Pulmonary-Allergy Drugs Advisory Committee Meeting for Use of ADVAIR DISKUS 500/50 in COPD

March 28, 2007

GlaxoSmithKline

Briefing Document

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EXECUTIVE SUMMARY

Introduction

ADVAIR DISKUS® is a combination product containing salmeterol, a long acting β_2-agonist, and fluticasone propionate, an inhaled corticosteroid. The purpose of this Document is to provide a summary of the clinical data supporting the supplemental NDA for ADVAIR DISKUS 500/50 for the treatment of airflow obstruction, reducing exacerbations, and improve survival.

ADVAIR has been approved for the treatment of chronic obstructive pulmonary disease (COPD) in over 80 countries worldwide, and for the treatment of asthma in over 130 countries. The safety profile of ADVAIR has been investigated through the clinical study program and has an excess of 29 million patient-years of post-marketing exposure. In addition, for the individual component treatments, the estimated cumulative exposure has reached 26 million patient-years for salmeterol and 34 million patient-years for fluticasone propionate.

In the US, ADVAIR DISKUS 250/50 was approved by the FDA on November 17th, 2003 for the twice-daily maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis. The supplemental NDA supporting this FDA approval demonstrated that both ADVAIR DISKUS 250/50 and ADVAIR DISKUS 500/50 improved lung function in patients with COPD; however, it was determined that the 500/50 strength did not differ substantially in either lung function parameters or in patient-related outcomes beyond ADVAIR 250/50.

This supplemental NDA provides additional efficacy data as well as long-term safety data on ADVAIR DISKUS 500/50 to support the approval of the following proposed indication:

"ADVAIR DISKUS 500/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema, and to increase survival and reduce exacerbations in patients with forced expiratory volume in 1 second (FEV_1) <60% of predicted [see Clinical Studies (14.2)].

Overview of COPD and Mortality

- COPD is a progressive disease and is one of the few major diseases with increasing mortality. In an analysis of a nationally representative US cohort with over 20 years follow-up, the presence of moderate COPD was associated with a 1.6 times greater risk of death. In addition, patients with severe COPD experienced a 2.7 times greater risk of death compared to the general population.
- The goals of therapy for patients with COPD include symptom management, prevention of disease progression and reduction of mortality. The demonstrable benefits of currently available therapies have been significant, but limited.

Currently, FDA approved medications for the treatment of COPD have been approved on the basis of improvements to lung function.

- Studies on mortality after hospitalization for an acute exacerbation of COPD have shown a one-year mortality of 22% and a 2-year mortality of 36%. In addition, mortality has been shown to increase with the frequency of severe exacerbations, particularly if these require admission to a hospital.
- Reduction of mortality is one of the greatest unmet needs in the management of COPD. Previously, no pharmacological treatment has been shown to impact mortality in patients with COPD.

Overview of Clinical Program

Three pivotal studies [Studies SCO30003, SFCB3024, and SFCA3006] were submitted to the FDA to support the efficacy of ADVAIR 500/50 for the proposed indications. Each of these studies compared the effects of treatment with ADVAIR 500/50 with placebo and the individual components, salmeterol and fluticasone propionate, in patients with COPD.

Clinical Trial	Study Design Primary Endpoint Duration	Number of Patients	DISKUS Treatment/Dose(s) (mcg)	Key Inclusion Criteria
SCO30003 (TORCH) [Calverley, 2007]	R, DB, PC, PG All-cause mortality 3 years	6112	ADVAIR 500/50 BID SAL 50 BID FP 500 BID Placebo BID	≥ 10-pack year history; FEV_1 <60% predicted; <10% reversibility; No exacerbation history required
SFCB3024 (TRISTAN) [Calverley, 2003]	R, DB, PC, PG Lung function 1 year	1465	ADVAIR 500/50 BID SAL 50 BID FP 500 BID Placebo BID	≥10-pack year history; FEV_1 ≥25 to ≤70% predicted; <10% reversibility; Exacerbation history required
SFCA3006 [Mahler, 2002]	R, DB, PC, PG Lung function 6 months	674	ADVAIR 500/50 BID SAL 50 BID FP 500 BID Placebo BID	≥ 20-pack year history; FEV_1 <65% predicted but >0.70L; No reversibility criteria; Exacerbation history not captured; Symptoms of chronic bronchitis

R=randomized, DB=double-blind, PG=parallel-group, SAL=salmeterol, FP=fluticasone propionate, BID=twice daily

Study Population Results

- Overall, the demographic characteristics of patients were similar across the three studies (SCO30003, SFCB3024, and SFCA3006) with the exception of race in Study SCO30003. This latter study included approximately 12% of patients reporting their race as Asian versus ≤1% from both Studies SFCB3024 and SFCA3006.
- The population evaluated in all three studies were characteristic of patients with COPD GOLD stages II-IV.
- The proportion of patients completing treatment was consistently higher in the ADVAIR 500/50 group compared with placebo across all three studies.

- The differential withdrawal rate from study drug was particularly noteworthy in Study SCO30003 (44% of placebo-treated patients versus 34% of ADVAIR 500/50 treated patients withdrew by Week 156). After withdrawal, patients in Study SCO30003 could have switched to any COPD therapy but were still included in the primary endpoint analysis (all-cause mortality), based upon the treatment to which they were randomized, on an intent-to-treat basis.
- In Study SCO30003, regardless of whether patients withdrew, survival status was assessed up to 156 weeks after the start of study treatment. Complete survival status data for 6,111 patients have been included in the mortality analyses. Survival status was unknown for only 1 patient who was censored at 2 years at which time the patient was known to be alive.

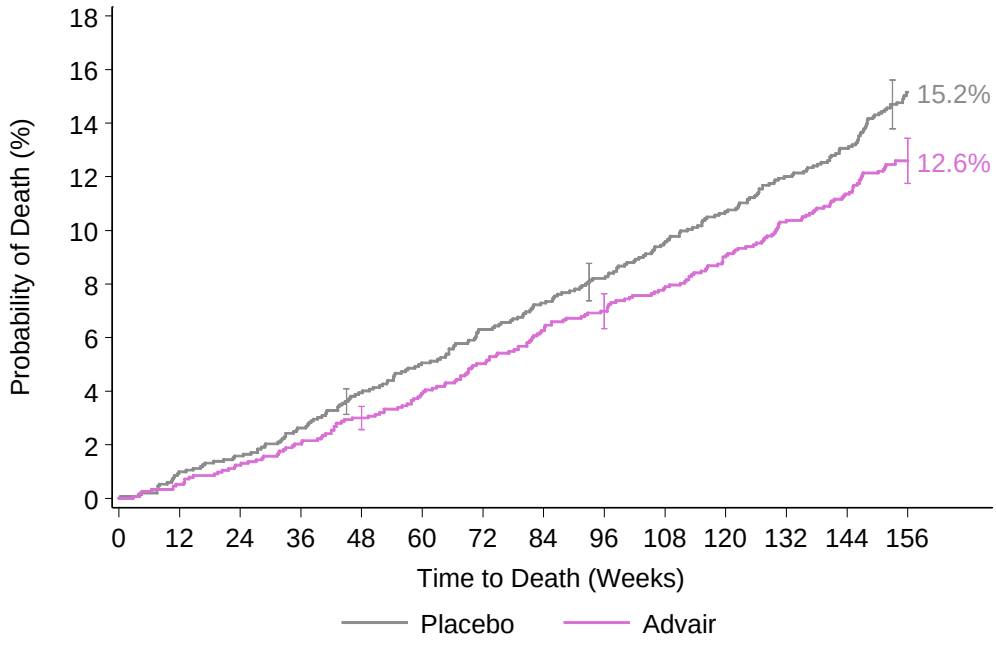
Efficacy Results

Mortality

Study SCO30003 was prospectively designed to assess mortality and the results are presented below.

- **All-cause mortality (primary endpoint)**: In Study SCO30003, ADVAIR 500/50 reduced the risk of dying at any time within 3 years from any cause by 17.5% compared with placebo (95% CI: 0%, 32%; p=0.052; adjusted for interim analyses) or an absolute risk reduction of 2.6%.

Study SCO30003



Note: Vertical bars represent standard error.

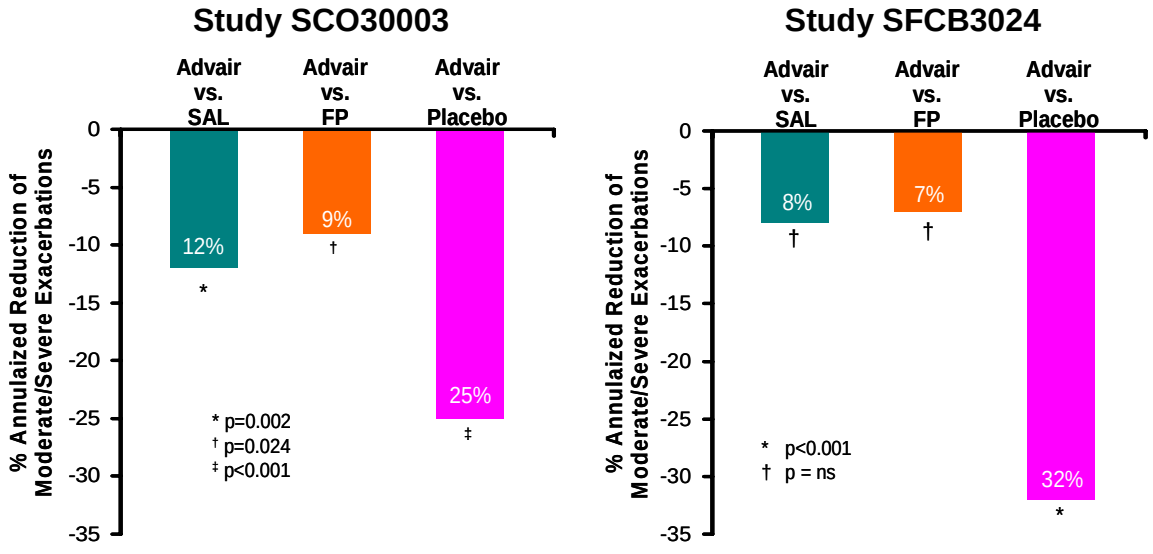
- **COPD-related mortality**: In a subset analysis of COPD-related deaths, the magnitude of response was similar to that seen for all-cause mortality. ADVAIR 500/50 reduced the risk of COPD-related deaths within 3 years by 22% compared with placebo (p=0.107).
- **On-treatment mortality**: In a subset analysis of deaths of patients remaining on treatment, the magnitude of response was similar to that seen for all-cause mortality. The risk of dying while on treatment was reduced by 23% with ADVAIR 500/50 compared with placebo (p=0.055).

Although not prospectively designed to assess mortality, fatal events on treatment for Study SFCB3024 and SFCA3006 are summarized below for completeness.

- In Study SFCB3024, there were 10 deaths in the placebo group, 5 deaths in the salmeterol group, 5 deaths in the fluticasone propionate group, and 4 deaths in the ADVAIR 500/50 group. In Study SFCA3006, there were three deaths in the placebo group and no deaths in the active treatment groups.

Moderate & Severe COPD Exacerbations

- In Study SCO30003, the rate of moderate and severe exacerbations was statistically significantly decreased by 25% in the ADVAIR 500/50 treatment group compared with placebo (95% CI: 19%, 31%; p<0.001).
- In Study SFCB3024, a similar magnitude of effect was obtained. The rate of moderate and severe exacerbations was significantly decreased by 32% in the ADVAIR 500/50 treatment group compared with placebo (95% CI: 17%, 43%; p<0.001).



- In Study SFCA3006, no significant differences in the rate of moderate or severe COPD exacerbations between treatment groups were observed. Analyses of moderate/severe COPD exacerbations should be interpreted with caution due to study design limitations: short duration of study (6-months) and the requirement for

patients to withdraw from treatment if they experienced an exacerbation that required oral corticosteroid or hospitalization, or if a patient experienced three exacerbations requiring antibiotics.

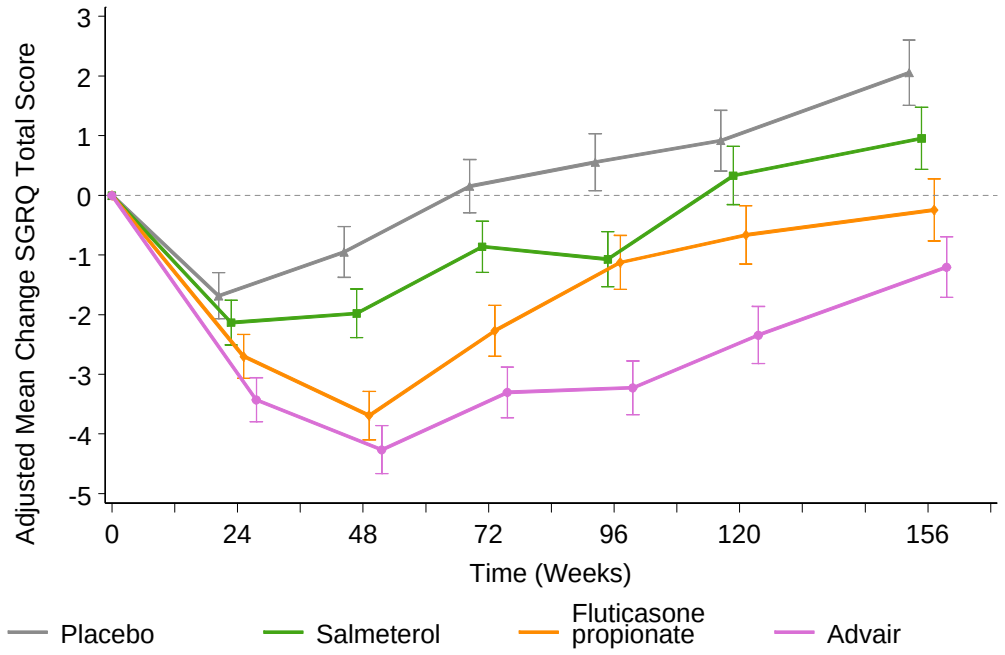
- The rate of moderate and severe exacerbations requiring treatment with systemic corticosteroids was statistically significantly decreased by 43% with ADVAIR 500/50 compared with placebo in Study SCO30003 (95% CI: 36%, 49%; p<0.001) and by 45% in Study SFCB3024 (95% CI: 29%, 58%; p<0.001).
- The rate of severe exacerbation (requiring hospitalization) was statistically significantly decreased by 17% with ADVAIR 500/50 compared with placebo in Study SCO30003 (95% CI: 2%, 29%; p=0.028).

Health-Related Quality of Life

Health outcome results are presented from Studies SCO30003 and SFCB3024 from the St George's Respiratory Questionnaire (SGRQ) and from Study SFCA3006 from the Chronic Respiratory Disease Questionnaire (CRQ).

- In Study SCO30003, health-related quality of life, as assessed by the St. George's Respiratory Questionnaire (SGRQ) total score, was improved for the ADVAIR 500/50 treatment group compared with placebo (average difference -3.1; p<0.001) over 3 years.

Study SCO30003



Note: Vertical bars represent standard error.

- In Study SFCB3024, the SGRQ total score was improved for the ADVAIR 500/50 treatment group compared with placebo (average difference -2.2, p<0.001) over 52 weeks.

