Table of Contents

DIVISION DIRECTOR MEMORANDUM

Date: April 4, 2007

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Products

To: Members, Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials for sNDA 21-077, application to add COPD indication for Advair Diskus 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg)

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on May 1, 2007. As members of the PADAC you provide important expert scientific advice and recommendations to the US Food and Drug Administration (the Agency) on various regulatory decisions, including approval of new indications for drugs already marketed in the United States. The upcoming meeting is to discuss the supplemental NDA from GlaxoSmithKline (GSK) to add a chronic obstructive pulmonary disease (COPD) indication to the labeling for Advair Diskus 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder).

Advair is a combination product containing fluticasone propionate, a fluorinated corticosteroid, and salmeterol xinofoate, a long-acting beta-adrenergic agonist, formulated as a dry powder for oral inhalation. Three dosage strengths of Advair Diskus are currently marketed in the United States; these are Advair 100/50, Advair 250/50, and Advair 500/50, containing 100 mcg, 250 mcg, and 500 mcg, of fluticasone propionate, respectively, and each with 50 mcg of salmeterol. In the United States, Advair is currently approved for use in patients with asthma and in patients with COPD. All three dosage strengths are indicated as maintenance treatment of asthma. Only one dosage strength, Advair 250/50, has a COPD indication. The indication is for maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis. Advair 500/50 is not recommended for use in COPD because the pivotal studies that formed the basis of approval of Advair 250/50 showed no additional benefit with the higher dose, and the higher corticosteroid dose could have the potential for additional adverse effects in susceptible patients. GSK is now proposing to add a COPD indication to the labeling for Advair 500/50. The proposed indication includes increased survival, reduction of exacerbations, and improvement of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. Both the claims for increased survival and reduction of exacerbations are novel for a COPD drug in the United States. Further, the current COPD indication is restricted to patients with chronic bronchitis, while the new claim would add patients with emphysema as well.

Attached are the background materials for the meeting. The background materials include two documents prepared by the Agency, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document, the currently approved product label for Advair, and an Agency

Guidance document titled "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products." The documents prepared by the Agency include a clinical summary and a statistical summary of the major clinical studies conducted by GSK to support this application. The materials prepared by the Agency contain findings and opinions based on reviews of the GSK submission. These represent preliminary findings and do not represent the final position of the Agency. Indeed, the input and advice we receive from you in this PADAC meeting will be an important part of our deliberations in coming to our final conclusions.

Support for the COPD indication for Advair 500/50 comes essentially from two studies conducted by GSK: a three-year study (SCO30003) primarily designed to show a survival benefit, and a one-year study (SFCB3024) primarily designed to show reduced airflow obstruction.

The proposed claim for increased survival is supported by one study, SCO30003. In a meeting between the Agency and GSK held in August 2000, prior to approval of the COPD indication for Advair 250/50 in the United States, the study protocol SCO30003 was discussed. At that time GSK was told that it might be possible to support an increased survival indication on the basis of one study, but the results would have to be robust and a sufficient number of patients would have to be enrolled in the United States to ensure that the results in the US population trended in the same direction as the overall results.

Subsequent sections of this memorandum summarize some relevant findings from the two pivotal studies, followed by key issues, and questions for discussion at the PADAC meeting.

Study SCO30003

Study SCO30003 was double-blind, placebo-controlled, parallel-group in design conducted in 466 centers in 42 countries around the world. There were 190 centers in the US contributing approximately 23% of the study patients. Patients enrolled in the study were 40 to 80 years of age with a diagnosis of COPD based on accepted criteria (ERS Consensus Statement). Patients were required to be current or former smokers with a smoking history of at least 10 pack-years, have a pre-bronchodilator FEV1 of <60%, a pre-bronchodilator FEV1/FVC ratio <70%, and less than 10% increase in FEV1 following 400 mcg albuterol administered by MDI. The study had a 2-week run-in period, a 3-year (156-week) randomized treatment period, a 2-week follow-up period, and involved a total of 16 clinic visits at 12-week intervals. The treatment groups were fluticasone 500 mcg plus salmeterol 50 mcg (FSC500/50), salmeterol 50 mcg (SAL50), fluticasone propionate 500 mcg (FP500), and placebo, all administered twice-daily from the Diskus device, along with permitted background therapy. The primary endpoint was all-cause mortality in patients treated with FSC500/50 compared with placebo. All patients were followed for 3 years for assessment of survival, including those who prematurely discontinued study drug. Patients who discontinued study drug were contacted by telephone every 12 weeks. The cause of death was initially assigned by the investigator using the information available. A blinded Clinical Endpoints Committee (CEC) reviewed the records and assigned a cause of death to a pre-

defined set of categories (cardiovascular, pulmonary, cancer-related, other, unknown), and also assessed if the death was COPD-related. Secondary endpoints were rates of moderate and severe COPD exacerbation, quality of life determined by Saint George's Respiratory Questionnaire (SGRQ), and spirometry measures. A patient was considered to have a COPD exacerbation if an investigator intervention was required for worsening COPD symptoms. A COPD exacerbation was defined as moderate if treatment with systemic corticosteroids or antibiotics or both was administered, and severe if hospitalization was required. Safety was assessed by recording adverse events, incidence of bone fractures, oropharyngeal examination in all patients, and bone mineral density and ophthalmologic assessments in selected US centers.

The original sample size was 3800 to detect a 5% difference in the primary endpoint with an 80% power. This sample size was calculated based on the assumption of a 20% placebo mortality in patients with a FEV1 of <60% (from a prior study). The assumption was modified and two re-estimations of the sample size were done such that the final sample size was 6040. This sample size provided 90% power to detect a 4.3% difference in the primary endpoint.

The study had two planned interim analyses of all-cause mortality. The first analysis occurred after approximately 300 deaths, and the second analysis occurred approximately at the mid-point between the first interim analysis and the end of the study. At the interim analyses a Safety and Efficacy Data Monitoring Committee (SEDMC) looked at the results of safety and efficacy and gave a recommendation to the Steering Committee as to whether the study or a specific treatment arm should be stopped prematurely. At the two interim analyses no stopping boundaries were crossed and the study was continued. Both the interim analyses occurred after the sample size re-estimations and were done as planned.

A total of 6184 patients were randomized approximately equally to the four treatment groups, received at least one dose of study drug, and constitute the ITT population. Data from 72 patients from 5 investigators were excluded to form a modified ITT population, MITT, which includes 6112 patients. The reasons for excluding these 5 centers are reasonable and were acceptable to the Agency. Dispositions of study patients are shown in Table 1. There were a large number of discontinuations in all treatment groups with more discontinuations from the placebo treatment group compared to the active treatment groups. The discontinuations in the placebo treatment group occurred relatively early in the course of the study compared to the active treatment groups (Figure 1). This disproportionate discontinuation in the placebo treatment group makes interpretation of the comparative data between active treatment groups and placebo treatment group somewhat complicated.

Table 1. Patient disposition, n (%), [Study SCO30003]

	Placebo	**SAL50**	**FP500**	**FSC500/50**
Randomized	1545	1542	1551	1546
Completed treatment	857 (55.5)	966 (62.7)	950 (61.3)	1014 (65.6)
Discontinued	688 (44.5)	576 (37.3)	601 (38.7)	532 (34.4)
Reasons for discontinuation				

	Placebo	SAL50	FP500	FSC500/50
Adverse event	368 (23.8)	304 (19.7)	366 (23.6)	292 (18.9)
Consent withdrawn	139 (9.0)	137 (8.9)	118 (7.6)	120 (7.8)
Lost to follow-up	21 (1.4)	15 (1.0)	24 (1.6)	29 (1.9)
Lack of efficacy	104 (6.7)	63 (4.1)	45 (2.9)	33 (2.1)
Did not fulfill entry criteria	4 (0.3)	3 (0.2)	5 (0.3)	3 (0.2)
Non-compliance	19 (1.2)	21 (1.4)	16 (1.0)	20 (1.3)
Others	32 (2.1)	33 (2.1)	25 (1.6)	33 (2.1)
Analysis population				
ITT population	1545	1542	1551	1546
MITT population	1524	1521	1534	1533

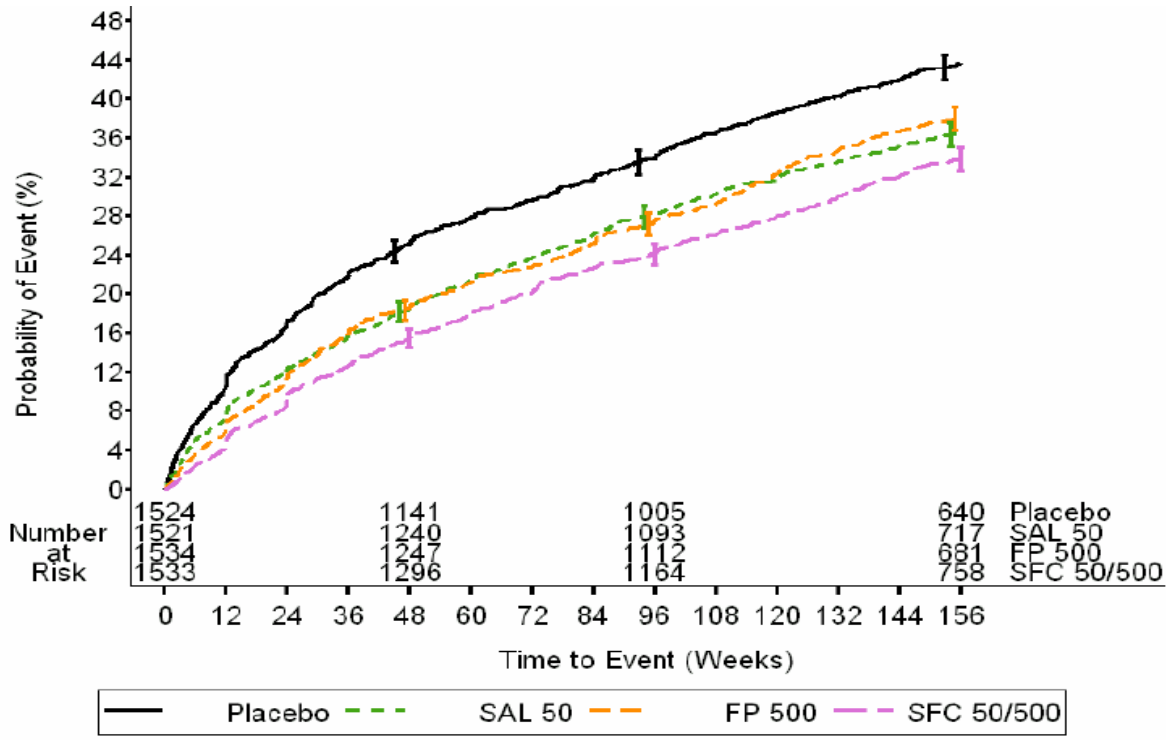

Figure 1. Time to study drug discontinuation – cumulative incidence curve (MITT), [Study SCO30003]

Survival status 3 years after initiation of study treatment was known for all patients in the MITT population except for one patient (this patient was in the FSC500/50 group and treated for 436 days). There were a total of 875 deaths that occurred in the MITT population within 3 years after start of the treatment. Causes of these deaths are shown in Table 2.

Table 2. Primary cause of death, n (%), [Study SCO30003]

	Placebo (n=1524)	SAL50 (n=1521)	FP500 (n=1534)	FSC500/50 (n=1533)
All death	231 (15.2)	205 (13.5)	246 (16.0)	193 (12.6)
COPD related death	91 (6.0)	93 (6.1)	106 (6.9)	72 (4.7)
Primary cause of death				
Cardiovascular	71 (4.7)	45 (3.0)	64 (4.2)	60 (3.9)
Pulmonary	74 (4.9)	80 (5.3)	91 (5.9)	61 (4.0)
Cancer	45 (3.0)	44 (2.9)	51 (3.3)	44 (2.9)
Others	23 (1.5)	22 (1.4)	30 (1.9)	11 (0.7)
Unknown	18 (1.2)	14 (0.9)	13 (0.8)	17 (1.1)

A summary of time to all-cause mortality for the four treatment groups within 3 years of treatment is shown graphically in Figure 2. The four treatment groups did not separate noticeably for the first 2 years of treatment; much of the separation occurred during the third year of treatment. The FP500 group and the placebo group were similar for the first 2 years, and then the FP500 group seemed to do worse than the placebo group. The FSC500/50 group and SAL50 group were similar for the first 2 years, and then the FSC500/50 group seemed to do better than the SAL50 group.

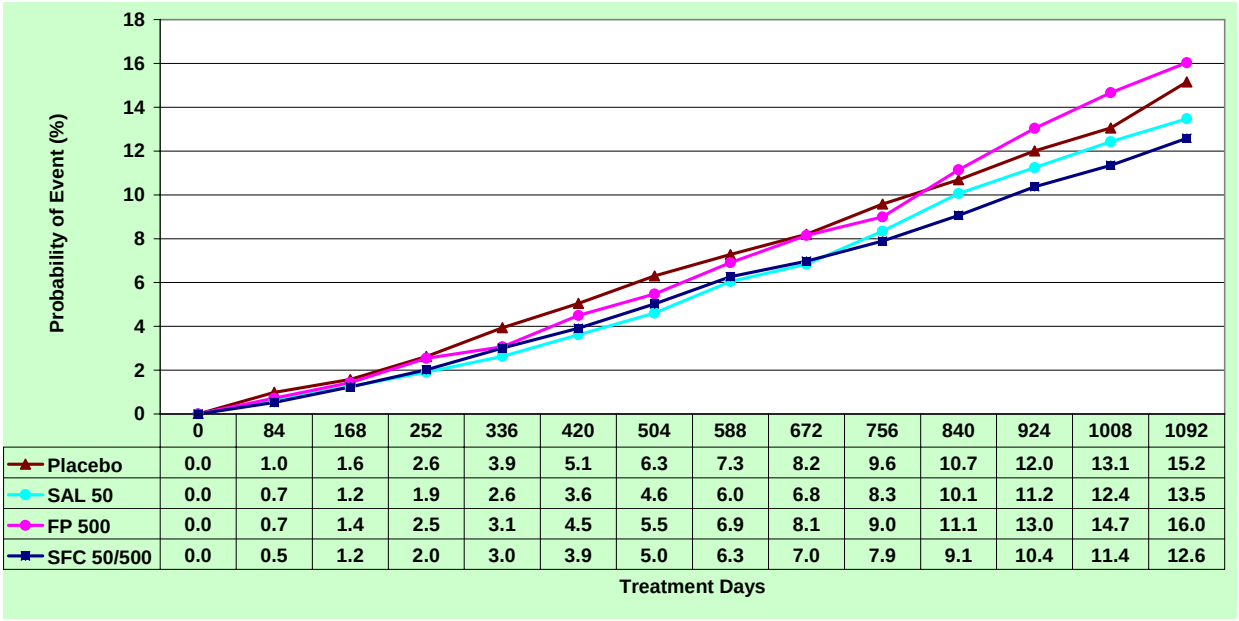

Figure 2. Time to all-cause mortality – cumulative incidence curve (MITT), [Study SCO30003]

The pre-specified primary analysis of time to all-cause mortality at 3 years stratified by smoking status for all treatment groups is shown in Table 3. For the primary comparison of FSC500/50 vs placebo the hazard ratio was 0.820 (unadjusted 95% CI was 0.677, 0.993) and unadjusted p-value was 0.041. Due to the interim analyses, this unadjusted p-value needs to

be compared to a significance level of 0.040. To allow comparison to the commonly used significance level of 0.05, the adjusted p-value was 0.052, and adjusted CI was 0.681, 1.002.

Table 3. Survival data analyses, [Study SCO30003]

	Placebo (n=1524)	**SAL50 (n=1521)**	**FP500 (n=1534)**	**FSC500/50 (n=1533)**
Deaths up to 3 years, n (%)				
Total	231 (15.2)	205 (13.5)	246 (16.0)	193 (12.6)
On treatment	116 (7.6)	106 (7.0)	140 (9.1)	102 (6.7)
During long term follow up	115 (7.5)	99 (6.5)	106 (6.9)	91 (5.9)
Log-rank analysis of time to all cause total death, % (95% CI)				
Probability of death by 3 years	15.2 (13.4, 17.0)	13.5 (11.8, 15.2)	16.0 (14.2, 17.9)	12.6 (10.9, 14.3)
Active treatment vs placebo				
Hazard ratio (95% CI)		0.88 (0.73, 1.06)	1.06 (0.89, 1.27)	0.82 (0.68, 0.99)
p-value (unadjusted) *		0.180	0.525	0.041
FSC500/50 vs components				
Hazard ratio (95% CI)		0.93 (0.77, 1.13)	0.77 (0.64, 0.93)	
p-value (unadjusted) *		0.481	0.007	

* Unadjusted p-value should be compared with adjusted significance level of 0.40 (adjusted for planned interim analyses)

Table 3 also shows the total deaths broken up as on treatment and during long-term follow up. On treatment deaths were those that occurred on or after the treatment start date and up to and including 14 days of stopping treatment. Deaths during long-term follow up were those that occurred more than14 days after stopping treatment. The hazard ratio for on treatment all-cause mortality for FSC500/50 vs placebo was 0.772 (95% CI was 0.59, 1.01) and the p-value was 0.055, which was not statistically significant. A drug with robust efficacy is expected to have a pronounced effect while patients are on treatment, which was not seen for FSC500/50 compared to placebo. On the other hand, early discontinuation that occurred more in the placebo treatment group in this study may underestimate the number of on treatment deaths in the placebo group.

On subgroup analysis of all-cause mortality based on regions, the survival improvement for US patients appeared to be low compared to non-US patients. The improvement of survival rate of FSC500/50 compared to placebo for the US was 1.6% (n=694). Survival improvement in Eastern Europe was 4% (n=578), Western Europe was 2.9% (n=952), Asia Pacific was 0% (n=376), and for other regions was 3.6% (n=457).

The prevalence and statistical analysis of moderate and severe exacerbations are shown in Table 4. All active treatment groups were statistically significantly better compared to the placebo group, and FSC500/50 was also statistically significantly better compared to the two other active treatment groups.

Table 4. Moderate and severe exacerbation data analyses, [Study SCO30003]

	Placebo (n=1524)	SAL50 (n=1521)	FP500 (n=1534)	FSC500/50 (n=1533)
Exacerbations in 3 years				
Number (%) of patients with at least one exacerbation	1057 (69.4)	1065 (70.0)	1055 (69.0)	1039 (67.8)
Number of exacerbations	3470	3258	3437	3224
Mean rate per patient per year	2.18	1.68	1.22	1.15
Negative binomial analysis of rate of exacerbation				
Mean number per year	1.13	0.97	0.93	0.85
Active treatment vs placebo				
Hazard Ratio (95% CI)		0.85 (0.78, 0.93)	0.82 (0.76, 0.89)	0.75 (0.69, 0.81)
p-value		<0.001	<0.001	<0.001
FSC500/50 vs components				
Hazard Ratio (95% CI)		0.88 (0.81, 0.95)	0.91 (0.84, 0.99)	
p-value		0.002	0.024	

SGRQ results were based on a subset of ITT patients who had completed a validated questionnaire and for whom a total score could be calculated. A total of 28 countries contributed to the population. In all of the treatment groups there was a decrease (improvement) in the total SGRQ score. The mean change from baseline of total SGRQ for active treatment minus placebo was -3.1, -2.0, and -1.0, for FSC500/50, SAL50, and FP500, respectively. Although the changes were statistically significant, none of the point estimates for mean changes crossed the 4 unit threshold that is considered to be clinically meaningful.

Post-bronchodilator FEV1 was available at baseline and for at least one follow-up visit in 5343 patients. In all treatment groups there was an increase in mean post-bronchodilator FEV1 at 24 weeks which gradually decreased thereafter. The mean change from baseline for post-bronchodilator FEV1 for active treatment minus placebo was 91.5, 47.4, and 41.5 mL, for FSC500/50, SAL50, and FP500, respectively. All active treatment groups were statistically significantly better compared to the placebo group, and FSC500/50 also was statistically significantly better compared to the two other active treatment groups.

Adverse events in this study were reported with similar frequency in all treatment groups if COPD exacerbations are included as adverse events. If COPD exacerbations are excluded, respiratory infections, both upper and lower, are increased in the FP500 and FSC500/50 groups. There were no remarkable changes in the ophthalmologic examination data and the reported changes in bone mineral density (BMD) were small. Patients with low BMD were advised to seek consultation, which may have influenced the decision about withdrawal from the study.

Study SFCB3024

Study SFCB3024 was double-blind, placebo-controlled, parallel-group in design conducted in 196 centers in 25 countries around the world. Unlike study SCO30003 there were no US centers in this study. Patients enrolled in the study were 40 to 80 years of age with a diagnosis of COPD based on accepted criteria (ERS Consensus Statement). Patients were required to be current or former smokers with a smoking history of at least 10 pack-years, have a pre-bronchodilator FEV1 of 25% to 70%, a pre-bronchodilator FEV1/FVC ratio <70%, less than 10% increase in FEV1 with 400 mcg albuterol administered by MDI, had coughed up sputum on most days during at least 3 months in 2 consecutive years, and a documented history of COPD exacerbation each year for the last 3 years including at least one exacerbation in the last year that required oral corticosteroids or antibiotics or both. The study had a 2-week run-in period, a 1-year (52-week) randomized treatment period, a 2-week follow-up period, and involved a total of 11 clinic visits. The treatment groups were the same as for study SCO30003. The primary endpoint was pre-bronchodilator FEV1 measured before the morning dose of study treatment at each clinical visit. Secondary endpoints were COPD exacerbation, and quality of life determined by SGRQ. A patient was considered to have COPD exacerbation if an investigator intervention was required for worsening COPD symptoms. COPD exacerbation was defined by the treatment that was administered. COPD exacerbation was assessed by the investigator at each clinical visit by reviewing patient daily record entries as well as by specific questioning, and categorized as mild, moderately severe, or severe. A mild exacerbation was defined as an exacerbation requiring increased use of relief albuterol MDI by more than 2 occasions per 24-hour period on two or more consecutive days compared with baseline and deemed clinically relevant by the investigator. A moderately severe exacerbation was defined as an exacerbation requiring treatment with antibiotics or oral corticosteroids, or both, either on the judgment of the investigator or according to predefined criteria. A severe exacerbation was defined as an exacerbation requiring hospitalization. Safety was assessed by recording adverse events, oropharyngeal examination, clinical laboratory evaluation, ECG, and assessment of HPA axis by serum cortisol.

A total of 1469 patients were randomized approximately equally to the four treatment groups, and 1465 patients received at least one dose of study medication and constitute the ITT population. Per-protocol (PP) population consisted of patients in the ITT who had no major protocol violation. Dispositions of study patients are shown in Table 5. There were a large number of discontinuations in all treatment groups with more discontinuations from the placebo treatment group compared to the active treatment groups. The discontinuations in the placebo treatment group occurred relatively early in the course of the study compared to the active treatment groups (Figure 3).

Table 5. Patient disposition, n (%), [Study SFCB3024]

	Placebo	**SAL50**	**FP500**	**FSC500/50**
Randomized	363	373	375	358
Completed treatment	221 (61)	253 (68)	266 (71)	269 (75)
Discontinued	140 (39)	119 (32)	108 (29)	89 (25)
Reasons for discontinuation				

	Placebo	SAL50	FP500	FSC500/50
Adverse event	68 (19)	61 (16)	55 (15)	46 (13)
Consent withdrawn	16 (4)	13 (3)	11 (3)	6 (2)
Lost to follow-up	8 (2)	8 (2)	8 (2)	8 (2)
Lack of efficacy	5 (1)	7 (2)	11 (3)	5 (1)
Did not fulfill entry criteria	3 (<1)	3 (<1)	3 (<1)	4 (1)
Non-compliance	7 (2)	5 (1)	11 (3)	5 (1)
Others	15 (4)	12 (3)	9 (2)	6 (2)
Analysis population				
ITT population	361	372	374	358
PP population	305	311	312	297

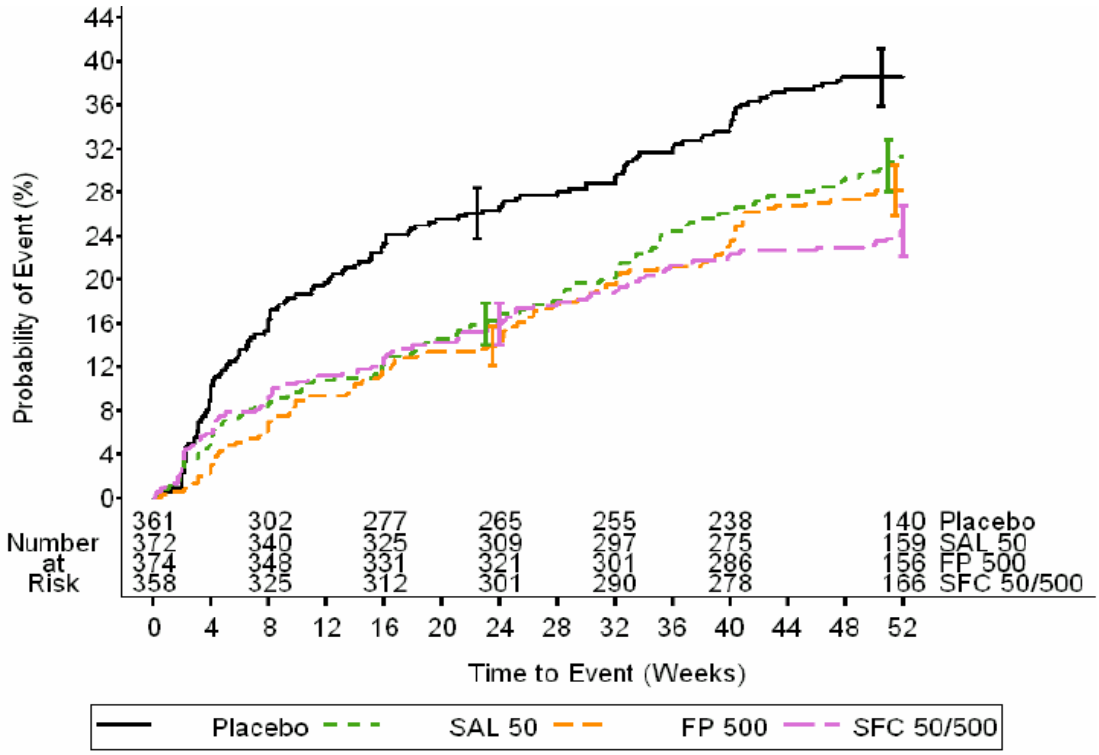

Figure 3. Time to study drug discontinuation – cumulative incidence curve (ITT), [Study SFCB3024]

Pre-bronchodilator FEV1 was the primary efficacy endpoint in this study. The change from baseline averaged over the 52 weeks of treatment was of primary interest. In all active treatment groups there was an increase in mean pre-bronchodilator FEV1 at 52 weeks (Table 6). All active treatment groups were statistically significantly better compared to the placebo group, and FSC500/50 also was statistically significantly better compared to the two other active treatment groups.

Table 6. Pre-bronchodilator (trough) FEV1 (mL) data analyses, [Study SFCB3024]

	Placebo (n=361)	SAL50 (n=372)	FP500 (n=374)	FSC500/50 (n=358)
Mean baseline FEV1	1266	1245	1260	1308
Mean change from baseline	-60	15	7	113
Active treatment - placebo				
Mean (95% CI)		60 (32, 88)	39 (11, 66)	133 (105, 161)
p-value		<0.001	0.006	<0.001
FSC500/50 - components				
Mean (95% CI)		73 (46, 101)	95 (67, 122)	
p-value		<0.001	<0.001	

The prevalence and statistical analysis of moderately severe and severe exacerbations are shown in Table 7. All active treatment groups were statistically significantly better compared to the placebo group, but FSC500/50 was not statistically significantly better compared to the two other active treatment groups.

Table 7. Moderately severe and severe exacerbation data analyses, [Study SFGB3024]

	Placebo (n=361)	SAL50 (n=372)	FP500 (n=374)	FSC500/50 (n=358)
Exacerbations in 1 year				
Number (%) of patients with at least one exacerbation	204 (56.5)	197 (53.0)	200 (53.5)	193 (53.9)
Number of exacerbations	382	366	374	331
Mean rate per patient per year	2.95	1.73	1.45	1.89
Negative binomial analysis of rate of exacerbation				
Mean number per year	1.51	1.12	1.11	1.03
Active treatment vs placebo				
Hazard Ratio (95% CI)		0.74 (0.62, 0.89)	0.74 (0.61, 0.88)	0.68 (0.57, 0.83)
p-value		0.001	0.001	<0.001
FSC500/50 vs components				
Hazard Ratio (95% CI)		0.92 (0.76, 1.11)	0.93 (0.77, 1.12)	
p-value		0.390	0.439	

SGRQ results were available at baseline and at the end of study for 318, 321, 340, and 320 patients in the placebo, SAL50, FP500, and FSC500/50 treatment groups, respectively. In all of the treatment groups there was a decrease (improvement) in the total SGRQ score. None of the point estimates for mean changes from baseline of total SGRQ for active treatment minus placebo crossed the 4 unit threshold that is considered to be clinically meaningful.

Adverse events in this study were reported with similar frequency in all treatment groups. The most common adverse event reported was COPD exacerbation. COPD exacerbation was most frequent in the placebo treatment group and least frequent in the FSC500/50 treatment group. Upper respiratory tract infection was as common in the placebo group as in the FSC500/50 group, although oropharyngeal candidiasis was three to four times more common in the FP500 group or FSC500/50 group than in either the placebo group or SAL50 group. Lower respiratory tract infections and pneumonia were common in the FP500 and

FSC500/50 groups. Serum cortisol value did not cross a predefined threshold value differentially in any of the treatment groups, though this is not the most sensitive measure of HPA axis integrity.

Key issues

The purpose of this PADAC meeting is to discuss the adequacy of the efficacy and safety data submitted by GSK to the Agency to support the approval of Advair Diskus 500/50 for COPD in the United States. While all clinical issues related to Advair are open for discussion, we are asking for a detailed deliberation on the claims of increased survival and reduction of exacerbation for Advair Diskus 500/50 in COPD patients. These two specific claims would be unique amongst all drugs that are currently approved in the United States for COPD. The drugs currently approved for COPD, including Advair 250/50, generally refer to the treatment of bronchospasm associated with COPD, intentionally focusing solely on the bronchodilator activity of the drugs because substantial evidence to support additional claims has not yet been provided for any drug. In the following paragraphs brief comments are made on the survival data and exacerbation data presented in previous sections of this document, followed by a brief comment on the overall safety findings.

Increased survival

The outcome of survival has essentially no measurement error and is considered clinically important. Support of an increased survival claim for Advair 500/50 comes from only one study, SCO30003. In this study, all but one of the 6112 patients were followed-up for survival status so there were essentially no missing data on this particular outcome. The cause of death was confirmed by an independent committee that reviewed all of the available data on all of the deaths. The survival outcome data of this study was well characterized and thoroughly analyzed.

In accord with our laws and regulations, the Agency usually requires more than one adequate and well-controlled study to provide independent substantiation of any finding that would results in a specific efficacy claim. In some situations, a single adequate and well-controlled study can support a specific new claim. The Agency's current thinking concerning the quantitative and qualitative standards for demonstrating the efficacy of a drug is articulated in a Guidance document titled "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products," which is included in this package. Some of the considerations in accepting a single study to support an efficacy claim include persuasive statistical findings, and consistency across study subjects. We would ask you to consider whether the results of study SCO30003 provide such evidence.

Study SCO30003 failed to show a statistically significant difference in survival between Advair 500/50 and placebo, with the unadjusted p-value being 0.041 versus the required significance level of 0.04. The primary analysis result was also not robust, being sensitive to small changes in the population analyzed. For example, by removing one country with the most favorable result (Iceland, n=41), the hazard ratio for all-cause mortality for Advair

500/50 vs placebo changes to 0.829 (95% CI 0.684, 1.005) and the p-value becomes 0.056. The finding also did not appear to be consistent across study subjects. On subgroup analysis based on regions, the survival improvement for US patients was low when compared to some other regions. Survival improvement of Advair 500/50 over placebo for the US was 1.6% compared to 4% for Eastern Europe. Furthermore, survival benefit of Advair 500/50 over placebo seemed to occur mostly during the third year of treatment (Figure 2), and was not primarily driven by patients who survived while on treatment but by patients who survived during long term follow up off treatment (Table 3). It is difficult to understand the attribution of the separation of the survival curves later in the study when many patients were off study treatments.

Although the primary comparison in study SCO30003 was between Advair 500/50 and placebo, the salmeterol and fluticasone treatment groups provide useful information. For a combination drug product, such as Advair, it is expected that each component would make a contribution to the claimed effect to justify the use of the combination product rather than one of its components. The rate and time course of discontinuations for the three active treatment groups were comparable in this study (Table 1, Figure 1), thus there is no confounder of early discontinuation when comparing the three active treatment groups. Advair 500/50 provided a favorable numerical trend of increased survival over both of its individual components, but its separation from salmeterol was marginal. Fluticasone appeared to be the worst performer of all the groups and had numerical trends even worse than placebo (Table 2, Table 3, Figure 2). This raises the question of whether Advair 500/50 provides substantial advantage in survival over salmeterol alone given the findings of this study and the known safety issues with fluticasone.

Reduction in exacerbations

COPD exacerbation has been linked to co-morbid conditions, can be life-threatening, and is believed to potentially contribute to permanent decrements in lung function. COPD exacerbation is an important clinical outcome measure. Although there is no clear consensus as to what constitutes an exacerbation, criteria often used to define an exacerbation include worsening of shortness of breath, increased sputum volume or purulence, worsening symptoms requiring changes in treatment or requiring urgent treatment or hospitalization.

Support for reduction in exacerbations for Advair 500/50 comes from two studies, SCO30003 and SFCB3024. In both studies exacerbation was defined in terms of use of medications or hospitalization. Although these are useful ways of capturing an exacerbation, there were some limitations, particularly in study SCO30003. In study SCO30003, COPD exacerbation was not defined or characterized precisely. There was no requirement for duration of an exacerbation and no limitation on how close two separate exacerbations could be to one another. The distinction between a COPD exacerbation and an adverse event was also somewhat blurred. As an extreme example, if an exacerbation led to death, and was counted as COPD related death, it would not be counted as an exacerbation if the exacerbation was not treated with antibiotics or corticosteroids or the patient hospitalized. In study SFCB3024 exacerbation was defined more robustly. Treatment of the exacerbation

was specified as a 10-day course of antibiotic or systemic corticosteroid treatment and 7 treatment free days were required between separate exacerbations.

Both studies were multinational and it is likely that there would be differences in the standard of care in various countries around the world and the threshold for starting antibiotics or systemic corticosteroids, and hospitalization would be different.

In both studies Advair 500/50 was statistically significantly better when compared to placebo for moderate and severe exacerbation (Table 4, Table 7). In study SCO30003 Advair 500/50 was also statistically significantly better when compared to both salmeterol and fluticasone given alone, but in study SFCB3024 Advair 500/50 was not statistically different when compared to either salmeterol alone or fluticasone alone.

The exacerbation program did not compare Advair 500/50 to a lower dose such as the currently approved Advair 250/50 dose; therefore, comparative risk-benefit assessment for different doses of Advair cannot be made. Note that the current airflow improvement indication for COPD is limited to Advair 250/50 because the pivotal studies that formed the basis of approval of Advair 250/50 for COPD showed no additional benefit with the higher dose, and the higher corticosteroid dose could have the potential for additional adverse effects.

Safety

The number of patients treated in these two studies was quite large and provides a rich source of safety information. In both studies middle age to elderly patients with a long smoking history and COPD were enrolled, and as expected there were a large number of deaths. Death was distributed across various categories of cardio-respiratory diseases, which is expected for this patient population. Death was the primary endpoint in study SCO30003, as discussed extensively before. In study SFCB3024 there were 24 deaths spread across the treatment groups.

Adverse events that were not fatal were also common in both studies. Adverse events were dominated by respiratory events, of which COPD exacerbations were the most numerous. COPD exacerbations were more frequent in the placebo-treated patients. Pneumonia was the second most common adverse event. Pneumonia was reported in 9%, 11%, 14%, and 16% of the patients in the placebo, SAL50, FP500, and FSC500/50 treatment groups, respectively, in study SCO30003. Pneumonia coded as a serious adverse event occurred in 69 (4%), 82 (5%), 121 (8%), and 138 (9%) of the patients in the placebo, SAL50, FP500, and FSC500/50 treatment groups, respectively. There was a clear predilection for pneumonia in the treatment arms containing fluticasone. While upper respiratory tract infection, such as candidiasis, is an acknowledged adverse effect of therapy with inhaled corticosteroid as a class, lower respiratory tract infection, such as pneumonia is not well described.

Other safety variables of interest that were evaluated in the studies were bone mineral density (BMD), ophthalmologic findings, and serum cortisol findings. BMD was measured in a subset of US patients enrolled in study SCO30003. Patients with low BMD withdrew earlier

than patients with normal BMD, thus the follow-up information at 3 years was very limited. Ophthalmologic findings including cataract and glaucoma, and serum cortisol data did not show any new, important concerns.

Questions

The purpose of this PADAC meeting is to discuss the relevant data and deliberate upon GSK's proposal to add a COPD indication for Advair Diskus 500/50 and gain claims for increasing survival and reducing exacerbations. At the meeting GSK will present an overview of the efficacy and safety data, followed by the Agency's presentation. There may also be presentations by other interested parties during the open public presentations.

Please keep in mind the following questions that will be discussed and deliberated upon following the presentations and discussion.

1. Do the data provide convincing, substantial evidence that Advair Diskus 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder) increases survival when used in the chronic treatment of patients with COPD?
    a) If not, what additional data should be obtained?
    b) Is additional dosing information needed (e.g., efficacy of Advair 500/50 vs. Advair 250/50)?

2. Do the data provide convincing, substantial evidence that Advair Diskus 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder) provide a clinically meaningful decrease in the rate of COPD exacerbation when used in the chronic treatment of patients with COPD?
    a) If not, what additional data should be obtained?
    b) Is additional dosing information needed (e.g., efficacy of Advair 500/50 vs. Advair 250/50)?

3. Do the data provide sufficient evidence that Advair Diskus 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder) provide substantial advantage on survival compared to salmeterol alone for the treatment of patients with COPD?

4. Does the increased incidence of respiratory tract infections and pneumonia seen in these studies warrant additional evaluation?

Please note that the questions above are preliminary and may change prior to the meeting. Final questions will be distributed on the day of the meeting. The main stem of all questions should generate a binary yes or no answer, and will be voted on by the voting members of the Committee.

We look forward to an informative and productive meeting and thank you for your time and commitment in this important public health service.

DRAFT Advisory Committee Questions
May 1, 2007

1) Do the data provide substantial convincing evidence that Advair Diskus (fluticasone/salmeterol inhalation powder) 500/50 mcg increases survival when used in the chronic treatment of patients with COPD?
    a. If not, what additional data should be obtained?
    b. Is additional dosing information needed (e.g., efficacy of Advair 500/50 vs. Advair 250/50)?

2) Do the data provide substantial convincing evidence that Advair Diskus (fluticasone/salmeterol inhalation powder) 500/50 mcg provides a clinically meaningful decrease in the incidence of COPD exacerbations when used in the chronic treatment of patients with COPD?
    a. If not, what additional data should be obtained?
    b. Is additional dosing information needed (e.g., efficacy of Advair 500/50 vs. Advair 250/50)?

3) Do the data provide sufficient evidence that Advair Diskus (fluticasone/salmeterol inhalation powder) 500/50 mcg provides substantial advantage for the treatment of patients with COPD when compared to salmeterol alone?

4) Does the increased incidence of respiratory infections and pneumonia seen in these studies warrant additional evaluation?

    a. If so, what additional data should be obtained?

PULMONARY - ALLERGY DRUGS ADVISORY COMMITTEE MEETING

May 1, 2007

CLINICAL BRIEFING DOCUMENT

NDA 21-077/s_029

ADVAIR DISKUS (Fluticasone/salmeterol) 500/50 mcg BID
to increase Survival and decrease Exacerbation Rate in
Chronic Obstructive Pulmonary Disease.

Primary Reviewer: Carol H. Bosken, M.D.
Secondary Reviewer: Lydia Gilbert-McClain, MD

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

TABLE OF ABRREVIATIONS

AE	Adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AUC	Area under the curve
BID	Twice a day
BMD	Bone Mineral Density
BMI	Body Mass Index
BQL	Below Quantitation Level
C_{10}	Concentration of salmeterol in blood 10 minutes after inhalation
C_{max}	Maximum concentration of a drug in the blood
CDRQ	Chronic Disease Respiratory Questionnaire
CEC	Clinical Endpoints Committee
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CV	Cardiovascular
DEXA	Dual Energy X-ray Absorptiometry
DPI	Dry Powder Inhaler
DRC	Daily Record Cards
DSI	Division of Scientific Investigation
ECG	Electrocardiogram
EQ-5D	European Quality of Life Questionnaire
ER	Emergency Room
ERS	European Respiratory Society
FEV_1	Forced Expired Volume in 1 second
FP	Fluticasone propionate 50 MCG bid
FSC	Fluticasone/salmeterol combination product, 500/50 mcg BID
GOLD	Glaxo Optimally Linked Database
GSK	GlaxoSmithKline
HLT	Higher Level Term
HPA-axis	Hypothalamic-Pituitary-Adrenal axis
HR	Hazard Ratio
ICS	Inhaled corticosteroids
ICU	Intensive Care Unit
ITT	Intention To Treat
LABA	Long-Acting Beta-Agonist
LTFU	Long Term Follow-up
LTOT	Long Term Oxygen Therapy
MedDRA	Medical Dictionary of Regulatory Activities
MID	Minimally Important Difference
MIDAS	Medications. Indications, Diagnoses, Adverse Events and Symptoms
MDI	Multidose Inhaler
MRC	Medical Research Council
NEC	Not Elsewhere Classified
NYHA	New York Heart Association
PD	Pharmacodynamic
PEFR	Peak expiratory flow Rate
PK	Pharmacokinetic
PP	Per-protocol
Pre-BD	pre-Bronchodilator
PRO	Patient-Reported Outcome
R&D	Research and Development
SAL	Salmeterol 50 mcg BID
SaO_2	Oxygen Saturation

SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SEDMC	Safety and Efficacy Data Monitoring Committee
SGRQ	Saint George's Respiratory Questionnaire
sNDA	Supplemental New Drug Application
SAE	Serious adverse event
SOC	System Organ Classification
VPC	Ventricular Premature Contraction

1 EXECUTIVE SUMMARY

1.1 Brief Overview of Clinical Program

Advair is a combination of fluticasone propionate, a fluorinated corticosteroid and salmeterol xinofoate a long-acting beta-adrenergic agonist, formulated as a dry powder for oral inhalation. The proposed indication is to prolong survival, decrease the exacerbation rate, and to relieve bronchial obstruction in patients with chronic obstructive pulmonary disease (COPD). The proposed dose is 500/50 mcg BID with a 250/50 mcg BID dose as an alternative. Advair, at the 250/50 mcg BID dose is currently approved for the relief of airflow obstruction in patients with COPD associated with chronic bronchitis. The pivotal trials supporting the relief of air flow obstruction indication documented the superiority of fluticasone/salmeterol 500/50 mcg BID to placebo and to each of the two components: Fluticasone (FP) 500 mcg BID and salmeterol (SAL) 50 mcg BID.

Support for the new indications in the current supplement is provided by two randomized, double-blind, placebo-controlled studies: One three-year trial (Study SCO30003) was designed to demonstrate a survival benefit for the fluticasone/salmeterol (FSC) combination product and to demonstrate a reduction in moderate/severe COPD exacerbations. An additional, one-year trial (Study SFCB3024) was submitted for replication of the reduction in exacerbations. Both of these studies included the results of pulmonary function testing to support the reduced airflow obstruction indication. In addition, the results of pulmonary function testing in Study SFCA3006, a study that was previously reviewed by the FDA, were referenced in further support of the reduction in airflow indication.

Study SCO30003 enrolled 6184 patients of whom 6112 were included in the ITT population. Vital status was ascertained for 6111 of the patients in the ITTP. Of these, 1533 patients received FSC. All 6184 were included in the safety population. Study SFCB3024 enrolled 1469 patients; however, 4 received no study medication so both the ITTP and safety population consisted of 1465 patients. Three hundred-sixty-one patients received FSC. Total treatment years of exposure to FSC was 3700 in Study SCO30003 and 302 years in Study SFCB3024, resulting in a total treatment exposure of 4002 years.

1.2 Efficacy

1.2.1 Mortality

The mortality assessment was based entirely on study SCO30003, a randomized, double-blind, placebo-controlled comparison of FSC to SAL, FP, and placebo. The patients were 40 to 80 years of age, with a clinical diagnosis of COPD and a FEV_1 % predicted of <60%. They were all current or former smokers and had a lifetime smoking history of at least 10 pack-years. Reversibility, defined as a ≥12% and ≥200 mL increase in FEV_1 compared to the predicted normal FEV_1 was present in less than 10% of the study population. The patients could not have been taking oral corticosteroids or long term oxygen therapy at the time of enrollment. Enrollment into this trial was international; 442 centers in 42 countries. Patients enrolled in the United States made up 23% of the study populations.

The vital status of all but one of the patients was documented at the three-year post initiation of treatment time point. A cause of death was assigned by a blinded Clinical Endpoint Committee (CEC) on the basis of all available clinical information. The CEC assigned a primary cause of death as cardiac, pulmonary, cancer, other, and unknown. An assessment was also made as to whether the death was COPD related, and the categories included possible, probable, and definite, as well as no and unknown. For the analysis of COPD-related deaths, all but the "no" and "unknown" categories were classified as COPD-related. Because follow-up was almost complete, but time on treatment was not, an analysis of on-treatment deaths was also performed.

Results

The three-year all-cause mortality was 15.2, 13.5, 16.0, and 12.6% in the placebo, SAL, FP, and FSC-treated patients, respectively. The difference between placebo and FSC was 2.6%. The unadjusted Hazard Ratio (95%) for death, comparing active treatment to placebo, was 0.879 (0.729, 1.061), 1.060 (0.886, 1.268), and 0.820 (0.677, 0.993) for the comparison with SAL, FP, and FSC, respectively. After adjustment for the interim analyses, the Hazard Ratio comparing FSC to placebo was 0.825 (0.681, 1.002) and the p-value was 0.052. Thus the primary efficacy outcome measure failed to reach the pre-specified significance level required to claim success. Of note was variation within subpopulations in the response to FSC. In the US population the difference in all-cause survival, comparing FSC to placebo, was only 1.6%. Patients with FEV_1 <40 % predicted and those who were older than 65 years of age had less of a response to FSC than those with a FEV_1 > 40% predicted and those ≤65 years of age.

The cause of death was cardiovascular in 4% of the patients, pulmonary in 5%, cancer in 3%, and "other" or "unknown" in the remainder. The distribution of cause of death was similar in the four treatment groups although 6% of the deaths were pulmonary in the FP treatment group compared to 5, 5, and 4% in the placebo, SAL, and FSC-treated patients, respectively

Deaths were categorized as COPD-related in 6.0, 6.1, 6.9, and 4.7% of the patients, respectively. The hazard ratio for death comparing active treatment to placebo was 1.013 (0.759, 1.352), 1.159 (0.876, 1.534), and 0.776 (0.776 (0.570, 1.057) for the comparison with SAL, FP, and FSC, respectively. On-treatment mortality was 7.6, 7.0, 9.1, and 6.7% in the placebo, SAL, FP, and FSC groups, respectively. The hazard ratio comparing FSC to placebo for on-treatment mortality was 0.772 (95% CI 0.570, 1.057).

1.2.2 COPD Exacerbations

COPD exacerbations were defined in both Study SCO30003 and SFCB3024 by the treatment that was administered. An exacerbation was moderate if it was treated with antibiotics or systemic corticosteroids, and severe if the patient was hospitalized. There was no further definition of exacerbation in study SCO30003; no requirement for specific symptoms, for duration of symptoms, for treatment of the exacerbation, or for a duration of symptom free time between individual events. In study SFCB3024 there was no single definition of an exacerbation, however, lists of symptoms that would suggest that various treatments would be appropriate, were included in the protocol. In addition, a symptom-free period of at least 7 days

was required between each exacerbation, and treatment of the exacerbation was specified to be a 10-day course of antibiotics or systemic corticosteroids.

Study SFCB3024 was similar to SCO30003 in that it was a randomized, double-blind placebo-controlled comparison of FSC to its component parts and placebo in the treatment of patients with COPD. The pulmonary function in this group was slightly less decreased than in study SCO30003; the FEV_1 was between 25 and 70% of predicted. The patients were required to have a history of chronic bronchitis and to have experienced at least one moderate or severe exacerbation in the 12 months prior to enrollment. There was no requirement for cough or sputum production in study SCO30003 and no requirement for previous exacerbations. Thus the tendency to exacerbations and perhaps the responsiveness of the patients enrolled in SFCB3024 may have been greater than in the patients enrolled into SCO30003. Patients were enrolled in SCFB3024 in Europe, S. Africa, Australia and Canada.

The exacerbation rate is highly variable among patients with COPD. Some patients suffer progressive deterioration of function without periodic acute increases in symptomatology while others have repeated bouts of increased shortness of breath and increased sputum production. This variability presents analytic problems which were handled differently in the two exacerbation studies. The Poisson distribution, commonly used to compare infrequent events over time, is thought to underestimate this variability and to inflate the importance of the difference in group means [1]. One solution to the problem is an analysis using what is called the negative binomial distribution, and this technique was used in study SCO30003. The Poisson distribution was used in study SFCB3024 so it is possible that there is some overestimation of the differences among the treatment groups that were seen in SCFB3024. On the other hand, because of the requirement for an exacerbation in the 12 months prior to enrollment, the variability of the study population should be somewhat less than of the general population of COPD patients. In both studies, exacerbations were counted only if they occurred during treatment with study drug.

Results

In study SCO30003, 70% of the patients experienced at least one moderate/severe exacerbation over the three-year treatment period. Using the negative binomial distribution to calculate the rates, there were 1.13, 0.97, 0.93, and 0.85 events/year in the placebo, SAL, FP, and FSC patients, respectively. The Hazard Ratio (95% CI) comparing FSC to placebo was 0.749 (0.689, 0.814, $p < 0.001$) and comparing FSC to SAL the Hazard ratio was 0.878 (0.808, 0.954, $p=0.002$). In study SFCB3024, 54% of the patients reported at least one exacerbation during the one year of treatment. The rates calculated with the Poisson distribution were 1.30, 1.04, 1.05, and 0.97 events / year. The Hazard Ratios (95% CI) comparing active treatment to placebo were 0.802 (0.694, 0.926), 0.807 (0.699, 0.931), and 0.746 (0.643, 0.865) for SAL, FP, and FSC respectively. All of the active treatments were significantly better than placebo at lowering the exacerbation rate. However, FSC was not superior to SAL or FP in this analysis. Thus the degree of improvement as expressed by the Hazard ratio comparing FSC to placebo was quite similar in the two studies (0.749 and 0.746) despite the differences in the characteristics of the patients enrolled.

Severe COPD exacerbations were reported for 25% of the patients in Study SCO30003. The calculated rate was 0.19, 0.16, 0.17, and 0.16 events / year in the placebo, SAL, FP, and FSC groups, respectively. The Hazard Ratio (95% CI) comparing FSC to placebo was 0.834 (0.710, 0.981) and the Hazard Ratios (95% CI) comparing FSC to the components were 1.022 (0.870, 1.200) for SAL and 0.954 (0.815, 1.117) for the comparison to FP. Only 120 (8.2%) of the patients in study SFCB3024 experienced a severe exacerbation in the one year of follow-up. The rates were estimated to be 0.07, 0.08, 0.06, and 0.07 events / year. No statistical analysis was performed on this outcome, but it appears that FSC did not affect the rates of severe exacerbations.

The rate of corticosteroid-treated exacerbations was decreased by treatment with FSC in both studies. In SCO30003 the calculated rates were 0.80, 0.64, 0.52, and 0.46 events / year in the placebo, SAL, FP, and FSC groups, respectively. In SFCB3024 the respective rates were 0.76, 0.54, 0.50, and 0.46 events / year. As was seen for the overall rates of moderate/severe exacerbations, the hazard ratios comparing FSC to placebo were similar in the two study populations: 0.568 in Study SCO30003 and 0.607 in Study SFCB3024. Systemic corticosteroid use was also tabulated in Study SCO30003. It was decreased by treatment with FSC as measured by the cumulative days of treatment: systemic corticosteroids were administered for a mean of 41.1, 38.7, 36.9, and 35.0 days in the placebo, SAL, FP, and FSC groups, respectively.

The rate of antibiotic-treated exacerbations was not submitted in Study SCO30003. Because respiratory infections were elevated in the FSC-treated patients, the FDA statistical reviewer calculated the rate of exacerbations treated with antibiotics alone and found them elevated in the FSC treated patients compared to placebo and SAL. The Hazard Ratio (95% CI) for time to antibiotic-only-treated exacerbations was 1.15 (1.03, 1.29) comparing FSC to placebo and 1.22 (1.09, 1.36) comparing FSC to SAL. The rate was comparable in the FSC and FP groups (HR = 0.96; 95% CI 0.86, 1.07). The rate of all antibiotic-treated exacerbations was submitted in Study SFCB3024 and they were 0.72, 0.65, 0.75, and 0.75 in the placebo, SAL, FP, and FSC groups, respectively. These rates were based on small number of events and no statistic was calculated. However, if anything, the rate was increased in the FSC-treated patients in this population as well.

In summary, treatment with FSC decreased the rate of moderate/severe exacerbations and the sub-group of moderate/severe exacerbations that were treated with corticosteroids when compared to placebo, and the reduction was similar in both studies. For both of these outcomes, FSC was superior to SAL and FP in study SCO30003, but all three drugs were equally efficacious in Study SFCB 3024. Severe exacerbations were reduced by FSC treatment in study SCO30003, but the reduction was not as great as that seen during treatment with SAL. On the other hand, antibiotic-treated exacerbations were actually elevated during FSC treatment.

It must be noted that the analysis of exacerbations is based on a subjective endpoint. While the administration of treatment and hospitalizations were objective events, the decision on the part of the investigator to institute any of the therapies was based on an assessment of the patient's status without a requirement for physiologic measurements. In addition, in Study SCO30003 there were no time limits on either the exacerbation or the treatment. This resulted in the inclusion of exacerbations of 1 day to more than one year in duration. While the distribution of

exacerbation duration among the treatment groups was approximately equal, this variability does raise the question of what exactly was being treated. It also raises a question about the adequacy of the treatment of the exacerbations. In study SFCB3024, a ten-day treatment course was prescribed by protocol whereas in Study SCO30003 at least some patients were treated for just one day with solumedrol. That those patients returned with another "exacerbation" one week later may be related more to the inadequacy of the treatment of the exacerbation than of the chronic treatment with study drug.

Differences in treatment practices were also suggested by the regional differences in exacerbation rates and duration reported in the regional groupings. The rate of moderate/severe exacerbations in the placebo-treated patients, calculated with the negative binomial model, was 1.18, 1.02, 0.70, 1.28, and 1.54 in the US, Asia, Eastern Europe, Western Europe, and Other regions, respectively. The respective difference between FSC and placebo was 0.21, 0.16, 0.07, 0.41, and 0.61 all favoring FSC. Likewise the duration of treated exacerbations varied between 14.3 and 19.7 days. Finally, severe exacerbations were defined by hospitalization, a decision which is not only affected by the clinical appearance of the patient but by societal policies governing the use of hospital facilities.

1.2.3 Saint George's Respiratory Questionnaire

The Saint George's Respiratory Questionnaire (SGRQ) was used to assess quality of life in both studies SCO30003 and SFCB3024. The difference in the total SGRQ score comparing FSC to placebo was 3.0 points in Study SCO30003 and 2.2 points in Study SFCB3024. Because the minimally important difference (MID) is generally taken to be 4.0 points, neither study provided support for a quality of life claim for FSC. The international nature of both pivotal studies also presented a problem in administering and interpreting the SGRQ. After initiation of the studies, it was noted that not all of the translated questionnaires had been validated. A retrospective validation project resulted in removal of some of the questionnaires from the analysis and the deletion of questions from questionnaires that were otherwise considered valid. Of the remaining validated questionnaires, some used a recall period of 12 months and others a recall period of 3 months. Analysis of subgroups based on those with and without all the questions and those using a 3 month or 12 month recall period failed to show any differences comparing active treatment to placebo that reached the MID.

1.2.4 Spirometry

In Study SCO30003 the FEV_1, measured 30 minutes after inhalation of albuterol, was the outcome of interest whereas in Study SFCB3024 the pre-albuterol FEV_1 was the primary functional outcome. The analysis in both of these studies was a repeated measures ANOVA which assessed the difference between active treatment and placebo averaged over the entire treatment period.

Study SFCA3006 was also submitted to support an indication for the relief of airflow obstruction. This study was previously reviewed by the FDA and will only be summarized here. It was a 24 week study comparing FSC 500/50 mcg BID to the components and placebo in patients with moderately severe COPD. The outcome variables were the pre-study medication

and 2 hour post-study medication FEV_1. These assessments were chosen because the study was submitted to support the first approval for a new indication of a combination product. It was therefore, important to measure the trough (pre-dose) FEV_1 (to assess the SAL contribution to efficacy) as well as the 2-hour post dose FEV_1 (to measure the FP contribution) in order to demonstrate that FSC was superior to each of the components. Having demonstrated the superiority of FSC to its components, it was only necessary to choose one of the measures to follow longitudinally in the more recent studies.

There were, however, other differences when comparing Study SCFA3006 to the other two pivotal trials. In study SCFA3006 the analysis was based on an endpoint comparison where only the last measurements (taken at 24 weeks or the last available value if the patient withdrew early) were included. Endpoint analyses were included as secondary outcomes in studies SCO30003 and SCFB3024 so these can be used for comparison. Of more concern is the difference in study populations. The patients enrolled in Study SCFA30006 were more reversible (54% of the population) than the patients enrolled in the other two studies (18 and 17% in Study Study SCO30003 and SFCB3024, respectively.

Results

In study SCO30003 the post bronchodilator FEV_1 increased in all of the treatment groups to a maximum at 24 weeks. Subsequently the values decreased over the rest of the treatment period. The early increase was greatest and the rate of fall smallest in the FSC-treated patients, and the early increase was smallest and rate of fall greatest in the placebo-treated patients. Both values were intermediate in the SAL and FP-treated patients. In the repeated measures analysis the mean change (SE) over the course of the trial was -62.3 (6.2), -20.9 (6.0), -15.0 (5.9), and 29.2 (5.8) mL for the placebo, SAL, FP, and FSC patients, respectively. The mean (SE) difference between FSC and placebo was 91.5 (8.5) mL. The mean (SE) difference between SAL and placebo was 41.5 (8.6) mL and between FP and placebo it was 47.4 mL (8.6).

In study SFCB3024 the pre-bronchodilator FEV_1 was the primary outcome measure. The mean change (SD) over the 52 weeks was -60 (272), 15 (255), 7 (272), and 113 (286) mL in the placebo, SAL, FP, and FSC groups, respectively. The mean (SE) difference comparing FSC to placebo in the repeated measures ANOVA was 133 (14.3) mL. The mean (SD) change in post-bronchodilator FEV_1 were -15 (248), 33 (249), 42 (274), and 108 (336) mL, and the mean (SE) difference comparing FSC to placebo in the repeated measure ANOVA was 76.1 (15.1) mL.

Study SFCA3006 compared the baseline, pre-treatment FEV_1 to the 2-hour post-treatment FEV_1 at six months. The values increased in all treatment groups, and the difference between FSC and placebo of 233 mL.

1.2.5 Summary and Conclusions

All-cause mortality over three years was 2.6% less in patients randomized to treatment with FSC compared to patients randomized to placebo treatment. In the statistical analysis that took into account the interim analyses, the p-value for this difference was 0.052. Thus the probability that this estimate is an accurate reflection of the population value is less than conventionally required to accept the result as true. The mean increase in 90% survival was 132 days or approximately 4

months. In the patients enrolled in the United States, the results were less impressive. The difference in survival was 1.6% at three years or 75 additional days of life.

The results for moderate/severe COPD exacerbation rates showed a decrease by all of the active treatments. FSC was also superior to SAL and FP in the three-year follow-up study. Although the definition of an exacerbation was less than optimal in Study SCO30003, there was clearly a decrease in the events measured and in the use of systemic corticosteroids. Pulmonary function was better in FSC-treated patients in three pivotal studies. Finally, the results of the SGRQ did not support an improvement in quality of life during FSC treatment in either study SCO30003 or SCFB3024.

1.3 Safety

The total treatment exposure to FSC in Study SCO30003 and SFCB3024 was 4002 years. All of the patients were 40 years of age or older and all were treated with the 500/50 mcg BID dose.

1.3.1 Deaths

Deaths were reviewed as the primary efficacy outcome in study SCO30003 (Section 1.2.1, pg 9). For the safety analysis, deaths were characterized by the adverse event that precipitated death, instead of the CEC-adjudicated cause of death. Using this categorization there were 533 deaths (133 [9%], 126 [8%], 160 [10%], and 114 [7%]) in the placebo, SAL, FP, and FSC groups, respectively, that resulted from an AE that started during randomized treatment. The MedDRA (Medical Dictionary of Regulatory Activities) preferred term of COPD was the most frequent event and was reported in 2.1, 2.0, 2.4, and 1.5% of the patients in the placebo, SAL, FP, and FSC groups, respectfully. Respiratory failure was the next most common event and occurred in 0.8, 1.0, 1.4, and 0.5% of the placebo, SAL, FP, and FSC patients, respectfully. All other events occurred in less than 1.0% of the patients in any treatment groups. In order of overall frequency, Sudden death/Cardiac arrest, MI/Acute MI, Pneumonia, Lung neoplasm, and Cerebrovascular accident were reported in ≥ 5 patients in any active treatment group. COPD, Respiratory failure, and Pneumonia were most common in the FP treatment group. If Adverse events with onset within 14 days of stopping treatment are tabulated then 9.9, 9.0, 11.9, and 9.4% of the placebo, SAL, FP, and FSC patients, respectively, died of an AE with onset during or immediately following randomized treatment (pg 38).

There were 24 deaths in study SFCB3024 (1 year of treatment), most of which were cardiovascular. Death was ascribed to a pulmonary, non-cancer cause in 3 placebo and 1 SAL-treated patient.

1.3.2 Adverse Events

In both studies, the adverse events (AEs) were reported as percentage of patients affected and as the rate of the event / 1000 years of drug exposure. The rates were included to adjust for differing lengths of time on study medication. In Study SCO30003, AEs were reported separately for those that occurred during study treatment, those that occurred during the two weeks following termination of treatment with study drug, and those that occurred more than two

weeks after the patient had stopped study treatment. MedDRA lists adverse events by preferred term (the most specific) grouped under Higher Level Terms (HLT) which are in turn grouped under system organ classifications (SOC). Analyzing events by HLT may reveal relationships to treatment that can not be detected when infrequent events (each preferred term) are analyzed separately. The respiratory events observed in study SCO30003 were tabulated by preferred term, by HLT, and in a grouping of "Lower respiratory tract infections of bronchitis or pneumonia" This was a non-MedDRA classification created for this application, and it included the pneumonia and bronchitis preferred terms.

In general, all of the summaries of adverse events were dominated by respiratory events and of the respiratory events, exacerbations of COPD were the most numerous. In most of the tabulations (serious events, non-serious events, respiratory events) COPD exacerbations were most frequent in the placebo-treated patients. Only in the tabulation of serious AEs in study SFCB3024 were COPD exacerbations more frequent in the FSC patients (8% of the patients [99.3 events/1000 treatment-year]) than in the placebo patients (5% of the patients [89.6 events / 1000 treatment-year]). Since moderate/severe exacerbations were decreased (Section 1.2.2) this suggests a substantial increase in mild exacerbations in the FSC treated patients in this study. This finding was not replicated in study SCO30003 where the rate of adverse event COPD exacerbations paralleled the rate of moderate/severe exacerbations reported in the efficacy review.

In the listing of serious adverse events by preferred term, pneumonia was the second most common event after COPD. It occurred in 69 (4%), 82 (5%), 121 (8%), and 138 (9%) of the patients treated with placebo, SAL, FP, and FSC, respectively. The respective rates were 23.5, 24.1, 41.9, and 47.3 events / 1000 treatment-years. In the tabulation of common adverse events ($\geq$ 5% of patients in any active treatment group), in order of frequency, COPD, Nasopharyngitis, Upper respiratory infection, and Pneumonia were all more common in the FSC-treated patient than in placebo or SAL treated patients. The rate for Nasopharyngitis was similar in patients treated with FP and FSC. Headache was most common in the placebo-treated patients but bronchitis was more common in the FSC-treated patients. A potentially important but uncommon event was Cerebrovascular accident, which was seen more frequently in the fluticasone-containing regimens: 2.7, 2.5, 5.1, and 3.2 events / 1000 treatment-years in the placebo, SAL, FP, and FSC groups, respectively. The overall number of events was small (N=45) and no clinical correlates could be found for the preponderance of events in the FP group.

Respiratory Tract Adverse Events

In a listing of serious respiratory events by HLT in Study SCO30003, Bronchospasm and obstruction was most frequent and occurred at a rate of 261.4, 230.5, 267.5, and 257.6 events /1000 treatment years in the placebo, SAL, FP, and FSC-treated patients, respectively. In this grouping, Lower respiratory tract infections was the second most common category and was reported as 35.1, 32.9, 56.3, and 61.6 event / 1000 treatment years in the placebo, SAL, FP, and FSC-treated patients, respectively. Respiratory failure was third and was reported as 13.4, 10.8, 14.1, and 1.8 events / 1000 treatment years in the placebo, SAL, FP, and FSC-treated patient, respectively. Chest pain and pneumothorax were reported as serious AEs at low frequency (<10 events / 1000 treatment-years), but in more FSC patients than placebo. Grouping common

respiratory adverse events (≥ 3% of patients in any active treatment group) by HLT orders Upper respiratory tract infections (251, 226, 275, and 285 events / 1000 treatment years) second after COPD (929, 766, 782, 672 events / 1000 treatment-years), followed by Lower respiratory tact infections (146, 141, 186, and 195 events /1000 treatment years) and Lower respiratory tract signs and symptoms (50, 51, 73, and 72 events / 1000 treatment years. Breathing abnormalities (57, 47, 43, and 25 events / 1000 treatment-years) and Respiratory failure (15, 14, 17, and 13 events / 1000 treatment years) followed the pattern of COPD and were less frequent in the FSC-treated patients (For less common events, see Table 13. pg 45). The pattern of events was similar in Study FSCB 3024. Bronchospasm and obstruction and Breathing disorders were less frequent in the FSC treated patient and infections, both upper respiratory and lower respiratory were increased in the fluticasone-containing regimens.

Respiratory Tract Infections

Examination of AEs of lesser frequency showed the expected increase in oropharyngeal candidiasis, dysphonia, and oropharyngeal pain in fluticasone- treated patients. These events are all grouped under Upper respiratory tract infections in MedDRA, and the number of expected events was sufficient to explain the increased incidence of the Upper respiratory tract infections HLT. They are all included in the current label, and the category was not further explored. "Lower respiratory tract infections of pneumonia and bronchitis" included all of the pneumonia, lung infection and bronchitis terms other than COPD and Infective exacerbation of chronic obstructive pulmonary disease that occurred in the database. (For complete list of preferred terms see Table 54, pg 105.) This combined group of events was reported in 20, 21, 24, and 29 % of the patients in the placebo, SAL, FP, and FSC groups, respectively. The respective rates were 151.9, 147.0, 192.1, 204.6 events / 1000 treatment-years. In a time-to-event analysis the hazard ratio comparing active treatment to placebo was 0.995 (0.851, 1.164), 1.190 (1.024, 1.384) and 1.375 (1.189, 1.591) in the placebo, SAL, FP, and FSC groups, respectively. The hazard ratio comparing FSC to its components was 1.384 (1.199, 1.597) for SAL and 1.154 (1.007, 1.324) for FP.

To further describe the type of lower respiratory tract infection that was responsible for the adverse events, an analysis was performed of the pneumonia cases alone. Pneumonias were reported in 9, 11, 14, and 16% of the in the placebo, SAL, FP, and FSC groups, respectively. The respective rates were 51.9, 51.5, 84.4, and 87.6 events / 1000 treatment-years. The hazard ratio for time to first pneumonia was 1.088 (0.867, 1.365), 1.533 (1.240, 1.894) and 1.639 (1.331, 2.017) for the comparisons of SAL, FP, and FSC to placebo, respectively. In the comparison of FSC to its components the Hazard was increased in comparison to SAL but not in comparison to FP. No analysis of non-pneumonia lower respiratory tract was presented. In order to explore this issue further, the FDA statistician performed a time-to-event analysis on the events included in the list of "Lower respiratory tract infections of pneumonia or bronchitis" that were not included in the "Pneumonia" analysis. The incidence of this event was 16, 15, 16, and 19%, and the hazard ratio (95% CI) comparing FSC to placebo was 1.23 (1.02, 1.23). Bronchitis, including acute, bacterial and viral (N=660) occurred in 11, 12, 12, and 14% of the patients, and the hazard ratio (95% CI) comparing FSC to placebo was 1.24 (0.99, 1.55). The importance of the increase in respiratory tract infections is suggested by the increased incidence of antibiotic-only treated exacerbations in the FSC-treated population.

Other Adverse Events of Interest

Bone disorders and bone fractures were reported in a few more FP and FSC patients than in the placebo and SAL groups. The rate of bone disorders was 27.5, 28.9, 29.3, and 32.2 events / 1000 treatment years and the rate of fractures was 18.6, 20.4, 20.3, and 22.4 events / 1000 treatment-years in the placebo, SAL, FP, and FSC groups, respectively. Bone mineral density (BMD) was measured at the hip and spine in a subset of patients enrolled in the United States. Baseline values were higher in the SAL (0.893 gm/cm^3) and FSC (0.905 g/cm^3) than in the placebo (0.854 g/cm^3) and FP (0.853 g/cm^3) groups, and patients with low BMD at baseline withdrew earlier than patients with normal BMD at baseline. In all, only 42% (277/658) of the patients enrolled in the sub-study were examined at three years. The BMD of the hip in those who had repeated determinations showed a decrease throughout the study, and the rate of decrease was not markedly different among the treatment groups. BMD measured at the spine actually increased in the SAL group and remained unchanged in the other treatment groups. Thus there was minimal evidence of any affect of active treatment on bone metabolism.

Ophthalmic AEs, including cataract and glaucoma, were slightly elevated in the FSC treatment group in Study SCO30003. The overall rates were 13.7, 17.8, 15.8 and 18.6 events / 1000 treatment years. Ophthalmic examination showed no clinically meaningful differences during the three-year trial. However, the examinations were not precise enough to demonstrate a change in the size of cataracts. Because more than 60% of the patients had cataracts at baseline the population available for the follow-up examinations was small. The rate of development of glaucoma did not differ among the treatment groups.

In study SFCB3024 the pattern of adverse events was similar to that seen in study SCO30003. The patients in this study provided a much shorter observation period (307 vs. 3000 years) and there were fewer events to analyze. However pneumonia did occur at slightly higher rates in the active treatment groups. Pneumonia was reported as a serious AE in 3 (<1%), 9 (2%), 9 (2%), and 7 (2%) of the patients in the placebo, SAL, FP, and FSC groups, respectfully.

1.3.3 Other Safety Issues

In Study SCO30003, serum cortisol was measured in 83 patients at selected sites in the US. There were enough samples to calculate a cortisol AUC for 76 patients. The Cortisol AUC was reduced by 21 and 22% by FP and FSC, respectively. The hazard ratio comparing active treatment to placebo was 1.0 (0.769, 1.31), 0.786 (0.58, 1.07), and 0.784 (0.594, 1.04) for SAL, FP, and FSC, respectively.

There were no clinically important changes in laboratory values, vital signs or ECGs in either of the two pivotal trials.

In summary in this large population of middle age to elderly patients with a long smoking history and COPD, death was distributed, as expected across various categories of cardiorespiratory diseases. When categorized by the AE that was thought to cause the death the most common events that started while the patients were still on study medications were pulmonary. Pulmonary events (COPD [N=126], Respiratory failure [N=61], and Pneumonia [N=39]) were

reported 226 times compared to 108 cardiac events (Sudden death [N=43], Cardiac failure [N=25], and MI [N=40]). The proportion of pulmonary AEs in this list is interesting given that the CEC attributed almost as many deaths to cardiac as to pulmonary causes. The CEC probably identified underlying causes of death rather than the precipitating episode.

Adverse events that were not fatal were also frequent in both study populations. COPD and terms that were associated with breathlessness and respiratory failure were decreased in the FSC group in most of the tabulations. Of note, treatment with FP did not provide protection. As a matter of fact in several event-groupings the highest rate of COPD events was in the FP group. In addition, respiratory infections both upper and lower were clearly increased in the fluticasone-containing regimens. While upper respiratory tract involvement with candida is an acknowledged adverse event during therapy with ICS as a class, the role of lower respiratory tract infections has not been as well described. Events labeled as some form of pneumonia, lung infection, or bronchitis were all elevated in patients in the fluticasone-containing regimens. It is odd that FSC treatment appears to decrease the rate of COPD exacerbations, but increase the rate of respiratory infections which are thought to be an etiologic factor for those same exacerbations. Either the infections remain and the patients respond differently or sense the changes in the lungs differently, or infections may be less important in etiology than previously thought.

2 INTRODUCTION AND BACKGROUND

2.1 Currently Available Treatment for Indications

There is no currently approved pharmacologic therapy for the prolongation of life or for decreasing exacerbations in patients with COPD. Smoking cessation, oxygen therapy, and lung volume reduction therapy are the only modalities shown to improve survival. There are several drug classes available for the relief of bronchospasm: ß-adrenergic agents, anticholinergic agents, and combinations of the two, and methylxanthines (Table 1). Other than theophylline, all of the drugs are administered by inhalation.

Table 1. Currently Available Drugs for the Treatment of COPD.

Drug class	Brand name	Formulation	Dosing
ß-adrenergic agonist	Albuterol	MDI	QID
	Salmeterol [Serevent]	DPI	BID
	Formoterol [Foradil Aerolizer]	DPI	BID
	Formoterol [Brovana]	Inhalation solution	BID
Anti-cholinergic	Ipratropium [Atrovent]	MDI	QID
	Titropium [Sprivia]	MDI	QD
Methylxanthine	Theophylline [Uniphyl]	Tablet	QD
Combination product	Ipratropium/albuterol [Combivent]	MDI	QID
	Fluticasone/salmeterol [Advair]	DPI	BID
Symbicort	Budesonide/Formoterol	MDI	BID

Advair, at a dose of 250/50 mcg BID is approved for the maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis. Higher doses are not recommended due to failure to document additional improvement in pulmonary function as compared to the 250/50 mcg BID dose.

2.2 Presubmission Regulatory Activity

Advair (FSC), as a dry powder inhaler, was first approved for the treatment of asthma in August 2000. Approved doses include 100/50, 250/50 and 500/50 mcg BID with the recommended starting dose dependent upon disease severity. Advair is approved for asthma for patients 4 years of age and older. A supplement for the treatment of COPD (NDA 21-077/ SE_003) was first submitted to the agency in May 2001 and was the subject of a pulmonary advisory committee meeting in January 2002. The supplement was ultimately approved in November 2003 after 2 review cycles. The approved indication is for the maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis and the approved dose is 250/50 mcg. The Applicant agreed to conduct two additional clinical trials as post-marketing commitments. One was a two-year study to assess bone mineral changes after two years of treatment with 250/50 mcg BID and one was a one-year study to assess the effect of FSC 250/50 mcg BID on the exacerbation rate in patients with moderate to severe COPD.

In August of 2000, prior to approval of the COPD indication, there was a meeting with the Agency to discuss protocol SCO30003, a study designed to show increased survival in patients with COPD who were treated with FSC 500/50. At that time, the Applicant was told that it

might be possible to support approval of a mortality indication on the basis of one study, but that the results would have to be robust. The Agency agreed that it would be acceptable to include patients enrolled outside of the United States, but that a sufficient number would have to be enrolled in the United States to make sure that the trend in the results in the US population was in the same direction as that of the rest of the patients. The Agency also noted that it was not appropriate to enroll patients into SCO30003 who had participated in study SFCB3024.

A statistical analysis plan (SAP) was submitted to the Agency in May of 2005. This plan differed from the original protocol in several aspects: 1) In the mortality analysis the comparison between FSC and placebo was followed by a comparison between FSC and SAL, not a comparison between FSC and FP; 2) COPD exacerbation rate replaced COPD-related mortality as the most important secondary outcome, and only FSC and SAL were included in the analysis plan; and 3) the Applicant proposed to analyze exacerbation rate and response to SGRQ in the absence of a statistically significant improvement in survival. The Agency responded that the overall Type I error would have to be maintained for the entire study meaning that all of the outcomes had to be included in the hierarchical plan. In addition, the Agency noted that a single study would not be sufficient to support the exacerbation or quality of life indications.

3 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

3.1 Tables of Clinical Studies

Table 2. Studies Reviewed in Detail

Study	Design	Dosage	Duration	N	Patients	Evaluations
SCO30003	R, DB, PC	FSC 500/50 FP 500 SAL 50 Placebo	156 Weeks	6184	FEV1 <60% predicted FEV1/FVC <70%	Survival Exacerbations FEV1
SFCB3024	R, DB, PC	FSC 500/50 FP 500 SAL 50 Placebo	52 Weeks	1469	FEV1 25 to 70% predicted FEV1/FVC <70%	FEV1 Exacerbations SGRQ
SFCA3006	R, DB, PC	FSC 500/50 FP 500 SAL 50 Placebo	24 Weeks	691	FEV1 <65% predicted, but >0.7 L FEV1/FVC <70%	FEV1

3.2 Review Strategy

Study SCO30003 was reviewed in detail for the primary endpoint of all-cause mortality as well as for secondary endpoints of COPD mortality and on-treatment mortality. COPD exacerbations were enumerated in both Study SCO30003 and SFCB3024. The former was of 3 year's duration and the later of one year's duration. Both were of sufficient duration and size to evaluate the effect of Advair for this indication (Table 2). All three of the primary trials measured the FEV_1 for evidence that Advair at the dose of 500/50 mcg BID was effective in the treatment of

bronchospasm. They were all reviewed to assess this indication. A quality of life claim is not being requested. However, the results of the Saint George's Respiratory Questionnaire are referred to in the proposed label, and these results were reviewed in study SCO30003 and SCFB3024.

Study SFCA3006 was reviewed in detail by the FDA with the original supplement to NDA 21-077, and was not reviewed again. The only data that is relevant to this application are the results of the pulmonary function testing, and these results are included in the Integrated Review of Efficacy (pg 32). The results of Study SFCA3006 are also not discussed in the safety section because infectious events associated with COPD exacerbations were not recorded as adverse events: they were treated as being part of the exacerbation. Since the primary adverse event that in the other two studies was an increase in the incidence of respiratory infections, the results of Study SCFA3006 can only serve to dilute the findings in SCO30003 and SFCB3024.

Twenty-two additional studies were submitted. Of these, 10 have not been completed and the study reports consist of only synopses of the study design and a listing of serious adverse events. Of the remaining 12 trials, 2 were small clinical pharmacology studies, and 4 efficacy trials did not include a placebo. Six remaining supportive trials were randomized and placebo-controlled trials (Table 3). However, none of the studies was of sufficient duration to evaluate survival and none measured the exacerbation rate. These studies can only be used to support the bronchodilation indication, and none is superior to the three primary studies all of which measured spirometry for at least 6 months. Of note, none of these studies made a direct comparison between the 500/50 BID and 250/50 BID dose of Advair.

Finally, 5 epidemiology studies were submitted to support the decreased mortality indication. The applicant refers to them in the ISE as "observational data from patients treated in real-world clinical practice…" If there were no randomized trial, evidence from epidemiologic studies might be seen as supportive. However, the results from epidemiology studies would not supplant or override the results of a randomized comparison. Therefore, these epidemiology trials were not reviewed.

Notation

The tables and figures in this review come directly from the body of the study reports unless indicated otherwise. References are to the Study Report or to post-text tables in the Study Report. Page references without other notation refer to other pages within this review. Reviewer analyses and tables are in italics. MedDRA terms are printed in 10-point Century Gothic font to distinguish them from general use of such terms as COPD and lower respiratory tract infection. In referring to results in the different drug treatment, a number and (%) are frequently used. These are the number of patients and percentage of patients in the respective treatment group that are affected. For example, "Pneumonia SAEs were reported in 86 (6%), 99 (6%), 150 (10%), and 157 (10%) of the placebo, SAL, FP, and FSC patients, respectively" means that 86/1544 (5.57%) of the patients in the placebo safety population reported pneumonia. Adverse events are described as having an onset during randomized treatment (patient taking placebo, FSC, SAL, or FP at onset of AE) to distinguish the treatment period from the time of treatment of the exacerbation with systemic corticosteroids and/or antibiotics. The combination product is refered to as FSC 500/50 in the review. It is called SFC 50/500 in the GSK submission and this nomenclature remains on the graphs copied from the submission.

4 INTEGRATED REVIEW OF EFFICACY

4.1 Indication

The proposed indication is stated as "ADVAIR 500/50 mcg twice daily is indicated for the maintenance treatment of airflow obstruction, increasing survival, and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD).

An alternative dose is ADVAIR DISKUS 250/50 mcg BID".

4.2 Methods

Efficacy was assessed with double-blind randomized clinical trials. Study SCO30003 compared the effect of FSC 500/50 mcg, to FP 500 mcg, SAL 50 mcg and placebo, all administered twice daily for three years, on survival. Secondary efficacy outcomes included COPD exacerbation rate, quality of life measures including the SGRQ, and pulmonary function.

Study SFCB3024 compared the effect of FSC 500/50 mcg, FP 500 mcg, SAL 50 mcg, and placebo, all administered twice daily for one year, on pulmonary function. Secondary efficacy outcomes included COPD exacerbation rate and quality of life measures including the SGRQ.

Study SFCA3006 was reviewed in the original supplement for treatment of COPD. It compared the effect of FSC 500/50 mcg, FP 500 mcg, and SAL 50 mcg, and placebo, all administered twice daily for six months, on pulmonary function.

4.3 General Discussion of Endpoints

4.3.1 Mortality

The primary efficacy outcome in Study SCO30003 was all-cause mortality at three years. This outcome has essentially no measurement error and is generally considered clinically important. In this particular study all but one of the 6112 patients were followed-up for vital status so there was essentially no missing data in the mortality analysis. The cause of death was confirmed by a clinical end points committee (CEC) that reviewed all of the available data on all of the deaths. The result of this deliberation was a categorization of deaths as pulmonary, cardiac, cancer, other, or unknown. A further distinction was made between COPD-related and non-COPD-related deaths. COPD-related deaths included some sudden deaths and deaths at home in patients with severe end-stage COPD. Cases were classified as possibly and probably COPD-related if the details did not allow for a definitive diagnosis. For analysis of the secondary efficacy outcome of COPD-related death, all definitive, probable and possible cases were included as COPD-related. The Intention-To-Treat (ITT) population included all of the patients regardless of how long they had been on therapy. In the entire population 62% stayed on study drug for three years or were still taking study drug at the time of death. As a confirmatory analysis all-cause on-treatment deaths were also compared. Thus, the mortality outcome of this population was well characterized and thoroughly analyzed.

4.3.2 COPD Exacerbation Rate

COPD is characterized by episodic worsening of symptoms in some patients. The change in symptoms may be mild, requiring only an increase in the amount of short acting bronchodilator taken for a few days to severe with respiratory distress and respiratory failure. COPD exacerbations have been related to the quality of life of patients with COPD [2], and are considered an important clinical outcome measure [3]. Although there is no clear consensus on what constitutes an exacerbation, most definitions include some combination of shortness of breath and increased sputum production. For research purposes, when quantitation is important, time limits are usually imposed such as a requirement for symptoms for more than two days.

In Study SCO30003, COPD exacerbations were defined only in terns of severity. They were called moderate if they were treated with antibiotics or systemic corticosteroids and severe if the patient required hospitalization, but there was no primary definition of an exacerbation. There was no requirement for a minimum number of symptoms or duration of illness, and there was no limitation on how close two separate exacerbations could be to one another. Neither the data sheets nor the case report forms contain any clinical information other than the dates of the exacerbations and an indicator variable for treatment (antibiotic, corticosteroid, hospitalization). The case report forms include listings of adverse events. Each of these listings is followed by the question, "Does this event meet the definition of a protocol defined moderate/severe COPD Exacerbation?" The response requires the details of treatment. COPD exacerbations could have been reported as "COPD exacerbation" or any one of 122 other diagnoses ranging from common cold to pneumonia to abdominal pain.

The requirement for treatment with antibiotics and/or systemic corticosteroids was clearly intended as a measure of severity, and presumably adverse events listed as a cold but not an exacerbation were less severe than a cold that was listed as an exacerbation, but the criteria by which this distinction was made were not specified. Lacking a definition of the event itself, interpretation of the data could be difficult. As an example, the definition meant that cases considered to be COPD exacerbations by the investigator and that resulted in death (i.e., serious) were not included in the exacerbation count if for any reason (i.e., end of life decision) the patient was not treated. This was even true if the deaths were adjudicated as COPD-related.

Another anomaly in the analysis of COPD exacerbations in this study was the distinction between exacerbations treated with antibiotics and those treated with corticosteroids. While treatment with either was sufficient to categorize the exacerbation as moderately severe, randomization was permitted for patients who had had an exacerbation treated with antibiotics during the run-in but not for patients who had had an exacerbation treated with corticosteroids. The exception for exacerbations during the run-in that were treated with antibiotics meant that some of the exacerbations started before the study treatment started. In addition, antibiotic treatment and exacerbations treated with antibiotics were not reported separately, as were treatment with corticosteroids and the incidence of corticosteroid-treated exacerbations.

Perhaps more important from the quantitative point of view is the failure to put limits on the duration or proximity of exacerbations. Some investigators reported exacerbations that lasted for months and were treated with several individual courses of therapy separated by up to months of

no treatment. Other investigators administered one day of solumedrol several times in one month and counted each treatment as a separate exacerbation. Similar variability occurred in withdrawal rates: some patients were withdrawn after one exacerbation while others stayed on blinded study treatment through 30 exacerbations. Guidelines suggested that patients could be withdrawn after 2 severe and 3 moderate exacerbations, but practice clearly varied among the investigators.

Because this was a multinational study it would be anticipated that there would be differences in the standard of care in various regions around the world. Even if randomization balanced differences in treatment styles across the study treatment groups, there is still the possibility that regional variation in baseline health and the response to treatment could affect the interpretation of the overall results of the study. Robust results in one region that were not repeated in the other regions could make it difficult to generalize the results of the overall analysis. All of the judgments about treatment are at least somewhat subjective; each one depends upon a personal interaction between a patient and physician. In COPD patients with very poor pulmonary function these decisions are often not based on laboratory or other objective data, but rather on a general impression of the patient's status. Finally, the designation of "Severe" exacerbation rested solely on the need for hospitalization, an endpoint that is related to socioeconomic and policy decisions that are only remotely related to an individual patient's health status.

Study SFCB3024 had a slightly more robust definition of exacerbation. Although no specific symptom complex was required, a list of symptoms that could indicate the need for treatment with antibiotics and/or corticosteroids was provided as guidance. Treatment of the exacerbation was specified as a ten-day course of antibiotics and/or systemic corticosteroids and 7 treatment-free days were required between separate exacerbations.

4.3.3 Health Outcomes

The Saint George's Respiratory Questionnaire (SGRQ) was used to assess quality of life in studies SCO30003 and SFCB3024. This is a patient reported outcome (PRO) measure that has been used extensively to evaluate changes in the quality of life of patients with respiratory diseases. A change or difference from placebo of 4 units (maximum possible score of 100) has been taken as the minimally important difference (MID). While the instrument has been translated into numerous languages, the validation of these translated instruments has been incomplete. In an attempt to address the issue a retrospective validation project was conducted in Study SCO30003. The questionnaires were reviewed by investigators in the local sites and back translated into English. COPD patients were interviewed to assess their comprehension of the questionnaire. The results of these two processes were returned to the questionnaire developer for further review. At the end of this process, 5 country-language combinations (in some countries the questionnaire was given in more than one language) were declared invalid. In an additional 14 of the questionnaires considered valid, at least one question was excluded from the analysis. To adjust for this variability in questionnaire format subset analyses were performed of the responses to questionnaires without modification. Finally, the original SGRQ required patients to recall events over the previous 3 months while many of the translations required recall over the previous 12 months. There are numerous discussions in the literature discussing the difficulty in accurate recall over prolonged periods of time [4, 5], and some of the

patients that participated in the validation process spontaneously mentioned that the 12-month recall was to long for accurate recollections. Again, this problem was addressed with subset analyses separating questionnaires that required the longer recall from those that employed the shorter recall period.

4.3.4 Spirometry

The FEV_1 was measured in all three studies using standard methodology. In SCFB3024 the efficacy outcome of interest was the pre-bronchodilator measurement and in study SCO30003 it was the post-bronchodilator measurement. Both are standard measures of pulmonary function and each has been used to compare different drug treatments over time. In Study SCFA3006 both the baseline pre-treatment and the 2-hour post-study drug FEV_1 values were assessed.

4.4 Study Design

All of the studies (SCO30003, SFCB3024, and SFCA3006) that form the primary basis of this review were randomized, double-blind and placebo-controlled. In all three studies placebo treatment was compared to treatment with salmeterol 50 mcg BID (SAL), fluticasone 500 mcg BID (FP) and fluticasone/salmeterol 500/50 mcg BID (FSC). In all three, the study population consisted of middle-age to elderly patients with a clinical diagnosis of COPD who were current or former smokers. The patients enrolled into SCO30003 were not required to have a specified number of exacerbations prior to enrollment, nor did they have to have a history of chronic cough or sputum production. By comparison, the patients enrolled into SFCB3024 were required to have a past history of exacerbations including 1 in the 12 months prior to enrollment and to have had a history of cough and sputum production that would indicate the presence of chronic bronchitis. Both of these factors could make the patients enrolled in SFCB3024 more prone to exacerbations and possibly more sensitive to treatment than the average patient with COPD.

Studies SCO30003 and SFCB3024 were multinational, although SFCB3024 did not enroll patients in Asia or the United States. SFCA3006 was carried out at multiple sites in the US. All of the analyses for study SCO30003 were adjusted for region which included the following: USA, Asia, Western Europe, Eastern Europe, and Other. The “Other” group included sites in Canada, South America, South Africa, and Australia/New Zealand. The sites in study SFCB3024 were aggregated into groups of one or two countries except for Canada which was divided into three geographic regions, each of which was a separate aggregate.

While the enrollment and treatment assignment was randomized there was a possible bias in early withdrawal that was introduced by the study design of SCO30003. Almost half of the patients in the United States were enrolled in a sub-study to measure changes in bone mineral density during treatment. Patients with pathologically low BMD were referred for consultation, and it is possible that knowledge of this result could have affected the investigator’s decisions about early withdrawal. (See the discussion of withdrawals in Section 5.2.3)

4.5 Efficacy Findings

4.5.1 Demographics

4.5.1.1 Study SCO30003

The ITT population was divided into 1524 placebo-treated, 1521 SAL-treated, 1534 FP-treated, and 1533 FSC-treated patients. Of the entire ITT population 23% were recruited in the United States, 12% in Asia, 19% in Eastern Europe, 31% in Western Europe, and 15% in the Other region. These proportions were maintained in the distribution among treatment groups within each region. The patients had a mean age of 65 years, 82% were white, and 75% were male. These characteristics were evenly distributed across the treatment groups.

The characteristics of the COPD history were also evenly distributed across the treatment groups. The duration was <10 years in 66% of the patients, and the MRC dyspnea score was 1 or 2 (2= short of breath when hurrying on the level or walking up a slight hill) in 50%. Fifty-two percent had a moderate or severe exacerbation and 18% had been hospitalized for an exacerbation in the 12 months prior to enrollment. Fifty-seven percent of the patients were former smokers and 43% were still actively smoking: the mean pack years was 47 to 49. Fifty-one percent of the placebo patients had taken inhaled corticosteroids in the 12 months prior to enrollment. This compares to 45, 47, and 45% of the SAL, FP, and FSC-treated patients respectively. As an index of concomitant disease, 6 or 7% of the patients in each treatment group reported a prior history of a myocardial infarction.