- In Study SFCA3006, health-related quality of life, as assessed by the overall Chronic Respiratory Disease Questionnaire (CRQ) score, was improved for the ADVAIR 500/50 treatment group compared with placebo (average difference 5.3; p=0.007) at Endpoint.
- There were strong and consistent trends of improvement on health-related quality of life across all three studies with ADVAIR 500/50 although the Minimal Important Difference (change from baseline of at least -4 units on the SGRQ or an improvement of at least 10 in Overall CRQ score) was not achieved with either questionnaire.
- In Study SCO30003, the odds for patients treated with ADVAIR 500/50 achieving the Minimal Important Difference on the SGRQ were nearly twice those of placebo (odds ratio: 1.86; 95% CI: 1.58, 2.18; p<0.001).

Pulmonary Function

FEV_1 results are presented from Studies SCO30003, SFCB3024, and SFCA3006.

- In Study SCO30003, a significant improvement in post-bronchodilator FEV_1 compared with placebo was demonstrated for ADVAIR 500/50 (average difference 92mL; p<0.001) over 3 years.
    - *Post hoc* analysis in Study SCO30003 demonstrated the rate of decline in FEV_1 was -39mL/year for ADVAIR compared with -55mL/year for placebo (p<0.001).
- In Study SFCB3024, a significant improvement in pre-bronchodilator FEV_1 (average difference 133mL; p<0.001) and post-bronchodilator FEV_1 (average difference 76mL; p<0.001) relative to placebo was demonstrated for ADVAIR 500/50 treatment over 52 weeks.
- In Study SFCA3006, a significant improvement in pre-dose FEV_1 (average difference 159mL; p<0.001) and post-dose FEV_1 (average difference 231mL; p<0.001) relative to placebo was demonstrated for ADVAIR 500/50 at Endpoint.

Safety Results

- The safety of ADVAIR 500/50 has been extensively evaluated with up to three years of exposure. This translates to 4,066 patient years of exposure from Studies SCO30003, SFCB3024, and SFCA3006 combined.
- The pharmacologically predictable local side effects of inhaled corticosteroids such as oral candidiasis and dysphonia were reported more commonly in patients treated with ADVAIR 500/50 and fluticasone propionate 500 mcg than in those treated with salmeterol 50 mcg or placebo.
- In SCO30003, there was an increased risk of pneumonia as evidenced by the AEs and SAEs in the fluticasone propionate containing arms. The overall incidence of pneumonia AEs in Study SCO30003 was markedly higher in the ADVAIR 500/50 (16%) and fluticasone propionate 500 mcg (14%) treatment groups than in the salmeterol 50 mcg (11%) and placebo (9%) groups. The number of deaths while on

treatment which were attributable to pneumonias, as adjudicated by the Clinical Endpoints Committee, was 7 in the placebo group, 9 in the salmeterol 50 mcg group, 13 in the fluticasone propionate 500 mcg group, and 8 in the ADVAIR 500/50 group. Treatment with ADVAIR 500/50 in COPD was not associated with an increased risk of dying from pneumonia. The observed risk of pneumonia has been included in the proposed label for ADVAIR 500/50 which is detailed in Section 7.1.3.

- There was no statistically significant difference for any active treatment compared with placebo in the time to the first reported bone disorder or bone fracture AE. The number of patients reporting each individual AE included within the category of bone disorders or bone fracture AEs was low. These data do not indicate clinically relevant differences with ADVAIR 500/50 on bone. This conclusion is further supported by detailed serial BMD examinations of the hip and lumbar spine from a subset of patients in Study SCO30003 (N=658). Analyses revealed no significant difference in the rate of bone loss between any active treatment and placebo.
- There was no statistically significant difference for any active treatment compared with placebo in the time to the first reported eye disorder AE. The incidence of AEs of eye disorders was low across treatment groups. These data do not indicate clinically relevant differences with ADVAIR 500/50 on the eye. This conclusion is further supported by detailed ophthalmic examinations performed in a subset of patients from Study SCO30003 that demonstrated no evidence for a difference between active treatments and placebo in the number of patients who developed cataracts or glaucoma during the study.
- HPA-axis effects were assessed in all three pivotal studies. Serum and urine cortisol data suggest the potential for ADVAIR 500/50 to impact basal HPA-axis homeostasis. However, compared with placebo, the ability of patients receiving ADVAIR 500/50 to respond to acute physiologic stress as assessed by cosyntropin stimulation was not impaired.
- No evidence was observed for a higher rate of cardiac AEs with ADVAIR 500/50 in Study SCO30003. Notably, the incidence of deaths due to cardiovascular causes in Study SCO30003 was numerically higher for placebo than for any of the active treatments. This was further supported by cardiac monitoring (ECG and Holter) conducted in Studies SFCB3024 and SFCA3006 which showed no evidence of an increased risk of cardiac events with ADVAIR 500/50 therapy.
- No clinically significant effects were observed in any treatment group on clinical laboratory parameters following 52 weeks of exposure (Study SFCB3024) or following 24 weeks of exposure (Study SFCA3006). Prospective assessment of bruising on the volar surface of the forearm (Study SFCB3024) was low and demonstrated no significant differences between any of the active treatment groups and placebo.

Summary of Benefit-Risk

The results from the clinical program indicate that ADVAIR 500/50 has a favorable benefit to risk ratio for the treatment of patients with COPD and can be summarized as follows:

- Treatment with ADVAIR 500/50 reduced the risk of dying at any time within 3 years by 17.5% compared with placebo (95% CI: 0%, 32%; p=0.052; adjusted for interim analyses). The absolute reduction in risk between ADVAIR 500/50 and placebo (2.6%) indicates that one death is prevented for every 39 patients treated for 3 years. This treatment effect was seen despite the withdrawal of over one-third of patients who could have switched to any COPD therapy.
- The statistically significant and clinically important improvements in COPD morbidity, measured by exacerbation rate, health status, and lung function, in conjunction with the mortality benefit, demonstrates a consistent and robust benefit of ADVAIR 500/50 for patients with COPD.
- No clinically relevant treatment differences were observed for eye disorders, HPA axis disorders, bone disorders (including changes in bone mineral density), or cardiac events.
- The pharmacologically predictable local side effects of ICS, such as oral candidiasis and dysphonia, were reported more commonly in patients receiving ICS-containing treatments compared with placebo.
- The increased incidence of pneumonia in ADVAIR 500/50 and fluticasone propionate 500 mcg treated patients is the most relevant and potentially significant risk associated with ADVAIR 500/50. However, from the SAE narratives in Study SCO30003, there was no evidence of an increase in opportunistic infections where cultures were obtained, and the clinical response to conventional antibiotics also suggests that the pneumonias were not atypical or opportunistic. Most importantly, treatment with ADVAIR 500/50 in COPD did not appear to increase the risk of dying from pneumonia. This may be because exacerbations and pneumonias have similar presentations and are therefore treated early in their course. The observed risk of pneumonia has been included in the proposed label for ADVAIR 500/50 which is detailed in Section 7.1.3.

Taking into consideration the above points, the benefit-risk profile is considered to be favorable and support the following proposed indication:

"ADVAIR DISKUS 500/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema, and to increase survival and reduce exacerbations in patients with forced expiratory volume in 1 second (FEV_1) <60% of predicted."

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Abbreviations Used in this Document

ACTH	Adrenocorticotropic Hormone
AE	adverse event
ANCOVA	Analysis of Covariance
ATS	American Thoracic Society
AUC_{12}	Area Under the Response-time Curve for 12 Hours After Dosing
bd	Twice daily
BMD	Bone mineral density
BMI	Body Mass Index
CEC	Clinical Endpoint Committee
CI	Confidence Interval
C_{min}	Minimum Concentration Over the Sampling Interval
COPD	Chronic Obstructive Pulmonary Disease
CRQ	Chronic Respiratory Disease Questionnaire
DEXA	Dual Energy X-ray Absorptiometry
ECCS	European Community for Coal and Steel
ERS	European Respiratory Society
ECG	Electrocardiogram
FEV_1	Forced Expiratory Volume in one second
FP 500	Fluticasone propionate 500 mcg
FVC	Forced Vital Capacity
GOLD	Global initiative for Obstructive Lung Disease
GSK	GlaxoSmithKline
HPA	Hypothalamic-Pituitary-Adrenal
HRQOL	Health-Related Quality of Life
ICS	Inhaled Corticosteroid
ITT	Intent-to-Treat (Efficacy)
kg	Kilogram
m	Meter
MID	Minimal Important Difference
ISOLDE	Inhaled Steroids in Obstructive Lung Disease in Europe
LABA	Long Acting β_2-Agonist
LTOT	Long term Oxygen Therapy
mcg	micrograms
MDI	Metered-Dose Inhaler
mL	millilitres
N, n	Number of patients
NDA	New Drug Application
NNT	Number Needed to Treat
SAE	Serious Adverse Event
SAL 50	Salmeterol 50 mcg
SD	Standard Deviation
SEDMC	Safety and Efficacy Data Monitoring Committee
SFC 50/500	Salmeterol/fluticasone propionate 50/500 mcg
SGRQ	St George's Respiratory Questionnaire
TORCH	TOwards a Revolution in COPD Health
US	United States

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1. INTRODUCTION AND BACKGROUND

1.1. Introduction

ADVAIR DISKUS® (salmeterol [SAL]/fluticasone propionate [FP]; SFC) is a combination product containing salmeterol, a long acting β_2-agonist (LABA), and fluticasone propionate, an inhaled corticosteroid (ICS). The purpose of this Document is to provide a summary of the clinical data supporting the supplemental NDA for ADVAIR DISKUS 500/50 for the treatment of airflow obstruction, reducing exacerbations, and improving survival.

ADVAIR® has been approved for the treatment of chronic obstructive pulmonary disease (COPD) in over 80 countries worldwide, and for the treatment of asthma in over 130 countries. The safety profile of ADVAIR has been investigated through the clinical study program and has an excess of 29 million patient-years of post-marketing exposure. In addition, for the individual component treatments, the estimated cumulative exposure has reached 26 million patient-years for salmeterol and 34 million patient-years for fluticasone propionate.

1.2. Overview of Chronic Obstructive Pulmonary Disease

1.2.1. Burden of Disease

The exact prevalence of COPD is not well characterized due to variable disease definitions over time and a high proportion of undiagnosed disease; however, COPD affects millions of individuals in the US and data suggest that the prevalence is rising. The US Centers for Disease Control and Prevention (CDC) estimates that as many as 24 million individuals in the US had evidence of impaired lung function (FEV_1/FVC <70%) in 2000; only 10 million of those with evidence of impaired lung function (42%) reported a physician diagnosis of COPD [Mannino, 2002].

COPD is a progressive disease and is one of the few major diseases with increasing mortality in the US over the last 20 years. The age-adjusted annual death rate for COPD increased 67%, from 40.7 per 100,000 in 1980 to 66.9 per 100,000 in 2000 [Mannino, 2002]. The Global Burden of Disease Study [Murray, 1997] ranked COPD as the 6th leading cause of mortality and the 12th leading cause of morbidity world-wide. These figures are expected to rise, with COPD becoming the third leading cause of mortality and the fifth leading cause of morbidity by the year 2020.

A major cause of mortality in patients with COPD is acute exacerbation. Studies on mortality after hospitalization for an acute exacerbation of COPD have shown a one-year mortality of 22% and a 2-year mortality of 36% [Almagro, 2002; Groenewegen, 2003]. In addition, mortality increases with the frequency of severe exacerbations, particularly if these require admission to a hospital [Soler-Cataluña, 2005].

Compared to the general population, patients with COPD also experience greater all-cause mortality. In an analysis of a nationally representative US cohort with over 20

years follow-up, the presence of moderate COPD was associated with a 1.6 times greater risk of death; patients with severe COPD experienced 2.7 times greater risk of death [Mannino, 2003]. An analysis of UK cohort similarly found all-cause mortality rates elevated in patients with COPD compared to the general population [Soriano, 2000]. After five years of follow-up, 80% of men without COPD were living—compared to 72% of men with mild COPD and 65% of men with moderate COPD. Survival in women with mild and moderate COPD was also lower (78% and 71%, respectively), compared to women without COPD (86%). For both men and women, significantly greater mortality was observed with increasing COPD severity. Only 24% of male patients and 30% of female patients with severe COPD survived after five years. Patients with severe COPD died an average of four years before the age and sex-matched reference population [Soriano, 2000].

COPD is also associated with considerable morbidity. COPD-related morbidity can be estimated by using hospitalization rates, as well as the total costs attributed to caring for patients with the disease. Since 1990, hospitalizations for COPD have increased among all age groups, with a 62% increase among 65-74 year olds. An estimated 726,000 hospital discharges were reported in 2000, a discharge rate of 40.8 per 10,000 population [Mannino, 2002]. According to recent estimates, in 2004 the annual cost to the US for COPD was $37.2 billion [NHLBI Chartbook, 2004]. This included $20.9 billion in direct healthcare expenditures, $7.4 billion in indirect morbidity costs and $8.9 in indirect mortality costs. Analysis of patients covered by a US managed care organization showed that annual inpatient and outpatient expenditure per patient with COPD was significantly higher than expenditure per age-matched patient without COPD ($11,680 vs. $5815, $p<0.001$) [Mapel, 2000]. As the disease progresses, so does its economic cost. A five-year study of 413 patients with COPD in the US demonstrated that healthcare costs rise significantly with the severity of disease [Hilleman, 2000]. The median healthcare cost per patient-year for patients in the milder COPD category (FEV_1 >50% predicted) was $1,681 compared to $10,812 per patient-year for those in the most severe COPD category (FEV_1 <35% predicted).

1.2.2. Pathophysiology of COPD

COPD is a disease state characterized by the presence of airflow obstruction due to emphysema or chronic bronchitis. Emphysema and chronic bronchitis are complex pathophysiological conditions and frequently co-exist in the same patient. Emphysema is associated with the destruction of the walls of the alveoli with abnormal permanent enlargement of the airspaces distal to the terminal bronchioles and loss of alveolar attachments. As a result, elasticity of the lung tissue is lost, causing airways to collapse and obstruction of airflow. Chronic bronchitis is associated with inflammation of the respiratory bronchioles, enlargement of bronchial mucous glands accompanied by dilation of gland ducts. Goblet cell size and number are increased, and there may be both metaplasia and hypertrophy of airway smooth muscle. As a result, there is plugging of the respiratory bronchioles with mucus, and distortion due to fibrosis [ATS, 1995].

Persistent reduction in expiratory flow and a progressive deterioration in lung function characterize COPD. Inflammation, fibrosis, goblet cell metaplasia, and smooth muscle hypertrophy in terminal bronchioles, as well as loss of alveolar attachments to

bronchioles due to alveolar destruction are important causes of airflow obstruction. Although expiratory airflow may improve significantly with treatment, by definition, expiratory airflow will never normalize and will progressively worsen with time. Patients with COPD have shortness of breath, initially appearing as dyspnea on exertion and then progressing insidiously. Progressively increasing productive cough and sputum production are also symptomatic manifestations of COPD. Patients most often modify their lifestyles to compensate for the dyspnea and activity limitation associated with reduced expiratory airflow [Petty, 2000]. In addition to these symptoms, periods of acute deterioration due to viral or bacterial exacerbations lead to considerable morbidity and mortality from the disease.

1.2.3. Unmet Medical Need and Current Therapies

Key problems in patients with COPD include:

1. **Symptoms and exacerbations**: COPD symptoms, particularly breathlessness and cough, can be disabling. Superimposed on these baseline symptoms are acute exacerbations that often require treatment with antibiotics, oral corticosteroids or both, and may be so severe as to require hospitalization or threaten life. Exacerbations are a major cause of morbidity and mortality in COPD. Recovery from exacerbations is sometimes incomplete, rendering the patient more vulnerable to repeated exacerbations and a more rapid decline in health status and lung function [Seemungal, 2000; Pauwels, 2001]. The incidence of COPD exacerbations is a predictor of the risk of dying from COPD [Soler-Cataluña, 2005; Almagro, 2002; Sapey, 2006].
2. **Gradual disease progression**: COPD progression causes worsening lung function and symptoms, and eventually respiratory failure and early death. Smoking cessation helps slow the rate of deterioration but, even in ex-smokers, continued inflammation and a slow downward drift in lung function is common [Hogg, 2004; Scanlon, 2000].
3. **Increased mortality**: COPD is associated with higher mortality rates from both respiratory and non-respiratory causes [Holguin, 2005; Soriano, 2005].

Prevention of COPD is the ideal outcome and, in the long term, initiatives to reduce smoking are likely to prevent many cases. Smoking cessation, which has been shown to slow the rate of decline in lung function by 30ml/yr over an 11 year period, remains a primary objective of treatment [Anthonisen, 2002]. However, smoking cessation after reaching an advanced disease stage unfortunately does not prevent the ongoing inflammatory process [Hogg, 2004]. Even with the prominence of anti-smoking programs, the burden of COPD is set to increase for at least two decades [Murray, 1997].

The goals of therapy for patients with COPD include symptom management, prevention of disease progression and reduction of mortality [Global Initiative for Chronic Obstructive Lung Disease, 2006]. The demonstrable benefits of currently available therapies have been significant, but limited. Currently, FDA approved medications for the treatment of COPD have been approved on the basis of improvements in lung function.

For symptomatic management, current COPD guidelines recommend LABAs for patients with moderate to severe COPD and ICS for patients with severe COPD and repeated exacerbations [Global Initiative for Chronic Obstructive Lung Disease, 2006]. Therapy is add-on, with patients taking more than one therapy as COPD progresses. Combination therapies of LABA and ICS not only provide the benefits of both treatments in a convenient single inhaler but have also been shown to provide better improvement in COPD symptoms than the individual components alone [Calverley, 2003a; Calverley, 2003b; Hanania, 2003; Mahler, 2002].

No treatment (other than smoking cessation) has been shown to have an important impact on disease progression. In addition, no non-surgical interventions, other than smoking cessation and long-term oxygen therapy (LTOT) in those with hypoxemia, have been shown to impact mortality in patients with COPD [Anthonisen, 2005; Crockett, 2001]. Thus, reduction of mortality is one of the greatest unmet needs in the management of COPD.

1.3. Regulatory History

The current COPD indication for ADVAIR DISKUS 250/50 is as follows:

… " *currently 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."

This information was added to the ADVAIR Prescribing Information on November 17th, 2003 as a result of a supplemental NDA that was submitted to the FDA in 2001. The supplemental NDA supporting this FDA approval demonstrated that both ADVAIR DISKUS 250/50 and ADVAIR DISKUS 500/50 improved lung function in patients with COPD; however, it was determined that the 500/50 strength did not differ substantially in either lung function parameters or in patient-related outcomes beyond ADVAIR 250/50.

This supplemental NDA provides additional efficacy data as well as long-term safety data on ADVAIR DISKUS 500/50 to support the approval of the following proposed indication:

"ADVAIR DISKUS 500/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema, and to increase survival and reduce

exacerbations in patients with forced expiratory volume in 1 second (FEV_1) <60% of predicted [see Clinical Studies (14.2)].

Prior to approval, the data in the application was discussed at a Pulmonary-Allergy Drugs Advisory Committee meeting on January 17th, 2002. At the conclusion of the meeting the members voted to recommend approval of ADVAIR DISKUS for the treatment of COPD but the discussion at the meeting included the following key issues:

- As the studies were only 6-months long there is not sufficient long-term efficacy or safety data and this should be reflected in the labeling
- Concerns of ocular manifestations and bone mass decrease in the COPD population
- COPD patients are more vulnerable to adverse effects
- The improvement in FEV1 was not associated with a consistent reduction in symptoms

GSK has conducted three key studies with ADVAIR DISKUS 500/50 in patients with COPD and taken together the data from these studies address many of the issues that were raised at the January 17th, 2002 Advisory committee meeting.

- SFCA3006- 6-month US study that was included in the original US COPD submission.
- SFCB3024- 1 year study conducted outside the US to support European registration that was ongoing when the original US COPD submission was submitted.
- SCO30003- 3 year global study that completed March, 2006. The study design for SCO30003 was discussed with the FDA on August 4, 2000 and the FDA comments were incorporated into the protocol. In addition, the statistical analysis plan was submitted to the FDA for comment prior to un-blinding the data.

The efficacy and safety data from these three key studies are presented in this briefing document and comprise the basis of the clinical program for the current supplemental NDA under consideration at the FDA. As the design, and in particular the size and duration of these studies, was not similar enough to allow for integration of the data it was agreed with the FDA to examine the data from the studies individually.

2. OVERVIEW OF CLINICAL PROGRAM

2.1. Introduction

Three pivotal studies (Studies SCO30003, SFCB3024, and SFCA3006) were submitted to the FDA to support the efficacy of SFC 50/500 for the proposed indications. Each of these studies compared the effects of treatment with SFC 50/500 with placebo and the individual components, SAL 50 and FP 500, in patients with COPD.

Table 1 summarizes the overall study characteristics of all three clinical trials.

Table 1 Description of Pivotal Efficacy and Safety Studies

Protocol No.	No. Study Center Location(s)	Study Start; Enrollment Status and Date; Total Enrollment /Target Enrollment	Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Patients by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)
SCO30003	444 centers in 42 countries[a]	07 Sep 2000; Completed; 08 Nov 2005; [b]6184/6040	age 40-80 years; FEV_1 <60% predicted; FEV_1/FVC ratio ≤70%; Poor reversibility of airflow obstruction[c]	SFC 50/500, SAL 50, FP 500, or placebo; inhalation powder via DISKUS; BID; 156 weeks	[d]SFC 50/500: 1533/1011; SAL 50: 1521/960; FP 500: 1534/947; Placebo: 1524/851	[d]4631 M/1481 F; 65.0 (40-86)	All-cause mortality of all patients in the ITT Population within 3 years after the start of treatment
SFCB3024	196 centers in 25 countries[e]	20 Aug 1998; Completed; 12 Dec 2000; [b]1469/1500	age 40-79 years; FEV_1 ≥25 to ≤70 predicted; FEV_1/FVC ratio ≤70%; Poor reversibility of airflow obstruction [c]	SFC 50/500, SAL 50, FP 500, or placebo; inhalation powder via DISKUS; BID; 52 weeks	[d]SFC 50/500: 358/269; SAL 50: 372/253; FP 500: 374/266; Placebo: 361/221	[d]1060 M/405 F; 63.2 (38-79)	Change from Baseline in morning pre-bronchodilator FEV_1 measured at each clinic visit.
SFCA3006	69 centers in the US	24 Sep 1998; Completed; 05 May 2000; [b]691/700	≥ 40 years of age; FEV_1 <65% predicted but >0.70L[f]; FEV_1/FVC ratio ≤70%	SFC 50/500, SAL 50, FP 500, or placebo; inhalation powder via DISKUS; BID; 24 weeks	[d]SFC 50/500: 165/113; SAL 50: 160/115; FP 500: 168/100; Placebo: 181/112	[d]445 M/229 F; 63.5 (40-90)	Mean change from Baseline at Endpoint in morning pre-dose FEV_1 and 2-hour post-dose FEV_1.

a. The study was conducted in 172 centers in the US, 132 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 57 centers in other regions (Australia, New Zealand, South Africa, Canada, Argentina, Brazil, Chile, Mexico).

b. Total enrollment represents the number of patients randomized (i.e., the Safety population).

c. Defined as a less than 10% increase in FEV_1 as a percentage of the predicted normal value, 30 minutes after inhalation of 400μg salbutamol/albuterol via MDI and VOLUMATIC/ELLIPSE spacer.

d. For Studies SCO30003 and SFCB3024, the number of patients represents the ITT population. For Study SFCA3006, the number of patients represents the ITT Population excluding Investigator 1403.

e. Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Lithuania, Netherlands, New Zealand, Norway, Poland, Russia, South Africa, Spain, Sweden, Switzerland, and United Kingdom.

f. Or FEV_1 ≤0.70L and >40% but still <65% of the predicted normal value according to Crapo et al. [Crapo, 1981].

2.2. Study Design

2.2.1. Study SCO30003

The primary objective of the SCO30003 study was to determine the effects on mortality of SFC 50/500 compared with placebo when added to usual COPD therapy (defined as any treatment, other than inhaled corticosteroids, inhaled long-acting bronchodilators, and long term oral corticosteroids).

GSK, in collaboration with an external steering committee, designed the 3-year study, SCO30003 (TORCH: TOwards a Revolution in COPD Health), based upon a *post-hoc* analysis of mortality rates from the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study. A reduced mortality rate in patients with COPD was suggested in those receiving FP compared with those receiving placebo during the 3-year ISOLDE study [Waterhouse, 1999]. Although the ISOLDE study was not designed to investigate mortality, the data provided the rationale on which to base a definitive mortality study. It was further hypothesised that co-administration of FP with salmeterol might have greater efficacy than FP alone. Following the initiation of TORCH, data from observational pharmaco-epidemiology studies were published supporting the hypothesis that LABA/ICS combination therapies may significantly reduce mortality in patients with COPD [Soriano, 2002; Soriano, 2003; Mapel, 2006].

Study SCO30003 was a multicenter, randomized, double-blind, parallel group, placebo-controlled study in 6,112 (the ITT efficacy population) patients with COPD treated for a period of 156 weeks (3 years). Patients were randomized in a 1:1:1:1 ratio to one of the following four treatment groups: SFC 50/500, SAL 50, FP 500, and placebo. Study treatments were provided as inhalation powders administered as one inhalation from the DISKUS device twice daily.

The study consisted of a 2-week run-in period, a 156-week (3-year) randomized treatment period (including follow-up if patients were prematurely withdrawn from treatment) and a 2-week follow-up period, and involved a total of 16 clinic visits. During the treatment period, clinic visits occurred at 12-weekly intervals. The 2-week follow-up period occurred after stopping double-blind treatment, regardless of when that occurred. All patients were followed for 156 weeks (3 years) following the initiation of treatment for assessment of survival, including those who prematurely discontinued study drug.

Patients were required to have an established clinical history of COPD according to the ERS Consensus Statement [Siafakas, 1995], be 40 to 80 years of age, and have a current or prior history of ≥10-pack years of cigarette smoking. Patients were required to have a baseline (pre-bronchodilator) FEV_1 <60% of predicted normal, poor reversibility of airflow obstruction (defined as an increase of <10% of the predicted normal FEV_1 value 30 minutes after inhalation of 400mcg salbutamol/albuterol), and an FEV_1/FVC ratio of ≤70%.

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. 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.

2.2.2. Study SFCB3024

Study SFCB3024 was a multicenter, randomized, double-blind, parallel-group, placebo-controlled trial in 1465 (the ITT efficacy population) patients with COPD treated for a period of 52 weeks. Patients were randomized in a 1:1:1:1 ratio to one of the following four treatment groups: SFC 50/500, SAL 50, FP 500, or placebo. Study treatments were provided as inhalation powders administered as one inhalation from the DISKUS device twice daily.

The study included a 2-week run-in period, a 12-month (52-week) treatment period and a 2-week follow-up period. The total study duration was 56 weeks (13 months) and involved 11 clinic visits (or 12 clinic visits if the run-in period was repeated). The 2-week follow-up period followed either completion of the treatment period or withdrawal from the study.

Patients were required to have an established clinical history of COPD according to the ERS Consensus Statement [Siafakas, 1995], be 40 to 79 years of age, have a current or prior history of ≥10-pack years of cigarette smoking, had a history of cough productive of sputum on most days for at least 3 months of the year, for at least 2 years. Patients were required to have a documented history of COPD exacerbations each year for the previous 3 years, including at least one exacerbation in the last year that required oral corticosteroids and/or antibiotics. Patients were required to have a baseline (pre-bronchodilator) FEV_1 of ≥25 to ≤70% of predicted normal, poor reversibility of airflow obstruction (defined as an increase of <10% of the predicted normal FEV_1 value 30 minutes after inhalation of 400mcg salbutamol), and an FEV_1/FVC ratio of ≤70%.

At entry into the run-in period, patients discontinued inhaled corticosteroids and long-acting inhaled bronchodilators. At the start of the run-in period, the patient's usual prn relief medication was replaced with inhaled salbutamol (provided by the Sponsor) for prn use throughout the trial. Patients who had any changes in COPD medication (other than prn use of salbutamol), received systemic corticosteroids or antibiotic therapy or were hospitalized for COPD/lower respiratory tract infection during the run-in period were excluded from entry into the treatment period.

2.2.3. Study SFCA3006

Study SFCA3006 was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study in 674 (the ITT efficacy population) patients with COPD treated for a period of 24 weeks. Patients were randomized in a 1:1:1:1 ratio to one of the following four treatment groups: SFC 50/500, SAL 50, FP 500, and placebo. Study treatments were provided as inhalation powders administered as one inhalation from the DISKUS device twice daily.

The study included a single-blind 2-week run-in period and a 24-week double-blind treatment period. The total study duration was 26 weeks and involved eleven treatment visits throughout the 6-month double-blind treatment period.

Patients had to meet the ATS definition of COPD [Gardner, 1988], be at least 40 years of age, have a current or prior history of ≥20-pack years of cigarette smoking, and have a history of cough productive of sputum on most days for at least 3 months of the year, for at least 2 years, that was not attributable to another disease process. Patients were required to have a baseline FEV_1 <65% of predicted normal, but >0.70L or FEV_1 ≤0.70L and >40% of predicted normal with an FEV_1/FVC ratio of ≤70%. Patients also had to achieve a score of ≥2 (moderate dyspnea) on the Modified Medical Research Council (MMRC) Dyspnea Scale [ATS News, 1982] at Screening and have minimal symptoms of chronic bronchitis (morning cough and sputum) at Baseline.

At entry into the run-in period, patients discontinued inhaled corticosteroids and long-acting inhaled bronchodilators. At the start of the run-in period, the patient's usual prn relief medication was replaced with inhaled albuterol (provided by the Sponsor) for use throughout the trial. During the 2-week, single-blind, run-in period, patients received placebo via the DISKUS twice daily and prn albuterol.

2.3. Efficacy Measures

The key efficacy parameters are displayed in Table 2 and are described in the following sections.

Table 2 Key Efficacy Assessments in Studies SCO30003, SFCB3024, and SFCA3006

Efficacy Measures	SCO30003	SFCB3024	SFCA3006
Mortality	X		
Exacerbations	X	X	
Health Outcomes	X	X	X
FEV1	X	X	X

2.3.1. Mortality

The primary endpoint was all-cause mortality at 156 weeks after treatment started for each patient regardless of the time on treatment. This endpoint was only prospectively studied in SCO30003.