Looking at the baseline medical conditions by geographic region, prior use of inhaled corticosteroids was lowest in Asia (25%) and highest in Western Europe (64%) with the other regions in between. A prior history of myocardial infarction was reported in 12% of the US population but only in 2% of the Asian population. Patients in the other regions reported a history of myocardial infarction in 5 to 6% of the patients. On the other hand, cardiovascular disease of any type was reported at baseline in 59, 37, 58, 48, and 48% of the patients in the US, Asia, Eastern Europe, Western Europe and the Other region, respectively, suggesting that the discrepancy in cardiovascular disease was less than the difference in prevalence of myocardial infarction.

Reviewer: The differential in incidence in myocardial infarction is probably overestimated due to changes in the manner of collection of this data over the course of the study (see Reviewer note pg 77 for details). If all prevalent serious cardiac diseases are analyzed the prevalence was actually highest in Eastern Europe. The baseline prevalence was 39.6, 39.9, 65.6, 41.4, and 32.7 in the US, Asian, Eastern European, Western European, and Other populations, respectively.

Pulmonary function was moderate to severely reduced in the population as a whole and in each of the treatment groups. The mean pre-bronchodilator FEV_1 was 1111 mL and the mean percent predicted was 40%. The range in FEV_1 was 240 to 2800 mL or 7 to 101% predicted. (There were only 38 patients [0.62%] with FEV_1 % predicted >60% which were protocol violations). The mean post-bronchodilator FEV_1 was 44% predicted and was 10% higher than the pre-bronchodilator value. Eighteen percent of the patients were reversible if "Reversible" is defined

as a >12% and >200 mL increase in FEV_1 after inhalation of albuterol and the change in FEV_1 is compared to the pre-bronchodilator value.

4.5.1.2 Study SFCB3024

There were 1465 patients who were randomized to receive placebo (N=361), SAL (N=372), FP (N=374), or FSC (N=358) for 52 weeks. The patients had a mean age of 63 years, 99% were Caucasian, 73% were male, and the mean dyspnea score was 2.7. Fifty-eight, 62, 56, and 65% had a history of COPD for ten years or less and 47, 51, 53, and 48% were current smokers in the placebo, SAL, FP, and FSC groups, respectively. The mean baseline FEV_1 % predicted in each of the treatment groups was 44 to 45%, and mean reversibility ranged between 8.0 and 8.9%. Fifty-one percent had taken ICS prior to enrollment.

4.5.1.3 Study SFCA3006

The ITT population consisted of 674 patients who were randomized to receive placebo (N=181), SAL (N=160), FP (N=168), or FSC (N=165) for 24 weeks. The patients had a mean age of 63 years, 93% were Caucasian, 66% were male, and 35% had a dyspnea score > 2. The mean duration of COPD was 5.5 years and 48% were current smokers. The mean baseline pre-bronchodilator FEV_1 was 1226 mL and the mean FEV_1 % predicted in each of the treatment groups was 40 to 41%. The mean response to bronchodilators using the pre-bronchodilator measured value as the baseline was 19 to 20%. Fifty-four percent of the patients enrolled in the study were reversible. Twenty-five percent of the patients were taking ICS at screening.

4.5.1.4 Summary

Within each study, the demographic and COPD characteristics were evenly distributed across the treatment groups. Comparing the populations across studies shows general consistencies with a few minor deviations (Table 3). Notably, the population enrolled in Study SCO30003 included somewhat fewer Caucasians and the pulmonary function was slightly poorer than the patients enrolled into the other studies. The patients enrolled into Study SCFA3006 had fewer males, a low level of ICS use at baseline, and a high prevalence of hyperresponsiveness when compared to the other two study populations.

Table 3. Demographic Characteristics of the Study Populations

	SCO30003	**SFCB3024**	**SFCA3006**
N	6112	1465	674
Age, mean years	65	63	63
Male, %	76	72	66
Caucasian, %	82	99	93
Chronic bronchitis	+/-	+	+
Dyspnea score	50% >2	Mean = 2.7	35% >2
Duration of COPD, % <10 yr	66	60	Mean = 5.5
Current smokers, %	43	51	48
ICS prior to enrollment, %	48	49	25
Baseline pre-BD FEV_1, mL	1111	1269	1227
Baseline pre-BD FEV_1, % predicted	40	45	40
Reversible, % of patients	18	17	54

4.5.1 Mortality (Study SCO30003)

After three years of follow-up the unadjusted mortality was 15.2, 13.5, 16.0, and 12.6 % in the placebo, SAL, FP, and FSC-treated patients, respectively (Table 4), and the difference between morality in FSC and placebo was 2.6%. The statistical comparison of FSC and placebo (hazard ratio [HR] = 0.820) had a nominal significance of 0.041 prior to adjustment for the interim analyses. After adjustment, the p-value was 0.052 (HR=0.825). Survival was better after treatment with FSC when compared to treatment with FP. However, it was not better than treatment with SAL. The mortality results varied by geographic region: the difference in mortality comparing FSC to placebo was 1.6, 0.0, 4.0, 2.9 and 3.6% in the United States, Asia, Eastern Europe, Western Europe, and Other, respectively.

Table 4 . All-cause Mortality in Study SCO30003

	Placebo (N=1524)	**SAL 50 (N=1521)**	**FP 500 (N=1534)**	**FSC 500/50 (N=1533)**
Number of Deaths	231	205	246	193
Probability of death by 156 weeks (%)	15.2	13.5	16.0	12.6
95% CI	13.4, 17.0	11.8, 15.2	14.2, 17.9	10.9, 14.3
Active Treatment vs. Placebo				
Hazard ratio		0.879	1.060	0.820
95% CI		0.729, 1.061	0.886, 1.268	0.677, 0.993
p-value		0.180	0.525	0.041
FSC 500/50 vs. Components				
Hazard ratio		0.932	0.774	
95% CI		0.765, 1.134	0.641, 0.934	
p-value		0.481	0.007	
FSC vs. Placebo after adjustment for interim analyses				
Hazard ratio				0.825
95% CI				0.681, 1.002
p-value				0.052

The lack of robustness of these results is shown by a sensitivity analysis that removes outlying points. Repeating the analysis after the removal of patients enrolled at one site (21 patients treated with placebo or FSC at site 39401) resulted in a substantial change in the hazard ratio (See FDA statistical review for details). Other clinical variables also affected the difference in survival comparing placebo to FSC to placebo. If the population is divided in half by FEV_1 or FEV_1 % predicted, patients with an $FEV_1 < 1000$ mL or a $FEV_1\% < 40\%$ predicted had a minimal response to FSC. Similarly, patients older than 65 years of age had a very small response to FSC. Women appeared to respond better than men, but most of this effect is eliminated if age and pulmonary function and smoking history were used for adjustment.

Over the three years of observations 875 (14.3%) patients died. The cause of death was adjudicated to be cardiac in 3 -5% of the population, pulmonary in 4 – 6% and cancer in 3%. The remainder was “Other” or “Unknown” (Table 5). The distribution of cause of death was similar across the treatment groups, although the SAL patients had a relatively low cardiovascular mortality (2.9 % compared to 4.7, 4.0, and 3.9% in the placebo, FP and FSC-treated patients) and there was a somewhat higher mortality due to pulmonary causes in the FP-treated patients (5.9% compared to 4.9, 5.3, and 4.0% in the placebo, SAL and FSC-treated patients).

Table 5. Adjudicated Cause of Death in ITTP

	N	All	Cardio-vascular	Pulmonary	Cancer	Other/ Unknown
Placebo	1524	231 (15.2)	71 (4.7)	74 (4.9)	45 (2.9)	41 (2.7)
Salmeterol	1521	205 (13.5)	45 (2.9)	80 (5.3)	44 (2.9)	36 (2.4)
Fluticasone	1534	246 (16.0)	61 (4.0)	91 (5.9)	51 (3.3)	43 (2.8)
Advair	1533	193 (12.6)	60 (3.9)	61 (4.0)	44 (2.9)	28 (1.8)
	N	**All**	**Cardio-vascular**	**Pulmonary**	**Cancer**	**Other/ Unknown**
USA	1388	188 (13.5)	45 (3.2)	57 (4.1)	46 (3.3)	40 (2.9)
Asia/Pacific	758	140 (18.5)	25 (3.3)	75 (9.9)	22 (2.9)	18 (2.4)
E Europe	1154	187 (16.2)	65 (5.6)	57 (4.9)	41 (3.6)	24 (2.1)
W Europe	1908	207 (10.8)	67 (3.5)	54 (2.8)	47 (2.5)	39 (2.0)
Other	904	153 (16.9)	35 (3.9)	63 (7.0)	28 (3.1)	27 (2.9)

The distribution of causes of death by region showed that 5.6% of the patients in Eastern Europe died of cardiovascular causes compared to 3.2, 3.3, 3.5, and 3.9% of the patients enrolled in the United States, Asia, Western Europe, and the Other region, respectively. On the other hand, 9.9% of the patients enrolled in Asia died of pulmonary causes compared to 4.1, 4.9, 2.8, and 7.0% of the patients in the United States Eastern Europe, Western Europe, and the Other region, respectively.

Approximately 41% of the deaths were determined to be COPD-related. The three-year COPD-related death rate was 6.0, 6.1, 6.9, and 4.7% in the placebo SAL, FP, and FSC groups, respectively. Pneumonia was the second most common cause of a pulmonary death and occurred in 13, 15, 21 and 15 patients in the placebo, SAL, FP, and FSC groups, respectively. None of the comparisons between placebo and active treatment was statistically significant. The Kaplan-Meier adjusted probability of on-treatment death was 10.5, 9.0, 11.5, and 8.1%, respectively.

4.5.2 COPD Exacerbation Rate (Study SCO30003 and Study SFCB3024)

In study SCO30003, 70% of the patients experienced at least one exacerbation while they were taking study medication. Using the negative binomial distribution the COPD exacerbation rate in study SCO30003 was 1.13, 0.97, 0.93, and 0.85 events per year in the placebo, SAL, FP, and FSC groups, respectively (Table 6). The hazard ratio (95% CI) comparing active treatment to placebo was 0.858 (0.784, 0.927), 0.823 (0.758, 0.894), 0.749 (0.689, 0.814) for the comparison to SAL, FP, and FSC, respectively. All of the active treatments were significantly better than placebo in decreasing the rate of moderate/severe exacerbations. The rate in the FSC-treated patients was also significantly less than the rate in the SAL and FP treatment-groups. Twenty-five percent of the patients experienced severe exacerbations. The modeled rates were 0.19, 0.16, 0.17, and 0.16 events / year in the placebo, SAL, FP, and FSC groups, respectively. The hazard ratio (95% CI) for a severe events comparing FSC to placebo was 0.834 (0.710, 0.981) but the hazard ratio comparing FSC to SAL was 1.022 (0.870, 1.200). The hazard ratio

comparing FSC to FP was 0.954, which was not statistically significant. The rate of exacerbations that were treated with systemic corticosteroids was 0.80, 0.64, 0.52, and 0.46 events / year in the placebo, SAL, FP, and FSC-treated patients. The active treatments were all superior to placebo in decreasing the number of exacerbations that were treated with corticosteroids and FSC treatment was superior to SAL and FP.

Reviewer: The rate of antibiotic-treated exacerbations was not included in the application. However, according to the FDA statistical reviewer, the rate of exacerbations treated with antibiotics alone was increased in the FSC group. The Hazard ratio (95% CI) comparing FSC to placebo was 1.15 (1.09, 1.36).

The exacerbation rate in study SFCB3024, modeled using the Poisson distribution, was 1.30, 1.04, 1.05, and 0.97 in the placebo, SAL, FP, and FSC groups, respectively (Table 6). The difference between FSC and placebo was thus, 0.33 events / year which compared favorably to the difference between FSC and placebo in study SCO30003 (0.28 events per year). There were too few severe exacerbations to allow for statistical inference. However, the rate was not reduced in the FSC group when compared to placebo: there were 0.07, 0.08, 0.06, and 0.07 events/year in the placebo, SAL, FP, and FSC groups, respectively. The rate of events that were treated with corticosteroids was 0.76, 0.54, 0.50, and 0.46 events/year in the placebo, SAL, FP, and FSC patients, respectively. All of the active treatment groups had lower rates than the placebo-treated patients, but the rate during FSC treatment was not lower in FSC than during SAL or FP treatment. Exacerbations treated with antibiotics were also not decreased by treatment with FSC. The rates of antibiotic-treated exacerbations were 0.72, 0.65, 0.75, and 0.76 events per year in the placebo, SAL, FP, and FSC groups respectively.

Reviewer: The Poisson distribution used in study SFCB3024 is thought to over estimate the difference in exacerbation rates due to an underestimate of the intra-patient variability [1]. However, the effectiveness of FSC as measured by the hazard ratio was remarkably similar in the two studies considering the different patient characteristics and different analysis methods.

Table 6. Summary of COPD Exacerbation Rates (events/year)

	Placebo	SAL	FP	FSC	Hazard Ratio FSC/Placebo
Moderate/Severe					
SCO30003*	1.13	0.97	0.93	0.85	0.749
SCFB3024**	1.30	1.04	1.05	0.97	0.746
Severe					
SCO30003*	0.19	0.16	0.17	0.16	0.834
SCFB3024, **	0.07	0.08	0.08	0.07	---
Corticosteroid-treated					
SCO30003*	0.80	0.64	0.52	0.46	0.568
SCFB3024**	0.76	0.54	0.50	0.46	0.607
Antibiotic-treated					
SCO30003, %†† (Antibiotic only)	0.32	0.31	0.39	0.37	1.15
SCFB3024** (Antibiotic with or without corticosteoids)	0.72	0.65	0.75	0.75	---

* Rates calculated using the negative binomial distribution; ** Rates calculated using the Poisson distribution
† † Calculated by FDA statistical reviewer

4.5.3 Quality of Life

The Total scores from the Saint George's Respiratory Questionnaire (SGRQ) failed to reach a clinically meaningful difference between placebo and active treatment (at least 4 points) in either Study SCO30003 (N=3911) or SCFB3024 (N=1299). In study SCO30003 the score decreased (improved) over the first 6 months in all of the treatment groups and then gradually increased over the remaining 2 ½ years. The mean change over the course of the study was 1.31, -0.44, -0.93, and -1.81 in the placebo, SAL, FP, and FSC groups, respectively. After correction for smoking status, age, sex, baseline FEV_1, baseline SGRQ, region, visit and including a treatment by visit interaction term and a SGRQ by visit interaction term the change was 0.2, -0.8, -1.8, and -3.0. Thus, the most favorable analysis of the data resulted in a difference between placebo and FSC of 3.2. The largest changes were in the symptom scores where the difference between FSC and placebo wad 3.6 units. Questionnaires without scoring modification were available for 1126 patients (18% of the ITT population). The results were in the same direction as for the larger group, though the difference comparing FSC to placebo was only 2.8 points.

In study SFCB3024 the changes were smaller with a difference between active treatment and placebo in the repeated measures analysis of -2.2, -1.1, and -1.4 for the SAL, FP, and FSC groups, respectively. Comparing the scores at the endpoint also indicated a greater improvement in the SAL-treated patients than in any other treatment group.

The results of the SGRQ have to be assessed in the light of the finding that not all of the questions in the original document could be translated into all of the languages of the patient populations in Study SCO30003. In addition, many of the questionnaires used a 12-month recall compared to the 3-month recall used in the original UK English document. Not only are the results likely to differ using the two different recall periods, the patients who participated in the validation process told the investigators that 12 months was too long to remember details. Since the questionnaire was administered every 6 months, the 12-month recall period covered overlapping periods of time. Finally, the validation process did not occur until after SFCB3024 had been completed. Therefore, there is no information or provision for adjustment of the results in the earlier study.

4.5.4 Pulmonary Function

In both SCO30003 and SFCB3024 spirometry was performed throughout the treatment course. In study SCO30003, 5343 (87.4%) of the patients had a measurement at baseline and at least one follow-up determination. Fifty-nine percent had measurements at the 156-week time point. In all the treatment groups, the post-bronchodilator FEV_1 increased over the first six months to a peak of 4, 30, 36, and 71 mL in the placebo SAL, FP, and FSC patients respectively. The FEV_1 then gradually declined in all of the treatment groups over the rest of the treatment period. The mean raw change at 156 weeks was -127, -61, -62, and -7 mL in the placebo, SAL, FP, and FSC groups, respectively (Table 7). After adjustment for smoking status, age, sex, baseline FEV_1, BMI, region, visit, and for baseline FEV_1 by treatment group and treatment group by visit interaction terms the calculated values were -62, -21, -15, and 29 mL, respectively. The rate of decline after 6 months was the same in all of the active treatment groups, but it was 13 to 16 mL/year less than the decline in the placebo patients. All of the active treatments were

statistically superior to placebo, and FSC was superior to both SAL and FP in maintaining pulmonary function.

In study SFCB3024 the mean baseline pre-bronchodilator FEV_1 was 1266, 1245, 1260, and 1308 mL in the placebo, SAL, FP, and FSC groups, respectively. This was comparable to the values obtained in Eastern (1226 mL) and Western Europe (1204 mL) in study SCO30003, but was approximately 200 mL higher than the overall mean in Study SCO30003. Comparing baseline to week 52 using a repeated measures ANOVA and adjusting for center, age, sex, smoking status, visit, and treatment the change was -60, 15, 7, and 113 mL, respectively (Table 7). Comparing the function-time curves, this increase in FEV_1 seen in SFCB3024 is consistent with the increase seen in the first 6 months of SCO30003. The increase in SCO30003 was stable over the following 6 months in the FSC group and fell slightly in the SAL and FP patients. In all of the spirometry analyses pulmonary function was maintained better with active treatment that with placebo, and FSC was superior to SAL or FP.

Table 7. Summary of Change in FEV_1 (mL) in Studies SCO30003, SFCB3024 and FSCB3006.

	Placebo	SAL	FP	FSC	FSC-Placebo
SCO30003 (3 years of follow-up)*					
Baseline 30 min post-albuterol FEV_1, mL	1257	1231	1233	1236	
Δ 24 weeks	4	30	36	71	67
Δ 156 weeks	-127	-61	-62	-7	91
SCFB3024 (1 year of follow-up)*					
Baseline pre-albuterol FEV_1, mL	1266	1245	1260	1308	
Δ 24 weeks	-37	52	16	122	
Δ 52 weeks	-60	15	7	113	133
Baseline 30 min post-albuterol FEV_1, mL	1379	1346	1363	1419	
Δ 24 weeks	33	70	78	124	
Δ 52 weeks	-15	33	42	108	76
SCFA3006 (6 weeks follow-up) †					
Baseline pre-dose FEV_1, mL	1282	1192	1174	1254	
Δ 24 weeks	-4	107	109	156	160
2 hours post-dose FEV_1, mL					
Δ 24 weeks	28	233	138	261	233

* Raw values for change from baseline and repeated measures ANOVA means for FSC-placebo.
† Endpoint analysis. The endpoint post-bronchodilator FEV_1 was compared to the baseline pre-bronchodilator FEV_1

In Study SCFA3006 the pre and post-dose FEV_1 were measured over 6 months. The analysis was performed on the difference between the endpoint and baseline values with no adjustment for missing values (the last measured FEV_1 was the outcome measure). This type of analysis is particularly problematic because the drop-out was relatively high. The protocol required patients to be withdrawn if they experience one hospitalization or one exacerbation that required treatment with systemic corticosteroid. As a result, only 65% of the patients remained on study treatment for the 6-month treatment period. The original medical reviewer noticed that the reversibility of this group of patients was high (54% of the patients with an increase in FEV_1 after albuterol of >12% and >200 mL) compared to the usual COPD population (reversibility closer to 30% of the population). The mean reversibility was 19 to 20% in the various treatment groups. In the 361 patients designated reversible the mean reversibility was 28 to 31%. In the 313 non-reversible patients the mean reversibility was 8 to 10%.

In the ITT population, the mean change in pre-dose FEV_1 was -4, 107, 109, and 156 mL in the placebo, SAL, FP, and FSC groups, respectively (Table 7). The overall difference in mean change in FEV_1 was 160 mL comparing FSC to placebo. All of the differences comparing active treatment to placebo were significant and FSC was significantly more efficacious than SAL or FP. The response in the reversible group was larger than in the patients who were not reversible. The mean change in the pre-dose FEV_1 in the reversible group was -1, 132, 123, and 191 mL in the placebo SAL, FP, and FSC groups, respectively. In the non-reversible patients the changes were -8, 80, 93, and 116 mL, respectively.

The changes in the 2-hour post-dose FEV_1 were numerically somewhat larger than for the pre-dose values. The mean change from baseline was 28, 233, 138, and 261 mL in the placebo SAL, FP, and FSC groups, respectively. The difference in mean change in post-dose FEV_1 comparing FSC to placebo was 233 mL. Division of the patients into reversible and non-reversible again demonstrated a greater effect in the reversible patients. The mean change in the reversible group was 29, 287, 161, and 319 mL in the placebo SAL, FP, and FSC groups, respectively. In the non-reversible patients the changes were 28, 175, 111, and 195 mL, respectively.

Reviewer: The spirometry data are difficult to compare because of the variation in the timing of the measurements and the methods of analysis used. In Study SCO30003 and SCFB3024 the post-albuterol FEV_1 was compared at each visit to the baseline pre-treatment post-albuterol FEV_1. In Study SFCB3024 the pre-albuterol FEV_1 was evaluated in the same way. In Study SFCA3006 the two-hour post-(study)treatment FEV_1 at each visit was compared to the pre-treatment FEV_1 at baseline. The results of SFCA3006 combine the increase that would be expected comparing a trough-to-peak value and the change with time whereas Studies SCO30003 and SCFB3024 only measured the secular change.

4.5.5 Resource Utilization

In study SCO30003 approximately 60% of the patients required unscheduled medical attention at some time during the trial. Usage was not consistently affected by any of the treatments. The SAL patients had the lowest usage of out-patient clinic visits, general ward admissions and ICU admissions. They spent 647 days/ 1000 years exposure less in hospital than the placebo patients and 155 days less than the FSC-treated patient. On the other hand the FSC patients had the fewest ER visits and office visits. Both the SAL and FSC-treated patients had approximately half the number of ER visits as the placebo patients. Time in the ICU was longest for the FSC group (169, 105, 150, and 186 days/1000 years of exposure, for the placebo, SAL, FP, and FSC patients, respectively).

In study SFCB3024, a smaller study conducted for only one year, resource utilization was less and some of the numbers are very small. However, the FSC patients had more office visits that any of the other groups and more general ward days than the placebo patients. Intensive care unit (ICU) days were 2, 25, 0, and 14 in the placebo, SAL, FP, and FSC groups respectively, but there were very few observations and two patients were responsible for 80% of the reported 41 days.

4.5.6 Efficacy Conclusions

In a well conducted study of 6112 patients followed for three years, FSC was shown to have a slight, statistically borderline advantage over placebo and FP treatment in all-cause mortality. The difference in survival comparing FSC to SAL did not look different. The 90% survival time was approximately 4 months longer with FSC and 2 months longer with SAL compared to placebo. Looking at sub-populations, the response to FSC was restricted to patients with FEV_1 % predicted >40%, age <65 years, and those with a smoking history >42 pack-years. Approximately 42% of the deaths were COPD-related. There were fewer COPD deaths in the FSC group (hazard ratio compared to placebo = 0.776) and more in the SAL (hazard ratio compared to placebo=1.013) and FP (hazard ratio compared to placebo=1.159) patients. None of the hazard ratio for COPD-related deaths approached statistical significance. The mortality difference between FSC and placebo was less in the United States patients (1.6% 3-year mortality or 90% survival difference of 75 days) than the mean for the ITT population.

Comparing FSC treatment to placebo in the three-year trial, the difference in moderate/severe exacerbations was 0.28 events / year or approximately 1 every three years. The rate of exacerbations was also significantly reduced when comparing FSC to SAL or FP. The exacerbation rates and response to FSC were similar in study SFCB3024 in which treatment continued for 1 year. However, FSC was not superior to SAL or FP. In the 3-year study, the rate of severe (requiring hospitalization) exacerbations was reduced to approximately the same degree in all of the treatment groups, though the formal analysis showed slight superiority of SAL to FSC (Hazard ratio FSC to SAL = 1.022 (95% CI 0.693, 1.200). In the 1-year study the numbers were too small to make a statistical analysis of severe events. However, severe exacerbations were not reduced in the FSC group compared to placebo. In both studies the rate of exacerbations treated with systemic corticosteroids was decreased in all of the active treatment groups. As in the analysis of all moderate/severe exacerbations, FSC was superior to SAL and FP in the reduction of corticosteroid-treated exacerbations in the 3-year study, but not the 1-year study. Antibiotic-treated exacerbations were actually higher in the FSC group in both studies.

The other efficacy outcomes were the SGRQ for quality of life and spirometry. The FEV_1 showed the least deterioration in the FSC-treated patients and the most deterioration was seen in the placebo group. The changes in FEV_1 for patients treated with SAL or FP were similar and intermediate between the placebo and FSC changes. The difference between placebo and active treatment in the SGRQ total score did not reach a clinically meaningful level in any of the treatment groups in either of the studies.

In summary, FSC appears to have a small beneficial effect on some patients with COPD. Life may be extended by a few months, and exacerbations may be decreased by one every three years. On the other hand, severe exacerbations were not decreased and antibiotic-treated exacerbations were increased in the FSC-treated patients. Pulmonary function was better maintained during treatment with FSC than during any of the other treatments and this was consistent across the three studies. In none of the studies was an improvement in quality of life documented.

5 INTEGRATED REVIEW OF SAFETY

5.1 Methods

5.1.1 Extent of exposure (dose/duration)

In the three studies summarized in the safety review, the total years of exposure was more than 3500 in all of the treatment groups. The total exposure to fluticasone/salmeterol was 4066 years (Table 8).

Table 8. Summary of Exposure to Study Drugs

	Placebo		Salmeterol		Fluticasone		Fluticasone/ Salmeterol	
Study	**Mean (weeks)**	**Total (years)**	**Mean (weeks)**	**Total (years)**	**Mean (weeks)**	**Total (years)**	**Mean (weeks)**	**Total (years)**
SCO30003	110.8	3278	119.5	3531	119.5	3555	124.9	3700
SCFB3024	38.7	268	43.1	307	43.9	315	44.0	302
Sub-total		3546		3838		3870		4002
SCFA3006	18.0	64	20.2	64	18.1	60	19.7	64
Total		3610		3902		3930		4066

5.1.2 Characterization of Adverse Events

In Study SCO30003 adverse events were categorized by time period: they started while the patient was taking randomized study medication or, in the case of withdrawal, started after termination of study medication. The post-treatment period was further divided into the two weeks following termination of study medication ("Post-treatment period"), and the time period between two weeks after stopping randomized medication and three years after initiating randomized medication ("Long Term Follow-up" [LTFU]). For the safety analysis, deaths were categorized by the adverse event that precipitated the death: there were on-treatment-AE related deaths, Post-treatment-AE related deaths, and LTFU-AE related deaths. If an adverse event occurred during randomized treatment and led to the patient's withdrawal and he/she died before the end of the study but after withdrawal, the death was ascribed to an on-treatment adverse event. There are more adverse event-associated deaths than actual deaths because some adverse events persisted through two or more treatment periods. For instance, if the adverse event, itself, persisted through the randomized treatment period into the LTFU the death was tabulated three times. Also, more than one adverse event could have been an immediate precursor to death such as cardiac arrest and arrhythmia. This resulted in tabulating two AE-related deaths.

In Study SFCB3024 the two weeks after stopping study medication was called the "Post-treatment" period.

Because the primary focus of adverse event reporting was on those with onset during randomized treatment, the events were reported as an incidence (% of patients affected) and as an event rate / 1000 treatment years. This adjustment accounted for the variable time on randomized treatment among the treatment groups. Adverse events were recorded for all treatment periods, but the completeness of the reporting varied in the LTFU (See detailed study report for details, Reviewer note pg 95). For this reason this review will only discuss AEs in the LTFU that were fatal.

5.2 Findings

5.2.1 Deaths

For the safety analysis in Study SCO30003, the deaths of patients enrolled at the sites that were excluded from the ITTP due to data irregularities as well as the 29 deaths that occurred beyond 3 years after starting study medications were included (N=911 deaths). Two deaths occurred in the LTFU that were the result or an AE present at enrollment and these were included in the ITT population. Adverse events that started during randomized treatment resulted in 533 deaths: 133 (9%), 126 (8%), 160 (10%), and 114 (7%) in the placebo, SAL, FP, and FSC groups, respectively. There were 11 diagnoses characterized as common (reported in ≥5 patients in any active treatment group): COPD, Respiratory failure, Acute respiratory failure, Myocardial infarction, Cardiac failure, Cardiac arrest, Acute myocardial infarction, Lung neoplasm, Pneumonia, Sudden death, and Cerebrovascular accident (Table 9). One-hundred fifty-six patients died of COPD (32, 32, 38, and 24 in the placebo, SAL, FP, and FSC groups, respectively). The next most common event was Respiratory failure, reported in 7 (<1%), 12 (<1%), 17 (1%), and 6 (<1%) of the placebo, SAL, FP, and FSC patients, respectfully. Pneumonia was the cause of death in 9 (<1%), 10 (<1%), 12 (<1%), and 8 (<1%) of the placebo, SAL, FP, and FSC patients respectively. Death during treatment due to cardiac event was slightly more common in the placebo-treated patients. The cancer deaths were primarily located in the lung (38) with only 2 breast cancers, and 10 colorectal cancers.

Table 9. Summary of Adverse Events (MedDRA preferred term) that Started During Randomized Treatment and Resulted in Death in Study SCO30003*

Number (%) Patients Reporting Events	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	FSC 500/50 (N=1546)	Total (N=6184)
Any Event	133 (8.6)	126 (8.2)	160 (10.3)	114 (7.4)	533 (8.6)
COPD	32 (2.1)	32 (2.1)	38 (2.4)	24 (1.5)	156 (2.5)
Respiratory failure/ Acute respiratory failure	13 (0.8)	15 (1.0)	22 (1.4)	8 (0.5)	61 (1)
Pneumonia	9 (0.6)	10 (0.6)	12 (0.8)	8 (0.5)	39 (0.6)
Sudden Death/Cardiac arrest	14 (0.9)	12 (0.8)	9 (0.6)	8 (0.5)	43 (0.7)
Cardiac failure	7 (0.4)	7 (0.4)	5 (0.3)	6 (0.4)	25 (0.4)
MI/Acute MI	14 (0.9)	6 (0.4)	11 (0.7)	9 (0.6)	40 (0.6)
Lung neoplasm malignant	6 (0.4)	10 (0.6)	11 (0.7)	11 (0.7)	38 (0.6)
Cerebrovascular accident	0	1 (0.1)	5 (0.3)	3 (0.2)	9 (0.1)

* Adapted from Table 42, pg 119 if ISS.

Fewer than 3% of the patients suffered AEs in the two weeks post treatment that resulted in death: 35 (2%), 22 (1%), 31 (2%), 36 (2%) of the placebo, SAL, FP, and FSC patients, respectively. Of these, pneumonia accounted for 4, 2, 3, and 6 deaths in the placebo, SAL, FP, and FSC patients, respectively. In the long-term follow-up period 311 AEs were reported that resulted in death. The most common event was COPD (15, 17, 14, and 12 patients in the placebo, SAL, FP, and FSC groups, respectively). Of the other causes of death that occurred in more than 5 individuals in an active treatment group, respiratory failure occurred in more placebo patients (14 compared to 6, 9, and 7 in the SAL, FP, and FSC groups, respectively) and

pneumonia occurred least frequently in the placebo patients (0 compared to 5, 9, and 6 in the SAL, FP, and FSC groups, respectively).

Reviewer: In the efficacy and adverse event analysis an "on-treatment" death is a death that occurred within two weeks of stopping study medication, but an "on-treatment" AE had to occur during randomized treatment. This assumes that there is an important differential in the potential for adverse events as opposed to deaths due to a drug reaction in the two weeks post-treatment termination. We performed an alternative analysis in which all the adverse events reported in the randomized treatment period and in the two weeks following treatment were combined. Further we ascribed only one adverse event to each death. We took the first reported event on the assumption that it would be the most likely to be associated with treatment. This categorization (Table 10) suggested that approximately half of the deaths occurred on treatment or in close proximity (49.4, 51.2, 55.5, and 51.7% in the placebo, SAL, FP, and FSC groups, respectively). An additional 17% of the deaths (15.1, 13.9, 17.3, and 20.3 % in the placebo, SAL, FP, and FSC groups, respectively) occurred after stopping study medication, but following an AE with an onset during active treatment, and 31% percent of the deaths (35.6, 29.5, 27.2, and *28.1% in the placebo, SAL, FP, and FSC groups, respectively) occurred more than 2 weeks after stopping therapy, following an AE that also occurred more than 2 weeks after stopping therapy.*

Table 10. ***Relationship of AE Onset to Death ****

	Placebo N=1544		*SAL N=1542*		*FP N=1552*		*FSC N=1546*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
AE during & death during†	*118*	*7.6*	*110*	*7.1*	*141*	*9.1*	*105*	*6.8*
AE during & death in LTFU†	*36*	*2.3*	*30*[&]	*1.9*	*44*	*2.8*	*41*[&]	*2.6*
AE in LTFU & death in LTFU	*85*	*5.5*	*75*	*4.9*	*69*	*4.4*	*57*	*3.7*
Total	*239*	*15.4*	*215*	*13.9*	*254*	*16.3*	*203*	*13.1*

** The percentages are percent of the treatment group population.*

† An AE or death during occurred within 2 weeks of stopping randomized medication.

[&] *Includes one death from an AE that was present at the time of enrollment.*

In study SFCB3024 there were 24 deaths: 15 occurred during the treatment period and 9 in the two weeks following termination of treatment. There were 10, 5, 5, and 4 deaths during treatment in the placebo, SAL, FP, and FSC groups. Most were cardiovascular (4, 3, 3, and 2 in the placebo, SAL, FP, and FSC patients, respectively. Four were due to cancer (2, 1, 1, and 0 in the placebo, SAL, FP, and FSC patients, respectively. There were 3 deaths attributed to COPD in the placebo patients and one in an FP patient.

5.2.2 Other Serious Adverse Events

The most frequent serious adverse event (SAE) in both studies SCO30003 and SFCB3024 was listed as Chronic obstructive pulmonary disease (Table 11). Protocol-defined moderate/severe exacerbations were discussed in the efficacy review (Section 4.3.2; pg 24). Tabulating all SAEs in Study SCO30003 that occurred during randomized treatment and entered as MedDRA preferred term COPD showed 339 (22%), 307 (20%), 318 (20%), and 298 (19%) of these events in the placebo, SAL, FP, and FSC patients, respectively. There were 11 other common SAEs events (occurring in ≥ 1% of the patients in any active treatment group in either study):

Pneumonia, Lobar pneumonia, Respiratory failure, Myocardial infarction, Atrial fibrillation, Chest pain, Congestive, Cardiac failure, Lung neoplasm, Cerebrovascular accident, and Pneumothorax. The most common event after COPD, and the only other event that occurred in 5% of the patients, was Pneumonia. It was reported as an SAE in 69 (4%), 82 (5%), 121 (8%), 138 (9%). The rate of Pneumonia events was 23.5, 24.1, 41.8, and 47.3 events per 1000 treatment-years. Respiratory failure or myocardial infarction was reported in 1 – 2% of the patients and all other serious events were reported in 1% or less of the patients.

There were an additional 227 serious events in the two weeks following termination of study treatment. The incidence was similar in the treatment groups. If the pneumonias that were reported as serious events in the 2-week post treatment period (8, 5, 6, and 9) are added to those that occurred during active treatment the total is 77 (5.0%), 82 (5.3%), 127 (8.2%), and 147 (9.5%) in the placebo, SAL, FP, and FSC groups, respectively.

In Study SFCB3024 the incidence of serious AEs was low, even given the shorter treatment period. However, the incidence, as well as rate of COPD events, was higher in the FSC-treated patients than placebo: 5% (90 events/1000 treatment years in placebo and 8% (99 events/1000 treatment-years for the FSC treated patients.

Subgroup analysis of SAEs showed that pneumonia occurred in 16% of the FSC-treated patients over 75 years of age compared to 7% of those <65 years of age. The respective incidences of pneumonia in the placebo-treated patients were 4 and 7%. Thus the difference between FSC and placebo was 9% for those over 75 years of age and 3% for those <65 years of age. Cardiac serious events were slightly more common in patients >75 years of age and this was most marked in the placebo and SAL groups. Cardiac events (myocardial infarction, atrial fibrillation, cardiac failure occurred in 1% or fewer of the patients <65 years of age, but in up to 4% of the placebo and SAL patients > 75 years of age.

Serious respiratory events were tabulated separately. (See Section 5.2.6.1 Respiratory Tract Adverse Events, pg 48.)

Table 11. Serious Adverse Events That Started During Treatment and Reported in ≥1% of Patients in Any Active Treatment Group

	SCO30003				SCFB3024			
MedDRA preferred term	Placebo N=1544	SAL N=1542	FP N=1552	FSC N=1546	Placebo N=361	SAL N=372	FP N=374	FSC N=358
Any Event	627 (41) 430.8	622 (40) 398.2	655 (90) 437.1	659 (89) 412.2	54 (15) 283.6	69 (19) 338.8	55 (15) 228.6	62 (17) 274.8
COPD	339 (41) 167.5	307 (20) 145.6	318 (20) 150.8	298 (19) 134.6	19 (5) 89.6	34 (9) 136.8	25 (7) 88.9	29 (8) 99.3
Pneumonia	69 (4) 23.5	82 (5) 24.1	121 (8) 41.9	138 (9) 47.3	3 (<1) 11.2	4 (1) 13.0	7 (2) 22.2	6 (2) 19.9
Lobar pneumonia	11 (<1) 4.0	9 (<1) 2.5	23(1) 7.0	15 (<1) 4.3	0	2 (<1) 6.5	0	0
Respiratory Failure	23 (1) 7.9	29 (2) 8.8	32 (2) 10.1	26 (2) 7.3	1 (<) 3.7	0	0	0
Myocardial infarction	20 (1) 6.7	27 (2) 7.6	19 (1) 5.6	20 (1) 5.9	1 (<1) 3.7	2 (<1) 6.5	1 (<1) 3.2	3 (<1) 9.9
Atrial fibrillation	20 (1) 6.7	23 (1) 6.5	15 (<1) 4.8	16 (1) 5.4	0	2 (<1) 6.5	0	1 (1) 3.3
Chest pain	8 (<1) 3.1	17 (1) 5.4	23 (1) 6.8	23 (1) 7.3	0	0	0	2 (<1) 6.6
Cardiac failure, congestive	18 (1) 6.7	18 (1) 7.1	15 (<1) 5.6	17 (1) 5.9	0	1(<1) 3.3	0	0
Cardiac failure	15 (<1) 5.5	18 (1) 7.6	16 (<1) 4.8	14 (1) 3.8	2 (<1) 7.5	2 (<1) 6.5	0	0
Lung neoplasm	12 (<1) 3.7	17 (1) 4.8	20 (1) 5.6	13 (<1) 3.5	2 (<1) 7.5	0	1 (<1) 3.2	0
Cerebrovascular accident	9 (<1) 2.7	8 (<1) 2.5	16 (1) 5.1	12 (<1) 3.2	2 (<1) 7.5	1 (<1) 3.3	1 (<1) 3.2	1 (<1) 3.3
Pneumothorax	7 (<1) 3.1	10 (<1) 3.1	8 (<1) 2.5	16 (1) 4.6	2 (<1) 7.5	0	0	0

5.2.3 Dropouts and Other Significant Adverse Events

5.2.3.1 Overall Profile of Dropouts

The primary reason for withdrawal was an adverse event which occurred in 24, 20, 24, and 19 % of the placebo, SAL, FP, and FSC patients, respectively in Study SCO30003 and in 19, 16, 15, and 13% of the respective treatment groups in Study SFCB3024 (Table 12). These drop-out rates are quite similar, especially considering that SCO30003 was three times as long as SFCB3024. However, it is consistent with the finding in SCO30003 of a relatively high drop-out during the first year, especially in the placebo-treated patients, with a gradual leveling off in the later years of the study. Lack of efficacy was more common as a reason for withdrawal of patients treated with placebo than patients in the active treatment groups in Studies SCO30003: in Study SFCB3024 withdrawal for lack of efficacy was similar in all of the treatment groups.

Loss to follow-up, protocol violations and lack of compliance were uncommon in both of the studies, but consent withdrawn was the reason for withdrawal in 8-9% of the patients in SCO30003 compared to 2-4% of the patients in Study SFCB3024. Withdrawal of consent could be related to any number of issues. In Study SCO30003, Bone Mineral Density (BMD) was measured in 658 (47%) of the patients enrolled in the United States. Patients with low density (T-score <-2) were sent for a consultation, and it is possible that knowledge of the low scores prompted patients to withdraw consent. Likewise, knowledge of low scores could affect the investigator's decision to withdraw a patient. There was no requirement to withdraw a patient after a specified number of exacerbations, and some patients were withdrawn after one event while others experienced as many as 30 events on study medication. Even if a patient was not withdrawn specifically because they had a low BMD, the decision to withdraw during an exacerbation (or any other time) could have been affected by knowledge of the BMD score. In support of this, patients in the BMD population with low scores withdrew earlier than patients in that population with normal values.

In the whole ITT population withdrawal was higher in patients who had taken corticosteroids in the 12 months prior to enrollment, and that tendency was particularly marked in the patients who were randomized to placebo. The withdrawal rate was very similar in all of the treatment groups in the patients who had not been treated with corticosteroids in the 12 months prior to admission (37, 33, 36, and 34% in the placebo, SAL, FP, and FSC patients, respectively). In the patients treated with inhaled corticosteroids during the 12 months prior to admission, the withdrawal rate was 50, 40, 40, and 34% in the placebo, SAL, FP, and FSC patients, respectively. Higher withdrawal in patients previously treated with ICS was seen in all of the study-treatment groups, although the absolute rates were highest in the placebo patients. The withdrawal category "Consent withdrawn" was not notably different when comparing the study-treatment groups as a whole. However, a higher percentage (30%) of the US population withdrew for this reason compared to 15, 17, 19, 13, and 18% of the population in Asia, Eastern Europe, Western Europe, and the "Other" region.

Table 12. Patient Disposition in Studies SCO30003 and SFCB3024

	SCO30003				SCFB3024			
	Placebo N=1544	**SAL N=1542**	**FP N=1552**	**FSC N=1546**	**Placebo N=361**	**SAL N=372**	**FP N=374**	**FSC N=358**
Completed Treatment	857 (56)	966 (63)	950 (61)	1014 (66)	221 (61)	253 (68)	266 (71)	269 (75)
Withdrawn	687 (44)	576 (37)	602 (39)	532 (34)	140 (39)	119 (32)	108 (29)	89 (25)
Reason for Withdrawal								
Adverse event	368 (24)	304 (20)	366 (24)	292 (19)	68 (19)	61 (16)	55 (15)	46 (13)
Consent withdrawn	139 (9)	137 (9)	118 (8)	120 (8)	16 (4)	13 (3)	11 (3)	6 (2)
Lost to follow-up	21 (1)	15 (<1)	24 (2)	29 (2)	6 (2)	8 (2)	8 (2)	8 (2)
Lack of efficacy	104 (7)	63 (4)	45 (3)	33 (2)	10 (3)	13 (3)	12 (3)	12 (3)
Lacked entry criteria	4 (<1)	3 (<1)	5 (<1)	3 (<1)	18 (5)	5 (1)	2 (<1)	2 (<1)
Non-compliance	19 (1)	21 (1)	16 (1)	20 (1)	3 (<1)	3 (<1)	4 (1)	4 (1)
Other	32 (2)	32 (2)	25 (2)	33 (2)	7 (2)	5 (1)	5 (1)	5 (1)
Missing	0	0	3 (<1)	2 (<1)	12 (3)	11 (3)	6 (2)	6 (2)

5.2.3.2 Adverse events associated with dropouts

The most common adverse event leading to withdrawal was COPD and it was most frequent in the placebo patients in both of the studies: 11, 9, 7, and 5% of the patients in Study SCO30003 and 12, 9, 7, and 6% of the patients in study SCFB3024 treated with placebo, SAL, FP, and FSC, respectively, withdrew due to COPD. Withdrawal from Study SCO30003 was higher in the FSC group for the indication of dysphonia, pneumonia, and malignant lung neoplasms although these conditions accounted for 2% or less of the withdrawals in any of the treatment groups. Malignant lung neoplasms led to withdrawal of 6, 13, 12, and 11 of the patients in the placebo, SAL, FP, and FSC groups, respectively: the corresponding rates were 1.8, 3.7, 3.4, or 3.0 events/1000 treatment years.

5.2.4 Common Adverse Events

5.2.4.1 Eliciting adverse events data in the development program

Patients were queried for adverse events at all clinic visits. After the patient had had a chance to spontaneously report events he/she was asked the following standard questions:

- "Have you had any (other) medical problems since your last visit/assessment?"
- "Have you taken any new medicines, other than those given to you within this study since your last visit/assessment?"

5.2.4.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were classified using the MedDRA dictionary in Study SCO30003 and the MIDAS dictionary for Study SFCB3024. However, for the ISS the events in Study SFCB3024 were recoded using MedDRA and all of the summary tables show the MedDRA coded term. Some of the events of special interest (e.g., bone demineralization) were evaluated with protocol specified laboratory examinations. However, the diagnosis of pneumonia was not prospectively defined, and there was no requirement for Chest x-rays to confirm the diagnosis. This might be particularly problematic in a multinational study where the use of technology could vary. In Study SCO30003 the appropriate terms were grouped for the pneumonia analysis.

5.2.4.3 Incidence of common adverse events

Common events for this analysis were those that occurred in ≥3% of the patients in any of the active treatment groups. They occurred in 90, 90, 90, and 89% of the placebo, SAL, FP, and FSC patients, respectively in Study SCO30003. In Study SFCB3024 they were reported for 78, 79, 81, and 80% of the placebo, SAL, FP, and FSC patients, respectively. Events that occurred in ≥3% of the FSC patients and in more FSC than placebo patient (incidence and rate /1000 treatment years) in one of the studies are listed in Table 13. Total exposure to study drug in Study SCO3003 was 3278, 3531, 3555, and 3700 treatment-years in the placebo, SAL, FP, and FSC groups, respectively. In Study SFCB3024 total exposure was 268, 307, 315, and 302 treatment-years, respectively.

The majority of events were respiratory but Depression, Muscle spasm, Dizziness, Abdominal pain, and Cataract were also increased in the FSC group, although the incidence was low. The respiratory events (other than COPD exacerbation) were all conditions associated with infection or with direct irritation of the upper airway. The incidence of Nasopharyngitis was slightly higher in SCO30003, but the rate was lower than in SFCB3024. If events coded Nasopharyngitis, Pharyngitis and Pharyngolarygeal pain are grouped, then the rate of this combined events was 114.6, 117, 136.8, and 126.5 events / 1000 treatment years in Study SCO30003. Upper respiratory tract infections, Pneumonia, and Bronchitis were less frequent in SFCB3024, and the trend to higher rates in the fluticasone-treated patients was less marked. In study SCO30003 the rate of Pneumonia in the FSC-treated patients was almost double the placebo rate. As expected, candidiasis was more common in the fluticasone-treated patients. If Oral candidiasis, Oropharyngeal candidiasis and Candidiasis are combined, the event occurred at a rate of 22.0, 17.3, 83.3, and 70.4 events / 1000 treatment-years in the placebo, SAL, FP, and FSC patients, respectively. Events that occurred at a rate of ≥3% but less frequently in the FSC-treated patients include COPD, Headache, Back pain, Hypertension, Dyspnea, Diarrhea, Insomnia, Constipation, Arthralgia, Peripheral edema, Urinary tract infection, Nausea, Pain in extremity, Gastroesophageal reflux, and Dyspepsia.

5.2.4.4 Common adverse event tables

Table 13. Adverse Events Occurring in at Least 3% of the FSC Patients and in More FSC than Placebo Patients (incidence and rate) in at Least One of the Studies

	SCO30003				SCFB3024			
N (%) Events/1000 treatment-years	**Placebo N=1544**	**SAL N=1542**	**FP N=1552**	**FSC N=1546**	**Placebo N=361**	**SAL N=372**	**FP N=374**	**FSC N=358**
Any Event	1385 (90) 2981.7	1381 (90) 2767.2	1395 (90) 2964.8	1381 (89) 2868.1	283 (78) 3783.6	295 (79) 3524.4	302 (81) 4181.0	285 (80) 3615.9
Nasopharyngitis	165 (11) 85.7	191 (12) 88.1	206 (13) 96.8	215 (14) 96.8	30 (8) 153.0	28 (8) 133.6	48 (13) 250.8	41 (11) 162.3
Upper Respiratory Tract Infection	170 (11) 100.7	165 (11) 80.4	168 (11) 88.0	213 (14) 104.9	15 (4) 63.4	10 (3) 48.9	13 (3) 54.0	10 (3) 39.7
Pneumonia	112 (7) 39.4	133 (9) 41.6	185 (12) 69.2	207 (13) 71.1	7 (2) 26.1	7 (2) 54.0	15 (4) 53.0	11 (3) 53.0
Bronchitis	91 (6) 48.5	97.6 (6) 35.1	102.7 (7) 59.6	121 (8) 54.3	5 (1) 26.1	5 (1) 16.3	5 (1) 25.4	11 (3) 53.0
Sinusitis	76 (5) 31.1	66 (4) 28.6	101 (7) 41.4	93 (6) 36.8	7 (2) 37.3	8 (2) 29.3	13 (3) 50.8	13 (4) 53.0
Cough	68 (4) 24.7	76 (5) 26.3	91 (6) 36.0	94 (6) 34.1	20 (6) 85.8	12 (3) 48.9	16 (4) 63.5	13 (4) 49.7
Chest pain	59 (4) 22.9	72 (5) 24.1	72 (5) 27.0	93 (6) 30.8	5 (1) 18.7	11 (3) 45.6	13 (3) 41.3	11 (3) 36.4
Influenza	66 (4) 31.4	69 (4) 26.3	86 (6) 28.7	82 (5) 28.6	21 (6) 89.6	19 (5) 91.2	16 (4) 57.1	25 (7) 99.3
Oral candidiasis	27 (2) 11.0	28 (2) 9.9	106 (7) 45.9	84 (5) 36.8	6 (2) 26.1	10 (3) 35.8	37 (10) 107.8	28 (8) 129.1
Diarrhea	50 (3) 20.1	66 (4) 23.5	65 (4) 20.0	68 (4) 21.1	8 (2) 33.6	6 (2) 22.8	12 (3) 41.3	5 (1) 16.6
Depression	42 (3) 14.3	42 (3) 12.5	46 (3) 14.1	55 (4) 14.9	2 (<1) 7.5	3 (<1) 9.8	4 (1) 12.7	1(<1) 3.3
Bronchitis acute	48 (3) 26.5	48 (3) 20.1	59 (4) 29.5	73 (5) 31.4	2 (<1) 7.5	1 (<1) 6.5	3 (<1) 9.5	3 (<1) 23.2
Muscle spasm	35 (2) 12.8	37 (2) 13.0	46 (3) 14.3	66 (4) 22.2	3 (<1) 11.2	8 (2) 42.3	6 (2) 25.4	9 (3) 33.1
Dizziness	43 (3) 16.8	40 (3) 12.7	42 (3) 12.9	56 (4) 17.3	2 (<1) 7.5	7 (2) 29.3	4 (1) 12.7	4 (1) 16.6
Dysphonia	12 (<1)	15 (<1)	52 (3)	67 (4)	2 (<1)	1 (<1)	8 (2)	7 (2)

	3.7	4.8	17.4	20.8	7.5	3.3	34.9	33.1
Pyrexia	26 (2) 9.2	43 (3) 19.5	37 (2) 12.7	55 (4) 18.9	10 (3) 52.2	6 (2) 32.6	10 (3) 34.9	10 (3) 49.7
Lower respiratory tract infection	46 (3) 20.1	46 (3) 19.0	43 (3) 21.4	53 (3) 23.1	15 (4) 67.2	9 (2) 35.8	16 (4) 88.9	19 (5) 102.6
Rhinitis	32 (2) 11.9	44 (3) 16.7	46 (3) 15.8	46 (3) 14.3	5 (1) 18.7	8 (2) 26.1	13 (3) 54.0	7 (2) 26.5
Respiratory tract infection	36 (2) 14.3	38 (2) 19.0	30 (2) 13.2	44 (3) 17.0	3 (<1) 11.2	2 (<1) 6.5	9 (2) 31.7	8 (2) 29.8
Abdominal pain	28 (2) 10.4	40 (3) 13.3	38 (2) 11.5	40 (3) 13.0	2 (<1) 7.5	5 (1) 19.5	3 (<1) 9.5	6 (2) 19.9
Pharyngitis	24 (2) 7.9	23 (1) 7.4	30 (2) 11.3	25 (2) 7.0	5 (1) 18.7	6 (2) 25.4	5 (1) 19.0	11 (3) 43.0
Cataract	27 (2) 9.2	37 (2) 12.5	29 (2) 8.4	48 (3) 13.8	0	2 6.5	0	0
Dyspepsia	24 (2) 9.2	32 (2) 13.0	36 (2) 12.9	39 (3) 13.0	3 (<1) 18.7	6 (2) 22.8	2 (<1) 12.7	4 (1) 13.2
Oropharyngeal candidiasis	10 (<1) 3.1	10 (<1) 3.4	27 (2) 15.5	25 (2) 16.8	1 (<1) 3.7	2 (<1) 6.5	6 (2) 25.4	9 (3) 39.7

5.2.5 Less Common Adverse Events

5.2.5.1 Bone Disorders

In Study SCO30003 the incidence of bone disorders was very slightly higher in the FSC treatment group: 77 (5%), 85 (6%), 90 (6%), 105 (7%) were reported in the placebo, SAL, FP, and FSC patients, respectively. The corresponding rates, adjusted for time on treatment, were 27.5, 28.9, 29.3, and 32.2 events/1000 treatment years.

Bone fractures were reported in 57 (3.7%), 61 (4.0%), 65 (4.2%), and 78 (5%) of the placebo, SAL, FP, and FSC patients, respectively. The respective rates were 18.6, 20.4, 20.3, and 22.4 events/1000 treatment years. The incidence of non-traumatic bone fractures was actually lower in the FSC group (Kaplan-Meier probability of 1.7% at three years) compared to 1.8, 2.5, and 1.7% in the placebo, SAL and FP groups, respectively. The Kaplan-Meier probability of traumatic fracture was 3.5, 3.1, 3.7, and 4.7 % in the placebo, SAL, FP, and FSC treatment groups.

In Study SFCB3024 the incidence of bone disorders was similar in all of the treatment groups, but the number of events was very low. Events were reported in 8 (2%), 4 (1%), 7 (2%), and 5 (1%) of the patients in the placebo, SAL, FP, and FSC groups, respectively.

5.2.5.2 Ophthalmic Adverse Events

Overall, 2-4% of the patients enrolled in Study SCO30003 reported ophthalmic adverse events. Adjusting for time on treatment, the rates were 13.7, 17.8, 15.8, and 18.6 events/1000 treatment-years in the placebo, SAL, FP, FSC groups, respectively. In a time to first eye event analysis the hazard ratio (95% CI) comparing the active treatment to placebo was 1.228 (0.830, 1.743), 1.156 (0.755, 1.769), and 1.462 (0.978, 2.187) in the placebo, SAL, FP, and FSC groups, respectively. The incidence of some form of cataract and glaucoma were both slightly elevated in the FSC group. Cataract occurred in 2.2, 2.8, 2.3, and 3.4% of the placebo, SAL, FP, and FSC patients, respectively. The respective incidence of glaucoma was 0.4, 0.7, 0.9, and 0.8%.

The incidence of eye disorders in SFCB3024 was very low. Events were reported in 1 placebo, 4 SAL, 2 FP, and 1 FSC patients, respectively.

5.2.5.3 HPA-axis Disorders

HPA-axis disorders were uncommon and were reported in a total of 7 patients in the two studies combined: 2 placebo, 1 SAL, 3 FP, and 1 FSC patient.

5.2.5.4 Cerebrovascular Events

In Study SCO30003, patients treated with FP were seen to have more Cerebrovascular accidents than the patients in the other groups. The overall rates were low, but FP-treated patients had higher rates that either the SAL or FSC, treated patients. The rates overall were 3.7, 3.1. 6.8, and 4.1 events/1000 treatment-years in the placebo, SAL, FP, and FSC patients,

respectively. The rate of severe Cerebrovascular accident AEs was also elevated in the FP group. Of the cerebrovascular adverse events, 7.4, 12.5, 35.1, and 16.7% were fatal in the placebo, SAL, FP, and FSC patients, respectively. Additional analyses were performed using different combinations of MedDRA terms and demographic variables were assessed but no explanation could be found for this finding.

5.2.6 Other Search Strategies

5.2.6.1 Respiratory Tract Adverse Events

Serious Respiratory Tract Adverse Events

Respiratory tract adverse events were further explored by grouping serious respiratory events by MedDRA Higher Level Term (HLT). Grouping the events permitted comparisons when the number of events in each preferred term was too small to provide a basis to draw conclusions. Overall, the incidence of severe respiratory events in study SCO30003 was similar in all of the treatment groups with rates of 261.4, 230.5, 267.5, and 257.6 events / 1000 treatment-years in the placebo, SAL, FP, and FSC patients, respectively (Table 14). Note that this tabulation includes Bronchospasm and obstruction, most of which were also counted as COPD exacerbations in the efficacy analysis. Lower respiratory tract infections were clearly elevated in the fluticasone-containing regimens. The rates were 35.1, 32.9, 56.3, and 61.6 events per 1000 treatment-years in the placebo, SAL, FP, and FSC groups, respectively. Respiratory failure and lung neoplasms were slightly less frequent in the FSC group, but respiratory signs and symptoms and pneumothorax/pleural effusion were more common.

Table 14. Serious Respiratory Adverse Events in Study SCO30003 (MedDRA HLT)

[Rate per Thousand Treatment-years]	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	FSC 500/50 (N=1546)
Any Respiratory Event	261.4	230.5	267.5	257.6
Bronchospasm and obstruction	168.4	146.7	151.3	135.4
Lower respiratory tract infections, NEC	35.1	32.9	56.3	61.6
Respiratory failure	13.4	10.8	14.1	10.8
Lower respiratory tract neoplasms	9.8	9.1	10.4	7.6
Respiratory signs and symptoms, NEC	4.6	6.5	7.3	7.8
Pneumothorax and pleural effusion	3.7	4.2	2.8	6.2

A similar pattern of serious respiratory adverse events was seen in Study SCFB3024; 240 patients reported serious respiratory events of which 107 were due to COPD. Again, pneumonia was the second most common event (3 (<1%), 9 (2%), 9 (2%), and 7 (2%) of the placebo, SAL, FP, and FSC patients, respectively.

Non-Serious Respiratory Tract Adverse Events

If all respiratory adverse events that were coded in the MedDRA System Organ Class (SOC) of Respiratory, thoracic and mediastinal disorders (Table 15) are tabulated by HLT, a similar pattern emerges in Study SCO30003. The overall incidence of respiratory events was similar in all of the treatment groups with a slight excess (events/1000 treatment-years) in the placebo and

FP groups: placebo (1660) SAL (1456) FP (1604) and FSC (1518). The rate of Bronchospasm and obstruction, the category under which a majority of the COPD exacerbations were classified, was decreased in the FSC-treated patients as were other diagnoses that might be associated with exacerbations (Breathing abnormalities, and Respiratory failure). The rate of adverse respiratory events excluding these three HLTs was 659, 629, 762, and 798 events/1000 treatment-years in the placebo, SAL, FP, and FSC patients, respectively. The excess events in the fluticasone-containing regimens was seen primarily in the infectious disease categories (Upper respiratory tract infection NEC and Lower respiratory tact infection NEC) although, many of the less frequent events (Respiratory tract signs and symptoms) were also elevated in the FSC-treated patients.

Table 15. All Respiratory Tract Adverse Events (MedDRA HLT) with Onset During Randomized Treatment Listed Under the MedDRA SOC Respiratory, Thoracic, and Mediastinal in Study SCO30003*

	SCO30003			
Percentage of Patients Rate/1000 treatment years	**Placebo N=1544**	**SAL N=1542**	**FP N=1552**	**FSC N=1546**
Any Event	83 1660	82 1456	82 1604	83 1518
Bronchospasm & Obstruction	63 929	61 766	60 782	57 672
Upper Respiratory Tract Infection, NEC	27 251	28 226	32 275	34 285
Lower Respiratory Tract Infection, NEC	19 146	20 141	24 186	28 195
Upper Respiratory Tract Signs and Symptoms	8 50	8 51	11 73	12 72
Breathing abnormalities	9 57	8 47	8 43	7 35
Cough	7 43	7 40	8 55	9 55
Respiratory Signs & Symptoms	5 31	6 31	6 34	7 37
Viral Upper Respiratory Tract Infection	5 36	5 30	6 33	6 34
Respiratory failure	3 15	3 14	3 17	3 13
Respiratory tract infections, NEC	3 15	3 21	2 14	3 19
Lower Respiratory Tract Neoplasms	2 12	2 11	3 12	3 12
Nasal Congestion & inflammation	2 12	2 14	3 15	3 15
Pulmonary Hypertension	1 9	2 8	2 8	2 8
Nasal disorders, NEC	1 7	1 6	1 5	1 7
Bronchial conditions	1 6	1 7	1 6	2 8
Pneumothorax and pleural effusion	1 6	<1 5	<1 4	2 8
Paranasal sinus disorders	1 5	1 6	<1 4	1 7

Thoracic Musculoskelatal disorders	<1 2	<1 3	1 5	<1 4
Respiratory Tact Disorders, NEC	<1 3	<1 4	<1 4	1 7
Lower Respiratory Tract Signs & symptoms	<1 3	<1 0.8	<1 3	<1 2

* * From Table 78 (pg 186) of ISS

Table 16 is in the same format as Table 15, above. It lists the MedDRA-coded terms for the respiratory events for study SFCB3024 with the exclusion of events that were reported in <1% in all treatment groups. The pattern reported for Study SCO30003 is repeated: the incidence of Bronchospasm and obstruction was lowest in the FSC-treated patients, but the incidence and rate of upper and lower respiratory infections was higher in the FSC-treated patients. Of note, the incidence of most of these events was lower, but the rates/1000 treatment-year were higher in Study SFCB3024 than in Study SCO30003. This is compatible with the shorter duration of SFCB3024 (lower incidence of events) and the increased susceptibility of the patients enrolled into SFCB3024 to exacerbations. The requirement for a history of chronic bronchitis and for a history of at least one moderate/severe exacerbation in the 12 months prior to admission would select patients expected to have a high rate of events.

Table 16. Adverse Respiratory Events Listed by MedDRA HLT in Study SFCB3024*

	SCFB3024			
Percentage Rate/1000 treatment years	**Placebo N=361**	**SAL N=372**	**FP N=374**	**FSC N=358**
Any Event	71 2258	66 1915	70 2206	69 2040
Bronchospasm & Obstruction	54 1332	51 1160	51 1089	49 964
Upper Respiratory Tract Infection, NEC	16 280	16 254	23 454	23 351
Lower Respiratory Tract Infection, NEC	8 134	8 121	11 191	13 258
Upper Respiratory Tract Signs and Symptoms	8 127	5 68	7 140	8 129
Breathing abnormalities	3 52	3 39	2 38	3 30
Cough	4 68	5 79	5 76	8 312
Respiratory Signs & Symptoms	2 22	3 49	4 48	3 36
Viral Upper Respiratory Tract Infection	6 90	5 91	4 57	7 99
Respiratory tract infections, NEC	1 15	<1 10	3 41	2 30
Nasal congestion and inflammations	<1 19	<1 3	1 19	1 17
Nasal disorders, NEC	1 15	1 16	<1 19	<1 7

* From Table 78 (pg 186) of ISS

Respiratory Tract Infections

In the report for Study SCO30003 there is an analysis of "Lower respiratory tract infection of pneumonia or bronchitis". This grouping was performed by the Applicant and included all of the pneumonia, bronchitis, and lung infection events other than COPD that were included in the application (See Table 54, pg 105, for list of preferred terms). Using this grouping, the outcome "Lower respiratory infections of pneumonia and bronchitis" was clearly elevated in both the FP and FSC treatment groups. The Hazard Ratio (95% CI) comparing active treatment to placebo was 0.995 (0.851, 1.164), 1.190 (1.024, 1.384), and 1.375 (1.189, 1.591) for the comparison with SAL, FP, and FSC. Furthermore, the Hazard Ratio (95% CI) was also high when comparing FSC to SAL (1.384 [1.199, 1.597]) and FP (1.154 [1.007, 1.324]).

Pneumonia

The elevated risk of lower respiratory tract infection was further investigated by grouping only pneumonia events in the time to event analysis in Study SCO30003. The following MedDRA terms were used in this included: Bronchopneumonia, Pneumonia, Lobar pneumonia, Lung infection, Pneumonia bacterial, Pneumonia chlamydial, Pneumonia necrotizing, Pneumonia staphylococcal, Pneumonia streptococcal, Superinfection lung, Pneumonitis, Pneumonia primary atypical, Bronchopneumopathy, Lung infection pseudomonal, and Pneumocystis jiroveci pneumonia. These aggregated conditions were reported in 9, 11, 14, and 16% of the placebo, SAL, FP, and FSC patients, respectively. The rates adjusted for time on treatment were 51.9, 51.5, 84.4 and 87.6 events/1000 treatment-years in the placebo, SAL, FP, and FSC groups, respectively. The hazard ratio (95% CI) comparing active treatment to placebo was 1.088 (0.867, 1.365), 1.533 (1.240, 1.894), and 1.639 (1.331, 2.017) for the comparison to SAL, FP, and FSC, respectively. The hazard ratio (95% CI) comparing FSC to SAL was 1.508 (1.237, 1.838) and 1.068 (0.891, 1.280) comparing FSC to FP.

In Study SFCB3024 the incidence of pneumonia was not markedly different among the treatment groups; however the number of events was relatively small. There were only 8 (2%), 17 (5%), 19 (5%), and 17 (5%) in the placebo, SAL, FP, and FSC treatment groups, respectively.

Reviewer: It is stated in the ISS that the increased incidence of lower respiratory infectious events was entirely accounted for by the increased incidence of pneumonia. However, no analysis of non-pneumonia, lower respiratory infections was performed. Because of the potential importance of this group of events in the natural history of COPD, the FDA statistical reviewer repeated the analysis using the Applicant's group of "Lower respiratory tract infection of pneumonia and bronchitis" excluding pneumonia. In a time-to-event analysis, this group of respiratory infections was also elevated in the FSC-treated patients: 16, 15, 16, and 19% three-year probability in the placebo, SAL, FP, and FSC groups, respectively. The hazard ratio (95% CI) comparing FSC to placebo was 1.23 (1.02, 1.23). The probability of any form of bronchitis (Bronchitis, Bronchitis acute, Bronchitis bacterial, Bronchitis viral), was 11, 11, 12, and 14% in the respective treatment groups. The hazard ratio (95% CI) comparing FSC to placebo was 1.24 (0.99, 1.55). Thus, while the differences were not as marked for the other respiratory infections as for pneumonia, they were consistently elevated in the FSC-treated patients.

The argument that non-pneumonia respiratory infections were not increased in a clinically important manner was supported with an analysis that grouped the "Lower respiratory tract

infection of pneumonia or bronchitis" and all of the COPD exacerbations that were treated with antibiotics. There was no difference in the time-adjusted incidence of this outcome among the treatment groups.

Reviewer: The above analysis is not appropriate because there were over 10,000 COPD exacerbations treated with antibiotics, and approximately ½ of these were also treated with corticosteroids. In many areas, clinical practice dictates that COPD exacerbations be treated with both modalities without documentation that infection is an etiologic factor. Thus inclusion of the large number of events treated with both corticosteroids and antibiotics probably includes many patients in whom infection was not primary. In an analysis conducted by the FDA statistical reviewer of COPD exacerbations treated with antibiotics alone, the incidence was found to be significantly increased in the FSC-treated patients compared to placebo (See Detailed Study review, pg 85 and FDA statistical review).

5.2.7 Special Safety Studies

5.2.7.1 Bone Mineral Density

Bone mineral density (BMD) was measured in 658 patients enrolled in the United States. A baseline and 3-year follow-up value were available in 277 patients. The measurements at baseline in the total hip were highest in the SAL group (0.908 g/cm^2) and lowest in the FP group (0.850 gm/cm^2). The mean value in the Placebo group was 0.878 g/cm^2 and in the FSC group it was 0.899 gm/cm^2. The adjusted percent change from baseline was -3.1, -1.7, -2.9, and -3.2% in the placebo, SAL, FP, and FSC groups, respectively. The repeated measures analysis of percent change in BMD showed a ratio of active treatment to placebo (95% CI) of 1.14 (0.996, 1.032), 1.0017 (0.934, 1.032) and 0.9987 (0.9812, 1.017) for the comparison with SAL, FP, and FSC, respectively. For the measurements at the lumbar spine, there were 270 patients with baseline and end-of-study scans for comparison. The mean values at baseline were 1.008, 1.058, 0.974, and 1.014 g/cm2 in the placebo, SAL, FP, and FSC patients, respectively. The repeated measures analysis of percent change in BMD showed a ratio (95% CI) comparing active treatment to placebo of 1.015 (0.998, 1.032), 0.997 (0.980, 1.014), and 0.997 (0.981, 1.013) for the comparison with SAL, FP, and FSC, respectively.

Thus there was not a dramatic difference among the treatment groups in the change in BMD with treatment. One caveat in this regard is that there was a higher drop-out among patients with lower BMD at baseline. Therefore, the analysis may under estimate the changes in the population as a whole because a susceptible sub-group withdrew early.

5.2.7.2 Ophthalmologic Examinations

In Study SCO30003 ophthalmologic examinations were conducted by optometrists at selected centers in the USA. The study report states that "Examinations were conducted with established methodology". Using these procedures, most of the patients had cataracts at baseline (64, 71, 64, and 61% of the placebo, SAL, FP, and FSC patients, respectively. Of the 188 patients remaining who had no cataracts at baseline, 21, 15, 17, and 26% of the placebo, SAL, FP, and FSC patients

developed cataracts during the trial. In a logistic regression of the number of patients developing cataract, the odds ratio (95% CI) for FSC compared to placebo was 1.395 (0.542, 3.590).

Eight percent or fewer of the patients had glaucoma at baseline. Of the 525 remaining patients without glaucoma at baseline, 2, 0, 5, and 2% of the patients in the placebo, SAL, FP, and FSC groups developed glaucoma during the treatment period.

Reviewer: The ophthalmic examinations were performed by trained optometrists, but a protocol was not used for the examination. By not using a systematic examination such as the LOCS III system prevalent cataract could not be followed for growth. Sixty percent of the patient in Study SCO30003 had cataracts at baseline and these patients were excluded from the analysis

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6 OVERALL ASSESSMENT

6.1 Conclusions

The difference between FSC and placebo in all-cause, 3-year mortality was small (2.6%) and not substantially better than the difference between SAL and placebo (1.7%). The differences between active treatment and placebo were even less in the on-treatment mortality analysis and in the all death analysis of the US population. The finding of a lower than expected mortality in this disease may reflect improved general supportive care to patients enrolled in a clinical study.

FSC did consistently decrease the incidence of moderate/severe COPD exacerbations and moderate/severe exacerbations that were treated with systemic corticosteroids. The effect on severe exacerbations was less marked and the incidence of antibiotic-treated infections was actually increased. The increase in antibiotic-treated exacerbations is consistent with the increase in pneumonia and other lower respiratory tract infections that was well documented in Study SCO30003. It is somewhat difficult to understand how the COPD exacerbation rate can be decreased while a major component of exacerbations (i.e. infections) is increased. This alone, suggests that there is still much to learn about the pathophysiology and natural history of COPD and that treatment with FSC should be reserved to patients most likely to respond.

Pulmonary function was better during treatment with FSC than with any of the other treatments in all three pivotal studies. This would be expected given the previously documented efficacy of the 250/50 mcg BID dose.

APPENDICES
(Review of Individual Study Reports)

1 STUDY # SCO30003

A multicenter, randomized, double-blind parallel group, placebo-controlled study to investigate the long-term effects of fluticasone/salmeterol propionate (SERETIDE™/VIANI™/ADVAIR™) 500/50 mcg bd, salmeterol 50 mcg bd and fluticasone propionate 500 mcg bd, all delivered via the DISKUS™ /ACCUHALER™ inhaler, on the survival of patients with chronic obstructive pulmonary disease (COPD) over 3 years of treatment.

1.1 Protocol

1.1.1 Administrative

Dates: September 7, 2000 to November 8, 2005

Centers: 466 in 42 countries including 190 in the US, 134 in Western Europe, 46 in Eastern Europe, 37 in Asia/Pacific, and 59 in other areas. Of these, 442 enrolled patients, including 171 in the US, 132 in Western Europe, 46 in Eastern Europe, 36 in Asia/Pacific and 57 in "Other" areas. The Other designation included Canada, Australia, New Zealand, 4 countries in South America and South Africa.

Steering Committee: The co-chairmen were Peter Calverley, a site investigator in the UK and Kate Knobil, Vice President of Respiratory Medicine at GSK. Additional members were site Principal investigators (PI) from the United States (2), Denmark (1) and Australia (1); The study leader and statistician from GSK; and Paul Jones and Neil Pride from the UK and Romain Pauwels from Denmark.

Safety and Efficacy Data Monitoring Committee (SEDMC):
Reuben Cherniak, Respiratory clinician, National Jewish Medical and Research Center, Denver, Colorado, US
Anne Whitehead, Statistician, University of Reading, Reading, UK
Thomas Similowski, Respiratory clinician Hôpital Pitie Saltperiere, Paris, Fr.
John Cleland, Cardiologist, Castle Hill Hospital, Hull, UK

Clinical Endpoints Committee (CEC):
Robert A. Wise, Respiratory clinician, John Hopkins University, Baltimore, MD, US
Lorcan McGarvey, Respiratory clinician, Grosvenor Road, Belfast, Northern Ireland, UK
Matthias John, Medical Director, Barmer Ostseeklinik, Prerow, Germany

1.1.2. Objective/Rationale

The primary objective of this study was to demonstrate a significant reduction in all-cause mortality in COPD patients treated with fluticasone/salmeterol propionate 500/50mcg (FSC 500/50) compared with placebo, when added to usual COPD therapy.

Secondary objectives were:

- To show a significant reduction in COPD morbidity with FSC 500/50 compared with placebo, as measured by the rate of moderate and severe exacerbations
- To show a significant difference in Quality of Life with FSC 500/50 compared with placebo, as measured by the St. George Respiratory Questionnaire (SGRQ)
- To investigate and compare the number of adverse events in each treatment group.

1.1.3 Study Design

This was a multi-center, randomized, double-blind, parallel-group, placebo-controlled trial. Following a 2-week run-in period, eligible patients were randomized to 3 years (156 weeks) of treatment with fluticasone/salmeterol 500/50 (FSC), Salmeterol 50 mcg (SAL), fluticasone 500 mcg (FP), or placebo, all treatments administered twice daily. Patients were randomized in a 1:1:1:1 ratio after stratification by smoking status (current vs former). Patients who discontinued study treatment before 3 years had survival status assessed at 3 years (156 weeks or 1092 days) after beginning study treatment. The patients were seen every 12 weeks for a maximum of 16 visits (One pre randomization, 14 on treatment, and 1 follow up visit 2 weeks after stopping therapy). Patients who stopped study treatment were contacted by telephone every 12 weeks. The vital status was ascertained and the patient was queried about study drug-related severe adverse events, COPD exacerbations, and concomitant medications.

The primary endpoint of this study was all-cause mortality amongst all patients in the ITT Population within 3 years after the start of treatment. Secondary efficacy endpoints were the rate of moderate and severe COPD exacerbations (moderate defined as requiring treatment with systemic corticosteroids and/or antibiotics and severe defined as requiring hospitalization) and quality of life assessed with the SGRQ. Safety evaluations included adverse event monitoring, bone mineral density measurements and ophthalmic examinations performed on a subset of the study population in the U.S.

1.1.4 Study Population

Inclusion Criteria

1. Male or female out-patients, aged 40-80 years inclusive, with a baseline (pre-bronchodilator) FEV_1, <60% of predicted normal.

2. An established clinical history of COPD (COPD defined, in accordance with the ERS Consensus Statement [Siafakis, 1995], as a disorder characterized by decreased maximum expiratory flow and slow forced emptying of the lungs, which is slowly progressive, mostly irreversible, and does not change markedly over several months)

3. Current or former smokers with a smoking history of at least 10 pack-years (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years). (Former smokers were defined as those who had stopped smoking for at least 6 months prior to Visit 1. Former smokers were eligible to enter the study provided they had at least 10 pack years' smoking history).

4. Poor reversibility of airflow obstruction. (Poor reversibility defined as less than 10% increase in FEV_1 as a percentage of normal predicted, 30 minutes after inhalation of 400rncg salbutamol via metered-dose inhaler (MDI) and VOLUMATIC™ spacer (ELLIPSE™ spacer for US centers).

5. Baseline (pre-bronchodilator) FEV_1/FVC ratio <70%

6. Able to use a DISKUS/ACCUHALER inhaler and relief medication correctly

7. A signed and dated written informed consent was obtained prior to participation.

8. Able to comply with the requirements of the protocol.

9. A female was eligible to enter and participate in this study if she was of-
   a. non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who was post-menopausal); or,
   b. child-bearing potential, had a negative pregnancy test (urine or serum) at screening, and agreed to one of the following:
   - Complete abstinence from intercourse for the duration of the study
   - Sterilization
   - Sterilization of male partner
   - Implant of levonorgestrol
   - Injectable progestogen
   - Oral contraceptive (combined or progestogen only)
   - Any intrauterine device (IUD) with published data showing that the lowest failure rate was less than 1% per year
   - Any other methods with published data showing that the lowest failure rate was less than I% per year
   - Barrier method only if used in combination with any of the above acceptable methods.

Exclusion Criteria

1. In the opinion of the investigator, there was a current diagnosis of asthma

2. Current respiratory disorders other than COPD (e.g., lung cancer, sarcoidosis, tuberculosis, lung fibrosis)

3. Chest X-ray indicating diagnosis other than COPD that could have interfered with the study (chest X-ray taken up to 6 months before entry to the treatment period)

4. Had lung-volume reduction surgery and/or a lung transplant

5. Requirement for long term oxygen therapy (LTOT) at the start of the study (LTOT was defined as oxygen therapy prescribed for 12 hours or more per day)

6. Was receiving long-term oral corticosteroid therapy at screening (Long-term therapy was defined as continuous use for greater than 6 weeks. Courses of oral corticosteroids separated by a period of less than 7 days were considered as continuous use.)

7. Serious, uncontrolled disease (including serious psychological disorders) likely to interfere with the study and/or likely to cause death within the 3-year study duration

*8. Received any other investigational drugs in the last 4 weeks before entry to Visit 1. Patients previously enrolled into Study SFCB3024 could have been recruited to this trial 4 weeks after stopping their previous study medication.

9. Had, in the opinion of the investigator, evidence of alcohol, drug or solvent abuse

10. Known or suspected hypersensitivity to inhaled corticosteroids, bronchodilators or Lactose

11. Known deficiency of α-1 antitrypsin

12. Previously had been enrolled into the Run-in Period

**Reviewer: Entry into SCO30003 after treatment in SCFB3024 was removed from the protocol in Amendment 3 (November 15, 2000). However, the last patient treated in SCFB3024 was enrolled into SCO30003 on May 16, 2002.*

Randomization Criteria

Patients who had an exacerbation of COPD during the run-in period that required systemic corticosteroid therapy and/or hospitalization were not eligible for randomization. There was no other requirement for clinical stability, and patients who started antibiotics for a COPD exacerbation were not disqualified.

Continuation Criteria

A patient could be withdrawn from treatment at his/her request, for an adverse event or lack of efficacy if the investigator thought it would have been detrimental for the patient to continue. Investigators were encouraged to treat exacerbations with non-study drugs and keep the patient in the study. However, ≥ 3 exacerbations requiring corticosteroid treatment or ≥ 2 exacerbations requiring hospitalization during a 6 month period were considered excessive and could be an indication for withdrawal from treatment.

The survival of all patients was recorded even if they withdrew prematurely from the treatment protocol.

1.1.5 Study Procedures

Treatment

The following blinded study medications were provided by the International Clinical Supplies Department of GSK Research and Development:

- Salmeterol xinafoate (GR33343G)/fluticasone propionate (CCI18781) combination product 500/50mcg strength DISKUS/ACCUHALER inhaler (formulated with lactose)
- Salmeterol xinafoate (GR33343G) 50mcg strength DISKUS/ACCUHALER inhaler (formulated with lactose)
- Fluticasone propionate (CCI18781) 500mcg strength DISKUS/ACCUHALER inhaler (formulated with lactose)
- Placebo DISKUS/ACCUHALER inhaler to match (formulated with lactose).

Each DISKUS/ACCUHALER contained 60 doses of study medication or placebo and all of the canisters had an identical appearance. Ventolin (salbutamol) was provided as relief medication.

Medications for other chronic diseases and for COPD were permitted throughout the study with the following exceptions:

- Inhaled or systemic corticosteroids
- Long acting bronchodilators including long acting ß-adrenergic agonists and long acting anticholinergics.
- LTOT was not permitted at Visit 1

Baseline Assessments

Demographic variables included the gender, ethnicity, date of birth, height, weight history of COPD, patient-reported number of exacerbations in the previous 12 months that required systemic corticosteroids and/or antibiotics and/or hospitalizations, history of myocardial infarction, Medical Research Council (MRC) dyspnea scale, oxygen saturation measured with an oximeter, smoking history current medical conditions, medication history and prior participation in study SFCB3024.

The MRC Dyspnea Score was graded as follows:

1. I only get breathless with strenuous exercise
2. I get short of breath when hurrying on the level or walking up a slight hill
3. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking at my own pace on the level
4. I stop for breath after walking about 100 yards or after a few minutes on the level
5. I am too breathless to leave the house or I am breathless when dressing or undressing

Smoking history was quantified by pack-years and by current or former status. To be a former smoker, the patient had to have refrained from smoking for at least 6 months prior to visit 1. Pack-years were calculated as number of cigarettes smoked/day divided by 20 times the number

of years smoking. One cigar was equivalent to 7 cigarettes and one gram of tobacco was equivalent to one cigarette.

Efficacy Evaluation

The primary efficacy outcome was all-cause mortality at 3 years. Patients who were lost to follow-up had their survival status checked by telephone at 12-weekly intervals. The patients agreed at the beginning of the study to allow continued follow-up in the event of study drug termination prior to three years of treatment, A cause of death was assigned by the investigator using the information at hand and he/she made an assessment as to whether, the death was COPD-related. The CEC reviewed the CRF and other available evidence and assigned a cause of death to a pre-determined set of categories (cardiovascular, pulmonary, cancer-related, other, unknown). The CEC also assessed whether the cause was COPD related and quantitated the certainty of this assessment with the terms "Yes", "Probably", "Possibly", "Unlikely", "No" or "Unknown". Deaths assigned a "Yes", "Probably" or "Possibly" by the CEC were classed as COPD-related deaths for analysis purposes. COPD-related deaths included such conditions as sudden death in a patient with severe COPD who were found dead at home and did not have an autopsy.

The secondary outcomes were the rate of moderate and severe COPD exacerbations and quality of life as determined by the Saint George's Respiratory Questionnaire (SGRQ).

A COPD exacerbation was defined as moderate if treatment with systemic corticosteroids and/or antibiotics was administered and severe if hospitalization was required. Patients with worsening COPD symptoms were told to increase their usual medication for COPD and to contact the investigator as soon as possible if there was no relief. The site investigator was encouraged to maximize non-study treatments (theophylline, short-acting anticholinergics, and short-acting ß-adrenergic agonists). Any treatment with short courses of systemic corticosteroids and/or antibiotics was recorded in the CRF. Moderate and severe COPD exacerbations were also reported as AEs or SAEs as appropriate. The exacerbation rate was calculated by taking the number of exacerbations that the patient had while on the study divided by the number of 13-week periods that the patient was on the study and that number was multiplied by 4 to arrive at an annual rate. Exacerbations that occurred after a patient was taken off of study medication were not included in the outcome assessment.

Other efficacy endpoints included COPD-related mortality, on-treatment morality, a composite endpoint (severe COPD exacerbation, LTOT, or on treatment mortality), post-bronchodilator FEV_1, number of withdrawals from treatment, time to first moderate or severe exacerbation, rate of severe exacerbations, time to first severe exacerbation rate of moderate and severe exacerbations requiring systemic corticosteroids, time to first moderate or severe exacerbations requiring systemic corticosteroids. Deaths occurring within 14 days of stopping study medication were considered on-therapy deaths while deaths occurring more than14 days after the stop of therapy were considered long-term follow-up deaths.

Spirometry was performed before and 30 minutes after inhalation of 400 mcg salbutamol. Reversibility was described in terms of the percentage of the predicted normal FEV_1 and was calculated as follows:

$$\text{Reversibility} = \frac{\text{Post-bronchodilator } FEV_1 - \text{Pre-bronchodilator } FEV_1}{\text{Predicted normal } FEV_1} \times 100$$

Only the post-bronchodilator FEV_1 was assessed at 24-weekly intervals throughout the follow-up.

Reviewer: By relating the change in FEV_1 to the predicted FEV_1 instead of the actual pre-bronchodilator FEV_1 the sponsor has based the exclusion criteria on a minimum estimate of reversibility. Reversibility calculated as a percentage of measured pre-bronchodilator FEV_1 is included in the datasets and will be referred to in this review.

Health Outcomes Evaluation

The Saint George's Respiratory Questionnaire was self-administered in countries and in languages in which the questionnaire was available at the start of the study. The questionnaire was completed at 24-weekly intervals (every other visit) prior to the patient obtaining the results of their spirometry. At some time during the course of the study, the Applicant learned that the questionnaires used were not identical to the questionnaires that Oxford Outcomes (a questionnaire developer) designated as optimal. Therefore, to assure that the translations used were optimal, the Applicant contracted Oxford Outcomes to conducted linguistic validation studies.

The validation process started with a review of the original questionnaire (UK English) by researchers in the study country and back translation into English. At the same time, the questionnaires were piloted with 5 COPD patients who were queried about their comprehension. The results of these two studies were referred back to Oxford Outcomes and the questionnaire developer, Dr. Paul Jones. Both made recommendations whether or not the question as posed in the translated questionnaire was an acceptable rendition of the original English version. As a result of this review, 33 of the original 38 country-language combinations (the questionnaires were administered in more than one language in some countries) were declared valid.

Reviewer: The process of "validation" was entirely retrospective. No questions were changed, but some were dropped, and up to 5 of the 50 questions were eliminated from questionnaires certified as "valid". In total, 14/33 (45% of the questionnaires were not identical to the original English version due to some modification of the scoring (Table 2 in Attachment 1, pg 5317 of the study report). One of the most important of these was the time frame for recall. The original questionnaire poses questions with a three month recall, but most of the translations ask for recall of 12 months. During the validation studies, the patients repeatedly told the investigators that the 12-month recall period was too long The manner in which differences of opinion between Oxford Outcomes and the Developer was resolved is not clear. It appears that problems were resolved by sub-set analysis: A separate analysis was performed that included only questionnaires without altered questions and another sub-set analysis was performed on questionnaires that used the 12-month recall.

The European Quality of Life Questionnaire (EQ-5D) was also self-administered every 24 weeks. This questionnaire is made up of 5 questions with a three-point grading scale (no problem, some of moderate problem(s), unable, or extreme problem). The final score ranges

between 0 for death and 1 for perfect health. Additionally, the patients were asked to grade their overall health on a visual analog scale.

Health resource utilization was queried at each visit. The patients were asked if they had sought medical treatment for COPD or a COPD-related episode since the previous visit, the type of healthcare professional contacted, date of contact, number of visits, hospitalization and number of days hospitalized. Estimates were acceptable if the patient could not recall the exact number of visits. The investigator referred to his/her records to verify or supplement information given by the patient if necessary.

Safety Evaluation

Safety was assessed with adverse events, pregnancy tests, incidence of bone fractures, oropharyngeal examinations in all centers, and bone mineral density and ophthalmologic assessments in selected US centers. Oropharyngeal examination was performed at each visit, although, the results were not recorded in the CRF. Clinical evidence of candidiasis was reported as an adverse event. The location of any reported bone fracture and whether or not it was traumatic was recorded. A non-traumatic bone fracture was defined as a fracture caused by a fall from less than a standing height. Adverse events were collected during treatment with study medication. During the long-term follow-up only severe, drug-related adverse events were recorded. COPD exacerbations were also listed as adverse events.

Bone mineral density was measured using dual energy x-ray absorptiometry (DEXA) at 75 sites (600 patients) in the United States. The T- and Z- scores were estimated by the manufacturer's software. For the hip data, T- and Z- Score, bone mineral content, area and BMD were only derived if all hip measurements (Femoral neck, Wards Triangle, Trochanter and shaft/Intertrochanter were adequate. For the spine, T and Z-Scores were only derived if all spine measurements (L_1-L_4) were adequate. Bone mineral content, area, and BMD were derived if at least one spine measurement was adequate.

BMD data were summarized by visit and as change from baseline. The log transformed ratio of measured to baseline was also calculated and expressed as a percentage change from baseline as follows:

$$\text{Percentage change from Baseline} = 100 * (\exp[\log\{\text{actual/baseline}\}]-1)$$

Baseline BMD was adjusted by concomitant therapy designed to affect BMD. Patients were classified as taking 1) bisphosphonates, 2) calcium or Vitamin D, or 3) nothing prior to the institution of randomized medication. BMD testing was scheduled for baseline, and 48, 84, and 156 weeks of therapy. An 8-week window around the projected test date was used to group patients for analytic purposes. Because some of the data were obtained at time-points beyond +/- 8 weeks, a supportive analysis was performed using a 16-week window.

Measurements of the total hip and the L_1-L_4 regions of the spine were completed at Visit 2, 6, 11, and 16. Patients with a T-score <-1.5 at baseline were referred for consultation. After the first year of double-blind treatment, any patient with a T-score <-2.0 or a bone mineral density loss of $\geq$ 8% were referred for consultation. After the second year of double-blind treatment, any

patient with a T-score <-2.0 or a bone mineral density loss of ≥ 10% was referred for consultation.

Ophthalmic examinations were to be conducted by board certified optometrists at approximately 75 centers in the United States. "Examinations were conducted with established methodology. Irregular findings (i.e., presence of cataracts and/or glaucoma) were identified and monitored". A prospective protocol was not employed. Ophthalmic examinations were conducted at Visit 2 (baseline), 6, 11, and 16 (end-of-study). To maintain consistency, the same optometrist was to perform each patient's initial and follow-up examination where possible. Any family history of cataract or glaucoma was recorded in the CRF.

PK/PD and pharmacogenetic studies were performed at the same selected sites in the United States where the BMD and ophthalmic examinations were performed. Blood for SAL, FP, and cortisol were obtained at Visit 5 (36 weeks).

1.1.6 Statistical Analysis Plan

Sample Size

The original sample size calculation was based on the assumption of a 20% placebo mortality in patients with an FEV_1% <60% (From ISOLDE study FLIT78). The treatment difference in that study comparing placebo to fluticasone 500 mcg alone was 4.4% after one year and 9.7% after 3 years. With these assumptions, the planned enrollment was 3800 to detect a difference of 4.3% with an 80% power. In November 2000, prior to enrollment of any patients in the United States, enrollment was increased to 5040 in order to increase the power to 90%. In May 2002, on the basis of a blinded analysis of overall mortality, and prior to the first interim analysis, the sample size was increased to 6040. The applicant anticipated that 440 deaths in the placebo and FSC groups would provide 90% power to detect the 4.3% difference (83 vs 87.3%) equivalent to a hazard ratio of 0.728.

Interim Analyses & Adjustments for Multiple Comparisons

The first interim analysis was planned to occur after 300 deaths and the second to occur midway between the first interim analysis and the expected end of the trial. The first interim analysis occurred in July 2003 and the second in June 2004. In each instance the SEDMC reviewed the un-blinded data and allowed the study to proceed. The statistical analysis of survival, but not the other efficacy outcomes made corrections for these additional looks at the data. (For a detailed review of these procedures and calculations see the Statistical Review.)