2.3.1.1. Assignment of Cause of Death

Accurate assignment of the cause of death was essential and was conducted centrally by an independent Clinical Endpoint Committee (CEC). The CEC was comprised of independent physicians with relevant expertise and was responsible for categorising the primary cause of death for all patients who died during the study by reviewing all available information in a blinded fashion. This ensured consistency in cause of death

assignment between the study centres. 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. Cause of death was assigned by the CEC to a set of pre-determined categories: cardiovascular, pulmonary, cancer related, other, or unknown. In addition, the CEC assessed whether each death was COPD-related, which included those cases where it was judged that the patient would not have died were it not for the existence of COPD.

2.3.2. Moderate & Severe COPD Exacerbations

In Studies SCO30003, SFCB3024, and SFCA3006, COPD exacerbations were those events where worsening COPD symptoms were serious enough to require intervention as determined and assessed by the study investigator. Severity of COPD exacerbation was specified per protocol (Table 3).

Table 3 Definition of Moderate and Severe COPD Exacerbations

Protocol No.	Moderate Exacerbation	Severe Exacerbation
SCO30003	Patients who experienced worsening COPD symptoms were told to contact the investigator or primary care physician immediately and report to the clinic as soon as possible if there was no satisfactory relief despite increased salbutamol/albuterol (or other relief medication) usage. Moderate exacerbations were those exacerbations treated with systemic corticosteroids and/or antibiotics.	Required hospitalization for treatment
SFCB3024	Required 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.	Required emergency hospital treatment
SFCA3006	Required, per investigator judgment, either oral antibiotics and/or oral or inhaled corticosteroids. Additionally, a patient was considered to have a moderate exacerbation if he/she experienced an AE related to a respiratory/airway infection (e.g., cold, flu, upper respiratory tract infection [URTI], lower respiratory infection [LRI]) where antibiotics or corticosteroids were administered.	Required inpatient admission for treatment

Study SFCA3006 evaluated COPD exacerbations; however, patients were required to withdraw from the study if the exacerbation required oral corticosteroid, hospitalization, or if a patient experienced three exacerbations requiring antibiotics. Due to this study design requirement and the relatively short study duration (6-months), the analyses of

moderate/severe COPD exacerbations from Study SFC3006 should be interpreted with caution.

2.3.3. Health Status

Study SCO30003, Study SFCB3024, and Study SFCA3006 all assessed the effect of SFC 50/500 on improving the quality of life in patients with COPD.

Health-related quality of life was analyzed with the St George's Respiratory Questionnaire (SGRQ) in Studies SCO30003 and SFCB3024 in those countries where a validated translation was available. The SGRQ [Jones, 1991] is a disease-specific patient completed questionnaire designed to measure the impact of respiratory disease and its treatment on the patient's health-related quality of life. As well as producing a total score, it is also possible to calculate scores for the individual domains of symptoms, activity and impacts. It has been used widely in studies of COPD patients and has been translated and validated for use in most major languages. Research has demonstrated that it is sensitive to change and interpretation of the results has been enhanced by determination of the score change necessary to achieve a clinically meaningful improvement in quality of life [Jones, 1991]. A decreased score on the SGRQ indicates an improvement in health-related quality of life, and an increased score indicates a poorer quality of life. A decrease of 4 points is currently considered the minimal important difference (MID) in this instrument.

Health-related quality of life was assessed in Study SFCA3006 using the Chronic Respiratory Disease Questionnaire (CRQ). The CRQ is an interviewer-administered disease-specific questionnaire designed to measure the impact of chronic respiratory disease and its treatments on the patient's health-related quality of life [Guyatt, 1987]. It is a 20-item questionnaire that evaluates quality of life across four domains: dyspnea (5 items), fatigue (4 items), emotional function (7 items) and mastery over the disease (4 items). For the dyspnea domain, at first administration the patient is asked to provide five specific activities that they perform regularly and which have been limited by the disease. These individualized activities were also used to evaluate the patient's dyspnea at subsequent visits. The responses to the 20 items were combined to provide an overall assessment of quality of life, as well as physical (sum of dyspnea and fatigue scores) and emotional (sum of emotional function and mastery over the disease scores) summary measures and scores for the individual domains. An increased score on the CRQ indicates an improvement in health-related quality of life, and a decreased score indicates a decline in quality of life. An improvement of at least 10 in Overall score is considered the MID in this instrument.

2.3.4. Pulmonary Function

In Study SFCB3024, pre-bronchodilator FEV_1 was the primary endpoint and post-bronchodilator FEV_1 was an additional endpoint. At each clinic visit, 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.

In Study SFCA3006, both pre-dose FEV_1 and 2-hour post-dose FEV_1 were primary endpoints conducted at each clinic visit.

In Study SCO30003, post-bronchodilator FEV_1 was conducted 30 minutes after inhalation of 400μg salbutamol via MDI and VOLUMATIC/ELLIPSE spacer at Visit 2 and at 24 weekly intervals thereafter (Visits 4, 6, 8, 10, 12 and 15) and also at Visit 16.

2.4. Safety Measures

Safety data are presented from the three pivotal studies (SCO30003, SFCB3024, SFCA3006) in this Briefing Document with the predominant focus being on the results from Study SCO30003 due to its size and duration.

2.5. Statistical Methods

2.5.1. Analysis Populations

The **Intent-to-Treat - Efficacy (ITT) Population** consisted of all patients who were randomized to treatment and received as least one dose of study medication, with the exception of patients recruited at sites that were closed as the result of audit findings or other information that indicated noncompliance with GCP. In Study SCO30003, a total of 72 patients from 5 sites were excluded, in SFCA3006, a total of 17 patients from 1 site were excluded, and in SFCB3024, a total of 4 patients from 4 sites were excluded on this basis. The ITT population was used for efficacy analyses.

The **Safety Population** consisted of all patients who were randomized to treatment and who received at least one dose of trial medication. This population used data from the excluded sites described above. The Safety Population was used for analyses of safety data.

The **Health Outcomes Population** was a subset of the ITT Population from SCO30003, and consisted of patients participating in countries where translations of the SGRQ questionnaire were considered to be linguistically valid for the population and who completed at least one questionnaire. For SFCB3024 and SFCA3006, the ITT Population was used for the Health Outcomes population. The Health Outcomes Population was used for Health Outcomes analyses.

The **Ophthalmic and Skeletal Safety Population** was a subset of the Safety Population from SCO30003 and consisted of patients from the selected US centres where measurements were made of bone mineral density and ophthalmic examinations were conducted.

2.5.2. Mortality - Study SCO30003

The primary efficacy endpoint in Study SCO30003 was time to all-cause mortality at 3 years (i.e., 156 weeks). The primary analysis used the log-rank test, stratified by

smoking status. The pre-specified primary treatment comparison was SFC 50/500 vs. placebo.

There were two planned interim analyses for efficacy which were undertaken by an independent Safety and Efficacy Data Monitoring Committee (SEDMC). The Steering Committee and sponsor (GSK) remained blinded. The SEDMC recommended continuing the study on both occasions and no changes were made to the study as a result of these interim analyses.

The statistical approach described by Whitehead [Whitehead, 1999] was used in the design of the study to account for these interim analyses. The stopping rules for the interim analysis corresponded to the alpha-spending approach [Lan, 1983] with an O'Brien-Fleming stopping rule [O'Brien, 1979]. Because of the interim analyses, the final significance level needed to be more stringent than 0.05. Thus the adjusted p-value and the median unbiased estimate of the hazard ratio for the final analysis were calculated taking into account the previous interim analyses using discrete stage-wise ordering as described by Tsiatis, Rosner and Mehta [Tsiatis, 1984]. These adjustments were applied to the primary comparison of SFC 50/500 vs. placebo.

This analysis used the actual survival status of patients at 156 weeks regardless of whether they withdrew from the study before this time. Once withdrawn from the study, patients could have taken any medications prescribed by their physicians. One patient whose survival status was unknown at 156 weeks was included as censored at the timepoint at which the patient was last known to be alive.

A pre-specified supportive analysis of time to all-cause mortality at 3 years was performed using a Cox proportional hazards model, using covariates of treatment group, smoking status, age, sex, baseline FEV_1, BMI and region.

A log-rank test, stratified by country and participation in the Ophthalmic and Skeletal Safety sub-study in addition to smoking status was also produced as a supportive analysis in order to more fully account for the stratified nature of the randomization. This analysis was pre-specified prior to the unblinding of the study following a request from the FDA.

The primary endpoint of all-cause mortality was supported by the tertiary endpoints of time to COPD-related mortality and time to on-treatment mortality. These were analysed as for the primary endpoint using the log-rank test stratified by smoking status.

The primary cause of death and whether the death was COPD-related was determined by the CEC. Because of the issue of competing risks of death [Gooley, 1999; Satagopan 2004], survival estimates for time to COPD related death are presented as cumulative incidence curves rather than Kaplan-Meier estimates.

An on-treatment death was defined as any death occurring on or after the treatment start date and up to and including 14 days after the cessation of treatment. Patients who discontinued treatment were included as censored observations at the time of treatment discontinuation.

2.5.3. Moderate & Severe COPD Exacerbations

For Studies SCO30003, SFCB3024 and SFCA3006, a moderate/ severe exacerbation was defined as one requiring treatment with systemic corticosteroids or antibiotics or requiring hospitalization.

For Study SCO30003, the pre-specified analysis of rate of moderate/severe exacerbations used a generalized linear model. Specifically, the number of these exacerbations occurring during the treatment period was assumed to follow the negative binomial distribution [Agresti, 2002; Metcalfe, 2006]; this distribution assumes that, for each individual, exacerbations follow a Poisson process and that the rates for each patient follow a gamma distribution. The model included covariates of smoking status, age, sex, region, baseline FEV_1, BMI and previous exacerbation history, with time on treatment as an offset.

The original analysis of SFCB3024 used a Poisson model for exacerbations. However, the negative binomial model has the advantage over the simpler Poisson model in that the variability between patients is explicitly incorporated into the model. Analysis of exacerbations for SFCB3024 is therefore presented here using the negative binomial model for rates of moderate and severe exacerbations; conclusions from the two analyses are similar. Covariates in the analysis of SFCB3024 were smoking status, age, sex, center amalgamation, and baseline FEV_1.

The negative binomial analysis of COPD exacerbations described above for Study SCO30003 and Study SFCB3024 was repeated for Study SFCA3006 with age and Baseline FEV_1 as covariates included in the model. Rate analysis was not pre-defined for the SFCA3006 study but is provided for completeness. Caution should be used in interpreting the exacerbation data from Study SFCA3006 due to design limitations mentioned in Section 2.3.2.

Other exacerbation endpoints included rate of severe exacerbations and rate of moderate and/or severe exacerbations requiring treatment with systemic corticosteroids. Analyses of these endpoints used the negative binomial distribution as above.

2.5.4. Health Outcomes

2.5.4.1. Study SCO30003

Change from baseline in SGRQ total score was analyzed using a repeated measures analysis and included patients with a baseline SGRQ total Score and at least one on-treatment SGRQ total score. 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, baseline SGRQ total score and treatment by visit interactions were also fitted as categorical variables, patient was fitted as a random effect and the variance-covariance matrix was assumed to be unstructured. The change from baseline averaged over 3 years was of primary interest.

2.5.4.2. Study SFCB3024

Change from baseline in SGRQ total score was analyzed using a repeated measures analysis and included patients with a baseline SGRQ total Score and at least one on-treatment SGRQ total score. Treatment group was fitted as the explanatory variable, and smoking status, sex, center amalgamation, age and Baseline SGRQ total score were fitted as covariates. Visit was fitted as a categorical variable and the variance-covariance matrix was assumed to be unstructured. The change from baseline averaged over 52 weeks was of primary interest.

2.5.4.3. Study SFCA3006

Change from baseline in endpoint CRQ overall score was compared between treatment groups using ANCOVA. Treatment group was fitted as the explanatory variable, and investigator and baseline CRQ overall score were fitted as covariates. Endpoint CRQ overall score was defined as the final measurement for the patient.

2.5.5. Pulmonary Function

In Study SCO30003, post-bronchodilator FEV_1 was a tertiary efficacy endpoint. In Study SFCB3024, pre-bronchodilator FEV_1 was the primary efficacy endpoint and post-bronchodilator FEV_1 was an additional efficacy endpoint. In Study SFCA3006, both pre-dose FEV_1 and 2-hour post-dose FEV_1 were primary efficacy endpoints.

2.5.5.1. Study SCO30003

FEV_1 change from baseline was compared between treatment groups, using a mixed models repeated measures analysis. The analysis included patients with a baseline FEV_1 and at least one on-treatment FEV_1. Treatment group was fitted as the explanatory variable, and smoking status, age, sex, baseline FEV_1, BMI and region were fitted as covariates. Visit, baseline FEV_1 by visit, and treatment by visit interactions were also fitted as categorical variables, patient was fitted as a random effect and the variance-covariance matrix was assumed to be unstructured. The change from baseline averaged over 3 years was of primary interest.

2.5.5.2. Study SFCB3024

FEV_1 change from baseline 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. Treatment group was fitted as the explanatory variable, and smoking status, age, sex, center amalgamation and baseline FEV_1 were fitted as covariates. Visit was fitted as a categorical variable, and the variance-covariance matrix was assumed to be unstructured. The change from baseline averaged over 52 weeks was of primary interest.

2.5.5.3. Study SFCA3006

Change from baseline in endpoint FEV_1 was compared between treatment groups using analysis of covariance. Treatment group was fitted as the explanatory variable, and center and baseline FEV_1 were fitted as covariates. Endpoint FEV_1 was defined as the final evaluable on-treatment measurement for the patient.

2.5.6. Safety Analyses

Adverse events were summarised using the percentage of patients experiencing an event, and also the rate of AEs per 1000 treatment years. This was calculated by dividing the total number of events by the total treatment exposure in years, and multiplying by 1000.

Adverse events in the following event categories were considered to be adverse events of special interest: pneumonias, bone disorders, eye disorders and HPA axis disorders. Time to first pneumonia event, time to first bone disorder, and time to first eye disorder were compared between treatment groups using the log-rank test, stratified by smoking status. There were insufficient patients with HPA axis disorders to warrant a time to first analysis.

Measurements of serum cortisol were summarised by calculating the area under the response-time curve for 12 hours after dosing (AUC_{12}), using the linear trapezoidal area method and by the minimum concentration over the sampling interval, C_{min}. Analysis of variance was used to compare among treatments after log transformation. The difference in least square means and the 95% confidence interval were back transformed (i.e., exponential transformation) for expression as a percentage or ratio. Measurement of 24-hour urinary cortisol from Study SFCB3024 were also analysed after log transformation using analysis of covariance with covariates of smoking status, age, sex, center amalgamation and baseline.

Bone Mineral Density (BMD) measured at the total hip and BMD measured at the lumbar spine was analyzed separately after log transformation. The analysis was also repeated using untransformed data. BMD change from baseline was compared between treatment groups, using a mixed models repeated measures analysis. The analysis included patients with a baseline BMD and at least one on-treatment BMD. Treatment group was fitted as the explanatory variable, and smoking status, age, sex, log baseline BMD, BMI and baseline BMD therapy were fitted as covariates. Visit, baseline FEV_1 by visit, and treatment by visit interactions were also fitted as categorical variables, patient was fitted as a random effect and the variance-covariance matrix was assumed to be unstructured. Treatment effects were estimated at each visit. An analysis of covariance for measurements at each visit was also conducted as a supportive analysis using covariates as above.