Because of the multiplicity of treatments and outcomes, the Type I error was controlled with a sequential, hierarchical analysis plan. The primary analysis was the all-cause 3-year mortality comparing FSC 500/50 to placebo. If survival after treatment with FSC 500/50 was significantly better than after treatment with placebo at the 0.05 level after correcting for the interim analyses, then the rate of moderate and severe COPD exacerbations was compared between placebo and FSC 500/50. If the second comparison was significant then FSC 500/50 was compared to SAL 50 for the rate of moderate and severe exacerbations. If the third comparison was significant then FSC 500/50 was compared to placebo for the SGRQ and if this was significant then FSC 500/50 was compared to SAL for the SGRQ.

Study Populations

The study was divided into a "Total Population", "Safety Population", "ITTP" "Health Outcomes Population" "Ophthalmic and Skeletal Safety Population" and "Pharmacokinetics Population". All of these populations were defined prospectively using standard criteria. However, the ITTP did not include patients who had been enrolled in five sites that were excluded from the analysis. These 5 sites were excluded on the basis of audits that occurred prior to breaking the blind and that indicated that integrity of the data had been compromised. These patients (N=72) were included in the safety population.

The Health Outcomes Population consisted of patients participating in countries where SGRQ questionnaire translations were considered to be linguistically valid for the population and could potentially have a total score calculated for the population. To be included, a patient had to have completed at least one questionnaire. Patients were analyzed in the treatment group to which they were randomized. The Ophthalmic and Skeletal population was a subset of the safety populations and consisted of patients at selected sites in the United States who had any skeletal or ophthalmic data. Patients were analyzed in the treatment that they took for the majority of the study.

General analytic considerations

Because of the wide geographic reach of the study all analyses were adjusted by region as listed in Table 17.

Table 17. Description of Regional Classification Used in the Efficacy Analyses

Region	Countries
USA	USA
Asia/Pacific	China, Hong Kong, Malaysia, Philippines, Singapore, Taiwan, Thailand
Eastern Europe	Bulgaria, Croatia, Czech Republic, Hungary, Estonia, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, Ukraine
Western Europe	Austria, Belgium, Denmark, Finland, France, Germany, Greece, I eland, Italy, Netherlands, Norway, Spain, Sweden, UK
Other	Australia, New Zealand, Argentina, Brazil, Chile, Mexico, South Africa, Canada

In addition, age, sex, disease severity (post-bronchodilator FEV_1), and BMI were included in the efficacy analyses as covariates. The number of exacerbations (0; 1; ≥2) in the 12 months prior to screening was included in the efficacy analysis of exacerbations.

Subgroup analyses were performed on the following variables:

- Smoking status (current vs former)
- Age (<55; 55 to <65; 65 to <75; ≥75 years)
- Sex
- Ethnic origin (White; Black; Asian; American Hispanic; Other)
- Percent predicted FEV_1 (<30%; 30 to <50%; ≥ 50%)
- BMI (<20; 20 to <25; 25 to <29; ≥29)
- Region (Table 17)

Baseline values for exacerbation rate, SGRQ, and BMD were used for subset analysis of these variables. Age was also included in the analysis of BMD and family history of cataract and glaucoma were included in the analyses of the ophthalmic data.

The Saint George's Respiratory Questionnaire (SGRQ) contained 76 weighted items grouped into three component scores (Symptoms, Activity and Impacts). Each domain score was calculated by summation of the weighted values for the non-missing questions within each category, dividing by the maximum possible score for those non-missing questions for that domain and multiplying by 100. The total score was calculated by aggregating the weighted scores from all 76 items and dividing by the maximum possible score for the SGRQ and multiplying by 100. Some of the questionnaires that had been validated in languages other than English had questions excluded for linguistic reasons. If more than 25% of the questions were missing from a domain, then the domain score was set to missing. At each visit the patient was categorized as improved (+4), unchanged (> -4 to <+4), or deteriorated (<4) on the basis of the change in SGRQ from the previous visit. If the SGRQ could not be calculated for any visit the score at the last visit was carried forward unless the reason for not calculating the score was because the patient had died, was having an exacerbation, or had withdrawn due to an adverse event.

The BMI was calculated as follows: BMI = Weight in kg/ (height in meters)^2

The rate of bone fracture, cataracts, glaucoma, AEs, and resource utilization was calculated as follows:

> Rate = (number of events * 1000) / Total treatment exposure in years.

This was equivalent to the

> Rate = (number of events * 1000) / (number of patients in treatment group * mean treatment exposure in years)

A stepwise procedure was used to handle multiplicity issues. Only if the null hypothesis was rejected at the 0.05 level for the first comparison, was the next analysis performed. The order of comparisons is as follows:

- All-cause mortality comparing FSC to placebo
- Rate of moderate and severe on-treatment exacerbations comparing FSC to placebo
- Rate of moderate and severe on-treatment exacerbations comparing FSC to SAL
- Change in SGRQ comparing FSC to placebo
- Change in SGRQ comparing FSC to SAL

Reviewer: The original protocol submitted in June 2001 listed the efficacy outcome measures as all-cause mortality and SGRQ. COPD exacerbations were defined only as an indication for permitting additional medication (above blinded study medication) to treat the exacerbation. The above stepwise procedure is the same as proposed by GSK in their SAP (May 2005) with the

exception that the protocol requires that the first analysis reject the null hypothesis at the adjusted 0.05 level prior to proceeding to the next level.

Missing data was not a major issue with the mortality analysis because all but one of the 6112 patients had their vital status ascertained at day 1092. The repeated measures analysis, the primary analysis for the SGRQ, FEV_1 and BMD, did not explicitly use any form of imputation. All available data for a patient was used within the analysis and the method of analysis itself weighted the information according to the amount of information available. Individual study visits were analyzed for patients who provided data at baseline and at the individual study visit. However, if an interim SGRQ was not available, the last previous completed questionnaire was used to calculate the change in score.

Reviewer: The section for exacerbations in "5.8.6.1 Premature discontinuation and missing data" simply repeats the description of the calculation of the rates. It dose not discuss the procedures for patients who missed an interim visit, but were not discontinued. Since this was a recall variable, presumably the patient was simply asked to recall over the past 6 months instead of 3. Missing data is also an issue with the measurement of BMD because the rate of failure to obtain all of the follow-up scans was high and related to the baseline BMD.

Compliance and Protocol Violations

Any patient who did not fulfill the inclusion or exclusion criteria was considered to be a protocol violator. In addition, any patient who had an exacerbation during the run-in and required systemic corticosteroid therapy and any patient who received prohibited medication during active treatment was considered to be a protocol violator.

Compliance was calculated assuming that one dose of medication was taken on the day of randomization while two doses were taken on all other days:

Compliance = number of doses used / number of doses expected to be used.
Number of doses used = sum (number of doses taken at each visit)
= sum {(number inhalers returned x 60) – used doses in returned inhalers
Number of doses expected to be used = [2 x (treatment stop date-treatment start date)] +1

If the number of doses remaining in the canister was missing then it was assumed that no doses were remaining, but if the inhalers were not returned then it was assumed that no medication was used.

Efficacy Analysis

The primary efficacy endpoint was time to all-cause mortality within 3 years (156 weeks) comparing the FSC 500/50 and placebo treatment groups in the ITT population, using the log-rank test, stratified by smoking status. Time to death was calculated in days using the date of death and treatment start date. Adjusted p-values and the median unbiased estimate of the hazard ratio for the final analysis was calculated using discrete stage wise ordering to account for the interim analyses carried out previously (See statistical review for details of the calculations). A Cox proportional hazards model was carried out as a supportive analysis. The hazard ratio for the

FSC vs placebo comparison, along with 95% confidence limits were derived, using time to death as the outcome variable, and covariates of treatment group, smoking status, age, sex, baseline FEV_1, BMI and region.

Other mortality outcomes were COPD-mortality and on-treatment mortality. On-treatment mortality was calculated with the inclusion of all deaths that occurred during randomized treatment and for two weeks after stopping the medication. The follow-up time between two weeks after termination of randomized treatment and 1092 days was called the Long-Term Follow-up Period.

Analysis for rate of moderate and severe exacerbations used a generalized linear model. The number of moderate and severe exacerbations occurring during the treatment period was assumed to follow the Negative Binomial distribution. The model included covariates of smoking status, age, sex, BMI, baseline FEV_1, number of exacerbations reported in the 12 months prior to Screening (0, 1, 2 or more), and region, with time on treatment as an offset variable. The adjusted mean rates per year, pairwise treatment ratios and associated p-values and confidence limits were presented. A supportive analysis comparing the rate of exacerbations between treatment groups was performed using the non-parametric rank analysis of covariance stratifying for smoking status, with age, sex, baseline FEV_1, number of exacerbations reported in the 12 months prior to Screening, BMI, and region as covariates . Exacerbation rate per year was calculated for each patient as the number of exacerbations / time on study (in years).

Change from baseline FEV_1 was compared between treatment groups, using a repeated measures analysis and included patients with a baseline FEV_1 and at least one on-treatment FEV_1. This was the main analysis model, and the change from baseline averaged over 3 years was of primary interest. Treatment group was fitted as the explanatory variable, and smoking status, age, sex, baseline FEV_1, BMI and region were fitted as covariates. Visit was fitted as a categorical variable, and the variance-covariance matrix was assumed to be unstructured. The model was:

> Change in FEV_1 = Treatment group + smoking status + age + sex + baseline FEV_1+BMI + region + visit + treatment*visit+ baseline FEV_1*visit

A post hoc analysis of the rate of decline in FEV_1 over time was investigated using a random coefficients model. FEV_1 was fitted as the response variable with treatment group, smoking status, age, sex, baseline FEV_1, BMI, region, and time on treatment as fixed effects. In this analysis, time on treatment was treated as a continuous variable, and defined as the number of days which had elapsed since the start of treatment. Patient effects were assumed to be random. The random coefficients model allowed random variation between slopes of individual patients, as well as intercepts of individual patients.

Health Outcomes Assessment

The change from baseline in SGRQ total score was analyzed using repeated measures analysis and included patients with a baseline SGRQ total score and at least one on-treatment SGRQ total Score. This was the main analysis for this endpoint, and the change from baseline averaged over 3 years was of primary interest. Treatment group was fitted as the explanatory variable, and smoking status, age, sex, baseline FEV_1, baseline SGRQ total score, BMI and region were fitted

as covariates. Visit was fitted as a categorical variable, and the variance-covariance matrix was assumed to be unstructured. Each domain was analyzed separately and an additional analysis was performed on questionnaires that were valid without modification and those based on a questionnaire recall period of 12 months. The change in health status (improved, unchanged, deteriorated [± 4 points] on SGRQ) was also summarized.

Other efficacy measures included all cause mortality comparing SAL and FP to placebo and to FSC, COPD mortality, on-treatment mortality, other exacerbation endpoints, and a composite endpoint of severe COPD exacerbation, LTOT, or mortality on treatment.

Safety Analysis

Adverse events (AE) that had an onset during randomized treatment were summarized for the entire population and for patients reporting at least one AE per 1000 treatment years. In addition, the number and percentage of patients reporting respiratory AEs was tabulated. Deaths, serious AEs, and AEs resulting in withdrawal were reported separately. Deaths were tabulated separately for those who died during randomized treatment, during the two week after stopping randomized treatment, and for the long-term follow-up period (Between two weeks after stopping randomized treatment and 156 weeks after the start of randomized treatment). AEs of special interest (ocular events, bone disorders, HPA-axis disorders, and lower respiratory infections) were tabulated and the time to first event was calculated. Post hoc evaluation of physician reported pneumonias was also reported.

The BMD data were analyzed using repeated measures analysis where treatment group was fitted as the explanatory variable and terms for age, sex, smoking status log baseline BMD, MBI, baseline BMD therapy and visit were fitted as covariates. The model was used to estimate pairwise treatment differences, confidence intervals, and p-values for each visit. An ANCOVA that fitted percentage change in BMD as the response variable was presented as supporting evidence. Also a repeated measures analysis of absolute change in density was presented.

The results of the ophthalmic examinations were used to tabulate the incidence of glaucoma and cataracts at baseline and at each follow-up visit.

PK Analysis

PK/PD analyses were performed at 15 US centers on 83 patients (20, 24, 15, 24 placebo, SAL, FP, and FSC treatment, respectively). At visit 5 (week 36) blood was collected for FP and cortisol measurement immediately prior to dosing and at 0.5, 1, 2, 4, 8, 10, and 12 hour post dosing with study medication. Blood was also collected 10 minutes after the dose for SAL levels. The FP and cortisol AUC and Cmax were calculated.

1.2. Results

1.2.1 Study Population

Disposition

A total of 8554 patients were screened of whom 6184 (72%) were randomized and received at least one dose of study medication. The Safety Population was comprised of these patients,

assigned to the treatment which they had received for the majority of the treatment period and included 1544 patients treated with placebo, 1542 with SAL 50,
1552 with FP 500 and 1546 with SFC 50/500 (one patient randomized to placebo received FP 500 for the majority of the treatment period). Data from 72 patients recruited by five investigators (investigators 89726, 34560, 75625, 87278 and 54948) were excluded from the ITT Population, and thus the ITT Population included 6112 patients (99% of the Safety Population) and comprised 1524 placebo patients, 1521 SAL 50, 1534 FP 500, and 1533 SFC 50/500. The Health Outcomes Population, a subset of the ITT Population, included 4951 patients (80% of the Safety Population) and the Ophthalmic and Skeletal Safety Population included 658 patients (11%) from the Safety Population.

The Applicant responded to a query about the five excluded patients on December 15, 2006 (…\n21077\S_029\2006-12-15). Their explanation is as follows: Investigator 89726 enrolled 25 patients. Site auditors confirmed that on 2 occasions the site deliberately entered incorrect data into the CRF to enable ineligible patients to receive study medication. Investigator 34560 enrolled 8 patients. The site did not provide adequate patient follow-up or co-operation with the Applicant's monitors. There was no documentation that oropharyngeal exams were conducted. Three patients received incorrect study medication, and the site was unwilling to specify how many incorrect doses were taken by each patient. Follow-up information on SAEs was not provided after 7 months of requests, and the site refused monitors access to the drug storage area. Investigator 75625 enrolled 23 patients. Monitors confirmed that the study coordinator falsified the PI signature on 2 SAE forms and 1 patient's source note. Multiple instances of failure to sign notes and inappropriate backdating were detected. Investigator 87278 enrolled 3 patients. The PI at the site died and neither office staff, not patient records could be located. Investigator 54958 enrolled 13 patients. The PI was put on probation by the Texas Medical License Board for three years for "allegations that he did not meet the standard of care in examining diagnosing and treating a patient with pulmonary disease" and for failing "to properly examine, diagnose and treat patient X". The allegations also included inappropriate prescribing of narcotics.

Reviewer: All of the exclusions are acceptable.

Patients were screened at 466 centers in 42 countries and were randomized and treated at 444 centers in 42 countries (439 centers included in the ITT Population). Patients were screened at 190 centers in the USA, 134 in Western Europe, 46 in Eastern Europe, 37 in Asia Pacific and 59 in other regions. Patients were included in the ITT Population at 171 centers in the USA, 131 in Western Europe, 45 in Eastern Europe, 37 in Asia/Pacific, and 55 in other regions (Table 18). Patients enrolled in the United States made up 23% of the ITT population.

Table 18. Enrollment and Follow-up by Treatment and Geographic Region*

	Not Enrolled	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 500/50 (N=1533)
Total Population, N	2370	1545	1542	1551	1546
USA,	1636	348 (23)	351 (23)	350 (23)	352 (23)
Asia/Pacific	228	188 (12)	189 (12)	193 (12)	188 (12)
E. Europe	31	297(19)	296 (19)	293 (19)	293 (19)
W. Europe	280	478 (31)	475 (31)	481 (31)	477 (31)
Other	195	234 (15)	231 (15)	234 (15)	236 (15)
ITT Population, N		1524	1521	1534	1533
USA		345 (23)	346 (23)	348 (23)	349 (23)
Asia/Pacific		188 (12)	189 (12)	193 (13)	188 (12)
E. Europe		290 (19)	289 (19)	287 (19)	288 (19)
W. Europe		476 (31)	475 (31)	481 (31)	476 (31)
Other		225 (15)	231 (15)	225 (15)	232 (15)

* See section 1.1.6 (pg , above) for definition of geographic areas.

Amendment #3 (November 15, 2000) specified that patients could not be enrolled into Study SCO30003 who had been treated in Study SFCB3024 (Study 2, Pg 118). However, 346 patients were enrolled in this manner (97, 81, 70, and 98 in the placebo, SAL, and FP groups, respectively) between initiation of study SCO30003 and May 16, 2002. None of the patients enrolled in Asia or in the United States had participated in SFCB3024 while 8 to 13% of the patients in Europe and "Other" had.

Overall, 62% of the patients completed the 3 year treatment periods. The completion rate was lowest is the placebo-treated patients (56%) and highest is the FSC -treated patients (66%). Study treatment was continued for three years in 63 and 61% of the SAL and FP groups, respectively (Table 19). The distribution of withdrawals was similar for the health outcomes and ophthalmic/skeletal populations although the loss to follow-up was slightly higher in the Ophthalmic/Skeletal population.

Table 19. Patient Disposition

	Placebo	SAL 50	FP 500	FSC 500/50
Safety Population, N	**1544**	**1542**	**1552**	**1546**
Completed Treatment, %	56	63	61	66
Withdrawn prior to Week 156, %	44	37	39	34
ITT Population, N	**1524**	**1521**	**1534**	**1533**
Completed Treatment, %	56	63	62	66
Withdrawn prior to Week 156, %	44	36	38	34
Health outcomes population, N	**1231**	**1232**	**1248**	**1240**
Completed Treatment, %	54	61	60	64
Withdrawn prior to Week 156, %	45	39	40	35
Ophthalmic and Skeletal Safety populations, N	**164**	**166**	**163**	**165**
Completed Treatment, %	41	57	50	58
Withdrawn prior to Week 156, %	59	43	49	41

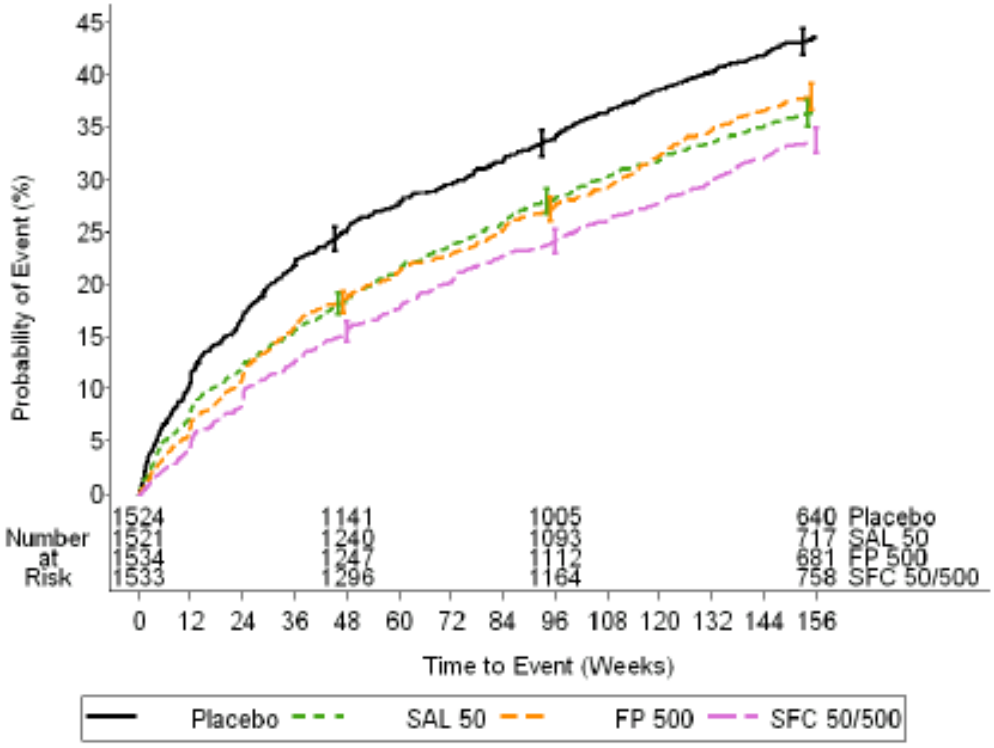
The withdrawal rate was significantly higher for the placebo patients than for any of the active treatment groups (Log-rank analysis – Table 20). In addition, the withdrawal rates for the SAL and FP treated patients were higher than for the FSC -treated patients.

Table 20. Log-Rank Analysis of Time to Premature Study Drug Discontinuation

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 500/50 (N=1533)
Number of patients discontinued	673 (44)	561 (37%)	587 (38)	522 (34)
Probability of discontinuation by 156 wks	43.5	36.4	38.1	33.7
95% CI	41.0, 46.0	34.0, 38.9	35.7, 40.5	31.4, 36.7
Active treatment vs. placebo				
Hazard ratio		0.782	0.808	0.693
95% CI		0.699, 0.875	0.723, 0.903	0.618, 0777
p-value		<0.001	<0.001	<0.001
FSC vs components				
Hazard ratio		0.887	0.856	
95% CI		0.787, 0.999	0.761, 0.963	
p-value		0.048	0.010	

A graph of the time to withdrawal is reproduced in Figure 1.

Figure 1. Rate of Withdrawal From Study Treatment *



* Study Report Figure 3; SFC = Advair

The most common reason for withdrawal was an adverse event (Table 21). This was more common in the placebo patients (24%) than in the other treatment groups, although the rate was essentially undistinguishable from that of the FP-treated patients (23%). Lack of efficacy was also more common in the placebo-treated patients.

Table 21. Reason for Withdrawal in the ITT Population

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 500/50 (N=1533)
Number of patients discontinued	673 (44%)	561 (37%)	587 (38%)	522 (34%)
Reason for discontinuation, %				
Adverse event	24	20	23	19
Consent withdrawn	9	9	7	8
Lost to follow-up	1	<1	2	2
Lack of efficacy	7	4	3	2
Did not fulfill entry criteria	<1	<1	<1	<1
Non-compliance	1	1	1	1
Other	2	2	1	2

In order to further evaluate drop-outs, the Applicant summarized the baseline FEV_1 and SGRQ for patients remaining in the study at each measurement point. The mean baseline value for both variables improved at each time point. This suggests that the patients remaining in the study had better pulmonary function and a higher quality of life than the patients who dropped out.

Reviewer: The rate of withdrawal was dependent upon geographic region as well as treatment regimen. Compared to patients enrolled in the United States (47.4%), drop-out was lower in Asia (31.9%), Eastern Europe (26.8%), and Western Europe (38.3%) It was essentially the same in the "Other" region (44.6%). In all regions the drop-out was greatest in the placebo group, however, the difference between placebo and FSC *also varied among the regions. In the US and Western Europe, the difference between placebo and FSC was 13 and 14%, respectively. In Asia, Eastern Europe and "Other" the difference was 6, 7, and 7%, respectively. (Based on the "wdw" variable in the subaccnt.xpt SAS transport file.)*

In the sub-population in the US in which BMD was measured, the mean baseline value was lower in the placebo and FP groups, than in the SAL and FSC-treated patients (See page 111). In addition, the drop-out rate was inversely related to the baseline BMD. Since patients with low BMD were referred for consultation and treatment of this abnormality, it is possible that this knowledge had some effect on withdrawal rates.

The drop-put rate was also related to prior steroid use. In patients who had taken either inhaled or oral corticosteroids in the 12 months prior to enrollment the drop-out rate was markedly elevated in the placebo-treated patients compared to FSC-treated patients (49, 41, 40, and 35% of the placebo, SAL, FP, and FSC patients, respectively). Drop-out in the SAL and FP groups was similar and intermediate. In patients who had not taken corticosteroids in the 12 months prior to enrollment there was little difference in drop-out among the study drug treatment-groups (37, 32, 36, and 32% of the placebo, SAL, FP, and FSC patients, respectively).

Protocol Deviations

The number of patients with protocol deviations was slightly lower in the *FSC* group than in the other treatment groups (Table 22). Fifty-one patients received an incorrect treatment during the study (12 (<1%), 13 <1%, 18 (1%), and 8 <1% in the placebo, SAL, FP. and *FSC* groups). All patients except one received no more than one incorrect packet.

Table 22. Protocol Violations in the ITT Population

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	*FSC* 500/50 (N=1533)
Number of patients with violations during run-in or active treatment	305 (20%)	299 (20%)	287 (19%)	260 (17%)
Use of ICS	12	9	9	8
Use of LABA	10	10	9	8
Long term (>6weeks) systemic corticosteroid use	5	4	4	4

The study blind was broken for 22 patients (10 [<1%], 4 [<1%], 3 [<1%], and 5 [<1%] of the placebo, SAL, FP, and *FSC* patients, respectively. The most common single reason for breaking the code was an emergency requiring further treatment. This occurred in 4 patients in the placebo group and 1 patient each in the SAL and FP groups.

Demographics and Medical History

Patient demographic variables are categorized by treatment group in Table 24 and by geographic region in Table 23. The mean age of the patients was 65 years, 82% were white, 75% were male, and the BMI was ≥ 29 kg/m^2 in 22%. These variables were evenly distributed across the treatment groups.

Table 23. Demographics by Treatment Group

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 500/50 (N=1533)
Age, years				
Mean (SD)	65.0 (8.2)	65.1 (8.2)	65.0 (8.4)	65.0 (8.3)
Range	40 - 85	40 - 86	40 - 82	40 - 80
Age Categories, (%)				
<65 years	44	43	44	43
≥65 years	56	57	56	56
Gender, % Male	76	76	75	75
Race, (%)				
White	82	82	82	82
Black	2	1	2	2
Asian	12	13	13	12
American Hispanic	3	3	3	3
Other	<1	<1	<1	<1
BMI, (%)				
<20 kg/m^2	13	14	13	15
20 to <29 kg/m^2	65	65	66	64
≥ 29 kg/m^2	22	22	22	22

More variability in populations was seen when they were categorized by geographic region (Table 24). The Asian/Pacific population, which made up 12% of the total, was older (mean age 69.9 years) and had a higher percentage of males (91%) than the other populations. Most of the Asian patients identified themselves as of Asian descent and only 3% had BMIs of ≥ 29 kg/m^2. By comparison, the US population contained only 60% males, 92% identified themselves as white, and the BMI was >29 kg/m^2 in 30%. Both of the European groups were overwhelmingly

white (99%) and the Eastern European group had a relatively younger age (63.2 years) with 53% less than 65 years of age.

Table 24. Demographic Variables by Geographic Region

	USA (N=1388)	Asia/Pacific (N=758)	E. Europe (N=1154)	W. Europe (N=1908)	Other* (N=904)
Age, years					
Mean (SD)	65.2 (8.2)	66.9 (7.3)	63.2 (8.5)	65.0 (8.3)	65.7 (8.3)
Range	40 - 80	41 - 80	40 - 81	40 - 86	41 - 81
Age Categories, (%)					
<65 years	44	33	53	44	41
≥65 years	56	66	45	56	60
Gender, % Male	60	91	84	78	72
Race, (%)					
White	92	<1	>99	>99	74
Black	6	0	0	<1	<1
Asian	<1	99	<1	<1	1
American Hispanic	1	0	0	0	19
Other	<1	<1	0	0	5
BMI, (%)					
<20 kg/m^2	10	35	9	9	15
20 to <29 kg/m^2	59	62	66	68	65
≥ 29 kg/m^2	30	3	25	23	20

* Other = Canada, S. Africa, Australia, New Zeeland, S America

The history of COPD also showed an even distribution of characteristics across treatment groups (Table 25). The duration of symptoms was 5 to 10 years in 30% of the patients, 52% had had a moderate exacerbation and 18% had had a severe exacerbation in the 12 months prior to screening. The rate of moderate/severe exacerbations was 1.2 / year in each of the treatment groups. Almost half (42, 44, 44, and 43%) had had no exacerbation in the year prior to enrollment. A plurality of the patients (42%) had an MRC Dyspnea score of 2, and 57% in all the groups were former as opposed to current smokers. Inhaled corticosteroids were used prior to study entry by 51, 45, 47, and 45% of the placebo, SAL, FP, and FSC patients, respectively. A prior myocardial infarction was reported by 6 to 7% of the patients in each treatment group.

Table 25. Medical History by Treatment Group

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 500/50 (N=1533)
Duration COPD, N (%)				
<5	547 (36)	527 (35)	544 (35)	553 (36)
5 to <10	458 (30)	466 (31)	480 (31)	450 (29)
10 to <15	263 (17)	273 (18)	265 (17)	261 (17)
≥ 15	256 (17)	255 (17)	245 (16)	269 (18)
Moderate COPD Exacerbation, %	801 (53)	788 (52)	806 (53)	786 (51)
Severe COPD Exacerbation, %	261 (17)	277 (18)	290 (19)	279 (18)
MRC Dyspnea Score, (%)				
1	128 (8)	110 (7)	108 (7)	110 (7)
2	643 (42)	645 (42)	642 (42)	660 (43)
3	466 (31)	473 (31)	509 (33)	493 (32)
4	219 (14)	235 (15)	228 (15)	207 (14)
5	67 (4)	57 (4)	44 (3)	63 (4)
Former Smokers, %	866 (57)	870 (57)	873 (57)	873 (57)

Mean Pack-years (SD)	48.6 (26.9)	49.3 (27.7)	49.2 (28.6)	47.0 (26.5)
Prior Medications taken within 12 months of enrollment, (%)	N=1523	N = 1520	N=1534	N=1532
ICS Only	338 (22)	273 (18)	306 (20)	292 (19)
LABA Only	118 (8)	137 (9)	130 (8)	137 (9)
ICS & LABA	449 (29)	413 (27)	414 (27)	435 (28)
Any ICS	787 (51)	686 (45)	720 (47)	727 (45)
Prior myocardial infarction	108 (7)	113 (7)	92 (6)	100 (7)

Reviewer: Two tabulations of prior ICS use are included in the application. The above figures are taken from text Table 19 (post text Table 6.035 [page 3001 of the study report]) that lists only medication taken within 12 months of enrollment. The number of patients taking ICS is more than the number reported in Text Table 23 (post-text Table 6.057 [pg 3161 of the study report]) even though Table 23 reports prior medication use at ***any time*** *prior to enrollment because Table 23 only includes medication that was ascribed by the investigator as treatment for COPD. The total difference for ICS use comparing the two tabulations is 548 patients who took ICS within the 12 months prior to enrollment but apparently did not take them for COPD. The condition being treated is not specified. However, by both tabulations, the placebo patients were taking slightly more ICS than the other groups prior to enrollment.*

As with the demographic variables, the manifestations of COPD varied more among the geographic regions than among treatment groups (Table 26). Patients enrolled in Eastern Europe had slightly longer histories of COPD and 56% had a moderate exacerbation in the 12 months preceding screening. This compares to 47% of patients in the US who had moderate exacerbations in the same time period. Hospitalization for an acute exacerbation was reported for 24% of the Eastern European patients, but only 12% of the US patients. Of the patients from Asia, 29% were hospitalized compared to 17 and 13% in Western Europe and in the group characterized as "Other". The Eastern Europeans also had higher MRC Dyspnea scores with 41% reaching the level of 3 compared with 26 to 33% of the other regions. The use of ICS prior to enrollment did not correlate with any of the other variables. Only 25% of the patients in Asia were treated with ICS (with or without LABA) as compared to 64% of the patients in Western Europe. Use of ICS in the other regions was between 45 and 58% of the patients. A past history of myocardial infarction was reported in twice as many of the US population (12%) as in the patients enrolled in Europe and "Other" (5-6%) areas. Only 2% of Asian patients had a past history of MI.

Table 26. COPD History by Geographic Region

	USA (N=1388)	**Asia/Pacific (N=758)**	**E. Europe (N=1154)**	**W. Europe (N=1908)**	**Other* (N=904)**
Duration COPD, %					
<5	591 (43)	335 (44)	312 (27)	574 (30)	359 (40)
5 to <10	443 (32)	207 (27)	339 (29)	585 (31)	280 (31)
10 to <15	207 (15)	92 (12)	225 (19)	401 (21)	137 (15)
≥ 15	147 (11)	124 (16)	278 (24)	348 (18)	128 (14)
COPD Moderate Exacerbation, n (%)	656 (47)	368 (49)	651 (56)	1028 (54)	478 (53)
COPD Severe Exacerbation, n (%)	171 (12)	220 (29)	281 (24)	321 (17)	114 (13)
MRC Dyspnea Score, n (%)					
1	107 (8)	79 (10)	54 (5)	138 (7)	78 (9)

2	582 (42)	334 (44)	450 (39)	857 (45)	367 (41)
3	388 (28)	202 (27)	476 (41)	638 (33)	237 (26)
4	252 (18)	112 (15)	136 (12)	226 (12)	163 (18)
5	56 (4)	31 (4)	38 (3)	47 (2)	59 (7)
Former Smokers, n (%)	791 (57)	514 (68)	568 (49)	1053 (55)	556 (62)
Mean Pack-years (SD)	58.9 (31.0)	46.7 (29.2)	38.8 (19.0)	45.6 (25.3)	52.9 (27.7)
Prior Medications, (%)					
ICS Only	249 (18)	111 (15)	224 (19)	377 (20)	248 (28)
LABA Only	184 (13)	41 (5)	95 (8)	158 (8)	44 (5)
ICS & LABA	433 (31)	78 (10)	187 (16)	836 (44)	177 (20)
Any ICS	682 (49)	189 (25)	411 (45)	1213 (64)	425 (58)
Prior Myocardial Infarction, N (%)	169 (12)	15 (2)	61 (5%)	111 (6)	57 (6)

* Other= Canada, S. America, S. Africa, and Australia/New Zealand

Reviewer: Comparing the incidence of myocardial infarction among the regions is not unbiased because a baseline history of myocardial infarction was not added to the protocol until Amendment 7 in May of 2001. The study was initiated in Europe in September 2000, and patients were not enrolled in the US until in July of 2001, after 2297 patients had been enrolled in Europe. The early enrollees would not have been specifically queried about myocardial infarction and would, for that reason, probably under report it. A past history of myocardial infarction is only one way to assess the background of cardiovascular disease in the population. The SAS transport file …\\med_cont.xpt contains a list of concomitant medical conditions present at baseline. There are 3274 conditions labeled as "Cardiovascular". However, over 1000 of the entries are for uncomplicated hypertension, peripheral vascular disease, and a miscellany including palpitations, heart murmur, and migraine headaches. If these conditions are removed, the remaining cardiovascular diagnoses were valvular disease, arrhythmia, coronary artery disease, ischemic cardiovascular disease, and heart failure. The distribution of these more serious conditions was uniform across the treatment groups (45.7, 47.7, 42.1, and 43.7% of the patients in the placebo, SAL, FP, and FSC groups respectively). However, the distribution across the regions was quite skewed. By this definition, 66% of the Eastern Europeans had a serious cardiovascular condition at entry to the study compared to 39.6, 39.9, 41.4, and 32.7% of the US, Asian, Western European, and "Other" patients, respectively.

Pulmonary function as assessed by FEV_1 was moderate to severely reduced in all of the treatment groups (Table 27). The mean pre-bronchodilator FEV_1 was approximately 1100 mL which was 40 to 41% of predicted. The range in FEV_1 was 240 to 2800 mL and the range in the FEV_1 % predicted was 7.3 to 101.3%. (38 patients had an FEV_1 % predicted > 60%, which was a protocol violation [See pg 55 for inclusion criteria]). The post bronchodilator FEV_1 was 44% of predicted which was 10% higher than the pre-bronchodilator value. Post-randomization, only the post bronchodilator values were presented. The post bronchodilator FEV_1 was unchanged when comparing Visit 1 (screening) to Visit 2 (Baseline).

Table 27. Pulmonary Function at Baseline by Treatment Group

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 500/50 (N=1533)
Visit #1 (Screening)				
Pre-BD FEV_1, mL (mean [SD])	1122 (400)	1103 (389)	1116 (391)	1123 (404)
% predicted Pre-BD FEV_1, mean (SD)	40 (11.8)	40 (12.1)	41 (12.1)	41 (12.0)
Pre-BD FVC, mL (mean [SD])	2342 (747)	2295 (732)	2341 (778)	2331 (753)
Pre-BD Fev_1/ FVC, mean (SD)	0.49 (10.9)	0.49 (10.8)	0.49 (10.7)	0.49 (10.8)
Post-BD FEV_1, mL (mean [SD])	1223 (421)	1205 (409)	1217 (414)	1224 (422)
% predicted Post-BD FEV_1, mean (SD)	44 (12.3)	44 (12.6)	44 (12.3)	44 (12.3)
FEV_1 Reversibility (mL)	101 (105)	101 (111)	101 (104)	101 (10.3)
Reversibility, % Pre-BD FEV_1	10.1 (10.7)	10.3 (11.4)	10.0 (11.1)	10.1 (10.7)
Reversibility, % predicted FEV_1	3.7 (3.7)	3.7 (3.9)	3.7 (3.7)	3.6 (3.6)
Visit #2 (Baseline)				
Post-BD FEV_1	1229 (446)	1211	1230	1233
% predicted Post-BD FEV_1, mean (SD)	44 (13.1)	44 (13.3)	45 (13.3)	45 (14.0)
Post-BD FEV_1, % in category				
<30 % predicted	14	17	14	16
30 to <50 % predicted	51	49	51	47
≥ 50 % predicted	35	34	35	37

Pulmonary function categorized by geographic region showed the lowest FEV_1 (both absolute and percent predicted) in the Asia population (Table 28). Reversibility was highest in the US patients (13.2%) and lowest in the Western European group (8.0%).

Table 28. Pulmonary Function at Baseline by Region*

	USA (N=1388)	Asia (N=758)	E. Europe (N=1154)	W. Europe (N=1908)	Other* (N=904)
Visit #1 (Screening)					
Pre-BD FEV1,mL	1060 (403)	920 (338)	1226 (382)	1204 (379)	1042 (389)
% predicted Pre-BD FEV1	38.9 (12.5)	36.2 (12.0)	41.9 (10.9)	43.0 (11.2)	38.5 (12.0)
Pre-BD FVC, mL	2250 (742)	1932 (611)	2447 (758)	2437 (714)	2396 (823)
Pre-BD Fev1/ FVC	0.47 (10.8)	0.48 (10.4)	51.1 (10.3)	50.1 (10.5)	44.4 (10.8)
Post-BD FEV1, mL	1182 (422)	1013 (362)	1323 (406)	1292 (400)	1150 (416)
% predicted Post-BD FEV1	43.3 (12.8)	39.9 (12.8)	45.2 (11.4)	46.2 (11.8)	42.4 (12.5)
Reversibility, % Pre-BD FEV1	13.2(12.1)	11.0 (11.2)	8.5 (10.0)	8.0 (9.7)	11.4 (11.1)
Visit #2 (Baseline)					
Post-BD FEV_1, mL	1197 (452)	1032 (398)	1330 (438)	1294 (427)	1155 (439)
% predicted Post-BD FEV_1	43.9 (14.1)	40.6 (13.9)	45.4 (12.4)	46.2 (12.9)	42.6 (13.6)
Post-BD FEV_1, % in category**					
<30	17	25	11	11	19
30 to <50	48	48	51	48	52
≥ 50	34	27	39	40	29

* Summary of post-Text table 6.046, pg 3080. ** The values represent mean (SD) except for Post-BD FEV1 in categories of severity.

Reviewer: Oxygen saturation was available for 4178 of the patients. This represented approximately 68% of the patients in each of the treatment groups. However, this variable was obtained much more frequently in the United States than in the other areas: 91.6, 60.4, 48.4, 72.8, and 55.3% of the patients in the United States, Asia, E. Europe, W. Europe, and Other,

respectively. There was very little variability in the oxygen saturation across either the treatment groups or the regions. The range in mean values was 93 to 94%. Only 196 (4.7% of the patients with the measurement) had a saturation <90%.

The SGRQ was obtained in 3911 (64%) patients (924, 980, 1005, and 1002 of the placebo, SAL, FP, and FSC patients respectively). However, this included only 1126 (18.4%) who received questionnaires that did not have scoring modifications.
The SGRQ Total Score ranged between 48.9 and 49.9.

Reviewer: The distribution of baseline characteristics by region is important because of possible regional differences in diagnosis and treatment. When interpreting adverse events and the severity of adverse events/exacerbations, the baseline incidence of concomitant complaints might suggest differences in reporting frequency. The definition of an exacerbation was entirely dependent upon the treatment administered. If there was a systematic difference in the use of corticosteroids or antibiotics by region, this could influence the rate of exacerbation reporting. As an example of this, the number of concomitant medical conditions at screening varied considerably among the geographic regions. Of the patients enrolled in the United States, 49.3% were reported to have had more than 5 concomitant conditions compared to 2.2, 2.4, 2.2, and 9.6% of the patients enrolled in Asia, Eastern Europe, Western Europe, and Other, respectively. Conversely, only 0.6% of the patients enrolled in the United States were reported to have had no concomitant diseases compared with 30.3, 22.1, 18.7, and 13.7% of the patients enrolled in Asia, Eastern Europe, Western Europe, and Other, respectively. The differences were less extreme, but still large, if a severe category of concomitant disease was analyzed.

The baseline pulmonary function suggested that the patients enrolled in Europe were slightly less impaired as measured by the pre-bronchodilator FEV_1 (41.9 and 43.0% predicted compared to less than 40% in the other groups) and the FEV_1/FVC (51.1 and 50.1% compared to less than 50% in the other groups) although the reversibility was less (8.5 and 8.0% in Europe and >10% in the other region). However the duration of COPD was longer in Eastern Europe and the exacerbation rate was higher in all of the regions compared to the patients enrolled in the United States.

Treatment Compliance

Compliance was defined by the number of doses remaining in the medication canisters. Mean overall compliance was good in all of the treatment groups (Table 29).

Table 29. Compliance with Medication in the ITT Population

	Placebo (N=1524)	**SAL 50 (N=1521)**	**FP 500 (N=1534)**	**FSC 500/50 (N=1533)**
Mean Overall compliance (SD)	88.5 (24.6)	89.1 (21.6)	88.4 (22.2)	88.7 (21.0)
Percentage compliance	% of patients			
<50%	7	5	6	5
>50 to 80%	15	14	13	15
>80 to 100%	56	58	59	60
>100 to 120%	19	21	19	18
>120%	3	1	2	2

Reviewer: Compliance also varied by region. It was 84.4, 88.9, 94.3, 86.4, and 90.8% in the United States, Asia, Eastern Europe, Western Europe, and Other, respectively.

1.2.2 Efficacy Results

Primary Efficacy Outcome

The primary endpoint was all-cause mortality in the Intent To Treat Population (ITTP) within 3 years (i.e. 156 weeks or 1092 days) after the start of study treatment. There were a total of 927 deaths in the entire study population: 16 occurred in patients who were not randomized, 7 occurred in patients recruited at the excluded sites, and 29 were known to have occurred after the three-year time point. Therefore there were 875 deaths included in the ITT analysis. The survival status was known for all patients except one, an FSC- treated patient who was treated for 436 days and censored at the time of loss to follow-up.

Within three years of the start of treatment, there were 231 (15.2%), 205 (13.5%), 246 (16.0%), and 193 (12.6%) deaths in the placebo, SAL, FP, and FSC groups, respectively (Table 30). Therefore the difference between placebo and FSC was 2.6% over three years or approximately 0.87% per year. The unadjusted p-value was 0.041 for the comparison between FSC and placebo. The comparison between SAL and placebo and FP and placebo were not statistically significant. However the difference between FSC and SAL was also not statistically significant (HR = 0.932, p-value = 0.481). The results are presented graphically in Figure 2.

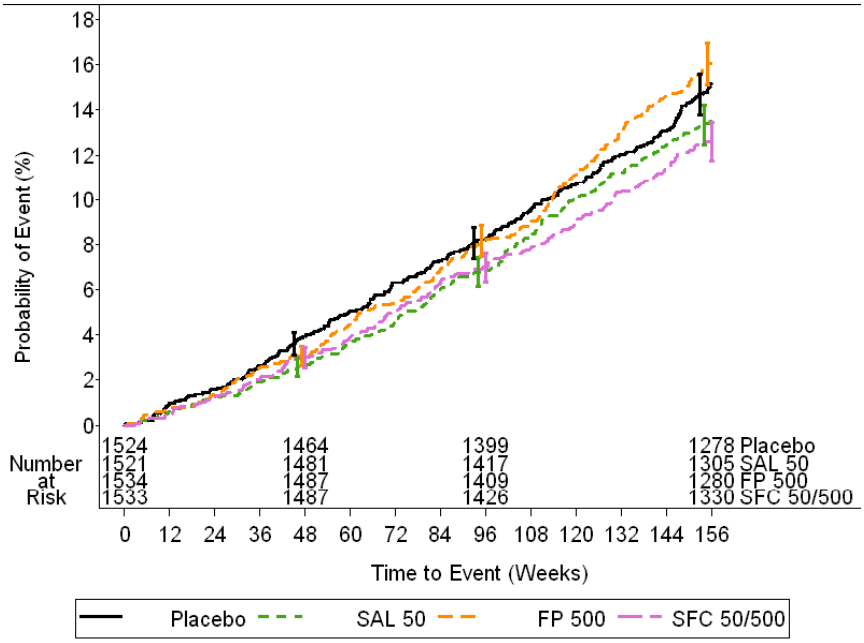
Table 30. Summary of Survival Data (without adjustment for interim analyses)

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 500/50 (N=1533)
Number of Deaths	231	205	246	193
Probability of death by 156 weeks (%)	15.2	13.5	16.0	12.6
95% CI	13.4, 17.0	11.8, 15.2	14.2, 17.9	10.9, 14.3
Active Treatment vs. Placebo				
Hazard ratio		0.879	1.060	0.820
95% CI		0.729, 1.061	0.886, 1.268	0.677, 0.993
p-value		0.180	0.525	0.041
FSC 500/50 vs. Components				
Hazard ratio		0.932	0.774	
95% CI		0.765, 1.134	0.641, 0.934	
p-value		0.481	0.007	

Reviewer: It took s 777, 834, 795, and 909 days for 10% of the placebo, SAL, FP, and FSC patients,, respectively, to die. Therefore, the difference in 90% survival comparing FSC to placebo was 132 days.

Mortality in the US population was 13.9%, 14.5%, 13.5%, and 12.3% in the placebo, SAL, FP, and FSC patients, respectively. The difference in survival comparing placebo to FSC in the US population was thus 1.6% over three years or 0.53% per year. The time to 90% survival was 870, 759, 902, and 945 days in the placebo, SAL, FP, and FSC groups, respectively. The difference in 90% survival comparing FSC to placebo in the United States population was 75 days.

Figure 2. All Cause Mortality at Three Years*[$]



*The number at risk does not reflect the number of patients remaining on treatment. At three years there were 851, 960, 947, and 1011 patients in the Placebo, SAL, FP, and FSC groups still being actively followed. & = Study report Figure 8; SFC=Advair

Inference based on the all-cause mortality outcome required adjustment for the interim analyses. When the appropriate adjustments were made (see FDA statistical review for details), the p-value for the difference in survival between patients treated with placebo and with Advair was 0.052 (Table 31).

Table 31. Log-Rank Analysis of Time to All-Cause Mortality at 3 years (ITT Population)

	Placebo (N=1524)	**FSC 500/50 (N=1533)**
Number of deaths	231	193
Probability of death by 156 weeks (%)	15.2	12.6
95% CI	13.4, 17.0	10.9, 14.3
FSC 500/50 vs placebo		
Adjusted Hazard ratio (95% CI)	0.825 (0.681, 1.002)	
p-value adjusted for interim analyses	0.052	

Reviewer: Survival was calculated on the basis of reports of death through 3 years. These were available for 6,111 patients. Because of withdrawal from the study, the patients were not on the treatment protocol throughout the three-year period. Patients were considered withdrawn at the time of death (228 [26.7%]) or could have been withdrawn earlier. This left 647 deaths that occurred at some time after withdrawal from study treatment (The long-term follow-up). The time off study drug ranged from 1 to 1091 days with a mean of 442.8 days. The mean duration off study drug ranged from 157.7 days for FSC treated patients to 244.7 days for placebo-treated patients. The value also varied among the regions: it was 264, 106, 88.6, 222, and 230 days for the United States, Asia, Eastern Europe, Western Europe and Other, respectively.

A supporting log-rank analysis was performed with the data stratified by smoking status and country. This resulted in a hazard ratio of 0.815 (p=0.036) when comparing FSC to placebo. A Cox proportional hazards model adjusted for smoking status, age sex, region, baseline FEV_1 and BMI gave a hazard ratio of 0.811 (95% CI = 0.670, 0.982).

Reviewer: A sensitivity analysis in which the results of clinical centers with exceptionally good results for the placebo-FSC comparison were removed singly from the analysis showed that both the hazard ratio and the estimate of significance were influenced by small changes in the database. For instance, removal of patients enrolled at site 39401 (N=21 treated with FSC or placebo) resulted in an increase of the hazard ratio for the remaining 3,036 patients treated with FSC to 0.826 and an unadjusted p-value of 0.051. See FDA statistical review for further details.) In addition, one of these influential sites (Site 34758) employed three investigators with a financial conflict of interest.

The primary cause of death was COPD-related in 6.0, 6.1, 6.9, and 4.7% of the placebo, SAL, PF, and FSC patients, respectively. Other causes of death were cardiovascular in 5, 3, 4, and 4% of the placebo, SAL, PF, and FSC patients, respectively; pulmonary in 5, 5, 6, and 4% of the placebo, SAL, PF, and FSC patients, respectively; and cancer in 3% of each treatment group (Table 32). COPD-related deaths were more numerous than COPD deaths because some cases of sudden death and cardiovascular collapse were ascertained as COPD-related by the CEC.

Table 32. Primary Cause of Death

	Placebo (N=1524)	**SAL 50 (N=1521)**	**FP 500 (N=1534)**	**FSC 500/50 (N=1533)**
Number of Deaths, N (%)	231(15.2)	205 (13.5)	246 (16.0)	193 (12.6)
COPD-related * Deaths, N (%)	91 (6.0)	93 (6.1)	106 (6.9)	72 (4.7)
Primary Cause of Death				
Cardiovascular	71 (5)	45 (3)	61 (4)	60 (4)
Congestive heart failure	5	5	6	7
Myocardial infarction	11	3	5	9
Stroke	6	6	15	7
Sudden death	45	30	29	35
Other	4	2	6	2
Pulmonary	74 (5)	80 (5)	91 (6)	61 (4)
COPD	60	64	67	43
Pneumonia	13	15	21	15
Pulmonary embolism	0	0	0	2
Other	1	1	3	1
Cancer	45 (3)	44 (3)	51 (3)	44 (3)
Lung	33	27	34	26
Breast	0	0	0	2
Colorectal	0	4	3	3
Other	12	13	14	13
Other	23	22	30	11
Unknown	18	14	13	17

* COPD-related deaths included conditions such as cardiac arrest and sudden death in patients with severe pulmonary disease who died at home and who did not have an autopsy (See Section 1.1.5, pg above). The number includes the "COPD" deaths listed under "Pulmonary".

For the purposes of the on-treatment mortality analysis, on-treatment was defined as any death that occurred within 2 weeks of discontinuation of randomized study medication. By this definition almost half of the deaths occurred after termination of treatment: 49.8, 48.3, 43.1, and 47.1% of the placebo, SAL, FP, and FSC patients, respectively (Table 33). The distribution of cause-of-death was similar for patients dying while on study drug and those who died after more than 14 days off of the study drug.

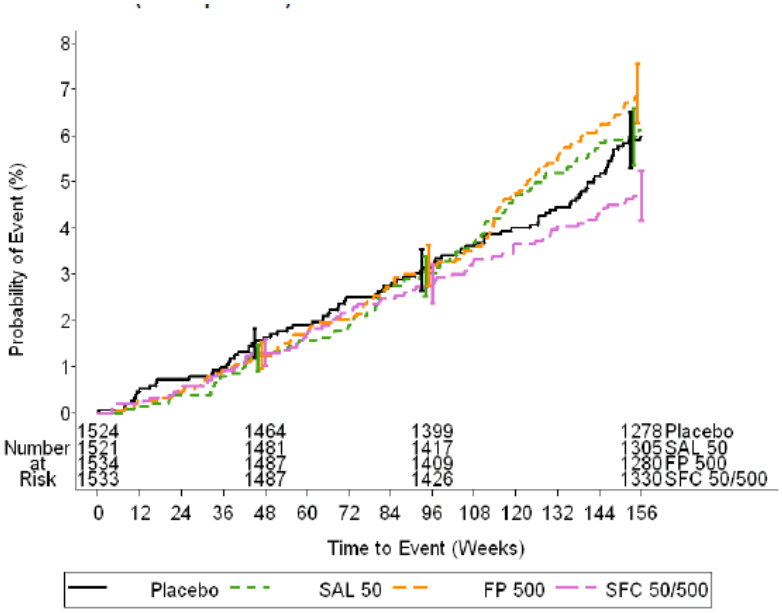
Table 33. Cause of Death by Treatment Status at the Time of Death

	Placebo (N=1524)	**SAL 50 (N=1521)**	**FP 500 (N=1534)**	**FSC 500/50 (N=1533)**
On Treatment Deaths*	116 (7.6)	106 (7.0)	140 (9.1)	102 (6.7)
COPD-related deaths	48 (3.1)	50 (3.3)	59 (3.8)	37 (2.4)
Primary cause of death				
Cardiovascular	47	33	43	47
Pulmonary	42	42	51	36
Cancer	16	17	18	11
Other	4	12	22	3
Unknown	7	2	6	5
Long-term follow-up deaths	115 (7.5)	99 (6.5)	106 (6.9)	91 (5.9)
COPD-related deaths	43 (2.8)	43 (2.8)	47 (3.1)	35 (2.3)
Primary cause of death				
Cardiovascular	24	12	18	13
Pulmonary	32	38	40	25
Cancer	29	27	33	33
Other	19	10	8	8
Unknown	11	12	7	12

* Includes deaths occurring within 14 days of study drug discontinuation

The Competing Risk estimates of death by 156 weeks showed a COPD-related mortality of 6.0, 6.1, 6.9, and 4.7% for placebo, SAL, FP, and FSC respectively. As can be seen from Figure 3, there was no difference in COPD-mortality by the two-year time-point, at which point 30% of the patients had been lost to follow-up. Loss to follow-up continued during the last year with only 61% of the patients remaining under treatment on day 1092.

Figure 3. COPD Mortality During 3-year Follow-up*



* Study report Figure 9; SFC=Advair

The COPD mortality was not significantly reduced by any of the active treatments (Table 34).

Table 34. Death Rates and Hazard Ratios for COPD Mortality

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 50500 (N=1533)
COPD-related deaths **95% CI**	91 (6.0) 4.8, 7.2	93 (6.1) 4.9, 7.3	106 (6.9) 5.6, 8.2	72 (4.7) 3.6, 5.8
Active treatment vs. placebo **Hazard ratio** **95% CI** **p-value**		1.013 0.759, 1.352 0.932	1.159 0.876, 1.534 0.300	0.776 0.570, 1.057 0.107
Active treatment vs. placebo **Hazard ratio** **95% CI** **p-value**		0.766 0.563, 1.042 0.089	0.670 0.497, 0.904 0.008	

Reviewer: The shape of the COPD-related survival curve is somewhat unusual in that the four treatment lines overlap until late in the course. Only after more than two years of treatment in the case of SAL and FP, and after more than 2 ½ years after treatment with placebo do the lines diverge from the FSC line. This may be related to the relatively small number of COPD-related deaths. On the other hand, more of the patients in the placebo and SAL treatment groups had been off therapy for longer than one year (>30% of the patients who died) than the FSC patients (15% of the patients who died) suggesting that the increased death rates in the SAL and placebo groups were not related to study drug treatment.

On treatment mortality was defined as any death occurring on or after the treatment start date and up to and including 14 days of stopping treatment. The number (%) of these deaths was 116 (7.6), 106 (7.0), 140 (9.1), and 102 (6.7) in the placebo, SAL, FP. And FSC- treated patients, respectively. An additional 1, 3, 1, and 1 patient in the placebo, SAL, FP and FSC- treated

patients, respectively, died after three years and they were included in the analysis of on-treatment deaths. The analysis was performed on all of the patients (including those who died after 3 years), but the Kaplan-Meier estimates included in Study report text table 41 (reproduced here as Table 35) were based on those who died by 3 years. The hazard ratio comparing FSC to placebo was 0.772 (95% CI 0.59, 1.01 [p=0.055]).

Table 35. Log-Rank Analysis of On-treatment Deaths *

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 500/50 (N=1533)
On-treatment deaths	117 (7.7)	109 (7.2)	141 (9.2)	103 (6.7)
Probability of death	10.5	9.0	11.5	8.1
95% CI	8.7, 12.3	7.3, 10.6	9.7, 13.3	6.5, 9.6
Active treatment vs. placebo				
Hazard ratio		0.858	1.100	0.772
95% CI		0.661, 1.113	0.861, 1.406	0.592, 1.006
p-value		0.248	0.445	0.055
FSC vs. components				
Hazard ratio		0.898	0.701	
95% CI		0.686, 1.175	0.544, 0.904	
p-value		0.433	0.006	

*** Reproduced from Table 40, pg 133 of Study Report**

Secondary efficacy outcome measures

At least one moderate or severe exacerbation was experienced while on study medication by 70% of the patients: 48% experienced 1 to 3 exacerbations, and 22% experienced 4 or more. Almost one third of the patients (31, 30, 31, and 32% in the placebo, SAL, FP and FSC groups, respectively) reported no exacerbation during treatment with study drug. The annual exacerbation rate calculated with the negative binomial model was 1.13, 0.97, 0.93, and 0.85 events per year for the placebo, SAL, FP, and FSC groups respectively (Table 36). The ratio of events comparing FSC to placebo was 0.749 (95% CI = 0.689, 0.814; p<0.001). The ratio of events comparing FSC to SAL was 0.878 (95% CI = 0.808, 0.954; p = 0.002) and the ratio of events comparing FSC to FP was 0.910 (95% CI = 0.838, 0.988; p = 0.024)

Table 36. Rate of Moderate and Severe Exacerbations from the Negative Binomial Model.

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 500/50 (N=1533)
Mean number/year from model	1.13	0.97	0.93	.85
Active treatment vs. placebo				
Ratio		0.858	0.823	0.749
95% CI		0.784, 0.927	0.758, 0.894	0.689, 0.814
p-value		<0.001	<0.001	<0.001
FSC vs. components				
Hazard ratio		0.878	0.910	
95% CI		0.808, 0.954	0.838, 0.988	
p-value		0.002	0.024	

The Kaplan-Meyer estimate of the probability of an exacerbation by 156 weeks was 78.4, 76.0, 78.0, and 74.8% for the placebo, SAL, FP, and FSC groups, respectively. The hazard ratio comparing FSC to placebo was 0.860 (95% CI = 0.790, 0.937) using this analysis. The hazard ratio (HR) for SAL was 0.923 (95% CI = 0.847, 1.005) and for FP was 0.918 (95% CI= 0.843,

1.000). FSC did not increase the time to the first exacerbation when compared to SAL (HR =0.933, 95% CI = 0.856, 1.016) or FP (HR=0.934, 95% CI = 0.857, 1.018)

A post hoc Andersen-Gill analysis was performed to compare the time to each moderate or severe exacerbation among the treatment groups. This analysis showed a decreased incidence of moderate to severe exacerbations for all of the active treatment groups and FSC was significantly better than FP, but not SAL. The hazard ratio (95% CI) comparing FSC to placebo was 0.784 (0.718, 0.857) using this analysis. The hazard ratio (95% CI) for SAL was 0.847 (0.772, 0.929) and for FP was 0.866 (0.718, 0.857). (See Statistical review for details).

Approximately 25% of the patients experienced a severe exacerbation at some time during the study. The annual rate of severe exacerbations with an onset during blinded treatment, calculated with the negative binomial model was 0.19, 0.16, 0.17, and 0.16 events per year for the placebo, SAL, FP, and FSC groups, respectively (Table 37). The ratio of events comparing FSC to placebo was 0.834 (95% CI = 0.710, 0.981; p=0.028). The ratio of events comparing FSC to SAL was 1.022 (95% CI = 0.870, 1.200; p = 0.790) and the ratio of events comparing FSC to FP was 0.954 (95% CI = 0.815, 1.117; p = 0.559).

Table 37. Rate of Severe COPD Exacerbations calculated using the Negative Binomial

	Placebo (N=1524)	**SAL 50 (N=1521)**	**FP 500 (N=1534)**	**FSC 500/50 (N=1533)**
Mean number/year from model	0.19	0.16	0.17	0.16
Active treatment vs. placebo				
Ratio		0.816	0.875	0.834
95% CI		0.693, 0.962	0.744, 1.028	0.710, 0.981
p-value		0.016	0.104	0.028
FSC vs. components				
Hazard ratio		1.022	0.954	
95% CI		0.870, 1.200	0.815, 1.117	
p-value		0.079	0.559	

The time to the first severe exacerbation did not differ among the treatment groups. The Kaplan-Meyer estimate of the probability of an exacerbation by 156 weeks was 32.8, 29.2, 31.6, and 30.6% for the placebo, SAL, FP, and FSC groups, respectively.

Using the Andersen-Gill procedure, only SAL showed a benefit in the time to each severe exacerbation. The hazard ratio (95% CI) comparing FSC to placebo was 0.992 (0.790, 1.078). The hazard ratio (95% CI) for SAL was 0.850 (0.725, 0.998) and for FP was 0.949 (0.814, 1.108).

The rate of exacerbations requiring corticosteroid therapy was lower in the active treatment groups than in the placebo-treated patients, and treatment with FSC was superior to the other active treatments. From the negative binomial analysis, exacerbations rates were 0.80, 0.64, 0.52, and 0.46 for the placebo, SAL, FP, and FSC-treated patients, respectively. The ratio of exacerbations comparing FSC to placebo was 0.568 (95% CI= 0.506, 0.637).

All of the calculated exacerbation rates were similar during the first 26 weeks to the rates observed during the rest of the study

Reviewer: The rate of antibiotic-treated or antibiotic-only treated exacerbations was not calculated. However, the FDA statistical reviewer determined that the hazard ratio for antibiotic-only-treated exacerbations (moderate exacerbations) comparing FSC to placebo was 1.15 (95% CI=1.03, 1.29) and the ratio comparing FSC to SAL was 1.22 (95% CI=1.09, 1.36). There is a further discussion of respiratory tract infections see adverse events of special interest (pg 105).

All of the calculations related to exacerbation rate are dependent upon an undefined outcome. There were no clinical criteria for defining an exacerbation other than treatment, and no post hoc clinical description was provided. Other than a categorical variable for treatment, the only piece of data presented is the duration of the exacerbation. The mean duration of the 13,309 events where duration was recorded was 17.5 days with a range of 1 to 474 days. (Note: the exacerbation file contains one record for patient 1973 for an exacerbation lasting from March 25, 2002 – April 9, 2004 or 747 days. This exacerbation is listed as occurring between March 25, and April 9, 2002 in the respiratory adverse event file. In addition, in the exacerbation file the long exacerbation overlaps with another one listed as lasting from March 1 – March 17, 2004. The 747-day exacerbation in the exacerbation file probably represents a data entry error.) The episodes lasted less than 6 days in 8.5% of the cases and longer than 30 days in 11.7% of the cases. The episodes were shortest in the SAL treatment group (16.9 days) compared with 18.2, 17.5, and 18.1 days in the placebo, FP, and FSC groups, respectively. The duration varied considerably by region. The mean duration was 14.3 days in Asia compared with 16.0 days in Eastern Europe, 17.6 days in Western Europe, 19.0 days in the United States, and 19.7 days in the "Other" group.

There was also no requirement that episodes be separated by a minimum time period. The exclusion criteria define continuous oral corticosteroid use as occurring unless two episodes are separated by at least 7 days, and the protocol for Study SFCB3024 (pg 123) required exacerbations to be separated by at least 7 days to be designated as separate exacerbations. A random review of case report forms submitted with the Study SCO30003 study report showed that treatment patterns varied widely. Some investigators reported very long episodes with multiple courses of treatment interspersed with long periods with no treatment and reported this as a single exacerbation. Other investigators reported three separate exacerbations that lasted for one day each and occurred within a week of one another.

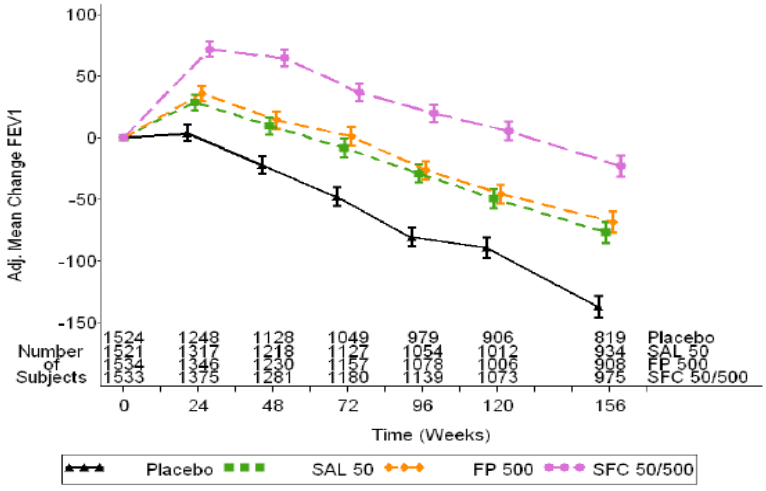
Because the definition of an exacerbation rested solely on treatment, exacerbations that were not treated (e.g., as an end-of life decision) were not counted as a COPD exacerbations even though the death was classified as a COPD-related death. Since antibiotic treatment during the run-in did not disqualify the patient from randomization, some of the exacerbations started prior to the start of study medication. Of the 13,389 exacerbations, 10,203 were classified with the MedDRA preferred term as Chronic obstructive pulmonary disease: the others were listed as Bronchitis, Pneumonia, Bronchitis acute, Upper respiratory tract infection, Lower respiratory tract infection and 117 other, uncommon, conditions. The respiratory adverse events not classified as an exacerbation were classified with similar terms, although infections were listed more frequently. The requirement for treatment with antibiotics or systemic corticosteroids was intended to

classify the exacerbation as a moderate as opposed to a mild exacerbation. However, when treatment is used as the only recorded criteria of an exacerbation it is unclear how the primary designation was made by the investigators. The database contains cases with pneumonias categorized as severe and lasting for several weeks that were not classified as moderate exacerbations. Why such an episode would not be treated with antibiotics is unclear.

Spirometry

An FEV_1 was available at baseline and for at least one follow-up visit in 5343 patients. Of these, 3636 had repeat determinations at 156 weeks (819, 934, 908, and 975 in the placebo, SAL, FP, and FSC groups, respectively). In all treatment groups there was an increase in mean post-bronchodilator FEV_1 at Week 24 with maximum changes of 4, 30, 36, and 71 mL in the placebo, SAL, FP, and FSC groups, respectively. The post-bronchodilator FEV_1 gradually decreased thereafter with a mean change in the raw value at 156 weeks of -127, -61, -62, and -7 mLs for the placebo, SAL, FP, and FSC-treated patients (Figure 4).

Figure 4. Change in post-bronchodilator FEV1*



Data source: Figure 7.044
Note: Vertical bars represent standard errors

* Study Report Figure 12. Adjustment is for smoking status, age, sex, baseline FEV_1, region, visit, baseline FEV1 by visit and treatment group by visit interaction.; SFC=Advair

In the repeated measures ANOVA the changes from baseline were of -62, -21, -15, and 29 mL for the placebo, SAL, FP, and FSC groups respectively (Table 38). The supporting analysis of covariance at each visit showed similar differences.

Table 38 . Repeated Measures ANOVA Change in Post-bronchodilator FEV_1

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 500/50 (N=1533)
Number of patients	1261	1334	1356	1392
Baseline Raw mean (SD)	1257 (444)	1231 (431)	1233 (437)	1236 (455)
Adjusted mean change (SE)	-62.3 (6.2)	-20.9 (6.0)	-15.0 (5.9)	29.2 (5.8)
Active treatment minus placebo (SE)		41.5 (8.6)	47.4 (8.6)	91.5 (8.5)
95% CI		24.6, 58.3	30.5, 64.2	74.9, 108.2
p-value		<0.001	<0.001	<0.001
FSC vs. components (SE)		50.1 (8.4)	44.2 (8.3)	
95% CI		33.7, 66.5	27.9, 60.5	
p-value		<0.001	<0.001	

The rate of decline in FEV_1 was analyzed using a random coefficients model. The mean adjusted rate of decline in FEV_1 was 55, 42, 42, and 39 mL/year in the placebo, SAL, FP, and FSC groups, respectively. The rate of decline was decreased by all of the active treatments to approximately the same degree. Compared with placebo, the rate of decline was decreased by 13 mL/yr by SAL and FP and by 16 mL/ yr by FSC.

Composite Endpoint

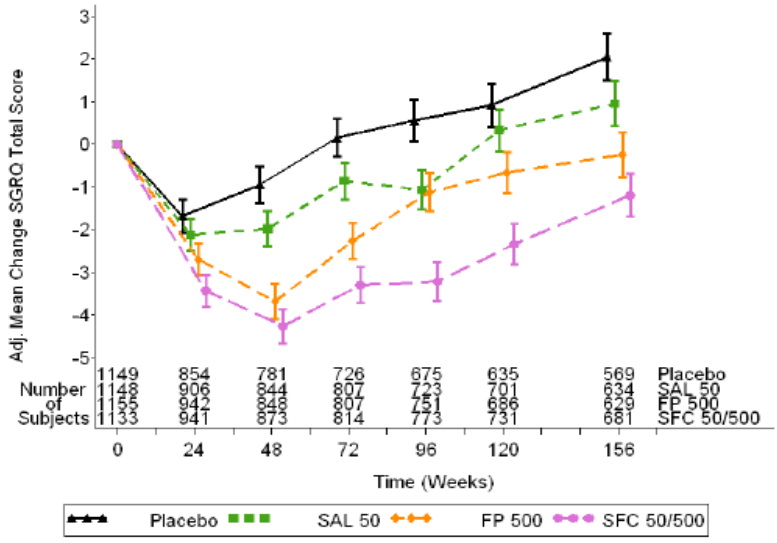
The composite endpoint consisted of on-treatment mortality, severe COPD exacerbations on treatment, and initiation of LTOT. An event was identified when any of the three conditions occurred on therapy even if the event occurred after 3 years. The hazard ratio ((5% CI) for this endpoint comparing FSC to placebo was 0.888 (0.782, 1.009). The hazard ratio comparing SAL to placebo was 0.879 (0.772, 0.999) and the hazard ratio comparing FP to placebo was 0.964 (0.850, 1.093).

Health Outcomes

According to the study protocol, the Saint George's Respiratory Questionnaire (SGRQ) was the second key secondary outcome (exacerbation rate was the first). These results were obtained from the Health Outcomes Population which was the subset of the ITT population who had completed a validated questionnaire (see Appendix Section 1.1.5 Study Procedures, Health Outcomes Evaluations, pg. 60) and for whom a total score could be calculated. Twenty-eight countries (387 centers) contributed to the population.

The mean total SGRQ scores were 49.0, 49.9, 49.5, and 48.9 in the placebo, SAL, FP, and FSC groups, respectively (Table 39). In all of the treatment groups there was a decrease (improvement) in the Total Score at 24 weeks (Figure 5). The mean change was -1.74, -2.31, -2.92, and -3.3 in the placebo, SAL, FP, and FSC groups, respectively. At 156 weeks, the mean changes from baseline were 1.31, -0.44, -0.93, and -1.81, respectively. Adjusting for smoking status, age sex, baseline FEV_1, baseline SGRQ total score, region, visit, baseline SGRQ by visit and treatment group by visit interaction resulted in a mean change averaged over the 3 year treatment period of 0.2, -0.8, -1.8, and -3.0 units for the placebo, SAL, FP, and FSC groups respectively (Figure 5 and Table 40). The average difference comparing FSC to placebo was -3.1 (95% CI = -4.1, -2.1). The comparison between SAL and FP to placebo was –1.0 (95% CI = -2.0, 0.0) and -2.9 (95% CI = -2.9, -1.0), respectively. The difference between FSC and SAL and FP was -2.2 and -1.2, respectively.

Figure 5. Change in SGRQ*



Source Data: Figure 7.026
Note: Vertical bars represent standard errors

* Study Report Figure 11; SFC=Advair

Table 39. Difference Between Treatment Groups in the Change in SGRQ During Treatment

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 500/50 (N=1533)
Number of patients	924	980	1005	1002
Baseline Raw mean (SD)	48.4 (17.5)	49.4 (16.6)	49.5 (17.3)	48.7 (17.1)
Adjusted mean change (SE)	0.2 (0.37)	-0.8 (0.35)	-1.8 (0.35)	-3.0 (0.35)
Active treatment minus placebo (SE)		-1.0 (0.51)	-2.0 (0.51)	-3.1 (0.50)
95% CI		-2.0, 0.0	-2.9, -1.0	-4.1, -2.1
p-value		0.057	<0.001	<0.001
FSC vs. components (SE)		-2.2 (0.49)	-1.2 (0.049)	
95% CI		-3.1, -1.2	-2.1, -0.2	
p-value		<0.001	0.017	

As a form of sensitivity analysis, only questionnaires that had no scoring modifications were reviewed. Results were available for 268, 289, 287, and 282 patients in the placebo, SAL, FP, and FSC groups, respectively. The results showed a smaller, but similar order of responsiveness. The adjusted mean change from baseline was 0.0, -0.8, -1.4, and -2.7 in the placebo, SAL, FP, and FSC groups, respectively. The difference between FSC and placebo -2.7, and the difference between FSC and its components was -2.0 for the comparison with SAL and -1.4 for the comparison with FP.

Using an a priori cut off of 4 units as a clinically significant change in status, the patients were classified as improved (+4 unit change in SGRQ), not changed (+/- <4 unit change in SGRQ) and deteriorated (-4 unit change in SGRQ). In the FSC group 31% improved compared with

21% in the placebo group. Twenty-seven and 28% improved in the SAL and FP groups, respectively (Table 40).

Table 40 . Categorical Analysis of Changes in SGRQ

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 500/50 (N=1533)
Number of patients	1149	1148	1155	1133
Improvement	247 (21)	312 (27)	325 (28)	353 (31)
No change	241 (21)	246 (21)	279 (24)	309 (27)
Deterioration	661 (58)	590 (51)	551 (48)	471 (42)
Odds ratio for active treatment to placebo (SE)		1.32 (0.11)	1.50 (0.12)	1.86 (0.15)
95% CI		1.13, 1.56	1.28, 1.75	1.58, 2.18
Odds ratio for FSC vs. components (SE)		1.40 (0.11)	1.24 (0.01)	
95% CI		1.20, 1.64	1.60, 1.45	

Changes in the Domain (Symptoms, Activity, and Impact) scores were similar to those for the Total scores. In no case was the adjusted mean difference between active treatment and placebo ≥ 4 units.

Sub-Group Analysis

The applicant used interaction term for smoking status, region, FEV_1, age, sex, ethnic origin and BMI in a Cox Proportional Hazards analysis to assess sub-group effects on mortality. According to this analysis (taking a p-value of 0.05 as the definition of a positive interaction) there was no significant affect of sub-group on the relative efficacy of FSC.

The interaction p-value for smoking status (Smoker vs. no-smoker) was 0.586. The death rate was lowest in the FSC group in both the smokers and non-smokers. However the difference in mortality between placebo and FSC-treated patients was 3.9% in smokers and 1.6% in former smokers.

Reviewer: The smoking analysis performed by the applicant is based on the current smoking status of the patients and not on the cumulative smoking history. However, in the survival analyses, pack-years smoked had a more significant effect on mortality than did current smoking status. In a Cox regression with treatment group, smoker had no effect on mortality (HR = 0.966) whereas pack-years smoked as a continuous or categorical variable had a significant effect in almost all divisions of the data. Entered into the regression with treatment group, a smoking history of >42 pack-years increased mortality by 26% compared to patients with a smoking history of 42 or fewer pack-years. The difference in mortality comparing FSC to placebo was 1.5% in the patients with the lower smoking history and 3.5% in those with the higher cumulative pack-years. Of note, being an active smoker was protective in patients with a lower pack-year history. This probably occurred because active smokers were healthier and younger. This interpretation is supported by the ablation of the effect of current smoking when a measure of pulmonary function and age were included in the regression.

Dividing the population by region showed that mortality was generally high in Asia, Eastern Europe and in the "Other" group. As noted by the Applicant, the mortality was less in the FSC

than in the other treatment groups except for the Asians in which group the mortality was the same (Table 41). However, the difference between placebo and FSC treatment varied among the groups. The difference between FSC and placebo ranged from 0 in the Asian population to 4.0 in the Eastern European population. The difference in mortality between placebo and FSC was 1.7% in the US population.

Table 41 . Regional Variation in Probability of Death

	N	Placebo 1524	Salmeterol 1521	Fluticasone 1534	FSC 1534	Placebo-FSC
USA	**1388**	345 13.9	346 14.5	348 13.5	349 12.3	**1.7**
Asia/Pacific	**758**	188 17.6	189 15.9	193 22.8	188 17.6	**0**
E Europe	**1154**	290 17.9	289 14.5	287 18.5	288 13.9	**4.0**
W Europe	**1908**	476 11.3	475 9.9	481 13.7	476 8.4	**2.9**
Other	**904**	225 19.6	222 16.2	225 16.0	232 16.0	**3.6**

Reviewer: The cause of death, analyzed by region, showed a death from cardiovascular causes in 45 (3.3%), 25 (3.3%), 65 (5.6%), 67 (3.5%), and 35 (3.9%) of the US, Asian, Eastern European, Western European, and Other populations respectively. Pulmonary deaths were reported in 57(4.1%), 75 (9.9%), 57(4.9%), 54 (2.8%), and 63 (7.0%) of the US, Asian, Eastern European, Western European, and Other populations, respectively.

The interaction p-value for percent predicted FEV_1 (divided into groups of <30, 30 - <50, and >=50% predicted) was 0.402. Using this division of function, the difference in mortality between placebo and *FSC* was 6.4, 0.6, and 3.6% in the low, medium, and hi-FEV_1 groups.

Reviewer: The group of patients with FEV_1 <30% had only 214 to 260 patients per region. This is in comparison to 500+ and 700+ in the other lung function groups. In this sick population it is likely that there was substantial variability in functional measurements and 200 patients per analysis group may not be large enough for a stable estimate of the effect of treatment. In a Cox regression including treatment group, the patients with an FEV_1 % predicted >40% had approximately half of the mortality (HR= 0.534) of the patients with an FEV_1 of <40% predicted. Comparing the effect of FSC to placebo treatment showed a difference of 1.4% for the patients with a baseline FEV_1 of <=40% predicted and the comparison showed a difference of 3.7% for the patients with an FEV_1 of >40% predicted.

The interaction p-value for age was 0.120. The applicant divided the treatment group into 10-year age categories (<55, 55-64, 65-74, and >74 years). This division resulted in analysis cells of less than 200 patients for those younger than 55 and older than 74 years. The difference in mortality between FSC and placebo was 2.7, 3.8, 0.9, and 5.1% in the young through older groups, respectively.

Reviewer: Again, the small analysis groups may be giving a false impression. Dividing the group at age 65 resulted in a mortality difference between FSC and placebo of 3.5% in the younger group and 1.9% in the older patients.

The interaction p-value for gender was 0.671, and the difference in mortality comparing FSC to placebo was 3.1% for men and 0.9% for women. There were 361 to 382 women per analysis group. BMI was grouped into those <20, 20 to <25, 25- <29, and >=29. Mortality was highest in those with a BMI <20. The difference in mortality between FSC and placebo was 0.5, 4.7, 1.6, and 3.0% in the low to high BMI groups, respectively. Mortality was higher in the FSC patients than in the Placebo group with a BMI <20.

Including interaction terms in the negative binomial calculation of exacerbation rate suggested no differential effect of subgroup. The rate of moderate/severe exacerbations was higher in former smokers than in current smokers, but in each smoking category the rates were lower in the FSC than the placebo-treated patients. The difference between FSC and placebo was 0.34 exacerbations/year in the current smokers and 0.39 exacerbations/year in the former smokers.

The rate of exacerbations was highest in the "Other" region and lowest in Eastern Europe. In all of the regions the rates were lower in the FSC-treated than in the placebo-treated patients. Using the capped exacerbation rate the difference between FSC and placebo was 0.281, 0.126, 0.2507, 0.471, and 0.691 in the US, Asian, Eastern European, Western European, and Other populations, respectively.

Reviewer: The rate of exacerbations (calculated by the FDA statistical reviewer using the negative binomial distribution) during placebo treatment was 1.18, 1.02, 0.70, 1.28, and 1.54 episode/year in the US, Asia, Eastern Europe, Western Europe, and the Other region. In all of the regions the rate was lower in the FSC-treated patients. The difference between the rate in the placebo and FSC-treated patients was 0.21, 0.16, 0.07, 0.41, and 0.61 episodes/year in the US, Asia, Eastern Europe, Western Europe, and the Other region. The low placebo exacerbation rate in Eastern Europe is interesting in light of the fact that historical exacerbation rate during the 12 months prior to enrollment was the highest of all the regions (See Table , pg above).

Exacerbations were more frequent in patients with poor pulmonary function at baseline, but the rate was less in patients treated with FSC than in the patients in other treatment groups at each level of pulmonary function. The difference between FSC and placebo was 0.30, 0.39, and 0.39 in the patients with a baseline FEV_1 % predicted of <30%, 30 to <50%, and ≥50%, respectively.

Reviewer: The difference in the rate of moderate/severe exacerbations in the entire population comparing FSC to placebo was 0.28 so the distribution of differences by pulmonary function group is probably in error.

The rate of exacerbations was highest in patients over 75 years of age and lowest in those less than 55, and the rate was lower in the FSC-treated patients than in the other treatment groups in all of the age categories. The difference between FSC and placebo was 0.28, 0.35, 0.34, and 0.67 in those <55, 55-64, 65-74, and ≥74 years old, respectively.

The rate of exacerbations was higher in women than men, and the rate was lower in the FSC-treated patients than in the other treatment groups in both genders. The difference between FSC and placebo was 0.36 and 0.44 in the men and women, respectively

Reviewer: Significant interactions were defined by the finding of a p-value of <0.05 for an interaction term for each variable. The usual p-value to use for this purpose is 0.10. Using a subset analysis it appears that there are substantial differences in responsiveness in various subgroups. Of clinical relevance is the poor response in patients with a FEV_1 % predicted <40%, those who were older than 65 years of age and those with very long smoking histories. All of this supports the unsurprising conclusion that patients with long term, severe, COPD have a very small reversible component to their disease process. In this sub-set it is possible that adverse events will outweigh any benefit seen in the survival function.

1.2.3 Health care utilization

Unscheduled health care contacts occurred in 3700 (60.5%) of the patients (Table 42). For all of the variables listed, other than ER visits and Office calls, the SAL group had the lowest number of contacts when corrected for the duration of treatment. ER visits and office calls occurred slightly less frequently in the FSC group than in any of the other treatment groups. The patients treated with SAL also had the shortest hospital and ICU stays (1490 and 105 days/1000 years of exposure, respectively). The FSC patients stayed in the hospital for a mean of 1,645 days/1000 years of exposure and they stayed in the ICU for 186 days/1000 years of exposure. The ICU stay for the FSC-treated patients was longer than any of the other treatment groups.

Table 42. Health Care Utilization.

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 500/50 (N=1533)
Unscheduled health care contacts, n (%)	949 (62)	918 (60)	937 (61)	896 (58)
Rate/1000 years of exposure				
ER Visits	143	75	81	72
Out-patient clinic visits	245	196	197	209
General ward admissions	200	172	195	180
ICU admissions	18	15	16	17
Office calls	593	450	603	426
Number of days/1000 years of exposure				
General ward	2137	1490	1987	1645
ICU	169	105	150	186

Reviewer: There were differences in health care utilization by region. Western Europe had the lowest mortality and the second lowest exacerbation rate. They also had a low incidence of ER use (5.8% of patients compared to 17.2, 12.9, 24.5% of the patients in the US, Other, and Asia, respectively). E Europe had an even lower incidence of ER use (3.5%) despite a mortality of 16.2%. Patients in the US had the second lowest mortality (13.5%), but a relative high ER use (17.2%). They were admitted to the hospital at a rate that was close to the group average, but the hospital stay was short (3.5 days compared with 5.8, 9.2, 4.4, and 7.8 for the patients in W Europe, E. Europe, Other and Asia, respectively). Admission to the ICU in the US was also near

the median, but again the stay was very short (2.9 days compared with 7.0, 4.4, 4.2, and 6.1 days in W Europe, E. Europe, Other and Asia, respectively.

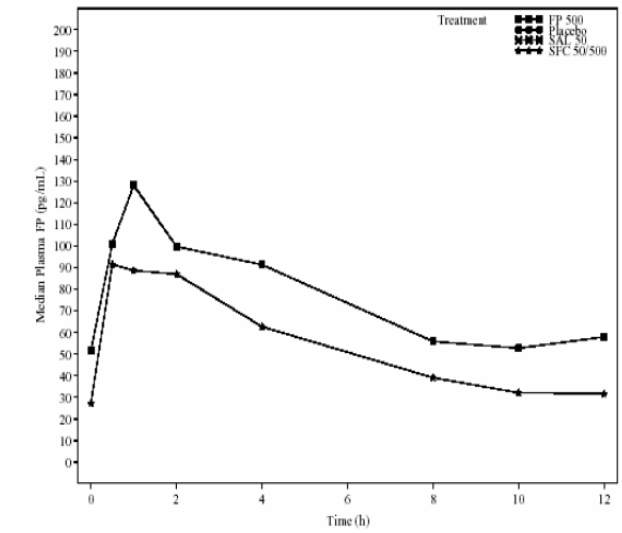
Pharmacokinetics

The PK/PD analysis was performed on 83 patients recruited at 15 sites in the United States. Compared to the population as a whole, the patients were slightly younger (48% < 65 years), more were female (29%), and they had a shorter history of COPD (46% <5 years). More of the PK population were active smokers (50.6%) and more had extremely poor pulmonary function (25% with FEV_1% predicted <30%) than the larger population. These differences were quantitatively small and not expected to change the results of the PK/PD analysis. There were 20, 24, 15, and 24 patients treated with placebo, SAL, FP, and FSC, respectively, in the PK population. Inhaled corticosteroids had been taken in the 12 months prior to enrollment in 60, 54, 26, and 63% of the patients in the placebo, SAL, FP, and FSC groups respectively. One, 0, 1, and 3 patients, respectively, took an ICS during the course of the trial.

Blood was collected at Visit 5 (week 36 of treatment) immediately pre-dose and at 0.5, 1, 2, 4, 8, 10, and 12 hours post-dose for plasma FP and cortisol. Blood was obtained from the 83 patients at all the planned time points except for four patients who did not provide a 12-hour sample. Of the 158 samples provided by the 20 placebo patients, two had measurable levels of fluticasone (139 and 129 pg/mL). These samples represented single measurable levels in two patients. No explanation for the finding could be found. There were 118 samples in the FP and 192 samples in the FSC-treated patients. Only 3% of the samples in the active treatment groups had no measurable FP.

The shape of the FP-time curves was similar in the two active treatment groups (Figure 6) although the peak was somewhat higher in the FP than the FSC group.

Figure 6. Plasma FP



FP exposure was slightly lower after inhalation of FSC compared with an identical dose of fluticasone inhaled as a single component (Table 43). However, the 90% confidence interval was broad and none of the differences was significant.

Table 43. Fluticasone PK analysis

	Fluticasone PK		Analysis	
Treatment	**FP**	**FSC**	**Ratio**	**90% CI**
C_{max}, pg/mL	115 (88,173)	105 (93, 147)	0.91	0.676, 1.22
T_{max}, hr	1.0 (0. 2.1)	1.0 (0, 4.0)	0	0, 1
AUC_{last}, pg hr/mL	790 (612, 1340)	736 (631, 1096)	0.93	0.659, 1.32
$T_{1/2}$, hr	7.0 (0.09, 0.11)	6.2 (5.6, 7.5)		

The 83 patients had single measurements for salmeterol ten minutes post-dose. The 20 placebo patients all had non-quantifiable levels, but one FP patient had a level close to the lower limits of quantitation (26.3 pg/mL). The measurements were below the level of quantitation in 8/24 SAL and 2/24 FSC patients. The remaining samples showed values ranging from 25.5 to 127 pg/mL. The SAL concentration at 10 minutes (C_{10}) was 82% higher following FSC compared to that following SAL. The C_{10} was 53.3 pg/mL and 29.4 pg/mL in the SAL and FSC patients, respectively. The geometric least squares mean ratio (90% CI) was 1.82 (1.32, 2.50).

Pharmacodynamics

The serum cortisol levels reach a minimum at 12 hours post dose in 49 (60%) of the patients and at 10 hours post-dose in 18 (22%). The cortisol AUC_{12} was calculated in 76 patients. Six patients (2, 1, 3 in the placebo FP, and FSC groups, respectively) did not have an adequate 12-hour sample. Serum cortisol was 21 and 22% lower after FP and FSC, respectively, when compared with placebo. However, because of the wide spread in the values, none of the comparisons was statistically significant (Table 44).

Table 44. Serum cortisol *

	Placebo (N=20)	**SAL (N= 24)**	**FP (N= 15)**	**FSC (N =23)**
Cmin, geometric mean	152	135	117	112
Ratio vs plbo		0.888	0.768	0.732
95% CI		0.623, 1.25	0.518, 1.14	0.515, 1.04
FSC vs. components		0.829	0.953	
95% CI		0.592, 1.16	0.650, 1.40	
AUC_{12}	3048	3423	2679	2672
Ratio vs. plbo		1.0	0.786	0.784
95% CI		0.769. 1.31	0.58, 1.07	0.594, 1.04
FSC vs. components		0.781	0.997	
95% CI		0.603, 1.01	0.741, 1.34	

* Taken from post-text Table 12.3, pg 8655

1.2.3. Safety

1.2.3.1 Exposure

Mean exposure to study medication was 775 days for placebo, 836 days for SAL, 837 for FP, and 874 for FSC (Table 45). Mean exposure was similar in the ITT and Health Outcomes Populations. In the Skeletal Safety and Ophthalmic Population mean exposure was lower: 661 days for placebo, 782 days for SAL, 765 days for FP, and 865 days for FSC.

Table 45. Summary of Exposure to Study Drug

	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	FSC 500/50 (N=1546)
Mean (SD) exposure, weeks	110.8 (59.9)	119.5 (55.7)	119.5 (54.8)	124.9 (51.6
Total treatment-years of exposure	3278	3531	3555	3700
Ratio of exposure comparing active to placebo treatment		1.08	1.08	1.13
Range of Exposure, n (%)				
≤ 12 weeks	160 (10%)	118 (8)	100 (6)	68 (4)
>12-≤24 weeks	99 (6)	71 (5)	77 (5)	68 (4)
>24-≤48 weeks	126 (8)	98 (7)	116 (8)	103 (7)
>48- ≤72 weeks	70 (5)	83 (5)	67 (5)	74 (5)
>72-≤96 weeks	75 (5)	71 (4)	76 (5)	65 (4)
>96-≤120 weeks	69 (4)	59 (4)	74 (5)	60 (4)
>120-≤144 weeks	54 (4)	50 (4)	68 (4)	63 (4)
>144-≤156 weeks	246 (16)	272 (18)	291 (19)	285 (18)
>156 weeks	645 (42)	720 (47)	683 (45)	760 (49%)

1.2.3.2 Adverse Events

Reviewer: Adverse event reporting was divided into events that occurred during randomized treatment, during the two weeks after stopping treatment, and in the LTFU (between two weeks after stopping treatment and 3 years following starting treatment). There are 44,434 events listed in the adverse events data sets (ae_all1.xpt and ae_all2.xpt combined). Of these, 40,706 are coded as treatment phase "During". Only 1040 are reported for the 2-week post treatment phase and another 1080 for the LTFU. The protocol required recording only serious, drug-related adverse events in the LTFU. However, in the data set approximately half (523/1080) of these events are recorded as not serious. The overall low incidence of events in the LTFU and the inclusion of non serious events suggest that adverse event reporting in the LTFU was not as intense as during randomized treatment and that reporting may not have been consistent. Adverse events that occurred during the LTFU will only be discussed for fatal events because the fatal events were all followed-up.

Because the time on treatment varied among the treatment groups, events were reported as the rate of events /1000 treatment-years in addition to the incidence (% of patients reporting the event). Examination of the rates is also useful in the discussion of rare events. Sometimes a differential can be detected in the rate that would not be seen if the incidence were reported only as <1%. Of note, the incidence and rate do not always correlate well. This is because of the

wide range of the number of events per patient. As with exacerbations (Range 0 to 30 per patient) the range for non-COPD-exacerbation-adverse events was high: 0-72 events/patient.