3. STUDY POPULATION OF PIVOTAL CLINICAL STUDIES

3.1. Patient Accountability

Overall, the reasons for withdrawal were similar across the three studies (SCO30003, SFCB3024, and SFCA3006). The most common reason for withdrawal was adverse event and the proportion of patients withdrawing due to adverse events was higher in the placebo treatment group than in the SFC 50/500 treatment group. More patients in the placebo treatment group withdrew due to lack of efficacy than in the SFC 50/500 treatment group across all three studies.

In Study SCO30003, regardless of whether patients withdrew, survival status was assessed up to 156 weeks after the start of study treatment. Complete survival status data for 6,111 patients have been included in the mortality analyses. Survival status was unknown for only 1 patient who was censored at 2 years at which time the patient was known to be alive.

A summary of patient disposition in Study SCO30003, SFCB3024, and SFCA3006 are presented in Table 4, Table 5, and Table 6, respectively.

Table 4 Patient Accountability – Study SCO30003

	Placebo (N=1524) n (%)	SAL 50 (N=1521) n (%)	FP 500 (N=1534) n (%)	SFC 50/500 (N=1533) n (%)
Completed	851 (56)	960 (63)	947 (62)	1011 (66)
Withdrawn prior to Week 156	663 (44)	554 (36)	584 (38)	517 (34)
Withdrawn after Week 156	10 (<1)	7 (<1)	3 (<1)	5 (<1)
Reason for withdrawal prior to Week 156:				
Adverse event	363 (24)	301 (20)	360 (23)	287 (19)
Consent withdrawn	135 (9)	132 (9)	115 (7)	118 (8)
Lost to follow-up	18 (1)	13 (<1)	24 (2)	27 (2)
Lack of efficacy	102 (7)	63 (4)	45 (3)	33 (2)
Did not fulfill entry criteria	4 (<1)	2 (<1)	4 (<1)	3 (<1)
Non-compliance	18 (1)	17 (1)	16 (1)	20 (1)
Other	23 (2)	26 (2)	20 (1)	29 (2)

Note: These are reasons for withdrawal from double blind treatment phase and does not prevent determining survival status at 3 years.

Table 5 Patient Accountability – Study SFCB3024

	Placebo (N=361) n (%)	SAL 50 (N=372) n (%)	FP 500 (N=374) n (%)	SFC 50/500 (N=358) n (%)
Completed	221 (61)	253 (68)	266 (71)	269 (75)
Withdrawn after randomization	140 (39)	119 (32)	108 (29)	89 (25)
Reason for withdrawal:				
Adverse event	68 (19)	61 (16)	55 (15)	46 (13)
Consent withdrawn	16 (4)	13 (3)	11 (3)	6 (2)
Lost to follow-up	6 (2)	8 (2)	8 (2)	8 (2)
Lack of efficacy	18 (5)	5 (1)	7 (2)	2 (<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	12 (3)	11 (3)	8 (2)	6 (2)

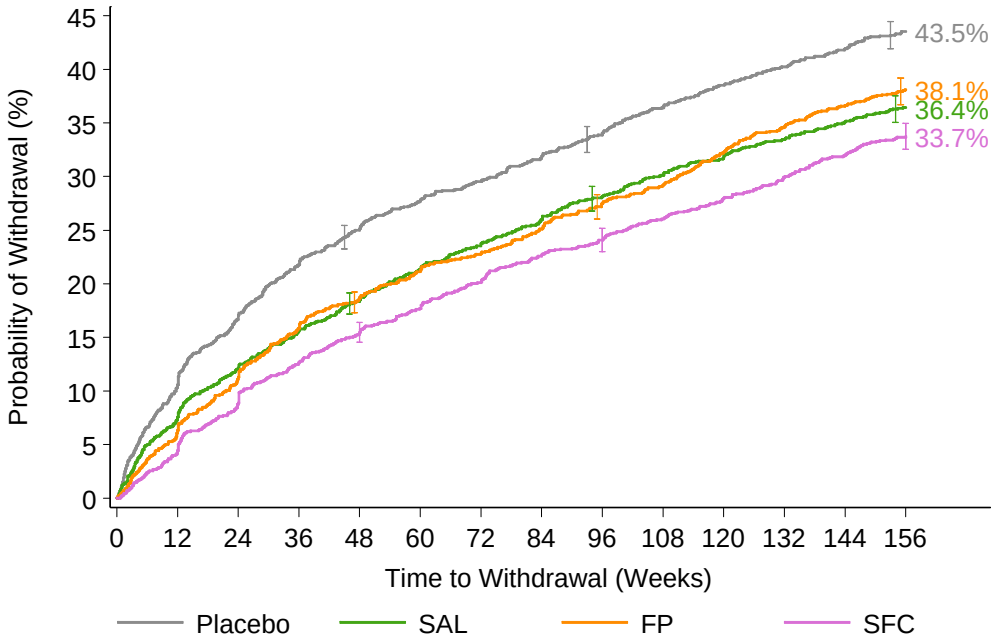
Table 6 Patient Accountability – Study SFCA3006

	Placebo (N=181) n (%)	SAL 50 (N=160) n (%)	FP 500 (N=168) n (%)	SFC 50/500 (N=165) n (%)
Completed	112 (62)	115 (72)	100 (60)	113 (68)
Withdrawn	69 (38)	45 (28)	68 (40)	52 (32)
Reason for withdrawal:				
Adverse event	17 (25)	11 (24)	21 (31)	11 (21)
Consent withdrawn	11 (16)	4 (9)	5 (7)	10 (19)
Lost to follow-up	2 (3)	1 (2)	3 (4)	1 (2)
Lack of efficacy	11 (16)	7 (16)	3 (4)	3 (6)
COPD Exacerbation	16 (23)	9 (20)	17 (25)	14 (27)
Protocol violation	8 (12)	10 (22)	14 (21)	8 (15)
Other	4 (6)	3 (7)	5 (7)	5 (10)

The differential withdrawal rates between placebo- and SFC 50/500-treated patients were noteworthy in Study SCO30003 (44% of placebo-treated patients withdrew by Week 156 compared with 34% of SFC 50/500-treated patients) and SFCB3024 (39% of placebo-treated patients withdrew compared with 25% of SFC 50/500-treated patients).

Figure 1 presents the cumulative incidence curve for premature study drug discontinuations in Study SCO30003.

Figure 1 Time to Premature Study Drug Discontinuation - Cumulative Incidence Curve – Study SCO30003



Note: Vertical bars represent standard error.

This differential withdrawal is particularly important when considering the primary and secondary efficacy results for Study SCO30003.

- Primary efficacy outcome: After withdrawal, patients could have switched to any COPD therapy but were still included in the primary endpoint analysis, based upon the treatment to which they were randomized. Consequently, patients withdrawn from placebo could have been receiving active treatment (including SFC) for a significant period of the study. This may have reduced the apparent treatment effect for the primary outcome.
- Secondary efficacy outcomes: Previous studies in patients with COPD have demonstrated that withdrawal may not be random but biased towards patients randomised to placebo and patients with worse health at baseline [Jones, 2003; Calverley, 2003c]. This was also seen in Study SCO30003 where higher withdrawal rates in the placebo group and in patients with worse baseline health status and lung function meant that, over time, patients who remain in the study and continue to contribute to the secondary endpoint analyses in the placebo group had better baseline disease severity than the active treatment groups.

Despite the fact that approximately 99% of patients were receiving usual COPD care (excluding ICS, inhaled long-acting bronchodilators and long-term oral corticosteroids), there was a significant difference in withdrawal between placebo and active treatments favoring SFC 50/500. After withdrawal, patients could switch to any COPD therapy but were still assessed for survival status at 3 years post-randomisation.

3.2. Demographic and Baseline Characteristics

Overall, the demographic characteristics of patients were similar across the three studies (SCO30003, SFCB3024, and SFCA3006) with the exception of race in Study SCO30003. This latter study included approximately 12% of patients reporting their race as Asian versus ≤1% from both Studies SFCB3024 and SFCA3006. Eighty-two percent (82%) to 99% of patients across the treatment groups were White. The majority of patients were male (61% to 76%). The average age ranged from 62 to 65 years, the average BMI ranged from 25kg/m^2 to 27kg/m^2, and the proportion of patients who were former smokers ranged from 46% to 57%.

A summary of the demographic characteristics of patients in Study SCO30003, SFCB3024, and SFCA3006 are presented in Table 7.

Table 7 Demographic Characteristics

	SCO30003 (3 years duration)				SFCB3024 (52 weeks duration)				SFCA3006 (24 weeks duration)			
	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	SFC 50/500 (N=1533)	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	SFC 50/500 (N=358)	Placebo (N=181)	SAL 50 (N=160)	FP 500 (N=168)	SFC 50/500 (N=165)
Age, years												
n	1524	1521	1534	1533	361	372	374	358	181	160	168	165
Mean ± SD	65 ± 8	65 ± 8	65 ± 8	65 ± 8	63 ± 9	63 ± 9	64 ± 9	63 ± 9	64 ± 8	64 ± 9	64 ± 9	62 ± 9
Median (range)	66.0 (40 – 85)	66.0 (40 – 86)	66.0 (40 – 82)	66.0 (40 – 80)	64.0 (40 - 79)	64.0 (38 – 79)	64.0 (40 – 79)	63.5 (40 – 78)	64.0 (44 – 90)	64.0 (40 – 84)	65.5 (42 – 82)	62.0 (40 – 86)
Age Group, n (%)												
<65 years	671 (44)	660 (43)	677 (44)	665 (43)	184 (51)	196 (53)	190 (51)	193 (54)	91 (50)	81 (51)	76 (45)	98 (59)
65 - 74 years	669 (44)	670 (44)	648 (42)	683 (45)	143 (40)	144 (39)	140 (37)	138 (39)	72 (40)	61 (38)	67 (40)	56 (34)
≥75 years	184 (12)	191 (13)	209 (14)	185 (12)	34 (9)	32 (9)	44 (12)	27 (8)	18 (10)	18 (11)	25 (15)	11 (7)
Sex, n (%)												
Female	361 (24)	361 (24)	377 (25)	382 (25)	92 (25)	111 (30)	114 (30)	88 (25)	45 (25)	57 (36)	65 (39)	62 (38)
Male	1163 (76)	1160 (76)	1157 (75)	1151 (75)	269 (75)	261 (70)	260 (70)	270 (75)	136 (75)	103 (64)	103 (61)	103 (62)
Race, n (%)												
White	1249 (82)	1250 (82)	1253 (82)	1254 (82)	358 (99)	366 (98)	370 (99)	355 (99)	166 (92)	152 (95)	156 (93)	156 (95)
Black	25 (2)	20 (1)	24 (2)	26 (2)	0	0	1 (<1)	0	11 (6)	6 (4)	8 (5)	7 (4)
Asian	190 (12)	192 (13)	196 (13)	191 (12)	2 (<1)	0	2 (<1)	3 (<1)	3 (2)	1 (<1)	2 (1)	2 (1)
American Hispanic	50 (3)	45 (3)	48 (3)	50 (3)	0	1 (<1)	0	0	Not collected	Not collected	Not collected	Not collected
Other	10 (<1)	14 (<1)	13 (<1)	12 (<1)	1 (<1)	5 (1)	1 (<1)	0	1 (<1)	1 (<1)	2 (1)	0
BMI, kg/m^2												
n	1524	1521	1534	1533	361	372	374	358	181	160	168	165
Mean ± SD	25 ± 5	25 ± 5	25 ± 5	25 ± 5	26 ± 4	26 ± 5	26 ± 4	26 ± 5	27 ± 6	27 ± 7	26 ± 5	27 ± 5
BMI Group, n (%)												
<20kg/m^2	199 (13)	206 (14)	194 (13)	225 (15)	37 (10)	31 (8)	33 (9)	26 (7)	11 (6)	20 (13)	13 (8)	10 (6)
20 - <25kg/m^2	574 (38)	576 (38)	580 (38)	571 (37)	143 (40)	133 (36)	124 (33)	153 (43)	48 (27)	46 (29)	62 (37)	53 (32)
25 - <29kg/m^2	409 (27)	406 (27)	422 (28)	405 (26)	110 (30)	114 (31)	141 (38)	108 (30)	61 (34)	46 (29)	53 (32)	46 (28)
≥29kg/m^2	342 (22)	333 (22)	338 (22)	332 (22)	71 (20)	94 (25)	76 (20)	71 (20)	61 (34)	48 (30)	40 (24)	56 (34)

	SCO30003 (3 years duration)				SFCB3024 (52 weeks duration)				SFCA3006 (24 weeks duration)			
	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	SFC 50/500 (N=1533)	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	SFC 50/500 (N=358)	Placebo (N=181)	SAL 50 (N=160)	FP 500 (N=168)	SFC 50/500 (N=165)
Smoking Status, n (%)												
Former	866 (57)	870 (57)	873 (57)	873 (57)	190 (53)	181 (49)	176 (47)	172 (48)	84 (46)	86 (54)	91 (54)	89 (54)
Current	658 (43)	651 (43)	661 (43)	660 (43)	171 (47)	191 (51)	198 (53)	186 (52)	97 (54)	74 (46)	77 (46)	76 (46)

3.2.1. Baseline Pulmonary Function

Table 8 presents the baseline mean percent predicted FEV_1 values for each of the three pivotal studies (SCO30003, SFCB3024, and SFCA3006). The patients in these studies encompass GOLD stages II-IV [Global Initiative for Chronic Obstructive Lung Disease, 2006].

Table 8 Baseline Percent Predicted FEV_1

	Placebo	SAL 50	FP 500	SFC 50/500
SCO30003 % Predicted Post-Bronchodilator FEV_1				
n Mean ± SD Median (range)	1524 44 ± 13 44 (11 - 103)	1521 44 ± 13 44 (12 - 96)	1534 45 ± 13 45 (12 - 95)	1533 45 ± 14 44 (12 - 156)
SFCB3024 % Predicted Pre-Bronchodilator FEV_1				
n Mean ± SD Median (range)	361 48 ± 14 47 (16 – 86)	371 48 ± 14 47 (20 – 84)	374 49 ± 14 47 (18 – 84)	354 49 ± 15 47 (22 – 94)
SFCA3006 % Predicted Pre-Dose FEV_1				
n Mean ± SD Median (range)	181 40 ± 13 39 (17 – 82)	159 39 ± 13 38 (15 – 74)	166 39 ± 12 39 (15 – 71)	162 40 ± 14 38 (13 – 95)

Table 9 presents the mean reversibility as a percent of predicted pre-bronchodilator FEV_1 and as a percent of pre-bronchodilator FEV_1 for the three primary studies.

Table 9 Mean Baseline Reversibility

	Percent Reversibility based on predicted normal FEV_1[1] Mean ± SD	Percent Reversibility by ATS Definition[2] Mean ± SD
SCO30003	3.7 ± 3.7	10.2 ± 11.0
SFCB3024	3.5 ± 4.3	8.3 ± 10.2
SFCA3006	7.7 ± 5.7	20.1 ± 15.3

1. 100 * (post-bronchodilator FEV1 – pre-bronchodilator FEV1) / predicted normal FEV1. All predicted normal values were taken from the European Community for Coal and Steel (ECCS) tables [Quanjer, 1993].
2. 100 * (post-bronchodilator FEV1 – pre-bronchodilator FEV1) / pre-bronchodilator FEV1.

The entry criteria for Studies SCO30003 and SFCB3024 required patients to be poorly reversible as defined by change in FEV_1 <10% of predicted normal FEV_1 ; however, poor reversibility was not an entry criterion in Study SFCA3006. Based on the ATS definition of reversibility (bronchodilator response of 200ml and ≥12% improvement in FEV1 over baseline of the study population), 44% to 49% of patients were non-reversible in Study SFCA3006 compared with 81% to 83% of patients in Study SCO30003 and 82% to 84% of patients in Study SFCB3024. These differential entry criteria must be considered when pulmonary function characteristics are compared across the studies. However, it is worth noting that approximately 73% of patients in Study SFCA3006 would be

considered poorly reversible when using the same definition applied in the other 2 studies (i.e., an increase in percent predicted FEV_1 of <10%, 30 minutes after inhalation of 400μg salbutamol).

4. EFFICACY RESULTS

4.1. Mortality

Improving survival in patients with COPD is currently one of the greatest unmet needs for patients with this disease. To date, smoking cessation, long-term oxygen therapy (LTOT) in patients with hypoxemia, and lung reduction surgery for selected patients with emphysema have been the only interventions shown to improve survival.

Study SCO30003 is the first study to prospectively investigate the effects of pharmacotherapy on all-cause mortality in patients with COPD. All cause mortality was selected a priori as the primary endpoint in this study as defining a patient's precise cause of death is difficult and patient to investigator bias. A precedent has been set for this approach in previous congestive heart failure and acute myocardial infarction mortality studies. COPD-related mortality (as determined by the Clinical Endpoints Committee) was also analyzed to ensure that any effect seen on all-cause mortality was supported by a trend in events related to COPD and not unrelated events. Finally, on-treatment mortality was analyzed as an additional supportive analysis in order to ensure the data demonstrated the same trend of effects from the all-cause mortality. An on-treatment death was defined as any death occurring on or after the treatment start date and up to and including 14 days after the cessation of treatment.

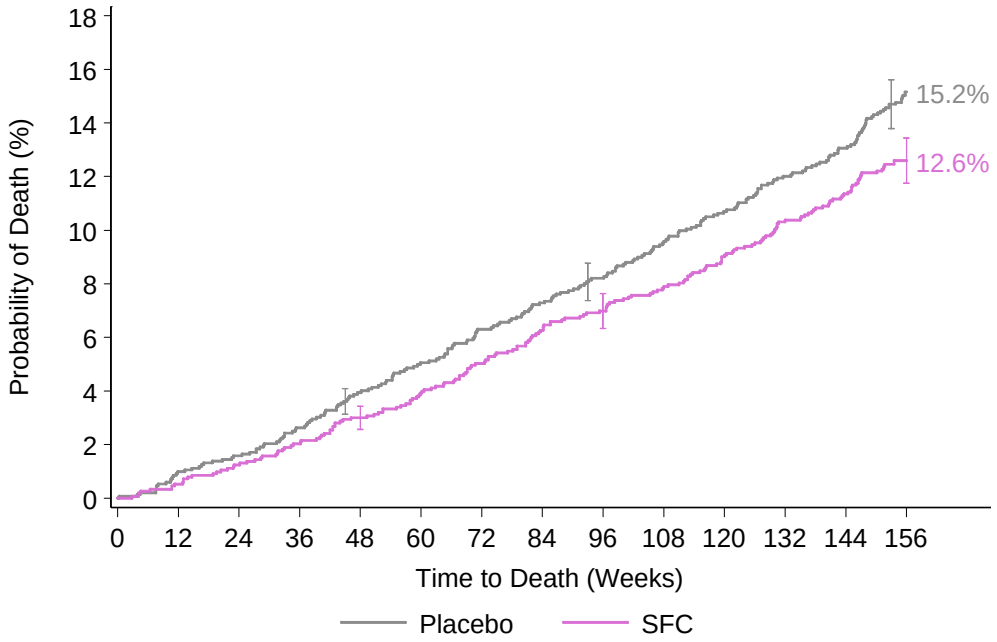
4.1.1. All-Cause Mortality

Study SCO30003 was prospectively designed to assess mortality. The primary endpoint was all-cause mortality among all patients in the ITT Population within 3 years after the initiation of study treatment. The primary objective was to demonstrate a significant reduction in all-cause mortality in COPD patients treated with SFC 50/500 compared with placebo, when added to usual COPD therapy.

Regardless of whether patients withdrew, survival status was assessed up to 156 weeks after the start of study treatment. Complete survival status data for 6,111 patients have been included in the mortality analyses. Survival status was unknown for only 1 patient who was censored at 2 years at which time the patient was known to be alive.

A total of 875 deaths occurred in the ITT Population within 3 years after the initiation of treatment. A summary of the time to death from all causes for placebo vs. SFC 50/500 within 3 years of treatment initiation in Study SCO30003 is shown graphically in Figure 2.

Figure 2 **Time to All-Cause Mortality for Placebo and SFC 50/500 - Cumulative Incidence Curve – Study SCO30003**



Note: Vertical bars represent standard error.

The withdrawal rates presented in Section 3.1, Figure 1 could have led to an underestimate of the primary efficacy outcome of all-cause mortality. After withdrawal, patients could have switched to any COPD therapy but were still included in the primary endpoint analysis, based upon the treatment to which they were randomized, on an intent-to-treat basis. Consequently, patients withdrawn from placebo could have been receiving active treatment (including ADVAIR) for a significant period of the study. This may have reduced the apparent treatment effect for the primary outcome.

The log-rank analysis of time to all-cause mortality at 3 years stratified by smoking status for the primary comparison of SFC 50/500 vs. placebo for patients in Study SCO30003 is presented in Table 10.

Table 10 Time to All-Cause Mortality for SFC 50/500 vs. Placebo - Log-rank Analysis – Study SCO30003

	Placebo (N=1524)	SFC 50/500 (N=1533)
Number of Deaths, n (%)	231 (15.2)	193 (12.6)
Number Censored, n (%)	0	1 (<1)
Number Alive, n (%)	1293 (84.8)	1339 (87.3)
Probability of Death by 156 weeks (%)[a] (95% CI)	15.2 (13.4, 17.0)	12.6 (10.9, 14.3)
SFC 50/500 vs. Placebo:		
Adjusted Hazard Ratio (95% CI)[b]	0.825 (0.681, 1.002)	
Adjusted p-value [b]	0.052	
Unadjusted Hazard Ratio (95% CI)	0.820 (0.677, 0.993)	
Unadjusted p-value	0.041	
Adjusted Significance Level [c]	0.040	

Note: Log-rank test stratified by smoking status

a. Kaplan-Meier Estimate.

b. Adjusted for the planned interim analyses.

c. Adjusted for the planned interim analyses. Significance level to which unadjusted p-value should be compared.

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 SFC 50/500. The unadjusted hazard ratio for time to all-cause mortality for SFC 50/500 vs. placebo was 0.820 (95% CI: 0.677, 0.993) and the unadjusted p-value was 0.041. Due to the interim analyses, this unadjusted p-value needs to be compared to a significance level of 0.04. To allow comparison to the commonly used significance level of 0.05, the hazard ratio and the p-value were adjusted. The adjusted hazard ratio for SFC 50/500 vs. placebo was 0.825 (95% CI: 0.681, 1.002), representing a 17.5% reduction in the risk of dying at any time within 3 years for SFC 50/500 compared with placebo. The log-rank p-value adjusted for the interim analyses was 0.052. There was an absolute risk reduction of 2.6% for SFC 50/500 compared with placebo, which equates to a 3-year NNT (number needed to treat) of 39 to prevent one death.

Similar reductions in all-cause mortality for SFC 50/500 compared with placebo were observed in two supporting analyses; 1) a log-rank analysis stratified by smoking status, country and participation in the Ophthalmic and Skeletal Safety (OSS) sub-study (Table 11), and 2) Cox proportional hazards analysis adjusted for smoking status, age, sex, region, Baseline FEV_1 and BMI (Table 12).

Table 11 presents the log-rank analysis of time to all-cause mortality at 3 years for SFC 50/500 vs. placebo.

Table 11 Time to All-Cause Mortality for SFC 50/500 vs. Placebo Log-rank Analysis – Study SCO30003

	Placebo (N=1524)	SFC 50/500 (N=1533)
Number of Deaths, n (%)	231 (15.2)	193 (12.6)
Probability of Death by 156 weeks (%)[a] (95% CI)	15.2 (13.4, 17.0)	12.6 (10.9, 14.3)
SFC 50/500 vs. Placebo: Hazard Ratio (95% CI) p-value	0.815 (0.673, 0.987) 0.036	

Note: Log-rank test stratified by smoking status, country and participation in the OSS sub-study (86 stratification variables).

a. Kaplan-Meier Estimate.

The hazard ratio for SFC 50/500 vs. placebo was 0.815 (95% CI: 0.673, 0.987), representing an 18.5% reduction in the risk of dying at any time within 3 years for SFC 50/500 compared with placebo (p=0.036).

Table 12 presents the Cox proportional hazards analysis of time to all-cause mortality at 3 years for SFC 50/500 vs. placebo.

Table 12 Time to All-Cause Mortality for SFC 50/500 vs. Placebo - Cox Proportional Hazards Analysis – Study SCO30003

	Placebo (N=1524)	SFC 50/500 (N=1533)
Number of Deaths, n (%)	231 (15.2)	193 (12.6)
Probability of Death by 156 weeks (%)[a] (95% CI)	15.2 (13.4, 17.0)	12.6 (10.9, 14.3)
Probability of Death by 156 weeks (%)[b] (95% CI)	12.6 (11.0, 14.2)	10.3 (8.9, 11.8)
SFC 50/500 vs. Placebo: Hazard Ratio[b] (95% CI)[b] p-value[b]	0.811 (0.670, 0.982) 0.031	

Note: Cox proportional hazards model adjusted for smoking status, age, sex, region, Baseline FEV_1, and BMI

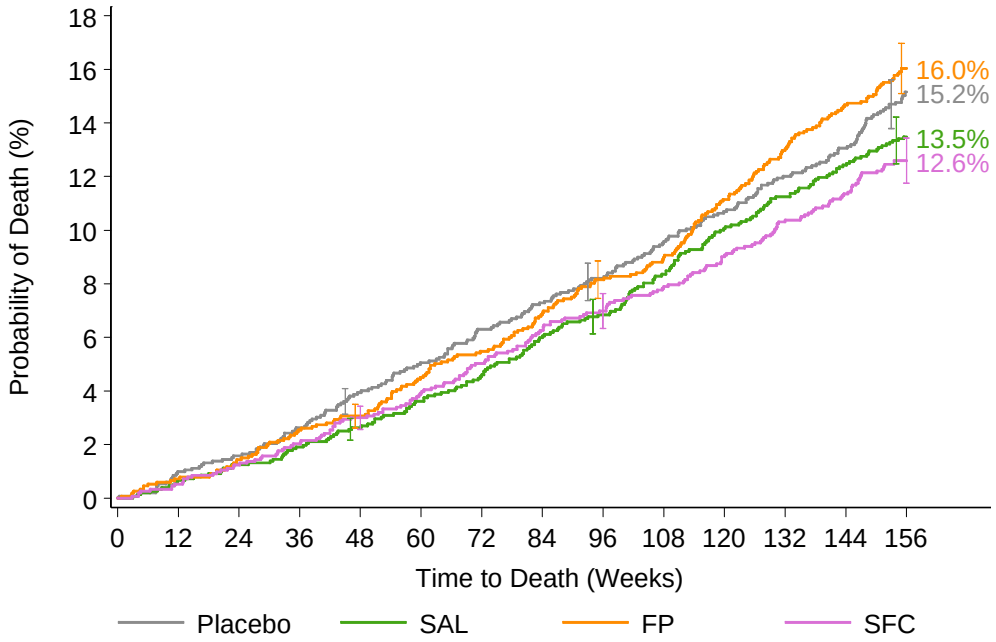
a. Kaplan-Meier Estimate.

b. Cox proportional hazards model estimate at mean age, FEV_1, BMI, and proportional coefficients for smoking status, sex, and region.

The hazard ratio for SFC 50/500 vs. placebo was 0.811 (95% CI: 0.670, 0.982), representing an 18.9% reduction in the risk of dying at any time within 3 years for SFC 50/500 compared with placebo (p=0.031).

A summary of the time to death from all causes for all treatment groups in Study SCO30003 is shown graphically in Figure 3.

Figure 3 **Time to All-Cause Mortality in All Treatment Groups - Cumulative Incidence Curve – Study SCO30003**



Note: Vertical bars represent standard error.

The log-rank analysis of time to all-cause mortality at 3 years stratified by smoking status for patients in all treatment groups in Study SCO30003 is presented in Table 13.

Table 13 Time to All-cause Mortality - Log-rank Analysis – Study SCO30003

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	SFC 50/500 (N=1533)
Number of Deaths, n (%)	231 (15.2)	205 (13.5)	246 (16.0)	193 (12.6)
Number Censored, n (%)	0	0	0	1 (<1)
Number Alive, n (%)	1293 (84.8)	1316 (86.5)	1288 (84.0)	1339 (87.3)
Probability of Death by 156 weeks (%)[a]	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[b]:				
Hazard Ratio		0.879	1.060	0.820[b]
(95% CI)		(0.729, 1.061)	(0.886, 1.268)	(0.677, 0.993)
p-value		0.180	0.525	0.041[b]
SFC 50/500 vs. Component:				
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

Note: The unadjusted values are presented here so results are calculated in a similar way to those for other treatment comparisons.

a. Kaplan-Meier Estimate.

b. SFC vs. Placebo comparison is not adjusted for the planned interim analyses. The adjusted values for the SFC50/500 comparison with placebo were Hazard Ratio of 0.825; 95% CI: 0.681, 1.002; p=0.052.

There was a statistically significant 23% reduction in the risk of dying for any reason at any time within 3 years for SFC 50/500 compared with FP 500 (hazard ratio 0.774; p=0.007); there was a 7% reduction in the risk of dying for any reason at any time within 3 years for SFC 50/500 compared with SAL 50 (hazard ratio 0.932; p=0.481).

The mortality rate for SAL 50 alone or FP 500 alone did not differ significantly from placebo treatment (p=0.180 and p=0.525, respectively).

4.1.2. Primary Cause of Death and COPD-related Mortality

The Clinical Endpoints Committee (CEC) categorised the primary cause of each death as cardiovascular, pulmonary, cancer related, other, or unknown, and assessed whether each death was COPD-related (Table 14; McGarvey, 2007).