Adverse events were reported in at least 89% of the patients during randomized treatment in each treatment group (Table 46). Serious events were reported in 41 to 43% and 18 to 24% of events resulted in withdrawal of the patient. The overall incidence was similar in all of the treatment groups with a slight preponderance of serious events and drug-related events in the FSC group. Events leading to withdrawal were more frequent in the placebo group.

Table 46. Overall Summary of AEs that Started During Treatment in Safety Population

Number (%) Patients Reporting Events	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	FSC 500/50 (N=1546)
N (%) /Patients Reporting Events				
All AE	1385 (90)	1381 (90)	1395 (90)	1381 (89)
SAEs	627 (41)	622 (40)	655 (42)	659 (43)
Drug-related AEs *	207 (13)	187 (12)	302 (19)	285 (18)
AEs leading to withdrawal	367 (24)	315 (20)	356 (23)	272 (18)
SAEs leading to withdrawal	216 (14)	212 (14)	242 (16)	201 (13)
Rate / 1000 treatment years				
All AEs	2981.7	2767.2	2964.8	2868.1
SAEs	430.8	398.2	437.1	412.2
Drug-related AEs	102.5	107.3	152.2	157.6

** Relationship to drug treatment assessed by investigators

Reviewer: As discussed below, all of the AE tabulations were dominated by respiratory events, and COPD exacerbations were the most frequent type of respiratory AE. According to the protocol, all moderate/severe exacerbations should have been reported as adverse events. However, many of the adverse events categorized as COPD were the same events that were analyzed as COPD exacerbations as an efficacy endpoint. If COPD exacerbations are removed from the tabulation (percentage of patients with events taken from post-text Table 7.028, pg 2820 of study report) 61.2, 62.4, 65.7, and 64.5% of the placebo, SAL, FP, and FSC groups, respectively, reported adverse events.

AEs, listed by MedDRA preferred term, which occurred in more than 5% of any treatment groups and that had an onset during randomized treatment are summarized in Table 47. In general, events that could be thought of as related to some form of deterioration of COPD (COPD, dyspnea, respiratory failure) were decreased in the FSC group compared to placebo. On the other hand, almost all events associated with infections (upper as well as lower respiratory) were increased in the FSC group as compared to placebo and to the SAL-treated patients. The FP treated patients also had an increased incidence of infections. (For a detailed discussion of respiratory infectious adverse events see Events of Special Interest [pg 104].)

Table 47. Adverse Events (MedDRA preferred term) Occurring During Randomized Treatment Group in at Least 5% of any Active Treatment Group

Number (%) Patients Reporting Events Rate per Thousand Treatment-years	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	FSC 500/50 (N=1546)
COPD	969 (63) 919.8	932 (60) 757.3	928 (60) 775.8	879 (57) 666.5
Nasopharyngitis	165 (11) 85.7	191 (12) 88.1	206 (13) 96.8	215 (14) 96.8
Upper respiratory tract infection	170 (11) 100.7	165 (11) 80.4	168 (11) 88.0	213 (14) 104.9
Pneumonia	112 (7) 39.4	133 (9) 41.6	185 (12) 69.2	207 (13) 71.1
Headache	115 (7) 81.8	100 (6) 58.6	115 (7) 59.6	111 (7) 50.3
Bronchitis	91 (6) 48.5	97 (6) 50.1	102 (7) 51.2	121 (8) 54.3
Back pain	94 (6) 37.5	97 (6) 35.1	96 (6) 35.2	96 (6) 37.0
Hypertension	77 (5) 25.3	92 (6) 27.5	89 (6) 26.2	82 (5) 23.0
Sinusitis	76 (5) 31.1	66 (4) 28.6	101 (7) 41.4	93 (6) 36.8
Cough	68 (4) 24.7	76 (5) 26.3	91 (6) 36.0	94 (6) 34.1
Influenza	66 (4) 31.4	69 (4) 31.4	86 (6) 28.7	82 (5) 28.6
Chest pain	59 (4) 22.9	72 (5) 24.1	72 (5) 27.0	93 (6) 30.8
Dyspnea	72 (5) 31.7	71 (5) 24.1	66 (4) 23.3	56 (4) 18.1
Pharyngolaryngeal pain	57 (4) 21.0	55 (4) 21.5	77 (5) 28.7	61 (4) 22.7
Oral candidiasis	27 (2) 11.0	28 (2) 9.9	106 (7) 45.9	84 (5) 36.8
Acute bronchitis	48 (3) 26.5	48 (3) 20.1	59 (4) 29.5	73 (5) 31.4

Dysphonia and oropharyngeal candidiasis are known to be adverse reactions associated with inhaled corticosteroid. Tabulating the events that occurred at a frequency of 1 to 5% of the patients confirmed the elevated rates in both corticosteroid-containing treatment groups. Dysphonia occurred at a rate of 3.7, 4.8, 17.4, and 20.8 events/1000 treatment years in the placebo, SAL, FP, and FSC groups, respectively. Oropharyngeal candidiasis was reported at a rate of 3.1, 3.4, 15.5, and 16.8 events /1000 treatment years, respectively. Candidiasis, which could include infection outside of the oropharynx, was reported at a rate of 7.9, 4.0, 21.9, 16.8 events/1000 treatment-years.

Reviewer: Note that candidiasis is reported here under three different MedDRA preferred terms: Oral candidiasis in >5% of patients, and Candidiasis and Oropharyngeal candidiasis in 1-5% of patients. The ae_all.xpt also includes three other preferred terms that could have been included in this group (Oral fungal infection, Oropharyngitis fungal and Pharyngeal candidiasis).

Fifty-one events were recorded in these categories. To fully describe the extent of possible upper airway fungal disease, the 12 events recorded as Fungal esophagitis or Esophageal candidiasis might have been included. All of these infrequent events other than Oropharygitis fungal were elevated in the fluticasone-containing treatment regimens.

Contusions were also reported at a low frequency, but more often in the fluticasone-containing regimens. A combination term that included bruise, contusion, bruising of arm bruising of leg, contusion of hip, bruising of chest, bruising of hand, contusion of back, contusion of chest wall, contusion of knee, bruise of head, contusion of elbow, bruising of face, bruising of foot, bruising of thigh, contusion of ankle, and contusion or wrist was reported in 19 (1%), 16 (1%), 20 (1%), 30 (2%) if the patients in the placebo, SAL, FP, and FSC groups, respectively. The respective rates were 6.4, 5.7, 13.5, and 11.4 events / 1000 treatment-years.

Low incidence events (reported in 1-5% of the patients and > 50% more frequent than in the placebo patients) were also tabulated. Muscle spasms, pyrexia, contusions, vomiting hemoptysis, nasal congestion, myalgias, hypokalemia, laryngitis, vertigo, gastroenteritis, coronary artery disease, hypercholesterolemia, pruritus, cataract and conjunctivitis occurred more frequently in FSC-treated than in placebo-treated patients. Contusions, myalgia, malignant lung neoplasms, hemorrhoids, anorexia, gastroenteritis, gastritis, viral infection, lobar pneumonia, diverticulitis, chest wall pain, cerebrovascular accident, fatigue, and skin laceration, were reported more frequently with FP, and pyrexia, nasal congestion, rhinorrhea, diverticulitis, fatigue, coronary artery disease, hypercholesterolemia, gout, pruritus, and conjunctivitis were reported more frequently in patients treated with SAL.

Of the events that occurred in 1-5% of the patients, the rates did not differ greatly among the treatment groups and most of those that were seen more frequently in the active treatment groups are already included in the approved label. However, the increased rate of cerebrovascular accident that was reported in the FP group (6.8 events/1000 treatment years compared to 3.7, 3.1, and 4.1 in the placebo, SAL, and FSC groups) was not expected. Therefore the Applicant tabulated adverse events coded to the MedDRA higher level terms of "Central Nervous System Hemorrhages and Cerebrovascular Accidents". These events were reported in 27 (2%), 16 (1%), 37 (2%), and 24 (2%) of the placebo, SAL, FP, and FSC patients, respectively. The respective rates were 9.5, 5.4, 11.0, and 6.8/1000 treatment years. The Applicant did not find an explanation for this finding.

According to the investigator's assessment, drug-related AEs occurred during randomized treatment in 13, 12, 19, and 18% of the placebo, SAL, FP, and FSC patients, respectively. According to this analysis, the excess events in the FP and FSC groups were entirely due to candidiasis and dysphonia.

Reviewer: Of the 785 pneumonias reported, only 5 were considered to be drug-related by the site investigators.

Subgroups

There were regional differences in the overall adverse event rate with the lowest rates in all treatment groups in Eastern Europe and the highest rates in the US (Table 48).

Table 48. **Overall Rate of Adverse Events by Region***

	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	FSC 500/50 (N=1546)
USA	329/348 (95)	331/351 (94)	335/350 (96)	340/352 (97)
Asia/Pacific	176/188 (94)	176/189 (93)	185/193 (96)	174/188 (93)
Eastern Europe	249/297 (84)	238/296 (80)	239/293 (82)	225/293 (77)
Western Europe	421/477 (88)	426/475 (90)	413/482 (86)	421/477 (88)
Other	210/234 (90)	210/231 (91)	223/234 (95)	221/236 (94)

*Reproduced from post-Text Table 8.025

Reviewer: When the number of events was tabulated, the differences were greater. The US population reported 11.2 events per patient compared to 3.3 events per patient in Eastern Europe. The other regions were intermediary: 7.1 events per patients in Asia, 5.0 in Western Europe and 6.8 in the Other group (This is the total number of AEs from the ae_all.xpt data sets divided by the number of patients in the treatment group). The variability was not as high when comparing serious AES. There were 1.1, 1.3, 0.86, 0.88, and 0.89 serious events per patient in the US, Asia, Eastern Europe, Western Europe, and Other, respectively. While the patients in the US reported the most AEs overall in most of the SOCS, the pattern for severe respiratory AEs was different. In Asia 0.77 severe respiratory events were recorded per patient compared to 0.29 in the US and 0.35, 0.38, and 0.37 events/patient in Eastern Europe, Western Europe, and Other, respectively. These rates are not adjusted for the length of time on treatment. However, it is unlikely that time on study medication can explain the differences in event rate because Eastern Europe had the lowest event rate and the longest time on study (mean = 919 days). The length of time on study medication for the other regions was 765, 896, 821, and 777 days for the US, Asian, W European and Other population, respectively.

The population was divided by age, sex, smoking and pulmonary function status as in the efficacy analysis (Pg 89). No effect of the subgroup analysis on the rate of adverse events using this categorization was seen.

Reviewer: The overall number of adverse events (without adjustment for time on study medication) was not markedly different in any subgroup. Overall events were slightly more common in patients older than 75 years (90-93%) compare to those <55 years (85-87%) patients with FEV_1 % predicted <30% (92 – 95%) compared to those with an FEV_1% > 50% (86-89%), Smoking status and pack-years had a negligible effect on adverse events. (Data taken from post-text Table 8.025, pg 4544 of study report.)

Fatal Adverse Events

In the primary efficacy analysis, death was tabulated for all patients in the ITTP who died within three years following the initiation of randomized treatment (N=875 deaths). A supportive analysis was performed of the time to "on-treatment" deaths which included any death that occurred within 2 weeks of stopping study drug but within 156 weeks of starting therapy (N=474 deaths). For the safety analysis, the 6 deaths of patients enrolled at the sites that were excluded from the ITTP due to data irregularities, as well as the 29 deaths that occurred beyond 3 years after starting study medications were included (N=911 deaths). The events were grouped by the

date of onset of the adverse event that preceded the death, not by the date of death, and the adverse event was as reported by the site investigator, not the cause of death adjudicated by the CEC. The time periods that the Applicant reported were "During treatment". "Post treatment" which was made up of the 2 weeks after stopping medication, and the Long Term Follow-up Period (LTFU) which consisted of the time from 2 weeks after stopping medication to 3 years after starting treatment. In the Applicant's tabulation there are more adverse events leading to death than deaths. This is because some adverse events persisted through the randomized treatment period into the LTFU and such a death was associated with three adverse event-treatment groupings. Also, more than one adverse event could have been an immediate precursor to death such as cardiac arrest and arrhythmia. Two patients died in the LTFU of adverse events that began prior to enrollment: one SAL treated patient had congestive cardiac failure and one FSC patient had metastatic rectal cancer. These two deaths are included in the 875 ITTP.

During Treatment

Adverse events that occurred during randomized treatment and resulted in death at any time during follow-up were reported for 533 patients (133 [9%], 126 [8%], 160 [10%], and 114 [7%] in the placebo, SAL, FP, and FSC groups, respectively) (Table 49). Using the MedDRA preferred term to classify the events, no individual AE was reported in >3% of the population. Deaths following any respiratory AE were more frequent in the FP group (94 [6%] compared to 71 [5%], 71 [5%], and 63 [4%] in the placebo, SAL, and FSC groups). The respective rates/100 treatment years were 27.8, 24.6, 31.8, and 19.2, respectively.

Table 49. Serious Adverse Events (classified by MedDRA preferred term) that Started During Treatment and Resulted in Death in at Least 5 Patients*

Number (%) Patients Reporting Events	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	FSC 500/50 (N=1546)	Total (N=6184)
Any event	133 (9)	126 (8)	160 (10)	114 (7)	533 (8.6)
COPD	32 (2.1)	32 (2.1)	38 (2.4)	24 (1.5)	156 (2.5)
Pneumonia	9 (0.6)	10 (0.6)	12 (0.8)	8 (0.5)	39 (0.6)
Respiratory failure	7 (0.4)	12 (0.8)	17 (1.1)	6 (0.4)	42 (0.7)
Acute Respiratory failure	6 (0.4)	3 (0.2)	5 (0.3)	2 (0.1)	16 (0.3)
Sudden Death	8 (0.5)	6 (0.4)	4 (0.3)	4 (0.3)	22 (0.4)
Myocardial infarction	8 (0.5)	5 (0.3)	6 (0.4)	7 (0.4)	26 (0.4)
Acute myocardial infarction	6 (0.4)	1 (<0.1)	5 (0.3)	2 (0.01)	14 (0.2)
Cardiac failure	7 (0.4)	7 (0.4)	5 (0.3)	6 (0.4)	25 (0.4)
Cardiac arrest	6 (0.4)	6 (0.4)	5 (0.3)	4 (0.3)	21 (0.3)
Lung neoplasm malignant	6 (0.4)	10 (0.6)	11 (0.7)	11 (0.7)	38 (0.6)
Cerebrovascular accident	0	1 (0.1)	5 (0.3)	3 (0.2)	9 (0.1)

. * Taken from Study Report Table 94, pg189.

Post Treatment

There were 124 AEs reported in the two weeks following treatment that resulted in death: 35 (2%), 22 (1%), 31 (2%), and 36 (2%) in the placebo, SAL, FP, and FSC groups, respectively.

Cardiac arrest was the only event reported in 5 or more patients: 5, 2, 2, and 3 in the placebo, SAL, FP, and FSC groups, respectively.

Reviewer: Thirty-eight of the 124 patients reported with a fatal AE during the post treatment period also had a fatal AE during treatment. The first, on-treatment AE is the most likely to be related to treatment and later AEs less so, although drug effect may persist, and two weeks post treatment is a reasonable period to include in the "on-treatment" period. Excluding the two patients who died in LTFU of a pre-existing condition that was not known about at enrollment, there were 909 deaths. If we attribute the cause of death to the first AE and include those patients who suffered the first fatal AE within two weeks of stopping treatment, then 623 patients died following an AE with an onset during or close to randomized treatment. There were 154 (10.0%), 139 (9.0%), 185 (11.9%) and 145 (9.4%) such patients in the placebo, SAL, FP, and FSC groups, respectively. The incidence of death in this analysis shows slightly less difference among the treatment groups than the on-treatment survival analysis (Appendix Section 1.2.2, pg 82). This is because there were slightly more patients in the FSC group with fatal AEs with onset in the two weeks after stopping therapy (30 patients compared to 21, 13, and 22 in the placebo, SAL, and FP groups, respectively. Of the AE-on-treatment-related deaths, 474 of the deaths were on-treatment, suggesting that 149 patients died more than two weeks after suffering an AE that was ultimately fatal. This happened to 36, 29, 44, and 40 of the patients in the placebo, SAL, FP, and FSC groups, respectively. AEs with onset more than 2 weeks after stopping treatment occurred in 85 (5.5%), 75 (4.9%), 69 (4.4%), and 57 (3.7%) of the placebo, SAL, FP, and FSC patients, respectively. (All of the above calculations are based on a rearrangement of the data in post-text Table 8.029, pg 4559 of the study report. This analysis is summarized in Table 9, pg 45, above. Note that Table 9 includes the two patients with AE that originated prior to study treatment.)

Three hundred eleven patients (92 [6%], 78 [5%], 77 [5%], and 64 [4%] in the placebo, SAL, FP, and FSC groups, respectively) died of an AE that started more than two weeks after stopping study medication. COPD was the only event recorded in >1% in any of the treatment groups: 92 (6%), 78 (5%), 77 (5%), 64 (4%) in the placebo, SAL, FP, and FSC groups, respectively.

Serious Adverse Events

SAEs (fatal and non-fatal) that started during treatment were reported in 2,563 patients: 627 (41%), 622 (40%), 655 (42%), 659 (43%) of the placebo, SAL, FP, and FSC patients, respectively (Table 50). This was equivalent of a rate of 430.8, 398.2, 437.1, and 412.2 events/1000 treatment-years, respectively. COPD was more common (167.5 events/1000 treatment-years) in the placebo patients than in those given active treatment: 145.6, 150.8, and 134.6 events/1000 treatment years in the SAL, FP, and FSC groups, respectively. Pneumonia was reported more frequently (events/1000 treatment-years) in the FP (41.8) and FSC (47.3) groups compared to placebo (23.5) and SAL (24.1) groups. (For further discussion of respiratory infectious AE see Section Events of Special Interest, pg 104). Non-specific chest pain was more frequent in the FP and FSC groups, and there was a high rate of cerebrovascular events in the FP group.

Table 50. Summary of Serious Adverse Events (Fatal and non-fatal) in Study SCO30003 (MedDRA preferred term)

Number (%) Patients Reporting Events [Rate per Thousand Treatment-years]	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	FSC 500/50 (N=1546)
COPD	339 (22) 167.5	307 (20) 145.6	318 (20) 150.8	298 (19) 134.6
Pneumonia	69 (4) 23.5	82 (5) 24.1	121 (8) 41.8	138 (9) 47.3
Respiratory failure	23 (1) 7.9	29 (2) 8.8	32 (2) 10.1	26 (2) 7.3
Myocardial infarction	20 (1) 6.7	27 (2) 7.6	19 (1) 5.6	20 (1) 5.9
Atrial fibrillation	20 (1) 6.7	23 (1) 6.5	15 (<1) 4.8	16 (1) 5.4
Lobar pneumonia	11 (<1) 4.0	9 (<1) 2.5	23 (1) 7.0	15 (<1) 4.3
Cardiac failure congestive	18 (1) 6.7	18 (1) 7.1	15 (<1) 5.6	17 (1) 5.9
Cardiac failure	15 (<1) 5.5	18 (1) 7.6	16 (1) 4.8	14 (<1) 3.8
Lung neoplasm malignant	12 (<1) 3.7	17 (1) 4.8	20 (1) 5.6	13 (<1) 3.2
Cerebrovascular accident	9 (<1) 2.7	8 (<1) 2.5	16 (1) 5.1	12 (<1) 3.2
Chest pain	8 (<1) 3.1	17 (1) 5.4	23 (1) 6.8	23 (1) 7.3
Pneumothorax	7 (<1) 3.1	10 (<1) 3.1	8 (<1) 2.5	16 (1) 4.6

To further investigate the cerebrovascular events, the applicant tabulated SAEs coded to the MedDRA HLT of "Central Nervous System Hemorrhages and Cerebrovascular Accidents." These events were reported in 19 (1%), 13 (<1%), 31 (2%), and 21 (1%) of the placebo, SAL, FP, and FSC patients, respectively. The respective rates/1000 treatment years were 6.1, 4.0, 9.3, and 5.7. Fatal events occurred in 2, 2, 13, and 4 of the placebo, SAL, FP, and FSC groups, respectively. The Applicants stated that a thorough review of the records "suggest that the findings are not consistent with a specific FP effect.

Reviewer: Vascular CNS events were not common and at these rates, random variation in the populations may explain the findings. However, this category of event is important because of the serious outcomes, especially in the FP group; 70.3, 81.2, 83.8, and 87.5% of the placebo, SAL, FP, and FSC groups, respectively. The percentage of the events that were fatal was 7.4, 12.5, 35.1, and 16.7%, respectively.

In the two-week post-treatment period, 206 patients (60, 40, 56, and 71 in the placebo, SAL, FP and FSC groups) reported a serious AE. COPD, pneumonia, respiratory failure, and cardiac arrest were the only SAEs reported in five or more patients in any treatment group and the incidence was roughly similar in the four treatment groups.

Adverse Events Leading to Withdrawal

Adverse events resulted in withdrawal of 1,310 patients (367 [24%], 315 [20%], 356 [23%], and 272 [18%] in the placebo, SAL, FP, and FSC groups, respectively. The only events that occurred at >1% were COPD, pneumonia, and respiratory failure (Table 51). COPD and respiratory failure were more common in the placebo group and pneumonia was more common in the FSC group.

Table 51. Adverse Events with an Onset During Active Treatment that Resulted in Withdrawal of at Least 1% of the Patients

Number (%) Patients Reporting Events [Rate per Thousand Treatment-years]	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	FSC 500/50 (N=1546)
COPD	169 (11) 51.6	144 (9) 40.8	114 (7) 32.1	81(5) 21.9
Pneumonia	17 (1) 5.2	21 (1) 5.1	23 (1) 5.3	26 (2) 7.0
Respiratory failure	10 (<1) 3.1	18 (1) 5.1	19 (1) 5.3	9 (<1) 2.4

Dysphonia and oral candidiasis were more common causes of withdrawal in the FP and FSC groups, however the incidence was <1%. Adverse events with onset during randomized treatment that were classified as vascular cerebrovascular events and that resulted in withdrawal of the patient were reported in 43 patients: 5 (<1%), 3 (<1%), 18 (1%), and 7 (<1%) in the placebo, SAL, FP, and FSC groups, respectively.

Other Adverse Events of Special Interest

Respiratory

Overall, respiratory events were reported in 82 or 83% of the patients in each treatment group during randomized treatment. The most frequent MedDRA preferred term was Chronic Obstructive Lung Disease and it was reported in 63, 60, 60, and 57% of the placebo, SAL, FP, and FSC patients, respectively (Table 53). Dyspnea was also more common in the placebo-treated patients (31.7 events/1000 treatment years) than in the other treatment groups (24.1, 23.3, and 18.1 events /1000 treatment-years in the placebo, SAL, FP, and FSC groups, respectively). On the other hand, events that could be related to infection were all increased in the FSC-treated patients. This includes Nasopharyngitis, Upper respiratory tract infection, Pneumonia, Bronchitis, Sinusitis, Cough, Oral candidiasis, Bronchitis acute, Candidiasis, and Oropharyngeal candidiasis. (Refer to Table 47 [pg 97] for rates). Influenza was reported in 5% of the FSC-treated patients compared to 4% of the placebo-treated patients, but the rate in the FSC group was actually lower (28.6 compared to 31.7 events/1000 treatment years in the placebo patients). The pattern of serious and fatal respiratory events was similar to the pattern for the common and non-serious events.

Combining similar preferred terms into MedDRA High Level Term (HLT) can result in groupings that show relationships between events and treatment when the number of events in each preferred term is small. The HLTs of Bronchospasm and obstruction, Breathing

abnormalities, and Respiratory failure were each infrequent in the FSC group compared to the placebo-treated patients (Table 52). On the other hand, as in the overall grouping, infectious processes were increased in the FSC group. Upper respiratory tract infections NEC, Lower respiratory tract infections NEC, Upper respiratory tract signs and symptoms NEC, Respiratory tract infections NEC, and Nasal congestion and inflammation were all increased in the FSC-treated patients. The rate of upper and lower respiratory tract infection in the FP- treated patients was similar to the rate in the FSC patients.

Table 52. Respiratory Adverse Events (MedDRA HLT) with an Onset During Randomized Treatment and Reported by at Least 1% of the Population)*

Number (%) Patients Reporting Events [Rate per Thousand Treatment-years]	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	FSC 500/50 (N=1546)
Any respiratory event	1280 (82) 1659.9	1267 (82) 1456.2	1269 (82) 1603.9	1278 (83) 1518.4
Bronchospasm and obstruction	979 (63) 928.9	941 (61) 766.1	935 (60) 781.7	885 (57) 672.2
Upper respiratory tract infection NEC	411 (27) 251.1	439 (28) 226.3	491 (32) 275.1	519 (34) 285.4
Lower respiratory tract infection NEC	291 (19) 146.4	309 (20) 140.8	367 (24) 185.7	432 (28) 195.4
Breathing abnormalities	137 (9) 57	121 (8) 47.0	118 (8) 43.6	104 (7) 35.4
Cough	111 (7) 42.7	105 (7) 40.2	125 (8) 55.1	138 (9) 54.6
Respiratory signs and symptoms	81 (5) 31.1	85 (6) 30.6	89 (6) 33.8	108 (7) 37.0
Viral upper respiratory infection	80 (5) 36.0	81 (5) 30.3	99 (6) 32.9	98 (6) 33.8
Respiratory failure	44 (3) 15.3	42 (3) 13.6	50 (3) 17.4	42 (3) 12.7
Respiratory tract infections NEC	39 (3) 15.3	44 (3) 21.0	32 (2) 13.8	48 (3) 18.6
Lower respiratory tract neoplasms	38 (2) 11.6	36 (2) 11.0	40 (3) 11.5	41 (3) 12.4
Nasal congestion and inflammation	34 (2) 11.6	34 (2) 14.2	39 (3) 15.2	48 (3) 14.6

* Only events that occurred in ≥3% of the patients are shown in this table. Taken from Study Report Table 92. pg 183, which is based on post-text Table 8.012.

Reviewer: In MedDRA respiratory infections are coded both as infectious processes and as respiratory diseases. The applicant has submitted two separate SAS transport files, one for "All AEs" and one for "Respiratory AEs". Post-text Table 8.008, derived from the All AE dataset, shows 4287 (69.3%) of the patients with respiratory AEs, listed by preferred term. Post-text Table 8.012 in the Study Report was taken from the Respiratory AE data sheet. It shows a respiratory event as occurring in 5094 (82.4%) of the patients. This discrepancy occurs because post-text Table 8.012 includes the pneumonia and bronchitis events that are listed under the Infections and infestations SOC in Table 8.008.

The pattern of serious respiratory events (MedDRA HLT) was similar to the pattern for the common and non-serious events. The rates of Bronchospasm and obstruction were lower (events/1000 treatment-years) in the FSC-treated patients (135.4) compared to the placebo (168.4), SAL (146.7) and FP (151.3) patients, while the rates of Lower respiratory tract infection NEC were lower in the placebo patients (35.1, 32.9, 56.3, and 61.6 events/1000 treatment-years in the placebo, SAL, FP, and FSC groups, respectively) (Table 53).

Table 53. Serious Respiratory Adverse events by MedDRA HLT

Rate per Thousand Treatment-years	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	FSC 500/50 (N=1546)
Any Respiratory Event	261.4	230.5	267.5	257.6
Bronchospasm and obstruction	168.4	146.7	151.3	135.4
Lower respiratory tract infections, NEC	35.1	32.9	56.3	61.6
Respiratory failure	13.4	10.8	14.1	10.8
Lower respiratory tract neoplasms	9.8	9.1	10.4	7.6
Respiratory signs and symptoms, NEC	4.6	6.5	7.3	7.8
Pneumothorax and pleural effusion	3.7	4.2	2.8	6.2

Lower Respiratory Tract Infections

In addition to MedDRA groupings, an analysis was preformed on the ad hoc grouping of "Lower respiratory tract infection of pneumonia or bronchitis". The MedDRA preferred terms that were included in this event-group are listed in Table 54. There were 304 (20%), 322 (21%), 380 (24%), and 446 (29%) events in the placebo, SAL, FP, and FSC groups respectively. Adjusting for time on treatment resulted in rates of 151.9, 147.0, 192.1, and 204.6 events/1000 treatment-years, respectively.

Table 54. MedDRA Preferred Terms for the Components of the "Lower Respiratory Tract Infections of Pneumonias and Bronchitis" Adverse Events of Special Interest †

	SCO30003			
Number of patients reporting at least one event	**Placebo N=1544**	**SAL N=1542**	**FP N=1552**	**FSC N=1546**
Any event	304	322	380	446
Pneumonia*	112	133	185	207
Bronchitis	91	97	102	121
Bronchitis acute	48	48	59	73
Lower Respiratory Tract infection	46	46	43	53
Lobar pneumonia*	14	12	28	19
Bronchopneumonia*	6	10	10	13
Lung infection*	6	5	4	8
Pulmonary tuberculosis	6	4	6	5
Infective exacerbation of COPD	1	7	2	3
Superinfection lung*	3	3	2	5
Tuberculosis	4		2	7
Bronchiectasis	1	1	2	4
Bronchitis bacterial	1	1	3	2
Bronchitis viral	1	1	2	3
Pneumonitis*			1	3
Pneumonia bacterial*	1	1		1

Pneumonia primary atypical*			1	2
Respiratory moniliasis			1	2
Bronchopulmonary aspergillosis			2	
Cryptogenic organizing pneumonia		1		1
Pneumonia staphylococcal*			1	1
Bronchopneumopathy*				1
Bronchopulmonary aspergillosis allergic			1	1
Lung infection pseudomonal*				
Obliterative bronchiolitis		1		
Pneumocystis jiroveci pneumonia*				1
Pneumonia chlamydial*	1			
Pneumonia necrotizing*				1
Pneumonia streptococcal*				1

† Reproduced from post-test Table 8.052 (pg 4734 of study report) *Events included in the analysis of pneumonias

The hazard ratio (95% CI) for time-to first lower respiratory tract infections of pneumonias and bronchitis was 1.375 (1.189, 1.591) comparing FSC to placebo (Table 55). The Hazard ratio (95% CI) comparing SAL and FP to placebo were 0.995 (0.851, 1.164) and 1.190 (1.024, 1.384), respectively.

Table 55. Log-Rank Analysis of Time to First Lower Respiratory Tract Infection of Pneumonia or Bronchitis

	Placebo (N=1524)	**SAL 50 (N=1521)**	**FP 500 (N=1534)**	**FSC 500/50 (N=1533)**
Number of events (%)	304 (20)	322 (21)	380 (24)	446 (29)
Probability of event by 156 weeks (%)	25.8	25.5	30.3	34.4
95% CI	23.3, 28.4	23.0, 27.9	27.7, 32.9	31.8, 37.1
Active treatment minus placebo (SE)				
Hazard ratio		0.995	1.190	1.375
95% CI		0.851, 1.164	1.024, 1.384	1.189, 1.591
FSC vs components (SE)				
Hazard ratio		1.384	1.154	
95% CI		1.199, 1.597	1.007, 1.324	

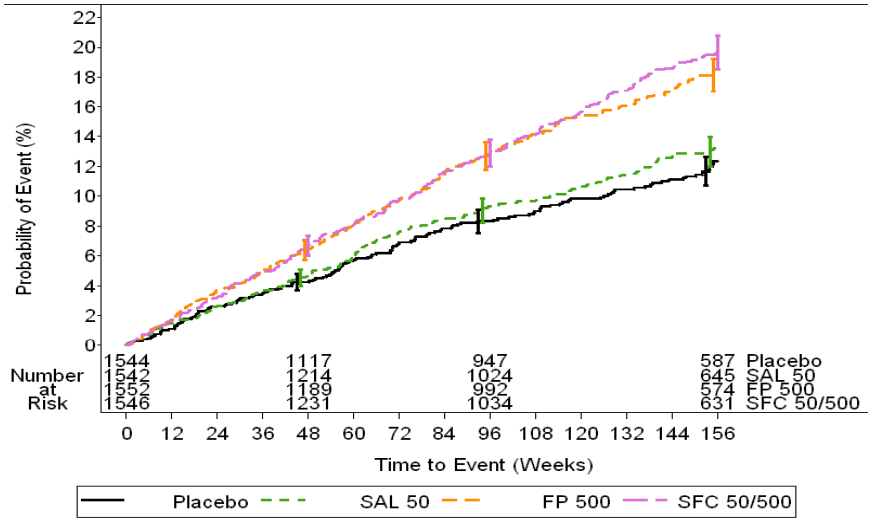
The Applicant contended that all of the difference between FSC and placebo in the lower respiratory tract infections was due to differences in the incidence of pneumonia. For this analysis they grouped the MedDRA preferred terms listed with an asterisk in Table 56. These physician diagnosed pneumonias were reported to have occurred in 139 (9%), 162 (11%), 224 (14%), and 248 (16%) of the placebo, SAL, FP, and FSC patients, respectively. When adjusted for time on treatment the respective rates were 51.9, 51.5, 84.4, 87.6 per 1000 treatment-years. The log-rank analysis of time to first pneumonia showed a hazard ratio (95% CI) of 1.639 (1.33, 2.01) comparing FSC to placebo. The Hazard ratio (95% CI) comparing SAL and FP to placebo were 1.088 (0.867, 1.365) and 1.533 (1.240, 1.894), respectively (Table 56). The results are

Table 56. Log-Rank Analysis of Time to First Pneumonia

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	FSC 500/50 (N=1533)
Number of events (%)	139 (9)	162 (11)	224 (14)	248 (16)
Probability of event by 156 weeks (%)	12.3	13.3	18.3	19.6
95% CI	10.4, 14.3	11.4, 15.2	16.1, 20.4	17.4, 21.9
Active treatment minus placebo (SE)				
Hazard ratio		1.088	1.533	1.639
95% CI		0.867, 1.365	1.240, 1.894	1.331, 2.017
FSC vs. components (SE)				
Hazard ratio		1.508	1.068	
95% CI		1.237, 1.838	0.891, 1.280	

presented graphically in Figure 7.

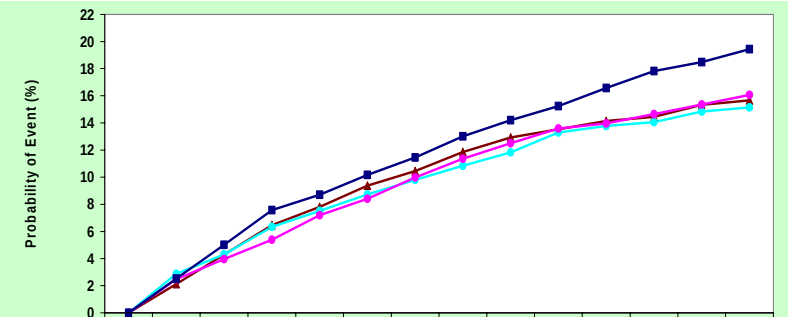
Figure 7. Time to First Pneumonia Event with Onset During Randomized Treatment*



* Study Report Figure 15; SFC=Advair

Reviewer: To explore the possibility that non-pneumonia infectious events were important, the FDA statistical reviewer repeated the time-to event analysis in two ways: 1) using the above classification of disease, the time to all respiratory infections excluding pneumonia was calculated, as was 2) the time to the onset of bronchitis, including acute, bacterial, and viral bronchitis. For the analysis of all events excluding pneumonia the three year probability was 16.0, 15.0, 16.0, and 19% for the placebo, SAL, FP, and FSC groups, respectively. The Hazard ratio (95% CI) comparing FSC to placebo was 1.23 (1.02, 1.23). The survival curve for onset of non-pneumonia lower respiratory tract infection is shown in Figure 8.

Figure 8. Non-pneumonia Lower Respiratory Adverse Events



	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo	0.00	2.13	4.30	6.47	7.81	9.38	10.46	11.86	12.92	13.52	14.14	14.46	15.33	15.66
SAL 50	0.00	2.87	4.32	6.34	7.51	8.72	9.81	10.84	11.82	13.29	13.77	14.06	14.84	15.14
FP 500	0.00	2.48	3.96	5.39	7.20	8.40	9.99	11.36	12.50	13.59	13.96	14.65	15.35	16.07
SFC 50/500	0.00	2.52	5.02	7.57	8.70	10.17	11.45	13.02	14.20	15.24	16.56	17.83	18.48	19.44

Treatment Days

In the analysis of bronchitis events the calculated three-year probability was 11, 12, 12, and 14%. The Hazard ratio (95% CI) comparing FSC to placebo was 1.24 (0.99, 1.55). Therefore, the incidence of non-pneumonia lower respiratory infectious events was also elevated in the patients treated with FSC.

The number of upper respiratory tract infections (excluding all preferred terms that referred to candidiasis and dysphonia) was also increased in the fluticasone-treated patients; however, statistical analysis was not performed on this outcome. There were 0.58, 0.58, 0.66, and 0.70 events/patient reported for the placebo, SAL, FP, and FSC groups respectively.

Serious pneumonia events were also increased in the FSC-treated patients. Pneumonia SAEs were reported in 86 (6%), 99 (6%), 150 (10%), and 157 (10%) of the placebo, SAL, FP, and FSC patients, respectively. The Hazard ratio (95% CI) for serious pneumonia comparing FSC to placebo was 1.645 (1.265, 2.140) and the ratios for SAL and FP were 1.068 (0.800, 1.426) and 1.635 (1.254, 2.131). Fatal pneumonias occurred in 10, 11, 15, and 12 patients in the placebo, SAL, FP, and FSC patients, respectively.

There was no protocol-driven definition of pneumonia, however, cases with a positive chest X-ray, were also more common in the FP and FSC-treated patients. Pneumonia was more common in older patients, those with poorer pulmonary function, and those with a low BMI.

Reviewer: Pneumonia was also reported more frequently in the United States than in Eastern Europe. Taking the designation Pneum = "Y" from the respiratory AE datasheet the incidence of pneumonia was 19.8, 18.8, 10.8, 16.7, and 12.7% in the US, Asia, E Europe, W Europe, and Other, respectively.

To assess the impact of lower respiratory infections, COPD exacerbations that were treated with antibiotics were combined with the "Lower respiratory tract infections of pneumonias and bronchitis" that is summarized in Table 54 (pg 105). Using this categorization, there were 951 (62%), 958 (62%), 991 (64%), and 1009 (65%) patients in the placebo SAL, FP and FSC groups

that had lower respiratory tract infections that were treated with antibiotics. When adjusted for time on treatment, the rates were 878.0, 737.8, 881.0, and 812.7 events/1000 treatment-years, respectively. The Applicant concluded from this analysis that lower respiratory tract infection excluding pneumonia was not significantly impacted by treatment with FSC.

Reviewer: The analysis combining all lower respiratory tract infections AND all exacerbations treated with antibiotics dilutes the effect of infection because it includes COPD exacerbations treated with both corticosteroids and antibiotics. Since many severe exacerbations are treated with both drug classes even if there is not good evidence of infection, this is not an accurate way to assess the impact of the increased incidence of infections. In an independent analysis of the rate of exacerbations treated with antibiotics alone, it was seen that the rate in the FSC-treated patients was 20% higher than the placebo group and 22% higher than in the SAL group. (See FDA statistical review for details.) This suggests that the increased incidence of infection is clinically relevant.

Bone Disorders

Bone disorders were reported in 357 patients: 77 (5%), 85 (6%), 90 (6%), and 105 (7%) of the placebo, SAL, FP, and FSC groups respectively. Adjustment for time on treatment resulted in rates of 27.5, 28.9, 29.3, and 32.2 events/1000 treatment-years, respectively. The Hazard ratio (95% CI) for SAL, FP and FSC compared to placebo were 1.024 (0.752, 1.393), 1.083 (0.799, 1.468) and 1.218 (0.908, 1.634), respectively.

Bone fractures were reported in 261 patients: 57 (3.7%), 61 (4.0%), 65 (4.2%), 78 (5.0%) of the placebo, SAL, FP, and FSC patients, respectively (Table 57). When corrected for time on therapy the respective rates were 18.6, 20.4, 20.3, and 22.4 events/1000 treatment-years. The rates differed for traumatic and non-traumatic fractures. The incidence of non-traumatic fractures was actually lower in the FSC group (5.9 / 1000 treatment-years) compared with 6.1, 9.6, and 6.5 / 1000 treatment years in the placebo, SAL and FP groups.

Table 57. Incidence of Fractures Reported as Adverse Events

	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	FSC 500/50 (N=1546)
All fractures	57 (3.7)	61 (4.0)	65 (4.2)	78 (5.0)
Rate per 1000 Treatment-yrs	18.6	20.4	20.3	22.4
Non Traumatic fractures	20 (1.3)	29 (1.9)	21 (1.4)	21 (1.4)
Rate per 1000 Treatment-yrs	6.1	9.6	6.5	5.9
Traumatic fractures	39 (2.5)	37 (2.4)	45 (2.9)	58 (3.8)

The Kaplan Meier estimate of probability of fracture at 3 years was 5.1, 5.1, 5.4, and 6.3% in the placebo, SAL, FP, and FSC groups, respectively. The hazard ratio (95% CI) for fracture comparing active treatment to placebo was 0.995 (0.693, 1.427), 1.056 (0.740, 1.507), and 1.223 (0.869, 1.720) for SAL, FP, and FSC, respectively. The Kaplan Meier estimate of probability of non-traumatic fracture at 3 years was 1.8, 2.5, 1.7, and 1.7% in the placebo, SAL, FP, and FSC groups, respectively. The hazard ratio (95% CI) for fracture comparing active treatment to placebo was 1.353 (0.766, 2.393), 0.696 (0.525, 1.788), and 0.931 (0.505, 1.718) for SAL, FP, and FSC, respectively. The Kaplan Meier estimate of probability of traumatic fracture at 3 years was 3.5, 3.1, 3.7, and 4.7% in the placebo, SAL, FP, and FSC groups, respectively. The hazard

ratio (95% CI) for fracture comparing active treatment to placebo was 0.878 (0.560, 1.378), 1.068 (0.696, 1.640), and 1.328 (0.855, 1.993) for SAL, FP, and FSC, respectively.

Treatment with drugs that could increase bone mineral density was distributed evenly across the treatment groups (14, 14, 14, and 15% of the patients in the placebo, SAL, FP and FSC treatment groups, respectively.

Eye Disorders

Some form of eye disorder was seen in 2 to 4% of the population (Table 58). When adjusted for time on treatment, the rate for any event was slightly higher in the active treatment than in the placebo-treated patients: 13.7, 17.8, 15.8, and 18.6 events/1000 treatment years in the placebo, SAL, FP, and FSC groups, respectively. The rates for cataract were slightly elevated in the SAL and FSC groups whereas glaucoma was slightly more frequent in all of the active treatment groups. The Kaplan Meier probability of an eye event at 3 years was 3.6, 4.3, 4.1, and 5.2% in the placebo, SAL, FP, and FSC groups, respectively. The hazard ratio for developing an eye event comparing FSC to placebo was 1.462 (95% CI=0.978, 2.187). The hazard ratios (95% CI) for SAL and FP were 1.228 (0.806, 1.873) and 1.156 (0.755, 1.769, respectively).

Table 58. Eye Adverse Events

Number (%) Patients Reporting Events [Rate per Thousand Treatment-years]	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	FSC 500/50 (N=1546)
Any event	38 (2) 13.7	50 (3) 17.8	48 (3) 15.8	63(4) 18.6
Cataract	27 (2) /9.2	37 (2)/12.5	29 (2)/8.4	48 (3)/13.8
Cataract operation	6 (<1)/1.8	6 (<1)	5 (<1) /2.3	5 (<1)/1.4
Cataract nuclear	1 (<1)/0.3	0	1 (<1)/0.3	0
Cataract subcapsular	0	0	1 (<1) /0.3	0
Total cataract	34 (2.2)	43 (2.8)	36 (2.3)	53 (3.4)
Glaucoma	4 (<1)/1.2	8 (<1)/2.3	12 (<1)/3.9	10(<1)/2.7
IOP Increased	2 (<1)/0.6	3 (<1)/0.8	1 (<1)/0.3	0
Ocular hypertension	2 (<1)/0.6	0	0	1(<1)/0.3
Angle closure glaucoma	0	0	1 (<1)/0.3	1(<1)/0.3
Borderline glaucoma	0	0	0	1(<1)/0.3
Total glaucoma	6 (0.4)	11(0.7)	14 (0.9)	13 (0.8)

HPA-Axis Disorders

See Pharmacodynamic discussion on page 94. In addition, two cases of Cushing's syndrome were reported in the placebo group and one case each of adrenal insufficiency and steroid withdrawal syndrome in the FP group.

Pregnancies

As expected because of the mean age of the study population, no patient became pregnant during the study.

Corticosteroid Treatment

Throughout the three-year trial corticosteroid use was highest in the placebo patients (Table 60). Eleven percent of the placebo patients took ICS during randomized treatment and this increased

to 43% during LTFU. Fifty-two percent of the placebo patients took systemic corticosteroids during the randomized treatment period and this dropped to 22% in the LTFU. In the FSC group, 8 % took additional ICS during randomized treatment and this increased to 40% in the long-term follow-up period. Forty-seven percent of the FSC patients took systemic corticosteroids during the active treatment period and this decreased to 15% during follow-up.

Table 59. Use of Corticosteroids During 3 Years of the Study

		Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	FSC 500/50 (N=1546)
ICS	**During, n (%)/** **No. Courses** **Duration (SD)***	161 (11) 211 54.8 (114.0)	133 (9) 166 43.0 (108.6)	128 (8) 155 46.1 (81.0)	115 (8) 142 42.7 (93.3)
	LTFU, n (%)**	660 (43)	655 (43)	559 (39)	613 (40)
Systemic	**During, n (%)** **No. courses** **Duration (SD)***	793 (52) 2353 41.1 (66.8)	747 (49) / 2117 38.7 (66.3)	724 (47) 1956 36.9 (61.8)	713 (47%) 1788 35.0 (55.3)
	LTFU, n (%)**	340 (22)	281 (18)	260 (17)	237 (15)

* Mean cumulative days of treatment with corticosteroid

** LTFU = Long term follow-up. From two weeks after termination of randomized treatment to 156 weeks following initiation of therapy

Laboratory Results

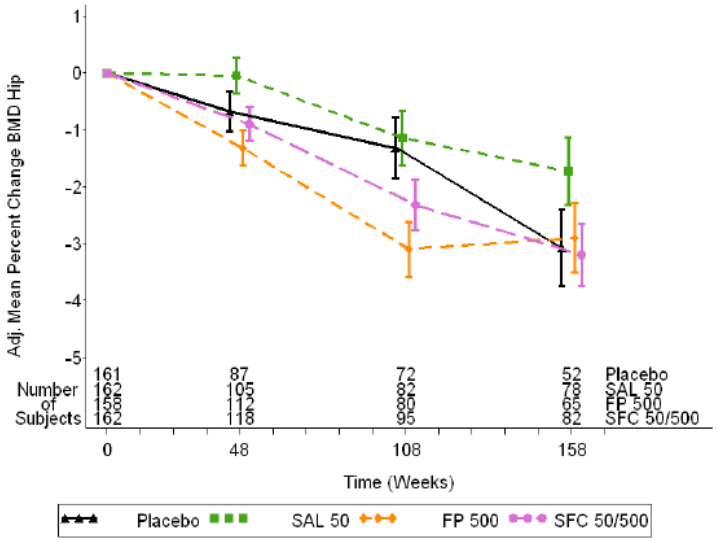
Routine laboratory examinations were not performed.

Bone Mineral Density

Bone mineral density was measured with dual energy x-ray absorptiometry (DEXA) in 658 (47.4%) of the patients enrolled in the United States: follow-up was complete in 277 (52, 78, 65, and 82 in the placebo, SAL, FP, and FSC groups, respectively). Measurements were made of the total hip and the L1-L4 spine at baseline and after 48, 108, and 156 weeks. In the Skeletal Safety Population slightly more placebo than active treatment patients took medications that could improve BMD at some time prior to or during the trial: 74 (45%), 68 (41%), 68 (42%), and 64 (39%) of the placebo, SAL, FP, and FSC patients, respectively. However, the increased use of BMD -promoting medication started prior to enrollment in the placebo patients and starting BMD therapy during the trial was actually less common in the placebo patient (16%) than in the other treatment groups (20, 21, and 22% in the placebo, SAL, FP, and FSC groups. This may be related to the fact that more of the placebo patients were taking inhaled corticosteroids 73 (45%) compared to the active treatment groups (64 [39%], 56 [34%], and 56 [34%] of the SAL, FP, and FSC patients, respectively).

Baseline values for the hip BMD were higher in the SAL (0.893 gm/cm^2) and the FSC (0.905 g/cm^2) than in the placebo (0.854 g/cm^2) and FP (0.853 g/cm^2) groups, and there was a gradual decline in BMD over the course of the study in each treatment group. At week 158 the raw mean percent change from baseline was -3.2, -1.4, -2.4, and -2.9% in the placebo, SAL, FP, and FSC groups, respectively. These rates underestimate the degree of loss of mineral because patients with low BMD at baseline dropped out earlier than patients with high BMD. Figure 9 shows the fall in BMD adjusted for smoking status, age, sex, BMI, BMD therapy, visit, and log baseline BMD.

Figure 9. Adjusted Mean Percent Change in BMD at the Total Hip*



* Study Report Figure 18; SFC=Advair

Reviewer: Because of the high differential drop-out the FDA statistical reviewer repeated the analysis including only the patients who had baseline measurement and who completed the study. In this analysis the change from baseline of the raw mean values was -2.71, -1.06, -2.35, and -2.49 in the placebo, SAL, FP, and FSC-treated patients, respectively, and the difference between FSC and placebo was -0.24. As in the primary analysis, the patients treated with SAL lost less bone mineral.

A repeated measures analysis of percent change in BMD at the total hip showed no difference between any active treatment and placebo. The absolute change in BMD showed similar changes. The active vs. placebo ratio (95% CI) for percent change in BMD was 1.014 (0.996, 1.032), 1.002 (0.984, 1.020), and 0.999 (0.981, 1.017) for the SAL, FP, and FSC treatment groups, respectively. A confirmatory analysis was performed using only patients who had not received a BMD active drug and the results were similar. Analyses of changes at each visit were similar for all of the analytic techniques. As suggested in Figure 9, BMD at 108 weeks was relatively low in the FP group. However, the values were very similar to those in the placebo and FSC groups by 158 weeks.

Results from patients treated with corticosteroids were analyzed by combining the FP and FSC groups (N=328) and comparing them to the combined placebo and SAL groups (N=330). Overall changes were small, but favored the non-steroid containing regimens (Table 60).

Table 60. Change in Hip BMD Comparing Patients Treated with Corticosteroids to Those Treated with Placebo or Salmeterol

	Steroid-non-steroid	95% CI
Percent change from Baseline*		
Week 158 (N = 130/147)	-0.82	-2.03, 0.39
Week 108 (N= 154/175)	-1.50	-2.45, -0.54
Week 48 (N=192/230)	-0.77	-1.40, -0.14
Overall (N=209/250)	-1.03	-1.83, -0.23

Absolute change from baseline		
Week 158	-0.0067	-0.0017, 0.003
Week 108	-0.0118	-0.020, -0.004
Week 48	-0.0056	-0.011, -0.000
Overall	-0.0080	-0.015, -0.002

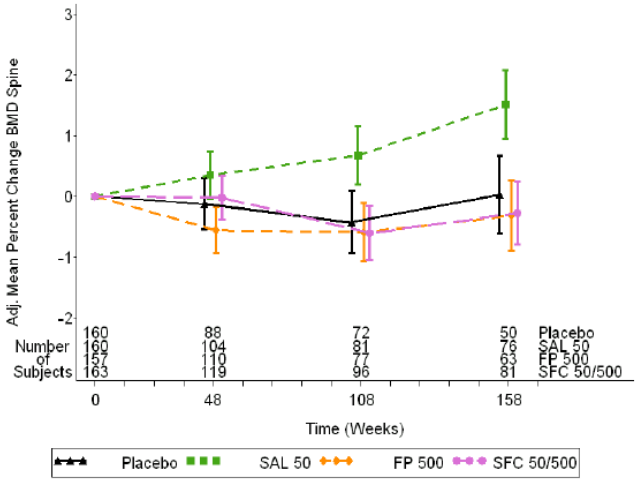
* N = # non-steroid / #steroid

Results using 16-week windows for analysis and those that looked at absolute changes were confirmatory.

Reviewer: The Skeletal Survey Population had a higher rate of withdrawal than the study as a whole, and the final study population was small compared to the parent study. This is doubly unfortunate because the baseline values for BMD varied among the treatment groups and withdrawal was correlated with baseline BMD. The BMD loss was relatively high in the placebo group. There were more females in the placebo group in this subset, but the females in the placebo group also had a more rapid loss of BMD than the females in the other treatment groups (see subset analysis below. Patients with a T-score of < -1.5 at baseline or < -2.0 at follow-up were supposed to be referred for "consultation". At baseline 37% of the patients had a low score at the hip and 38% has a low score at the spine. More patients in the placebo group had abnormally low scores at the hip 69 (43%) than did the patients in the active treatment groups (55 [34%], 62 [39%], and 53 [33%] of the SAL, FP, and FSC-treated patients, respectively). It is possible that knowledge of the low BMD measurement influenced the investigator's judgments about withdrawal of the patients from the study.

Similar to what was found for the hip, the baseline values for the lumbar spine BMD were higher in the SAL (1.042 gm/cm^2) and the FSC (1.034 g/cm^2) than in the placebo (1.003 g/cm^2) and FP (0.991 g/cm^2) groups. Changes over time were very small in the placebo, FP and FSC groups. BMD increased in the SAL group (Figure 10). At Week 158 (Visit 16), the raw mean percent change from baseline was 0.0, 1.4, -0.2, and -0.5% in the placebo, SAL, FP, and FSC groups, respectively. Baseline BMD of the lumbar spine was not different in those who completed therapy and those who withdrew.

Figure 10. Lumbar Spine BMD*



* Study Report Figure 19; SFC=Advair

The active vs. placebo ratio (95% CI) for percent change in lumbar spine BMD was 1.0145 (0.998, 1.032), 0.997 (0.980, 1.014), and 0.997 (0.981, 1.013) for the SAL, FP, and FSC treatment groups, respectively. The ratio comparing FSC to SAL was 0.982 (0.968, 0.997). Analyses of individual visits, of the absolute change in BMD and of the change after excluding patients who had received BMD active medications were all supportive.

Results from patients treated with corticosteroids were analyzed by combining the FP and FSC groups (N=328) and comparing them to the combined placebo and SAL groups (N=330). Overall changes were small, but favored the non-steroid containing regimens (Table 61).

Table 61. Change in Lumbar Spine BMD Score Comparing Patients Treated with Corticosteroids to Those Treated with Placebo or Salmeterol

	Steroid-non-steroid	95% CI
Percent change from Baseline*		
Week 158 (N=126/144)	-1.16	-2.27, -0.04
Week 108 (N=153/173)	-0.77	-1.70, 0.17
Week 48 (N=192/229)	-0.41	-1.17, 0.35
Overall	-0.78	-1.57, 0.01
Absolute change from baseline		
Week 158	-0.014	-0.025, -0.002
Week 108	-0.010	-0.019, -0.000
Week 48	-0.006	-0.014, -0.002
Overall	-0.010	-0.018, -0.002

* N = # non-steroid / #steroid

Subgroup Analysis

BMD loss was greater in patients 65 years or older compared to those younger than 65 in all of the treatment groups other than SAL. Bone loss was greater in females in the placebo and FSC groups than in the SAL and FP groups, but females in the FP and SAL groups had less bone loss. In the males, the loss was greatest in the FP group followed by the patients in the FSC and placebo groups. Of note, females made up 50% the placebo group compared to 34% of the FSC group (Table 62).

Table 62. Summary of Percent Change in Hip BMD by Subgroup.

	Placebo (N=164)	SAL 50 (N=166)	FP 500 (N=163)	FSC 500/50 (N=165)
<65 years of age, n	71	77	64	76
Mean change at week 158	-2.6	-2.3	-1.1	-1.5
>=65 years of age, n	93	89	99	89
Mean change at week 158	-3.7	-0.6	-1.1	-4.4
Female, n	78	67	74	57
Mean change at week 158	-4.3	-1.1	-1.9	-3.9
Male, n	86	99	89	108
Mean change at week 158	-2.2	-1.5	-2.9	-2.4

The Applicant commented on the apparent large fall in hip BMD in patients with a BMI <20 (-7.1%) and in those with a baseline BMD <0.72 (-8.2%). However, these subgroups contain only

20 and 21 patients each, making the reliability of the estimate suspect. There was no effect of smoking status or baseline FEV_1 on BMD.

Subgroup differences in the lumbar spine BMD were small and inconsistent.

Ophthalmic examination

Cataracts were present prior to randomization >60% of the patients: 105 (64%), 118 (71%), 105 (64%), and 101 (61%) of the placebo, SAL, FP, and FSC groups respectively. This left 188 patients without cataracts at baseline that could be evaluated. The number of patients developing cataracts/number without cataracts at baseline (%) was 10/47 (21%), 6/41 (15%), 8/47 (17%), and 14/53 (26%) in the placebo, SAL, FP, and FSC patients respectively. The respective rates were 108.3, 64.9, 72.0, and 94.1 events / 1000 treatment-years, respectively.

The incidence of glaucoma was low at baseline and during the course of the study. Glaucoma was present in 9 (5%), 9 (5%), 8 (5%), and 14 (8%) of the placebo, SAL, FP, and FSC patients at baseline, respectively. Adjusting for time on treatment it developed at a rate of 7.4, 0.0, 19.7 and 8.6 events/1000 treatment-years, respectively.

1.3. Summary and Discussion

In this randomized, placebo-controlled mortality trial, 6,112 patients were treated with placebo, SAL, FP, or FSC for up to 3 years. Approximately 60% of the patients continued on study medication throughout the 3 years of follow-up with more placebo patients withdrawing early in the course. Even if the patients withdrew from study medication, their vital status was ascertained every 12 weeks until death or completion of a three-year follow-up. All deaths were reviewed by the Clinical Endpoints Committee and the cause of death and relationship to COPD was determined. Patients were recruited world-wide and the analysis was adjusted for geographic region as follows: United States, Asia/Pacific, Eastern Europe, Western Europe, and Other.

At baseline the patients had a mean age of 65 years, 82% were white, and 75% were male. They had moderate to severe pulmonary dysfunction with a mean pre bronchodilator FEV_1 of 1100 mL and a mean FEV_1 % predicted of 41%. The duration of COPD was <10 years in 65% of the patients and 57% were former smokers. Fifty-two percent had had a COPD exacerbation in the 12 months prior to enrollment, and 45 to 51% had taken ICS in the 12 months prior to enrollment.

The all-cause mortality at 3 years was 15.2, 13.5, 16.0, and 12.6% in the placebo, SAL, FP, and FSC-treated patients, respectively. The difference between placebo and FSC was 2.6% or 0.87% per year. The Hazard ratio comparing FSC to placebo was 0.82 (95% CI=0.677, 0.993). This difference was significant at the 0.041 level before adjusting for the interim analyses. After correction, the p-value was 0.052. The difference in all cause mortality comparing FSC to placebo in the US population was 1.6%. This is compared to a difference of 4.0% and 3.6% in

Eastern and the "Other" region, respectively. Sub-group analysis showed than only patients with pulmonary function FEV_1 >40% predicted and patients in the age groups <65 years of age responded to FSC substantially better than to placebo. In addition, it was noted that removal of just a few patients who had been enrolled at sites with an unusually good response to FSC resulted in a substantial change in the hazard ratio and significance level of the difference between FSC and placebo in all-cause mortality.

Approximately 40% of the patients died of a COPD-related condition. The mortality from COPD was 6.0, 6.1, 6.9, and 4.7% for the placebo, SAL, FP, and FSC-treated patients, respectively. The hazard ratio comparing FSC to placebo was 0.776 (95% CI=0.570, 1.057) and the hazard ratio comparing FSC to SAL and FP was 0.776 (95% CI 0.563, 1.042) and 0.670 (0.497, 0.904), respectively. The survival curves for COPD mortality overlapped for more than 2 years. Only during the last 9 months of the study did FP and SAL mortality diverge from the placebo and FSC mortality, and it was only in the last 6 months that the placebo mortality increased. There were minor differences in the patients who died at the end of the treatment period compared to those who died earlier, but the numbers were too small to draw firm conclusions.

Moderate and severe exacerbations were reduced in all of the treatment groups. The modeled event rate was 1.13, 0.97, 0.93, and 0.85 exacerbations per year in the placebo, SAL, FP, and FSC groups, respectively. The hazard ratios compared to placebo were 0.858, 0.823, and 0.749 in the SAL, FP, and FSC groups, respectively. All of these comparisons were statistically significant at the $p<0.001$ level and the rate in the FSC groups was lower than the rates in the SAL and FP groups. The rate of severe exacerbations was decreased in the SAL and FSC groups. However, the hazard ratio comparing FSC to placebo was higher that the hazard ratio comparing SAL to placebo. The hazard rate for the comparison of FSC to SAL was 1.022 (95% CI=0.870, 1.200).

The inference to be drawn about the effectiveness of FSC in the reduction of exacerbations is less precise than it might have been due to the imprecise definition of an exacerbation. They were defined only by treatment and a severe exacerbation was defined as an exacerbation that required hospitalization. Treatment and hospitalization rates can be influenced by local patterns of care and socio-economic relationships. Given the multi-national nature of this study, local differences in care were not unexpected. Exacerbations were reported infrequently in Eastern Europe and relatively frequently in the United states, Western Europe and the Other region. The differences between placebo and FSC were greatest in the Other region and Western Europe and lowest in Eastern Europe.

Results of spirometric testing showed an improvement in post-bronchodilator FEV_1 at week 24 and then a gradual decline over the remainder of the study in all of the treatment groups. Using a repeated measures analysis, pulmonary function was maintained at a higher level in all of the active treatment groups than in the placebo-treated patient. The SGRQ declined over the first 24 weeks and then gradually increased in all of the treatment groups. Active treatment showed a statistical superiority over placebo treatment, however, in no treatment group and in none of the domains was the improvement 4 points, which is generally considered the minimal important clinical difference.

Adverse events occurred with similar frequency in all of the treatment groups if COPD exacerbations (which have already been quantitated in the efficacy analysis) are included as adverse events. If COPD exacerbations are excluded, it is clear that respiratory infections, both upper and lower respiratory tract, are increased in the groups treated with fluticasone. The Kaplan-Meier probability of pneumonia was 25.8, 25.5, 20.3, and 34.4% in the placebo, SAL, FP, and FSC patients, respectively. Although, not provided by the Applicant, it can be shown that the COPD exacerbations treated with antibiotics alone were also increased in the FSC group. Unscheduled health care visits occurred more frequently in the placebo-treated patients, but ICU admissions occurred with the same frequency in all of the treatment groups and the ICU stay was longest in the FSC group. There were no remarkable changes in the ophthalmic examination and the changes in BMD were small. However, the loss to follow-up was relatively high and may have been influenced by the testing provided. Because patients with low BMD were advised to seek consultation for the condition, this might have influenced subsequent decisions about withdrawal from the study.

In summary, there was a statistically equivocal increase in all-cause mortality that at best increased the 90% survival by 4 months. The difference between placebo and FSC treatment was less in the United States population. There were too few COPD-related deaths for robust statistical inference. Moderate exacerbations were decreased by all the active treatments, but severe exacerbations were improved by only SAL and FSC. In addition, the severe exacerbation rate appeared to be decreased more in the SAL group, and some indices of health care utilization, especially the time in the ICU favored treatment with SAL. Pulmonary function was better maintained during treatment with FSC than in any of the other treatment groups, but, infections adverse events were clearly increased in patients treated with FSC.

2 STUDY # SFCB3024

A multicenter, randomized, double-blind parallel group, placebo-controlled study to compare the efficacy and safety of the fluticasone/salmeterol combination product at a strength of 500/50 mcg bd with salmeterol 50 mcg bd alone and fluticasone 500 mcg bd alone, delivered via the DISKUS™ /ACCUHALER™ in the treatment of patients with chronic obstructive pulmonary disease (COPD) for 12 months.

2.1 Protocol

2.1.1 Administrative

Dates: August 20, 1998 to December 12, 2000

Centers: 196 in 25 countries excluding the US. There were 14 in Western Europe, 7 in Eastern Europe, and 4 in other areas.

2.1.2 Objective/Rationale

The primary objective of this study was to demonstrate a significant reduction in all-cause mortality in COPD patients treated with fluticasone/salmeterol propionate 500/50mcg (FSC 500/50) compared with placebo, when added to usual COPD therapy.

2.1.3 Study Design

This was a multicenter, randomized, double-blind placebo-controlled parallel group study in patients with poorly reversible COPD. During a 2-week run-in period, patients took only salbutamol (Ventolin) for symptomatic relief. At the end of the run-in, eligible patients were randomized to receive fluticasone/salmeterol 500/50 mcg BID (FSC), salmeterol 50 mcg BID (SAL), fluticasone 50 mcg BID (FP) or placebo for 52 weeks. Follow-up visits occurred at 2, 4, 8, 16, 24, 32, 40, and 52 weeks. The primary efficacy outcome measure was pre-dose FEV_1 comparing FSC to placebo. The Secondary efficacy outcomes were the number of moderate or severe COPD exacerbations and quality of life as determined by the Saint George's Respiratory Questionnaire.

2.1.4 Study Population

2.1.4.1 Inclusion Criteria

1. Male or female, aged 40-79 years inclusive.
2. An established clinical history of COPD (As per the European Respiratory Society (ERS) Consensus Statement which defines COPD as a disorder characterized by decreased maximum expiratory flow and slow forced emptying of the lungs, which is slowly progressive, mostly irreversible, and does not change markedly over several months).

3. Patients who had coughed up sputum on most days during at least 3 months in 2 consecutive years.
4. Current or ex-smokers with a smoking history of at least 10 pack-years (20 cigarettes per day for 10 years or 10 cigarettes per day for 20 years). (Ex-smokers were defined as those who had stopped smoking for at least 6 months prior to visit 1. Ex-smokers were eligible to enter the study provided they had at least 10 pack years smoking history).
5. Exacerbation history: A documented history of COPD exacerbations each year for the 3 years prior to visit 1, including at least one exacerbation in the last year prior to visit 1 that required oral corticosteroids and/or antibiotics.
6. Poor reversibility of airflow obstruction defined as an increase of less than 10% of the predicted normal FEV_1 value 30 minutes after inhalation of 400 mcg salbutamol via MDI and Volumatic Spacer.
7. A signed and dated written informed consent was obtained prior to participation.
8. A female was eligible to enter and participate in the study if she was:

(a) Of non-child-bearing potential (i.e. physiologically incapable of becoming pregnant, including any female who was pre-menarchal or post-menopausal); or

(b) Of child-bearing potential, was not lactating, had a negative pregnancy test (urine or serum) at screen, and agreed to one of the following contraceptive methods:

- Complete abstinence from intercourse for the duration of the study
- Female sterilization
- Sterilization of male partner
- Implant of levonorgetrel
- Injectable progestogen
- Oral contraceptive (combined or progestogen only)
- Any intrauterine device (IUD) with published data showing that the lowest failure rate is less than 1% per year
- Any other methods with published data showing that the lowest failure rate is less than 1% per year
- Barrier method only if used in combination with any of the above acceptable methods

2.1.4.2 Inclusion criteria for entry to the treatment period

1. Baseline (pre-bronchodilator) FEV_1 of $\geq$25 to $\leq$70% of predicted normal. This could be demonstrated at either visit 1 or visit 2 (or at visit 2A if the run-in period was repeated).
2. Poor reversibility of airflow obstruction defined as an increase of less than 10% of the predicted normal FEV_1 value 30 minutes after inhalation of 400mcg salbutamol via MDI and *Volumatic* spacer. This had to be demonstrated at visit 1 and visit 2 (and visit 2A if the run-in was repeated).
3. Baseline (pre-bronchodilator) FEV_1/FVC ratio < 70%. This could be demonstrated at either visit 1 or visit 2 (or at visit 2A if the run-in period was repeated).
4. Able to complete a daily record card and to use a mini-Wright peak flow meter correctly
5. Able to use a *Diskus* and relief medication correctly

2.1.4.3 Exclusion Criteria

1. In the opinion of the investigator there was a current diagnosis of asthma, eczema or allergic rhinitis
2. Known respiratory disorders other than COPD (eg: lung cancer, sarcoidosis, tuberculosis, lung fibrosis)
3. Chest X-ray indicating diagnosis other than COPD that might have interfered with the study (chest X-ray had to be taken at entry to the run-in period, or in the last 3 months before entry to the run-in period)
4. Requirement for regular (daily) or long term oxygen therapy (LTOT was defined as >12 hours oxygen/day)
5. Received systemic corticosteroids in the last 4 weeks before entry to the run-in period
6. Received antibiotic therapy or hospitalized for lower respiratory tract infection /COPD in the last 4 weeks before entry to the run-in period
7. Received inhaled corticosteroids at a dose of >1000 mcg/day (beclomethasone dipropionate, budesonide or flunisolide) or > 500 mcg/day (FP) in the last 4 weeks before entry to the run-in period
8. Had any changes in COPD medication in the last 4 weeks before entering the run-in period
9. Were receiving β-blockers (with the exception of topical betaxolol for the treatment of glaucoma; and the selective β-blocker celiprolol for the treatment of hypertension, provided the dosage did not exceed 200 mg/day)
10. Serious, uncontrolled disease (including serious psychological disorders) likely to have interfered with the study
11. Received any other investigational drugs in the last 4 weeks before entry to the run-in period
12. Had, in the opinion of the investigator, evidence of alcohol, drug or solvent abuse
13. Known or suspected hypersensitivity to inhaled corticosteroids, β2-agonist or lactose
14. Previously been enrolled to this study.

2.1.4.4 Exclusion criteria for entry to the treatment period

Had any changes in COPD medication (other than as required use of V*entolin*), received systemic corticosteroids or antibiotic therapy or was hospitalized for COPD/lower respiratory tract infection during the run-in period.

2.1.5 Study Procedures

2.1.5.1 Therapy

Concurrent Medications

The following COPD medications were allowed during the study:

- Inhaled salbutamol (*Ventolin*). Patients were required to withhold *Ventolin* for 6 hours prior to the morning PEFR readings and clinic visit spirometry.
- Anticholinergic agents were permitted provided they had been started prior to randomization and were used in constant dosage.
- Dose titration of methylxanthines (e.g., theophylline) was permitted to ensure the drug was at therapeutic plasma levels throughout the study. However patients were required to

withhold the use of these medications for 6 hours prior to the morning PEFR readings and clinic visit spirometry.

- Standardized short courses of oral corticosteroids and antibiotics were permitted for treatment of exacerbations.
- Mucolytics such as acetylcysteine were permitted provided they had been started prior to randomization and were used in constant dosage throughout the study.
- Sodium cromoglycate, nedocromil sodium and ketotifen were permitted provided they had been started prior to randomization and were used in constant dosage throughout the study.
- Oxygen therapy during a severe COPD exacerbation and for up to 4 weeks afterwards
- Self-medicated, intermittent oxygen therapy was permitted on entry to the study, or during the study, provided it was not continuous.

The following COPD medications were prohibited during the study:

- All inhaled and oral short-acting ß$_2$-agonists were stopped at entry to the run-in period
- Inhaled corticosteroids (other than the study medication) were stopped at entry to the run-in period.
- Long-acting ß$_2$-agonists (other than the study medication) were stopped at entry to the run-in period.
- Combination bronchodilators containing inhaled anticholinergics and a short-acting ß$_2$-agonist (eg: Combivent, Berodual, Duovent) were stopped at entry to the run-in period. If necessary, they were replaced with an inhaled anticholinergic alone at a regular daily dosage. The short-acting ß$_2$-agonist part of the combination was replaced by the relief *Ventolin* provided by the Sponsor.
- Systemic corticosteroids for any condition
- Beta blockers

Changes in Medication

Patients who had a change in their COPD medication (other than "as required" use of *Ventolin*) during the run-in period were not eligible to enter the treatment period and were required to be withdrawn.

During the treatment period, patients were not permitted to vary the dose or change their COPD medication (other than "as required" use of *Ventolin*), unless for the treatment of COPD exacerbations as described below. Anticholinergic agents, mucolytics, sodium cromoglycate, nedocromil sodium and ketotifen were all permitted medications in patients entering the study provided they were used in constant dosage and had been started prior to randomization. Methylxanthines were also permitted during the study as long as this therapy had started before randomization and dose-titration to plasma-levels was permitted during the study to ensure that therapeutic levels of the drug were maintained.

Treatment of Exacerbations of COPD

Exacerbations requiring antibiotics were treated with a 10-day course of oral antibiotics (dose and type according to local practice). Examples of suitable antibiotics included broad spectrum penicillins (e.g. amoxycillin clavulanate, amoxycillin, ampicillin), cephalosporins (e.g. cefuroxime), tetracyclines (e.g. doxycycline), quinolones (e.g.

ciprofloxacin), macrolides (e.g. clarithromycin, erythromycin) and co-trimoxazole).

Exacerbations requiring oral corticosteroids were treated with a standard course of prednisolone or prednisone tablets 30mg/day for 10 days, or methylprednisolone tablets 24mg/day for 10 days.

2.1.5.2 Assessments

Demographic information including gender, ethnic origin, date of birth, height, weight, duration of COPD, number of exacerbations in the previous 12 months that required oral corticosteroids and/or antibiotics or hospitalization; smoking history in pack years; assessment of dyspnea using the MRC Dyspnea Scale, current medical conditions and concurrent medications.

Spirometry was performed at each clinic visit prior to ingestion of study medication. FEV_1, FVC and FEV_1/FVC were measured before and 30 minutes after inhalation of 400 mcg salbutamol. Reversibility was calculated as a percentage of the predicted FEV_1.

The number and severity of COPD exacerbations were assessed by the investigator at each clinic visit, by reviewing the Daily Record Card (DRC) entries as well as specific questioning on AEs. Each COPD exacerbation was categorized according to one of the following three levels
of severity:

Mild: Defined as an exacerbation requiring increased use of relief *Ventolin* by > 2 occasions/24-hour period on 2 or more consecutive days compared with baseline (baseline = mean of last 10 days of run-in period) AND deemed clinically relevant by the investigator.

Moderately severe: Defined as an exacerbation requiring treatment with antibiotics and/or oral corticosteroids, EITHER as judged by the investigator OR according to the criteria given below:

Criteria for treating with antibiotics (for guidance): If there was evidence of chest infection i.e. two or more of the following symptoms: purulent sputum, increased sputum production, increased breathlessness.

Criteria for treating with oral corticosteroids (for guidance): If there was an increase in symptoms (increased cough, increased sputum production or increased breathlessness) and:

EITHER
i) Increased use of relief *Ventolin* by > 4 occasions/24-hour period on 2 or more consecutive days compared with baseline (baseline = mean of last 10 days of run-in period)
OR
ii) Morning PEFR decreased by > 50L/min on 2 or more consecutive days compared with baseline (baseline = mean of last 10 days of run-in period).

Severe: Requires hospitalization

If considered appropriate by the investigator, patients could be given a reserve supply of oral corticosteroids and/or antibiotics for use in the event of a moderately severe exacerbation. However, patients were not to self-medicate until they had contacted the investigator, either in person or by telephone. Individual courses of oral corticosteroid were classified as separate exacerbations only if they were administered more than one week apart. Any course started within one week of finishing a previous course was considered as part of that previous exacerbation.

COPD exacerbations were recorded on both the Exacerbation and the Adverse event form. Date of onset and resolution, outcome, and severity were recorded for all episodes. The date of resolution was the time at which the exacerbation had resolved, in the opinion of the investigator or the patient.

Patients were given Daily Record Cards (DRC) to be filled out daily. Each card was designed to collect four weeks of data. The following pieces of information were collected: Morning PEFR measure with a mini-Wright peak flow meter, Ventolin usage for the previous 24 hours, COPD symptom score (See Appendix for a copy of the score), night-time awakenings, time missed from work (none, half-day, full day), Use of other medication.

The Saint George's Respiratory Questionnaire (SGRQ) was completed at weeks 0, 2, 4, 8, 24, and 52 in those countries where a validated translation was available.

The following information was recorded on the COPD-related Unscheduled Healthcare Contacts form in the CRF: type of healthcare professional contacted (nurse/primary care physician/specialist physician); date of contact; number of visits/calls (in the case of primary care contacts); number of hospitalizations; and number of days hospitalized. The investigator prompted the patient to give answers which were as complete as possible. If the patient could not recall an exact figure, an estimate was acceptable. The investigator could refer to his/her records to verify or supplement information given by the patient, if necessary.

Safety was evaluated with adverse events (AEs), routine safety hematology and chemistry at baseline, 24 and 52 weeks, and fasting serum cortisol was measured at baseline and weeks 24 and 52. At selected centers 24-hour urines were collected for free cortisol measurement. Vital signs and a 12-Lead ECG were obtained at baseline and weeks 24 and 52. At each clinic visit the number of bruises of >5cm in diameter on the volar surface of each forearm was counted. Oropharyngeal examination was performed at each clinic visit.

2.1.6 Analysis

Adverse events were classified using MIDAS (Medications, Indications, Diagnoses, Adverse Events and Symptoms) and THERAPY (drugs) dictionaries on GOLD (Glaxo Optimally Linked Database).

Reviewer: These are old disease classification systems and it is not clear how they compare to the MedDRA classification used in study SCO30003. However, the events were reclassified for the ISS so they could be compared to the events in the other studies.

Sample Size

Assuming a standard deviation of 0.35 L for a repeated measures analysis of FEV_1, it was estimated that 250 patients per treatment arm would provide 90% to detect a difference in FEV_1 of 0.10 L with a Type I error of <5%. Two hundred fifty patients would also provide a power of 90% to detect a difference in exacerbation rate of at least 15% assuming that the incidence of COPD exacerbation on placebo would be at least 60%

Analysis Populations

The Intent-to-Treat (ITT) Population consisted of all patients enrolled who received at least one dose of study medication. The Per-Protocol (PP) population consisted of patients in the ITT population who had no major protocol violations. The Safety Population consisted of everyone in the ITT population.

Covariates in the efficacy analyses included age, sex, center, and when available, smoking status. The centers were included in the analysis in groups of 1 or two countries. There was a large enrollment from Canada so it was divided into three geographic regions so the site units would be of approximately the same size. Subgroups based on sex, age, treatment and center were analyzed by looking for interactions with a statistical significance of 0.10. Additional analyses were performed to assess the importance of baseline smoking status, use of inhaled corticosteroids at screening, baseline use of long acting beta agonists, baseline percent of predicted FEV_1, history of atopy, and baseline reversibility. For the analyses, individual sites were grouped by country or area to provide 34-95 patients per site-group. All the sites from one country were included in the same group except for Canada which was divided into three regions (East, Mid section, and West).

The Applicant accepted as a satisfactory outcome the result that FSC was superior to SAL and FP or FSC was superior to placebo. To protect the Type I error with this combined endpoint, the FSC vs. SAL and FSC vs. FP comparisons were conducted at the two-sided $p \leq 0.04$ level and the FSC vs. placebo was conducted at the $p \leq 0.01$ level.

If a patient withdrew prior to 52 weeks the number of COPD exacerbations was imputed for 52 weeks. The number of 4 week periods that the patient was on treatment was rounded up to the next integer. The number of COPD exacerbations was then divided by the number of 4 week periods and the result multiplied by 13.

For DRC data, the baseline was taken as the average of the values recorded for the 10 days prior to randomization.

Major protocol violators were excluded from the PP population. Major protocol violations included any breach of the inclusion and exclusion criteria, patients whose treatment compliance was <50%, and patients enrolled in site 13494 because the data could not be verified. Patients were excluded from some of the analyses under the following circumstances: those who failed to

withhold bronchodilators prior to spirometry testing were excluded from the spirometry results, those whose study medication was unblinded were excluded after the time of the un-blinding. Patients with >3 moderate, or > 2 severe exacerbations who had not been withdrawn from the treatment protocol were excluded from the PP analysis at the time of the third moderate or second severe exacerbation. Patients who had received the wrong study medication or patients who had taken expired medication were excluded from the PP analysis, but they were included in the ITT analysis.

Compliance was calculated as the number of doses of study drug used/number of doses expected to be used. Assuming that treatment started on the evening of randomization the doses expected is calculated is as follows:

[2 * (treatment stop date – randomization visit date) +1] – 1

The number of doses used is 60 – number of doses remaining. If the DISKUS was not returned, it was assumed that no drug had been taken.

Efficacy Analysis

For the FEV_1 efficacy analysis a repeated measures model included time as a categorical parameter. The main model is as follows:

FEV_1 = Baseline FEV_1 + center + age + sex + smoking status + visit + treatment.

This model was repeated with a treatment* visit interaction term. An additional analysis was performed with the last observation carried forward, and another with only completers. An endpoint analysis was performed as the change from baseline in FEV_1 using an analysis of covariance (ANCOVA) model, adjusting for the effects of sex, center, ate and baseline FEV_1.

The number of moderate/severe COPD exacerbations experienced by the patient during the treatment period was analyzed using a maximum likelihood based analysis, assuming the Poisson distribution, with time on treatment as an offset variable. The model included adjustment for the effects of smoking status, sex, centre amalgamation, age and baseline FEV_1 (mL). The analysis was not adjusted for baseline exacerbation rate.

The SGRQ was administered at baseline and weeks 2, 4, 8, 24, and 52 of treatment. A transformed score was calculated for each of the three sub-scales of the questionnaire (symptoms, impacts, and activity) and the overall total score, in accordance with the developers scoring guidelines. The total score was analyzed using repeated measures analysis. The model included adjustment for the effects of smoking status, sex, centre age and baseline SGRQ total score. The ITT population was used for the analysis. An Endpoint analysis was also performed on the change from baseline in SGRQ total score using an ANCOVA model adjusting for the effects of sex, center, age, and baseline SGRQ. All of the analyses were repeated for each of the three sub-scores.

Other efficacy measures included the post-bronchodilator FEV_1 and results of the DRC recordings. The following variables were summarized from the DRC:

- Mean cough score
- Percentage of days with mild or no cough
- Mean breathlessness score
- Percentage of days with breathless only on at least moderate exertion
- Mean sputum production
- Percentage of day with mild or no sputum production
- Mean sputum color
- Percentage of days with colorless or no sputum produced
- Mean number of night-time awakenings
- Percentage of nights with no awakenings

Mean scores were analyzed for each time interval using ANCOVA including covariates of age, sex, center, smoking status, and baseline score. The following time intervals were analyzed:

- Weeks 1-12
- Weeks 13-24
- Weeks 25-36
- Weeks 37-52

Bronchodilator use was presented as median use for each patient and as the percentage of days with no relief bronchodilator use during each of the above time periods. The number of withdrawals and time to withdrawal was summarized. The mean PEFR was summarized for each time interval.

Exacerbations were further analyzed as the number of severe exacerbations, the time to the first moderate/severe exacerbation, number of patients with at least one moderate/severe exacerbation, number of exacerbations requiring corticosteroids, number of exacerbations requiring antibiotics.

Unscheduled health care visits were summarized and the patient's percentage of days missed from work/usual activities was calculated. Data were summarized over the 1-52 week interval as well as the three-month intervals listed above.

Safety Analysis

Adverse events were collected during treatment with double blind study medication and after discontinuation of the medication in case of withdrawal. Deaths, serious AEs and pregnancies were tabulated. Of note, adverse events were recorded using the MIDAS dictionary. For hematology and chemistry safety blood levels, shift table were prepared to show change in values in and out of the normal ranges. Threshold limits for each analyte were determined by the Clinical Research group of GlaxoWellcome (now GSK) prior to beginning the study. The Upper Threshold Limit ranged from 1.05 to 5.0 times the ULN, and the Lower Threshold Limit ranged between 0.75 and 0.95 times the LLN depending on the analyte.

HPA-Axis Assessment

Serum cortisol was measured at Baseline and at Weeks 24 and 52. The raw data were log-transformed prior to analysis. Cortisol levels were analyzed using ANCOVA with covariates of smoking status, age, sex, center, and log baseline cortisol. A 24-hour urinary cortisol was measured at baseline and at Weeks 24 and 52. The ratio of urinary cortisol concentration to creatinine concentration was summarized by visit and the ratios were log-transformed prior to analysis.

2.2. Efficacy Results

2.2.1 Study Population

Disposition

A total of 1974 patients were recruited of whom 1469 were randomized to receive treatment. Subsequently 4 patients were found to have received no medication so the ITT population consisted of 1465 individuals. The PP population comprised 1225 patients. After randomization 456 patients were withdrawn: 140 (39%), 119 (32%), 108 (29%), and 89 (25%) of the placebo SAL, FP, and FSC groups, respectively (Table 63). The largest number of withdrawals was due to adverse events and the rate of events was greatest in the placebo-treated patients: 19, 16, 15, and 13% in the placebo, SAL, FP, and FSC patients, respectively.

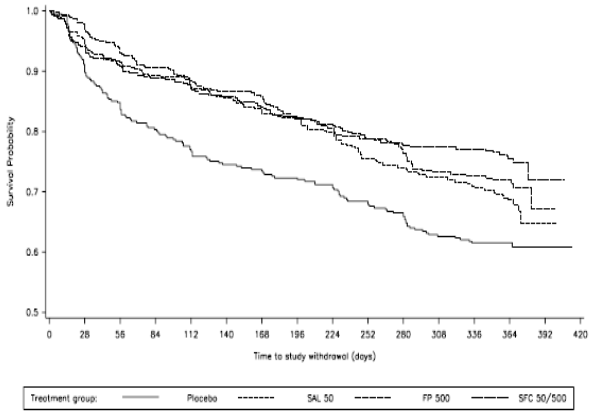
Table 63. Disposition of Patients in Study SFCB3024

	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Total withdrawals, n(%)	140 (39)	119 (32)	108 (25)	89 (25)
Reason for withdrawal, %				
Adverse event	19	16	15	13
Consent withdrawn	4	3	3	2
Protocol violation	3	3	1	3
Lack of efficacy	5	1	2	<1
Lost to follow-up	2	2	2	2
Non-compliance	2	1	3	1
Did not fulfill inclusion criteria	<1	<1	<1	1
Other	3	3	2	2

Reviewer: By way of comparison, the drop-out rate in Study SCO30003 was 44, 37, 38, and 34% for the placebo, SAL, FP, and FSC patients. The drop-out rate was not much higher in SCO30003 than SFCB3024 and the former was three times longer than the latter.

As in Study SCO30003, most of the adverse events and withdrawals were due to COPD exacerbations. AEs that were not COPD exacerbations were more frequent in the active treatment groups than in the placebo-treated patients. (See Adverse Events, pg 137.) Withdrawal occurred earlier in the placebo patients than in the active treatment groups (Figure 11).

Figure 11 . Withdrawal from TRISTAN by Treatment Group*



* Post-text Figure F11 from Study Report ; SFC=Advair

The incidence of major protocol violations was similar across the treatment groups: 16, 16, 17, and 17% in the placebo, SAL, FP, and FSC groups, respectively. Calculated treatment compliance of <70% (based on dose-counts in returned DISKUS) was the most common cause of exclusion from the PP population and this occurred slightly more frequently in the FSC group (10% compared to 8% in each of the other treatment-groups). The other most common protocol violations were failure to stop ICS at screening, reversibility of airflow too high, Baseline FEV_1/FVC >70%, and received ICS at an excess does in the 4 weeks prior to screening. Ninety-eight patients in the ITT population were excluded from the analysis at specific dates (6-7% of each treatment group).

Demographics

The demographic characteristics were similar across the treatment groups (Table 64). The majority of the patients were male, the mean age (SD) was 63 (8.6) years, 72% were male and ≥99% were Caucasian. Atopy was present in 5% or less of the patients, the mean MRC Dyspnea Score was 2.6, 25% of the patients had symptoms of COPD for <5 years, and 51% were taking ICS as screening. Fifty-one % continued to smoke and the mean pack-years ranged from 40-44 in the former smokers and 41 – 46 in the current smokers. Most of the patients (77, 78, 80, and 76% of the placebo, SAL, FP, and FSC patients, respectively) reported at least one additional medical condition. The most common concurrent condition was some form of heart disease that was reported in 40-45% of each treatment group. The number of exacerbations reported in the year prior to admission was not provided.

Table 64. Demographics in Study SFCB3024

	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Age, years				
Mean (SD)	63.4	63.2	63.5	62.7
Range	40 - 79	38 - 79	40 - 79	40 - 78
Gender, % Male	75	70	70	75
Race, % White	>99	98	99	>99
BMI, Mean	25.5	26.2	25.7	25.5

(Range)	(16.2-43.5)	(16.4-44.4)	(13.8-45.0)	(14.2-45.2)
Atopy, %	5	3	3	3
MRC Dyspnoea Score				
Mean (Range)	2.7 (1-5)	2.7 (1-5)	2.5 (1-5)	2.6 (1-5)
Duration of COPD,%				
< 5 years	25	26	25	23
5-10 years	33	36	31	42
> 10 years	42	38	45	34
Taking ICS at Screening, %	52	49	54	50
Taking LABA at Screening, %	38	42	40	42
Taking ICS and LABA, %	26	29	29	27
Current smokers, %	47	51	53	48
Pack-years				
Former smoker	44 (10-150)	41 (10-140)	42 (10-105)	41 (10-159)
Current smoker	43 (12-120)	47 (11-120)	41 (10-110)	43 (10-124)

Reviewer: Compared to SCO30003 these patients are 2 years younger and more are Caucasian. The history of COPD was slightly longer (The duration of COPD was <5 years in at least 35% of the patients in SCO30003 and a similar percentage (34-36%) has a history of >10 years) despite the higher FEV_1 – see below.

2.2.2 Efficacy

Primary Efficacy Outcome

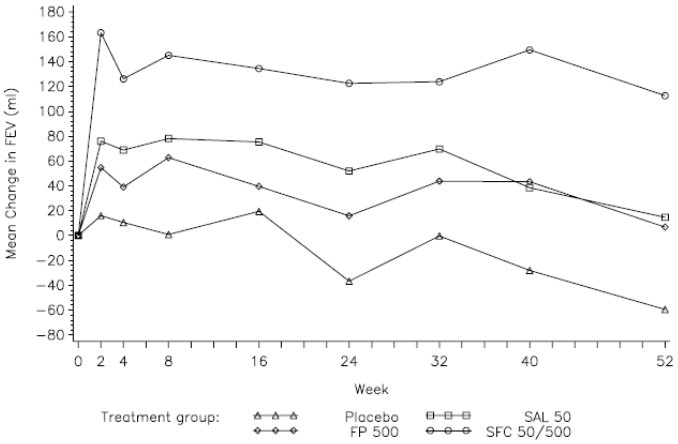
The primary efficacy outcome was the pre-bronchodilator FEV_1. The mean FEV_1 and FEV_1 % predicted was 1266 (44.2%), 1245 (44.3%), 1260 (45.0%) and 1308 (44.8%) in the placebo, SAL, FP, and FSC groups, respectively. The raw change and % change in FEV_1 at 52 weeks were -60 (-3%), 15 (2%), 7 (2%) and 113 (10%) in the placebo, SAL, FP, and FSC patients, respectively (Table 65). The primary analysis used a repeated measures model without a treatment by time interaction. The calculated mean (95% CI) difference between FSC and placebo was 133 mL (105, 161). The differences for SAL and FP were 60 (32, 88) and 39 (11, 66) mL, respectively. The change in FEV_1 during treatment was significantly better in all of the active treatment groups compared to placebo at the $p<0.001$ level. The change in FEV_1 during treatment with FSC was also significantly greater than during treatment with SAL or FP. The mean (95% CI) difference between FSC and the components was 73 (46, 101) and 95 mL (67, 122) for SAL and FP, respectively. The results are presented graphically in Figure 12.

Table 65. Pre-bronchodilator, Trough FEV_1

	Placebo (N=361)	**SAL 50 (N=372)**	**FP 500 (N=374)**	**FSC 500/50 (N=358)**
Baseline FEV1, mL	1266	1245	1260	1308
% predicted	44.2	44.3	45.0	44.8
Week 52, N	216	255	267	269
Change from Baseline, mL (%)	-60 (-3)	15 (2)	7 (2)	113 (10)
Baseline FEV1, N	353	361	371	345
Repeated measures analysis. mL	1260	1241	1261	1308

Adjusted mean over week 1-52	1264	1323	1302	1396
Active Treatment –Placebo		60	39	133
95% CI		32, 88	11, 66	105, 161
p-value		<0.001	<0.001	<0.001
FSC – Components, mL		73	95	
95% CI		46, 101	67, 122	
p-value		<0.001	<0.001	

Figure 12. Pre-bronchodilator, Trough FEV_1*



* Post-text Figure F2 of Study Report; SFC=Advair

When the model was run with the addition of a treatment by visit interaction, a significant (p=0.017) difference was noted in the effect of treatment with time. However, the effect of FSC was significantly better than placebo and the components at each time point. In this analysis the difference between FSC and placebo ranged from 116 to 167 mL.