Table 14 Cause of Death up to 3 Years as Classified by the Clinical Endpoint Committee (ITT population) – Study SCO30003

	PLA (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	SFC 50/500 (N=1533)
All Deaths	231 (15%)	205 (14%)	246 (16%)	193 (13%)
Primary cause of death				
Cardiovascular	71 (5%)	45 (3%)	61 (4%)	60 (4%)
Pulmonary	74 (5%)	80 (5%)	91 (6%)	61 (4%)
Cancer	45 (3%)	44 (3%)	51 (3%)	44 (3%)
Other	23 (2%)	22 (1%)	30 (2%)	11 (<1%)
Unknown	18 (1%)	14 (<1%)	13 (<1%)	17 (1%)
COPD-related deaths	91 (6%)	93 (6%)	106 (7%)	72 (5%)

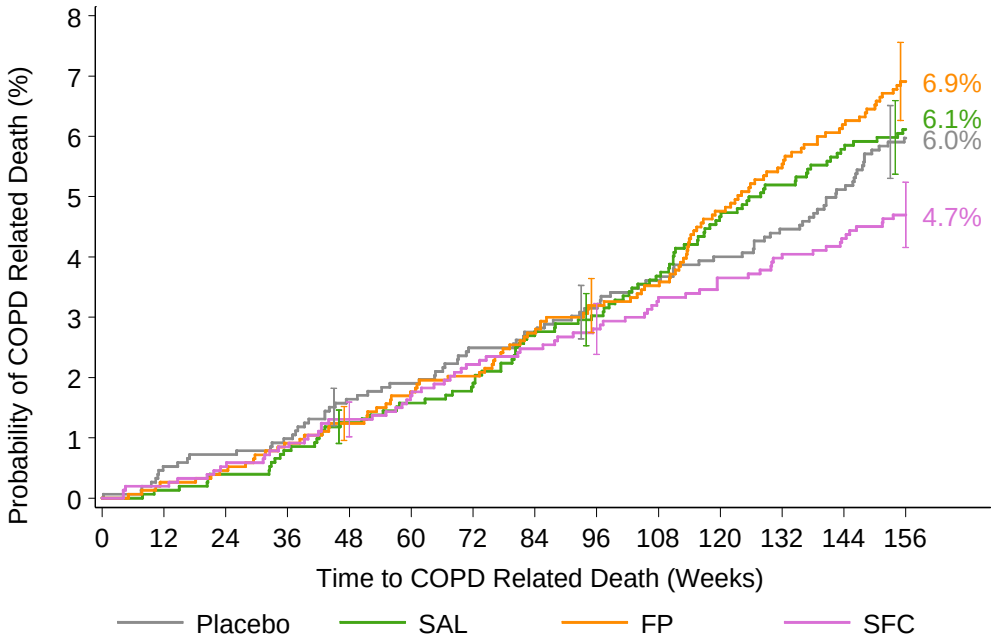
The majority of deaths in the study (62%) were considered to have a cardiovascular or pulmonary cause (Table 14). Although no analyses were performed, trends in the incidence of cardiovascular and pulmonary deaths appeared consistent with the reduction in all-cause mortality for SFC 50/500 compared with placebo.

For each death that occurred in the study, the CEC gathered all available documentation and made an assessment of the primary cause of death and whether or not the death was COPD-related by a set of a priori criteria. These criteria were that COPD was the primary cause of death; or the terminal event was hypercapnic respiratory failure or failure to be liberated from a ventilator; or if the patient likely would have survived if COPD was not present. While a death may be related to the patient's COPD, it may not have been the primary cause of death. Overall, 41% of all deaths were considered to be COPD-related in Study SCO30003 (Table 14).

4.1.3. COPD-Related Mortality

A summary of time to COPD-related mortality at 3 years for patients in Study SCO30003 is presented graphically in Figure 4.

Figure 4 **Time to COPD-Related Death - Cumulative Incidence Curve – Study SCO30003**



Note: Vertical bars represent standard error.

The log-rank analysis of time to COPD-related mortality at 3 years stratified by smoking status for patients in Study SCO30003 is presented in Table 15.

Table 15 **Time to COPD-Related Mortality – Log-rank Analysis – Study SCO30003**

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	SFC 50/500 (N=1533)
Number of Deaths, n (%)	91 (6.0)	93 (6.1)	106 (6.9)	72 (4.7)
Number Censored, n (%)	140 (9.2)	112 (7.4)	140 (9.1)	122 (8.0)
Number Alive, n (%)	1293 (84.8)	1316 (86.5)	1288 (84.0)	1339 (87.3)
Probability of Death by 156 weeks (%)[a] (95% CI)	6.0 (4.8, 7.2)	6.1 (4.9, 7.3)	6.9 (5.6, 8.2)	4.7 (3.6, 5.8)
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
SFC 50/500 vs. Component:				
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

a. Competing Risk Estimate.

The Competing Risk estimates of the probability of death by 156 weeks was 4.7% for SFC 50/500 compared with 6.0% for placebo, 6.1% for SAL 50, and 6.9% for FP 500.

Although the study was not powered to detect a difference in COPD-related mortality, a notable trend in favor of SFC 50/500 vs. placebo was observed. The hazard ratio for SFC 50/500 vs. placebo was 0.776 (95% CI: 0.570, 1.057), representing a 22% reduction in the risk of dying at any time within 3 years from a COPD-related cause for SFC 50/500 compared with placebo (p=0.107). The effects of SAL 50 and of FP 500 were similar to those of placebo treatment (p=0.932 and p=0.300, respectively). There was a 23% reduction in the risk of dying at any time within 3 years from a COPD-related cause for SFC 50/500 compared with SAL50 (p=0.089) and a 33% reduction in risk for SFC 50/500 compared with FP 500 (p=0.008).

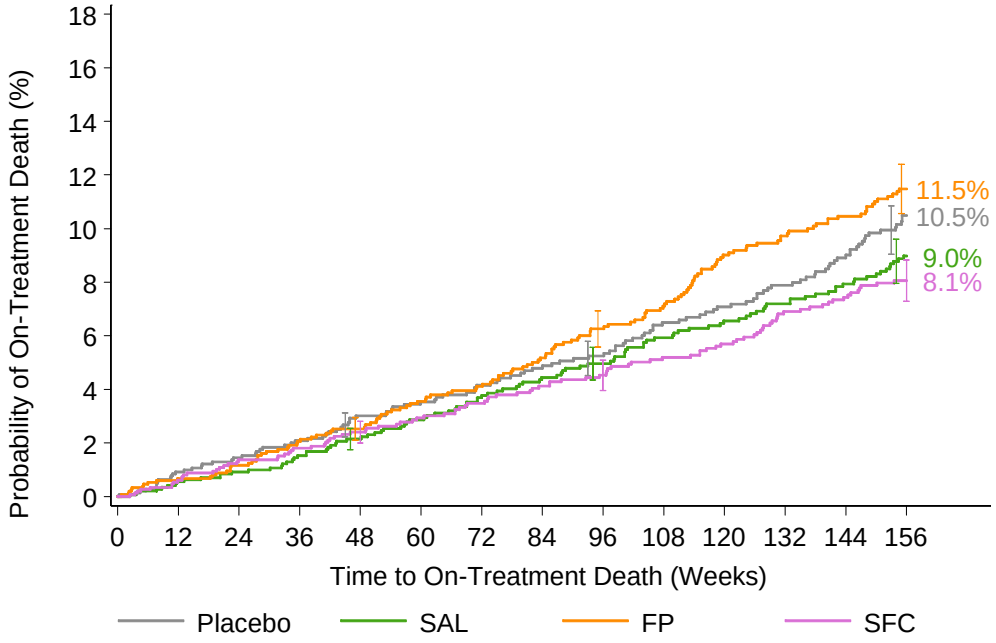
Although not specifically powered, this analysis supports the primary efficacy analysis of all-cause mortality by demonstrating a consistent magnitude of response for reducing the risk of dying from a COPD-related cause at anytime within 3 years for SFC 50/500 as compared with placebo.

4.1.4. On-Treatment All-Cause Mortality

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.

Kaplan-Meier estimates of survival probabilities for time to on-treatment all-cause mortality are displayed graphically in Figure 5.

Figure 5 Time to On-Treatment Death - Cumulative Incidence Curve – Study SCO30003



Note: Vertical bars represent standard error.

Kaplan-Meier probabilities of on-treatment death at 3 years stratified by smoking status for patients in Study SCO30003 are presented in Table 16.

Table 16 Time to On-Treatment All-Cause Mortality – Log-rank Analysis – Study SCO30003

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	SFC 50/500 (N=1533)
Number of Deaths, n (%)	117 (7.7)	109 (7.2)	141 (9.2)	103 (6.7)
Number Censored, n (%)	1407 (92.3)	1412 (92.8)	1393 (90.8)	1430 (93.3)
Probability of Death by 156 weeks (%)[a] (95% CI)	10.5 (8.7, 12.3)	9.0 (7.3, 10.6)	11.5 (9.7, 13.3)	8.1 (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
SFC 50/500 vs. Component:				
Hazard Ratio		0.898	0.701	
(95% CI)		(0.686, 1.175)	(0.544, 0.904)	
p-value		0.433	0.006	

Note: Analysis date is treatment stop date for all patients. Log-rank test stratified by smoking status

a. Kaplan-Meier Estimate.

The hazard ratio for on-treatment mortality for SFC 50/500 vs. placebo was 0.772 (95% CI: 0.592, 1.006), representing a 23% reduction in the risk of dying at any time on-treatment for SFC 50/500 compared with placebo (p=0.055). The effects of SAL 50 and of FP 500 were similar to those of placebo treatment (p=0.248 and p=0.445, respectively). The effects of SAL 50 and SFC 50/500 were also similar (p=0.433), but there was a 30% reduction in the risk of dying at any time on-treatment for SFC 50/500 compared with FP 500 (p=0.006).

Although not specifically powered, this analysis supports the primary efficacy analysis of all-cause mortality by demonstrating a clear trend for a reduction in the risk of dying while still on treatment (or within 14 days of stopping treatment) for SFC 50/500 compared with placebo.

4.1.5. Deaths Reported in Studies SFCB3024 and SFCA3006

Although not prospectively designed to assess mortality, fatal events on treatment for Study SFCB3024 and SFCA3006 are summarized below for completeness.

- In Study SFCB3024, there were 10 deaths in the placebo group, 5 deaths in the salmeterol group, 5 deaths in the fluticasone propionate group, and 4 deaths in the SFC 50/500 group.
- In Study SFCA3006, there were 3 deaths in the placebo group and no deaths in the active treatment groups.

4.2. Moderate & Severe COPD Exacerbations

COPD exacerbations are closely associated with symptomatic and physiological deterioration and impaired health status [Seemungal, 1998; Seemungal, 2000]. Furthermore, the likelihood of further exacerbations increases following the occurrence of a COPD exacerbation [Seemungal, 2000]. High frequency of COPD exacerbations is associated with a rapid decline in lung function and increased risk of hospitalization and death [Donaldson, 2002; Garcia-Aymerich, 2001; Soler-Cataluña, 2005].

Study SCO30003 and Study SFCB3024 provide evidence to support the use of SFC 50/500 in decreasing the rate of moderate and severe exacerbations in patients with COPD. Additional analyses of rate of COPD exacerbation requiring systemic corticosteroids and rate of severe COPD exacerbation are presented.

4.2.1. Moderate and Severe COPD Exacerbations

The majority of patients in both Studies SCO30003 (70% of patients) and SFCB3024 (54% of patients) experienced at least one moderate or severe exacerbation while on study treatment.

The rate of moderate and severe exacerbations was analyzed in Study SCO30003 and SFCB3024 using a negative binomial model (See Section 2.3.2 for further details) and is presented in Table 17.

The negative binomial analysis of COPD exacerbations for Study SCO30003 and Study SFCB3024 was repeated for Study SFCA3006. This analysis was not pre-defined for the SFCA3006 study but is provided for completeness. Caution should be used in interpreting this data due to design limitations mentioned in Section 2.3.2.

Table 17 Analysis of Rate of Moderate and Severe COPD Exacerbations

Study (Duration)	Efficacy Endpoint	Statistical Analysis	Treatment Arm	N	Active Treatment vs. Placebo		SFC 50/500 vs. Component	
					Comparison	p-value	Comparison	p-value
Rate of Moderate and Severe COPD Exacerbations [Rate Ratio (95% CI)]								
SCO30003 (3 years)	Secondary	Negative Binomial analysis adjusted for smoking status, age, sex, region, Baseline FEV_1, BMI and Baseline exacerbations	Placebo	1524	--	--	--	--
			SAL 50	1521	0.853 (0.784, 0.927)	<0.001	0.878 (0.808, 0.954)	0.002
			FP 500	1534	0.823 (0.758, 0.894)	<0.001	0.910 (0.838, 0.988)	0.024
			SFC 50/500	1533	0.749 (0.689, 0.814)	<0.001	--	--
SFCB3024 (52 weeks)	Secondary	Negative Binomial analysis adjusted for smoking status, age sex, amalgamated center and Baseline FEV_1	Placebo	361	--	--	--	--
			SAL 50	371	0.742 (0.617, 0.893)	0.001	0.921 (0.763, 1.111)	0.390
			FP 500	374	0.736 (0.612, 0.885)	0.001	0.929 (0.771, 1.120)	0.439
			SFC 50/500	356	0.684 (0.566, 0.826)	<0.001	--	--
SFCA3006 (24 weeks)	Secondary	Negative Binomial analysis adjusted for age and Baseline FEV_1	Placebo	181	--	--	--	--
			SAL 50	159	0.864 (0.615, 1.215)	0.402	1.083 (0.770, 1.523)	0.648
			FP 500	166	0.964 (0.688, 1.350)	0.830	0.971 (0.692, 1.364)	0.866
			SFC 50/500	163	0.936 (0.669, 1.309)	0.699	--	--

In Study SCO30003, the ratio of the exacerbation rate for SFC 50/500 to the rate for placebo was 0.749 (95% CI: 0.689, 0.814), which represents a statistically significant 25% decrease in rate compared with placebo (p<0.001) and corresponds to a number needed to treat of four to prevent one exacerbation in 1 year. SFC 50/500 treatment also significantly reduced the exacerbation rate compared with SAL 50 (12% reduction; p=0.002) and FP 500 (9% reduction; p=0.024).

Similar results were found in Study SFCB3024 for the rate of moderate and severe COPD exacerbations. The ratio of the exacerbation rate for SFC 50/500 to the rate for placebo was 0.684 (95% CI: 0.566, 0.826), which represents a statistically significant 32% decrease in rate compared with placebo (p<0.001). The exacerbation rate with SFC 50/500 was lower compared with SAL 50 (8% reduction; p=0.390) and FP 500 (7% reduction; p=0.439).

4.2.2. Other Exacerbation Endpoints

4.2.2.1. Rate of COPD Exacerbations Requiring Systemic Corticosteroids

Approximately 50% of patients in SCO30003 and 36% of patients in SFCB3024 experienced at least one exacerbation requiring treatment with systemic corticosteroids while on study treatment.

In Study SCO30003, the ratio of the exacerbation rate, from negative binomial analysis, on SFC 50/500 to the rate on placebo was 0.568 (95% CI 0.506, 0.637) which represented a 43% decrease in rate compared with placebo (p<0.001) corresponding to a number needed to treat of 3 to prevent one exacerbation requiring treatment with systemic corticosteroids in 1 year. Treatment with SAL 50 and FP 500 also reduced the exacerbation rate by 20% and 35%, respectively (p<0.001). SFC 50/500 treatment also reduced the exacerbation rate by 29% compared with SAL 50 (p<0.001) and by 13% compared with FP 500 (p=0.017). These results are summarised in Table 18.