In the endpoint analysis the mean difference (SE between active treatment and placebo was 49.8 (20.1), 43.1 (20.0), and 140.2 (20.4) for SAL, FP, and FSC, respectively. The mean difference (SE) between FSC and the components was 90.3 (20.3) and 97.1 (20.1) for the comparison with SAL and FP, respectively. The completers analysis showed similar results.

In a sub-group analysis, neither age nor smoking status affected the results. The interaction term for baseline FEV_1 and treatment was not significant. However, there was a trend for increased responsiveness in the upper quartile of FEV_1 (Table 66).

Table 66. Relationship Between Response to FSC and Baseline Percent Predicted FEV_1

	Lower Quartile	**Median**	**Upper Quartile**
Baseline FEV_1, % predicted	33	44	55
Treatment difference, mL	113	132	151
95% CI	77, 149	104, 160	116, 186

The results of the per-protocol analysis were similar to the results of the primary analysis. The mean difference (SE) between active treatment and placebo was 79.3 (20.2), 48.9 (20.0), and

165.2 (20.2) mL in the SAL, FP, and FSC groups, respectively. The mean difference (se) between FSC and the components was 86.0 (20.2) and 116 (20.0) for the comparison with SAL and FP, respectively.

Secondary efficacy outcome measures

Overall, 54% of the patients experienced a moderate/severe exacerbation during the year of follow-up. The number of moderate and/or severe COPD exacerbations / year was higher in the placebo than the active treatment groups (Table 67). The Hazard ratio (95% CI) comparing the active components to placebo was 0.802 (0.694, 0.926), 0.807 (0.699, 0.931), and 0.746 (0.643, 0.865) for SAL, FP, and FSC, respectively. However, treatment with FSC was not significantly better than SAL or FP at reducing the rate of moderate/severe COPD exacerbations. The ratio (95% CI) of FSC to the components was 0.930 (0.801, 1.080) and 0.925 (0.797, 1.073) for SAL and FP respectively.

Table 67. Number of Moderate/Severe COPD Exacerbations per Year

	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
	361 1.30	371 1.04	374 1.05	356 0.97
Ratio active/placebo **95% CI** **p-value**		0.802 0.694, 0.926 0.003	0.807 0.699, 0.931 0.003	0.746 0.643, 0.865 <0.001
Ratio of FSC over Components **95% CI** **p-value**		0.930 0.801, 1.080 0.343	0.925 0.797, 1.073 0.343	

The number of exacerbations varied widely by country. The annual rate in the placebo group ranged from 0.42 per year in Russia to 4.84 per year in Australia. In five of the 24 countries the exacerbation rate was higher in the FSC-treated patients than in the placebo patients. Overall, 42, 44, 46, and 47% of the placebo, SAL, FP, and FSC patients had no exacerbation in the year of follow-up. Therefore, there was a significant decrease in the rate of moderate/severe exacerbations in all of the treatment groups because one moderate/severe exacerbation in the 12 months prior to enrollment was an inclusion criterion

The number of moderate and/or severe COPD exacerbations / year that required treatment with corticosteroids was higher in the placebo than the active treatment groups (Table 68). The Hazard ratio (95% CI) comparing the active components to placebo was 0.712 (0.593, 0.854), 0.656 (0.544, 0.791), and 0.607 (0.500, 0.736) for SAL, FP, and FSC, respectively. However, as for the analysis of the overall incidence of moderate/severe exacerbations, treatment with FSC was not significantly better than treatment with SAL or FSC at reducing the rate of moderate/severe COPD exacerbations. The ratio (95% CI) of FSC to the components was 0.853 (0.699, 1.039) and 0.925 (0.755, 1.133) for SAL and FP respectively.

Table 68. Moderate/Severe Exacerbations Requiring Oral Corticosteroids

	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Baseline, N	361	371	374	356
Mean number/year from model	0.76	0.54	0.50	0.46
Ratio active/placebo		0.712	0.656	0.607
95% CI		0.593, 0.854	0.544, 0.791	0.500, 0.736
Ratio of FSC over Components		0.853	0.925	
95% CI		0.699, 1.039	0.755, 1.133	

The number of moderate and/or severe COPD exacerbations / year that required treatment with antibiotics was similar in all of the treatment groups and the Applicant did not perform any statistical analysis of these results (Table 70).

Reviewer: In light of the TORCH results it is interesting to note that the rate of antibiotic-treated exacerbations is actually higher in the FSC group than in any of the other groups, although not statistically significant.

Table 69. Exacerbations Requiring Antibiotics

	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Baseline, N	361	371	374	356
Mean number / year from model	0.72	0.65	0.75	0.76

The number of patients with severe COPD exacerbations was small (0.07, 0.08, 0.06, and 0.07 events/year in the placebo, SAL, FP, and FSC groups, respectively) and not patient to statistical analysis. From Table 70 it appears that a higher percentage of the patients treated with placebo (94% compared with 91, 92, and 91% of the SAL, FP, and FSC patients) had no severe exacerbations than those in the active treatment groups, although, more of the placebo patients had 2 or more exacerbations.

Table 70. Patients with Severe Exacerbations

	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Baseline, N	361	372	374	358
Patients with Severe Exacerbations, n (%)				
0	338 (94)	337 (91)	344 (92)	326 (91)
1	18 (5)	29 (8)	27 (7)	30 (8)
2	4 (1)	4 (1)	3 (<1)	2 (<1)
>3	4 (<1)	2 (<1)	0	0

The time to first moderate/severe exacerbation showed a similar order of responsiveness as the rate of exacerbations. The time to first event was shorter in the placebo patients, but all of the active treatment groups were similar.

In a sub-group analysis of age and baseline $FEV_{1,}$ no interaction was found with the exacerbation rate. However, a statistically significant (p=0.002) interaction between center amalgamation and exacerbation rate was noted. Seven of the 24 Center groupings had a higher rate of exacerbations in the FSC-treated patients than the placebo patients. To assess the regional differences, the Applicant compared the ratio of FSC to placebo exacerbation rate to the difference between the FSC and placebo SGRQ. In a qualitative analysis they say there is no correlation.

Reviewer: If the ratios and differences are changed into categorical variables (SGRQ difference <0 = FSC superior and exacerbation ratio <1 = FSC superior) then the correspondence between SGRQ and FSC is 17 of the 21 center amalgamations with both variables for all the centers.

The interaction coefficient between smoking status and treatment was not significant, however, the difference between FSC and placebo was somewhat greater in the former than the current smokers. The ratio of moderate/severe COPD exacerbations comparing FSC to placebo was 0.695 in the former smokers and 0.800 in the current smokers.

Other secondary outcome measures

The post-bronchodilator FEV_1 improved more over the treatment period in the actively treated patients than in the placebo group. In a repeated measures analysis, the mean difference (95% CI) between active treatment and placebo was 28 (-1, 57), 46 (17, 75), and 76 (47, 106) mL in the SAL, FP, and FSC groups, respectively. The mean difference (95% CI) between FSC and the components was 48 (19, 77) and 31 (2, 60) mL for the comparison with SAL and FP, respectively.

Results of the patient-recorded symptoms showed more improvement in the FSC-treated patients than in the other treatment groups (Table 71). None of the treatments affected sputum color or volume.

Table 71. Symptom Scores that Varied with Treatment.

	FSC-placebo	FSC- SAL	FSC - FP
Mean cough score	√		
Breathless			
Mean Score	√	√	√
% Days breathless only on Mod exertion	√		
Night time awakenings			
Number	√	√	
% Nights without	√	√	
Bronchodilator use			
Median use	√	√	√
% days with no use	√	√	√

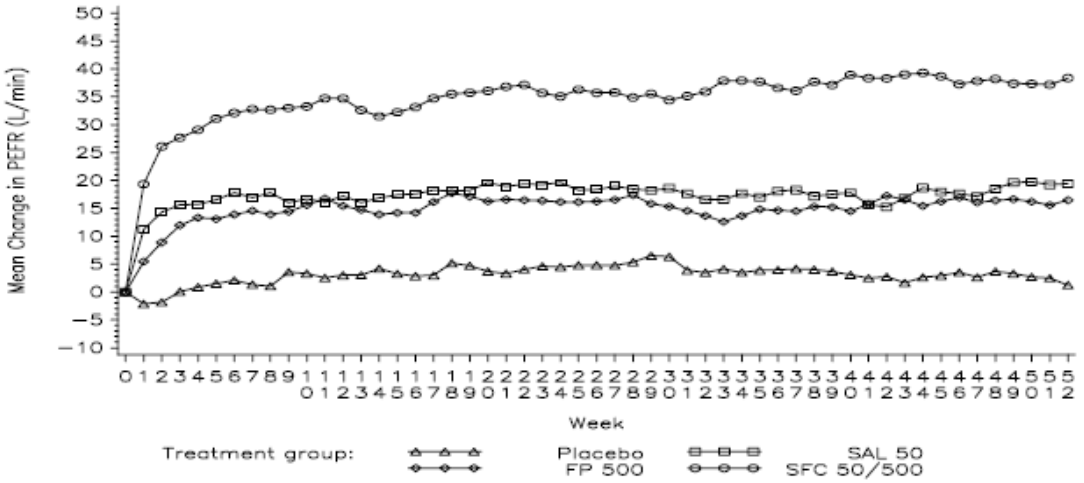
The time to withdrawal was significantly shorter in the placebo-treated patients than those in the active treatment groups (Table 72). However, there was no difference comparing FSC to the components.

Table 72. Time to Withdrawal

	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Active Treatment-Placebo				
Hazard ratio		0.733	0.654	0.560
95% CI		0.573, 0.938	0.508, 0.842	0.429, 0.732
FSC-Components				
Hazard ratio		0.761	0.859	
95% CI		0.577, 1.005	0.646, 1.138	

Changes in the daily PEFR were derived from the DRC-recorded values. At all time points the values were higher for the active treatment groups than for the placebo-treated patient. The values for the FSC patients were also higher than those in the patients treated with either of the components.

Figure 13. Daily Peak Expiratory Flow Rate*



* Post-text F12 if Study Report; SFC=Advair

The pre-bronchodilator FVC improved more over the treatment period in the actively treated patients than in the placebo group. In a repeated measures analysis, the mean difference (SE) between active treatment and placebo was 86.8 (24.6), 61.1 (24.4), and 155 (24.9) mL in the SAL, FP, and FSC groups, respectively. The mean difference (SE) between FSC and the components was 68.1 (24.7) and 93.9 (24.5) mL for the comparison with SAL and FP, respectively.

2.2.3 Health Outcomes

The SGRQ was available at baseline and at the end of the study for 318, 321, 340, and 320 patients in the placebo, SAL, FP, and FSC patients, respectively. Patients enrolled in Denmark, Iceland, and Lithuania were excluded due to the unavailability of a validated questionnaire. The fall in score (improvement) was greatest in the FSC group (Table 73). However, in the repeated measures analysis neither the total score nor any of the domains was the difference from placebo

clinically meaningful (>4 units). In the endpoint analysis only the symptom score showed >4 unit superiority of FSC over placebo.

Table 73. Comparison of Drug Regimens using the Repeated Measures Analysis of SGRQ over 52 Weeks

	FSC-placebo	FSC- SAL	FSC - FP
Total	-2.2	-1.1	-1.4
Symptoms	-2.2	-2.1	-1.6
Impact	-2.7	-0.8	-1.5
Activity	-2.3	-1.7	-2.0
Endpoint ANOVA			
Total	-2.5	-1.6	-1.9
Symptoms	-4.6	-4.4	-3.9
Impact	-1.8	-0.7	-1.4
Activity	-2.8	-1.6	-2.6

A greater proportion of patients treated with FSC showed a 4-point or greater improvement (46%) than did the placebo (38%) or FP (40%). However 47% of the SAL treated patients improved by 4 or more points.

The change in SGRQ showed a relationship to the exacerbation rate (Table 74). Those who had no exacerbations had a clinically meaningful (FP was close to 4) fall in SGRQ, and those with more than 1 exacerbation had no change, very small improvements, or a deterioration in the score. For patients with 0-1 exacerbation, the FSC, but not the other groups had an improvement in SGRQ.

Table 74. Relationship Between SGRQ and Exacerbation Rate

	Change in SGRQ			
Number of Exacerbations	**Placebo**	**SAL**	**FP**	**FSC**
0	-4.5	-4.9	-3.8	-5.9
>0-1	-2.0	0.4	-3.7	-4.3
>1-2	0.7	-1.2	0.3	-0.7
>2-3	4.1	-1.8	2.5	-1.3
>3	4.3	1.1	0.5	2.9

Reviewer: The results of the SGRQ must be taken in conjunction with later developments in instrument development. In SCO30003 questionnaires were excluded from several of the countries represented in SFCB3024 and modified questionnaires were administered in additional countries. It is not entirely clear which groups were duplicated because the language is not identified in SFCB3024 (i.e., In SCO30003 the Russian language questionnaire was excluded in Finland, but not the Finnish language instrument.) However, it is clear that the validation was not as complete in this early study.

2.2.4 Resource Utilization

Unscheduled COPD-related healthcare contacts varied by treatment group. While the number of phone calls was lowest in the FSC group, office visits, ER days, hospital days, and ICU days were all higher in the FSC group than in the placebo-treated patients (Table 76).

Table 75. Unscheduled COPD-related Healthcare Contacts

	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Telephone contacts	197	160	165	135
Office visits	174	166	197	202
Out-patient visits	77	74	71	70
ER days	25	32	22	28
Total hospitalizations	29	35	30	31
General hospital ward days	218	351	232	231
ICU days	2	25	0	14

The applicant claims that the reason for the apparent increased resource utilization in the active treatment groups is due to a few outliers. They also note that part of the reason that the number of events was higher in the active treatment groups was because they stayed on treatment longer. They therefore, converted the visits to number per 10,000 treatment exposure days. This transformation resulted in rates that were lower for the FSC group than the placebo group in all categories other than ICU days. The number of ICU days/10,000 treatment exposure days was 0.2 for the placebo treated patients and 1.3 for the FSC group. The number of office visits was also higher in the FSC group, even after adjusting for time on study (17.8, 14.8, 17.1, and 18.3 visits/10,000 treatment-days in the placebo, SAL, FP, and FSC groups, respectively.

Reviewer: While there are relatively few entries for ICU days (two patients [1 SAL with a 25 day stay and 1 FSC with an 8-day stay] account for most of the time in the ICU), there are enough general ward days to support the general impression of fewer hospital days in the placebo group.

The percentage of days with no time off from work/normal activities was slightly higher for the FSC treated patients: 85.6, 84.5, 85.2, and 89.9 percent for the placebo, SAL, FP, and FSC groups, respectively.

2.2.5 Safety

Mean exposure to study drug was 271, 301, 307, and 308 days in the placebo, SAL, FP, and FSC groups, respectively (Table 77).

Table 76. Exposure

(%) Patients Reporting Events	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Treatment days, mean	271	301	307	308
Range	1-413	2-401	4-399	1-407

Range of exposure, %				
<14 days	2	3	<1	3
15-28 days	8	3	2	3
29-112 days	13	7	9	7
113-224 days	6	7	8	6
225-364 days	32	37	39	34
>364 days	39	43	42	46

Adverse Events

Overall, 1165 (80%) of the patients reported a total of 4505 adverse events during the treatment period. Events were more common in the FP group (81% compared with 78, 79, and 80% of the Placebo, SAL, and FSC patients, respectively). Events classified as drug-related by the site investigators were particularly common in the FP group (19% compared with 14, 12, and 16% in the Placebo, SAL, and FSC groups, respectively (Table 77).

Table 77. Summary of Adverse events reported in Study SFCB3024

(%) Patients Reporting Events Number of Events	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Any event	283 (78) 1014	295 (79) 1082	302 (81) 1317	285 (80) 1092
Serious adverse event	54 (15)	69 (19)	55 (15)	62 (17)
Drug-related adverse event*	49 (14)	46 (12)	70 (19)	58 (16)
Withdrawn due to the event	66 (18)	58 (16)	51 (14)	41 (11)

* As assessed by the site investigator

The most common individual event reported was a COPD exacerbation (Table 78). COPD exacerbations were most common in the placebo patients (53%) and least frequent in the FSC group (49%) with SAL (51%) and FP (50%) reporting intermediate frequencies. Twenty-five, 28, 31, and 31% of the placebo, SAL, FP, FSC patients, respectively, reported non-COPD related adverse events. Upper respiratory tract infection was as common in the placebo patients as in the FSC-treated patients, although oropharyngeal candidiasis was three to four times more common in the fluticasone-treated patients than in either the placebo or SAL-treated patients. Lower respiratory tract infections and pneumonia were more common in the fluticasone-treated patients. Pneumonia occurred in more than twice the number of patients treated with FP (19 [5%]) and FSC (17 [5%]) than placebo (8 [2%]). The incidence of pneumonia was also increased in the SAL group (16 [4%]).

Table 78. Adverse Events Occurring in > 5% of the Patients in SCB3024

(%) Patients Reporting Events Number of Events	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Any event	78	79	81	80
COPD	53	51	50	49
Upper respiratory tract infection	12	9	15	12
Musculoskelatal pain	7	6	7	6
Lower respiratory tract infection	5	3	7	9
Viral respiratory tract infection	6	5	5	8
Headache	5	5	7	4

Candidiasis	2	2	7	8
Cough	6	3	4	4
Pneumonia	2	4	5	5
Throat irritation	6	3	5	4

In the two weeks following termination of treatment more patients in the FSC reported adverse events that in the other treatment groups, respectively (13, 13, 15, and 20% of the placebo, SAL, FP, and FSC patients). COPD exacerbations were also more common (2, 4, 4, and 7% of the patients in the placebo, SAL, FP, and FSC groups respectively).

Serious Adverse Events and Events Leading to Withdrawal

Deaths

Twenty-four patients died after randomization: 15 occurred during active treatment and 9 in the post-treatment period. There were 10, 5, 5, and 4 deaths in the placebo, SAL, FP, and FSC patients. Most of the deaths were cardiovascular (4, 3, 3, and 2 in the placebo, SAL, FP, and FSC groups, respectively). Cancer occurred in 2, 1, 1, and 0 of the placebo, SAL, FP, and FSC patients, and the death was ascribed to respiratory causes in 3 placebo and 1 SAL treated patient. The remaining deaths were ascribed to pancreatitis (placebo) unexpected (FP) and one each post-cardiac surgery and septicemia in the FSC group.

Serious Adverse Events

Two hundred forty patients reported serious adverse events during the treatment period. The most common cause was COPD (5, 9, 7, and 8% of the placebo, SAL, FP, and FSC patients, respectively), followed by pneumonia (Table 79). All other serious events occurred in less than 1% of the patients. However, myocardial infarction and fractures occurred more frequently in the FSC group. One, 2, 1, and 3 patients reported a myocardial infarction and 1, 0 2, and 3 patients reported serious fractures in the placebo, SAL, FP, and FSC groups. Cerebrovascular accidents were reported in 2, 1, 1, and 1 patient, respectively.

Table 79. Serious Adverse Events Occurring in >1% of the Patients.

(%) Patients Reporting Events Number of Events	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Any Serious event	54 (15)	69 (19)	55 (15)	62 (17)
COPD	19 (5)	34 (9)	25 (7)	29 (8)
Pneumonia	3 (<1)	9 (2)	9 (2)	7 (2)

Adverse Events Leading to Withdrawal

Events leading to withdrawal were most frequent in the placebo patients (Table 80). The most common events were COPD and breathing disorders which were also most common in the placebo group. Lower respiratory neoplasia, myocardial infarction, candidiasis, lower respiratory infection, fractures, and muscle cramps occurred sporadically.

Table 80. Adverse Events Resulting in Withdrawal

(%) Patients Reporting Events Number of Events	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Any event leading to withdrawal	66 (18)	58 (16)	51 (11)	41 (11)
COPD	44 (12)	32 (9)	27 (7)	20 (6)
Breathing disorders	3 (<1)	3 (<1)	1 (<1)	2 (<1)
Pneumonia	1(<1)	2 (<1)	3 (<1)	3 (<1)

Other Adverse Events

Events that are included in the current prescribing information were also tabulated. As expected, tremor, palpitations, and tachycardia occurred more frequently in the salmeterol treated patients. Candidiasis and hoarseness occurred most frequently in the fluticasone-treated patient. However throat irritation was more common in the placebo patients (Table 81).

Table 81. Adverse Events that are Current Included in the Approved Label

(%) Patients Reporting Events Number of Events	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Tremor	0	4 (1)	0	4 (1)
Palpitations	0	3 (<1)	2 (<1)	5 (1)
Headache	18 (5)	20 (5)	25 (7)	15 (4)
Tachycardia	1(<1)	6 (2)	1 (<1)	4 (1)
Other arrhythmias	2 (<1)	1 (<1)	0	1 (<1)
Arthralgia	6 (2)	7 (2)	5 (1)	5 (1)
Muscle cramp and spasms	2 (<1)	8 (2)	6 (2)	9 (3)
Candidiasis of mouth/throat	6 (2)	8 (2)	27 (7)	27 (8)
Hoarseness/dysphonia	3 (<1)	2 (<1)	8 (2)	6 (2)
Throat irritation	20 (6)	10 (3)	17 (5)	13 (4)

Pregnancies

No pregnancies occurred during the trial.

Laboratory Results

At the end of treatment, ≥97% of the patients had hematology values that were in the reference range or had not changed significantly from baseline. At the end of treatment ≥95% of the patients had chemistry values that were in the reference range or had not changed significantly from baseline.

A total of 67 patients had at least one abnormal hematology value that was considered to be clinically significant by the investigator on at least one occasion (Table 82). Forty-five (2-4% per treatment group) were not present at baseline. The only patient who had an abnormal value that was attributed to study medication was a patient taking salmeterol who had elevated lymphocytes, neutrophils and total white blood cell count.

Table 82. Summary of Abnormal Hematology Values

(%) Patients Reporting Events Number of Events	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Total with ≥1 clinically significant abnormality	18 (5)	11 (3)	15 (4)	23 (6)
Abnormality not present at baseline	11 (3)	8 (2)	10 (3)	16 (4)
Investigator attribution				
Disease under study	8 (2)	0	2 (<1)	5 (1)
Other concurrent disease	1 (<1)	4 (1)	4 (1)	6 (2)
Other concurrent medication	1 (<1)	0	0	1 (<1)
Possibly due to study medication	0	1 (<1)	0	0
Unknown	3 (<1)	3 (<1)	4 (1)	4 (1)

A total of 183 patients had at least one abnormal hematology value that was considered to be clinically significant by the investigator on at least on occasion (Table 83). Ninety-six were not present at baseline. The incidence was the same across the treatment groups. Most of the abnormalities were related to glucose levels and were attributed to other known diseases. The five cases that were possibly related to study drug treatment were all due to elevated cortisol levels (See below).

Table 83. Summary of Abnormal Chemistry Values

(%) Patients Reporting Events Number of Events	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Total with ≥1 clinically abnormality	47 (13)	49 (13)	45 (12)	42 (12)
Abnormality not present at baseline	23 (6)	22 (6)	27 (7)	24 (7)
Investigator attribution				
Disease under study	1 (<1)	1 (<1)	0	0
Other concurrent disease	9 (2)	11 (3)	11 (3)	11 (3)
Other concurrent medication	5 (1)	3 (<1)	2 (<1)	0
Possibly due to study medication	0	2 (<1)	2 (<1)	1 (<1)
Unknown	11 (3)	6 (2)	13 (3)	13 (4)

HPA-axis evaluation

Serum Cortisol

Eighteen patients had clinically significant serum cortisol values during the study, and 5 of these abnormalities were attributed to study medication. Of these five, two were receiving salmeterol, two were receiving FP and 1 was receiving FSC (Table 84).

Table 84. Clinically Significant Abnormal Cortisol Levels

Treatment	Visit	Serum Cortisol (nmol/L)	Investigator's Attribution
Placebo	10	795	Steroid course
	6	49	Concurrent medication
	2	679	No explanation
	11	73	Concurrent medication

SAL	10 7 7 7, 10 10	46 97 97 682, 689 741	Concurrent medication Concurrent medication **Trial medication** **Trial medication** Concurrent medication
FP	7 10 2 2,5 7 11 10	7 640 890 36 9 59 20	Unknown Concurrent disease **Trial medication** Steroid injection to knee Probable laboratory error **Trial medication** Inhibition of serum cortisol
FSC	11 10	834 599	No explanation **Trial medication**

In the placebo and SAL groups, 4% of the patients had cortisol values that were in the reference range at baseline and were low at the end of the study. In the FP and FSC groups it was 5 and 6%, respectively. The number of patients for whom the serum cortisol value was below the threshold value did not change substantially throughout the course of the study for any of the treatment groups. Fewer than 2% had values above the reference range at any time (Table 85).

Table 85. Patients with Cortisol Levels Beyond the Normal Range

(%) Patients Reporting Events Number of Events	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Baseline, N	354	361	366	351
N < Threshold Low	2 (<1)	3 (<1)	6 (2)	7 (<2)
N > Threshold High	3 (<1)	3 (<1)	5 (1)	1 (<1)
At any visit, N	319	337	343	322
N < Threshold Low	6 (2)	12 (4)	14 (4)	6 (2)
N > Threshold High	3 (<1)	3 (<1)	3 (<1)	4 (1)

The baseline geometric means of the morning serum cortisol were similar across the treatment groups: 359, 347, 336, and 340 nmol/ L in the placebo, SAL, FP, and FSC groups, respectively (Table 86). The geometric mean ratio for the Visit 10/Baseline values was slightly lower in the fluticasone-treated patients. However, the FSC and FP to placebo ratios were 90% or greater.

Table 86. Summary of Morning Serum Cortisol

(%) Patients Reporting Events Number of Events	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	FSC 500/50 (N=358)
Baseline , N	354	360	366	351
Geometric mean (nmol/L)	359	347	336	340
Visit 10:Geometric mean Ratio (n)	1.02 (62)	1.06 (251)	0.94 (262)	0.98 (290)
Visit 10: Column vs. Placebo				
Ratio		1.02	0.90	0.94
95% Confidence limits		0.94, 1.10	0.83, 0.97	0.86, 1.01
Visit 10: FSC vs. Column				
Ratio		0.92	1.04	
95% Confidence limits		0.85, 0.99	0.97, 1.12	

Urinary cortisol was reported as geometric mean 24-hour excretion corrected for creatinine concentration in 99, 107, 113, and 113 patients in the placebo, SAL, FP, and FSC groups, respectively. No assessment of the adequacy of the urine collection is provided. The geometric mean value was 25 nmol/L in all of the treatment groups. The ratio of geometric mean cortisol measured at visit 10 compared to the value at baseline (95% CI) was 0.99 (0.88. 1.11), 0.80 (0.72, 0.90), and 0.87 (0.70, 0.88) for the SAL, FP, and FSC groups, respectively.

12-Lead Electrocardiogram

At baseline the ECG was normal or abnormal but not clinically significant in 88, 91, 89, and 89% of the patients, respectively. Comparing Visit 10 to baseline the ECG had changed from normal to abnormal in 10 SAL patients compared with 5, 6, and 6 of the placebo, FP and FSC patients. ECGs went from abnormal at baseline to normal at Visit 10 in 7, 8, 9, and 6 of the placebo, SAL, FP, and FSC patients. Thus, the number of abnormalities was small in the entire group, but the SAL groups was the only one where more patients went from normal to abnormal than changed from abnormal to normal.

Vital Signs

There were no clinically meaningful changes in vital signs in any of the treatment groups.

Bruise Count

The bruise count was low at baseline (2-3%) and throughout the study in all of the treatment groups. There were, however, a few patients in the actively treated groups with counts of 5 – 15. There were no such patients in the placebo group, and 1, 2, and 4 in the SAL, FP, and FSC groups, respectively.

Oropharygeal Examination

At baseline 3 placebo and 1 SAL patient had clinical evidence of candidiasis. Over the course of the study, candidiasis was observed in 17, 21, 95, and 51 of the patient-visits in the placebo, SAL, FP, and FSC groups, respectively. Of those with clinical evidence of infection 7/13 (53.8%), 3/11 (27.3%), 44/69 (63.8%), and 24/39 (61.5%) of the placebo, SAL, FP, and FSC patients had positive cultures. Candidiasis was reported as an adverse event (see above, pg) in 23 of the FP and 22 of the FSC-treated patients.

2.3 Summary and Discussion

This randomized, double-blind treatment trial was originally powered for the primary endpoint of change in FEV_1. However, it is included in this application primarily to support the decrease in exacerbation indication for FSC. The study population is similar to the population in SCO30003, but there were also significant differences in the requirements for enrollment. In both studies patients were 40 to 79/80 years of age with a >10 pack-year smoking history, a clinical history of COPD and poor reversibility as defined by a < 10% increase in FEV_1 after inhalation of albuterol with the predicted FEV_1 as the denominator. SCO30003 enrolled patients with a FEV_1 % predicted of < 60% with no lower limit, while SFCB3024 enrolled patients with a FEV_1 % predicted of 25 - <70%. The mean FEV_1% predicted was 45% in SFCB3024 and 40%

in SCO30003: the FEV_1% was less than 25% of predicted in 712 (11.6%) of the patients treated in SCO30003. Reversibility was 3.6 to 3.7% in SCO30003 and 3.7 to 4.0 in SFCB3024.

Probably more important in evaluating the change in exacerbation rate was the requirement in SFCB3024 for a history of chronic bronchitis, and for a past history of exacerbations, including at least one in the 12 months prior to enrollment. The SCO30003 patients were not required to have chronic bronchitis and 48% of them denied having had an exacerbation in the 12 months prior to enrollment. Patients enrolled in SFCB3024 could not have received antibiotics or inhaled corticosteroids for the 4 weeks prior to screening or during the run-in. Patients enrolled in SCO30003 were permitted to be on chronic ICS and antibiotic use during the run-in was permitted for exacerbations. Systemic corticosteroids "at screening", however, the patients enrolled in SFCB3024 were prohibited from taking systemic corticosteroids for the 4 weeks prior to enrollment. Thus patients enrolled into SFCB3024 were more prone to have exacerbations due the underlying type of disease (chronic bronchitis and history of recent exacerbation), more care was exercised to be sure they were stable at admission.

Exacerbations were also defined and treated differently in the two trials. While specific symptoms were not required in either study, SFCB3024 provided guidelines for treatment with antibiotics and corticosteroids. If systemic corticosteroids were used, the treatment in SFCB3024 was prescribed as a 10-day course. Furthermore, episodes that occurred within 7 days of one another were treated as one exacerbation. In SCO30003 the definition and treatment of exacerbations was entirely dependent upon the investigators judgment: exacerbations could be of any length and there was no requirement for a specific time period between separate exacerbations. Finally, patients in SFCB3024 could have been given a supply of corticosteroids and/or antibiotics for home use. They were required to call the clinic prior to starting treatment. However, the freedom to start treatment without a visit to the clinic would tend to increase the use of these modalities. It has been shown that research patients do not always come to the clinic for treatment of COPD exacerbations even when they are explicitly told to do so and there is no cost involved [1]. The inconvenience of a clinic visit is probably responsible for some of the discrepancy. It is interesting that patients with >3 moderate or >2 severe exacerbations were excluded from the per-protocol analysis although they were included in the ITT analysis.

The analysis of moderate/severe exacerbations in SFCB3024 was minimally supportive of the results see in SCO30003. The number or exacerbations was on the same order of magnitude as that seen in SCO30003 and all of the active treatment groups had lower rates than the placebo patients. However, in none of the analyses or subgroups was FSC superior to SAL or FP. The number of patients with severe exacerbations was not unequivocally decreased by active treatment and time in the ICU was seven times longer for the FSC patients than for the placebo patients, though this is based on only a few patients.

The pattern of adverse events was similar in the two studies with COPD exacerbations more frequent in the placebo-treated patients, but with evidence of infection more frequent in the FSC-treated patients.

REFERENCES

1. Suissa S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006; 173:842-846.

2. Seemungal TAR, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease, Am J Respir Crit Care Med 1998;157:1418-1422.

3. Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, Anderson P, Morgan NA. Effect of systemic glucocorticoids on exacerbati0ns of chronic obstructive pulmonary disease. N Engl J Med 1999;.340:1941-7.

4. Redelmeier DA, Kahneman D. Patients' memories of painful medical treatments: real-time and retrospective evaluations of two minimally invasive procedures. Pain 1996; 66:3-8.

5. Stone AA, Broderick JE, Shiffman SS, Schwartz JE. Understanding recall of weekly pain from a momentary assessment perspective: absolute agreement, between- and within-person consistency, and judged change in weekly pain. Pain 2004; 107:61-69.

PULMONARY - ALLERGY DRUGS ADVISORY COMMITTEE MEETING

May 1, 2007

STATISTICAL BRIEFING DOCUMENT

NDA 21-077/s_029

ADVAIR DISKUS (Fluticasone/salmeterol) 500/50 mcg BID
to increase Survival and decrease Exacerbation Rate in
Chronic Obstructive Pulmonary Disease

Primary Reviewer: Feng Zhou, M.S.
Secondary Reviewer: Joy Mele, M.S.

Table of Contents

List of Tables

List of Figures

1. EXECUTIVE SUMMARY

ADVAIR DISKUS® (salmeterol [SAL]/fluticasone propionate [FP]; SFC) is a combination product containing SAL, a long acting β2-agonist (LABA), and FP, an inhaled corticosteroid (ICS) manufactured by GlaxoSmithKline group of companies. The DISKUS® formulation is a dry powder inhaler that is approved for the maintenance treatment of asthma in patients 4 years of age and older using doses of 100/50, 250/50, and 500/50 mcg administered twice daily. ADVAIR DISKUS® was also approved (November 17, 2003) for the maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis at a dose of 250/50mcg twice daily. The 250/50mcg dose is the only approved dose for the treatment of patients with COPD because the pivotal trials that formed the basis of approval showed no advantage of the 500/50mcg product over 250/50mcg. In addition, the label includes the proviso that the trials were conducted for 6 months and that efficacy beyond that time had not been documented.

The sponsor submitted this application on October 6, 2006 (NDA 21-077/S029) in support of the following proposed indications for the ADVAIR DISKUS® 500/50mcg dosage strength in the treatment of COPD:

- Twice daily maintenance treatment of airflow obstruction in patients with COPD
- Increasing survival and reducing exacerbations in patients with COPD

Note that the approved 250/50mcg dose was not included in the studies of this supplement, so the results here for 500/50mcg dose cannot be directly compared to results for the 250/50mcg dose.

This review focuses on the data from a 3-year pivotal clinical trial (Study SCO30003) and a one-year secondary study (SFCB3024). The statistical analyses looked at both the comparison of Advair (SFC50/500) to placebo (the primary comparison) and the comparison to its individual active ingredients: salmeterol (SAL50) and fluticasone (FP500). The primary endpoint was all cause mortality (survival rate) over a 3-year period where the status of all patients was ascertained regardless of whether patients remained on treatment. Other mortality endpoints included COPD-related mortality and on-treatment mortality over a 3-year period. An important secondary endpoint was moderate and severe COPD exacerbations which were measured over 3 years in the pivotal trial and over one year in the secondary study. The review also presents results by geographic regions (US vs. non-US) and various other subgroups.

1.1 Conclusions and Recommendations

Based on the evaluation of Study SCO30003, SFC50/500 demonstrated a borderline insignificant effect over placebo with a hazard ratio of 0.82 (95%CI: 0.68, 0.99; p=0.041). Due to the interim analyses, this unadjusted p-value needs to be compared to a significance level of 0.040. To allow comparison to the commonly used significance level of 0.05, the adjusted CI was 0.681, 1.002 and the adjusted p-value was 0.052. The absolute difference of cumulative incidence rates of all cause mortality at 3 years was -2.6% between SFC50/500 (12.6%) and placebo (15.2%). It

should be noted that usually highly significant results are required to demonstrate efficacy with a single study.

According to the proposed multiplicity adjustment procedure in the protocol of Study SCO30003 (See more details on section 3.1.7), secondary hypotheses would not be tested if the primary endpoint results were not significant at the 0.05 level. Since the primary endpoint was not significant at the 0.05 alpha level, secondary endpoints should not be tested. Nevertheless, since the results are borderline, it is important for the reader to see the nominal results for the secondary endpoints while understanding the context of these results under the protocol.

No notable difference in risk reduction for SFC50/500 compared with SAL50 was observed (risk reduction 7%, absolute risk difference of -0.9%, p=0.481). Compared with FP500, SFC50/500 reduced the risk by 23% (absolute risk difference of -3.4%, p=0.007).

SFC50/500 reduced the risk of COPD-related deaths within 3 years by 22% compared with placebo (SFC50/500 rate of 4.7% and placebo rate of 6.0%, p=0.107), which was consistent with the magnitude of the risk reduction seen for all-cause mortality. Although, SFC50/500 was not shown to be significantly different from placebo on COPD deaths, the results for SFC50/500 were notably better than either component. Similarly, an exploratory analysis of deaths occurring while patients were on treatment showed the risk of dying was reduced by 23% with SFC50/500 compared with placebo (p=0.055).

The magnitude of efficacy of SFC50/500 compared with placebo was smaller in the US population than non-US population with risk reductions of 13% and 19% for death and exacerbation, respectively, compared to 20% and 27% for the Non-US population.

There was no statistically significant evidence that treatment (SFC50/500 vs. placebo) effects varied with smoking status, baseline FEV_1, age, sex, ethnic origin, BMI or previous exacerbation history. Subjects who did not use ICS or OCS during the screening period or who were considered at low risk based on a composite baseline variable of no history of MI, no baseline COPD exacerbation and % predicted $FEV_1 > 40$, SFC50/500 showed a greater benefit due to SFC50/500 over placebo compared to subjects that may be characterized as less healthy .

Studies SCO30003 and SFCB3024 showed a reduction in exacerbations and an improvement in FEV_1 for SFC50/500 patients compared to placebo with a nominal p-value less than 0.05.

1.2 Brief Overview of Clinical Studies

The sponsor's submission included three studies as outlined in Table 1. The pivotal clinical trial supporting the above proposal was a recently completed 3-year, multi-national, and multi-center trial of Advair (Study SCO30003). Secondary studies were trials of one year (Study SFCB3024) and 6-month clinical trial (SFCA3006). Study SCO30003 was the only study of mortality. Besides mortality endpoint, Studies SCO30003 and SFCB3024 were similar in design except for sample size (n of 6,112 vs. 1,465) and treatment duration (3 years vs. 1 year). Each trial consists of four arms: Advair or SFC50/500 (50 mcg salmeterol and 500 mcg fluticasone),

SAL50 (50 mcg salmeterol), and FP500 (500 mcg fluticasone propionate). This reviewer focuses on studies SCO30003 and SFCB3024. Study SFCA3006 has been reviewed under a previous submission. The sponsor submitted this study under this NDA to demonstrate that SFC50/500 significantly improved the pre-dose FEV_1 and the 2-hour post-dose FEV_1 relative to placebo (study SFCA3006 did not evaluate COPD exacerbation as an efficacy endpoint).

Table 1 summarizes the design and statistical results for the primary efficacy endpoint for the three studies.

Table 1. Design and Statistical Results of Three Studies

Study (# of centers)	***Gender M/F Mean Age (Range)***	***Design***	***No of Subjects by Group Entered /Completed***	***Primary Efficacy Variable***	***Mean of PL – CIC 95% CI p-value***
SCO30003 444 centers in 42 countries 3 years study	4631 M /1481 F; 65.0 (40 - 86)	Randomized Multi-center Double-blind Parallel-group Placebo-controlled	SFC50/500: 1533/1011; SAL50: 1521/960; FP500: 1534/947; Placebo: 1524/851	All-cause mortality of all subjects in the ITT population within 3 years after the start of treatment	SFC50/500 vs. Placebo: Δ = -2.6% in Mortality Rate Hazard Ratio=0.820, 95%CI: (0.681, 1.002), p=0.052, adjusted for interim analyses SFC50/500 vs. SAL50: Δ = -0.9% in Mortality Rate Hazard Ratio=0.932, 95%CI: (0.77, 1.13), p=0.481 SFC50/500 vs. FP500: Δ = -4.6% in Mortality Rate Hazard Ratio=0.774, 95%CI: (0.64, 0.93), p=0.007
SFCB3024 196 centers in 25 countries 52 weeks study	1060 M /405 F; 63.2 (38 – 79)	Randomized Multi-center Double-blind Parallel-group Placebo-controlled	SFC50/500: 358/269; SAL50: 372/253; FP500: 374/266; Placebo 361/221	Change from Baseline in morning pre-bronchodilator FEV_1 measured at each clinic visit at 52 weeks	SFC50/500 vs. Placebo: Δ = 133mL in pre-bro. FEV_1 95% CI: (105, 161), p<0.001 SFC50/500 vs. SAL50: Δ = 73mL in pre-bro. FEV_1 95% CI: (46, 101), p<0.001 SFC50/500 vs. FP500: Δ = 95mL in pre-bro. FEV_1 95% CI: (67, 122), p<0.001
SFCA3006 69 centers in the US 6 months study	445 M /229 F; 63.2 (40 – 90)	Randomized Multi-center Double-blind Parallel-group Placebo-controlled	SFC50/500: 165/113; SAL50: 160/115; FP500: 168/100; Placebo 181/112	Mean Change from Baseline in morning pre-bronchodilator and 2-hour post-dose FEV_1	SFC50/500 vs. Placebo: A.M. pre-dosing: Δ=159 95%CI: (109, 209), p<0.001 SFC50/500 vs. SAL50: A.M. pre-dosing: Δ=67 95%CI: (15, 118), p=0.012 SAL50 vs. FP500: A.M. pre-dosing: Δ=54 95%CI: (3, 106), p=0.038

1.3 Statistical Issues and Findings

Primary Efficacy Variables – All Cause Mortality within 3 Years

The results of the pre-specified primary analysis (Table 2), time to all-cause mortality at 3 years stratified by smoking status, showed that SFC50/500 reduced the risk of all cause mortality compared with placebo (borderline p-value of 0.041 compared to 0.04) and compared with FP500 (p=0.007). No notable difference in risk reduction for SFC50/500 compared with SAL50 was observed (p=0.481).

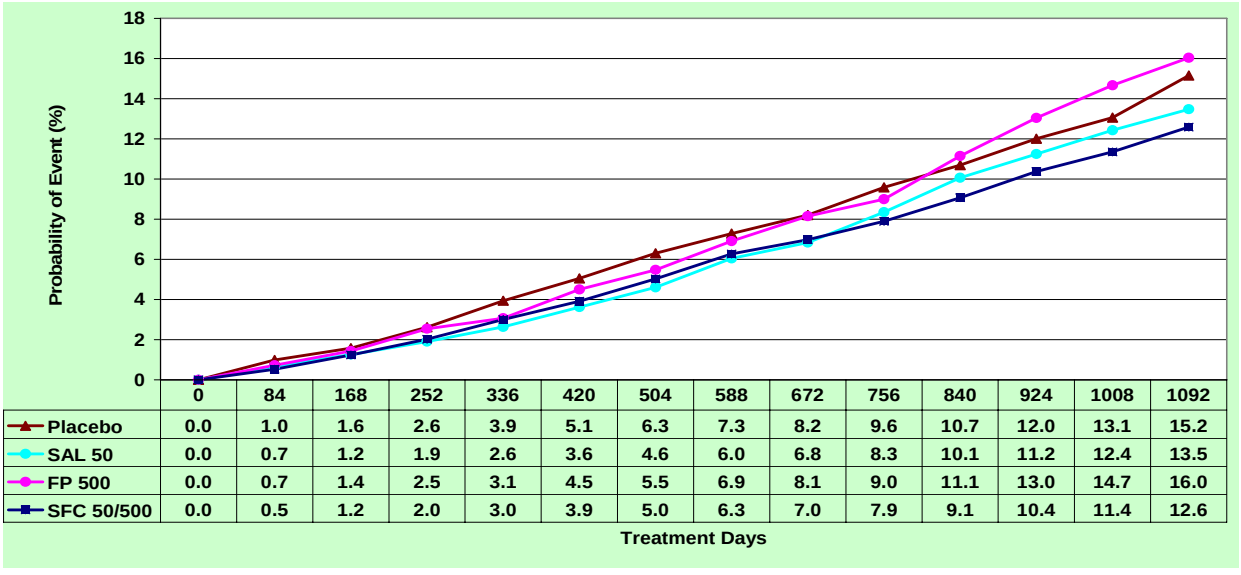
Table 2. Log-Rank Analysis of Time to All-Cause Mortality at 3 Years, Study SCO30003

	Placebo (N=1524)	***SAL50 (N=1521)***	***FP500 (N=1534)***	***SFC50/500 (N=1533)***
Number of deaths	231 (15.2%)	205 (13.5%)	246 (16.0%)	193 (12.6%)
Probability of deaths by 156 weeks (%)[1]	15.2	13.5	16.0	12.6
95% CI	(13.4, 17.0)	(11.8, 15.2)	(14.2, 17.9)	(10.9, 14.3)
Active treatment vs. placebo				
Hazard ratio		0.879	1.060	0.820
95% CI		(0.73, 1.06)	(0.89, 1.27)	(0.68, 0.99)
p-value[2]		0.180	0.525	0.041
SFC50/500 vs. components				
Hazard ratio		0.932	0.774	
95% CI		(0.77, 1.13)	(0.64, 0.93)	
p-value[2]		0.481	0.007	

Note: Log-Rank test stratified by smoking status. 1. Kaplan-Meier estimate. 2. Unadjusted p-value should be compared with adjusted significance level of 0.040 (adjusted for planned interim analyses)

As shown in Figure 1, the cumulative incidence curves of all cause mortality for the four treatments separated during the third year. The pink line (FP500) crossed several time with the red line (placebo) and the light blue line (SAL50) crossed several time with the dark blue line (SFC50/500) suggesting changes in the hazard rates over time.

Figure 1. Time to All-Cause Mortality– Cumulative Incidence Curve



	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo	0.0	1.0	1.6	2.6	3.9	5.1	6.3	7.3	8.2	9.6	10.7	12.0	13.1	15.2
SAL 50	0.0	0.7	1.2	1.9	2.6	3.6	4.6	6.0	6.8	8.3	10.1	11.2	12.4	13.5
FP 500	0.0	0.7	1.4	2.5	3.1	4.5	5.5	6.9	8.1	9.0	11.1	13.0	14.7	16.0
SFC 50/500	0.0	0.5	1.2	2.0	3.0	3.9	5.0	6.3	7.0	7.9	9.1	10.4	11.4	12.6

Other Mortality Endpoints – By cause mortality, COPD-related death and on-treatment death

Cause of death was classified by the Clinical Endpoint Committee (CEC). In addition, the CEC judged whether or not the death was related to the subject's COPD. A summary of cause of death for all deaths occurring in Study SCO30003 within 3 years of treatment start is provided in Table 3. The proportion of COPD-related deaths was lower in the SFC50/500 treatment group (4.7%) than in the placebo (6.0%), SAL50 (6.1%), or FP500 (6.9%) treatment groups.

Table 3. Cause of Death as Classified by the Clinical Endpoint Committee Up to 3 Years

	SCO30003 (n=6112)(%)			
	Placebo	***SAL50***	***FP500***	***SFC50/500***
Randomized patients	1524	1521	1534	1533
All death	231 (15.2)	205 (13.5)	246 (16.0)	193 (12.6)
COPD related death[1]	91 (6.0)	93 (6.1)	106 (6.9)	72 (4.7)
Primary cause of death				
Cardiovascular	71 (4.7)	45 (3.0)	64 (4.2)	60 (3.9)
Pulmonary	74 (4.9)	80 (5.3)	91 (5.9)	61 (4.0)
Cancer	45 (3.0)	44 (2.9)	51 (3.3)	44 (2.9)
Others	23 (1.5)	22 (1.4)	30 (1.9)	11 (0.7)
Unknown	18 (1.2)	14 (0.9)	13 (0.8)	17 (1.1)

1: Only included the adjudicated code: 'yes', 'probably' or 'possibly'.
Source code: death.sas; data source: endpoint.xpt.

SFC50/500 reduced the risk of COPD-related deaths within 3 years by 22% compared with placebo which was not statistically significant; however the results for SFC50/500 were notably better than either component (see Table 4).

Table 4. Log-Rank Analysis of Time to COPD-Related Mortality at 3 Years, Study SCO30003

	Placebo (N=1524)	***SAL50 (N=1521)***	***FP500 (N=1534)***	***SFC50/500 (N=1533)***
Number of deaths, n (%)	91 (6.0)	93 (6.1)	106 (6.9)	72 (4.7)
Number of censored, n (%)	140 (9.2)	112 (7.4)	140 (9.1)	122 (8.0)
Number of alive, n (%)	1293 (84.8)	1316 (86.5)	1288 (84.0)	1339 (87.3)
Probability of deaths by 156 weeks (%)[1]	6.3	6.4	7.3	4.9
95% CI	(5.1, 7.7)	(5.2, 7.7)	(6.1, 8.7)	(3.9, 6.1)
Active treatment vs. placebo				
Hazard ratio		1.103	1.159	0.776
95% CI		(0.759, 1.352)	(0.876, 1.534)	(0.570, 1.057)
p-value[2]		0.932	0.300	0.107
SFC50/500 vs. components				
Hazard ratio		0.766	0.670	
95% CI		(0.563, 1.042)	(0.497, 0.904)	
p-value[2]		0.089	0.008	

Note: Log-Rank test stratified by smoking status. 1. Kaplan-Meier estimate.

On-treatment deaths were defined as any death occurring on or after the treatment start date, and up to and including 14 days of stopping treatment (including those that occurred after 3 years from treatment start). An exploratory analysis of on-treatment deaths showed the risk of dying was reduced by 23% with SFC50/500 compared with placebo (p=0.055).

Secondary Endpoints - COPD Exacerbation and FEV_1

The efficacy evaluation of studies SCO30003 and SFCB3024 demonstrated statistically significant reductions in exacerbation and improvements in FEV_1 for SFC50/500 patients compared to placebo; only the results for exacerbations are shown here.

For SFCB3024, a history of exacerbation was required to enroll, while in Study SCO30003 this was not an entry criterion (see Table 36). However, in Study SCO30003, about 57% of the patients had 1 or more exacerbation in the year pervious to enrollment. To compare two studies, the results for subjects who had COPD exacerbation during the previous year for Study SCO30003 with the results for Study SFCB3024 are shown in Table 5. It can be seen the results are consistent for the combination product versus placebo across the two studies with a 29% risk reduction in the subgroup of patients from Study SCO30003 and a 32% risk reduction in Study SFCB3024. The mean number of exacerbation per year from model is similar in both studies, but SAL50 and FP500 had better effect in Study SFCB3024 compared to Study SCO30003. Overall, Study SCO30003 and Study SFCB3024 demonstrated statistically significant reductions in exacerbation for SFC50/500 patients compared to placebo.

Table 5. Negative Binomial Analysis of the Rate of Moderate and Severe Exacerbation

	Placebo	*SAL50*	*FP500*	*SFC50/500*
Study SCO30003 (MITT) for All Subjects				
N	1524	1521	1534	1533
Mean number per year from model	1.13	0.97	0.93	0.85
Ratio (Active TRT vs. Placebo)		0.853	0.823	0.749
95% CI		(0.784, 0.927)	(0.758, 0.894)	(0.689, 0.814)
p-value		<0.001	<0.001	<0.001
Ratio (SFC50/500 vs. Components)		0.878	0.910	
95% CI		(0.808, 0.954)	(0.838, 0.988)	
p-value		0.002	0.024	
Study SCO30003 for Subjects (MITT) who had COPD Exacerbation at Previous Year				
N	877	859	887	863
Mean number per year from model	1.49	1.24	1.21	1.06
Ratio (Active TRT vs. Placebo)		0.835	0.816	0.714
95% CI		(0.753, 0.925)	(0.738, 0.903)	(0.644, 0.791)
p-value		<0.001	<0.001	<0.001
Ratio (SFC50/500 vs. Components)		0.855	0.875	
95% CI		(0.772, 0.948)	(0.791, 0.967)	
p-value		0.003	0.009	
Study SFCB3024 (ITT) Rate of Moderately Severe and Severe Exacerbation				
N	361	371	374	356
Mean number per year from model	1.51	1.12	1.11	1.03
Ratio (Active TRT vs. Placebo)		0.742	0.736	0.684
95% CI		(0.617, 0.893)	(0.612, 0.885)	(0.566, 0.826)
p-value		0.001	0.001	<0.001
Ratio (SFC50/500 vs. Components)		0.921	0.929	
95% CI		(0.763, 1.111)	(0.771, 1.120)	
p-value		0.390	0.439	

Source cod: negb_anal.sas; Data: exacana.xpt; exacrt24.xpt;pops.xpt.

2. INTRODUCTION

2.1 Overview

ADVAIR DISKUS® (salmeterol [SAL]/fluticasone propionate [FP]; SFC) is a combination product containing SAL, a long acting β2-agonist (LABA), and FP, an inhaled corticosteroid (ICS). The DISKUS® formulation is a dry powder inhaler that is approved for the maintenance treatment of asthma in patients 4 years of age and older. The approved doses are 100/50, 250/50, and 500/50 mcg administered twice daily. ADVAIR DISKUS® is also approved (November 17, 2003) for the maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis. The 250/50mcg twice daily is the only approved dose for the treatment of patients with COPD because the pivotal trials that formed the basis of approval showed no advantage of the 500/50mcg product. In addition, the label includes the proviso that the trials were conducted for 6 months and that efficacy beyond that time had not been documented.

The sponsor submitted this application on October 6, 2006 (NDA 21-077/S029) in support of the following proposed indications for the ADVAIR DISKUS® 500/50mcg dosage strength in the treatment of COPD:

- Twice daily maintenance treatment of airflow obstruction in patients with COPD
- Increasing survival and reducing exacerbations in patients with COPD

The sponsor's submission included three studies as outlined in Table 6. Study SCO30003 was the only study with mortality as a primary endpoint. This reviewer focused on studies SCO30003 and SFCB3024. Study SFCA3006 reviewed under an earlier submission and is not reviewed here.

Table 6. Clinical Trials

Study/Center/ Study Period	***Study Design***	***Key Inclusion Criteria***	***No. of subjects by treatment group entered/completed***	***Primary Endpoints***
SCO30003 466 centers in 42 countries 07 Sep 2000 to 08 Nov 2005	Multi-center Randomized Double-blind Placebo-controlled Parallel- group	COPD diagnosis/history; Age 40-80 yrs; FEV1<60% predicted; FEV1/FEC ratio≤70%; Poor reversibility of airflow obstruction	SFC50/500: 1546/1014 SAL50: 1542/966 FP500: 1551/950 Placebo: 1545/857	All-cause mortality of all subjects in ITT population within 3 years after the start of treatment
SFCB3024 196 centers in 25 countries 20 Aug 1998 to 12 Dec 2000	Multi-center Randomized Double-blind Placebo-controlled Parallel- group	COPD diagnosis/history; Age 40-79 yrs; FEV1 ≥25% to ≤70% predicted; FEV1/FVC ratio ≤70%; Poor reversibility of airflow obstruction	SFC50/500: 358/269 SAL50: 373/253 FP500: 375/266 Placebo: 363/221	Change from baseline in morning pre-bronchodilator FEV1 measured at each clinic visit at 52 week
SFCA3006 69 centers in US 24 Sep 1998 to 05 May 2000	Multi-center Randomized Double-blind Placebo-controlled Parallel- group	COPD diagnosis/history; Age 40+ yrs; FEV1 <65% predicted but >.70L; FEV1/FVC ratio ≤70%;	SFC50/500: 165/113 SAL50: 160/115 FP500: 168/100 Placebo: 181/112	Mean change from baseline at endpoint in morning pre-dose FEV1 and 2-hour post-dose FEV1 at 6 month

2.2 Data Sources

Documents reviewed were accessed from the DCER document room at: \\...\N21077\S_029\

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy of Study SCO30003

3.1.1 Design

Study SCO30003 was a multinational, multi-center, randomized, double-blind, parallel-group, placebo-controlled study in subjects with COPD treated for a period of 156 weeks. The study subjects were outpatients, who fulfilled the study entry criteria. Subjects were stratified by smoking status and were centrally randomized in a 1:1:1:1 ratio to one of the following four treatment groups: SFC50/500, SAL50, FP500, and placebo. Study treatments were provided as inhalation powders administered as one inhalation from the DISKUS device twice daily.

Study SCO30003 consisted of a 2-week run-in period, a 156-week randomized treatment period (including follow-up if subjects were prematurely withdrawn from treatment) and a 2-week follow-up period, and involved a total of 16 clinic visits at 12-weekly intervals (at 0, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, and 156 weeks). The 2-week follow-up period occurred after stopping double-blind treatment, regardless of when that occurred. All subjects were followed for 156 weeks (3 years) following the initiation of treatment for assessment of survival, including those who prematurely discontinued study drug. All inhaled corticosteroids and inhaled long-acting bronchodilators were discontinued at entry to the 2-week run-in period. Salbutamol/albuterol was provided by the Sponsor for use as a relief medication as required (prn) throughout the trial.

The key inclusion criteria are as follow:

Table 7. The Key Inclusion Criteria for Study SCO30003

Male or Female aged 40 – 80
An established clinical history of COPD
Current or ex-smokers with a smoking history of at least 10 pack/yr
No exacerbation history required
Poor reversibility of airflow obstruction (defined as <10% of the predicted normal FEV1 30 minutes after inhalation of 400µg salbutamol via MDI and VOLUMATIC (ELLIPSE in US centers) spacer must be demonstrated at Visit 1)
Baseline (pre-bronchodilator) FEV_1/FVC ratio ≤ 70%
Baseline (pre-bronchodilator) FEV_1 % of predicted normal < 60%

3.1.2 Objective

The primary objective of Study SCO30003 was to demonstrate a significant reduction in all-cause mortality in COPD subjects treated with SFC50/500 compared with placebo, when added to usual COPD therapy.

The secondary objectives of this study were:

- To show a significant reduction in COPD morbidity with SFC50/500 compared to placebo, as measured by the rate of moderate and severe exacerbations
- To show a significant difference in quality of life with SFC50/500 compared to placebo, as measured by the St. George's Respiratory Questionnaire (SGRQ)
- To investigate and compare the number of Adverse Events (AE) in each treatment group.

3.1.3 Patient Disposition

Table 8 summarizes the patient's disposition in study SCO30003 using randomized treatment code (one subject- ID 1563 randomized to placebo received FP500 for the majority of the treatment period). A total of 8554 subjects were screened of whom 6184 (72%) were randomized in a 1:1:1:1 ratio into four treatment groups; 69% of patients who failed screening were in the USA. Data from 72 subjects recruited by five investigators (investigators' ID: 89726, 34560, 75625, 87278 and 54948) were excluded from the sponsor's ITT population, and thus the modified ITT (MITT) population included 6112 subjects (99% of the safety population) and comprised 1524 subjects randomized to placebo, 1521 randomized to SAL50, 1534 randomized to FP500, and 1533 randomized to SFC50/500. Across the four treatment groups, a total of 56% (placebo) to 66% (SFC50/500) of subjects completed the treatment period. The survival status of all patients, except one, was ascertained 3 years post-randomization regardless of whether the patient was on treatment.

Table 8. Patients' Accountability N (%), (ITT)

	Study SCO30003 (n=6184)			
	Placebo	***SAL50***	***FP500***	***SFC50/500***
Randomized patients	1545	1542	1551	1546
Completed treatment period	857 (55.5)	966 (62.7)	950 (61.3)	1014 (65.6)
Discontinued	688 (44.5)	576 (37.3)	601 (38.7)	532 (34.4)
Reason of early discontinuation				
Adverse event	368 (23.8)	304 (19.7)	366 (23.6)	292 (18.9)
Consent withdrawn	139 (9.0)	137 (8.9)	118 (7.6)	120 (7.8)
Lost to follow-up	21 (1.4)	15 (1.0)	24 (1.6)	29 (1.9)
Lack of efficacy	104 (6.7)	63 (4.1)	45 (2.9)	33 (2.1)
Did not fulfill entry criteria	4 (0.3)	3 (0.2)	5 (0.3)	3 (0.2)
Non-compliance	19 (1.2)	21 (1.4)	16 (1.0)	20 (1.3)
Others	32 (2.1)	33 (2.1)	25 (1.6)	33 (2.1)
Analysis Population				
ITT population	1545	1542	1551	1546
MITT population	1524	1521	1534	1533

Data: subaccnt.xpt, pops.xpt; Code: demo.sas.

The sponsor provided information as to the reasons for closing those five centers on December 15, 2006 upon the FDA review team's request. Table 9 displays the patients' enrollment and survival information for the five centers which were excluded from the ITT population. The reasons for excluding these five centers from the ITT population are reasonable to this reviewer; therefore the review focuses on the modified ITT (MITT) population (6112). After this point, all

tables and figures will represent in MITT population unless specified otherwise. The exclusion of these 72 patients (total of 7 deaths) from the mortality analysis changed the results from p=0.054 to p=0.041, See Table 21 for details.

Table 9. The Patients' Survival Information in Those Five Centers (Death/Enrollment)

Center	*Country*	*Date Closed*	*Reason for Site Exclusion*	*Placebo*	*SAL50*	*PF 500*	*SFC 50/500*	*Total*
89726	Slovakia	1/5/02	Falsification of data	0/7	0/7	0/6	1/5	1/25
34560	Canada	16/12/02	Failure to adequately follow-up subjects or co-operate with monitors	0/1	0/2	0/3	0/2	0/8
75625	Australia	24/6/04	Study monitor falsified PI's signature on at least 3 documents	1/8	1/7	0/6	0/2	2/23
87278	France	27/9/04	Investigator died and left no records	0/2	0/0	0/0	0/1	0/3
54948	USA	31/8/05	PI was on 3-year probation for previous episode of inadequate patient care	1/3	1/5	0/2	2/3	4/13

Figure 2 presents the cumulative incidence curve for premature study drug discontinuations in Study SCO30003. About 10% more placebo patients discontinued than SFC50/500 patients.

Figure 2. Time to Study Drug Discontinuation - Cumulative Incidence Curve

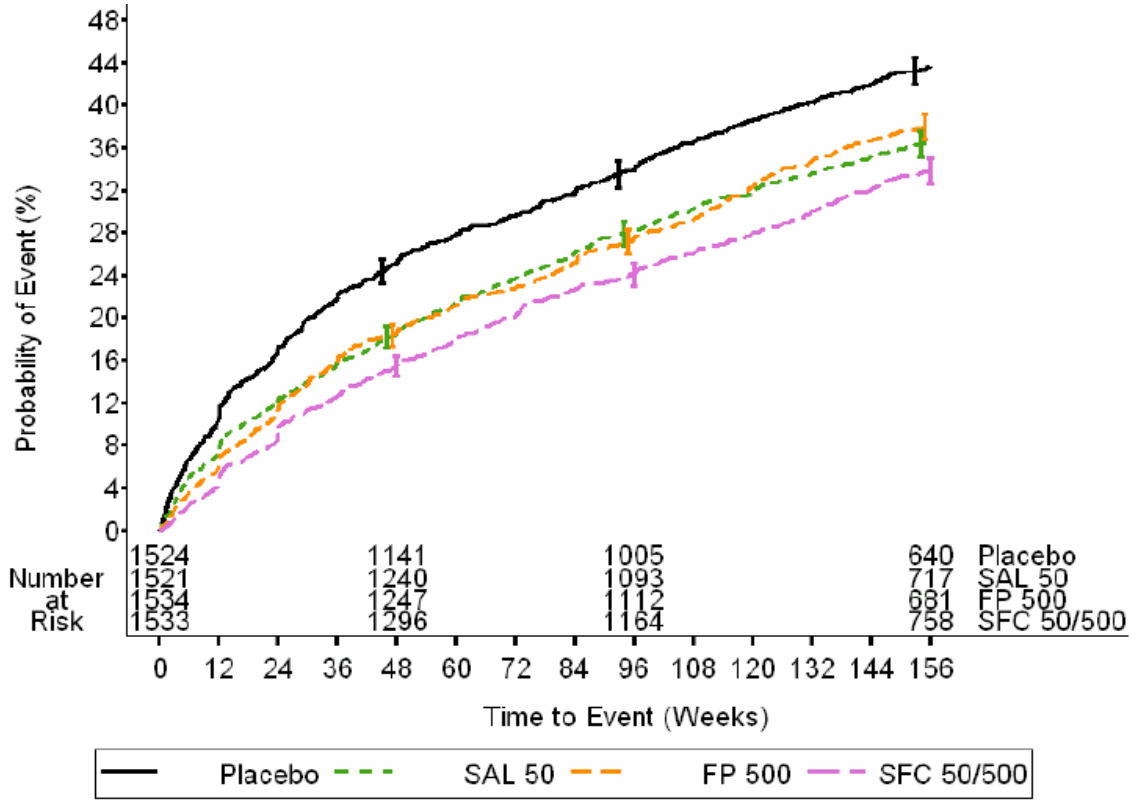
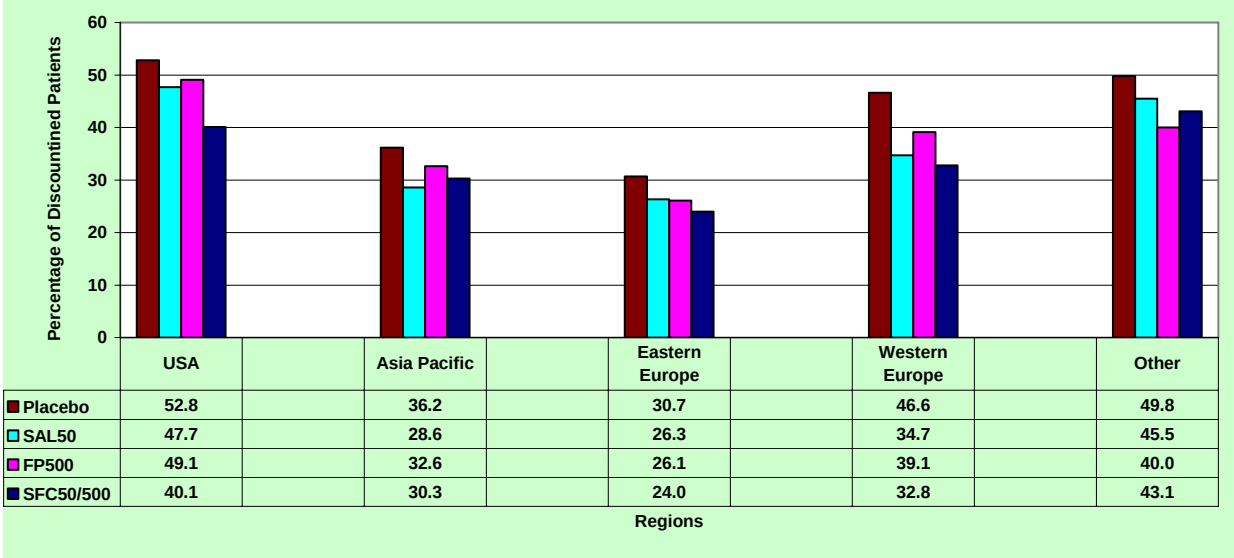


Figure 3 displays the percentage of discontinued patients by regions. USA had the highest dropout rate. The difference between SFC50/500 and placebo was 13% in Western Europe and 12.7% in USA.

Figure 3. Percentage of Discontinued Patients by Regions



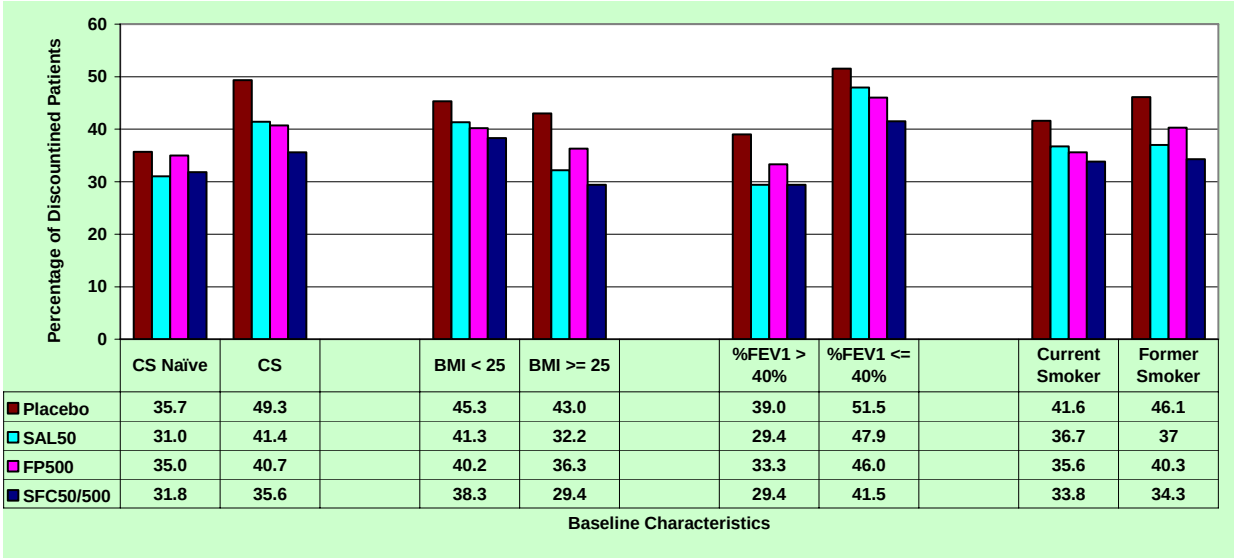
	USA	Asia Pacific	Eastern Europe	Western Europe	Other
Placebo	52.8	36.2	30.7	46.6	49.8
SAL50	47.7	28.6	26.3	34.7	45.5
FP500	49.1	32.6	26.1	39.1	40.0
SFC50/500	40.1	30.3	24.0	32.8	43.1

Regions

Source:discountinue.xls

Figure 4 displays the percentage of discontinued patients by baseline characteristics. There was a 12 -14% difference between SFC50/500 and placebo in dropout rate for subjects who took a corticosteroid (CS) during screening period, who were over weight, or who were former smokers.

Figure 4. Percentage of Discontinued Patients by Baseline Characteristics

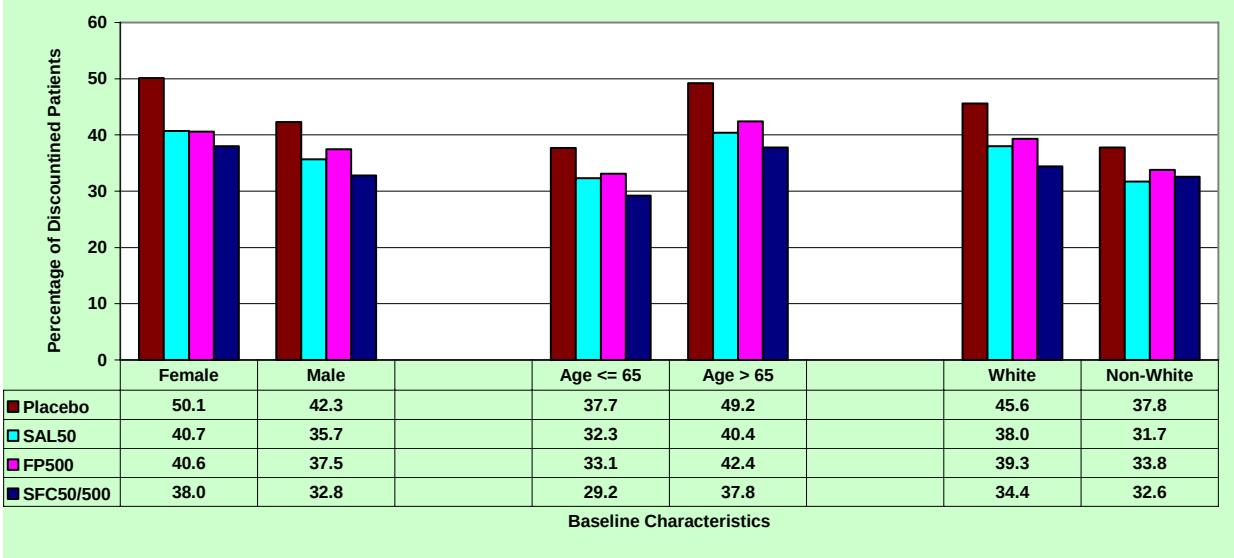


	CS Naïve	CS	BMI < 25	BMI >= 25	%FEV1 > 40%	%FEV1 <= 40%	Current Smoker	Former Smoker
Placebo	35.7	49.3	45.3	43.0	39.0	51.5	41.6	46.1
SAL50	31.0	41.4	41.3	32.2	29.4	47.9	36.7	37
FP500	35.0	40.7	40.2	36.3	33.3	46.0	35.6	40.3
SFC50/500	31.8	35.6	38.3	29.4	29.4	41.5	33.8	34.3

Baseline Characteristics

Figure 5 displays the percentage of discontinued patients by demographics. There was 12% difference between SFC50/500 and placebo in dropout rate for female subjects, older age (> 65) subjects, or White subjects.

Figure 5. Percentage of Discontinued Patients by Demographics



Source:discountinue.xls

So generally the dropout rate was greater in patients that might be considered at high risk.

3.1.4 Demographic and Baseline Characteristics

The demographics and baseline characteristics for all randomized patients (ITT) for study SCO30003 are summarized by treatment groups in Table 10. There was no important difference in baseline characteristics between the MITT and ITT population. Treatment groups were well-matched for demographic characteristics. The mean age of the subjects was 66 years and the majority (76%) was male. Most subjects (82%) were White. Only 13% of subjects had a BMI below 20kg/m^2. There was 23% US population.

The treatment groups were well-matched for lung function before the start of treatment. Overall, the mean baseline (value obtained at Visit 2, or that obtained at Visit 1 if Visit 2 was missing) pre-bronchodilator FEV_1 as a percentage of predicted was 40%. Notice that, the poor reversibility of airflow obstruction criteria was not well controlled during the enrollment, a high percentage of subjects had more than 10% pre-bronchodilator FEV_1 at visit 1. There were 5% of subjects participated in Study SFCB3024 in each treatment.

Table 10. ITT Subjects' Demographics and Baseline Characteristics by Treatment

	SCO30003 (n=8554) (%)			
	Placebo (n=1545)	**SAL50 (n=1542)**	**FP500 (n=1551)**	**SFC50/500 (n=1546)**
Regions				
USA	348 (22.5)	351 (22.8)	350 (22.6)	352 (22.8)
Asia Pacific	188 (12.2)	189 (12.3)	193 (12.4)	188 (12.2)
Eastern Europe	297 (19.2)	196 (19.2)	293 (18.9)	293 (18.6)
Western Europe	478 (30.9)	475 (30.8)	481 (31.0)	477 (30.9)
Other	234 (15.2)	231 (15.0)	234 (15.1)	236 (15.3)
Sex				
Female	369 (23.9)	366 (23.7)	383 (24.7)	382 (24.7)
Male	1176 (76.1)	1176 (76.3)	1168 (75.3)	1164 (75.3)
Race				
White	1270 (82.2)	1271 (82.4)	1270 (81.9)	1267 (82.0)
Asian	190 (12.3)	192 (12.5)	196 (12.6)	191 (12.4)
Black	25 (1.6)	20 (1.3)	24 (1.6)	26 (1.7)
American Hispanic	50 (3.2)	45 (2.9)	48 (3.1)	50 (3.2)
Others	10 (0.7)	14 (0.9)	13 (0.8)	12 (0.8)
Age				
Mean (SD)	64.5 (9.5)	65.1 (8.1)	65.2 (8.2)	65.0 (8.4)
Median	66	66	66	66
Range	36 – 87	40 – 85	40 – 86	40 – 82
<50	63 (4.1)	73 (4.7)	64 (4.1)	70 (4.5)
50 – 64	617 (39.9)	591 (38.3)	618 (39.9)	598 (38.7)
65+	865 (56.0)	878 (56.9)	869 (56.0)	878 (56.8)
BMI				
Mean (SD)	26.8 (6.5)	25.5 (5.2)	25.4 (5.2)	25.3 (5.1)
Median	26.1	25.0	24.8	24.8
Range	0 – 86	12 – 57	12 – 47	12 - 55
< 20	200 (12.9)	207 (13.4)	197 (12.7)	226 (14.6)
20 - < 25	579 (37.5)	580 (37.6)	588 (37.9)	572 (37.0)
25 - < 29	418 (27.1)	414 (26.9)	425 (27.4)	413 (26.7)
29+	348 (22.5)	341 (22.1)	341 (22.0)	335 (21.7)
Myocardial Infarction				
Yes	112 (7.2)	115 (7.5)	92 (5.9)	103 (6.7)
Smoking Status				
Current	664 (43)	657 (43)	666 (43)	667 (43)
Former	881 (57)	885 (57)	885 (57)	879 (57)
COPD Exacerbation in Previous Year				
0	658 (42.6)	677 (43.9)	654 (42.2)	680 (44.0)
1	391 (25.3)	365 (23.7)	396 (25.5)	374 (24.2)
>=2	496 (32.1)	500 (32.4)	501 (32.3)	492 (31.8)
% Predicted Pre-bronchodilator FEV1 at Visit 1				
Mean (SD)	40.4 (11.7)	39.9 (12.1)	40.5 (11.8)	40.7 (12.0)
Median	40.3	40.1	40.7	41.4
Range	11 – 70.3	11 – 101.3	7.3 – 76.6	13.1 – 79.5
>= 60%	12	9	9	11
Pre-bronchodilator FEV1/FVC Ratio at Visit 1				
Mean (SD)	48.6 (10.9)	48.8 (10.8)	48.6 (10.8)	48.8 (10.9)
Median	48.5	48.4	48.6	48.6
Range	20.6 – 77.1	16.9 – 77.9	19.6 – 81.8	18.8 – 80.5
> 70%	6	10	4	7
Reversibility % Pre-bronchodilator FEV1 at Visit 1				
Mean (SD)	10.1 (10.6)	10.4 (11.3)	10.1 (11.0)	10.1 (10.7)
Median	8.9	9.9	9.2	9.5
Range	-53.1 – 53.9	-62.2 – 51.4	-36.7 – 96.2	-35.4 – 64.5
>= 10%	706	770	719	754
Subjects Participated in Study SFCB3024	97 (6.3%)	81 (5.3%)	70 (4.5%)	98 (6.3%)

The baseline characteristics in the US population were different from other regions in terms of race, sex, COPD in previous year (50%; 60% for other regions), myocardial infarction (12.2%; 2-7% for other regions), and lung function test (see Table 11). In Asia, there were fewer female subjects (9%) compared to other regions (16% to 40%) and BMI was lower compared to other regions. Notice that, the poor reversibility of airflow obstruction criteria was not well controlled during the enrollment, a high percentage of subjects had more than 10% pre-bronchodilator FEV_1 at visit 1, particularly in the US (60%) and Asia (50%).

Table 11. ITT Subjects' Demographics and Baseline Characteristics by Region

	Study SCO30003 (n=8554) (%)				
	USA	***Asia Pacific***	***Eastern Europe***	***Western Europe***	***Other***
Enrollment					
Screening	3037	986	1210	2191	1130
Randomized	1401 (46.1)	758 (76.9)	1179 (97.4)	1911 (87.2)	935 (82.7)
Completed	733 (52.3)	516 (68.1)	845 (71.7)	1177 (61.6)	516 (55.2)
Discontinued	668 (47.7)	242 (31.9)	334 (28.3)	734 (38.4)	419 (44.8)
Sex					
Female	563 (40.2)	72 (9.5)	184 (15.6)	420 (22.0)	261 (27.9)
Male	838 (59.8)	686 (90.5)	995 (84.4)	1491 (78.0)	674 (72.1)
Race					
White	1288 (91.9)	2 (0.3)	1178 (99.9)	1908 (99.8)	702 (75.1)
Asian	2 (0.1)	754 (99.5)	1 (0.1)	2 (0.1)	10 (1.1)
Black	89 (6.4)	0	0	1 (0.1)	5 (0.5)
American Hispanic	19 (1.4)	0	0	0	174 (18.6)
Others	3 (0.2)	2 (0.3)	0	0	44 (4.7)
Age					
<50	53 (3.8)	18 (2.4)	79 (6.7)	83 (4.3)	37 (4.0)
50 – 64	559 (39.9)	233 (30.7)	535 (45.4)	760 (39.8)	337 (36.0)
65+	789 (56.3)	507 (66.9)	565 (47.9)	1068 (55.9)	561 (60.0)
BMI					
< 25	595 (42.5)	614 (81.0)	556 (47.2)	868 (45.4)	516 (55.2)
25+	806 (57.5)	144 (19.0)	623 (52.8)	1043 (54.6)	419 (44.8)
Myocardial Infarction					
Yes	171 (12.2)	15 (2.0)	63 (5.3)	111 (5.8)	62 (6.6)
Smoking Status					
Current	600 (42.8)	244 (32.2)	598 (50.7)	856 (44.8)	356 (38.1)
Former	801 (57.2)	514 (67.8)	581 (49.3)	1055 (55.2)	579 (61.9)
COPD Exacerbation in Previous Year					
0	714 (51.0)	311 (41.0)	438 (37.2)	794 (41.6)	412 (44.1)
1	322 (23.0)	172 (22.7)	304 (25.8)	503 (26.3)	225 (24.1)
>=2	365 (26.1)	275 (36.3)	437 (37.1)	614 (32.1)	298 (31.9)
% Predicted Pre-bronchodilator FEV1 at Visit 1					
Mean (SD)	38.9 (12.5)	36.2 (12.0)	42.0 (10.8)	43.0 (11.2	38.5 (11.9)
Median	38.9	34.8	42.1	43.6	38.5
Range	7.3 – 70	21.1 – 61.8	16 – 68.3	11 – 101.3	10.7 – 70.3
>= 60%	17	2	2	15	5
Pre-bronchodilator FEV1/FVC Ratio at Visit 1					
Mean (SD)	47.6 (10.9)	48.1 (10.4)	51.3 (10.4)	50.1 (10.5)	44.5 (10.8)
Median	47.2	48.2	51.2	50.0	43.2
Range	18.9 – 77.8	21.4 – 70.5	20.6 – 81.8	18.8 – 80.5	16.9 – 71.6
> 70%	11	1	2	12	1
Reversibility % Pre-bronchodilator FEV1 at Visit 1					
Mean (SD)	13.1 (12.1)	11.0 (11.2)	8.6 (10.0)	8.0 (9.7)	11.3 (11.0
Median	12.5	10.6	8.0	7.4	10.4
Range	-62.3 – 96.1	-33.7 – 53.9	-37.0 – 53.9	-38.3 – 47.1	-36.7 – 51.7
>= 10%	845	395	492	731	486

Data: subaccn.xpt; pops.xpt; lft_base.xpt; Code: Demog.sas

3.1.5 Statistical Methodologies

There were nine amendments to the original protocol dated 03 April 2000. Three amendments involved statistical issues.

Amendment 3, dated 15 November 2000, was applicable to all centers. This amendment: clarified the primary, secondary and other objectives of the study; increased the power of the study from 80% to 90% by increasing the population from 3800 to 5040 subjects; changed the key secondary endpoints from 1. COPD-related mortality; 2. Requirement for LTOT to 1. Rate of moderate and severe COPD exacerbations; 2. Quality of Life (SGRQ).

Amendment 8, dated 17 May 2002, was applicable to all centers. This amendment: increased the sample size from 5040 to 6040 based on the lower than expected death rate; increased the number of sites from approximately 350 to approximately 450; added collection of all fatal SAEs during long-term follow-up in addition to study drug-related SAEs; redefined the trigger for the first interim analysis by changing the timing of the first interim analysis from when 3/4 of enrolment has been met until we have had approximately 300 deaths; corrected minor protocol inaccuracies;

Amendment 9, dated 13 January 2006, was applicable to all centers. This amendment: added an additional objective (investigation of COPD-related mortality, on-treatment mortality and the composite endpoint of 'treatment failure') and clarified the planned statistical analyses.

1. Changed the study secondary objective by putting salmeterol first in the comparison order:
   From " To demonstrate a significant reduction in all-cause mortality in COPD subjects treated with following, in addition to usual COPD therapy:
   ADVAIR vs. fluticasone propionate
   ADVAIR vs. salmeterol
   fluticasone propionate vs. placebo
   salmeterol vs. placebo"

   To: " To demonstrate a significant reduction in all-cause mortality in COPD subjects treated with following, in addition to usual COPD therapy:
   ADVAIR vs. salmeterol
   ADVAIR vs. fluticasone propionate
   falmeterol vs. placebo
   fluticasone propionate vs. placebo"

2. Changed the definition of the ITT population:
   'The Intent-to Treat – Efficacy population will consist of all subjects in the safety population, with the exception of subjects recruited at sites which were closed down as the results of audit findings or other information which implied that the integrity of the data had been composed. These subjects will be excluded from the ITT population (and

all efficacy analyses), and this decision will be formally documented prior to un-blinding of the trial. …"

3. Added a multiple comparisons:
   "To handle multiplicity issues with respect to the effect of ADVAIR 50/500 on COPD mortality and morbidity the following ordered hierarchy (i.e. gatekeeper approach) for the primary and secondary endpoints and treatment comparisons will be applied:
   a. All-cause mortality within 3 years
      ADVAIR vs. placebo
   b. Rate of moderate and severe COPD exacerbations
      ADVAIR vs. placebo
      ADVAIR vs. salmeterol
   c. Quality of Life determined using the ST. George's Respiratory Questionnaire (SGRQ)
      ADVAIR vs. placebo
      ADVAIR vs. salmeterol …"

4. "The rate of moderate and severe exacerbations will be analyzed using a Negative Binomial model, adjusting for region of recruitment, age, sex, baseline smoking status, BMI, number of exacerbations in the 12 months prior to screening and baseline disease severity and will also include a term for duration on treatment (to censorship or end of study as appropriate). For this analysis, data will not be imputed beyond end of study drug treatment."

The sponsor claimed that Amendment 9 was implemented after all subjects had completed the study but prior to un-blinding.

3.1.5.1 Efficacy Endpoints

Primary Efficacy Measurements

All Cause Mortality

The primary endpoint of this study was all-cause mortality comparing SFC50/500 with placebo at 3 years. In the case of subjects who prematurely withdrew from study treatment, survival status was noted at 12-weekly intervals until 156 weeks had elapsed since the subject started study treatment.

Assignment of Cause of Death

Assignment of the cause of death was essential and was conducted centrally by an independent committee in order to minimized regional bias. Categorization of cause of death was conducted by the Clinical Endpoint Committee (CEC). The CEC reviewed the CRF and survival data and all available documentation from the site (including death certificate, witness account, discharge summary and autopsy reports) for all deaths reported and categorized the cause of death according to a set of pre-determined categories. The categorization of death assigned by the CEC was the primary basis for all analyses of cause of death or COPD-related death.

Interim Analyses and Safety Reviews

The study had two planned interim analyses of all cause mortality in addition to the final analysis. An O'Brien-Fleming alpha spending function was used to compute stopping boundaries. The software of PEST4 was used to calculate the adjust values.

The first interim analysis was planned to be performed when approximately 300 deaths had occurred. The timing of the second interim analysis was fixed according to recruitment rates so as to fall approximately mid-way between the first interim and the final analysis.

The interim analyses, un-blinded to treatment allocation, were undertaken by the Safety and Efficacy Data Monitoring Committee (SEDMC). Following completion of each interim analysis, the SEDMC gave a recommendation to the Steering Committee as to whether the trial, or a specific treatment limb, should be stopped prematurely following review of the interim results for safety and efficacy. The Steering Committee, in conjunction with the Sponsor, decided whether to act on this recommendation.

In addition to the two planned interim analyses, the independent statistician on the SEDMC prepared un-blinded summary table of SAEs every six months. The SEDMC also could recommend increasing the overall trial size, or extending the period of follow-up, in order to ensure adequate power for the trial to give a definitive result. Such recommendations were to be made to the Steering Committee.

Secondary Efficacy Measurements

The secondary efficacy endpoints of this study were the rate of moderate and severe COPD exacerbations and quality of life as determined using the SGRQ.

Exacerbations of COPD

COPD exacerbations were assessed by the investigator at each clinic visit (12 weekly interval) while subjects remained on treatment. For the purpose of this study, an exacerbation of COPD is defined as:

- moderate if treated with systemic corticosteroids and/or antibiotics
- severe if hospitalization is required for treatment of the exacerbation

SGRQ

Quality of life was assessed using the SGRQ every 24 weeks at Visits 2, 4, 6, 8, 10, and 12 and also at Visit 15, in those countries where a linguistically valid translation was available. This reviewer did not analyze this variable because the FDA clinical team did not think the results warranted a statistical review.

Other Efficacy Measurements

Post-Bronchodilator FEV_1

Clinic post-bronchodilator FEV_1 was another efficacy measure assessed in this study. At Visit 2 and 24 weekly intervals thereafter and also at Visit 16, measurement of FEV_1 was taken 30 minutes after inhalation of 400μg salbutamol via MDI and **VOLUMATIC** spacer (**ELLIPSE** in US centers).

3.1.5.2 Statistical Methods

Survival Analysis

Main Model

The primary efficacy endpoint of time to all-cause mortality within 3 years (i.e. 156 weeks) was compared between the SFC50/500 and placebo treatment groups within the ITT population, using the log-rank test, stratified by smoking status. Time to death was calculated in days using the date of death and treatment start date. Adjusted p-values and the median unbiased estimate of the hazard ratio for the final analysis were calculated using discrete stagewise ordering to account for the interim analyses carried out previously.

Kaplan-Meier plots were presented showing the survival curves of the two treatment groups, along with the cumulative incidence curves.

Additional Analyses

A hazard ratio for the SFC50/500 vs. placebo comparison, along with 95% confidence limits was derived, using the following Cox proportional hazards model:

Log (hazard ratio) = Treatment group + smoking status + age + sex + baseline FEV1 + BMI + region

Survival curves and cumulative incidence curves of the two treatment groups from the Cox proportional hazards model were presented.

A log-rank test, stratified by smoking status, country and participation in the Ophthalmic and Skeletal Safety Population was also produced as a supportive analysis in order to account for the stratified nature of the randomization.

Repeated Measures Analysis

Repeated measures analyses were performed for FEV_1. These analyses assumed that the treatment difference can vary between visits (i.e., a treatment by visit interaction was included in the model), and separate estimates were produced at each visit. The estimated treatment differences at each visit were averaged with equal weights so as to obtain the overall treatment effect. Unstructured covariate structure has been used. The models used were the following:

Change from baseline in FEV_1 = Treatment group + smoking status + age + sex + baseline FEV_1 + baseline FEV_1 + BMI + region + visit + treatment*visit + baseline FEV_1 *visit

Calculation of Exacerbation Rates

Rate of Moderate and Severe COPD Exacerbations

Exacerbation rate per year was calculated for each subject as:

Rate of Exacerbation = Number of exacerbations / time on study (in years).

The number of moderate and severe exacerbations occurring during the treatment period was assumed to follow the Negative Binomial distribution. The Negative Binomial model included covariates of smoking status, age, sex, BMI, baseline FEV_1, number of exacerbations reported in the 12 months prior to Screening (0, 1, 2 or more), and region, with time on treatment as an offset variable. The adjusted mean rates per year, pairwise treatment ratios and associated p-values and confidence limits were presented. The primary analysis (negative binomial analysis) of exacerbation data used all available data for each subject while on treatment.

The sponsor proposed using Negative Binomial Model and commented that the negative binomial model has the advantage over the Poisson model in that the variability between subjects is explicitly incorporated into the model with a specific variability parameter that is estimated via maximum likelihood. If Y is the number of exacerbation and μ represents the mean of Y, then the probability density of response Y for the negative binomial distribution can be expressed as:

$$f(y) = \frac{\Gamma(y+1/k)}{\Gamma(y+1)\Gamma(1/k)} \frac{(k\mu)^y}{(1+k\mu)^{y+1/k}} \quad for\ y = 0,1,2,...$$

$$Dispersion = k$$

$$Var(y) = \mu + k\mu^2$$

This model was fitted to the data using SAS PROC GENMOD. The parameter k was estimated by maximum-likelihood and standard errors and p-values were calculated taking this estimation into account. The model included adjustments for smoking status, age, sex, baseline FEV_1, number of exacerbations reported in the 12 months prior to screening (0, 1, 2 or more) and region. In addition to the Negative Binomial Analysis (the pre-specified primary analysis), the sponsor did the following analyses:

- The non-parametric rank analysis of covariance stratifying for smoking status, with age, sex, baseline FEV_1, number of exacerbations reported in the 12 months prior to screening, BMI, and region as covariates to compare the rate of exacerbation between treatment groups.
- The Generalized Estimating Equations Analysis of Exacerbation Rates over Time.
- The Andersen-Gill model to analyze multiple exacerbation events for each subject.

Although this reviewer thinks the Negative Binomial is harder to interpret intuitively than Poisson in terms of exacerbation events as successes, this reviewer agrees with the sponsor's rationale for using the Negative Binomial. This reviewer also fit a Poisson regression model to compare with the results from the Negative Binomial model.

The adjusted means, pairwise treatment differences, p-values and 95% confidence limits for the treatment differences were summarized overall and for each visit, and presented graphically.

Multiplicity

Before Amendment 8, the sponsor did not mention any multiple adjustment method for testing primary and secondary variables. In Amendment 9 (SAP-1/13/06), the following ordered hierarchy for the primary and secondary endpoints and treatment comparisons was described:

- All-cause mortality within 3 years
  - ADVAIR vs. placebo

- Rate of moderate and severe COPD exacerbations
  - ADVAIR vs. placebo
  - ADVAIR vs. salmeterol
- SGRQ
  - ADVAIR vs. placebo
  - ADVAIR vs. salmeterol

Each endpoint will be tested at 0.05 level (gatekeeper approach)

Sample Size

A sample size of 3800 based on the assumptions shown in Table 12 was proposed in the original protocol. The assumptions were modified based on two re-estimations of the sample size such that a final sample size of 6040 was planned.

Table 12.The information of Sample Size Calculation

Protocol (Date)	***Sample Size***	***Δ and HR[1]***	***Assumption – death rate in placebo group***	***Power***
Original (4/3/00)	3800 (950 per group)	5% and 0.728	20% at 3 years	80%
Amendment 3 (11/15/01)	5040 (1260 per group)	5% and 0.728	20% at 3 years	90%
Amendment 8 (7/1/02)	6040 (1510 per group)	4.3% and 0.728	17% at 3 years	90%
Study Results (MITT)	**6112**	**2.6% and 0.820**	**15.2% at 3 years**	

1: Δ is true difference of SFC50/500 compared to a placebo morality rate at 3 years and HR is the *hazard ratio for treatment with SFC50/500 compared to placebo*.

Analysis Populations

The Intent-to-Treat (ITT) efficacy population consisted of all subjects who were randomized to treatment and received as least one dose of study medication, with the exception of subjects recruited at sites that were closed as the results of audit findings or other information that implied the integrity of the data had been compromised. All subjects were analyzed based on the treatment group to which they were randomized.

The Health Outcomes Population used for all SGRQ analyses was a subset of the ITT population, and consisted of subjects participating in countries where translations of the SGRQ questionnaire were considered to be linguistically valid for the population and could potentially have a total score calculated for the population, and who completed at least one questionnaire. All subjects were analyzed based on the treatment group to which they were randomized.

Multi-center Studies

For analysis purposes in this study, centers were combined into geographical regions (US, Asia Pacific, Eastern Europe, Western Europe, and Other) which were used in the assessment of treatment by region interactions. According to the sponsor, the process of amalgamation was performed and finalized prior to un-blinding of treatment allocations.

Treatment Comparisons

The primary interest of treatment comparison was between SFC50/500 and placebo. The following comparisons were also of interest:

- SFC50/500 vs. SAL50
- SFC50/500 vs. FP500

- FP500 vs. placebo
- SAL50 vs. placebo

Missing Data Handling

Premature discontinuation and missing data
For any subject who withdrew prematurely from the study, all available data up to the time of discontinuation were included in the analyses Mortality data continued to be collected for subjects who withdrew early, up to 3 years after the start of study treatment.

For the survival analysis of time to all-cause mortality and COPD-related mortality, subjects who were lost to follow-up were censored at the last time-point when they were known to be alive or 1092 days after treatment start, whichever was earlier. For on-treatment mortality analyses, subjects who had not died prior to treatment being stopped were censored at that point.

The repeated measures analysis was the primary analysis for FEV_1 assessments. It did not explicitly use any form of imputation, but all available data for a subject was used within the analysis and the method of analysis itself weighted the information for the complete analysis according to the amount of information available.

3.1.6 Sponsor's Results and Conclusions

The sponsor described their results and conclusion s as follows (p171, Study report of SCO30003):
"The primary endpoint of this study was all-cause mortality within 3 years after the start of treatment and the primary treatment comparison was for SFC50/500 versus placebo. Secondary efficacy endpoints were the rate of moderate and severe COPD exacerbations and quality of life determined using the SGRQ total score. As summarized below, SFC 50/500 demonstrated a greater beneficial effect than placebo on mortality and aspects of COPD morbidity such as exacerbations, health-related quality of life and pulmonary function. No definitive evidence of differential treatment effects on mortality, the rate of moderate and severe COPD exacerbations and health-related quality of life was observed across the different subgroups. A positive treatment effect was observed with SFC50/500 compared with placebo across subgroups on each of the three aforementioned efficacy parameters, but the magnitude of this response varied. In particular, the SFC50/500 treatment effect on mortality and the moderate and severe COPD exacerbation rate was lower in Asian subjects compared with the other subgroups. However, a variation in the magnitude of response may occur by chance. Although a reduced magnitude of response was observed in the smaller subgroup of Asian subjects across these endpoints, the data still demonstrate that treatment with SFC50/500 results in beneficial effects.

Mortality
• SFC50/500 reduced the risk of dying at any time within 3 years from any cause by

17.5% for SFC50/500 compared with placebo (unadjusted p-value 0.041, p-value adjusted for interim analyses 0.052). Results of two separate supporting analyses of all-cause mortality confirmed those seen in the primary analysis.
• There was a 23% reduction in the risk of dying at any time within 3 years from any cause for SFC50/500 compared with FP500 (p=0.007) but no notable difference in risk reduction for SFC50/500 compared with SAL50 was observed (risk reduction 7%, p=0.481).
• There was a 12% reduction in the risk of dying at any time within 3 years from any cause for SAL50 compared with placebo (p=0.180) but no notable difference in risk was observed for FP500 compared with placebo (risk increase 6%, p=0.525).
• There was no evidence that treatment effects varied for important subgroups (smoking status, age, sex, baseline FEV_1, BMI and region) in analyses of all-cause mortality.
• SFC50/500 reduced the risk of COPD-related deaths within 3 years by 22% compared with placebo (p=0.107), which was consistent with the magnitude of response seen for all-cause mortality.
• Similarly, while subjects remained on treatment, the risk of dying was reduced by 23% with SFC50/500 compared with placebo (p=0.055).

Exacerbations

• The rate of moderate and severe exacerbations was decreased by all active treatments in comparison with placebo (p<0.001); the reductions in exacerbation rates were 25% for SFC50/500, 15% for SAL50 and 18% for FP. SFC50/500 was more effective than SAL50 or FP500 in decreasing the moderate or severe exacerbation rate (12% reduction, p=0.002 for SAL50 and 9% reduction, p=0.024, for FP500).
• Three supporting analyses (non-parametric analysis of rate of moderate and severe exacerbations, an analysis of time to first moderate or severe exacerbation and an analysis of time to each moderate or severe exacerbation) gave similar results to those seen in this primary analysis for SFC50/500 compared with placebo.
• There was no evidence that treatment effects varied for important subgroups (smoking status, age, sex, baseline FEV_1, BMI, region and previous exacerbation history)in analyses of the moderate and severe exacerbation rate.
• The rate of severe exacerbations was decreased by 17% for SFC50/500 compared with placebo (p=0.028).
• The rate of exacerbations requiring systemic corticosteroid treatment was reduced by 43% for SFC50/500 compared with placebo (p<0.001)….

Pulmonary Function

• Over the entire treatment period, FEV_1 values were higher in subjects treated with SFC50/500 than for those treated with placebo (average difference over 3 years 92mL, p<0.001). Both SAL50 and FP500 were also more effective than placebo in effects on FEV_1 (average difference 42mL, p<0.001 for SAL50 and 47mL, p<0.001 for FP500).
• SFC50/500 was more effective than SAL50 or FP500 in improving FEV_1 (average difference 50 mL, p<0.001 for SAL50 and 44mL, p<0.001 for FP500).
• Post hoc analyses showed that the rate of decline in FEV_1 was reduced by all active treatments compared with placebo. The rate of decline was -55mL/year for placebo, -42mL/year for SAL50, -42mL for FP500 and -39mL/year for SFC50/500."

3.1.7 Reviewer's Efficacy Analysis

3.1.7.1 Mortality

The primary endpoint was all-cause mortality among all subjects in the MITT population within 3 years (i.e. 156 weeks or 1092 days) after the start of study treatment. Survival status 3 years after initiation of study treatment was known for all subjects in the MITT population exception one (subject 1021, treated with SFC50/500 for 436 days). This subject was censored at the time point at which he was last known to be alive (day 792). There were 927 deaths reported at any time in this study and the time at which they occurred in the study is summarized in Table 13. Twenty-nine subjects were known to have died more than 3 years after that start of study treatment. Thus 875 deaths occurred in the MITT population within 3 years after the start of treatment were the primary interest.

Table 13. Summary of Survival Status, N (%) (ITT)

	Placebo (N=1545)	***SAL50 (N=1542)***	***FP500 (N=1551)***	***SFC50/500 (N=1546)***	***Total (N=6184)***
MITT	1524	1521	1534	1533	6112
Deaths up to 3 years					
Total	**231 (15.2)**	**205 (13.5)**	**246 (16.0)**	**193 (12.6)**	**875 (14.3)**
Unknown	0	0	0	1 (0.1)	1
On-treatment	116 (7.6)	106 (7.0)	140 (9.1)	102 (6.7)	464 (7.6)
Long term follow up	115 (7.5)	99 (6.5)	106 (6.9)	91 (5.9)	411 (6.7)
Deaths post 3 years					
On-treatment	1 (0.1)	3 (0.2)	1 (0.1)	1 (0.1)	6 (0.1)
Long term follow up	5 (0.3)	5 (0.3)	7 (0.5)	6 (0.4)	23 (0.4)
Excluded ITT Subjects	21	21	17	13	72
Deaths	**2 (9.5)**	**2 (9.5)**	**0**	**3 (23.1)**	**7 (9.7)**
Non-Randomized					2370
Deaths					**16 (6.7)**

This reviewer confirmed the sponsor's primary analysis and supporting analyses which included the Log-Rank analysis of time to all-cause mortality stratified by smoking status, country, and participation in the Ophthalmic and Skeletal Safety (OSS) sub-study; the Cox's Proportional Hazards model adjusted for smoking status, age, sex, region, baseline FEV_1 and BMI.

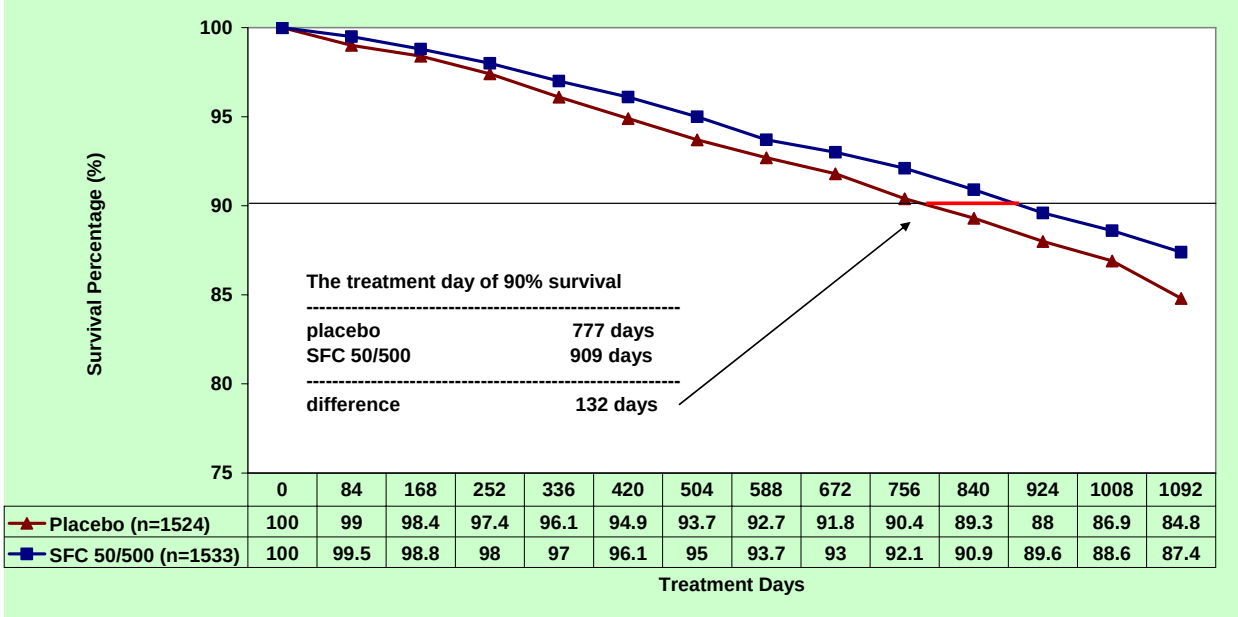
The primary efficacy analysis of time to all-cause mortality at 3 years using log-rank analysis stratified by smoking status for the primary comparison of SFC50/500 vs. placebo for subjects in Study SCO30003 is presented in Table 14. The Kaplan-Meier estimate of probability of death by 156 weeks was 15.2% (95% CI: 13.4, 17.0) for placebo, compared to 12.6% (95% CI: 10.9, 14.3) for SFC50/500. The hazard ratio for time to all-cause mortality for SFC50/500 vs. placebo was 0.820 (95% CI: 0.677, 0.993) and unadjusted p-value was 0.041. Due to the interim analyses, this unadjusted p-value needs to be compared to a significance level of 0.040. To allow comparison to the commonly used significance level of 0.05, the sponsor used PEST4 to calculate the adjust p-value and confidence interval. The adjusted CI was 0.681, 1.002 and adjusted p-value was 0.052. Figure 6 displays the Kaplan Meier estimates of survival probabilities for time to death from all causes.

Table 14. Primary Analysis of Time to All Cause Mortality at 3 Years

	Placebo (N=1524)	*SFC50/500 (N=1533)*
Number of deaths	231 (15.2%)	193 (12.6%)
Probability of deaths by 156 weeks (%)[1]	15.2	12.6
95% CI	(13.4, 17.0)	(10.9, 14.3)
Active treatment vs. placebo		
Hazard ratio		0.820
95% CI		(0.677, 0.993)
p-value[2]		0.041

Note: Log-Rank test stratified by smoking status. 1. Kaplan-Meier estimate. 2. Unadjusted p-value should be compared with adjusted significance level of 0.040 (adjusted for planned interim analyses)

Figure 6. Time to All Cause Death within 3 Years – Survival Distribution



	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo (n=1524)	100	99	98.4	97.4	96.1	94.9	93.7	92.7	91.8	90.4	89.3	88	86.9	84.8
SFC 50/500 (n=1533)	100	99.5	98.8	98	97	96.1	95	93.7	93	92.1	90.9	89.6	88.6	87.4

Source: kmest-death.xls; km_anal.sas

Issues to consider in the interpretation of the mortality results:

1. Sample size re-estimation -

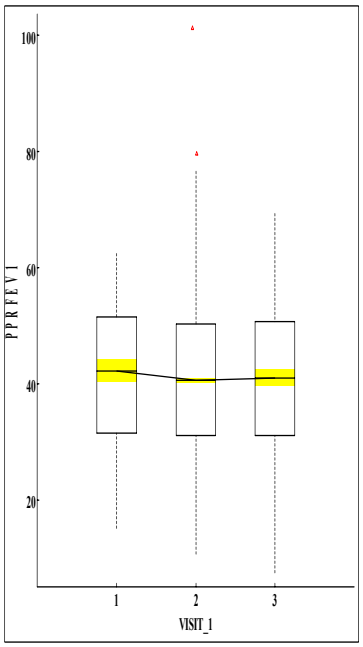
This study started September, 2000 and ended at November, 2005. Table 15 displays the main timeline of this study. The sponsor increased the sample size two times (11/15/00, 5/17/02). It is worth noting that both sample size re-estimations occurred prior to the first interim analysis. Figure 7 displays the lung function characteristics at baseline of subjects enrolled during three periods: 1. from the first enrollment (7 Sep. 2000) to the first increase in sample size (15 Nov. 2000); 2. from the first increase in sample size (15 Nov. 2000) to the second increase in sample size (17 May 2002); 3. from the second increase in sample size (17 May 2002) to the last enrollment. The box lots illustrate that patients enrolled after each increase in sample size had similar baseline characteristics to those already on study.

Table 15. Timeline of Study SCO30003

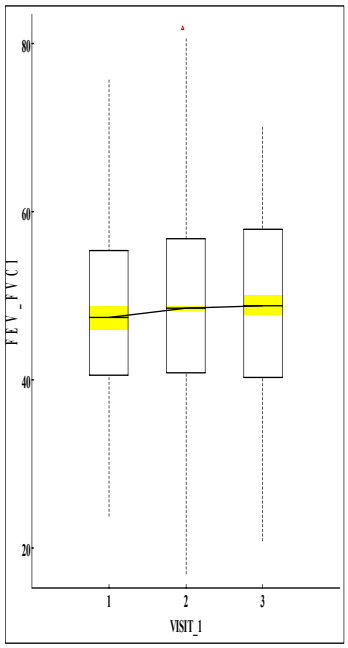
Date	Description	Cumulative Enrollment	Cumulative Death
03 April, 2000	The original protocol of SCO30003	0	
07 September, 2000	Began enrollment in Europe	1	0
15 November, 2000	Increased sample size from 3800 to 5040	261	0
05 July 2001	Enrolled first US subjects	2350	17
17 May, 2002	Increased sample size from 5040 to 6040	5660	140
30 September, 2002	Enrolled the last patient	6184	232
23 May, 2003	Performed the first interim analysis	6154	428
20 May, 2004	Performed the second interim analysis	6153	757
08 November, 2005	Completed study	6184	912
13 January, 2006	Finalized the statistical analysis plan		
06 October, 2006	Submitted NDA		

Data: subaccnt.xpt, pops.xpt; Source: demo.sas.

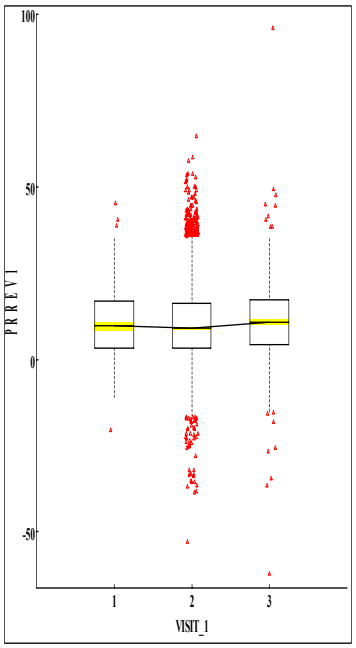
Figure 7. ITT Subjects' Lung Function Test at Baseline by Group by Enrollment Time



%Predicted Pre-bronchodilator FEV1



Pre-Bronchodilator FEV1/FVC Ratio



Reversibility %Predicted Pre-bronchodilator FEV1

Table 16 displays the results of log-rank analysis and Kaplan Meier estimates of survival probabilities for all cause mortality at 3 year grouped by enrollment time as described above (before the 2nd increasing sample size and after the 2nd sample size increasing). The percentage of death was higher after the 2nd sample size increasing which is displayed in Table 17. The percentage of death in the placebo group was higher than other treatment groups. Based on the evaluation, it seems that the sample size re-estimation was done appropriately and did not impact the integrity of the trial.

Table 16. Time to All Cause Mortality at 3 Years Grouped by Enrollment Time

Patients Enrollment Time (d/m/y)=>	***Before the 2nd Sample Size Increasing (7/9/00 – 16/5/02)***		***After the 2nd Sample Size Increasing (17/5/02 – 30/9/02)***	
	Placebo	***SFC50/500***	***Placebo***	***SFC50/500***
N	1396	1401	128	132
Number of deaths, n (%)	209 (15.0)	178 (12.7)	22 (17.2)	15 (11.4)
Probability of deaths by 156 weeks (%), 95%CI	15.0 (13.2, 17.0)	12.7 (11.1, 14.6)	17.2 (11.7, 4.9)	11.4 (7.0, 11.8)
Difference	2.3%		5.8%	
SFC50/500 vs. placebo				
Hazard Ratio	0.840		0.626	
95% CI	(0.688, 1.026)		(0.325, 1.206)	

Source: lr_anal.sas; data source: deaths.xpt, and pops.xpt.

Table 17. Mortality Results for Patients Added after the 2nd Sample Size Re-estimation

Patients Enrolled at Time=>	***After the 2nd Sample Size Increasing (16/5/02 – 8/11/05) (N=524)***				
	Placebo	***SAL50***	***FP500***	***SFC50/500***	***Total***
N	128	135	129	132	524
Death (%)	22 (17.2%)	18 (13.3%)	21 (16.3%)	15 (11.4%)	76 (14.5%)
Cancer	8	4	2	2	16
Cardiovascular	6	3	4	7	20
Pulmonary	2	10	9	4	25
Other	2	1	3	0	6
Unknown	4	0	3	2	9

1: Only included the adjudicated code: ‘yes’, ‘probably’ or ’possibly’.
Source code: death.sas; Data source: endpoint.xpt.

2. Interim analyses -

SEDMC recommended continuing the study based on the results from two interim efficacy analyses. No stopping boundaries have been crossed for the comparisons of SFC50/500 with placebo (Table 18). The interim analyses were done after the sample size re-estimation and were conducted as planned; there appears no impact on the integrity of the trial.

Table 18. Mortality Results for Two Interim Analyses and Final Analysis

	Interim Analysis 1 (23 May, 2003)		***Interim Analysis 2 (20 May, 2004)***		***Final Analysis (10 January 2006)***	
	Placebo	***SFC50/500***	***Placebo***	***SFC50/500***	***Placebo***	***SFC50/500***
N	1538	1540	1538	1539	1524	1533
Number of Death (%)	93 (6.1%)	80 (5.2%)	176 (11.4%)	148 (9.6%)	231 (15.2%)	193 (12.6%)
Difference	0.8%		1.8%		2.6%	
Hazard Ratio	0.833		0.820		0.820	
95% CI	(0.617, 1,123)		(0.659, 1.020)		(0.677, 0.993)	
p-value	0.228		0.074		0.041	

Source: lr_anal.sas; data source: ia1dat.xpt, ia2dat.xpt, deaths.xpt, and pops.xpt.

3. Supporting Mortality Analyses –

The sponsor provided the supporting Log-Rank Analysis stratified by smoking status, country, and participation in the Ophthalmic and Skeletal Safety (OSS) sub-study. But, this model didn't fit well. The likelihood ratio test for strata homogeneity was questionable since some strata had no events. In that case, the assumption of proportionality may not be satisfied. This reviewer did the Log-Rank Analysis stratified by smoking status, region and participation in the Ophthalmic and Skeletal Safety (OSS) sub-study. Two analysis results are presented in Table 19.

Table 19. Supporting Log-Rank Analysis of Time to All-Cause Mortality within 3 Years

SFC50/500 vs. placebo	***Stratified by Smoking Status, Participation in OSS, and Country[1]***	***Stratified by smoking Status, Participation in OSS, and Region[2]***
Hazard ratio (95% CI)	0.815 (0.673, 0.987)	0.824 (0.681, 0.998)
p-value[3]	0.036	0.047

1. The sponsor's reported log-Rank analysis results.
2. The reviewer's log-Rank analysis results.
3. Unadjusted p-value should be compared with adjusted significance level of 0.040 (adjusted for planned interim analyses)

Source: supt_lrana.sas.

Table 20 displays the supporting analysis using a Cox's Proportional Hazards model adjusted for smoking status, age, sex, region, baseline FEV_1 and BMI. Hazard ratio was 0.811 (95% CI: 0.670, 0.982) for SFC50/500 vs. placebo which represented a 19% reduction in the risk of dying at any time within 3 years.

Table 20. Supporting Cox's Proportional Hazards Analysis of Time to All-Cause Mortality within 3 Years

	Placebo (N=1524)	***SFC50/500 (N=1533)***
Number of deaths	231 (15.2%)	193 (12.6%)
Probability of death by 156 weeks (%) 95% CI[1]	15.2 (13.4, 17.0)	12.6 (10.9, 14.3)
Probability of death by 156 weeks (%) 95% CI[2]	12.6 (11.0, 14.2)	10.3 (8.9, 11.8)
SFC50/500 vs. placebo		
Hazard ratio (95% CI)		0.811 (0.670, 0.982)
p-value[3]		0.031

1. Kaplan-Meier estimate.
2. Cox's proportional hazards model estimate at mean age, FEV1, body mass index and proportional coefficients for smoking status, sex and region.
3. Unadjusted p-value should be compared with adjusted significance level of 0.040 (adjusted for planned interim analyses)

Source: supt_cox.sas.

Thus, the primary analysis and the two supporting analyses all showed very similar results with a reduction in the risk of dying at any time within 3 years of approximately 18% for SFC50/500 compared with placebo.

4. Multiplicity Issues -

In the protocol amendment 9 (Statistical Analysis Plan) (section 6.2.3.4), the sponsor proposed to handle multiplicity issues with respect to the effect of SFC50/500 on COPD mortality and morbidity. The following ordered hierarchy (i.e. gatekeeper approach) for the primary and secondary endpoints and treatment comparisons would be applied as follow:

- All-cause mortality within 3 years
  - SFC50/500 vs. placebo at α=0.05 (following adjustment for interim analyses)
- Rate of moderate and severe COPD exacerbation
  - SFC50/500 vs. placebo at α=0.05
  - SFC50/500 vs. SAL50 at α=0.05
- SGRQ
  - SFC50/500 vs. placebo at α=0.05
  - SFC50/500 vs. SAL50 at α=0.05

As an ordered hierarchy for the primary treatment comparisons for both the primary and secondary endpoints was applied, no further adjustments for multiple comparisons were required.

In the study report, the sponsor claimed that since the adjusted p-value of 0.052 for the primary endpoint of all-cause mortality was sufficiently close to the boundary of 0.05, the p-values for the secondary endpoint comparisons listed in the gatekeeper approach are being considered as inferential; these p-values were all $\leq$0.002.

According to the proposed multiplicity adjustment procedure in amendment 9, hypotheses is not tested if p-value of previous level of test is great than 0.05. Since the primary endpoint was not significant at 0.05 alpha level, no secondary endpoints should not be tested. This reviewer thinks the gatekeeper procedure as described in the protocol should be applied and that an adjusted p-value of 0.052 negates further testing.

5. Robustness of Study Results –

The primary efficacy analysis result was not robust, being sensitive to small changes in the analysis population. The results of primary efficacy analyses of the MITT (excluding five centers) and ITT population and with the removal of countries with the most favorable and least favorable results to SFC50/500 show that the risk reduction ranged from 17-19% and the absolute difference of death rates ranged from 2.4% to 2.7% (Table 21). One country's data can change the results as much as 7.7% (0.2/2.6) of the overall difference (2.6%).

Figure 8 displays the SFC50/500 survival over placebo by regions. The Eastern Europe had the most survival improvement. Asia showed no survival improvement. The difference between East Europe and Asia for the treatment effect is 4%.

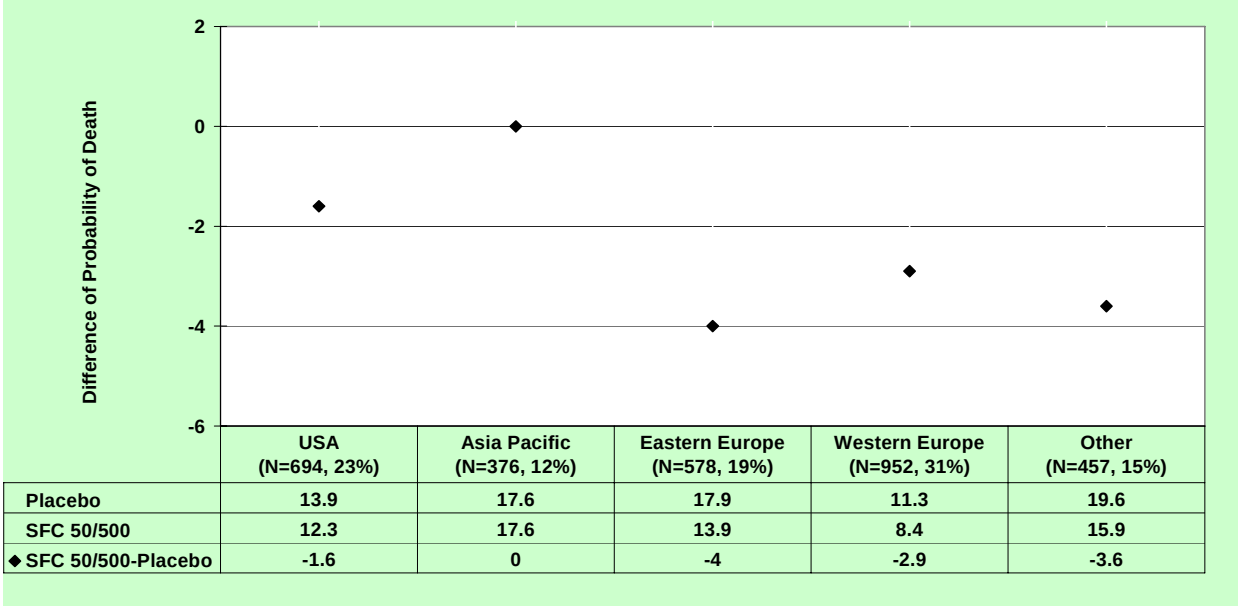
Table 21. Robustness of Analysis of Primary Endpoint

Population	*Placebo*	*SFC50/500*	*SFC50/500 vs. Placebo*	
ITT[1]	**N=1545**	**N=1546**	**Difference**	**Hazard Ratio[2]**
Number of deaths	233 (15.1%)	196 (12.7%)	2.4%	0.830
95% CI	(13.4, 17.0)	(11.2, 14.5)		(0.686, 1.004), p=0.054
MITT	**N=1525**	**N=1533**	**Difference**	**Hazard Ratio**
Number of deaths	231 (15.2%)	193 (12.6%)	2.6%	0.820
95% CI	(13.5, 17.1)	(11.0, 14.4)		(0.677, 0.993), p=0.041
MITT without Best country (Iceland n=41)	**N=1510**	**N=1521**	**Difference**	**Hazard Ratio**
Number of deaths	226 (15.0%)	191 (12.6%)	2.4%	0.829
95% CI	(13.3, 16.9)	(11.0, 14.3)		(0.684, 1.005), p=0.056
MITT without Worst country (Croatia n=34)	**N=1510**	**N=1516**	**Difference**	**Hazard Ratio**
Number of deaths	228 (15.1%)	188 (12.4%)	2.7%	0.807
95% CI	(13.4, 17.0)	(10.8, 14.2)		(0.666, 0.979), p=0.030

Source: lr_anal.sas; data source: deaths.xpt and pops.xpt,

1. The all ITT included the five centers which were excluded from the sponsor's ITT population.
2. Unadjusted p-value should be compared with adjusted significance level of 0.040

Figure 8. Difference of Probability (%) of Death between SFC50/500 and Placebo by Regions



	USA (N=694, 23%)	Asia Pacific (N=376, 12%)	Eastern Europe (N=578, 19%)	Western Europe (N=952, 31%)	Other (N=457, 15%)
Placebo	13.9	17.6	17.9	11.3	19.6
SFC 50/500	12.3	17.6	13.9	8.4	15.9
◆ SFC 50/500-Placebo	-1.6	0	-4	-2.9	-3.6

Source: cnt_efct.sas; data source: deaths.xpt and pops.xpt

6. All Cause Mortality - Other Treatment Comparison

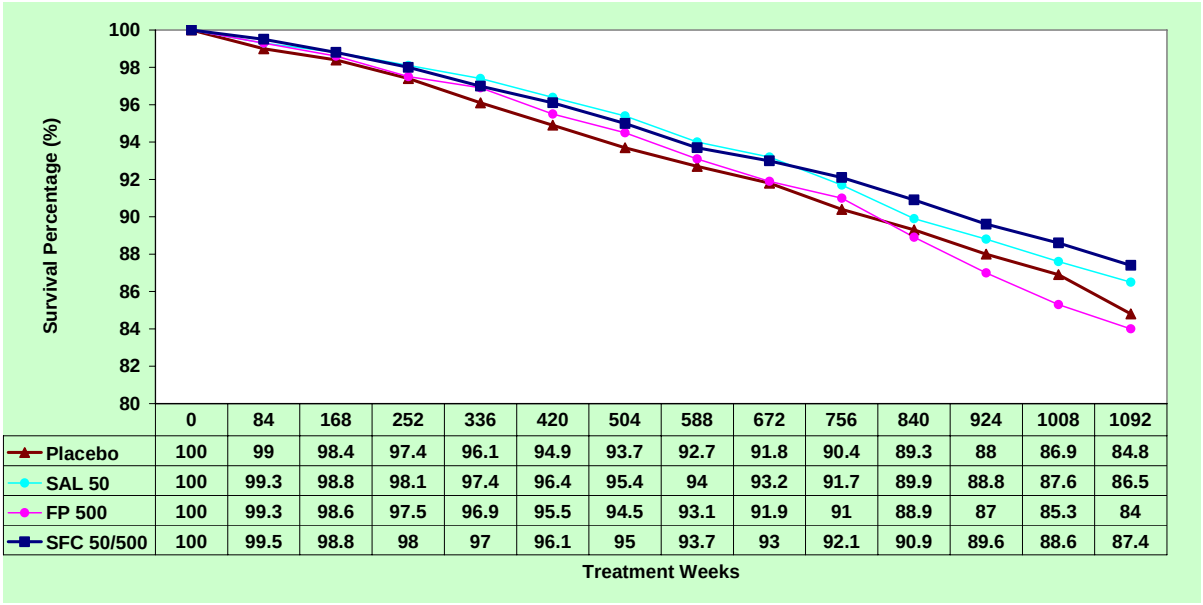
Compared with FP500, SFC50/500 reduced the risk by 23% within 3 years (absolute risk difference of -3.4%, p=0.007) but no notable difference in risk reduction for SFC50/500 compared with SAL50 was observed (risk reduction 7%, absolute risk difference of -0.9%, p=0.481) (Table 22). There was a non-significant 12% risk reduction of dying at any time within 3 years from any cause for SAL50 compared with placebo (absolute risk difference of -1.7%, p=0.180), while for FP500 compared with placebo, a risk increase of 6% was seen (absolute risk difference of +0.8%, p=0.525). Figure 9 graphically displays these results.

Table 22. Log-Rank Analysis of Time to All-Cause Mortality at 3 Years

	Placebo (N=1524)	*SAL50 (N=1521)*	*FP500 (N=1534)*	*SFC50/500 (N=1533)*
TRT Exp. (person yrs)	3238	3499	3532	3678
Number of deaths, n (%)	231 (15.2)	205 (13.5)	246 (16.0)	193 (12.6)
Number of censored, n (%)	0	0	0	1 (<1)
Probability of deaths by 156 weeks (%)[1]	15.2	13.5	16.0	12.6
95% CI	(13.4, 17.0)	(11.8, 15.2)	(14.2, 17.9)	(10.9, 14.3)
Active treatment vs. placebo				
Hazard ratio		0.879	1.060	0.820
95% CI		(0.729, 1.061)	(0.886, 1.268)	(0.677, 0.993)
p-value		0.180	0.525	0.041
SFC50/500 vs. components				
Hazard ratio		0.932	0.774	
95% CI		(0.765, 1.134)	(0.641, 0.934)	
p-value		0.481	0.007	

Note: Log-Rank test stratified by smoking status. 1. Kaplan-Meier estimate;

Figure 9. Time to All Cause Death within 3 Years – Survival Distribution



	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo	100	99	98.4	97.4	96.1	94.9	93.7	92.7	91.8	90.4	89.3	88	86.9	84.8
SAL 50	100	99.3	98.8	98.1	97.4	96.4	95.4	94	93.2	91.7	89.9	88.8	87.6	86.5
FP 500	100	99.3	98.6	97.5	96.9	95.5	94.5	93.1	91.9	91	88.9	87	85.3	84
SFC 50/500	100	99.5	98.8	98	97	96.1	95	93.7	93	92.1	90.9	89.6	88.6	87.4

kmest-death.xls; km_anal.sas

7. Primary Cause of Death, COPD-related Mortality, and On-treatment Mortality

COPD-related mortality and on-treatment mortality were other two pre-specified interested mortality endpoints. Table 23 displays the Clinical Endpoint Committee (CEC) categorized the primary cause of death as cardiovascular, pulmonary, cancer related, other, or unknown and the CEC determined whether the death was COPD-related using the following categories: Yes, Probably, Possibly, Unlikely, No or Unknown. Deaths assigned 'Yes', 'Probably' or 'Possibly' by the CEC were classified COPD-related deaths. Table 24 summarizes the log-rank analysis results of time to COPD -related mortality at 3 years. Within 3 years after the start of study treatment, 91 subjects (6.1%) in the SAL50 group and 106 subjects (6.9%) in the FP500 group had died, compared with 91 subjects (6.0%) in the placebo group. SFC50/500 reduced the risk of COPD-related deaths within 3 years by 22% compared with placebo (SFC rate of 4.7% and placebo rate of 6%, p=0.107), which was consistent with the magnitude of the risk reduction

seen for all-cause mortality. Although, SFC50/500 was not shown to be significantly different from placebo on COPD deaths, the results for SFC50/500 were notably better than either component. Figure 10 graphically displays these results.

Table 23. Cause of Death as Classified by the CEC at 3 Years in the Study

	SCO30003 (n=6112) (%)			
	Placebo	***SAL50***	***FP500***	***SFC50/500***
Randomized patients	1524	1521	1534	1533
All Death	231 (15.2)	205 (13.5)	246 (16.0)	193 (12.6)
COPD Related Death[1]	91 (6.0)	93 (6.1)	106 (6.9)	72 (4.7)
Primary Cause of Death				
Cardiovascular	71 (4.7)	45 (3.0)	64 (4.2)	60 (3.9)
Pulmonary	74 (4.9)	80 (5.3)	91 (5.9)	61 (4.0)
Cancer	45 (3.0)	44 (2.9)	51 (3.3)	44 (2.9)
Others	23 (1.5)	22 (1.4)	30 (1.9)	11 (0.7)
Unknown	18 (1.2)	14 (0.9)	13 (0.8)	17 (1.1)

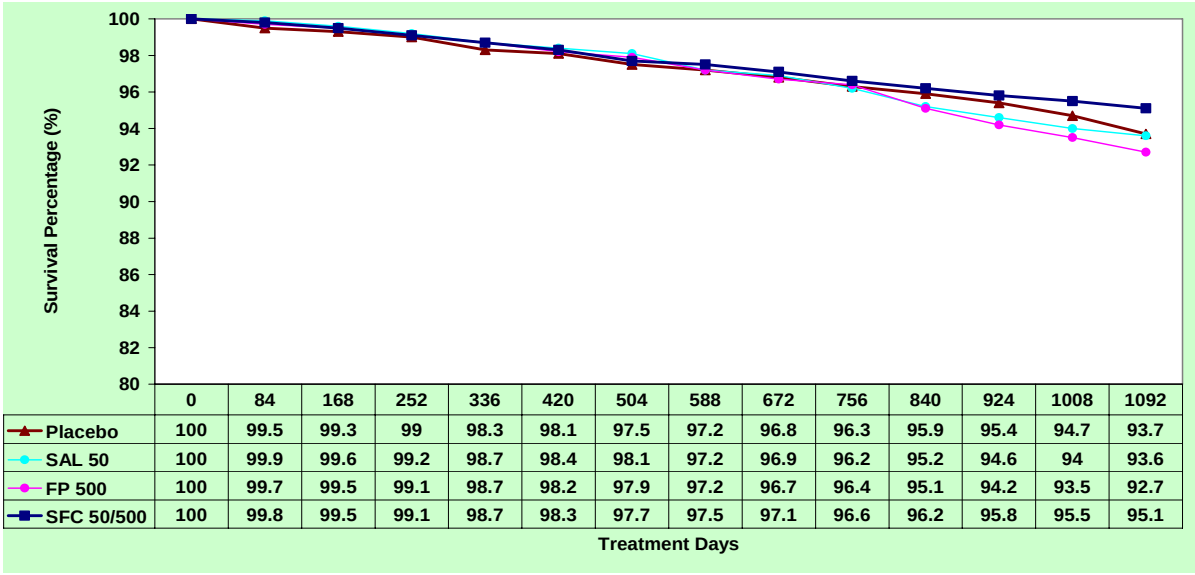
1: Only included the adjudicated code: 'yes', 'probably' or 'possibly'.
Source code: death.sas; Data source: endpoint.xpt.

Table 24. Log-Rank Analysis of Time to COPD-Related Mortality

	Placebo (N=1524)	***SAL50 (N=1521)***	***FP500 (N=1534)***	***SFC50/500 (N=1533)***
TRT Exp. (person yrs)	3238	3499	3532	3678
Number of deaths, n (%)	91 (6.0)	93 (6.1)	106 (6.9)	72 (4.7)
Probability of deaths by 156 weeks (%)[1]	6.3	6.4	7.3	4.9
95% CI	(5.1, 7.7)	(5.2, 7.7)	(6.1, 8.7)	(3.9, 6.1)
Active treatment vs. placebo				
Hazard ratio		1.013	1.159	0.776
95% CI		(0.759, 1.352)	(0.876, 1.534)	(0.570, 1.057)
p-value		0.932	0.300	0.107
SFC50/500 vs. components				
Hazard ratio		0.766	0.670	
95% CI		(0.563, 1.042)	(0.497, 0.904)	
p-value		0.089	0.008	

Note: Log-Rank test stratified by smoking status. 1. Kaplan-Meier estimate;

Figure 10. Time to COPD Related Mortality within 3 Years – Survival Distribution



	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo	100	99.5	99.3	99	98.3	98.1	97.5	97.2	96.8	96.3	95.9	95.4	94.7	93.7
SAL 50	100	99.9	99.6	99.2	98.7	98.4	98.1	97.2	96.9	96.2	95.2	94.6	94	93.6
FP 500	100	99.7	99.5	99.1	98.7	98.2	97.9	97.2	96.7	96.4	95.1	94.2	93.5	92.7
SFC 50/500	100	99.8	99.5	99.1	98.7	98.3	97.7	97.5	97.1	96.6	96.2	95.8	95.5	95.1

On-treatment deaths were defined as any death occurring on or after the treatment start, and up to 14 days of treatment stop (including 14 days). The on-treatment deaths also included those that occurred after 3 years from treatment start. In these analyses, the subject who died after 14 days of treatment stop would be censored and all on-treatment deaths were included, whether or not they occurred within 3 years after the start of treatment.

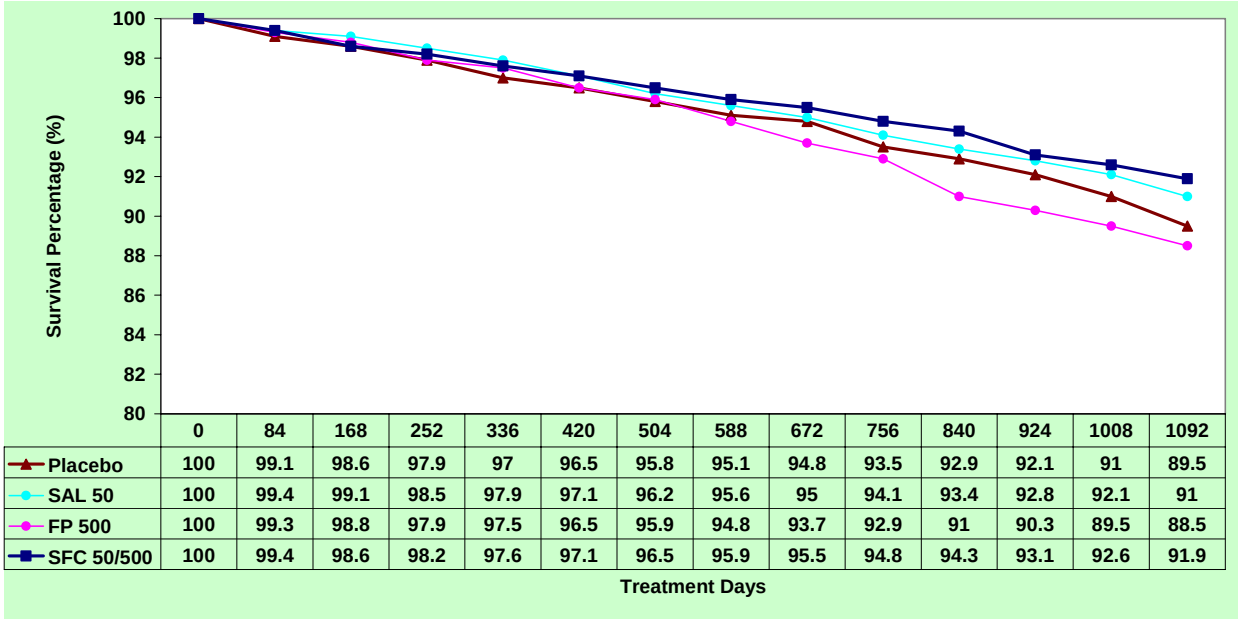
As shown on Table 25, the results of an analysis of deaths occurring while patients were on treatment showed the risk of dying was reduced by 23% with SFC50/500 compared with placebo (p=0.055). The effects of SAL50 and SFC50/500 were similar (hazard ratio=0.898, p=0.443) and SFC50/500 was statistically better than FP500 (hazard ratio=0.701, p=0.006). As shown in Figure 11, the light blue (SAL50) lied very close to dark blue line (SFC50/500). Four lines separated during the third year.

Table 25. Log-Rank Analysis of Time to On-treatment Mortality

	Placebo (N=1524)	*SAL50 (N=1521)*	*FP500 (N=1534)*	*SFC50/500 (N=1533)*
TRT Exp. (person yrs)	3238	3499	3532	3678
Number of deaths, n (%)	117 (7.7)	109 (7.2)	141 (9.2)	103 (6.7)
Probability of deaths by 156 weeks (%)[1]	10.5	9.0	11.5	8.1
95% CI	(8.7, 12.3)	(7.3, 10.6)	(9.7, 13.3)	(6.5, 9.6)
Active treatment vs. placebo				
Hazard ratio		0.858	1.100	0.772
95% CI		(0.661, 1.113)	(0.861, 1.406)	(0.592, 1.006)
p-value		0.248	0.445	0.055
SFC50/500 vs. components				
Hazard ratio		0.898	0.701	
95% CI		(0.686, 1.175)	(0.544, 0.904)	
p-value		0.433	0.006	

Note: Log-Rank test stratified by smoking status; 1. Kaplan-Meier estimate;

Figure 11. Time to On-Treatment Mortality within 3 Years – Survival Distribution



	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo	100	99.1	98.6	97.9	97	96.5	95.8	95.1	94.8	93.5	92.9	92.1	91	89.5
SAL 50	100	99.4	99.1	98.5	97.9	97.1	96.2	95.6	95	94.1	93.4	92.8	92.1	91
FP 500	100	99.3	98.8	97.9	97.5	96.5	95.9	94.8	93.7	92.9	91	90.3	89.5	88.5
SFC 50/500	100	99.4	98.6	98.2	97.6	97.1	96.5	95.9	95.5	94.8	94.3	93.1	92.6	91.9

kmest-death.xls; km_anal.sas

Compared to the primary analysis of SFC50/500 compared to placebo, the risk reduction differed by 5% (18% for primary and 23% for on-treatment), and the absolute difference of all cause mortality rate differed by 0.2%. The effect of SAL50 was closer to the effect of SFC50/500 for the on-treatment analysis. So the analyses did not differ notably.

7. Subgroups Analysis

Table 26 summarizes the results of log-rank test by sub-group of time to all-cause mortality at 3 years. Subjects who, aged younger than 65 years, raced in white, had myocardial infarction at baseline, current smoker, had no COPD exacerbation during the one year before study start, and baseline %predicted post-bronchodilator FEV1 > 40%, had more benefit of treatment of SFC50/500 compared than placebo. Healthier patients were benefit more.

Table 26. Survival Analysis of All Cause Mortality for 2 Treatments

Sub-group	*Group*	*Placebo*	*SFC50/500*	*Δ*	*HR*	*95% CI*	*PV*
Sex	F	43/361 (11.9%)	42/382 (11.0%)	-0.9%	0.932	(0.609, 1.426)	0.7460
	M	188/1163 (16.2%)	151/1151 (13.1%)	-3.0%	0.798	(0.644, 0.988)	0.0381
Age	<65	70/671 (10.4%)	45/665 (6.8%)	-3.7%	0.639	(0.439, 0.929)	0.0180
	≥65	161/853 (18.9%)	148/868 (17.1%)	-1.8%	0.893	(0.714, 1.116)	0.3206
Race	Non-white	54/275 (19.6%)	51/279 (18.3%)	-1.4%	0.947	(0.646, 1.389)	0.7806
	White	177/1249 (14.2%)	142/1254 (11.3%)	-2.8%	0.788	(0.632, 0.982)	0.0337
BMI	< 25	141/773 (18.2%)	121/796 (15.2%)	-3.0%	0.823	(0.646, 1.050)	0.1157
	≥25	90/751 (12.0%)	72/737 (9.8%)	-2.2%	0.803	(0.589, 1.094)	0.1640
Smoking Status	Current	103/658 (15.7%)	78/660 (11.8%)	-3.8%	0.744	(0.554, 0.998)	0.0480
	Former	128/866 (14.8%)	115/873 (13.2%)	-1.6%	0.881	(0.685, 1.133)	0.3216
Myocardial Infarction	No	202/1415 (14.3%)	169/1432 (11.8%)	-2.5%	0.816	(0.665, 1.001)	0.0500
	Yes	29/109 (26.6%)	24/101 (23.8%)	-2.8%	0.885	(0.515, 1.522)	0.6578
Taking ICS	No	116/721 (16.1%)	107/793 (13.5%)	-2.6%	0.832	(0.640, 1.082)	0.1708
	Yes	115/803 (14.3%)	86/740 (11.6%)	-2.7%	0.796	(0.602, 1.052)	0.1079
Taking OCS	No	173/1196 (14.5%)	140/1215 (11.5%)	-2.9%	0.786	(0.629, 0.983)	0.0341
	Yes	58/328 (17.7%)	53/318 (16.7%)	-1.0%	0.932	(0.642, 1.353)	0.7113
Taking LABA	No	151/949 (15.9%)	129/957 (13.5%)	-2.4%	0.841	(0.665, 1.063)	0.1467
	Yes	80/575 (13.9%)	64/576 (11.1%)	-2.8%	0.789	(0.568, 1.096)	0.1569
COPD Exac in Pre-year	0	93/647 (14.4%)	67/670 (10.0%)	-4.4%	0.674	(0.493, 0.923)	0.0134
	≥1	138/877 (15.7%)	126/863 (14.6%)	-1.1%	0.924	(0.726, 1.177)	0.5225
BL %pred post-br FEV1	> 40%	109/893 (12.2%)	89/943 (9.4%)	-2.8%	0.761	(0.575, 1.007)	0.0548
	≤ 40%	122/631 (19.3%)	104/590 (17.6%)	-1.7%	0.905	(0.697, 1.176)	0.4529

3.1.7.2 Exacerbations

The rate of moderate or severe exacerbation was a secondary endpoint for study SCO30003. Other exacerbation endpoints were time to first moderate or severe exacerbation, rate of severe exacerbations, time to first severe exacerbation, rate of moderate and severe exacerbations requiring systemic corticosteroids, time to first moderate or severe exacerbation requiring systemic corticosteroids.

Rate of Moderate and severe Exacerbations

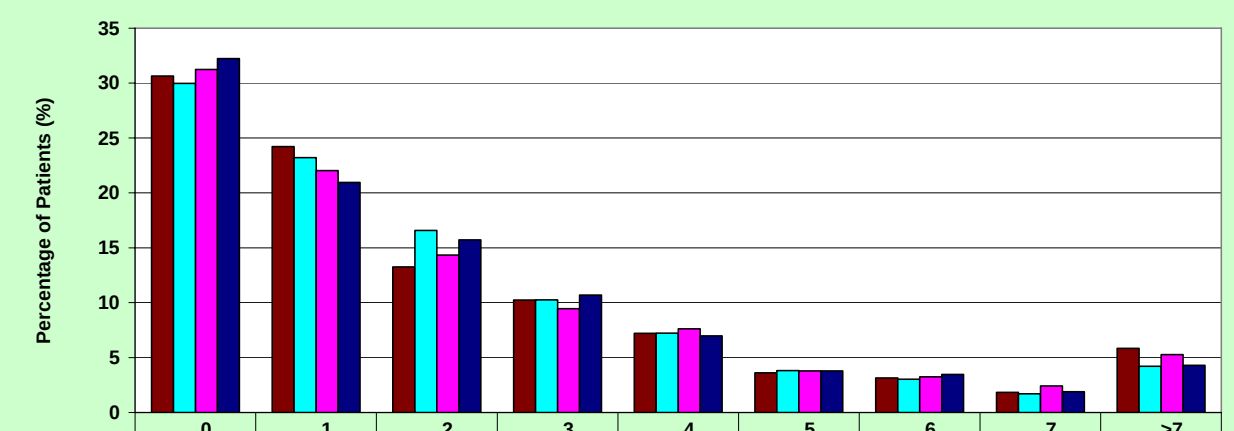
The prevalence of moderate and severe exacerbation is shown in Table 27. The majority of subjects (68% to 70%) experienced at least one moderate or severe exacerbation while on study treatment. Figure 12 displays the distribution of moderate and severe exacerbation of the study.

Table 27. Prevalence of Moderate and Severe Exacerbation

	Placebo	*SAL50*	*FP500*	*SFC50/500*
Study SCO30003 (3 years)				
No. patients	1524	1521	1534	1533
No. patients with at least one moderate and severe exacerbation (%)	1057 (69.4%)	1065 (70.0%)	1055 (68.8%)	1039 (67.8%)
No. moderate and severe exacerbation				
Total No.	3470	3258	3437	3224
Mean No. per patient	2.28	2.14	2.24	2.10
Range	0 – 30	0 – 28	0 – 21	0 – 28
Treatment Exposure, year				
Total person-years	3238	3499	3532	3678
Mean follow-up per patient	2.12	2.30	2.30	2.40
Median	2.98	2.99	2.99	2.99
Range	0.005 – 3.21	0.005 – 3.23	0.003 – 3.23	0.01 – 3.18

Source cod: exac_rate.sas; Data: exacana.xpt; pops.xpt

Figure 12. Distribution of Moderate and Severe Exacerbation



	0	1	2	3	4	5	6	7	>7
Placebo	30.6	24.2	13.3	10.2	7.2	3.6	3.1	1.8	5.8
SAL 50	30.0	23.2	16.6	10.3	7.2	3.8	3.0	1.7	4.2
FP 500	31.2	22.0	14.3	9.5	7.6	3.8	3.3	2.4	5.3
SFC 50/500	32.2	20.9	15.7	10.7	7.0	3.8	3.5	1.9	4.3

Source cod: rate of exac.xls; exac_rate.sas; Data: exacana.xpt; pops.xpt

From the negative binomial analysis, the rate of moderate and severe exacerbations is displayed in Table 28. The ratio of the exacerbation rate for SFC50/500 to the rate on placebo was 0.749 (95% CI 0.689, 0.814) which represented a 25% decrease in rate compared with placebo ($p<0.001$). Treatment with SAL50 and FP500 also reduced the rate compared with placebo, by 15% and 18%, respectively ($p<0.001$). SFC50/500 treatment reduced the exacerbation rate by 12% compared with SAL50 ($p=0.002$) and by 9% compared with FP500 ($p=0.024$).

Table 28. Negative Binomial Analysis of the Rate of Moderate and Severe Exacerbation

	Placebo	*SAL50*	*FP500*	*SFC50/500*
N	1524	1521	1534	1533
Mean number per year from model	1.13	0.97	0.93	0.85
Ratio (Active TRT vs. Placebo)		0.853	0.823	0.749
95% CI		(0.784, 0.927)	(0.758, 0.894)	(0.689, 0.814)
p-value		<0.001	<0.001	<0.001
Ratio (SFC50/500 vs. Components)		0.878	0.910	
95% CI		(0.808, 0.954)	(0.838, 0.988)	
p-value		0.002	0.024	

Source cod: negb_anal.sas; Data: exacana.xpt;pops.xpt.
a: Three subjects were excluded due to missing Baseline FEV_1 .

Table 29 displays the analysis results from the Poisson model. The analysis results were similar from two models. The estimated the mean number per year from Poisson model was slightly lower than Negative Binomial model. The ratio of the exacerbation rate for SFC50/500 to the rate on placebo was slightly higher.

Table 29. Poisson Analysis of the Rate of Moderate and Severe Exacerbation

	Placebo	*SAL50*	*FP500*	*SFC50/500*
N	1524	1521	1534	1533
Mean number per year from model	1.02	0.88	0.90	0.81
Ratio (Active TRT vs. Placebo)		0.856	0.877	0.797
95% CI		(0.816, 0.898)	(0.837, 0.920)	(0.760, 0.836)
p-value		<0.001	<0.001	<0.001
Raito (SFC50/500 vs. Components)		0.931	0.908	
95% CI		(0.887, 0.977)	(0.866, 0.953)	
p-value		0.004	< 0.001	

Source cod: poisson_anal.sas; Data: exacana.xpt; pops.xpt.
a: Three subjects were excluded due to missing baseline FEV_1 .

The results from negative binomial model and Poisson model were similar and demonstrated the SFC50/500 reduce the rate of moderate or severe exacerbation.

Table 30 display the *post hoc* sponsor's Andersen-Gill analysis of time to each moderate or severe exacerbation, which was fitted in SAS PROC PHREG with covariates of smoking status, age, sex, baseline FEV_1, number of previous exacerbation in the 12 months prior to screening, region and BMI. This analysis supports the results of the pre-defined primary analysis of exacerbation using the negative binomial model. The analysis results shows there was a

reduction in risk of exacerbation for SFC50/500 compared to placebo and some evidence of a greater effect of SFC50/500 compared to components (SAL50 and FP500). As shown in Table 30, SFC50/500 reduced the risk of moderate or severe exacerbations by 22% compared with placebo (hazard ratio 0.784; 95% CI: 0.718, 0.857; p<0.001), by 7% compared with SAL50 (p=0.088), and by 9% compared with FP500 (p=0.020). Treatment with SAL50 and FP500 also reduced the risk of moderate or severe exacerbations compared with placebo by 15% (p<0.001) and 13% (p<0.001), respectively.

Table 30. Andersen-Gill Analysis of Time to Each Moderate or Severe Exacerbation

	Placebo	*SAL50*	*FP500*	*SFC50/500*
N	1524	1521	1534	1533
Ratio (Active TRT vs. Placebo)		0.847	0.866	0.784
95% CI		(0.772, 0.929)	(0.793, 0.947)	(0.718, 0.857)
p-value		<0.001	0.001	<0.001
Ratio (SFC50/500 vs. Components)		0.926	0.905	
95% CI		(0.848, 1.012)	(0.833, 0.984)	
p-value		0.088	0.020	

Source cod: exac_ag_model.sas; Data: exacag1.xpt; exacag2.xpt; exacag3.xpt; pops.xpt

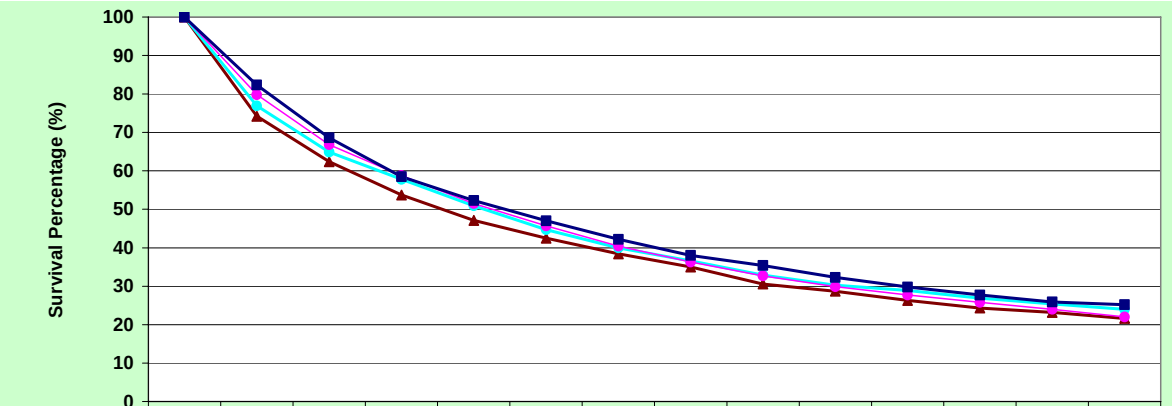
As shown in Table 31, the log-rank analysis of time to first moderate or severe exacerbation show that the hazard ratio for SFC50/500 vs. placebo was 0.860 (95%CI: 0.790, 0.937). This represented a 14% reduction in the risk of experiencing the first moderate or severe exacerbation at any time for SFC50/500 compared with placebo (p<0.001). SAL50 and FP500 numerically reduce the risk of experiencing a moderate or severe exacerbation compared to placebo, but didn't reach the statistical significance. The effects of SFC50/500 were similar to those of SAL50 and FP500.

Table 31. Log-Rank Analysis of Time to First Moderate/Severe Exacerbation

	Placebo	*SAL50*	*FP500*	*SFC50/500*
# of Subjects	1524	1521	1534	1533
# Subjects with at least one exacerbation (%)	1057 (69.4%)	1065 (70.0%)	1055 (69.0%)	1039 (67.8%)
Probability of exacerbation by 156 weeks1 95%CI[1]	78.4 (76.1, 80.7)	76.0 (73.7, 78.3)	78.0 (75.7, 80.2)	74.8 (72.4, 77.2)
Hazard Ratio (Active TRT vs. Placebo)		0.923	0.918	0.860
95% CI		(0.847, 1.005)	(0.843, 1.000)	(0.790, 0.937)
p-value		0.065	0.051	<0.001
Hazard Raito (SFC50/500 vs. Components)		0.933	0.934	
95% CI		(0.856, 1.016)	(0.857, 1.018)	
p-value		0.110	0.118	

Kaplan Meier estimates of time to first moderate or severe exacerbation is presented graphically in Figure 13. SAL50 and FP500 numerically reduce the risk of experiencing a moderate or severe exacerbation at any time, but didn't reach the statistical significance. The effects of SFC50/500 were similar to those of SAL50 and FP500.

Figure 13. Time to First Moderate or Severe Exacerbation – Survival Distribution



	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo	100	74.2	62.4	53.7	47.1	42.5	38.4	35	30.6	28.7	26.3	24.3	23.2	21.6
SAL 50	100	76.9	64.9	57.8	50.9	44.7	40	36.6	32.9	30.3	28.9	26.9	25.4	24
FP 500	100	79.8	66.8	58.8	51.5	45.7	40.4	36.3	32.7	29.9	27.7	25.8	24	22
SFC 50/500	100	82.3	68.6	58.5	52.3	47	42.2	38	35.4	32.3	29.8	27.7	25.9	25.2

Treatment Days

Source: kmest-exac.xls

Other Exacerbation Endpoints

The analysis results for the Rate of Severe Exacerbations using three models, Time to First Severe COPD Exacerbations are shown in Table 32. Approximately one quarter of subjects in each treatment group experienced at least one severe exacerbation while on study treatment. The rate of severe exacerbations from the negative binomial model was 0.19, 0.16, 0.17, and 0.16 for placebo, SAL50, FP500, and SFC50/500, respectively. Three models had similar results which showed that SAL50 statistically reduced the rate of severe exacerbation by 18% compared to placebo (p=0.016). From negative binomial model, SFC50/500 had 17% decrease in rate compared with placebo (p=0.028). The results from Poisson model and Andersen-Gill analysis did not support this result. FP500 only numerically reduced the rate of severe exacerbation compared with placebo by 12% (p=0.104). The log-rank analysis of time to first sever exacerbation shows that no differences were seen between any active treatment and placebo in time to first severe exacerbation.

Table 32. Analysis Results of the Other Exacerbation Endpoints

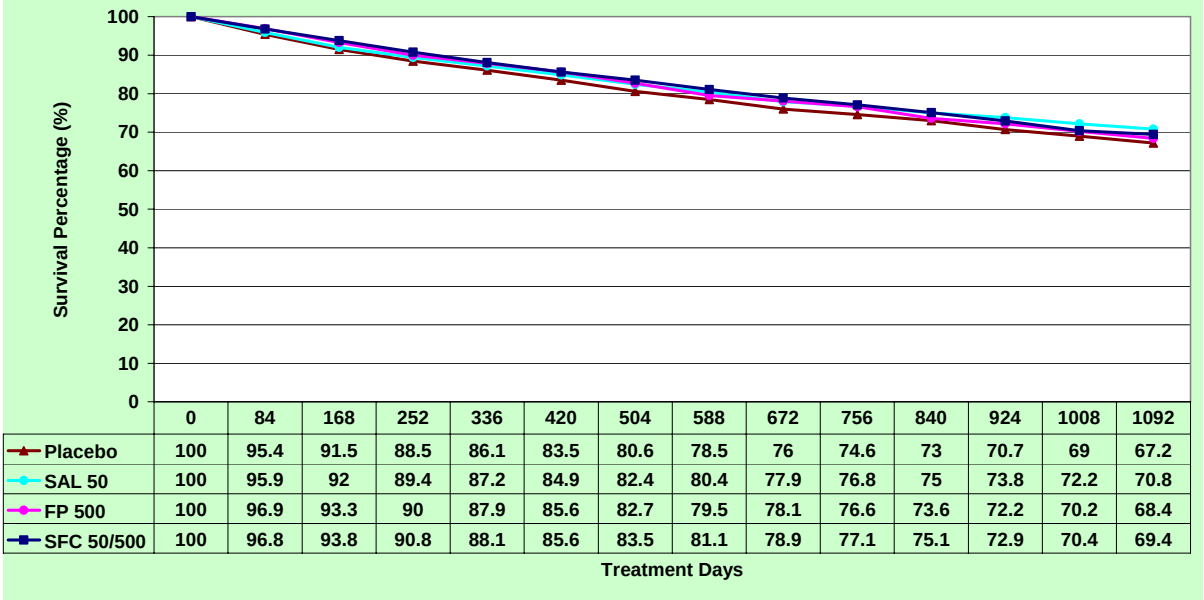
	Placebo	*SAL50*	*FP500*	*SFC50/500*
# of Subjects	1524	1521	1534	1533
Negative Binomial Analysis of the Rate of Severe Exacerbation				
Mean number per year from model	0.19	0.16	0.17	0.16
Ratio (Active TRT vs. Placebo)		0.816	0.875	0.834
95% CI		(0.693, 0.962)	(0.744, 1.028)	(0.710, 0.981)
p-value		0.016	0.104	0.028
Raito (SFC50/500 vs. Components)		1.022	0.954	
95% CI		(0.870, 1.200)	(0.815, 1.117)	
p-value		0.790	0.599	
Poisson Analysis of the Rate of Severe Exacerbation				

Mean number per year from model	0.16	0.14	0.16	0.15
Ratio (Active TRT vs. Placebo)		0.854	0.950	0.929
95% CI		(0.764, 0.954)	(0.853, 1.057)	(0.834, 1.035)
p-value		0.005	0.346	0.180
Raito (SFC50/500 vs. Components)		1.008	0.978	
95% CI		(0.976, 1.213)	(0.881, 1.087)	
p-value		0.128	0.685	
Andersen-Gill Analysis of Time to Each Severe Exacerbation				
Ratio (Active TRT vs. Placebo)		0.850	0.949	0.922
95% CI		(0.725, 0.998)	(0.814, 1.108)	(0.790, 1.078)
p-value		0.048	0.511	0.308
Raito (SFC50/500 vs. Components)		1.085	0.971	
95% CI		(0.924, 1.274)	(0.832, 1.134)	
p-value		0.322	0.714	
Log-Rank Analysis of Time to First Severe Exacerbation				
# Subjects with at least an exacerbation	394 (26%)	373 (25%)	400 (26%)	400 (26%)
Probability of exacerbation by 156 weeks1 95%CI[1]	32.8 (30.1, 35.6)	29.2 (26.6, 31.7)	31.6 (29.0, 34.2)	30.6 (28.0, 33.1)
Hazard Ratio (Active TRT vs. Placebo)		0.875	0.932	0.896
95% CI		(0.759, 1.008)	(0.811, 1.071)	(0.780, 1.030)
p-value		0.064	0.322	0.124
Hazard Raito (SFC50/500 vs. Components)		1.029	0.962	
95% CI		(0.893, 1.185)	(0.837, 1.105)	
p-value		0.694	0.579	

Source code: negb_anal.sas; exac_ag_model.sas;exac_lr_anal.sas; Data: exacana.xpt; pops.xpt
1: Kaplan Meier estimates

Figure 14 graphically shows there was no difference between treatment groups in Kaplan Meier estimates of time to first severe exacerbation.

Figure 14. Time to First Severe Exacerbation – Survival Distribution



	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo	100	95.4	91.5	88.5	86.1	83.5	80.6	78.5	76	74.6	73	70.7	69	67.2
SAL 50	100	95.9	92	89.4	87.2	84.9	82.4	80.4	77.9	76.8	75	73.8	72.2	70.8
FP 500	100	96.9	93.3	90	87.9	85.6	82.7	79.5	78.1	76.6	73.6	72.2	70.2	68.4
SFC 50/500	100	96.8	93.8	90.8	88.1	85.6	83.5	81.1	78.9	77.1	75.1	72.9	70.4	69.4

Source: kmest-exac.xls

Subgroup Analysis

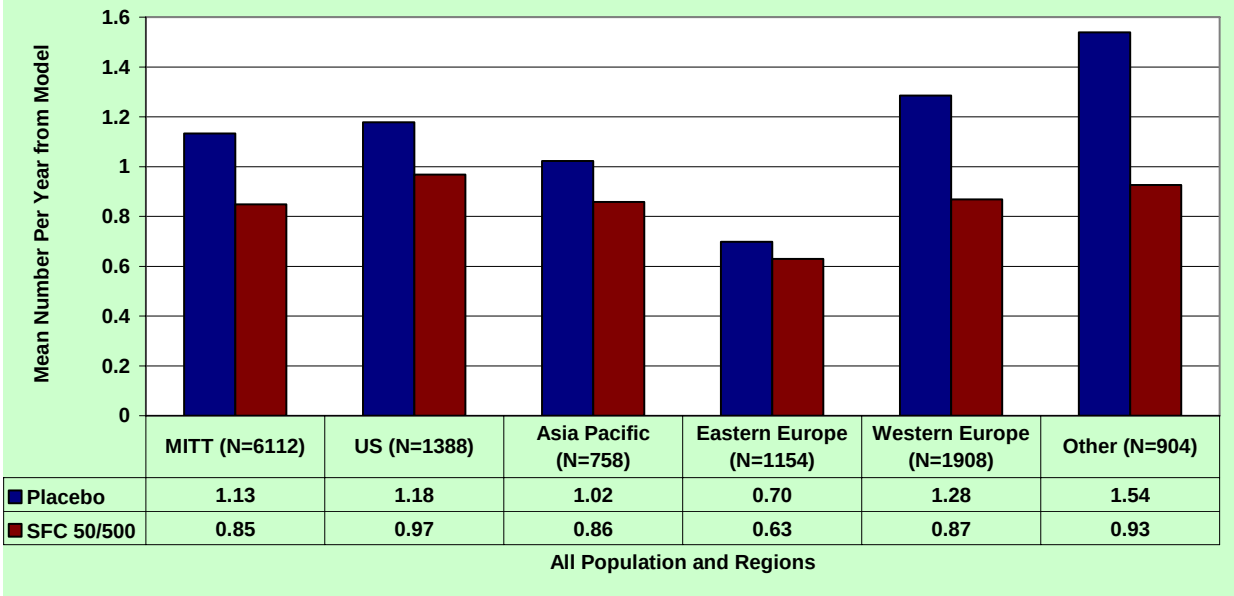
Using a Negative Binomial model for analysis of the rate of moderate and severe exacerbations, there was no significant evidence that treatment (SFC50/500 vs. placebo) effects varied with smoking status, baseline FEV_1, age, sex, ethnic origin, BMI or previous exacerbation history. As shown in Table 33, the p-value of region by treatment interaction was 0.012, previous COPD exacerbations by treatment interaction was 0.072, and previous used ICS or OCS by treatment interaction was less than 0.001.

Figure 15 graphically displays the rate of moderate and severe exacerbations estimated by the negative binomial model which shows the different pattern between four treatment groups in different region. Figure 16 graphically displays the ratio of SFC50/500 vs. placebo of rate of moderate and severe exacerbations estimated by the negative binomial model which shows the SFC 500/500 had better effect on the subjects who had previous COPD exacerbation or used ICS or OCS. Those results shows the interaction of region and previous COPD exacerbation was quantitative not qualitative.

Table 33. Summary of Interaction Tests for the Rate of Moderate and Severe Exacerbation

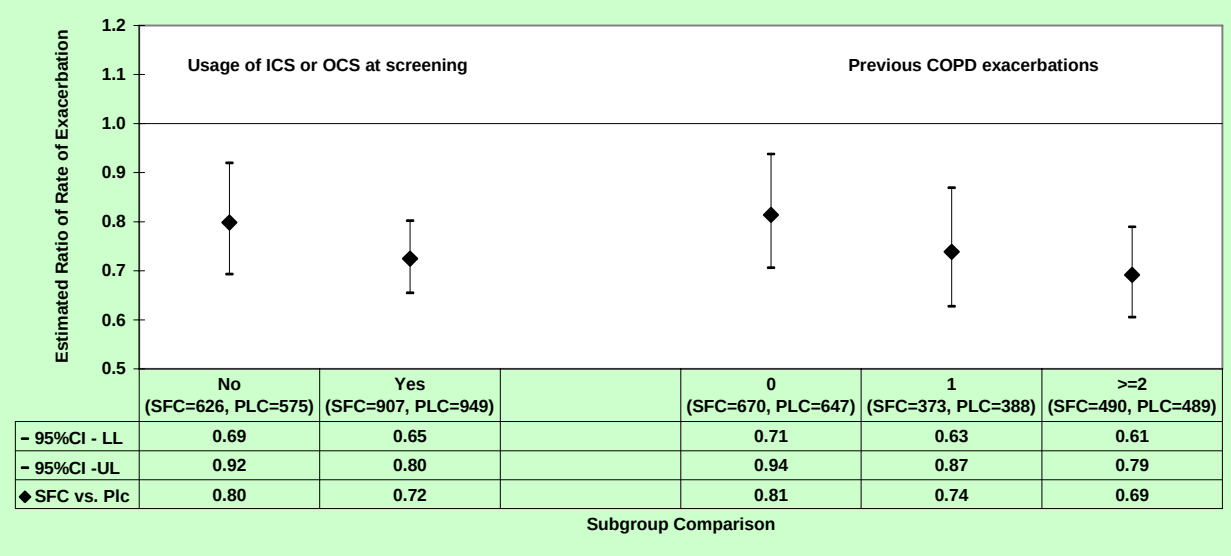
Interaction	*p-value*
Smoking status	0.570
Region	0.012
Percent Predicted FEV_1	0.271
Age	0.440
Sex	0.433
Ethnic origin	0.564
BMI	0.945
Previous COPD exacerbations	0.072
Previous used ICS or OCS	<0.001

Figure 15. Negative Binomial Analysis of the Rate of Moderate/Severe Exacerbation by Regions



Source: rate_of_exac.xls

Figure 16. Negative Binomial Analysis of the Rate of Moderate/Severe Exacerbation



	No (SFC=626, PLC=575)	Yes (SFC=907, PLC=949)		0 (SFC=670, PLC=647)	1 (SFC=373, PLC=388)	>=2 (SFC=490, PLC=489)
– 95%CI - LL	0.69	0.65		0.71	0.63	0.61
– 95%CI -UL	0.92	0.80		0.94	0.87	0.79
◆ SFC vs. Plc	0.80	0.72		0.81	0.74	0.69

Subgroup Comparison

Source: negbest.xls

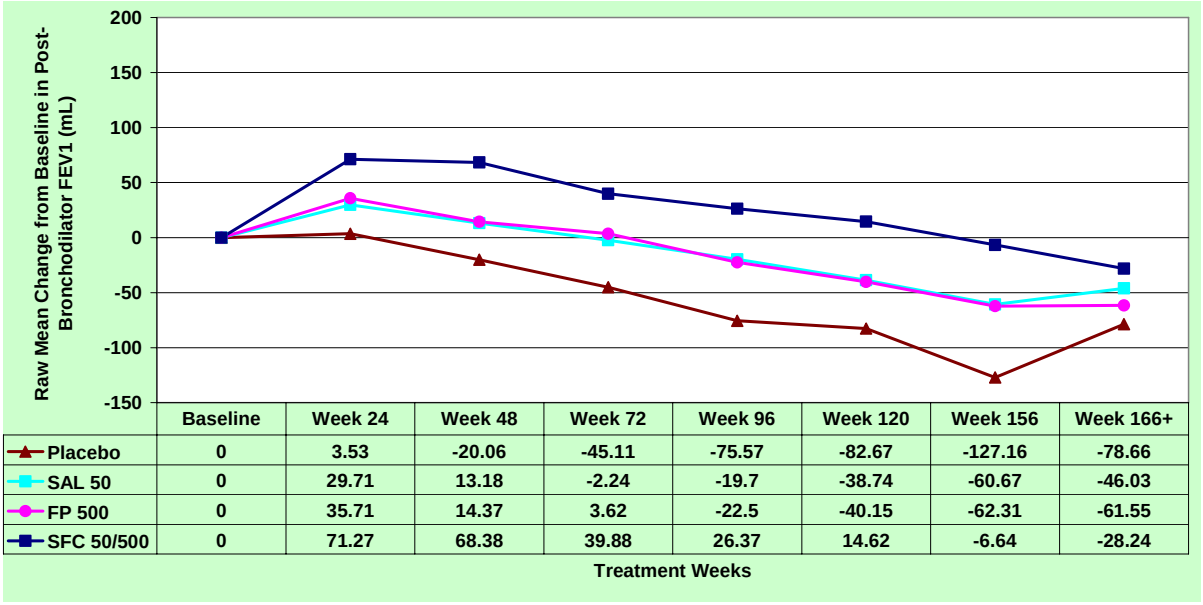
3.1.7.3 Pulmonary Function

Study SCO30003 provided the lung function assessment data to support the use of SFC50/500 in maintenance treatment of airflow obstruction in patients with COPD.

Clinic Post-bronchodilator FEV1

Post-bronchodilator FEV_1 was assessed as an "other" efficacy endpoint in Study SCO30003. The mean change in post-bronchodilator FEV_1 over time in Study SCO30003 is shown graphically in Figure 17.

Figure 17. Mean Change in Post-Bronchodilator FEV_1 over Time



	Baseline	Week 24	Week 48	Week 72	Week 96	Week 120	Week 156	Week 166+
Placebo	0	3.53	-20.06	-45.11	-75.57	-82.67	-127.16	-78.66
SAL 50	0	29.71	13.18	-2.24	-19.7	-38.74	-60.67	-46.03
FP 500	0	35.71	14.37	3.62	-22.5	-40.15	-62.31	-61.55
SFC 50/500	0	71.27	68.38	39.88	26.37	14.62	-6.64	-28.24

Treatment Weeks

The sponsor's summary of the repeated measures analysis of post-bronchodilator FEV_1 for subjects in Study SCO30003 is presented in Table 34. This reviewer couldn't confirm the sponsor's results because of a convergence problem when baseline FEV_1*visit term was included. This reviewer performed the repeated measures analysis without baseline FEV_1*visit. The result is displayed in Table 35, which shows the adjusted mean change averaged over the 3-year treatment period was -65mL for placebo, -27mL for SAL50, -26mL for FP500 and 15mL for SFC50/500. Over the entire treatment period, repeated measures analyses shows that improvements in post-bronchodilator FEV_1 were larger in the SFC50/500 comparing to placebo and both components. The average difference for SFC50/500 compared with placebo was 81mL (95% CI 64, 97mL; p<0.001), compared with SAL50 was 42mL (p<0.001), and compared with FP500 was 41mL (p<0.001). Mean FEV_1 was also higher than placebo for both SAL50 (39mL; p<0.001) and FP500 (39mL; p<0.001).

This reviewer also did an additional analysis using an ANCOVA model and the same covariates as in the sponsor's repeated measures analysis model to estimate the LS mean of change from baseline in post-bronchodilator FEV_1 at 3 years (Table 35). For subjects who prematurely discontinued, the LOCF method was used to define the post-bronchodilator FEV_1 at endpoint. The magnitude of the effect size for SFC50/500 and components compared to placebo were smaller than the sponsor's results. That difference was expected due to the informative dropout, in which, placebo had highest drop out rate among the four treatment group. FEV_1 declined over time.

Table 34. Repeated Measures Analysis of Post-Bronchodilator FEV1

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	SFC 50/500 (N=1533)
Number of subjects	1261	1334	1356	1392
Baseline Raw mean (SD)	1257 (444)	1231 (431)	1233 (437)	1236 (455)
Adjusted Mean Change from baseline (SE)	-62.3 (6.2)	-20.9 (6.0)	-15.0 (5.9)	29.2 (5.8)
Active treatment minus placebo (SE)		41.5 (8.6)	47.4 (8.6)	91.5 (8.5)
95% CI		24.6, 58.3	30.5, 64.2	74.9, 108.2
p-value		<0.001	<0.001	<0.001
SFC 50/500 minus components (SE)		50.1 (8.4)	44.2 (8.3)	
95% CI		33.7, 66.5	27.9, 60.5	
p-value		<0.001	<0.001	

Data Source: Table 7.065
Note: Repeated measures analysis adjusted for smoking status, age, sex, baseline FEV_1, BMI, region, visit, baseline FEV_1 by visit and treatment group by visit.

Table 35. LS Mean Change from Baseline in Post-Bronchodilator FEV_1(mL) at Endpoint

	Placebo	***SAL50***	***FP500***	***SFC50/500***
N	1524	1521	1534	1533
Repeated measure analysis[1]				
Number of Subject in the Analysis	1517	1512	1526	1515
Baseline Raw Mean (SD)	1228 (446)	1211 (430)	1229 (439)	1235 (459)
Adjusted Mean Change from Baseline (SE)[1]	-65.8 (6.4)	-26.7 (6.3)	-26.3 (6.3)	15.1 (6.2)

Active Treatment – Placebo (SE)		39.1 (8.4)	39.5 (8.4)	80.9 (8.4)
95% CI		(22.6, 55.6)	(23.0, 55.9)	(64.4, 97.3)
p-value		<0.001	<0.001	<0.001
SFC50/500 – Component (SE)		41.8 (8.3)	41.4 (8.3)	
95% CI		(25.5, 58.0)	(25.2, 57.6)	
p-value		<0.001	<0.001	
ANCOVA model using LOCF imputed the missing data at endpoint[2]				
N	1524	1521	1534	1533
Number of Subject in the Analysis	1357	1403	1411	1427
Baseline Raw Mean (SD)	1244 (444)	1222 (432)	1233 (437)	1235 (455)
Adjusted Mean Change from Baseline (SE)[2]	-83.4 (7.7)	-56.2 (7.6)	-58.7 (7.6)	-25.3 (7.5)
Active Treatment – Placebo (SE)		27.2 (10.1)	24.7 (10.1)	58.0 (10.0)
95% CI		(7.4, 46.9)	(4.9, 44.4)	(38.4, 77.7)
p-value		0.007	0.014	<0.001
SFC50/500 – Component (SE)		30.9 (9.9)	33.4 (9.9)	
95% CI		(11.4, 50.4)	(13.9, 52.9)	
p-value		0.002	<0.001	

Source cod: lft_anal.sas; Data: lftana.xpt; pops.xpt

1: Repeated measures analysis adjusted for smoking status, age, sex, baseline FEV1, BMI, region, visit, treatment by visit. 2: ANCOVA model adjusted for smoking status, age, sex, baseline FEV1, BMI, region, visit using LOCF imputed the missing data at endpoint.

3.1.7.5 Reviewer's Conclusion

The primary objective for study SCO30003 was to compare SFC50/500 to placebo for all-cause mortality within 3 years. Two secondary endpoints were the rate of moderate and severe COPD exacerbations and health-related quality of life using the SGRQ. The statistical methodologies in this study are adequate and appropriate. The sponsor provided results for primary analysis and supportive analyses which this reviewer confirmed.

Mortality

Based on the evaluation of Study SCO30003, SFC50/500 demonstrated a borderline insignificant effect over placebo with a hazard ratio of 0.82 (95%CI: 0.68, 0.99; p=0.041). Due to the interim analyses, this unadjusted p-value needs to be compared to a significance level of 0.040. To allow comparison to the commonly used significance level of 0.05, the adjusted CI was 0.681, 1.002 and the adjusted p-value was 0.052. The absolute difference of cumulative incidence rates of all cause mortality at 3 years was -2.6% between SFC50/500 (12.6%) and placebo (15.2%). It should be noted that usually highly significant results are required to demonstrate efficacy with a single study.

According to the proposed multiplicity adjustment procedure in the protocol of Study SCO30003 (See more details on section 3.1.7), secondary hypotheses would not be tested if the primary endpoint results were not significant at the 0.05 level. Since the primary endpoint was not significant at the 0.05 alpha level, secondary endpoints should not be tested. Nevertheless, since the results are borderline, it is important for the reader to see the nominal results for the secondary endpoints while understanding the context of these results under the protocol.

No notable difference in risk reduction for SFC50/500 compared with SAL50 was observed (risk reduction 7%, absolute risk difference of -0.9%, p=0.481). Compared with FP500, SFC50/500 reduced the risk by 23% (absolute risk difference of -3.4%, p=0.007).

SFC50/500 reduced the risk of COPD-related deaths within 3 years by 22% compared with placebo (SFC50/500 rate of 4.7% and placebo rate of 6.0%, p=0.107), which was consistent with the magnitude of the risk reduction seen for all-cause mortality. Although, SFC50/500 was not shown to be significantly different from placebo on COPD deaths, the results for SFC50/500 were notably better than either component. Similarly, an exploratory analysis of deaths occurring while patients were on treatment showed the risk of dying was reduced by 23% with SFC50/500 compared with placebo (p=0.055).

Exacerbations

Based on the evaluation of Study SCO30003, the rate of moderate and severe exacerbations was decreased by all active treatments in comparison with placebo (p<0.001); the reductions in exacerbation rates were 25% for SFC50/500, 15% for SAL50 and 18% for FP500. SFC50/500 was more effective than SAL50 or FP500 in decreasing the moderate or severe exacerbation rate (12% reduction, p=0.002 for SAL50 and 9% reduction, p=0.024, for FP500). The rate of severe exacerbations was decreased by 17% for SFC50/500 compared with placebo (p=0.028). The rate of exacerbations requiring systemic corticosteroid treatment was reduced by 43% for SFC50/500 compared with placebo (p<0.001).

There was no evidence that treatment effects varied for important subgroups (smoking status, age, sex, baseline FEV_1, BMI, region and previous exacerbation history) in analyses of the moderate and severe exacerbation rate.

Pulmonary Function

Over the entire treatment period, FEV_1 values were higher in subjects treated with SFC50/500 than for those treated with placebo (average difference over 3 years 92mL, p<0.001). Both SAL50 and FP500 were also more effective than placebo in effects on FEV_1 (average difference 42mL, p<0.001 for SAL50 and 47mL, p<0.001 for FP500). SFC50/500 was more effective than SAL50 or FP500 in improving FEV_1 (average difference 50 mL, p<0.001 for SAL50 and 44mL, p<0.001 for FP500).

3.2 Evaluation of Efficacy of Study SFCB3024

3.2.1 Design

Study SFCB3024 was a multinational, multi-center, randomized, double-blind, parallel-group, placebo-controlled study in subjects with COPD treated for a period of 52 weeks. The study subjects were outpatients, who fulfilled the study entry criteria. Subjects were stratified by smoking status and were centrally randomized in a 1:1:1:1 ratio to one of the following four treatment groups: SFC50/500, SAL50, FP500, and placebo. Study treatments were provided as inhalation powders administered as one inhalation from the DISKUS device twice daily. This study consisted of a 2-week run-in period, a 52-week randomized treatment period and a 2-week follow-up period, and involved a total of 11 clinic visits (at 0, 2, 4, 8, 16, 24, 32, 40, and 52 weeks). The 2-week follow-up period occurred after stopping double-blind treatment, regardless of when that occurred. All inhaled corticosteroids and inhaled long-acting bronchodilators were discontinued at entry to the run-in period. Salbutamol/albuterol was provided by the Sponsor for use as a relief medication as required (prn) throughout the trial.

The key inclusion criteria for study SFCB3024 are compared to the inclusion criteria for study SCO30003. The most notable difference is Inclusion 6 which was not required in study SCO30003.

Table 36. The Key Inclusion Criteria

		SCO30003	***SFCB3204***
1	Male or Female, Year of Age	40 – 80	40 – 79
2	An established clinical history of COPD	Yes	Yes
3	Subjects who had coughed up sputum on most days during at least 3 months in 2 consecutive years	No	Yes
4	Current or ex-smokers with a smoking history of at least	10 pack/yr	10 pack/yr
5	Poor reversibility of airflow obstruction (defined as <10% of the predicted normal FEV1 30 minutes after inhalation of 400µg salbutamol via MDI and VOLUMATIC (ELLIPSE in US centers) spacer must be demonstrated at Visit 1)	Yes	Yes
6	Exacerbation history: A documented history of COPD exacerbations each year for the last 3 years, including at least one exacerbation in the last year that required oral corticosteroids and/or antibiotics	No	Yes
7	Baseline (pre-bronchodilator) FEV_1/FVC ratio	≤ 70%	≤ 70%
8	Baseline (pre-bronchodilator) FEV_1 % of predicted normal	< 60%	≥25% to ≤70%

3.2.2 Objective

The primary objective of Study SFCB3204 was to compare the efficacy of SFC50/500 with salmeterol 50mcg bid alone, FP500mcg bid alone and placebo in the treatment of COPD.

3.2.3 Patient Disposition

Across the four treatment groups, a total of 61% to 75% of subjects completed the treatment period (Table 37). The proportion of subjects who withdrew from the treatment period was highest in the placebo treatment group (39%) and lowest in the SFC50/500 treatment group

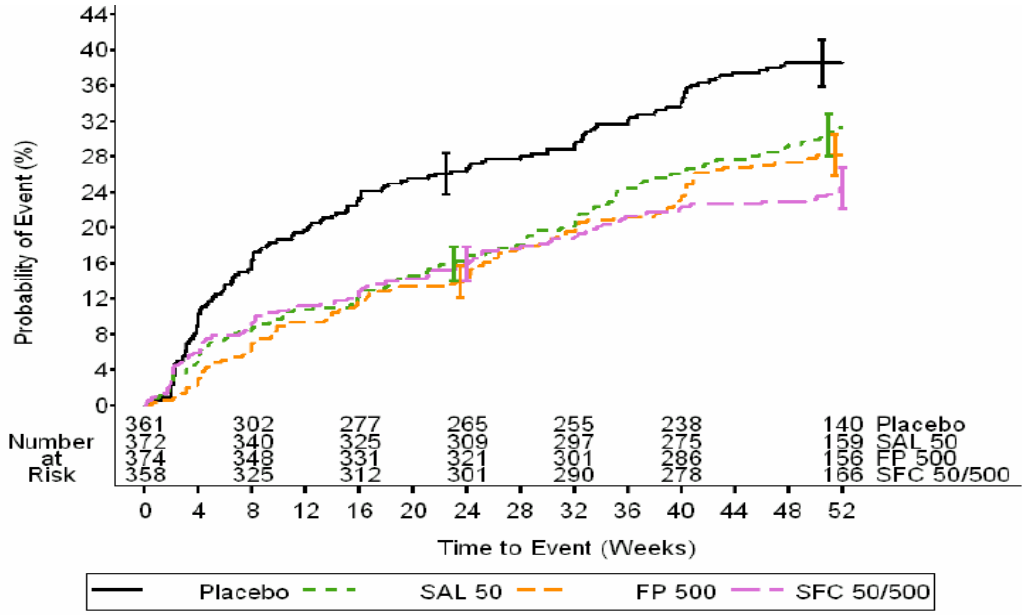
(25%) (Figure 18). There were four subject who did not receive any medication (ID #'s 5356, 5369, 5385, 5951) were excluded from the sponsor's ITT population. The most common reason for withdrawal was adverse event with the highest rate seen in the placebo group. There were 10 (3%) deaths in the placebo group compared to 4 (1%) in the SFC50/500 group.

Table 37. Patients' Accountability N (%)

	SFCB3024 (n=1469)			
	Placebo	***SAL50***	***FP500***	***SFC50/500***
Randomized patients	363	373	375	358
Completed treatment period	221 (61)	253 (68)	266 (71)	269 (75)
Discontinued	142 (39)	120 (32)	109 (29)	89 (25)
Reason of early discontinuation				
Adverse Event	68 (19)	61 (16)	55 (15)	46 (13)
Consent withdrawn	16 (4)	13 (3)	11 (3)	6 (2)
Lost to follow-up	8 (2)	8 (2)	8 (2)	29 (1.9)
Lack of efficacy	5 (1)	7 (2)	11 (3)	5 (1)
Did not fulfill entry criteria	3 (<1)	3 (<1)	3 (<1)	4 (1)
Non-compliance	7 (2)	5 (1)	11 (3)	5 (1)
Protocol violation	10 (3)	13 (3)	5 (1)	12 (3)
Other	15 (4)	12 (3)	9 (2)	6 (2)
Death	10 (3)	5 (1)	5 (1)	4 (1)
Analysis Population				
ITT[1]	361	372	374	358
PP	305	311	312	297

Data: demo2.xpt, pops.xpt; Code: demo.sas. 1: Four subjects were excluded from ITT population.

Figure 18. Time to Study Drug Discontinuation - Cumulative Incidence Curve



3.2.4 Demographic and Baseline Characteristics

Overall, the demographic characteristics of subjects in the study were will-matched between

treatment groups (Table 38). The majority of subjects were male (70% to 75%) and white (98% to 99%) with a mean age of 63 years (range 38 to 79 years), and an average BMI of 26kg/m2. At baseline, approximately half of subjects were former smokers (rage 47% to 53%).

The treatment groups were well-matched for pulmonary function before the start of treatment. Overall, the mean percent predicted pre-bronchodilator FEV_1 was approximately 44%.

Table 38. ITT Subjects' Demographics and Baseline Characteristics by Treatment

	SFCB3024 (n=1465)			
	Placebo (n=361)	***SAL50 (n=372)***	***FP500 (n=374)***	***SFC50/500 (n=358)***
Sex, n (%)				
Female	92 (25)	111 (30)	114 (30)	88 (25)
Male	269 (75)	261 (70)	260 (70)	270 (75)
Race, n (%)				
White	358 (99)	366 (98)	370 (99)	355 (99)
Black	0	0	1 (<1)	0
Asia/Others	3 (<1)	6 (2)	3 (<1)	3 (<1)
Age, n (%)				
Mean (SD)	63 (9)	63 (9)	64 (9)	63 (9)
Median	64	64	64	63.5
Range	40 - 79	38 – 79	40 – 79	40 – 78
<65	184 (51)	196 (53)	190 (51)	193 (54)
65+	177 (49)	176 (47)	184 (49)	165 (46)
BMI, kg/m2				
Mean (SD)	26 (4)	26 (5)	26 (4)	26 (5)
< 25	180 (50)	164 (44)	157 (42)	179 (50)
25+	181 (50)	208 (56)	217 (58)	179 (50)
Smoking Status, n (%)				
Current	171 (47)	191 (51)	198 (53)	186 (52)
Former	190 (53)	181 (49)	176 (47)	172 (48)
Duration of COPD (yr)				
<5 years	92 (25)	96 (26)	92 (25)	84 (23)
5 – 10 years	118 (33)	134 (36)	115 (31)	152 (42)
> 10 years	151 (42)	142 (38)	167 (45)	122 (34)
% Predicted Pre-bronchodilator FEV1 at Visit 1				
Mean (SD)	44.2 (13.7)	44.3 (13.8)	45.0 (13.6)	44.8 (14.7)
Median	42.2	42.9	44.9	44.3
Range	10.4 – 85.0	15.9 – 79.2	16.8 – 81.3	15.0 – 77.1
< 25% or > 70%	21 (5.8%)	31 (8.3%)	25 (6.7%)	41 (11.5%)
Reversibility % Pre-bronchodilator FEV1 at Visit 1				
Mean (SD)	8.1 (9.6)	8.1 (9.3)	8.4 (12.2)	8.8 (9.1)
Median	8.3	6.7	7.8	8.0
Range	-50.9 – 42.9	-29.7 – 37.0	-32.3 – 123.8	-17.8 – 35.1

Data: subaccn.xpt; pops.xpt; lft_base.xpt; Code: Demog.sas

3.2.5 Statistical Methodologies

3.2.5.1 Efficacy Endpoints

Primary Efficacy Measurements

Pre-Bronchodilator FEV_1

The primary efficacy endpoint was the clinic FEV_1 prior to use of salbutamol and measured before the morning dose of study medication at each clinic visit. At each clinic visit (0, 2, 4, 8,

16, 24, 32, 40, and 52 weeks), the highest of three technically acceptable measurements of FEV_1 was recorded before and 30 minutes after inhalation of 400µg salbutamol via MDI and **VOLUMATIC** spacer.

Secondary Efficacy Measurements
The secondary efficacy endpoints were the number of moderate and severe COPD exacerbations and quality of life as determined using the SGRQ.

Exacerbations of COPD
The exacerbation of COPD definition was more carefully described in Study SFCB3204 than in Study SCO30003. COPD exacerbations were assessed by the Investigator at each clinic visit (2, 4, 8, 16, 24, 32, 40, and 52 weeks) by reviewing the daily record card entries, as well as specific questioning on adverse events. Each COPD exacerbation was categorized according to one of three levels of severity (mild, moderately severe or severe):

- Mild: Defined as an exacerbation requiring increased use of relief salbutamol by >2 occasions per 24-hour period on two or more consecutive days compared with Baseline AND deemed clinically relevant by the Investigator.

- Moderately severe: Defined as an exacerbation requiring treatment with antibiotics and/or oral corticosteroids, EITHER as judged by the Investigator OR according to the criteria given below:

  Criteria for treating with antibiotics (for guidance): If there was evidence of chest infection (i.e., two or more of the following symptoms: purulent sputum, increased sputum production, increased breathlessness).

  Criteria for treating with oral corticosteroids (for guidance): If there was an increase in symptoms (increased cough, increased sputum production or increased breathlessness) and either:

  i) Increased use of relief salbutamol by >4 occasions per 24-hour period on two or more consecutive days compared with Baseline
  OR
  ii) Morning PEFR decreased by ≥50L/min on two or more consecutive days compared with Baseline.

- Severe: Defined as requiring emergency hospital treatment.

3.2.5.2 Statistical Methods

Analysis Populations
The Intent-to-Treat (ITT) efficacy population consisted of all subjects who were randomized to treatment and received at least one dose of study medication, with the exception of subjects recruited at sites that were closed as the results of audit findings or other information that implied

the integrity of the data had been compromised. For Study SFCB3204 all subjects were analyzed based on the treatment group to which they were randomized.

Treatment Comparisons

The primary interest of treatment comparison was between SFC50/500 and placebo. The following comparisons were also of interest:

- SFC50/500 vs. SAL50
- SFC50/500 vs. FP500
- FP500 vs. placebo
- SAL50 vs. placebo

Multi-center Studies

For analysis purposes in Study SFCB3204, center amalgamation were made by combining subjects from centers into groups of at least 20 subjects per center amalgamation, grouped based on geographical proximity of sites. According to the sponsor, the process of amalgamation was performed and finalized prior to unblinding of treatment allocations.

Efficacy Analysis

FEV_1

The change from Baseline in pre-bronchodilator FEV_1 was compared between treatment groups, using a repeated measures analysis which included subjects with a baseline FEV_1 and at least one on-treatment FEV_1. The change form Baseline averaged over 52 weeks was of primary interest. Treatment group was fitted as the explanatory variable, and smoking status, sex, center amalgamation, age and Baseline pre-bronchodilator FEV_1 were fitted as covariates. Visit was fitted as a categorical variable, and the variance-covariance matrix was assumed to be unstructured. This analysis was repeated for post-bronchodilator FEV_1. Treatment effects were estimated at each visit as well as a combined estimate across all visits.

FEV_1 = Treatment group + smoking status + age + sex + baseline FEV_1 + baseline FEV_1 + BMI + region + visit

Rate of Moderately Severe and Severe COPD Exacerbations

The rate of moderate and severe exacerbations was analyzed using a Poisson regression model as pre-specified in the protocol. In order to compare with Study SCO30003, this reviewer also performed analysis using Negative Binomial model. For Study SFCB3024, the time to first moderate or severe exacerbation was compared between treatment groups using a Cox proportional hazard model adjusted for age, sex, centre amalgamation, smoking status, and Baseline FEV_1.

Multiplicity

The primary objective of the study will be met if, for the primary efficacy endpoint, the following were satisfied:

SFC50/500 is superior to FP500 and superior to SAL50 at alpha = 0.04 (2-sided) or
SFC50/500 is superior to placebo at alpha = 0.01 (2-sided)

Sample Size

It was estimated that 250 evaluable subjects per treatment arm were required to detect a 15%

difference in the incidence of exacerbations between treatment groups at the 5% significance level with at least 90% power if the incidence of exacerbations on placebo was at least 60%.

3.2.6 Sponsor's Results and Conclusions

The sponsor's analysis of the primary efficacy endpoint of Study SFCB3204 is provided in following. (p173, Study report of SFCB3024):

"SFC50/500 produced significant improvements in lung function compared with placebo, salmeterol alone and FP alone. These improvements were accompanied by a significant reduction in the rate of moderate and/or severe COPD exacerbations compared to placebo and significant reductions in symptoms of breathlessness, use of relief medication and nighttime awakenings compared with placebo and one or both components."

3.2.7 Reviewer's Efficacy Analysis

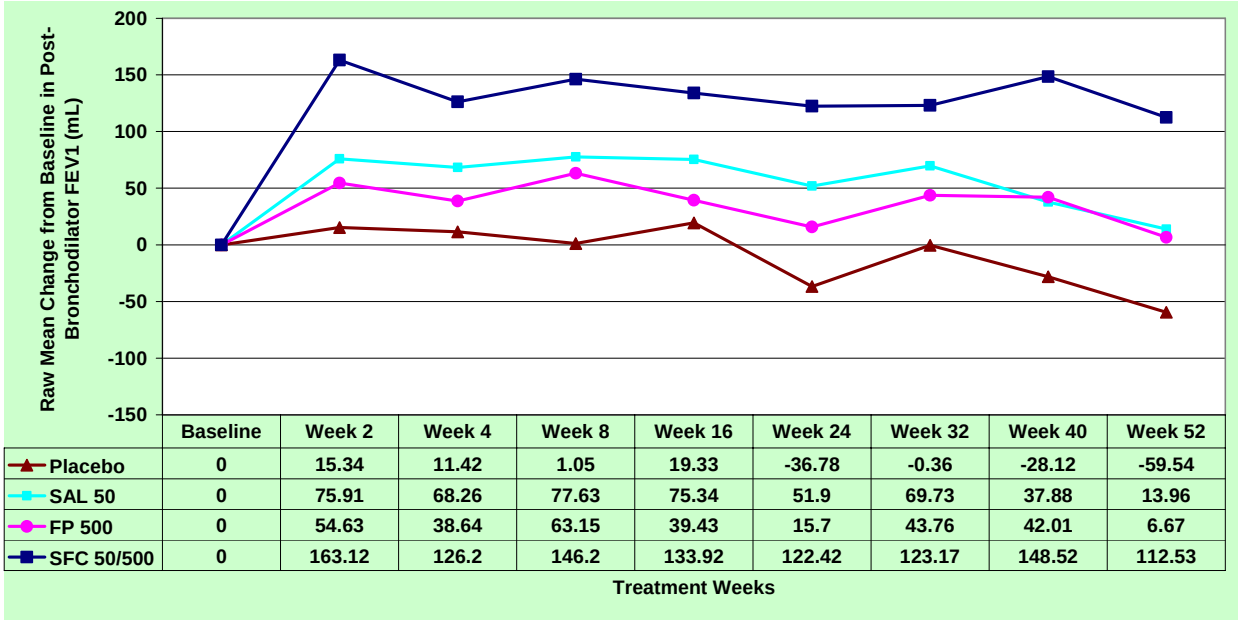
3.2.7.1 Pulmonary Function

Study SFCB3024 provided the lung function assessment data to support the use of SFC50/500 in maintenance treatment of airflow obstruction in patients with COPD. The pre-bronchodilator FEV_1 was the primary endpoint and post-bronchodilator FEV_1 was an "other" endpoint.

Clinic Pre-bronchodilator FEV1

The mean change in pre-bronchodilator FEV_1 over time in Study SFCB3024 is shown graphically in Figure 19 .

Figure 19. Mean Change in Pre-Bronchodilator FEV_1 over Time



	Baseline	Week 2	Week 4	Week 8	Week 16	Week 24	Week 32	Week 40	Week 52
Placebo	0	15.34	11.42	1.05	19.33	-36.78	-0.36	-28.12	-59.54
SAL 50	0	75.91	68.26	77.63	75.34	51.9	69.73	37.88	13.96
FP 500	0	54.63	38.64	63.15	39.43	15.7	43.76	42.01	6.67
SFC 50/500	0	163.12	126.2	146.2	133.92	122.42	123.17	148.52	112.53

The sponsor's summary of the results of the repeated measures analysis of pre-bronchodilator FEV_1 for subjects in SFCB3024 is presented in Table 39. Over 52 weeks, the SFC50/500 treatment group demonstrated a statistically significant improvement in pre-bronchodilator FEV_1 of 133mL relative to placebo ($p<0.001$). Improvement in pre-bronchodilator FEV_1 was also significantly greater in the SFC50/500 treatment group compared with the SAL50 and FP500 treatment groups (73.3mL to 94.5mL; $p<0.001$), and in the SAL50 (59.7mL; $p<0.001$) and FP500 (38.5mL; $p=0.006$) treatment groups when compared with placebo.

Table 39. Repeated Measures Analysis of Pre-Bronchodilator FEV1

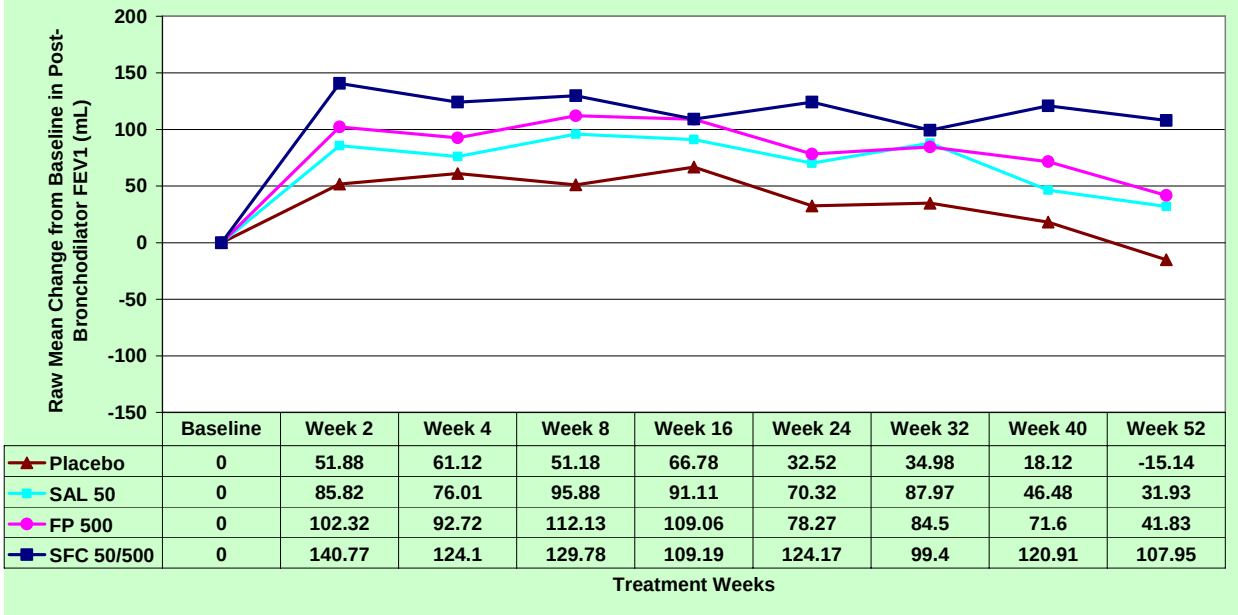
	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	SFC 50/500 (N=358)
Number of Subjects	353	361	371	345
Baseline Raw Mean (SD)	1260 (469)	1241 (447)	1261 (450)	1308 (532)
Raw Mean (SD)	1256 (492)	1299 (477)	1298 (469)	1441 (583)
Adjusted Mean (SE)	1264 (11)	1323 (11)	1302 (11)	1396 (11)
Active Treatment – Placebo (SE) (95% CI) p-value		59.7 (14.17) (31.9, 87.5) <0.001	38.5 (14.08) (10.9, 66.1) 0.006	133.0 (14.33) (104.9, 161.1) <0.001
SFC 50/500 – Component (SE) (95% CI) p-value		73.3 (14.20) (45.5, 101.2) <0.001	94.5 (14.12) (66.8, 122.2) <0.001	

Note: The repeated measures analysis was adjusted for smoking status, age, sex, amalgamated center and Baseline FEV_1.

Clinic Post-bronchodilator FEV1

Post-bronchodilator FEV_1 was assessed as an "other" efficacy endpoint in Study SFCB3024. The mean change in post-bronchodilator FEV_1 over time are shown graphically in Figure 20

Figure 20. Mean Change in Post-Bronchodilator FEV_1 over Time



	Baseline	Week 2	Week 4	Week 8	Week 16	Week 24	Week 32	Week 40	Week 52
Placebo	0	51.88	61.12	51.18	66.78	32.52	34.98	18.12	-15.14
SAL 50	0	85.82	76.01	95.88	91.11	70.32	87.97	46.48	31.93
FP 500	0	102.32	92.72	112.13	109.06	78.27	84.5	71.6	41.83
SFC 50/500	0	140.77	124.1	129.78	109.19	124.17	99.4	120.91	107.95

The sponsor's a summary of the repeated measures analysis of post-bronchodilator FEV_1 for subjects in SFCB3024 is presented in Table 40. It shows, over 52 weeks, the SFC50/500 treatment group demonstrated a statistically significant improvement in post-bronchodilator FEV_1 of 76mL relative to placebo ($p<0.001$). Improvement in post-bronchodilator FEV_1 was also significantly greater in the SFC50/500 treatment group compared with the SAL50 (48mL; $p=0.001$) or FP500 (31mL; $p=0.039$) treatment groups, and in the FP500 treatment group when compared with placebo (46mL; $p=0.002$).

Table 40. Repeated Measures Analysis of Post-Bronchodilator FEV1

	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	SFC 50/500 (N=358)
Number of Subjects	352	358	371	340
Baseline Raw Mean (SD)	1374 (477)	1339 (459)	1363 (461)	1420 (550)
Raw Mean (SD)	1419 (524)	1411 (498)	1448 (494)	1536 (601)
Adjusted Mean (SE)	1408 (11)	1436 (11)	1454 (11)	1484 (11)
Active Treatment – Placebo (SE) (95% CI) p-value		28.3 (14.87) (-0.9, 57.4) 0.058	45.6 (14.76) (16.6, 74.5) 0.002	76.1 (15.06) (46.6, 105.7) <0.001
SFC 50/500 – Component (SE) (95% CI) p-value		47.9 (14.94) (18.6, 77.2) 0.001	30.6 (14.82) (1.5, 59.7) 0.039	

Note: The repeated measures analysis was adjusted for smoking status, age, sex, amalgamated center and Baseline FEV_1.

This reviewer did an additional analysis using an ANCOVA model with the same covariates as in the sponsor's repeated measures analysis model to estimate the LS mean of change from baseline in post-bronchodilator FEV_1 at 52 weeks for Study SFCB3024 (Table 41). For the premature discontinued subject, the LOCF method was used for the post-bronchodilator FEV_1 at endpoint. The magnitude of the effect size for SFC50/500 and components compared to placebo were smaller than the sponsor's results. That difference was expected due to the informative dropout, in which, placebo had highest drop out rate among the four treatment group. FEV_1 declined over time.

Table 41. LS Mean Change from Baseline in Pre- or Post-Bronchodilator FEV_1(mL) at 52-Week

	Placebo	***SAL50***	***FP500***	***SFC50/500***
Pre-Bronchodilator FEV1 (mL)				
N	361	372	374	358
Number of Subject in the Analysis	353	361	371	345
Baseline Raw Mean (SD)	1260 (469)	1241 (447)	1261 (450)	1308 (532)
Adjusted Mean Change from Baseline (SE)	-46.0 (15.1)	2.7 (14.8)	-3.9 (14.6)	94.5 (15.3)
Active Treatment – Placebo (SE)		48.6 (20.1)	42.0 (20.0)	140.4 (20.3)
95% CI		(9.3, 88.0)	(2.9, 81.2)	(100, 180)
p-value		0.016	0.035	<0.001
SFC50/500 – Component (SE)		91.8	98.4	
95% CI		(52.2, 131)	(59.0, 138)	
p-value		<0.001	<0.001	

Post-Bronchodilator FEV1 (mL)				
N	361	372	374	358
Number of Subject in the Analysis	352	358	371	340
Baseline Raw Mean (SD)	1374 (477)	1339 (459)	1363 (460)	1420 (550)
Adjusted Mean Change from Baseline (SE)	-6.4 (15.7)	14.9 (15.4)	26.4 (15.2)	75.8 (15.9)
Active Treatment – Placebo (SE)		21.3 (20.9)	32.7 (20.7)	82.2 (21.2)
95% CI		(-19.7, 62.3))	(-7.9, 73.4)	(40.6, 123.7)
p-value		0.309	0.115	<0.001
SFC50/500 – Component (SE)		60.9 (21.1)	49.5 (20.9)	
95% CI		(19.5, 102.3)	(8.4, 90.5)	
p-value		0.004	0.018	

Source cod: lft.anal.sas; Data: lftana.xpt; pops.xpt

This additional analysis supports the results of the sponsor's repeated measure analysis. Both demonstrated that over the 52 weeks of the study, pre-bronchodilator FEV_1 in the SFC50/500 group was 133mL higher than that of the placebo group ($p<0.001$); 73 mL higher the SAL50 group ($p<0.001$) and 95 mL higher than the FP500 group ($p<0.001$).

3.2.7.2 Exacerbations

The rate of moderately severe and severe exacerbation was the secondary endpoint for Study SFCB3024. The COPD definition had three levels of severity (mild, moderately severe or severe). As part of the inclusion criteria, patients were required to have an exacerbation history.

Rate of Moderately Severe and Severe Exacerbations

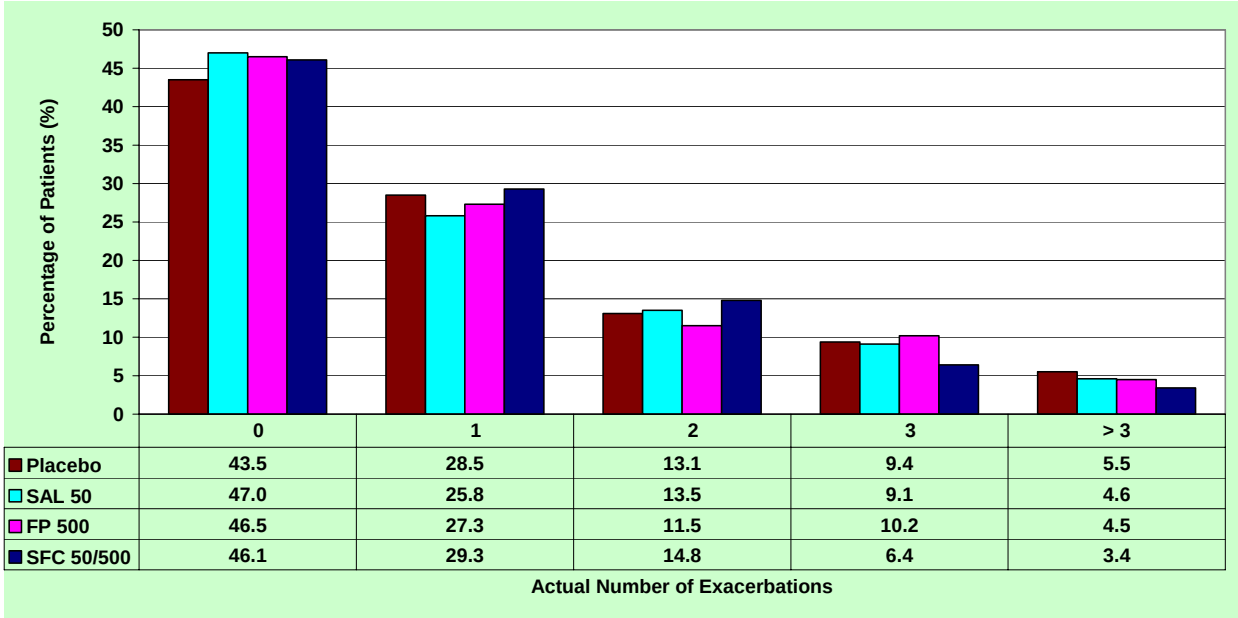
The prevalence of moderately severe and severe exacerbation is shown in Table 42. The majority of subjects (53% to 57%) experienced at least one moderately severe or severe exacerbation while on study treatment. Figure 21 displays the distribution of moderately severe and severe exacerbation of the study.

Table 42. Prevalence of Moderately Severe and Severe Exacerbation

	Placebo	***SAL50***	***FP500***	***SFC50/500***
No. patients	361	372	374	358
No. patients with at least one moderately severe and severe exacerbation (%)	204 (56.5%)	197 (53.0%)	200 (53.5%)	193 (53.9%)
No. moderately severe and severe exacerbation				
Total No.	382	366	374	331
Mean No. per patient	1.06	0.98	1.0	0.92
Range	0 – 5	0 – 4	0 – 6	0 – 6
Treatment Exposure, year				
Total person-years	267.8	307.2	314.7	302.0
Mean follow-up per patient	0.74	0.83	0.84	0.84
Median	0.99	1.00	1.00	1.00
Range	0.003 – 1.13	0.005 – 1.10	0.01 – 1.09	0.002 – 1.11

Source cod: exac_rate.sas; Data: exacrt24.xpt, pops.xpt

Figure 21. Distribution of Moderately Severe and Severe Exacerbation



Source cod: rate of exac.xls; exac_rate.sas; Data: exacrt24.xpt; pops.xpt

For Study SFCB3024, the Poisson analysis model was the pre-specified model for analysis of the rate of moderately severe and severe exacerbation. This reviewer also performed the negative binomial analysis. As shown in Table 43, the analysis results were similar from the two models. The ratio of the exacerbation rate for SFC50/500 to the rate on placebo was slightly higher using the binomial model than the Poisson model. Both analyses results demonstrated that SFC50/500 reduced the rate of moderate and severe exacerbations in comparison with placebo ($p<0.001$). From Poisson model, the reductions in exacerbation rates was 25% for SFC50/500, 20% for SAL50 and FP500 ($p<0.01$). Table 43 also displays the log-rank analysis of time to first moderately severe or severe exacerbation and the Andersen-Gill analysis of time to each moderately severe or severe exacerbation which demonstrated the reduction of rate of moderately severe or severe COPD exacerbation by all active treatments in comparison with placebo ($p<0.01$). The effect of SFC50/500 was similar when compared to the two components.

Table 43. Analysis Results of the Moderately Severe and Severe Exacerbation

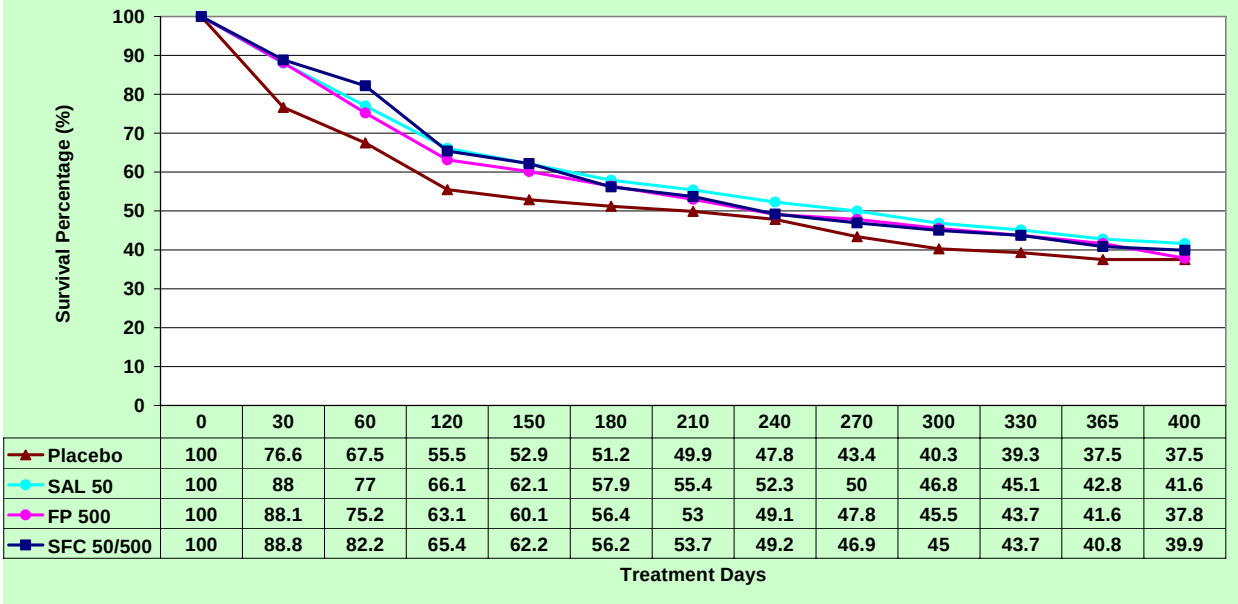
	Placebo	*SAL50*	*FP500*	*SFC50/500*
# of Subjects	361	371	374	356
Poisson Analysis of the Rate of Moderately Severe and Severe Exacerbation				
Mean number per year from model	1.34	1.07	1.08	1.00
Ratio (Active TRT vs. Placebo)		0.802	0.807	0.746
95% CI		(0.694, 0.927)	(0.699, 0.931)	(0.644, 0.865)
p-value		0.003	0.003	<0.001
Hazard Raito (SFC50/500 vs. Components)		0.930	0.925	
95% CI		(0.801, 1.080)	(0.797, 1.073)	
p-value		0.343	0.303	
Negative Binomial Analysis of the Rate of Moderately Severe and Severe Exacerbation				
Mean number per year from model	1.51	1.12	1.11	1.03

Ratio (Active TRT vs. Placebo)		0.742	0.736	0.684
95% CI		(0.617, 0.893)	(0.612, 0.885)	(0.566, 0.826)
p-value		0.001	0.001	<0.001
Raito (SFC50/500 vs. Components)		0.921	0.929	
95% CI		(0.763, 1.111)	(0.771, 1.120)	
p-value		0.390	0.439	
Log-Rank Analysis of Time to First Moderately Severe or Severe Exacerbation				
# Subjects with at least an exacerbation	204 (56.5%)	197 (53.0%)	200 (53.5%)	193 (53.9%)
Probability of exacerbation by 52 weeks1 95%CI[1]	62.5 (57.1, 67.9)	58.4 (52.8, 64.2)	62.2 (53.7, 70.7)	60.1 (54.5, 65.6)
Hazard Ratio (Active TRT vs. Placebo)		0.802	0.839	0.832
95% CI		(0.658, 0.977)	(0.690, 1.022)	(0.683, 1.014)
p-value		0.028	0.080	0.068
Hazard Raito (SFC50/500 vs. Components)		1.035	0.983	
95% CI		(0.848, 1.264)	(0.808, 1.199)	
p-value		0.733	0.869	
Andersen-Gill Analysis of Time to Each Moderately Severe or Severe Exacerbation				
Ratio (Active TRT vs. Placebo)		0.786	0.786	0.728
95% CI		(0.655, 0.944)	(0.656, 0.942)	(0.607, 0.874)
p-value		0.010	0.009	<0.001
Raito (SFC50/500 vs. Components)		0.927	0.927	
95% CI		(0.780, 1.101)	(0.781, 1,100)	
p-value		0.387	0.384	

Source code: negb_anal.sas; exac_ag_model.sas;exac_lr_anal.sas; Data: exacana.xpt; pops.xpt
1: Kaplan Meier estimates

Kaplan Meier estimates of time to first moderately severe or severe exacerbation are shown in are presented graphically in Figure 22. The larger separation between any active treatment and placebo is seen during the first 6 months of study. The effects of SFC50/500 were similar at those of SAL50 and FP500 during the entire study.

Figure 22. Time to First Moderately Severe or Severe Exacerbation – Survival Distribution



	0	30	60	120	150	180	210	240	270	300	330	365	400
Placebo	100	76.6	67.5	55.5	52.9	51.2	49.9	47.8	43.4	40.3	39.3	37.5	37.5
SAL 50	100	88	77	66.1	62.1	57.9	55.4	52.3	50	46.8	45.1	42.8	41.6
FP 500	100	88.1	75.2	63.1	60.1	56.4	53	49.1	47.8	45.5	43.7	41.6	37.8
SFC 50/500	100	88.8	82.2	65.4	62.2	56.2	53.7	49.2	46.9	45	43.7	40.8	39.9

Source: kmest-exac.xls

3.2.7.4 Reviewer's Conclusion

The primary endpoint for this study was pre-bronchodilator FEV_1 (mL) and the two secondary endpoints were the rate of moderately severe and severe COPD exacerbations and health-related quality of life using the SGRQ. The statistical methodologies in this study are adequate. The sponsor provided the pre-specified the primary analysis and the supportive analyses. This reviewer confirmed the sponsor's primary efficacy analysis results.

The primary analysis demonstrated that over the 52 weeks of the study, pre-bronchodilator FEV_1 in the SFC50/500 group was 133mL higher than that of the placebo group ($p<0.001$); 73 mL higher the SAL50 group ($p<0.001$) and 95 (mL) higher than the FP500 group ($p<0.001$).

From binomial model, the ratio of the moderately severe and severe exacerbation rate for SFC50/500 to the rate on placebo was 0.684 (95% CI 0.566, 0.826) which represented a 32% decrease in rate compared with placebo ($p<0.001$). Treatment with SAL50 and FP500 also reduced the rate compared with placebo, by 26% ($p<0.001$). The effect of SFC50/500 was similar compared to two components. These results were consistent with Study SCO30003.

3.3 Comparison of Study SCO30003 and Study SFCB3024

Study SCO30003 and Study SFCB3024 provide evidence to support the use of SFC50/500 in decreasing the rate of moderate and severe exacerbation in patients with COPD and improving lung function FEV_1. For SFCB3024, a history of exacerbation was required to enroll while in Study SCO30003 this was not an entry criterion (see Table 36). However, in Study SCO30003, about 57% of the patients had 1 or more exacerbation in the year pervious to enrollment. To compare two studies, the results for subjects who had COPD exacerbation during the previous year for Study SCO30003 with the results for Study SFCB3024 are shown in Table 44.

Overall, the majority of subjects, 68% to 70% in Study SCO30003 and 53% to 57% in Study SFCB3024, experienced at least one moderate or severe exacerbation while on study treatment.

Table 44. Prevalence of Moderate and Severe Exacerbation

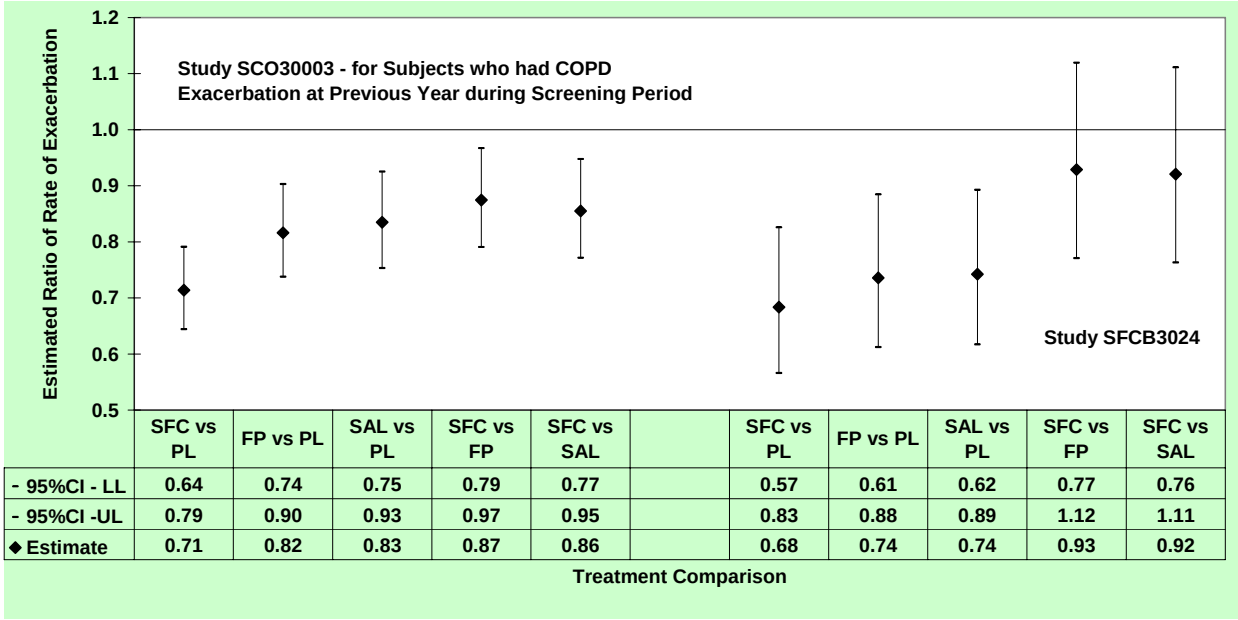
	Placebo	*SAL50*	*FP500*	*SFC50/500*
Study SCO30003 for Subjects who had COPD Exacerbation at Previous Year				
No. patients	887	859	887	863
No. patients with at least one moderate and severe exacerbation (%)	675 (76.1%)	661 (76.9%)	676 (76.2%)	634 (73.5%)
No. moderate and severe exacerbation				
Total No.	2454	2242	2475	2156
Mean No. per patient	2.80	2.61	2.79	2.50
Range	0 – 30	0 – 28	0 – 21	0 – 28
On treatment time, year				
Total person-years	1810	1948	2052	2027
Mean follow-up per patient	2.06	2.27	2.31	2.35
Study SFCB3024 (1 year) Moderately Severe and Severe Exacerbation				
No. patients	361	372	374	358
No. patients with at least one moderate and severe exacerbation (%)	204 (56.5%)	197 (53.0%)	200 (53.5%)	193 (53.9%)

No. moderate and severe exacerbation				
Total No.	382	366	374	331
Mean No. per patient	1.06	0.98	1.00	0.92
Range	0 – 5	0 – 4	0 – 6	0 – 6
On treatment time, year				
Total person-years	267.8	307.2	314.7	302.0
Mean follow-up per patient	0.74	0.83	0.84	0.84

Source cod: exac_rate.sas; Data: exacana.xpt; exacrt24.xpt, pops.xpt

From Figure 23 and the estimates below the figure, it can be seen the results are consistent for the combination product versus placebo across the two studies with a 29% risk reduction in the subgroup of patients from Study SCO30003 and a 32% risk reduction in Study SFCB3024. The mean number of exacerbation per year from model is similar in both studies, but SAL50 and FP500 had better effect in Study SFCB3024 compared to Study SCO30003. Overall, Study SCO30003 and Study SFCB3024 demonstrated statistically significant reductions in exacerbation for SFC50/500 patients compared to placebo.

Figure 23. Negative Binomial Estimated the Rate of Moderate and Severe Exacerbation



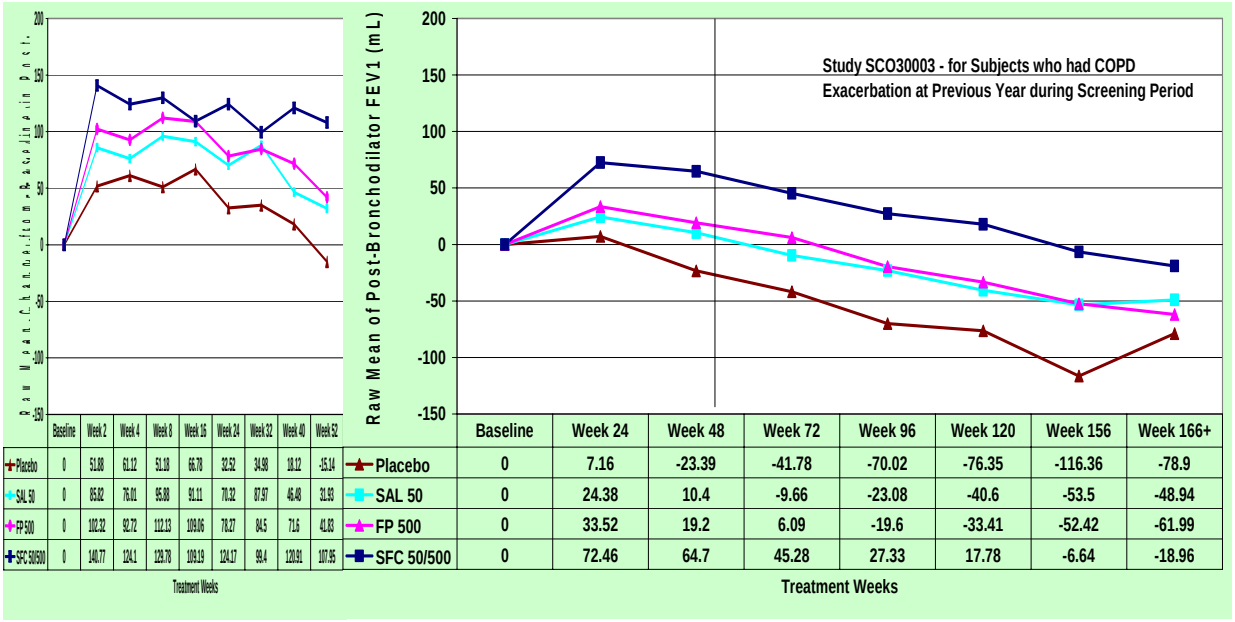
	SFC vs PL	FP vs PL	SAL vs PL	SFC vs FP	SFC vs SAL		SFC vs PL	FP vs PL	SAL vs PL	SFC vs FP	SFC vs SAL
- 95%CI - LL	0.64	0.74	0.75	0.79	0.77		0.57	0.61	0.62	0.77	0.76
- 95%CI -UL	0.79	0.90	0.93	0.97	0.95		0.83	0.88	0.89	1.12	1.11
◆ Estimate	0.71	0.82	0.83	0.87	0.86		0.68	0.74	0.74	0.93	0.92

Source: negbest.xls; data source: exacana.xpt, exacrt24.xpt, and pops.xpt

The mean change in post-bronchodilator FEV_1 over time in Study SCO30003 for subjects who had a COPD exacerbation in the previous year is shown graphically with results for Study SFCB3024 in Figure 24. Overall, the improvement in post-bronchodilator FEV_1 was smaller in Study CSO30003 compared to Study SFCB3024.

Figure 24. Mean Change in Post-Bronchodilator FEV_1 over Time

Study SFCO3024 **Study SCO30003**



	Baseline	Week 24	Week 48	Week 72	Week 96	Week 120	Week 156	Week 166+
Placebo	0	7.16	-23.39	-41.78	-70.02	-76.35	-116.36	-78.9
SAL 50	0	24.38	10.4	-9.66	-23.08	-40.6	-53.5	-48.94
FP 500	0	33.52	19.2	6.09	-19.6	-33.41	-52.42	-61.99
SFC 50/500	0	72.46	64.7	45.28	27.33	17.78	-6.64	-18.96

This reviewer performed the repeated measures analysis without the interaction term of baseline FEV_1*visit. This result is displayed in Table 45, which shows the magnitude of the effect size for SFC50/500 and components compared to placebo were similar in two studies

Table 45. LS Mean Change from Baseline in Post-Bronchodilator FEV_1(mL) at Endpoint

	Placebo	***SAL50***	***FP500***	***SFC50/500***
Study SCO30003 for Subjects who had COPD Exacerbation at Previous Year				
N	1524	1521	1534	1533
Number of Subject in the Analysis	872	853	883	855
Baseline Raw Mean (SD)	1190 (430)	1173 (436)	1188 (436)	1213 (456)
Adjusted Mean Change from Baseline (SE)[1]	-62.7 (8.7)	-32.7 (8.6)	-28.6 (8.4)	16.9 (8.5)
Active Treatment – Placebo (SE)		30.0 (11.5)	34.1 (11.4)	79.6 (11.4)
95% CI		(7.5, 52.5)	(11.8, 56.3)	(57.2, 102)
p-value		0.009	0.003	<0.001
SFC50/500 – Component (SE)		49.6 (11.3)	45.6 (11.2)	
95% CI		(27.5, 71.8)	(23.6, 67.5)	
p-value		<0.001	<0.001	
Study SFCB3024				
N	361	372	374	358
Number of Subject in the Analysis	353	361	371	345
Baseline Raw Mean (SD)	1374 (477)	1339 (459)	1363 (460)	1420 (550)
Adjusted Mean Change from Baseline (SE)[1]	23.2 (12.1)	53.8 (11.7)	67.6 (11.5)	97.8 (12.0)
Active Treatment – Placebo (SE)		30.6 (16.1)	44.4 (16.0)	74.6 (16.3)
95% CI		(-0.92, 62.2)	(13.1, 75.7)	(42.7, 106.6)
p-value		0.057	0.006	<0.001
SFC50/500 – Component (SE)		44.0 (16.0)	30.2 (15.9)	
95% CI		(12.6, 75.4)	(-0.94, 1.4)	
p-value		0.006	0.057	

Source cod: lft_anal.sas; Data: lftana.xpt; pops.xpt. 1: Repeated measures analysis adjusted for smoking status, age, sex, baseline FEV_1, BMI, region, visit, treatment by visit.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Others

A detailed subgroup analysis can be found in the individual study review section.

4.2 Other Special/Subgroup Populations

US Population -

This multinational study was conducted at 466 centers (444 had the randomized subjects) in 42 countries comprising 190 centers in USA, 134 centers in Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom), 46 centers in Eastern Europe (Bulgaria, Croatia, Czech Republic, Hungary, Estonia, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, Ukraine), 37 centers in Asia Pacific (China, Hong Kong, Malaysia, Philippines, Singapore, Taiwan, Thailand) and 59 centers in other regions (Australia, New Zealand, South Africa, Canada, Argentina, Brazil, Chile, Mexico). Figure 25 displays the results by country for the difference of cumulative incidence rate of death for SFC50/500 over placebo sorted by country size from smallest to largest (left to right), ranging from 18 to 694. US had the largest patient population (694) compared to other countries and the survival improvement was 1.6%. The difference varies from country to country, but for a trial with so many countries, this is expected.

Figure 25. Difference of Probability (%) of Death between SFC50/500 and Placebo by Country

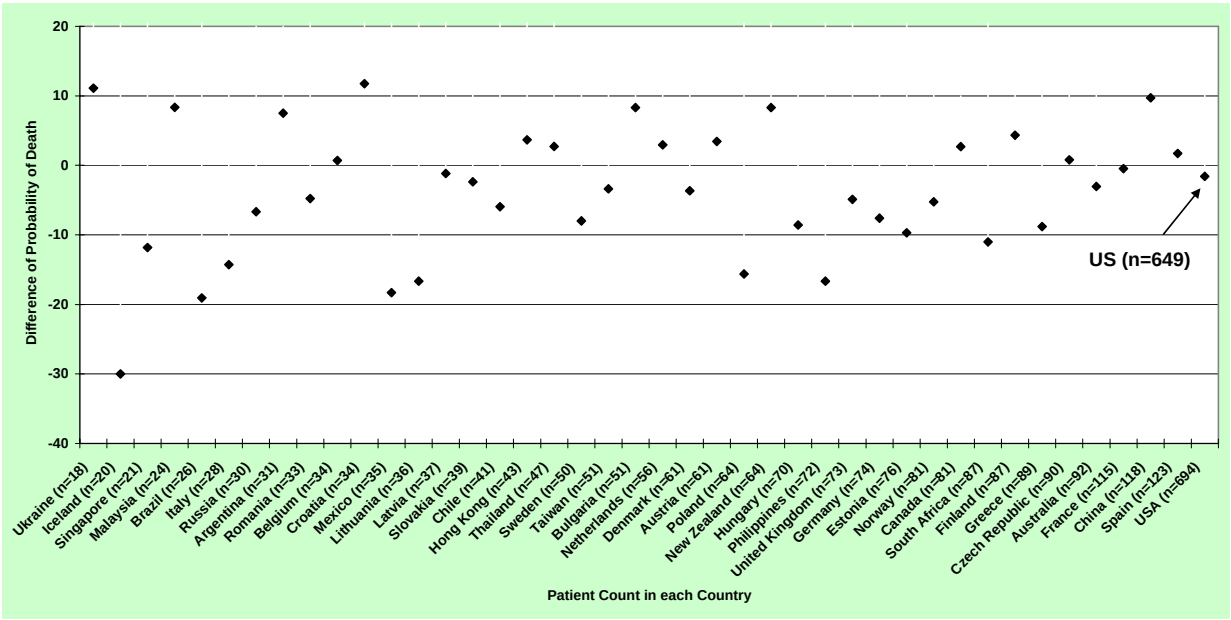
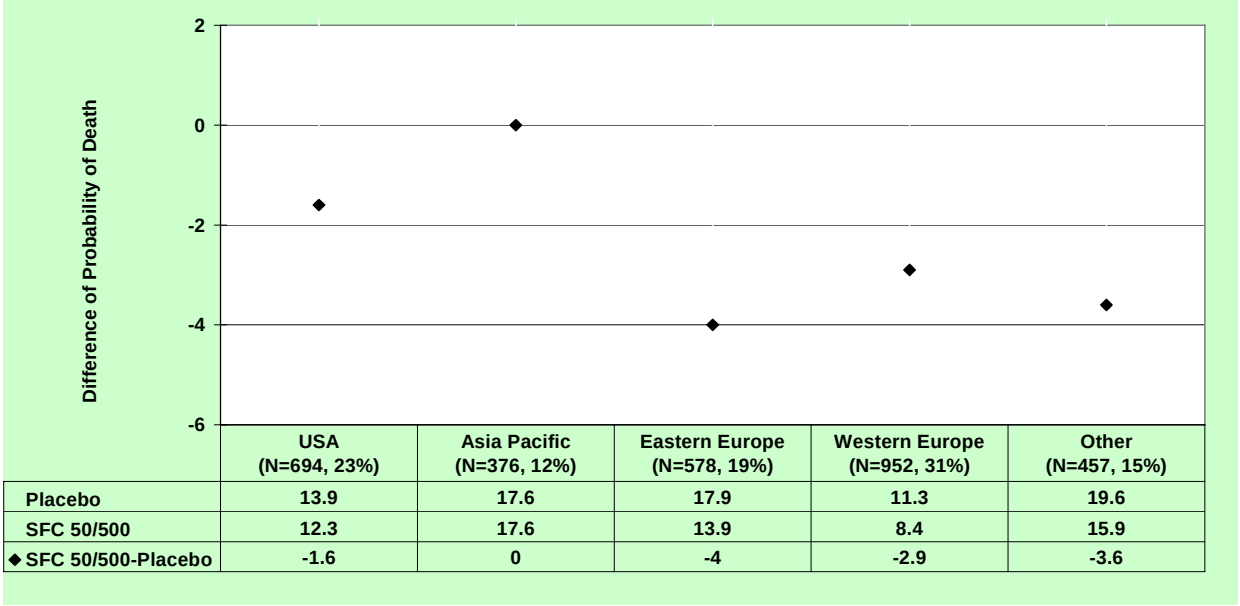


Figure 26 displays the SFC50/500 survival over placebo by regions. The Eastern Europe had the most survival improvement. Asia showed no survival improvement. The difference between East Europe and Asia for the treatment effect is 4%.

Figure 26. Difference of Probability (%) of Death between SFC50/500 and Placebo by Regions



	USA (N=694, 23%)	Asia Pacific (N=376, 12%)	Eastern Europe (N=578, 19%)	Western Europe (N=952, 31%)	Other (N=457, 15%)
Placebo	13.9	17.6	17.9	11.3	19.6
SFC 50/500	12.3	17.6	13.9	8.4	15.9
◆ SFC 50/500-Placebo	-1.6	0	-4	-2.9	-3.6

Source: cnt_efct.sas; data source: deaths.xpt and pops.xpt

Overall, the magnitude of efficacy size of SFC50/500 were lower in US population for the primary endpoint (mortality), secondary endpoint (moderate and severe COPD exacerbation), and other endpoint (post-bronchodilator FEV_1) (Table 46). The improvement of survival rate of SFC50/500 over placebo was low in US population (1.6%) compared to non-US population (2.9%); the reductions in exacerbation rates were lower in US population (18%) compared to those in non-US population (27%); over entire treatment period, LS Mean difference of changed from baseline in post-bronchodilator FEV_1 between two treatment was lower in US population (37 mL) compared to those in non-US population (58 mL).

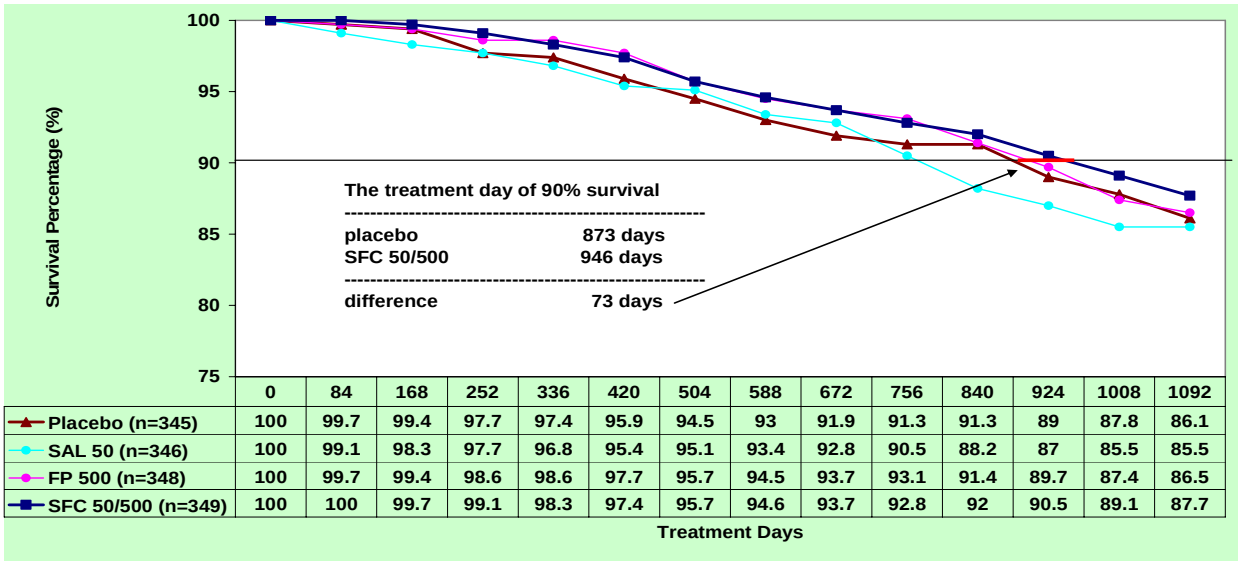
Table 46. Comparison between US and Non-US Population in Three Endpoints

	US Population		*Non-US Population*		*All Population*	
	Placebo	***SFC50/500***	***Placebo***	***SFC50/500***	***Placebo***	***SFC50/500***
N	345	349	1179	1184	1524	1533
TRT Exp. (person yrs)	661	817	2578	2861	3238	3678
(mean, yrs)	(1.92)	(2.34)	(2.19)	(2.42)	(2.12)	(2.40)
Mortality at Weeks 156						
# Death (%)	48 (13.9)	43 (12.3)	183 (15.5)	150 (12.7)	231(15.2)	193 (12.6)
Difference	1.6%		2.9%		2.6%	
HR (95%CI)	0.873 (0.578, 1.317)		0.806 (0.649, 1.000)		0.820 (0.677. 0.993)	
p-value	0.517		0.049		0.041	
Moderate and Severe COPD Exacerbations						
Mean number per year from model	1.18	0.97	1.11	0.82	1.13	0.85
Ratio (95%CI)	0.822 (0.699, 0.966)		0.732 (0.664, 0.806)		0.749 (0.689, 0.814)	
p-value	0.017		<0.001		<0.001	
Adjust Mean Change in Post-Bronchodilator FEV_1 (mL) at Weeks 156						
LS Mean (SE)	-87 (15.6)	-50 (15.3)	-80 (9.0)	-16 (8.7)	-83 (7.7)	-25 (7.5)
SFC – PL (95%CI)	37 (-6, 79)		63 (41, 86)		58 (38, 78)	
p-value	0.091		<0.001		<0.001	

Source: interim_ana.sas; data source: deaths.xpt, and pops.xpt

Figure 27 and Figure 28 displays the Kaplan Meier estimates of survival probabilities for time to death from all causes (only data up to 3 years (Week 156) are included) for US and Non-US population which graphically show the different pattern. In US, SAL50 had the highest mortality in US population and FP500 had the highest mortality in non-US population. It is worth noting that death rate was lower in the placebo group for US population compared to those in the Non-US population and dropout rate was higher in US population too.

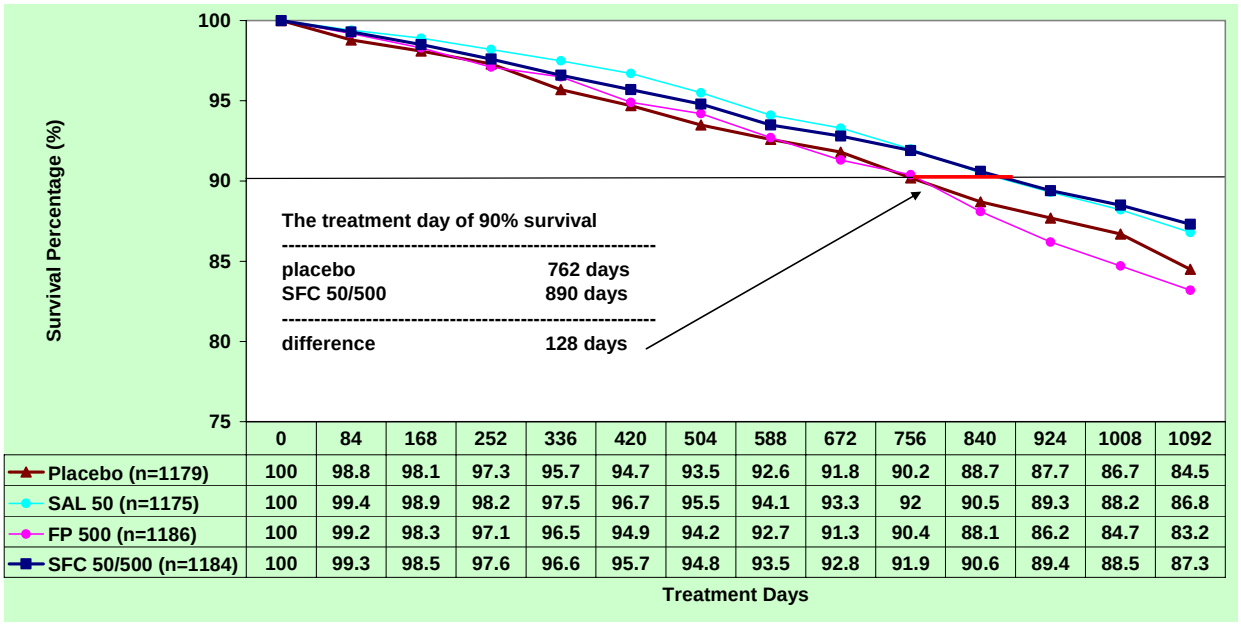
Figure 27. Time to All Cause Death – Survival Distribution for US



	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo (n=345)	100	99.7	99.4	97.7	97.4	95.9	94.5	93	91.9	91.3	91.3	89	87.8	86.1
SAL 50 (n=346)	100	99.1	98.3	97.7	96.8	95.4	95.1	93.4	92.8	90.5	88.2	87	85.5	85.5
FP 500 (n=348)	100	99.7	99.4	98.6	98.6	97.7	95.7	94.5	93.7	93.1	91.4	89.7	87.4	86.5
SFC 50/500 (n=349)	100	100	99.7	99.1	98.3	97.4	95.7	94.6	93.7	92.8	92	90.5	89.1	87.7

Source: kmest-death-region.xls; km_anal.sas

Figure 28. Time to All Cause Death – Survival Distribution for Non-US Population

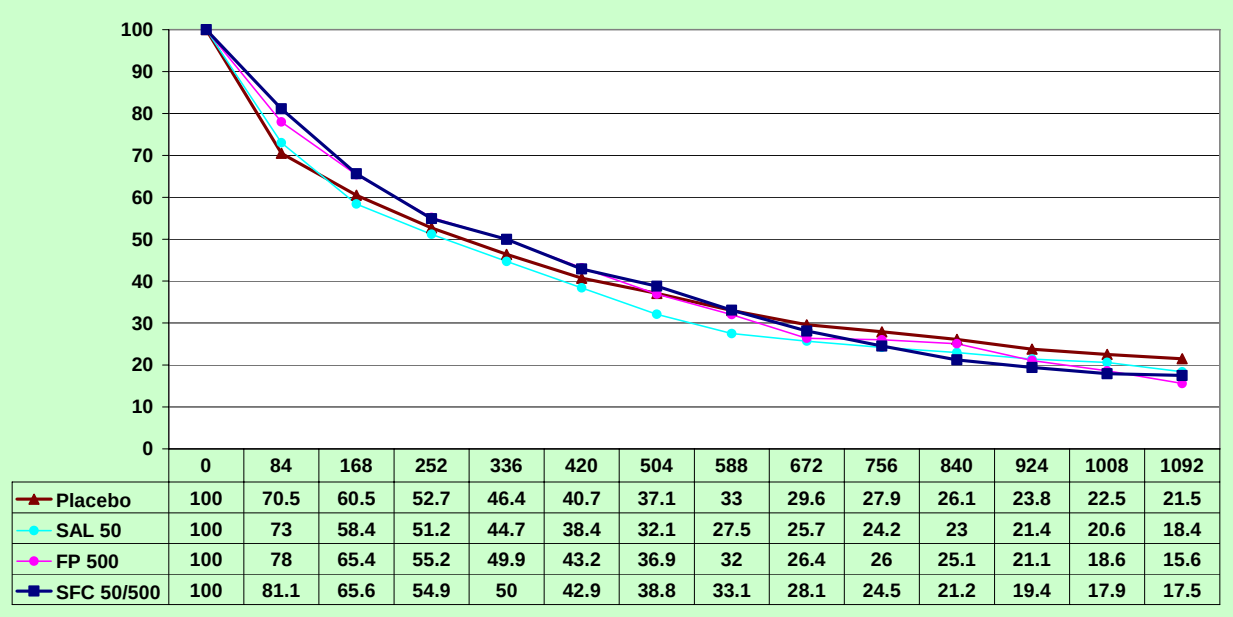


	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo (n=1179)	100	98.8	98.1	97.3	95.7	94.7	93.5	92.6	91.8	90.2	88.7	87.7	86.7	84.5
SAL 50 (n=1175)	100	99.4	98.9	98.2	97.5	96.7	95.5	94.1	93.3	92	90.5	89.3	88.2	86.8
FP 500 (n=1186)	100	99.2	98.3	97.1	96.5	94.9	94.2	92.7	91.3	90.4	88.1	86.2	84.7	83.2
SFC 50/500 (n=1184)	100	99.3	98.5	97.6	96.6	95.7	94.8	93.5	92.8	91.9	90.6	89.4	88.5	87.3

Source: kmest-death.xls; km_anal.sas

Figure 29 and Figure 30 display the time to first moderate or severe exacerbation for US or Non-US population which graphically show the different pattern. In US, SFC50/500 (dark blue) was better than placebo (dark red) in first half of the study period and worst then placebo in the second half of the study period (i.e. two lines crossed in the middle of study period). In non-US population, four lines are parallel during the study period.

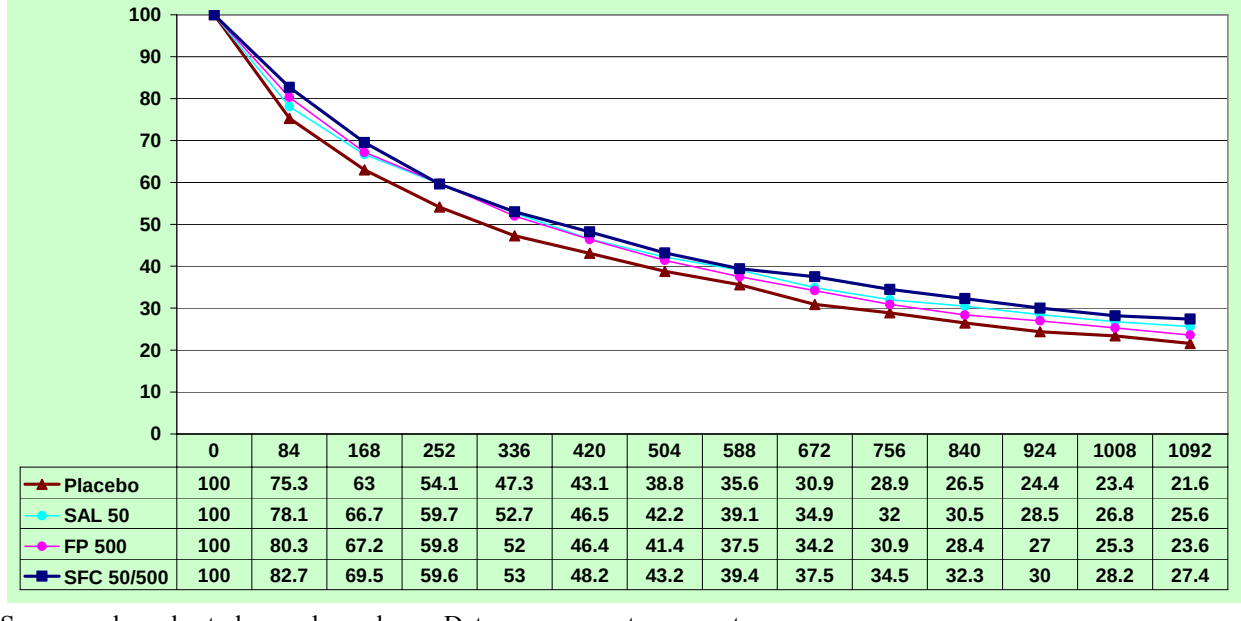
Figure 29. Time to First Moderate or Severe Exacerbation – Survival Distribution, US



	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo	100	70.5	60.5	52.7	46.4	40.7	37.1	33	29.6	27.9	26.1	23.8	22.5	21.5
SAL 50	100	73	58.4	51.2	44.7	38.4	32.1	27.5	25.7	24.2	23	21.4	20.6	18.4
FP 500	100	78	65.4	55.2	49.9	43.2	36.9	32	26.4	26	25.1	21.1	18.6	15.6
SFC 50/500	100	81.1	65.6	54.9	50	42.9	38.8	33.1	28.1	24.5	21.2	19.4	17.9	17.5

Source cod: negbest.xls; megb_anal.sas; Data: exacana.xpt; pops.xpt

Figure 30. Time to First Moderate or Severe Exacerbation – Survival Distribution, Non-US

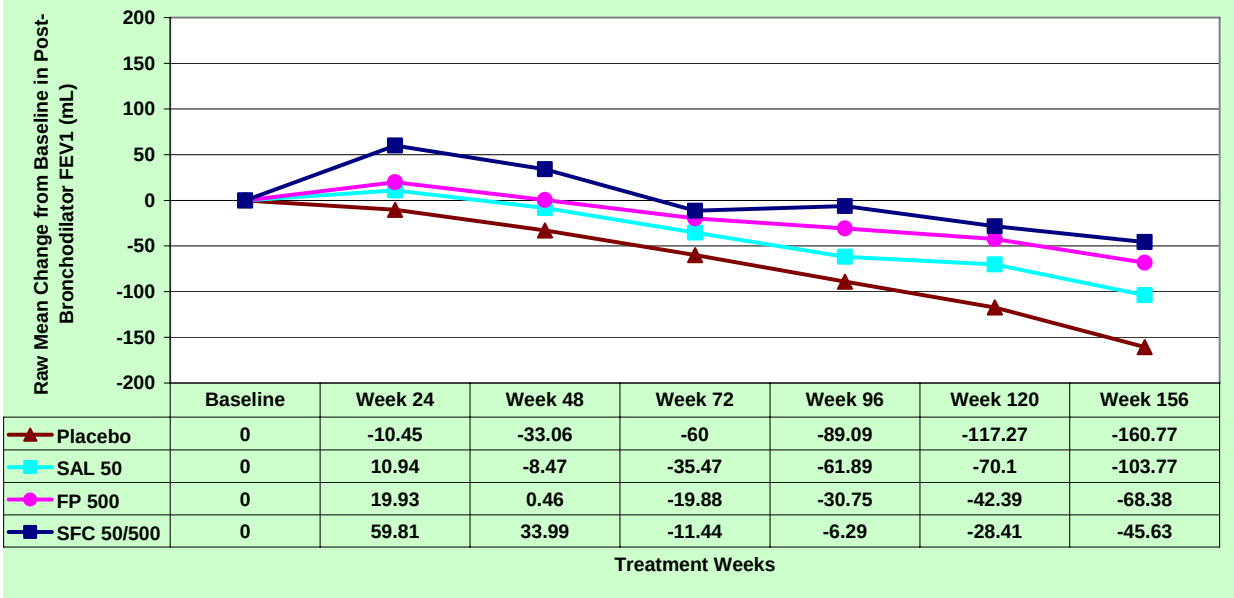


	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo	100	75.3	63	54.1	47.3	43.1	38.8	35.6	30.9	28.9	26.5	24.4	23.4	21.6
SAL 50	100	78.1	66.7	59.7	52.7	46.5	42.2	39.1	34.9	32	30.5	28.5	26.8	25.6
FP 500	100	80.3	67.2	59.8	52	46.4	41.4	37.5	34.2	30.9	28.4	27	25.3	23.6
SFC 50/500	100	82.7	69.5	59.6	53	48.2	43.2	39.4	37.5	34.5	32.3	30	28.2	27.4

Source cod: negbest.xls; megb_anal.sas; Data: exacana.xpt; pops.xpt

Figure 31 and Figure 32 display the mean change in post-bronchodilator FEV_1 over time in Study SCO30003 for US and non-US population which show the difference pattern. In US, four lines are parallel during the study period and SAL50 (pink line) had better effect than FP500 (light blue). In non-US population, four lines are parallel during the study period and SAL50 and FP500 had similar effect.

Figure 31. Mean Change in Post-Bronchodilator FEV_1 over Time, US Population

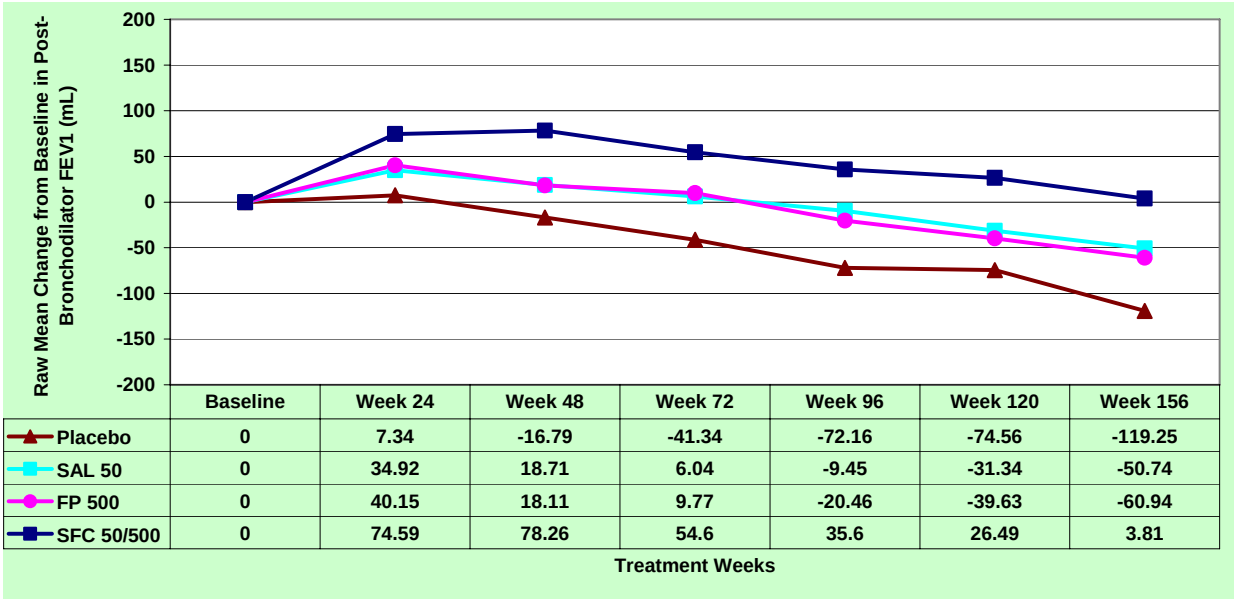


	Baseline	Week 24	Week 48	Week 72	Week 96	Week 120	Week 156
Placebo	0	-10.45	-33.06	-60	-89.09	-117.27	-160.77
SAL 50	0	10.94	-8.47	-35.47	-61.89	-70.1	-103.77
FP 500	0	19.93	0.46	-19.88	-30.75	-42.39	-68.38
SFC 50/500	0	59.81	33.99	-11.44	-6.29	-28.41	-45.63

Treatment Weeks

Source: lft.xls; lft_anal.sas. Data: lft.xpt; pops.xpt.

Figure 32. Mean Change in Post-Bronchodilator FEV_1 over Time, Non-US Population



	Baseline	Week 24	Week 48	Week 72	Week 96	Week 120	Week 156
Placebo	0	7.34	-16.79	-41.34	-72.16	-74.56	-119.25
SAL 50	0	34.92	18.71	6.04	-9.45	-31.34	-50.74
FP 500	0	40.15	18.11	9.77	-20.46	-39.63	-60.94
SFC 50/500	0	74.59	78.26	54.6	35.6	26.49	3.81

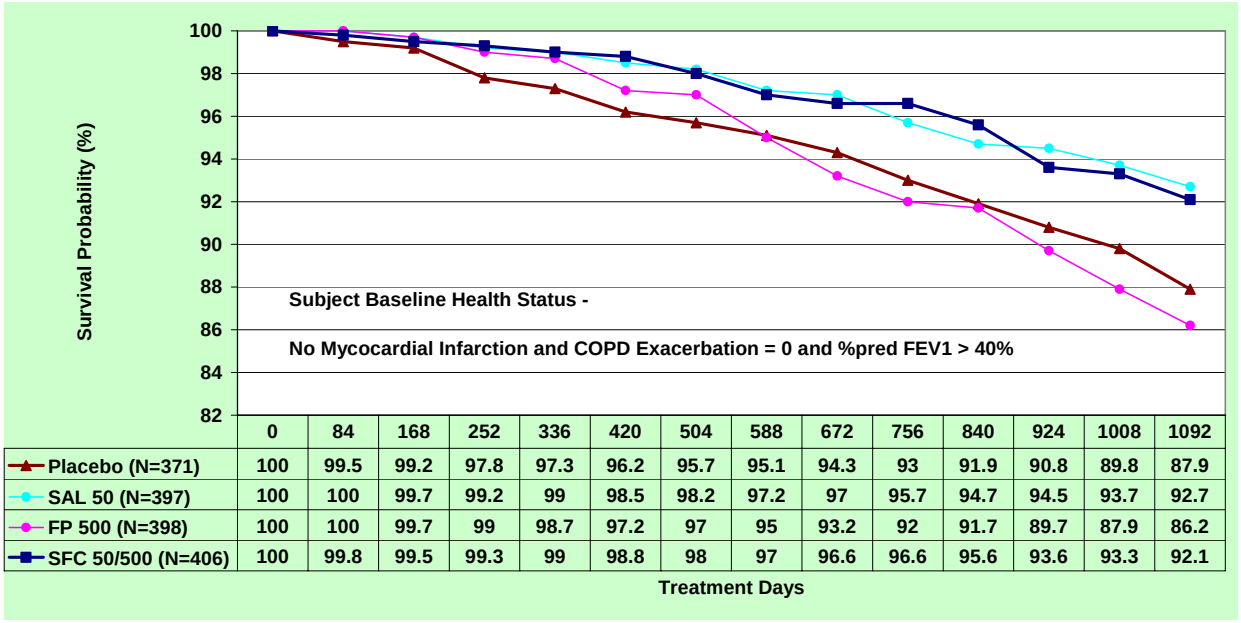
Treatment Weeks

Source: lft.xls; lft_anal.sas. Data: lft.xpt; pops.xpt.

Healthier Subjects or Steroid Naïve Subjects -

Figure 33 and Figure 34 display the Kaplan Meier estimates of survival probabilities for time to death from all cause (only data up to 3 years (Week 156) are included) by subject's health status at baseline. The healthier subjects had more benefit from the treatment of SFC50/500 compared to placebo than other subjects.

Figure 33. Time to All Cause Death – Survival Distribution, (Healthy Subjects)

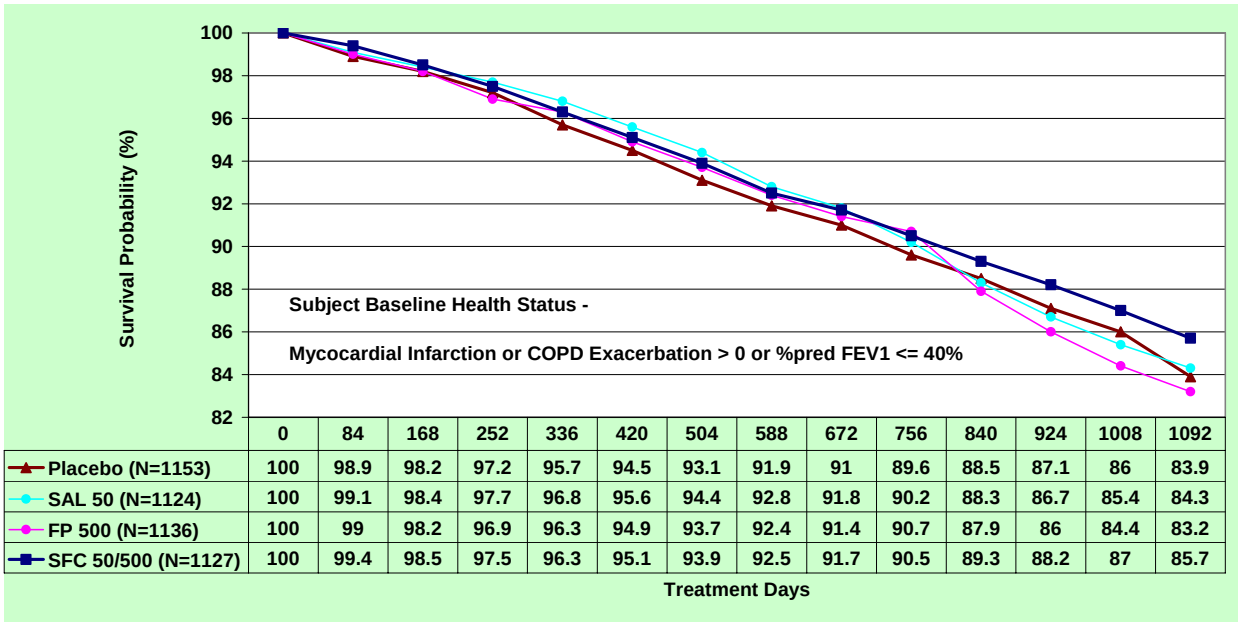


	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo (N=371)	100	99.5	99.2	97.8	97.3	96.2	95.7	95.1	94.3	93	91.9	90.8	89.8	87.9
SAL 50 (N=397)	100	100	99.7	99.2	99	98.5	98.2	97.2	97	95.7	94.7	94.5	93.7	92.7
FP 500 (N=398)	100	100	99.7	99	98.7	97.2	97	95	93.2	92	91.7	89.7	87.9	86.2
SFC 50/500 (N=406)	100	99.8	99.5	99.3	99	98.8	98	97	96.6	96.6	95.6	93.6	93.3	92.1

Treatment Days

KMest-death.xls; KM_anal.sas

Figure 34. Time to All Cause Death – Survival Distribution, (Un-Health Subjects)



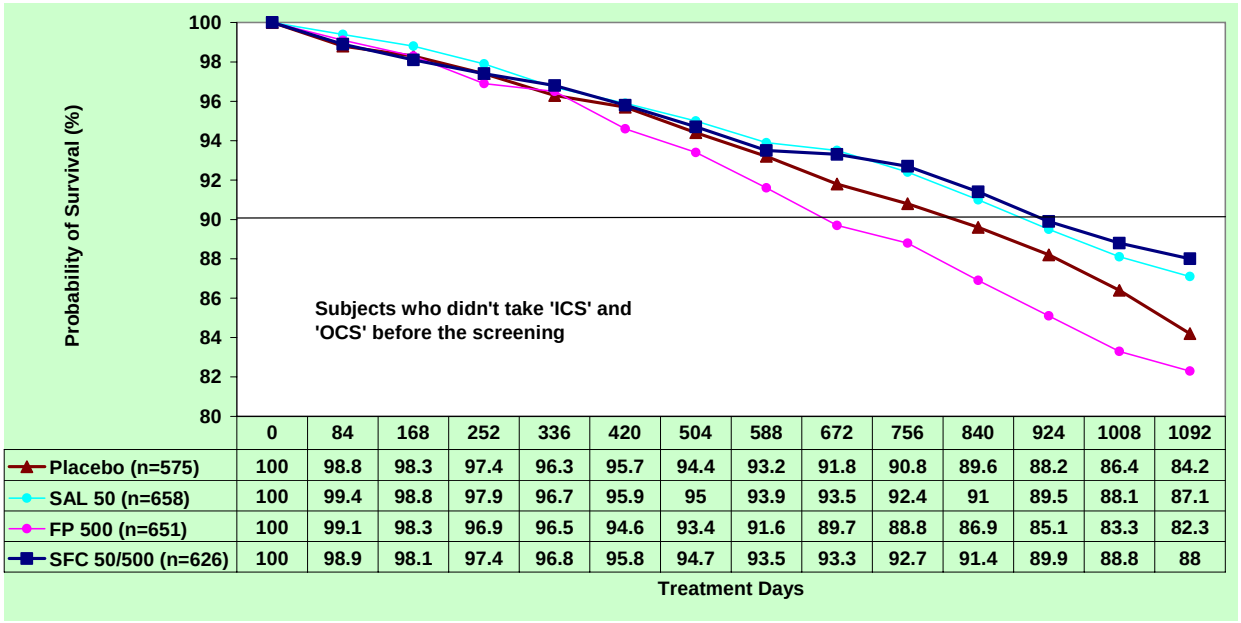
	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo (N=1153)	100	98.9	98.2	97.2	95.7	94.5	93.1	91.9	91	89.6	88.5	87.1	86	83.9
SAL 50 (N=1124)	100	99.1	98.4	97.7	96.8	95.6	94.4	92.8	91.8	90.2	88.3	86.7	85.4	84.3
FP 500 (N=1136)	100	99	98.2	96.9	96.3	94.9	93.7	92.4	91.4	90.7	87.9	86	84.4	83.2
SFC 50/500 (N=1127)	100	99.4	98.5	97.5	96.3	95.1	93.9	92.5	91.7	90.5	89.3	88.2	87	85.7

Treatment Days

KMest-death.xls; KM_anal.sas

Figure 35 and Figure 36 display the Kaplan Meier estimates of survival probabilities for time to death from all cause (only data up to 3 years (Week 156) are included) by subject's whether or not took steroid before the screening. The steroid Naïve had more benefit from the treatment of SFC50/500 compared to placebo than subjects who took severe subjects.

Figure 35. Time to All Cause Death – Survival Distribution (Steroid Naïve Subjects)

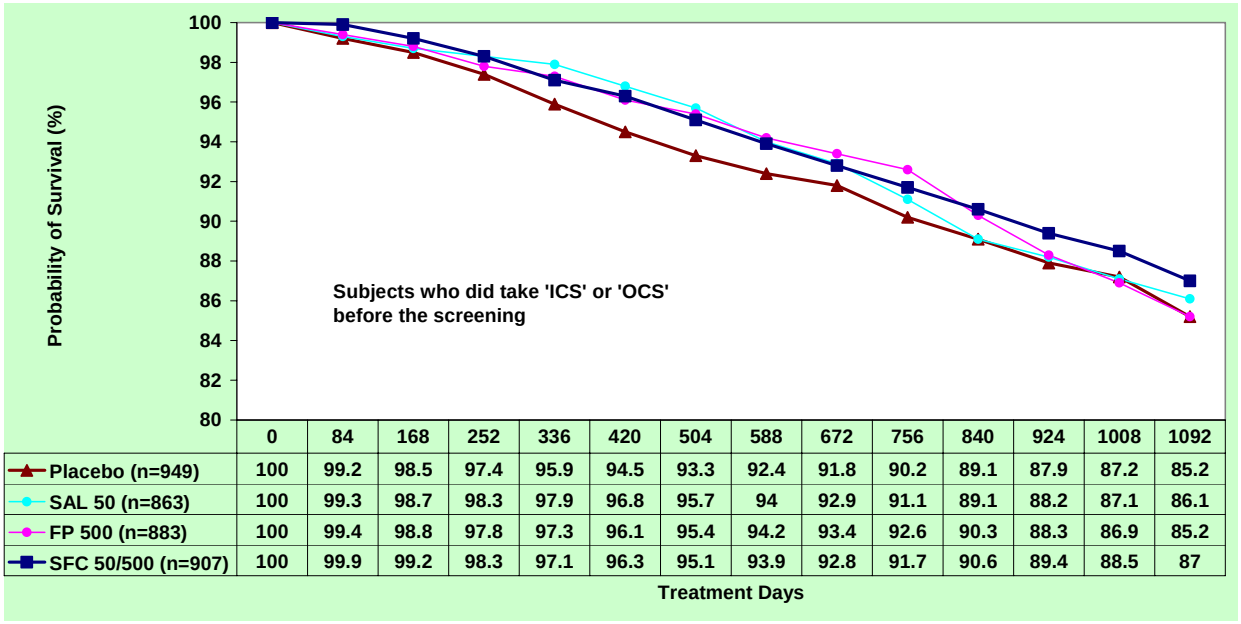


	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo (n=575)	100	98.8	98.3	97.4	96.3	95.7	94.4	93.2	91.8	90.8	89.6	88.2	86.4	84.2
SAL 50 (n=658)	100	99.4	98.8	97.9	96.7	95.9	95	93.9	93.5	92.4	91	89.5	88.1	87.1
FP 500 (n=651)	100	99.1	98.3	96.9	96.5	94.6	93.4	91.6	89.7	88.8	86.9	85.1	83.3	82.3
SFC 50/500 (n=626)	100	98.9	98.1	97.4	96.8	95.8	94.7	93.5	93.3	92.7	91.4	89.9	88.8	88

Treatment Days

KMest-death.xls; KM_anal.sas

Figure 36. Time to All Cause Death – Survival Distribution (Used Steroid Subjects)



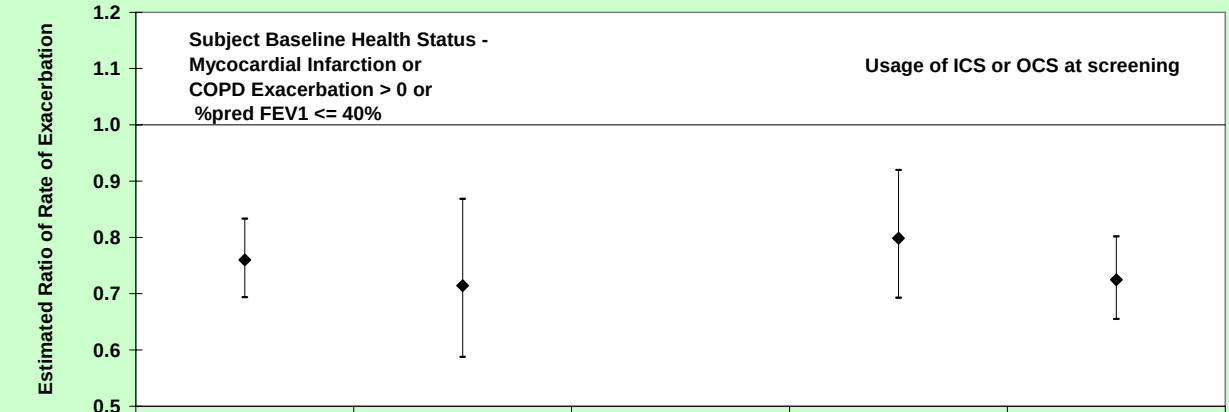
	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo (n=949)	100	99.2	98.5	97.4	95.9	94.5	93.3	92.4	91.8	90.2	89.1	87.9	87.2	85.2
SAL 50 (n=863)	100	99.3	98.7	98.3	97.9	96.8	95.7	94	92.9	91.1	89.1	88.2	87.1	86.1
FP 500 (n=883)	100	99.4	98.8	97.8	97.3	96.1	95.4	94.2	93.4	92.6	90.3	88.3	86.9	85.2
SFC 50/500 (n=907)	100	99.9	99.2	98.3	97.1	96.3	95.1	93.9	92.8	91.7	90.6	89.4	88.5	87

Treatment Days

kmest-death.xls; km_anal.sas

Figure 37 graphically displays the ratio of SFC50/500 vs. placebo of rate of moderate and severe exacerbations estimated by the negative binomial model which shows the SFC 500/500 had better effect on the subjects who were healthier at baseline or used ICS or OCS during the screening period.

Figure 37. Negative Binomial Analysis of the Rate of Moderate/Severe Exacerbation, Subgroups



	No (SFC=1127, Plc=1153)	Yes (SFC=406, Plc=371)		No (SFC=626, Plc=575)	Yes (SFC=907, Plc=949)
- 95%CI - LL	0.69	0.59		0.69	0.65
- 95%CI -UL	0.83	0.87		0.92	0.80
◆ SFC vs. Plc	0.76	0.71		0.80	0.72

Subgroup Comparison

Source: negbest.xls

5. SUMMARY AND CONCLUSIONS

Based on the evaluation of Study SCO30003, SFC50/500 demonstrated a borderline insignificant effect over placebo with a hazard ratio of 0.82 (95%CI: 0.68, 0.99; p=0.041). Due to the interim analyses, this unadjusted p-value needs to be compared to a significance level of 0.040. To allow comparison to the commonly used significance level of 0.05, the adjusted CI was 0.681, 1.002 and the adjusted p-value was 0.052. The absolute difference of cumulative incidence rates of all cause mortality at 3 years was -2.6% between SFC50/500 (12.6%) and placebo (15.2%). It should be noted that usually highly significant results are required to demonstrate efficacy with a single study.

According to the proposed multiplicity adjustment procedure in the protocol of Study SCO30003 (See more details on section 3.1.7), secondary hypotheses would not be tested if the primary endpoint results were not significant at the 0.05 level. Since the primary endpoint was not significant at the 0.05 alpha level, secondary endpoints should not be tested. Nevertheless, since the results are borderline, it is important for the reader to see the nominal results for the secondary endpoints while understanding the context of these results under the protocol.

No notable difference in risk reduction for SFC50/500 compared with SAL50 was observed (risk reduction 7%, absolute risk difference of -0.9%, p=0.481). Compared with FP500, SFC50/500 reduced the risk by 23% (absolute risk difference of -3.4%, p=0.007).

SFC50/500 reduced the risk of COPD-related deaths within 3 years by 22% compared with placebo (SFC50/500 rate of 4.7% and placebo rate of 6.0%, p=0.107), which was consistent with the magnitude of the risk reduction seen for all-cause mortality. Although, SFC50/500 was not shown to be significantly different from placebo on COPD deaths, the results for SFC50/500 were notably better than either component. Similarly, an exploratory analysis of deaths occurring while patients were on treatment showed the risk of dying was reduced by 23% with SFC50/500 compared with placebo (p=0.055).

The magnitude of efficacy of SFC50/500 compared with placebo was smaller in the US population than non-US population with risk reductions of 13% and 19% for death and exacerbation, respectively, compared to 20% and 27% for the Non-US population.

There was no statistically significant evidence that treatment (SFC50/500 vs. placebo) effects varied with smoking status, baseline FEV_1, age, sex, ethnic origin, BMI or previous exacerbation history. Subjects who did not use ICS or OCS during the screening period or who were considered at low risk based on a composite baseline variable of no history of MI, no baseline COPD exacerbation and % predicted $FEV_1 > 40$, SFC50/500 showed a greater benefit due to SFC50/500 over placebo compared to subjects that may be characterized as less healthy .

Studies SCO30003 and SFCB3024 showed a reduction in exacerbations and an improvement in FEV_1 for SFC50/500 patients compared to placebo with a nominal p-value less than 0.05.

-EOF-

PRESCRIBING INFORMATION

ADVAIR DISKUS® 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

ADVAIR DISKUS® 250/50
(fluticasone propionate 250 mcg and salmeterol* 50 mcg inhalation powder)

ADVAIR DISKUS® 500/50
(fluticasone propionate 500 mcg and salmeterol* 50 mcg inhalation powder)

***As salmeterol xinafoate salt 72.5 mcg, equivalent to salmeterol base 50 mcg**

For Oral Inhalation Only

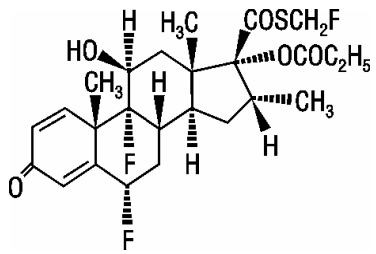
WARNING

Long-acting beta$_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see WARNINGS).

DESCRIPTION

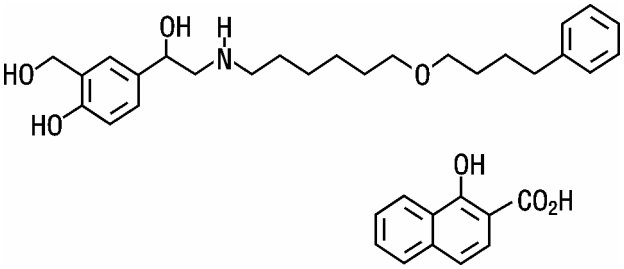
ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are combinations of fluticasone propionate and salmeterol xinafoate.

One active component of ADVAIR DISKUS 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 and the following chemical structure:



Fluticasone propionate is a 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.

The other active component of ADVAIR DISKUS is salmeterol xinafoate, a beta$_2$-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has the following chemical structure:



Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is $C_{25}H_{37}NO_4 \bullet C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are specially designed plastic devices containing a double-foil blister strip of a powder formulation of fluticasone propionate and salmeterol xinafoate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 100, 250, or 500 mcg of microfine fluticasone propionate and 72.5 mcg of microfine salmeterol xinafoate salt, equivalent to 50 mcg of salmeterol base, in 12.5 mg of formulation containing lactose (which contains milk proteins). Each blister contains 1 complete dose of both medications. 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.

Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS 100/50, 250/50, and 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean forced expiratory volume in 1 second [FEV_1] 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS® inhalation device was 82.4 L/min (range, 46.1 to 115.3 L/min).

Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to 50 years) patients with asthma inhaling maximally through the DISKUS device show mean PIF of 122.2 L/min (range, 81.6 to 152.1 L/min). Inhalation profiles for pediatric patients with asthma inhaling maximally through the DISKUS device show a mean PIF of 75.5 L/min (range, 49.0 to 104.8 L/min) for the 4-year-old patient set (N = 20) and 107.3 L/min (range, 82.8 to 125.6 L/min) for the 8-year-old patient set (N = 20).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

CLINICAL PHARMACOLOGY

Mechanism of Action: *ADVAIR DISKUS:* Since ADVAIR DISKUS contains both fluticasone propionate and salmeterol, the mechanisms of action described below for the individual components apply to ADVAIR DISKUS. These drugs represent 2 classes of medications (a synthetic corticosteroid and a selective, long-acting beta-adrenergic receptor agonist) that have different effects on clinical and physiological indices.

Fluticasone Propionate: Fluticasone propionate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Inflammation is also a component in the pathogenesis of chronic obstructive pulmonary disease (COPD). In contrast to asthma, however, the predominant inflammatory cells in COPD include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of corticosteroids in the treatment of COPD are not well defined and inhaled corticosteroids and fluticasone propionate when used apart from ADVAIR DISKUS are not indicated for the treatment of COPD.

Salmeterol Xinafoate: Salmeterol is a long-acting $beta_2$-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for $beta_2$-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on $beta_1$- and $beta_2$-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more selective for $beta_2$-adrenoceptors than albuterol. Although $beta_2$-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-adrenoceptors are the predominant receptors in the heart, there are also $beta_2$-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic

AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D_2, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

Pharmacokinetics: ***ADVAIR DISKUS:*** Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours and those of salmeterol were achieved in about 5 minutes.

In a single-dose crossover study, a higher than recommended dose of ADVAIR DISKUS was administered to 14 healthy adult subjects. Two (2) inhalations of the following treatments were administered: ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, and fluticasone propionate powder 500 mcg alone. Mean peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL, respectively, and of salmeterol averaged 200 and 150 pg/mL, respectively, indicating no significant changes in systemic exposures of fluticasone propionate and salmeterol.

The terminal half-life of fluticasone propionate averaged 5.33 to 7.65 hours when ADVAIR DISKUS was administered, which is similar to that reported when fluticasone propionate was given concurrently with salmeterol or when fluticasone propionate was given alone (average, 5.30 to 6.91 hours). No terminal half-life of salmeterol was reported upon administration of ADVAIR DISKUS or salmeterol given concurrently with fluticasone propionate.

Special Populations: Population Pharmacokinetics: A population pharmacokinetic analysis was performed for fluticasone propionate and salmeterol utilizing data from 9 controlled clinical trials that included 350 patients with asthma aged 4 to 77 years who received treatment with ADVAIR DISKUS, the combination of HFA-propelled fluticasone propionate and salmeterol inhalation aerosol (ADVAIR® HFA), fluticasone propionate inhalation powder (FLOVENT® DISKUS®), HFA-propelled fluticasone propionate inhalation aerosol (FLOVENT® HFA), or CFC-propelled fluticasone propionate inhalation aerosol. The population pharmacokinetic analyses for fluticasone propionate and salmeterol showed no clinically relevant effects of age, gender, race, body weight, body mass index, or percent of predicted FEV_1 on apparent clearance and apparent volume of distribution.

When the population pharmacokinetic analysis for fluticasone propionate was divided into subgroups based on fluticasone propionate strength, formulation, and age (adolescents/adults and children), there were some differences in fluticasone propionate exposure. Higher fluticasone propionate exposure from ADVAIR DISKUS 100/50 compared with FLOVENT DISKUS 100 mcg was observed in adolescents and adults (ratio 1.52 [90% CI 1.08, 2.13]). However, in clinical studies of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50 and FLOVENT DISKUS 100 mcg in adolescents and adults, no differences in systemic effects of

corticosteroid treatment (e.g., HPA axis effects) were observed. Similar fluticasone propionate exposure was observed from ADVAIR DISKUS 500/50 and FLOVENT DISKUS 500 mcg (ratio 0.83 [90% CI 0.65, 1.07]) in adolescents and adults.

Steady-state systemic exposure to salmeterol when delivered as ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR HFA 115/21 was evaluated in 127 patients aged 4 to 57 years. The geometric mean AUC was 325 pg•hr/mL [90% CI 309, 341] in adolescents and adults.

Gender: The population pharmacokinetic analysis involved 202 males and 148 females with asthma who received fluticasone propionate alone or in combination with salmeterol and showed no gender differences for fluticasone propionate pharmacokinetics.

The population pharmacokinetic analysis involved 76 males and 51 females with asthma who received salmeterol in combination with fluticasone propionate and showed no gender differences for salmeterol pharmacokinetics.

Pediatric Patients: The population pharmacokinetic analysis included 160 patients with asthma aged 4 to 11 years who received ADVAIR DISKUS 100/50 or FLOVENT DISKUS 100 mcg. Higher fluticasone propionate exposure (AUC) was observed in children from ADVAIR DISKUS 100/50 compared to FLOVENT DISKUS 100 mcg (ratio 1.20 [90% CI 1.06, 1.37]). Higher fluticasone propionate exposure (AUC) from ADVAIR DISKUS 100/50 was observed in children compared to adolescents and adults (ratio 1.63 [90% CI 1.35, 1.96]). However, in clinical studies of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50 and FLOVENT DISKUS 100 mcg in both adolescents and adults and in children, no differences in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed.

Exposure to salmeterol was higher in children compared to adolescents and adults who received ADVAIR DISKUS 100/50 (ratio 1.23 [90% CI 1.10, 1.38]). However, in clinical studies of up to 12 weeks' duration with ADVAIR DISKUS 100/50 in both adolescents and adults and in children, no differences in systemic effects of $beta_2$-agonist treatment (e.g., cardiovascular effects, tremor) were observed.

Hepatic and Renal Impairment: Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with hepatic or renal impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Drug Interactions: In the repeat- and single-dose studies, there was no evidence of significant drug interaction in systemic exposure between fluticasone propionate and salmeterol when given as ADVAIR DISKUS. The population pharmacokinetic analysis from 9 controlled clinical trials in 350 patients with asthma showed no significant effects on fluticasone propionate or salmeterol pharmacokinetics following co-administration with $beta_2$-agonists, corticosteroids, antihistamines, or theophyllines.

Fluticasone Propionate: Absorption: Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled

and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate from the DISKUS device in healthy volunteers averages 18%.

Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma (N = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone propionate inhalation powder using the DISKUS device. The mean fluticasone propionate plasma concentration was 110 pg/mL.

Peak steady-state fluticasone propionate plasma concentrations in patients with COPD averaged 53 pg/mL (range, 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily (N = 30) via the DISKUS device.

Distribution: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Metabolism: The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Elimination: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations: Gender: Full pharmacokinetic profiles were obtained from 9 female and 16 male patients with asthma given fluticasone propionate inhalation powder 500 mcg twice daily using the DISKUS device and from 14 female and 43 male patients with COPD given 250 or 500 mcg twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

Age: No relationship between fluticasone propionate systemic exposure and age was observed in 57 patients with COPD (aged 40 to 82 years) given 250 or 500 mcg twice daily.

Drug Interactions: Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18

healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{max}) averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and $AUC_{(0-\tau)}$ averaged 8.43 pg•hr/mL (range, 4.2 to 18.8 pg•hr/mL). Fluticasone propionate C_{max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range, 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased plasma fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Salmeterol Xinafoate: Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Absorption: Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of 167 pg/mL at 20 minutes and no accumulation with repeated doses.

Distribution: The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism: Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to α-hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4). Ketoconazole, a potent inhibitor of CYP3A4, essentially completely inhibited the formation of α-hydroxysalmeterol in vitro.

Elimination: In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was

eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days.

Drug Interactions: Salmeterol is a substrate of CYP3A4. In a repeat-dose study in 13 healthy subjects, concomitant administration of erythromycin (a weak CYP3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol C_{max} at steady state (ratio with and without erythromycin 1.4; 90% CI: 0.96, 2.03; p = 0.12), a 3.6-beat/min increase in heart rate (95% CI: 0.19, 7.03; p<0.04), a 5.8-msec increase in QTc interval (95% CI: -6.14, 17.77; p = 0.34), and no change in plasma potassium. Although no in vivo drug interaction studies have been conducted between salmeterol and more potent CYP3A4 inhibitors, caution should be exercised when salmeterol is concomitantly administered with CYP3A4 inhibitors, e.g., ketoconazole, ritonavir.

Pharmacodynamics: ***ADVAIR DISKUS: Adult and Adolescent Patients:*** Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four (4) studies were conducted in healthy adult subjects: (1) a single-dose crossover study using 2 inhalations of ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg given alone, (2) a cumulative dose study using 50 to 400 mcg of salmeterol powder given alone or as ADVAIR DISKUS 500/50, (3) a repeat-dose study for 11 days using 2 inhalations twice daily of ADVAIR DISKUS 250/50, fluticasone propionate powder 250 mcg, or salmeterol powder 50 mcg, and (4) a single-dose study using 5 inhalations of ADVAIR DISKUS 100/50, fluticasone propionate powder 100 mcg alone, or placebo. In these studies no significant differences were observed in the pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given as ADVAIR DISKUS, concurrently with fluticasone propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic effects of salmeterol were not altered by the presence of fluticasone propionate in ADVAIR DISKUS. The potential effect of salmeterol on the effects of fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis was also evaluated in these studies. No significant differences across treatments were observed in 24-hour urinary cortisol excretion and, where measured, 24-hour plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone propionate were not altered by the presence of salmeterol in ADVAIR DISKUS in healthy subjects.

Asthma: In clinical studies with ADVAIR DISKUS in adult and adolescent patients 12 years of age and older with asthma, no significant differences were observed in the systemic pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given alone or as ADVAIR DISKUS. In 72 adolescent and adult patients with asthma given either ADVAIR DISKUS 100/50 or ADVAIR DISKUS

250/50, continuous 24-hour electrocardiographic monitoring was performed after the first dose and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

In a 28-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 500/50 twice daily was compared with the concurrent use of salmeterol powder 50 mcg plus fluticasone propionate powder 500 mcg from separate inhalers or fluticasone propionate powder 500 mcg alone. No significant differences across treatments were observed in plasma cortisol AUC after 12 weeks of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

In a 12-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 250/50 twice daily was compared with fluticasone propionate powder 250 mcg alone, salmeterol powder 50 mcg alone, and placebo. For most patients, the ability to increase cortisol production in response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with ADVAIR DISKUS. One patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing, compared with 2 patients (6%) who received placebo, 2 patients (6%) who received fluticasone propionate 250 mcg, and no patients who received salmeterol.

In a repeat-dose, 3-way crossover study, 1 inhalation twice daily of ADVAIR DISKUS 100/50, FLOVENT DISKUS 100 mcg, or placebo was administered to 20 adolescent and adult patients with asthma. After 28 days of treatment, geometric mean serum cortisol AUC over 12 hours showed no significant difference between ADVAIR DISKUS and FLOVENT DISKUS or between either active treatment and placebo.

Chronic Obstructive Pulmonary Disease: In clinical studies with ADVAIR DISKUS in patients with COPD associated with chronic bronchitis, no significant differences were seen in pulse rate, blood pressure, potassium, and glucose between ADVAIR DISKUS, the individual components of ADVAIR DISKUS, and placebo. In a study of ADVAIR DISKUS 250/50, 8 patients (2 [1.1%] in the group given ADVAIR DISKUS 250/50, 1 [0.5%] in the fluticasone propionate 250 mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the placebo group) had QTc intervals >470 msec at least 1 time during the treatment period. Five (5) of these 8 patients had a prolonged QTc interval at baseline.

In a 24-week study, 130 patients with COPD associated with chronic bronchitis received continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of twice-daily treatment with either ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg, salmeterol powder 50 mcg, or placebo. No significant differences in ventricular or supraventricular arrhythmias and heart rate were observed among the groups treated with ADVAIR DISKUS 500/50, the individual components, or placebo. One (1) subject in the fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the group given ADVAIR DISKUS 500/50 experienced heart block. There were 3 cases of nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone propionate 500 mcg treatment groups).

Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in 101 patients with COPD receiving twice-daily ADVAIR DISKUS 250/50, fluticasone propionate

powder 250 mcg, salmeterol powder 50 mcg, or placebo. For most patients, the ability to increase cortisol production in response to stress, as assessed by short cosyntropin stimulation, remained intact with ADVAIR DISKUS 250/50. One (1) patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by high-performance liquid chromatography) after dosing, compared with 2 patients (9%) who received fluticasone propionate 250 mcg, 2 patients (7%) who received salmeterol 50 mcg, and 1 patient (4%) who received placebo following 24 weeks of treatment or early discontinuation from study.

Pediatric Patients: In a 12-week study in patients with asthma aged 4 to 11 years who were receiving inhaled corticosteroids at study entry, ADVAIR DISKUS 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 mcg administered twice daily via the DISKUS. The values for 24-hour urinary cortisol excretion at study entry and after 12 weeks of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol excretion was also similar between the 2 groups.

Fluticasone Propionate: Asthma: In clinical trials with fluticasone propionate inhalation powder using doses up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out with the DISKHALER® inhalation device in 64 patients with mild, persistent asthma (mean FEV_1 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

Chronic Obstructive Pulmonary Disease: In a 24-week study, the steady-state fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of patients with COPD associated with chronic bronchitis (n = 86) randomized to twice-daily fluticasone propionate inhalation powder via the DISKUS 500 mcg, fluticasone propionate inhalation powder 250 mcg, or placebo. Serial serum cortisol concentrations were measured across a 12-hour dosing interval following at least 4 weeks of dosing. Serum cortisol concentrations following 250 and 500 mcg twice-daily dosing were 10% and 21% lower than placebo, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

Salmeterol Xinafoate: Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium (see PRECAUTIONS: General). The cardiovascular effects (heart rate, blood pressure) associated with salmeterol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

Asthma: The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and adult patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month of therapy, and no clinically significant dysrhythmias were noted.

Chronic Obstructive Pulmonary Disease: In 24-week clinical studies in patients with COPD associated with chronic bronchitis, the incidence of clinically significant electrocardiogram (ECG) abnormalities (myocardial ischemia, ventricular hypertrophy, clinically significant conduction abnormalities, clinically significant arrhythmias) was lower for patients who received salmeterol (1%, 9 of 688 patients who received either salmeterol 50 mcg or ADVAIR DISKUS) compared with placebo (3%, 10 of 370 patients).

No significant differences with salmeterol 50 mcg alone or in combination with fluticasone propionate as ADVAIR DISKUS 500/50 was observed on pulse rate and systolic and diastolic blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign measurements after the first dose (N = 183) and after 12 weeks of therapy (N = 149). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar to those seen with placebo (see ADVERSE REACTIONS: Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis).

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical relevance of these findings is unknown.

CLINICAL TRIALS

Asthma: ***Adult and Adolescent Patients 12 Years of Age and Older:*** In clinical trials comparing ADVAIR DISKUS with the individual components, improvements in most efficacy endpoints were greater with ADVAIR DISKUS than with the use of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed similar results between ADVAIR DISKUS and the concurrent use of fluticasone propionate plus salmeterol at corresponding doses from separate inhalers.

Studies Comparing ADVAIR DISKUS to Fluticasone Propionate Alone or Salmeterol Alone: Three (3) double-blind, parallel-group clinical trials were conducted with ADVAIR DISKUS in 1,208 adolescent and adult patients (≥12 years, baseline FEV_1 63% to 72% of predicted normal) with asthma that was not optimally controlled on their current therapy. All treatments were inhalation powders, given as 1 inhalation from the DISKUS device twice daily, and other maintenance therapies were discontinued.

Study 1: Clinical Trial With ADVAIR DISKUS 100/50: This placebo-controlled, 12-week, US study compared ADVAIR DISKUS 100/50 with its individual components,

fluticasone propionate 100 mcg and salmeterol 50 mcg. The study was stratified according to baseline asthma maintenance therapy; patients were using either inhaled corticosteroids (N = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg) or salmeterol (N = 106). Baseline FEV_1 measurements were similar across treatments: ADVAIR DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and placebo, 2.15 L.

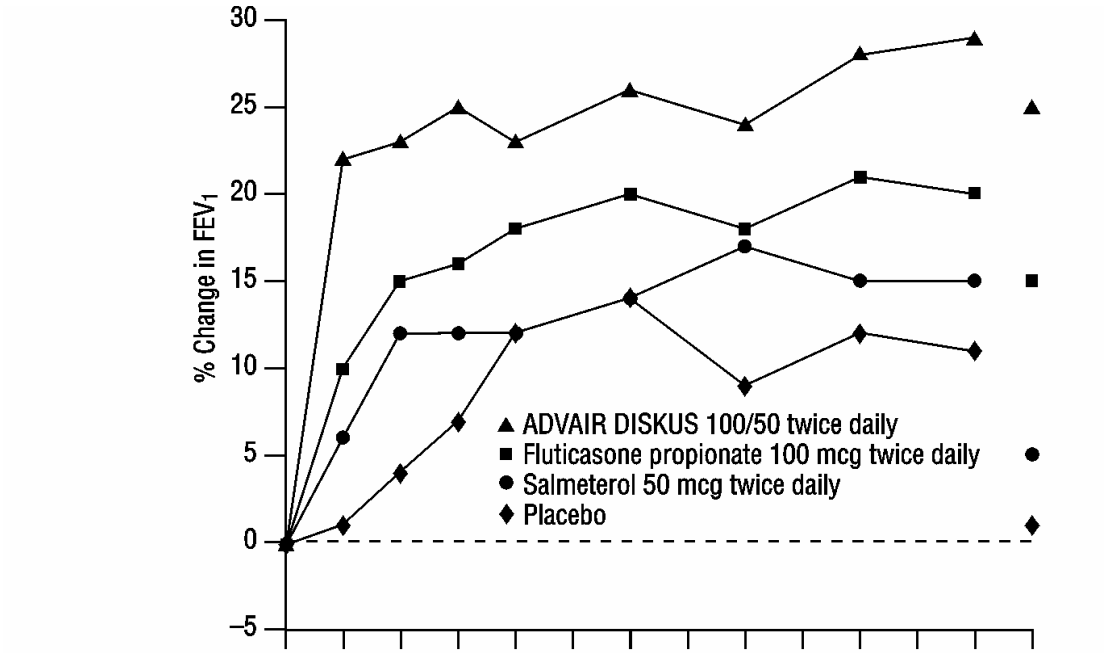
Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were utilized for this placebo-controlled study. Worsening asthma was defined as a clinically important decrease in FEV_1 or peak expiratory flow (PEF), increase in use of VENTOLIN® (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. As shown in Table 1, statistically significantly fewer patients receiving ADVAIR DISKUS 100/50 were withdrawn due to worsening asthma compared with fluticasone propionate, salmeterol, and placebo.

Table 1. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)

ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
3%	11%	35%	49%

The FEV_1 results are displayed in Figure 1. Because this trial used predetermined criteria for worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV_1 results at Endpoint (last available FEV_1 result) are also provided. Patients receiving ADVAIR DISKUS 100/50 had significantly greater improvements in FEV_1 (0.51 L, 25%) compared with fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L, 1%). These improvements in FEV_1 with ADVAIR DISKUS were achieved regardless of baseline asthma maintenance therapy (inhaled corticosteroids or salmeterol).

Figure 1. Mean Percent Change From Baseline in FEV_1 in Patients With Asthma Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)



	N												N	N
ADVAIR DISKUS 100/50	87						79						73	86
Fluticasone propionate 100 mcg	85						71						65	85
Salmeterol 50 mcg	86						59						51	86
Placebo	77						34						27	74

The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is shown in Table 2.

Table 2. Peak Expiratory Flow Results for Patients With Asthma Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)

Efficacy Variable*	ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
AM PEF (L/min)				
Baseline	393	374	369	382
Change from baseline	53	17	-2	-24
PM PEF (L/min)				
Baseline	418	390	396	398
Change from baseline	35	18	-7	-13

*Change from baseline = change from baseline at Endpoint (last available data).

The subjective impact of asthma on patients' perception of health was evaluated through use of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR DISKUS 100/50 had clinically meaningful improvements in overall asthma-specific quality of life as defined by a difference between groups of ≥0.5 points in change from baseline AQLQ scores (difference in AQLQ score of 1.25 compared to placebo).

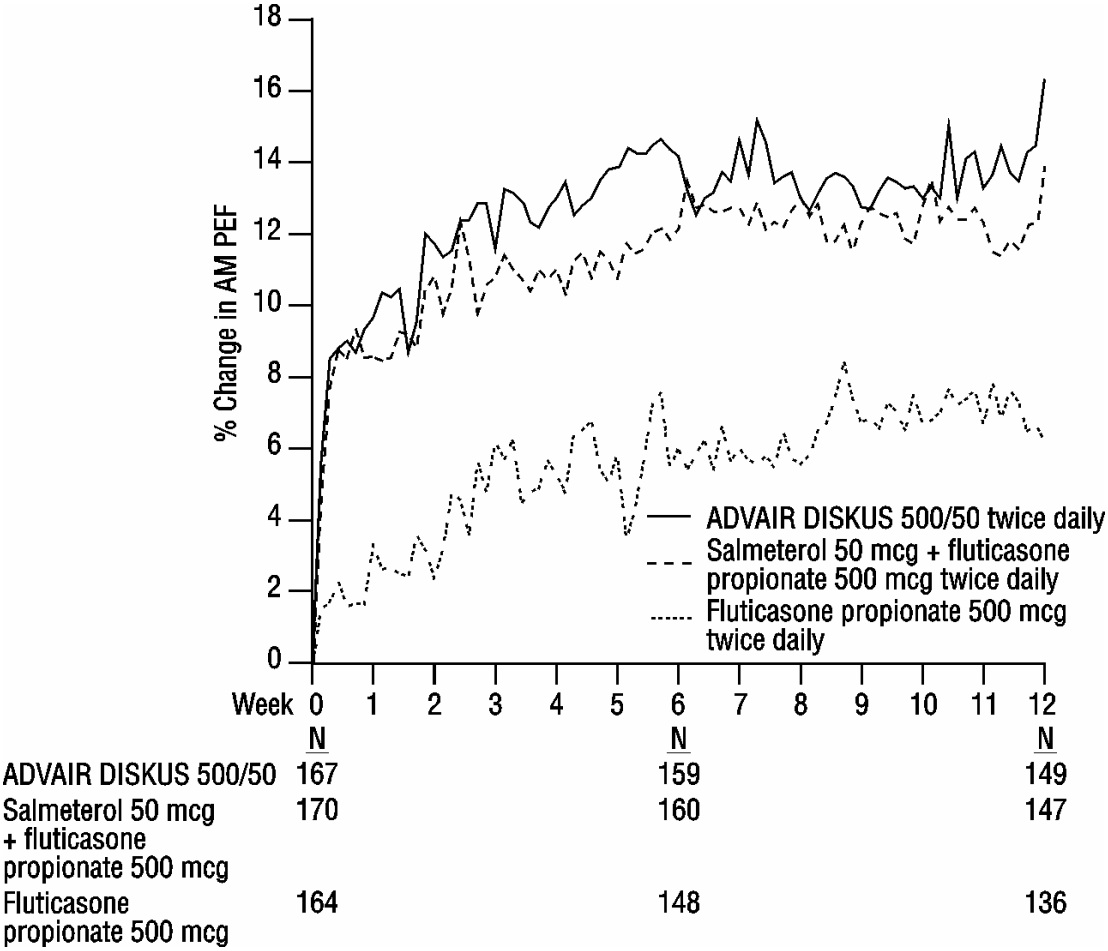
Study 2: Clinical Trial With ADVAIR DISKUS 250/50: This placebo-controlled, 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components, fluticasone propionate 250 mcg and salmeterol 50 mcg in 349 patients with asthma using inhaled corticosteroids (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100 to 1,600 mcg). Baseline FEV_1 measurements were similar across treatments: ADVAIR DISKUS 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

Efficacy results in this study were similar to those observed in Study 1. Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in FEV_1 (0.48 L, 23%) compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and placebo (decrease of 0.11 L, decrease of 5%). Statistically significantly fewer patients receiving ADVAIR DISKUS 250/50 were withdrawn from this study for worsening asthma (4%) compared with fluticasone propionate (22%), salmeterol (38%), and placebo (62%). In addition, ADVAIR DISKUS 250/50 was superior to fluticasone propionate, salmeterol, and placebo for improvements in morning and evening PEF. Patients receiving ADVAIR DISKUS 250/50 also had clinically meaningful improvements in overall asthma-specific quality of life as described in Study 1 (difference in AQLQ score of 1.29 compared to placebo).

Study 3: Clinical Trial With ADVAIR DISKUS 500/50: This 28-week, non-US study compared ADVAIR DISKUS 500/50 with fluticasone propionate 500 mcg alone and concurrent therapy (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from separate inhalers) twice daily in 503 patients with asthma using inhaled corticosteroids (daily doses of beclomethasone dipropionate 1,260 to 1,680 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; or fluticasone propionate inhalation aerosol 660 to 880 mcg [750 to 1,000 mcg inhalation powder]). The primary efficacy parameter, morning PEF, was collected daily for the first 12 weeks of the study. The primary purpose of weeks 13 to 28 was to collect safety data.

Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50, 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. As shown in Figure 2, morning PEF improved significantly with ADVAIR DISKUS 500/50 compared with fluticasone propionate 500 mcg over the 12-week treatment period. Improvements in morning PEF observed with ADVAIR DISKUS 500/50 were similar to improvements observed with concurrent therapy.

Figure 2. Mean Percent Change From Baseline in Morning Peak Expiratory Flow in Patients With Asthma Previously Treated With Inhaled Corticosteroids (Study 3)



	N	N	N
ADVAIR DISKUS 500/50	167	159	149
Salmeterol 50 mcg + fluticasone propionate 500 mcg	170	160	147
Fluticasone propionate 500 mcg	164	148	136

Onset of Action and Progression of Improvement in Asthma Control: The onset of action and progression of improvement in asthma control were evaluated in the 2 placebo-controlled US trials. Following the first dose, the median time to onset of clinically significant bronchodilatation (≥15% improvement in FEV_1) in most patients was seen within 30 to 60 minutes. Maximum improvement in FEV_1 generally occurred within 3 hours, and clinically significant improvement was maintained for 12 hours (see Figure 3).

Following the initial dose, predose FEV_1 relative to Day 1 baseline improved markedly over the first week of treatment and continued to improve over the 12 weeks of treatment in both studies.

No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR DISKUS 100/50 (Figures 3 and 4) or ADVAIR DISKUS 250/50 as assessed by FEV_1 following 12 weeks of therapy.

Figure 3. Percent Change in Serial 12-hour FEV_1 in Patients With Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)

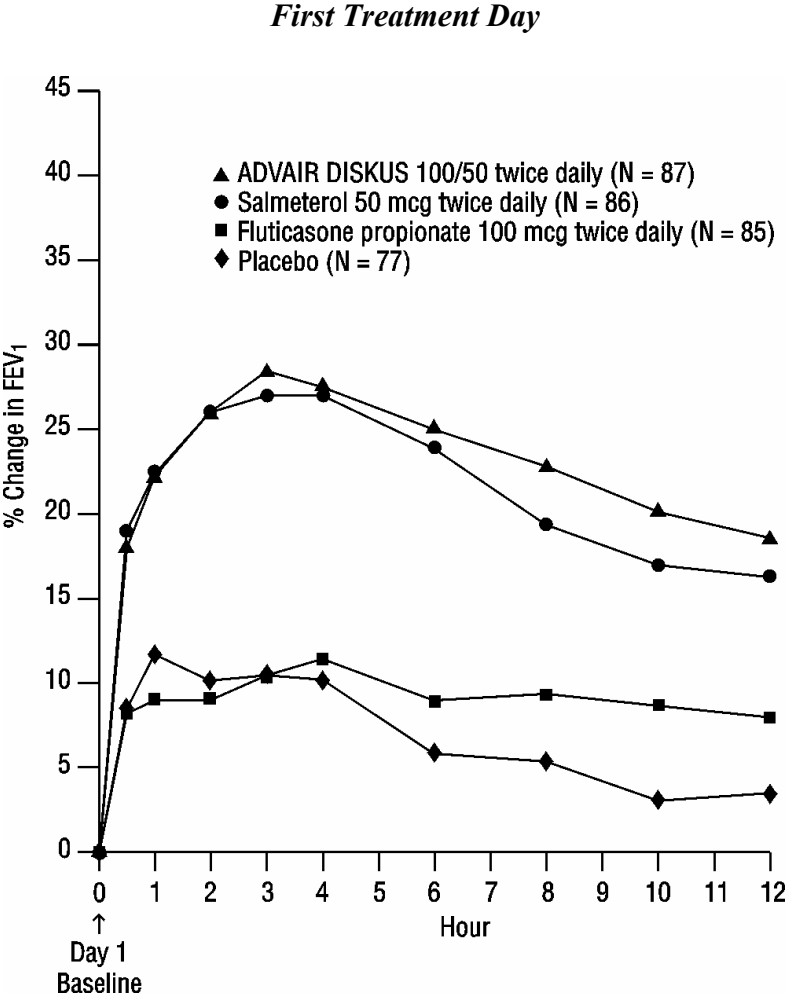
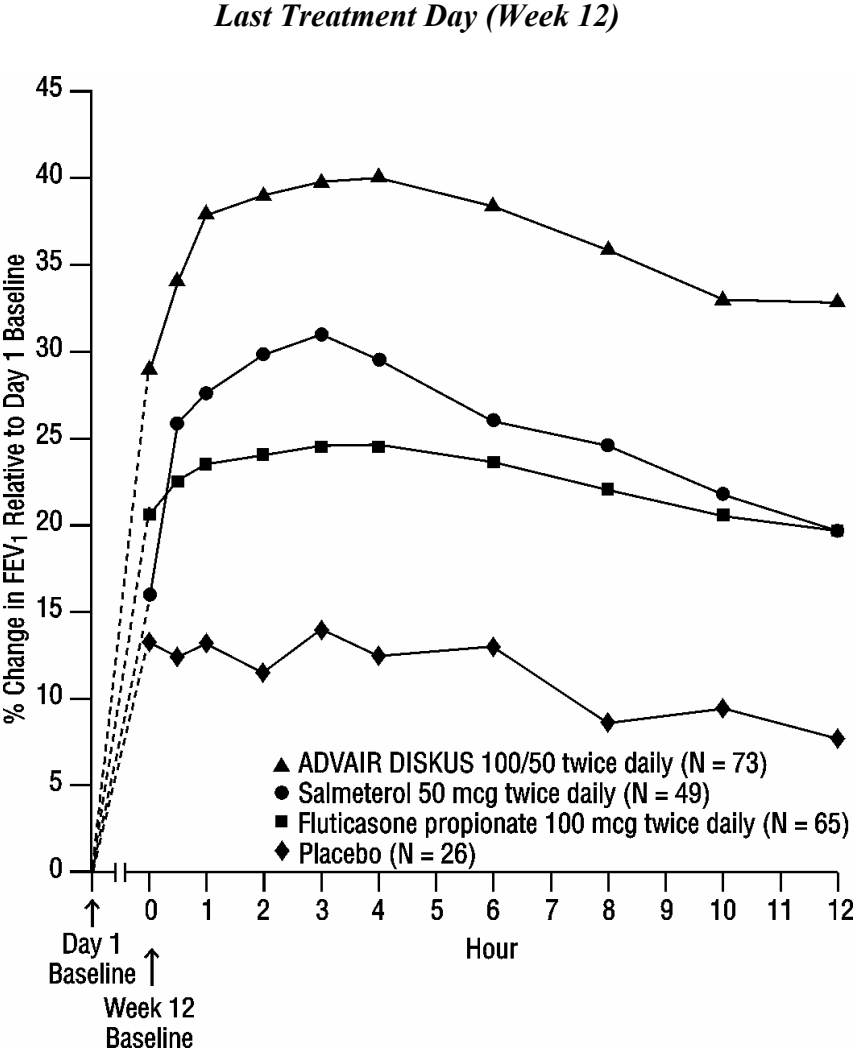


Figure 4. Percent Change in Serial 12-hour FEV_1 in Patients With Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)



Reduction in asthma symptoms, use of rescue VENTOLIN Inhalation Aerosol, and improvement in morning and evening PEF also occurred within the first day of treatment with ADVAIR DISKUS, and continued to improve over the 12 weeks of therapy in both studies.

Pediatric Patients: In a 12-week US study, ADVAIR DISKUS 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 mcg twice daily in 203 children with asthma aged 4 to 11 years. At study entry, the children were symptomatic on low doses of inhaled corticosteroids (beclomethasone dipropionate 252 to 336 mcg/day; budesonide 200 to 400 mcg/day; flunisolide 1,000 mcg/day; triamcinolone acetonide 600 to 1,000 mcg/day; or fluticasone propionate 88 to 250 mcg/day). The primary objective of this study was to determine the safety of ADVAIR DISKUS 100/50 compared with fluticasone propionate inhalation powder

100 mcg in this age-group; however, the study also included secondary efficacy measures of pulmonary function. Morning predose FEV_1 was obtained at baseline and Endpoint (last available FEV_1 result) in children aged 6 to 11 years. In patients receiving ADVAIR DISKUS 100/50, FEV_1 increased from 1.70 L at baseline (N = 79) to 1.88 L at Endpoint (N = 69) compared with an increase from 1.65 L at baseline (N = 83) to 1.77 L at Endpoint (N = 75) in patients receiving fluticasone propionate 100 mcg.

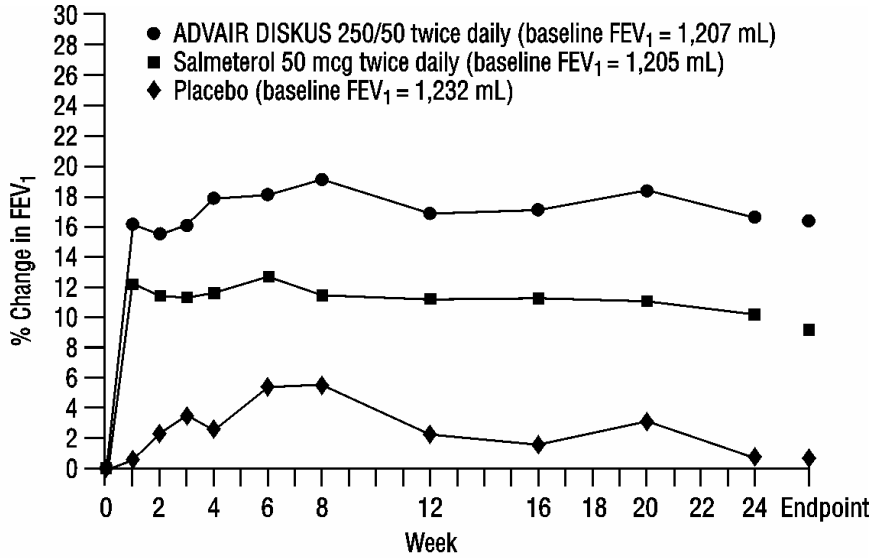
The findings of this study, along with extrapolation of efficacy data from patients 12 years of age and older, support the overall conclusion that ADVAIR DISKUS 100/50 is efficacious in the maintenance treatment of asthma in patients aged 4 to 11 years.

Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis: In a clinical trial evaluating twice-daily treatment with ADVAIR DISKUS 250/50 in patients with COPD associated with chronic bronchitis, improvements in lung function (as defined by predose and postdose FEV_1) were significantly greater with ADVAIR DISKUS than with fluticasone propionate 250 mcg, salmeterol 50 mcg, or placebo. The study was a randomized, double-blind, parallel-group, 24-week trial. All patients had a history of cough productive of sputum that was not attributable to another disease process on most days for at least 3 months of the year for at least 2 years. Study treatments were inhalation powders given as 1 inhalation from the DISKUS device twice daily. Maintenance COPD therapies were discontinued, with the exception of theophylline.

Figures 5 and 6 display predose and 2-hour postdose FEV_1 results. To account for patient withdrawals during the study, FEV_1 at Endpoint (last evaluable FEV_1) was evaluated. Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in predose FEV_1 at Endpoint (165 mL, 17%) compared with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL, 1%), demonstrating the contribution of fluticasone propionate to the improvement in lung function with ADVAIR DISKUS (Figure 5). Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in postdose FEV_1 at Endpoint (281 mL, 27%) compared with fluticasone propionate 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the contribution of salmeterol to the improvement in lung function with ADVAIR DISKUS (Figure 6).

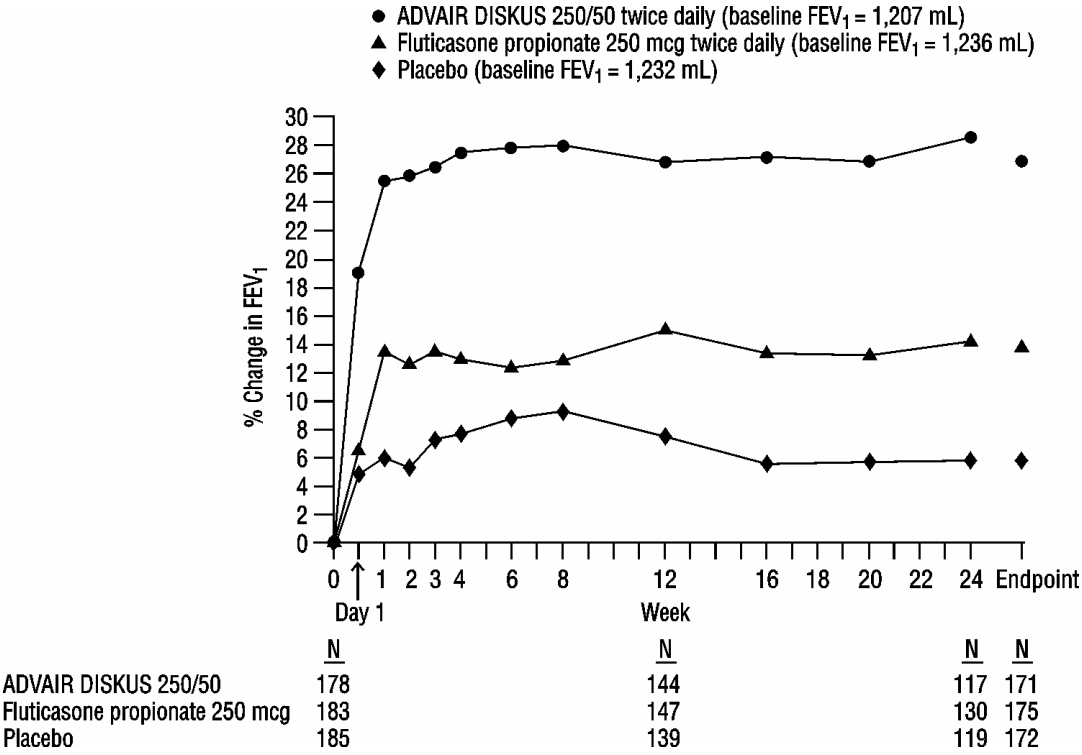
A similar degree of improvement in lung function was also observed with ADVAIR DISKUS 500/50 twice daily.

Figure 5. Predose FEV_1: Mean Percent Change From Baseline in Patients With COPD Associated With Chronic Bronchitis



	N		N		N	N
ADVAIR DISKUS 250/50	178		144		124	171
Salmeterol 50 mcg	177		135		119	168
Placebo	185		139		125	172

Figure 6. Two-Hour Postdose FEV_1: Mean Percent Changes From Baseline Over Time in Patients With COPD Associated With Chronic Bronchitis



Patients treated with ADVAIR DISKUS 250/50 or ADVAIR DISKUS 500/50 did not have a significant reduction in chronic bronchitis symptoms (as measured by the Chronic Bronchitis Symptom Questionnaire) or in COPD exacerbations compared to patients treated with placebo over the 24 weeks of therapy. The improvement in lung function with ADVAIR DISKUS 500/50 was similar to the improvement seen with ADVAIR DISKUS 250/50. Since there is evidence of more systemic exposure to fluticasone propionate from this higher dose and no documented advantage for efficacy, ADVAIR DISKUS 500/50 is not recommended for use in COPD.

The benefit of treatment of patients with COPD associated with chronic bronchitis with ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated.

INDICATIONS AND USAGE

Asthma: ADVAIR DISKUS is indicated for the long-term, twice-daily, maintenance treatment of asthma in patients 4 years of age and older.

Long-acting $beta_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. ADVAIR DISKUS is not indicated in

patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting beta$_2$-agonists.

ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:
ADVAIR DISKUS 250/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis.

ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50, are not recommended (see DOSAGE AND ADMINISTRATION: Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis).

The benefit of treating patients with COPD associated with chronic bronchitis with ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated. Patients who are treated with ADVAIR DISKUS 250/50 for COPD associated with chronic bronchitis for periods longer than 6 months should be reevaluated periodically to assess the continuing benefits and potential risks of treatment.

ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

ADVAIR DISKUS is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.

Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see DESCRIPTION and ADVERSE REACTIONS: Observed During Clinical Practice: *Non-Site Specific*).

WARNINGS

Long-acting beta$_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies.

A large placebo-controlled US study that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting beta$_2$-agonist–naive patients with asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared to placebo when added to usual asthma therapy. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355), which led to premature termination of the study. The results of the interim analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events (see Table 3 and Figure 7). In the total population, a higher rate of asthma-related death occurred

in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%; relative risk 4.37 [95% CI 1.25, 15.34]).

Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). In African Americans also, asthma-related death occurred at a higher rate in patients treated with salmeterol than those treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the relative risks of asthma-related death were similar in Caucasians and African Americans, the estimate of excess deaths in patients treated with salmeterol was greater in African Americans because there was a higher overall rate of asthma-related death in African American patients (see Table 3). Given the similar basic mechanisms of action of $beta_2$-agonists, it is possible that the findings seen in the SMART study represent a class effect.

The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other active ingredient in ADVAIR DISKUS, or other asthma-controller therapy modifies the risk of asthma-related death.

Table 3: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)

	Salmeterol n (%*)	Placebo n (%*)	Relative Risk† (95% Confidence Interval)	Excess Deaths Expressed per 10,000 Patients‡ (95% Confidence Interval)
Total Population§ Salmeterol: N = 13,176 Placebo: N = 13,179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Salmeterol: N = 9,281 Placebo: N = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
African American Salmeterol: N = 2,366 Placebo: N = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

* Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

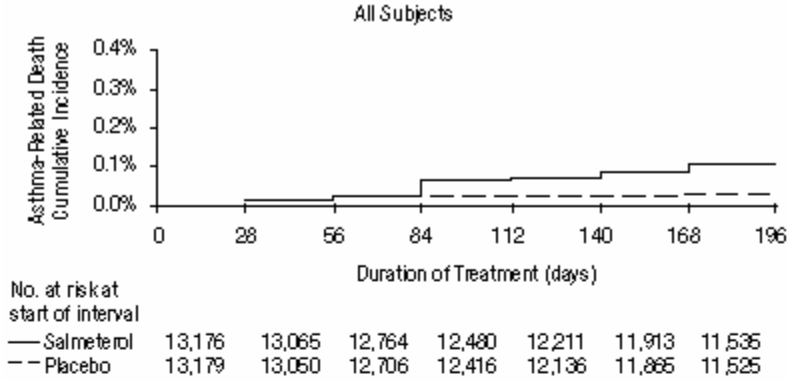
† Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the rate in the placebo group. The relative risk indicates how many more times likely an asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week treatment period.

‡ Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period.

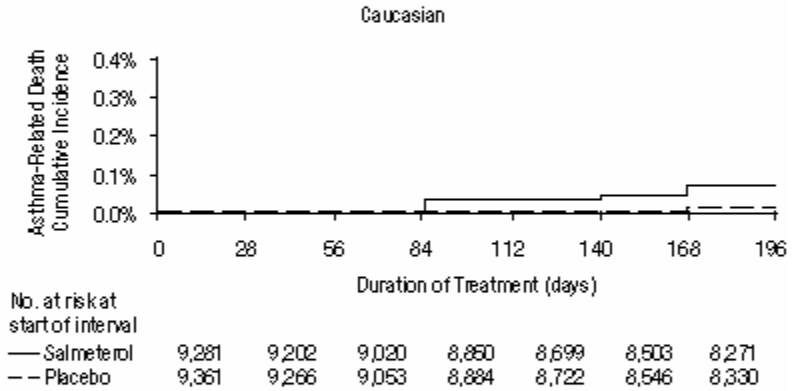
Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

§ The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population includes those patients whose ethnic origin was not reported. The results for Caucasian and African American subpopulations are shown above. No asthma-related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death occurred in the placebo group in the subpopulation whose ethnic origin was not reported (salmeterol n = 130, placebo n = 127).

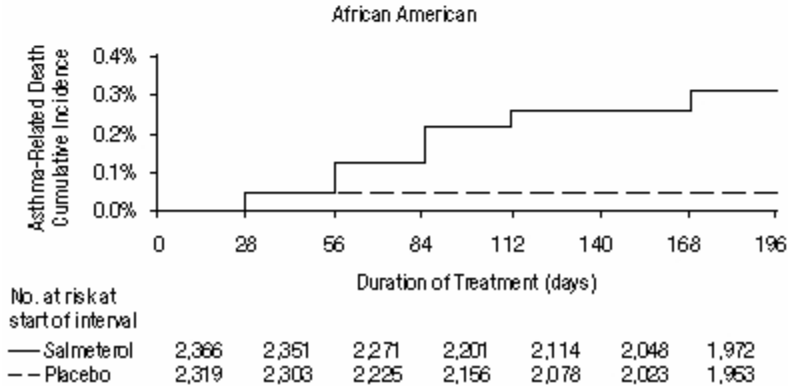
Figure 7. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART), by Duration of Treatment



No. at risk at start of interval							
Salmeterol	13,176	13,065	12,764	12,480	12,211	11,913	11,535
Placebo	13,179	13,050	12,706	12,416	12,136	11,865	11,525



No. at risk at start of interval							
Salmeterol	9,281	9,202	9,020	8,850	8,699	8,503	8,271
Placebo	9,361	9,266	9,053	8,884	8,722	8,546	8,330



No. at risk at start of interval							
Salmeterol	2,366	2,351	2,271	2,201	2,114	2,048	1,972
Placebo	2,319	2,303	2,225	2,156	2,078	2,023	1,953

A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate of asthma-related death was numerically, though not statistically significantly, greater in patients with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol (180 mcg 4 times daily) added to usual asthma therapy.

The SNS and SMART studies enrolled patients with asthma. No studies have been conducted that were adequate to determine whether the rate of death in patients with COPD is increased by long-acting beta$_2$-adrenergic agonists.

The following additional WARNINGS about ADVAIR DISKUS should be noted.

1. ADVAIR DISKUS should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide when salmeterol, a component of ADVAIR DISKUS, has been initiated in patients with significantly worsening or acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for inhaled, short-acting beta$_2$-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol contributed to these events.

2. ADVAIR DISKUS should not be used to treat acute symptoms. An inhaled, short-acting beta$_2$-agonist, not ADVAIR DISKUS, should be used to relieve acute symptoms of shortness of breath. When prescribing ADVAIR DISKUS, the physician must also provide the patient with an inhaled, short-acting beta$_2$-agonist (e.g., albuterol) for treatment of shortness of breath that occurs acutely, despite regular twice-daily (morning and evening) use of ADVAIR DISKUS.

When beginning treatment with ADVAIR DISKUS, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs. For patients taking ADVAIR DISKUS, inhaled, short-acting beta$_2$-agonists should only be used for symptomatic relief of acute symptoms of shortness of breath (see PRECAUTIONS: Information for Patients).

3. Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. The physician and patient should be alert to such changes. The patient's condition may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's inhaled, short-acting beta$_2$-agonist becomes less effective, the patient needs more inhalations than usual, or the patient develops a significant decrease in lung function, this may be a marker of destabilization of the disease. In this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of ADVAIR DISKUS with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation twice daily (morning and evening) of ADVAIR DISKUS.

4. ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid therapy. Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have

occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although inhaled corticosteroids may provide control of asthma symptoms during these episodes, in recommended doses they supply less than normal physiological amounts of glucocorticoid systemically and do NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

5. ADVAIR DISKUS should not be used in conjunction with an inhaled, long-acting $beta_2$-agonist. Patients who are receiving ADVAIR DISKUS twice daily should not use additional salmeterol or other inhaled, long-acting $beta_2$-agonists (e.g., formoterol) for prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma or the maintenance treatment of bronchospasm associated with COPD. Additional benefit would not be gained from using supplemental salmeterol or formoterol for prevention of EIB since ADVAIR DISKUS already contains an inhaled, long-acting $beta_2$-agonist.

6. The recommended dosage should not be exceeded. ADVAIR DISKUS should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias.

7. Paradoxical bronchospasm. As with other inhaled asthma and COPD medications, ADVAIR DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ADVAIR DISKUS, it should be treated immediately with an inhaled, short-acting bronchodilator; ADVAIR DISKUS should be discontinued immediately; and alternative therapy should be instituted.

8. Immediate hypersensitivity reactions. Immediate hypersensitivity reactions may occur after administration of ADVAIR DISKUS, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

9. Upper airway symptoms. Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving fluticasone propionate and salmeterol, components of ADVAIR DISKUS.

10. Cardiovascular disorders. ADVAIR DISKUS, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Salmeterol, a component of ADVAIR DISKUS, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical relevance of these findings is unknown.

11. Discontinuation of systemic corticosteroids. Transfer of patients from systemic corticosteroid therapy to ADVAIR DISKUS may unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

12. Immunosuppression. Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

13. Drug interaction with ritonavir. A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Drug Interactions* and PRECAUTIONS: Drug Interactions: *Inhibitors of Cytochrome P450*). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

PRECAUTIONS

General: *Cardiovascular Effects:* Cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of salmeterol, a component of ADVAIR DISKUS, and may require

discontinuation of ADVAIR DISKUS. ADVAIR DISKUS, like all medications containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in electrocardiograms (ECGs) have been seen infrequently in individual patients in controlled clinical studies with ADVAIR DISKUS and salmeterol. Clinically significant changes in systolic and/or diastolic blood pressure and pulse rate have been seen infrequently in individual patients in controlled clinical studies with salmeterol, a component of ADVAIR DISKUS.

Metabolic and Other Effects: Long-term use of orally inhaled corticosteroids may affect normal bone metabolism, resulting in a loss of bone mineral density (BMD). A 2-year study of 160 patients (females 18 to 40 and males 18 to 50 years of age) with asthma receiving chlorofluorocarbon-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar region L1 through L4. Long-term treatment effects of fluticasone propionate on BMD in the COPD population have not been studied.

In patients with major risk factors for decreased bone mineral content, such as tobacco use, advanced age, sedentary lifestyle, poor nutrition, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), ADVAIR DISKUS may pose an additional risk. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended, including prior to instituting ADVAIR DISKUS 250/50 and periodically thereafter. If significant reductions in BMD are seen and ADVAIR DISKUS 250/50 is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered. ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of COPD associated with chronic bronchitis, and higher doses, including ADVAIR DISKUS 500/50, are not recommended.

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS; therefore, regular eye examinations should be considered.

Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS.

Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through

intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with ADVAIR DISKUS at recommended doses.

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Fluticasone propionate, a component of ADVAIR DISKUS, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of ADVAIR DISKUS in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing ADVAIR DISKUS.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with ADVAIR DISKUS should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when fluticasone propionate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of ADVAIR DISKUS should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from the therapeutic use of corticosteroids, including inhaled corticosteroids. The effects of long-term treatment of children and adolescents with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known.

A 52-week, placebo-controlled study to assess the potential growth effects of fluticasone propionate inhalation powder (FLOVENT® ROTADISK®) at 50 and 100 mcg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (N = 76), 6.07 cm/year in the 50-mcg group (N = 98), and 5.66 cm/year in the 100-mcg group (N = 89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the study revealed growth rates at 52 weeks of

6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the 100-mcg group (n = 79). In children 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is: boys – 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year.

The clinical relevance of these growth data is not certain. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route, and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if growth appears slowed. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.

The long-term effects of ADVAIR DISKUS in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or longer. In clinical studies in patients with asthma treated for 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

In clinical studies with ADVAIR DISKUS, the development of localized infections of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on treatment with ADVAIR DISKUS, but at times therapy with ADVAIR DISKUS may need to be interrupted.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate, a component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see ADVERSE REACTIONS: Observed During Clinical Practice: *Eosinophilic Conditions*).

Chronic Obstructive Pulmonary Disease: ADVAIR DISKUS 250/50 twice daily is the only dosage recommended for the treatment of airflow obstruction in patients with COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50, are not recommended, as no additional improvement in lung function (defined by predose and postdose

FEV_1) was observed in clinical trials and higher doses of corticosteroids increase the risk of systemic effects.

The benefit of treatment of patients with COPD associated with chronic bronchitis with ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated. Patients who are treated with ADVAIR DISKUS 250/50 for COPD associated with chronic bronchitis for periods longer than 6 months should be reevaluated periodically to assess the continuing benefits and potential risks of treatment.

Information for Patients: Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document.

Patients being treated with ADVAIR DISKUS should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

It is important that patients understand how to use the DISKUS inhalation device appropriately and how it should be used in relation to other asthma or COPD medications they are taking. Patients should be given the following information:

1. **Patients should be informed that salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death.** They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other component of ADVAIR DISKUS, or other asthma-controller therapy modifies this risk.
2. ADVAIR DISKUS is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient in how it should be used). ADVAIR DISKUS is not meant to relieve acute asthma symptoms or exacerbations of COPD.
3. The physician should be notified immediately if any of the following signs of seriously worsening asthma occur:
   - decreasing effectiveness of inhaled, short-acting $beta_2$-agonists;
   - need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists;
   - significant decrease in lung function as outlined by the physician.
4. Patients should not stop therapy with ADVAIR DISKUS without physician/provider guidance since symptoms may recur after discontinuation.
5. Patients should be cautioned regarding common adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
6. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS, may increase the risk of some eye problems (cataracts or glaucoma). Regular eye examinations should be considered.

7. Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and should be told to monitor and, where appropriate, seek treatment for this condition.
8. When patients are prescribed ADVAIR DISKUS, other medications for asthma and COPD should be used only as directed by their physicians.
9. ADVAIR DISKUS should not be used with a spacer device.
10. Patients who are pregnant or nursing should contact their physicians about the use of ADVAIR DISKUS.
11. Patients should use ADVAIR DISKUS at regular intervals as directed. Results of clinical trials indicate significant improvement may occur within the first 30 minutes of taking the first dose; however, the full benefit may not be achieved until treatment has been administered for 1 week or longer. The patient should not use more than the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.
12. The bronchodilation from a single dose of ADVAIR DISKUS may last up to 12 hours or longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not be exceeded. Patients who are receiving ADVAIR DISKUS twice daily should not use salmeterol or other inhaled, long-acting $beta_2$-agonists (e.g., formoterol) for prevention of EIB or maintenance treatment of asthma or the maintenance treatment of bronchospasm in COPD.
13. Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult their physicians without delay.
14. Effective and safe use of ADVAIR DISKUS includes an understanding of the way that it should be used:
    - Never exhale into the DISKUS.
    - Never attempt to take the DISKUS apart.
    - Always activate and use the DISKUS in a level, horizontal position.
    - After inhalation, rinse the mouth with water without swallowing.
    - Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
    - Always keep the DISKUS in a dry place.
    - Discard **1 month** after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads "0"), whichever comes first.
15. For the proper use of ADVAIR DISKUS and to attain maximum improvement, the patient should read and carefully follow the Instructions for Using ADVAIR DISKUS in the Medication Guide accompanying the product.
16. Most patients are able to taste or feel a dose delivered from ADVAIR DISKUS. However, whether or not patients are able to sense delivery of a dose, you should instruct them not to exceed the recommended dose of 1 inhalation each morning and evening, approximately 12 hours apart. You should instruct them to contact you or the pharmacist if they have questions.

Drug Interactions: ADVAIR DISKUS has been used concomitantly with other drugs, including short-acting beta$_2$-agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with asthma or COPD, without adverse drug reactions. No formal drug interaction studies have been performed with ADVAIR DISKUS.

Short-Acting Beta$_2$-Agonists: In clinical trials with patients with asthma, the mean daily need for albuterol by 166 adult and adolescent patients 12 years of age and older using ADVAIR DISKUS was approximately 1.3 inhalations/day, and ranged from 0 to 9 inhalations/day. Five percent (5%) of patients using ADVAIR DISKUS in these trials averaged 6 or more inhalations per day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse reactions was observed among patients who averaged 6 or more inhalations per day.

In a COPD clinical trial, the mean daily need for albuterol for patients using ADVAIR DISKUS 250/50 was 4.1 inhalations/day. Twenty-six percent (26%) of patients using ADVAIR DISKUS 250/50 averaged 6 or more inhalations per day over the course of the 24-week trial. No increase in frequency of cardiovascular adverse reactions was observed among patients who averaged 6 or more inhalations of albuterol per day.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by adult and adolescent patients 12 years of age and older receiving ADVAIR DISKUS has not been completely evaluated. In clinical trials with patients with asthma, 39 patients receiving ADVAIR DISKUS 100/50, 250/50, or 500/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 304 patients receiving ADVAIR DISKUS without theophylline. Similar results were observed in patients receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily concurrently with a theophylline product (n = 39) or without theophylline (n = 132).

In a COPD clinical trial, 17 patients receiving ADVAIR DISKUS 250/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 161 patients receiving ADVAIR DISKUS without theophylline. Based on the available data, the concomitant administration of methylxanthines with ADVAIR DISKUS did not alter the observed adverse event profile.

Fluticasone Propionate Nasal Spray: In adult and adolescent patients 12 years of age and older taking ADVAIR DISKUS in clinical trials, no difference in the profile of adverse events or HPA axis effects was noted between patients taking FLONASE® (fluticasone propionate) Nasal Spray, 50 mcg concurrently (n = 46) and those who were not (n = 130).

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: ADVAIR DISKUS should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol, a component of ADVAIR DISKUS, on the vascular system may be potentiated by these agents.

Beta-Adrenergic Receptor Blocking Agents: Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma

should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics: The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical relevance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

Inhibitors of Cytochrome P450: Fluticasone propionate and salmeterol are substrates of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Drug Interactions*). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when ADVAIR DISKUS is coadministered with ketoconazole and other known potent cytochrome P450 3A4 inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility: *Fluticasone Propionate:*
Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 4 and 10 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to, respectively, the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

Salmeterol: In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose in adults and children based on comparison of the plasma area under the curves [AUCs]) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg (approximately 3 times the maximum recommended daily inhalation doses in adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 and 25 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis). No tumors were seen at 0.21 mg/kg (approximately 15 and 8 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in male and female rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

Pregnancy: ***Teratogenic Effects: ADVAIR DISKUS:*** Pregnancy Category C. From the reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using combinations of fluticasone propionate and salmeterol compared to toxicity data from the components administered separately. In mice combining 150 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) with 10 mg/kg orally of salmeterol (approximately 410 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) was teratogenic. Cleft palate, fetal death, increased implantation loss and delayed ossification were seen. These observations are characteristic of glucocorticoids. No developmental toxicity was observed at combination doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) and up to 1.4 mg/kg orally of salmeterol (approximately 55 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). In rats, no teratogenicity was observed at combination doses up to 30 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) and up to 1 mg/kg of salmeterol (approximately 80 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Combining 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) with 10 mg/kg orally of salmeterol (approximately 810 times the maximum recommended daily inhalation dose in adults on a

mg/m^2 basis) produced maternal toxicity, decreased placental weight, decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone. There are no adequate and well-controlled studies with ADVAIR DISKUS in pregnant women. ADVAIR DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Fluticasone Propionate: Pregnancy Category C. Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg (less than or equivalent to the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis), respectively, revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY).

Fluticasone propionate crossed the placenta following administration of a subcutaneous dose of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis), administration of a subcutaneous or an oral dose of 100 mcg/kg to rats (approximately equivalent to the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis), and administration of an oral dose of 300 mcg/kg to rabbits (approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Salmeterol: Pregnancy Category C. No teratogenic effects occurred in rats at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans. There are no adequate and well-controlled studies with salmeterol in pregnant women. Salmeterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice and rats (approximately 410 and 810 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

Use in Labor and Delivery: There are no well-controlled human studies that have investigated effects of ADVAIR DISKUS on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of ADVAIR DISKUS during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers: Plasma levels of salmeterol, a component of ADVAIR DISKUS, after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known whether fluticasone propionate, a component of ADVAIR DISKUS, is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) resulted in measurable radioactivity in milk.

Since there are no data from controlled trials on the use of ADVAIR DISKUS by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue ADVAIR DISKUS, taking into account the importance of ADVAIR DISKUS to the mother.

Caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.

Pediatric Use: Use of ADVAIR DISKUS 100/50 in patients 4 to 11 years of age is supported by extrapolation of efficacy data from older patients and by safety and efficacy data from a study of ADVAIR DISKUS 100/50 in children with asthma aged 4 to 11 years (see CLINICAL TRIALS: Asthma: *Pediatric Patients* and ADVERSE REACTIONS: Asthma: *Pediatric Patients*). The safety and effectiveness of ADVAIR DISKUS in children with asthma under 4 years of age have not been established.

Controlled clinical studies have shown that orally inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS, may cause a reduction in growth velocity in children and adolescents (see PRECAUTIONS: General: *Metabolic and Other Effects*). The growth of pediatric patients receiving orally inhaled corticosteroids, including ADVAIR DISKUS, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, each patient should be titrated to the lowest strength that effectively controls his/her asthma (see DOSAGE AND ADMINISTRATION: Asthma).

Geriatric Use: Of the total number of patients in clinical studies of ADVAIR DISKUS for asthma, 44 were 65 years of age or older and 3 were 75 years of age or older. Of the total number of patients in a clinical study of ADVAIR DISKUS 250/50 for COPD, 85 were 65 years of age or older and 31 were 75 years of age or older. For both diseases, no overall differences in safety were observed between these patients and younger patients, and other reported clinical experience, including studies of the individual components, has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other products containing $beta_2$-agonists, special caution should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by $beta_2$-agonists. Based on available data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR DISKUS in geriatric patients is warranted.

ADVERSE REACTIONS

Long-acting $beta_2$-adrenergic agonists, such as salmeterol, may increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (see WARNINGS). Salmeterol is a component of ADVAIR DISKUS. However, the data from this study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other component of ADVAIR DISKUS, or other asthma controller therapy modifies the risk of asthma-related death.

Asthma: ***Adult and Adolescent Patients 12 Years of Age and Older:*** The incidence of common adverse events in Table 4 is based upon 2 placebo-controlled, 12-week, US clinical studies (Studies 1 and 2). A total of 705 adolescent and adult patients (349 females and 356 males) previously treated with salmeterol or inhaled corticosteroids were treated twice daily with ADVAIR DISKUS (100/50- or 250/50-mcg doses), fluticasone propionate inhalation powder (100- or 250-mcg doses), salmeterol inhalation powder 50 mcg, or placebo.

Table 4. Overall Adverse Events With ≥3% Incidence in US Controlled Clinical Trials With ADVAIR DISKUS in Patients With Asthma

Adverse Event	ADVAIR DISKUS 100/50 (N = 92) %	ADVAIR DISKUS 250/50 (N = 84) %	Fluticasone Propionate 100 mcg (N = 90) %	Fluticasone Propionate 250 mcg (N = 84) %	Salmeterol 50 mcg (N = 180) %	Placebo (N = 175) %
Ear, nose, & throat						
Upper respiratory tract infection	27	21	29	25	19	14
Pharyngitis	13	10	7	12	8	6
Upper respiratory inflammation	7	6	7	8	8	5
Sinusitis	4	5	6	1	3	4
Hoarseness/dysphonia	5	2	2	4	<1	<1
Oral candidiasis	1	4	2	2	0	0
Lower respiratory						
Viral respiratory infections	4	4	4	10	6	3
Bronchitis	2	8	1	2	2	2
Cough	3	6	0	0	3	2
Neurology						
Headaches	12	13	14	8	10	7
Gastrointestinal						
Nausea & vomiting	4	6	3	4	1	1
Gastrointestinal discomfort & pain	4	1	0	2	1	1
Diarrhea	4	2	2	2	1	1
Viral gastrointestinal infections	3	0	3	1	2	2
Non-site specific						
Candidiasis unspecified site	3	0	1	4	0	1
Musculoskeletal						
Musculoskeletal pain	4	2	1	5	3	3
Average duration of exposure (days)	77.3	78.7	72.4	70.1	60.1	42.3

Table 4 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in either of the groups receiving ADVAIR DISKUS and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account. Rare cases of

immediate and delayed hypersensitivity reactions, including rash and other rare events of angioedema and bronchospasm, have been reported.

These adverse reactions were mostly mild to moderate in severity.

Other adverse events that occurred in the groups receiving ADVAIR DISKUS in these studies with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

Blood and Lymphatic: Lymphatic signs and symptoms.

Cardiovascular: Palpitations.

Drug Interaction, Overdose, and Trauma: Muscle injuries, fractures, wounds and lacerations, contusions and hematomas, burns.

Ear, Nose, and Throat: Rhinorrhea/postnasal drip; ear, nose, and throat infections; ear signs and symptoms; nasal signs and symptoms; nasal sinus disorders; rhinitis; sneezing; nasal irritation; blood in nasal mucosa.

Eye: Keratitis and conjunctivitis, viral eye infections, eye redness.

Gastrointestinal: Dental discomfort and pain, gastrointestinal signs and symptoms, gastrointestinal infections, gastroenteritis, gastrointestinal disorders, oral ulcerations, oral erythema and rashes, constipation, appendicitis, oral discomfort and pain.

Hepatobiliary Tract and Pancreas: Abnormal liver function tests.

Lower Respiratory: Lower respiratory signs and symptoms, pneumonia, lower respiratory infections.

Musculoskeletal: Arthralgia and articular rheumatism; muscle stiffness, tightness, and rigidity; bone and cartilage disorders.

Neurology: Sleep disorders, tremors, hypnagogic effects, compressed nerve syndromes.

Non-Site Specific: Allergies and allergic reactions, congestion, viral infections, pain, chest symptoms, fluid retention, bacterial infections, wheeze and hives, unusual taste.

Skin: Viral skin infections, urticaria, skin flakiness and acquired ichthyosis, disorders of sweat and sebum, sweating.

The incidence of common adverse events reported in Study 3, a 28-week, non-US clinical study of 503 patients previously treated with inhaled corticosteroids who were treated twice daily with ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation powder 500 mcg was similar to the incidences reported in Table 4.

Pediatric Patients: Pediatric Study: ADVAIR DISKUS 100/50 was well tolerated in clinical trials conducted in children with asthma aged 4 to 11 years. The incidence of common adverse events in Table 5 is based upon a 12-week US study in 203 patients with asthma aged 4 to 11 years (74 females and 129 males) who were receiving inhaled corticosteroids at study entry and were randomized to either ADVAIR DISKUS 100/50 or fluticasone propionate inhalation powder 100 mcg twice daily.

Table 5. Overall Adverse Events With ≥3% Incidence With ADVAIR DISKUS 100/50 in Patients 4 to 11 Years of Age With Asthma

Adverse Event	ADVAIR DISKUS 100/50 (N = 101) %	Fluticasone Propionate 100 mcg (N = 102) %
Ear, nose, & throat		
Upper respiratory tract infection	10	17
Throat irritation	8	7
Ear, nose, & throat infections	4	<1
Epistaxis	4	<1
Pharyngitis/throat infection	3	2
Ear signs & symptoms	3	<1
Sinusitis	3	0
Neurology		
Headache	20	20
Gastrointestinal		
Gastrointestinal discomfort & pain	7	5
Nausea & vomiting	5	3
Candidiasis mouth/throat	4	<1
Non-site specific		
Fever	5	13
Chest symptoms	3	<1
Average duration of exposure (days)	74.8	78.8

Table 5 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving ADVAIR DISKUS 100/50.

Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis: The incidence of common adverse events in Table 6 is based upon 1 placebo-controlled, 24-week, US clinical trial in patients with COPD associated with chronic bronchitis. A total of 723 adult patients (266 females and 457 males) were treated twice daily with ADVAIR DISKUS 250/50, fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder 50 mcg, or placebo.

Table 6. Overall Adverse Events With ≥3% Incidence With ADVAIR DISKUS 250/50 in Patients With Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis

Adverse Event	ADVAIR DISKUS 250/50 (N = 178) %	Fluticasone Propionate 250 mcg (N = 183) %	Salmeterol 50 mcg (N = 177) %	Placebo (N = 185) %
Ear, nose, & throat				
Candidiasis mouth/throat	10	6	3	1
Throat irritation	8	5	4	7
Hoarseness/dysphonia	5	3	<1	0
Sinusitis	3	8	5	3
Lower respiratory				
Viral respiratory infections	6	4	3	3
Neurology				
Headaches	16	11	10	12
Dizziness	4	<1	3	2
Non-site specific				
Fever	4	3	0	3
Malaise & fatigue	3	2	2	3
Musculoskeletal				
Musculoskeletal pain	9	8	12	9
Muscle cramps & spasms	3	3	1	1
Average duration of exposure (days)	141.3	138.5	136.1	131.6

Table 6 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving ADVAIR DISKUS 250/50 and were more common than in the placebo group.

These adverse reactions were mostly mild to moderate in severity.

Other adverse events that occurred in the groups receiving ADVAIR DISKUS 250/50 with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

Cardiovascular: Syncope.

Drug Interaction, Overdose, and Trauma: Postoperative complications.

Ear, Nose, and Throat: Ear, nose, and throat infections; ear signs and symptoms; laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection.

Endocrine and Metabolic: Hypothyroidism.

Eye: Dry eyes, eye infections.

Gastrointestinal: Constipation, gastrointestinal signs and symptoms, oral lesions.

Hepatobiliary Tract and Pancreas: Abnormal liver function tests.

Lower Respiratory: Breathing disorders, lower respiratory signs and symptoms.

Non-Site Specific: Bacterial infections, candidiasis unspecified site, edema and swelling, nonspecific conditions, viral infections.

Psychiatry: Situational disorders.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during worldwide use of any formulation of ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to ADVAIR DISKUS, fluticasone propionate, and/or salmeterol or a combination of these factors.

In extensive US and worldwide postmarketing experience with salmeterol, a component of ADVAIR DISKUS, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also occurred in a few patients with less severe asthma. It was not possible from these reports to determine whether salmeterol contributed to these events.

Cardiovascular: Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular tachycardia), ventricular tachycardia.

Ear, Nose, and Throat: Aphonia, earache, facial and oropharyngeal edema, paranasal sinus pain, throat soreness.

Endocrine and Metabolic: Cushing syndrome, Cushingoid features, growth velocity reduction in children/adolescents, hypercorticism, hyperglycemia, weight gain, osteoporosis.

Eye: Cataracts, glaucoma.

Gastrointestinal: Abdominal pain, dyspepsia, xerostomia.

Musculoskeletal: Back pain, cramps, muscle spasm, myositis.

Neurology: Paresthesia, restlessness.

Non-Site Specific: Immediate and delayed hypersensitivity reaction (including very rare anaphylactic reaction), pallor. Very rare anaphylactic reaction in patients with severe milk protein allergy.

Psychiatry: Agitation, aggression, depression.

Respiratory: Chest congestion; chest tightness; dyspnea; immediate bronchospasm; influenza; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

Skin: Contact dermatitis, contusions, ecchymoses, photodermatitis.

Urogenital: Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal candidiasis, vaginitis, vulvovaginitis.

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate, a component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a

condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. While ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid therapy, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see PRECAUTIONS: General: *Eosinophilic Conditions*).

OVERDOSAGE

ADVAIR DISKUS: No deaths occurred in rats given an inhaled single-dose combination of salmeterol 3.6 mg/kg (approximately 290 and 140 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis) and 1.9 mg/kg of fluticasone propionate (approximately 15 and 35 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis).

Fluticasone Propionate: Chronic overdosage with fluticasone propionate may result in signs/symptoms of hypercorticism (see PRECAUTIONS: General: *Metabolic and Other Effects*). Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. In mice, the oral median lethal dose was >1,000 mg/kg (>4,100 and >9,600 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis). In rats the subcutaneous median lethal dose was >1,000 mg/kg (>8,100 and >19,200 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis).

Salmeterol: The expected signs and symptoms with overdosage of salmeterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of salmeterol.

Treatment consists of discontinuation of salmeterol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of salmeterol. Cardiac monitoring is recommended in cases of overdosage.

No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg (approximately 240 and 110 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 190 and 90 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6,100 and 2,900 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis) and in rats at 1,000 mg/kg (approximately 81,000 and 38,000 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION

ADVAIR DISKUS should be administered by the orally inhaled route only (see Instructions for Using ADVAIR DISKUS in the Medication Guide accompanying the product). After inhalation, the patient should rinse the mouth with water without swallowing. ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid therapy.

Asthma: Long-acting $beta_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. ADVAIR DISKUS is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting $beta_2$-agonists.

ADVAIR DISKUS is available in 3 strengths, ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50, containing 100, 250, and 500 mcg of fluticasone propionate, respectively, and 50 mcg of salmeterol per inhalation.

ADVAIR DISKUS should be administered twice daily every day. More frequent administration (more than twice daily) or a higher number of inhalations (more than 1 inhalation twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. The safety and efficacy of ADVAIR DISKUS when administered in excess of recommended doses have not been established.

If symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

Patients who are receiving ADVAIR DISKUS twice daily should not use additional salmeterol or other inhaled, long-acting beta$_2$-agonists (e.g., formoterol) for prevention of EIB, or for any other reason.

Adult and Adolescent Patients 12 Years of Age and Older: For patients 12 years of age and older, the dosage is 1 inhalation twice daily (morning and evening, approximately 12 hours apart).

The recommended starting dosages for ADVAIR DISKUS for patients 12 years of age and older are based upon patients' current asthma therapy.

- For patients not adequately controlled on an inhaled corticosteroid, Table 7 provides the recommended starting dosage.
- For patients not currently on inhaled corticosteroids whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, the recommended starting dosage is ADVAIR DISKUS 100/50 or 250/50 twice daily (see INDICATIONS AND USAGE).

The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily.

For all patients it is desirable to titrate to the lowest effective strength after adequate asthma stability is achieved.

Table 7. Recommended Dosages of ADVAIR DISKUS for Patients With Asthma Aged 12 Years and Older Not Adequately Controlled on Inhaled Corticosteroids

Current **Daily Dose** of Inhaled Corticosteroid		Recommended Strength and Dosing Schedule of ADVAIR DISKUS
Beclomethasone dipropionate HFA inhalation aerosol	≤160 mcg	100/50 twice daily
	320 mcg	250/50 twice daily
	640 mcg	500/50 twice daily
Budesonide inhalation aerosol	≤400 mcg	100/50 twice daily
	800-1,200 mcg	250/50 twice daily
	1,600 mcg*	500/50 twice daily
Flunisolide inhalation aerosol	≤1,000 mcg	100/50 twice daily
	1,250-2,000 mcg	250/50 twice daily
Flunisolide HFA inhalation aerosol	≤320 mcg	100/50 twice daily
	640 mcg	250/50 twice daily
Fluticasone propionate HFA inhalation aerosol	≤176 mcg	100/50 twice daily
	440 mcg	250/50 twice daily
	660-880 mcg*	500/50 twice daily
Fluticasone propionate inhalation powder	≤200 mcg	100/50 twice daily
	500 mcg	250/50 twice daily
	1,000 mcg*	500/50 twice daily
Mometasone furoate inhalation powder	220 mcg	100/50 twice daily
	440 mcg	250/50 twice daily
	880 mcg	500/50 twice daily
Triamcinolone acetonide inhalation aerosol	≤1,000 mcg	100/50 twice daily
	1,100-1,600 mcg	250/50 twice daily

* ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid therapy.

Improvement in asthma control following inhaled administration of ADVAIR DISKUS can occur within 30 minutes of beginning treatment, although maximum benefit may not be achieved for 1 week or longer after starting treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, replacing the current strength of ADVAIR DISKUS with a higher strength may provide additional improvement in asthma control.

If a previously effective dosage regimen of ADVAIR DISKUS fails to provide adequate improvement in asthma control, the therapeutic regimen should be reevaluated and additional therapeutic options, e.g., replacing the current strength of ADVAIR DISKUS with a higher

strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be considered.

Pediatric Patients: For patients aged 4 to 11 years who are symptomatic on an inhaled corticosteroid the dosage is 1 inhalation of ADVAIR DISKUS 100/50 twice daily (morning and evening, approximately 12 hours apart).

Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis: The dosage for adults is 1 inhalation (250/50 mcg) twice daily (morning and evening, approximately 12 hours apart).

ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50, are not recommended, as no additional improvement in lung function was observed in clinical trials and higher doses of corticosteroids increase the risk of systemic effects.

If shortness of breath occurs in the period between doses, an inhaled, short-acting $beta_2$-agonist should be taken for immediate relief.

Patients who are receiving ADVAIR DISKUS twice daily should not use additional salmeterol or other inhaled, long-acting $beta_2$-agonists (e.g., formoterol) for the maintenance treatment of COPD or for any other reason.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see PRECAUTIONS: Geriatric Use) have been treated with ADVAIR DISKUS, efficacy and safety did not differ from that in younger patients. Based on available data for ADVAIR DISKUS and its active components, no dosage adjustment is recommended.

HOW SUPPLIED

ADVAIR DISKUS 100/50 is supplied as a disposable purple device containing 60 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional pack of 1 disposable purple device containing 28 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0695-02).

ADVAIR DISKUS 250/50 is supplied as a disposable purple device containing 60 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional pack of 1 disposable purple device containing 28 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0696-02).

ADVAIR DISKUS 500/50 is supplied as a disposable purple device containing 60 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional pack of 1 disposable purple device containing 28 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0697-02).

Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F), in a dry place away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation

device is not reusable. The device should be discarded 1 month after removal from the moisture-protective foil pouch or after all blisters have been used (when the dose indicator reads "0"), whichever comes first. Do not attempt to take the device apart.

GlaxoSmithKline
Research Triangle Park, NC 27709

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MEDICATION GUIDE

ADVAIR [*ad′vair*] DISKUS® 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

ADVAIR DISKUS® 250/50
(fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder)

ADVAIR DISKUS® 500/50
(fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder)

Read the Medication Guide that comes with ADVAIR DISKUS before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about ADVAIR DISKUS?

- **ADVAIR DISKUS contains 2 medicines:**
  - **fluticasone propionate (the same medicine found in FLOVENT®)**, an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
  - **salmeterol (the same medicine found in SEREVENT®)**, a long-acting beta$_2$-agonist medicine or LABA. LABA medicines are used in patients with asthma and chronic obstructive pulmonary disease (COPD). LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten.

This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.

- **In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in ADVAIR DISKUS), may increase the chance of death from asthma problems.** In a large asthma study, more patients who used salmeterol died from asthma problems compared with patients who did not use salmeterol. It is not known whether fluticasone propionate, the other medicine in ADVAIR DISKUS, changes your chance of death from asthma problems seen with salmeterol. Talk with your healthcare provider about this risk and the benefits of treating your asthma with ADVAIR DISKUS.

- **ADVAIR DISKUS does not relieve sudden symptoms. Always have a short-acting beta$_2$-agonist medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.**

- **Do not stop using ADVAIR DISKUS unless told to do so by your healthcare provider because your symptoms might get worse.**

- **ADVAIR DISKUS should be used only if your healthcare provider decides that another asthma-controller medicine alone does not control your asthma or that you need 2 asthma-controller medicines.**

- **Call your healthcare provider if breathing problems worsen over time while using ADVAIR DISKUS. You may need different treatment.**

- **Get emergency medical care if:**
  - **breathing problems worsen quickly, and**
  - **you use your short-acting beta$_2$-agonist medicine, but it does not relieve your breathing problems.**

What is ADVAIR DISKUS?

ADVAIR DISKUS combines an inhaled corticosteroid medicine, fluticasone propionate (the same medicine found in FLOVENT) and a long-acting beta$_2$-agonist medicine, salmeterol (the same medicine found in SEREVENT). ADVAIR DISKUS is used for asthma and chronic obstructive pulmonary disease (COPD) as follows:

<u>Asthma</u>

ADVAIR DISKUS is used long term, twice a day to control symptoms of asthma and to prevent symptoms such as wheezing in adults and children ages 4 and older.

ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT). Because LABA medicines, such as salmeterol, may increase the chance of death from asthma problems, ADVAIR DISKUS is not for adults and children with asthma who:

- are well controlled with another asthma-controller medicine, such as a low to medium dose of an inhaled corticosteroid medicine
- only need short-acting beta$_2$-agonist medicines once in awhile

Chronic Obstructive Pulmonary Disease (COPD)

ADVAIR DISKUS is used long term, twice a day in controlling symptoms of COPD and preventing wheezing in adults with COPD.

What should I tell my healthcare provider before using ADVAIR DISKUS?

Tell your healthcare provider about all of your health conditions, including if you:

- **have heart problems**
- **have high blood pressure**
- **have seizures**
- **have thyroid problems**
- **have diabetes**
- **have liver problems**
- **have osteoporosis**
- **have an immune system problem**
- **are pregnant or planning to become pregnant**. It is not known if ADVAIR DISKUS may harm your unborn baby.
- **are breastfeeding.** It is not known if ADVAIR DISKUS passes into your milk and if it can harm your baby.
- **are allergic to ADVAIR DISKUS, any other medicines, or food products**
- **are exposed to chickenpox or measles**

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. ADVAIR DISKUS and certain other medicines may interact with each other. This may cause serious side effects. Especially, tell your healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR® (ritonavir capsules) Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA® (lopinavir/ritonavir) Tablets contain ritonavir.

Know the medicines you take. Keep a list and show it to your healthcare provider and pharmacist each time you get a new medicine.

How do I use ADVAIR DISKUS?

See the step-by-step instructions for using the ADVAIR DISKUS at the end of this Medication Guide. Do not use the ADVAIR DISKUS unless your healthcare provider has taught you and you understand everything. Ask your healthcare provider or pharmacist if you have any questions.

- Children should use ADVAIR DISKUS with an adult's help, as instructed by the child's healthcare provider.

- Use ADVAIR DISKUS exactly as prescribed. **Do not use ADVAIR DISKUS more often than prescribed.** ADVAIR DISKUS comes in 3 strengths. Your healthcare provider will prescribe the one that is best for your condition.

- The usual dosage of ADVAIR DISKUS is 1 inhalation twice a day (morning and evening). The 2 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR DISKUS.

- If you miss a dose of ADVAIR DISKUS, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.

- Do not use a spacer device with ADVAIR DISKUS.

- Do not breathe into ADVAIR DISKUS.

- **While you are using ADVAIR DISKUS twice a day, do not use other medicines that contain a long-acting beta$_2$-agonist or LABA for any reason. Other LABA medicines include SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder) or FORADIL® AEROLIZER™ (formoterol fumarate inhalation powder).**

- Do not change or stop any of your medicines used to control or treat your breathing problems. Your healthcare provider will adjust your medicines as needed.

- Make sure you always have a short-acting beta$_2$-agonist medicine with you. Use your short-acting beta$_2$-agonist medicine if you have breathing problems between doses of ADVAIR DISKUS.

- **Call your healthcare provider or get medical care right away if:**
  - your breathing problems worsen with ADVAIR DISKUS
  - you need to use your short-acting beta$_2$-agonist medicine more often than usual
  - your short-acting beta$_2$-agonist medicine does not work as well for you at relieving symptoms

- you need to use 4 or more inhalations of your short-acting beta$_2$-agonist medicine for 2 or more days in a row
- you use 1 whole canister of your short-acting beta$_2$-agonist medicine in 8 weeks' time
- your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
- you have asthma and your symptoms do not improve after using ADVAIR DISKUS regularly for 1 week

What are the possible side effects with ADVAIR DISKUS?

- **ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT). In patients with asthma, LABA medicines, such as salmeterol, may increase the chance of death from asthma problems.** See "What is the most important information I should know about ADVAIR DISKUS?"

Other possible side effects with ADVAIR DISKUS include:

- **serious allergic reactions including rash; hives; swelling of the face, mouth, and tongue; and breathing problems.** Call your healthcare provider or get emergency medical care if you get any symptoms of a serious allergic reaction.
- **increased blood pressure**
- **a fast and irregular heartbeat**
- **chest pain**
- **headache**
- **tremor**
- **nervousness**
- **immune system effects and a higher chance for infections**
- **lower bone mineral density.** This may be a problem for people who already have a higher chance for low bone density (osteoporosis).
- **eye problems including glaucoma and cataracts.** You should have regular eye exams while using ADVAIR DISKUS.
- **slowed growth in children.** A child's growth should be checked often.
- **throat irritation**

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with ADVAIR DISKUS. Ask your healthcare provider or pharmacist for more information.

How do I store ADVAIR DISKUS?

- Store ADVAIR DISKUS at room temperature between 68° to 77° F (20° to 25° C). Keep in a dry place away from heat and sunlight.

- Safely discard ADVAIR DISKUS 1 month after you remove it from the foil pouch, or after the dose indicator reads "0", whichever comes first.
- **Keep ADVAIR DISKUS and all medicines out of the reach of children.**

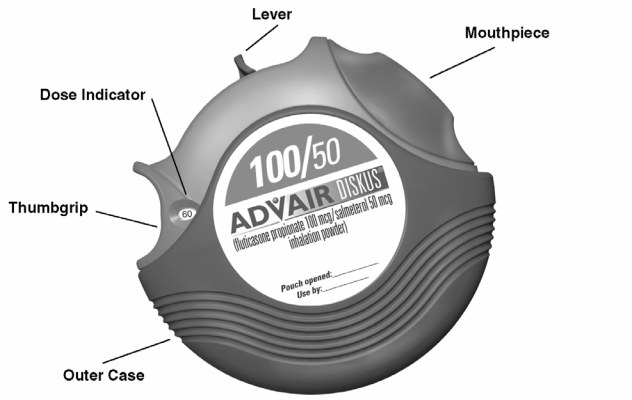
General Information about ADVAIR DISKUS

Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not use ADVAIR DISKUS for a condition for which it was not prescribed. Do not give your ADVAIR DISKUS to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about ADVAIR DISKUS. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ADVAIR DISKUS that was written for healthcare professionals. You can also contact the company that makes ADVAIR DISKUS (toll free) at 1-888-825-5249 or at www.advair.com.

Instructions for Using ADVAIR DISKUS

Follow the instructions below for using your ADVAIR DISKUS. **You will breathe in (inhale) the medicine from the DISKUS.** If you have any questions, ask your healthcare provider or pharmacist.



Take the ADVAIR DISKUS out of the box and foil pouch. Write the **"Pouch opened"** and **"Use by"** dates on the label on top of the DISKUS. **The "Use by" date is 1 month from date of opening the pouch.**

- The DISKUS will be in the closed position when the pouch is opened.
- The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose indicator number will decrease each time you use the DISKUS. After you have used 55 doses from the DISKUS, the numbers 5 to 0 will appear in **red** to warn you that there are only a few doses left *(see Figure 1)*. If you are using a "sample" DISKUS, the numbers 5 to 0 will appear in red after 23 doses.

Figure 1

Taking a dose from the DISKUS requires the following 3 simple steps: Open, Click, Inhale.

1. **OPEN**

   Hold the DISKUS in one hand and put the thumb of your other hand on the **thumbgrip**. Push your thumb away from you as far as it will go until the mouthpiece appears and snaps into position *(see Figure 2)*.

Figure 2

2. **CLICK**

Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the **lever** away from you as far as it will go until it **clicks** *(see Figure 3)*. The DISKUS is now ready to use.

Figure 3

Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the DISKUS is ready:**

- **Do not close the DISKUS.**
- **Do not tilt the DISKUS.**
- **Do not play with the lever.**
- **Do not move the lever more than once.**

3. **INHALE**

Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding the DISKUS level and away from your mouth *(see Figure 4)*. **Remember, never breathe out into the DISKUS mouthpiece.**

Figure 4

Put the mouthpiece to your lips *(see Figure 5)*. Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.

Figure 5

Remove the DISKUS from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable. Breathe out slowly.

The DISKUS delivers your dose of medicine as a very fine powder. Most patients can taste or feel the powder. Do not use another dose from the DISKUS if you do not feel or taste the medicine.

Rinse your mouth with water after breathing-in the medicine. Spit the water out. Do not swallow.

4. **Close the DISKUS when you are finished taking a dose so that the DISKUS will be ready for you to take your next dose.** Put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go *(see Figure 6)*. The DISKUS will click shut. The lever will automatically return to its original position. The DISKUS is now ready for you to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4.)

Figure 6

Remember:

- Never breathe into the DISKUS.
- Never take the DISKUS apart.
- Always ready and use the DISKUS in a level, flat position.
- Do not use the DISKUS with a spacer device.
- After each dose, rinse your mouth with water and spit the water out. Do not swallow.
- Never wash the mouthpiece or any part of the DISKUS. **Keep it dry.**
- Always keep the DISKUS in a dry place.
- Never take an extra dose, even if you did not taste or feel the medicine.

Rx only

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

References

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease. Updated 2005. http://goldcopd.com

Guidance for Industry: Providing Clinical Evidence of effectiveness for Human Drug and Biological Products. http://www.fda.gov/cder/guidance/

Suissa, S. Statistical Treatment of Exacerbations in Therapeutic Trials of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2006; 173: 842-846.