Table 18 Rate of Exacerbations Requiring Systemic Corticosteroids - Negative Binomial Analysis - ITT Population – Study SCO30003

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	SFC 50/500 (N=1533)
Mean number of exacerbations from model	0.80	0.64	0.52	0.46
Active treatment vs placebo				
Ratio		0.802	0.652	0.568
95% CI		0.716, 0.899	0.582, 0.731	0.506, 0.637
p-value		<0.001	<0.001	<0.001
SFC 50/500 vs components				
Ratio		0.708	0.870	
95% CI		0.631, 0.793	0.776, 0.976	
p-value		<0.001	0.017	

Note: Negative Binomial model adjusted for smoking status, age, sex, region, baseline FEV_1, BMI and baseline exacerbations.

In Study SFCB3024, the ratio of the exacerbation rate, from negative binomial analysis, on SFC 50/500 to the rate on placebo was 0.545 (95% CI 0.421, 0.705) which represented a 45% decrease in rate compared with placebo (p<0.001). Treatment with SAL 50 and FP 500 also reduced the exacerbation rate by 37% and 43%, respectively (p<0.001). These results are summarised in Table 19.

Table 19 Rate of Moderate and/or Severe COPD Exacerbations Requiring Oral Corticosteroids - Negative Binomial Analysis - ITT Population SFCB3024

	Placebo (N=361)	SAL 50 (N=371)	FP 500 (N=374)	SFC 50/500 (N=356)
Mean number of exacerbations from model	0.89	0.56	0.51	0.49
Active treatment vs placebo				
Ratio		0.627	0.572	0.545
95% CI		(0.490, 0.803)	(0.445, 0.734)	(0.421, 0.705)
p-value		<0.001	<0.001	<0.001
SFC 50/500 vs components				
Ratio		0.869	0.953	
95% CI		(0.670, 1.126)	(0.733, 1.238)	
p-value		0.287	0.717	

Note: Negative Binomial model adjusted for smoking status, age, sex, amalgamated center, and baseline FEV_1

4.2.2.2. Rate of Severe COPD Exacerbations

Approximately 26% of patients from Study SCO30003 and 8% of patients from Study SFCB3024 experienced at least one severe exacerbation (requiring hospitalization) while on study treatment.

In Study SCO30003 (Table 20), the ratio of the severe exacerbation rate for SFC 50/500 to the rate for placebo was 0.834 (95% CI: 0.710, 0.981), which represents a statistically significant 17% decrease in rate compared with placebo (p=0.028) corresponding to a number needed to treat of 32 to prevent one hospitalization in 1 year. The effects of SFC 50/500 and SAL 50, and of SFC 50/500 and FP 500 were similar (p=0.790 and p=0.559, respectively).

Table 20 Rate of Severe Exacerbations - Negative Binomial Analysis - ITT Population SCO30003

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	SFC 50/500 (N=1533)
Mean number of exacerbations 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
SFC 50/500 vs components				
Ratio		1.022	0.954	
95% CI		0.870, 1.200	0.815, 1.117	
p-value		0.790	0.559	

Note: Negative Binomial model adjusted for smoking status, age, sex, region, baseline FEV_1, BMI and baseline exacerbations.

In Study SFCB3024, there was no effect of treatment on rate of severe COPD exacerbations likely due to the small number of severe COPD exacerbations seen in this study.

4.3. Health Status

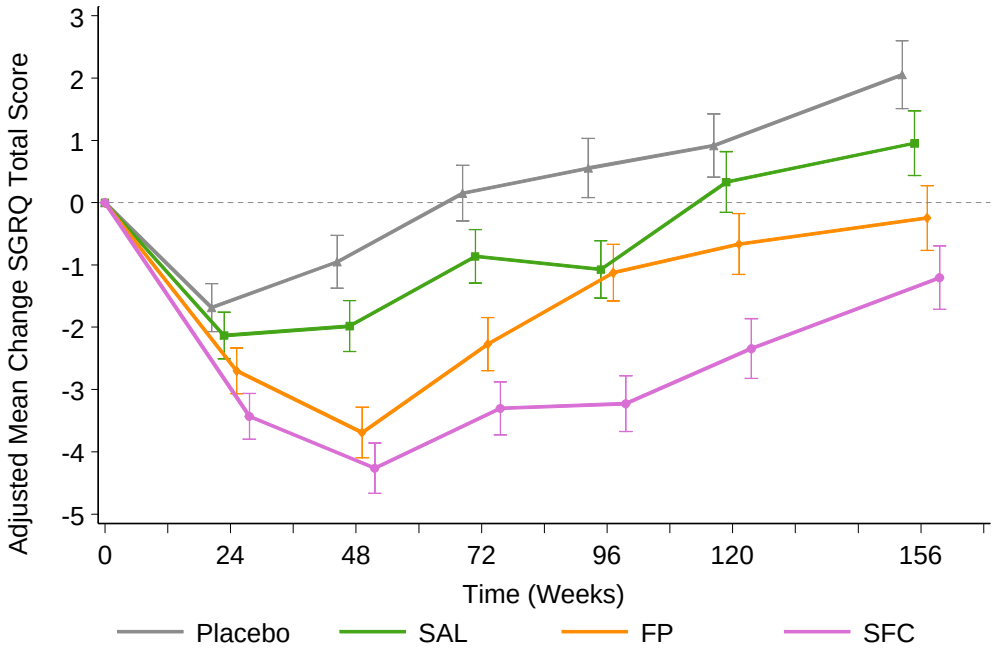
Health status scores provide measures of the impact of COPD on the patient. Health-related quality of life was analyzed with the St George's Respiratory Questionnaire (Studies SCO30003 and SFCB3024) and the Chronic Respiratory Disease Questionnaire (Study SFCA3006).

4.3.1. St George's Respiratory Questionnaire (SGRQ)

A decreased score on the SGRQ indicates an improvement in health-related quality of life, and an increased score indicates a poorer quality of life. A decrease of 4 points is currently considered the minimal important difference (MID) in this instrument.

In all treatment groups in Study SCO30003, there was a decrease from baseline (i.e. improvement) in mean SGRQ total score at Week 24 that was largest in the SFC 50/500 group (-3.30) and smallest in the placebo group (-1.74). The mean decrease was -2.31 in the SAL 50 group and -2.92 in the FP 500 group. At Week 156, the mean changes from baseline were 1.31 for placebo, -0.44 for SAL 50, -0.93 for FP 500 and -1.81 for SFC 50/500. A similar pattern was seen for adjusted mean changes (Figure 6).

Figure 6 **Adjusted Mean Change in SGRQ Total Score over Time - (Health Outcomes Population) Study SCO30003**



Note: Vertical bars represent standard errors
Note: From repeated measures analysis adjusted for smoking status, age, sex, baseline FEV_1, baseline SGRQ total score, region, visit, baseline SGRQ by visit and treatment group by visit interaction.

A summary of the repeated measures analysis of SGRQ total score for patients in Studies SCO30003 and SFCB3024 is presented in Table 21.

Table 21 SGRQ Total Score Overall - Repeated Measures Analysis - Study SCO30003 and Main Model Study SFCB3024

	SCO30003 (3 years duration)				SFCB3024 (52 weeks duration)			
	Placebo (N=1231)	SAL 50 (N=1232)	FP 500 (N=1248)	SFC 50/500 (N=1240)	Placebo (N=361)	SAL 50 (N=372)	FP 500 (N=374)	SFC 50/500 (N=358)
Number of Patients					318	320	340	320
Baseline Raw Mean (SD)	48.4 (17.5)	49.4 (16.6)	49.5 (17.3)	48.7 (17.1)	46.8 (16.2)	48.5 (16.9)	49.8 (15.8)	47.0 (15.8)
Raw Mean (SD)	48.4 (17.9)	48.3 (17.0)	47.4 (16.8)	45.8 (17.0)	45.8 (16.7)	46.0 (17.4)	47.5 (16.4)	43.6 (16.3)
Adjusted Mean (SE)	48.7 (0.37)	47.7 (0.35)	46.8 (0.35)	45.6 (0.35)	46.3 (0.5)	45.2 (0.4)	45.5 (0.4)	44.1 (0.5)
Active Treatment – Placebo (SE)		-1.0 (0.51)	-2.0 (0.51)	-3.1 (0.50)		-1.1 (0.59)	-0.8 (0.59)	-2.2 (0.59)
(95% CI)		(-2.0, 0.0)	(-2.9, -1.0)	(-4.1, -2.1)		(-2.3, 0.1)	(-2.0, 0.4)	(-3.3, -1.0)
p-value		0.057	<0.001	<0.001		0.068	0.174	<0.001
SFC 50/500 – Component (SE)		-2.2 (0.49)	-1.2 (0.49)			-1.1 (0.59)	-1.4 (0.59)	
(95% CI)		(-3.1, -1.2)	(-2.1, -0.2)			(-2.2, 0.1)	(-2.5, -0.2)	
p-value		<0.001	0.017			0.071	0.021	

Note: Lower SGRQ scores indicate better health status.

Note SCO30003: From repeated measures ANCOVA adjusted for smoking status, age, sex, Baseline FEV_1, BMI, Baseline SGRQ, region, Baseline SGRQ by visit and treatment by visit interaction.
SGRQs completed in a different language than that completed at Baseline are excluded.

Over 3 years in Study SCO30003, SGRQ total score improvements were significantly larger for the SFC 50/500 treatment group compared with placebo (-3.1; p<0.001) and significant improvements in SGRQ total score when compared with the SAL 50 (-2.2; p<0.001) and FP 500 (-1.2; p=0.017) treatment groups. At the end of the 3-year treatment period, on average SGRQ total scores for SFC 50/500 were still lower (i.e. better) than at baseline.

Over 52 weeks in SFCB3024, SGRQ total score improvements were significantly larger for the SFC 50/500 treatment group relative to placebo (-2.2; p<0.001) and significant improvements in SGRQ total score when compared with the FP 500 treatment group (p=0.021).

It is important to keep in mind that changes in SGRQ total score which do not achieve the 4-unit change are not necessarily clinically unimportant; for example, a patient may improve from having shortness of breath almost every day to only with respiratory infections, and may improve from having wheezing a few days a month to having no episodes of wheezing in the last 4 weeks, and this would constitute a change of 2 units [Borker, 2004].

For Study SCO30003, the proportions of patients in each treatment group showing an improvement (change from baseline of at least -4 units), deterioration (change from baseline of at least +4 points) or no change in health status as measured by the SGRQ total score are summarized in Table 22. In this analysis, the last observation was carried forward for patients who discontinued treatment prematurely unless they met another criterion for deterioration. At Week 156, the odds of a patient being clinically significantly better off were significantly greater for SFC 50/500 than placebo, SAL 50 or FP 500. The odds for SFC 50/500 patients having a significantly better health status were nearly twice those of placebo (odds ratio 1.86; 95% CI 1.58, 2.18; p<0.001).

Table 22 Proportional Odds Analysis of Change in Health Status Assessed by SGRQ Total Score (Health Outcomes Population) – Study SCO30003

	Placebo (N=1231)	SAL 50 (N=1232)	FP 500 (N=1248)	SFC 50/500 (N=1240)
Week 156				
Number of patients	1149	1148	1155	1133
Improvement, n (%)	247 (21%)	312 (27%)	325 (28%)	353 (31%)
No change, n (%)	241 (21%)	246 (21%)	279 (24%)	309 (27%)
Deterioration, n (%)	661 (58%)	590 (51%)	551 (48%)	471 (42%)
Odds ratio of 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
p-value		<0.001	<0.001	<0.001
Odds ratio of SFC 50/500 to components (SE)		1.40 (0.11)	1.24 (0.10)	
95% CI		1.20, 1.64	1.06, 1.45	
p-value		<0.001	0.006	

4.3.2. Chronic Respiratory Disease Questionnaire (CRQ)

An increased score on the CRQ indicates an improvement in health-related quality of life, and a decreased score indicates a decline in quality of life. An improvement of at least 10 in Overall score is considered the MID in this instrument.

A summary of the change from Baseline in overall CRQ score based on an ANCOVA model for patients in Study SFCA3006 is presented in Table 23.

Table 23 Change from Baseline in Overall CRQ Score – ANCOVA - Study SFCA3006

	Placebo (N=181)	SAL 50 (N=160)	FP 500 (N=168)	SFC 50/500 (N=165)
Active Treatment – Placebo				
Diff (SE)		3.8 (1.99)	0.5 (1.96)	5.3 (1.97)
Raw Diff		3.0 (2.04)	-0.2 (2.01)	5.0 (2.02)
(95% CI)		(-0.2, 7.7)	(-3.3, 4.4)	(1.5, 9.2)
p-value		0.060	0.784	0.007
SFC 50/500 – Component				
Diff (SE)		1.6 (2.04)	4.8 (2.01)	
Raw Diff		2.0 (2.08)	5.2 (2.05)	
(95% CI)		(-2.4, 5.6)	(0.8, 8.7)	
p-value		0.441	0.017	

Note: p values are based on an ANCOVA model: Change from Baseline = Baseline + treatment + Investigator.
Higher CRQ scores indicate better health status.

At Endpoint, overall CRQ score improvements were significantly larger for the SFC 50/500 treatment group relative to placebo (5.3; p=0.007). Improvement in overall CRQ score was also significantly greater in the SFC 50/500 treatment group compared with the FP 500 treatment group (4.8; p=0.017).

4.4. Pulmonary Function

Measurement of FEV_1 is a clinically important assessment due to its wide acceptance as a reproducible and objective indicator of disease severity and prognosis in COPD [ATS, 1991; Crapo, 1981; Kanner, 1996]. Moreover, FEV1 has been shown to be a sensitive endpoint for the measurement of the effects of the treatment of patients with COPD with both β-agonists and corticosteroids.

Studies SCO30003, SFCB3024 and SFCA3006 provide evidence to support the use of SFC 50/500 in maintenance treatment of airflow obstruction in patients with COPD. The primary data supporting improvement in lung function are provided by Studies SFCB3024 and SFCA3006, and supporting data are provided by Study SCO30003.

4.4.1. FEV_1 Measurements

In Study SFCB3024, pre-bronchodilator FEV_1 was the primary efficacy endpoint and post-bronchodilator FEV_1 was an additional efficacy endpoint. In Study SFCA3006, both pre-dose FEV_1 (to assess the contribution of FP to SFC) and 2-hour post-dose FEV_1 (to assess the contribution of SAL to SFC) were primary efficacy endpoints. In Study SCO30003, post-bronchodilator FEV_1 was an additional efficacy endpoint.

A summary of the analysis of pulmonary function in Studies SFCB3024, SFCA3006, and SCO30003 is presented in Table 24.

Table 24 Analysis of Pulmonary Function

Study (Duration)	Efficacy Endpoint	Statistical Analysis	Treatment Arm	N	Active Treatment vs. Placebo		SFC 50/500 vs. Component	
Pre-Bronchodilator or Pre-Dose FEV_1, mL [Treatment Difference (95% CI)]								
SFCB3024 (52 weeks)	Primary	Pre-bronchodilator FEV_1; repeated measures analysis adjusted for smoking status, age, sex, amalgamated center, and Baseline pre-bronchodilator FEV_1; average difference over 52 weeks.	Placebo	361	--	--	--	--
			SAL 50	372	60 (32, 88)	<0.001	73 (46, 101)	<0.001
			FP 500	374	39 (11, 67)	0.006	95 (67, 122)	<0.001
			SFC 50/500	358	133 (105, 161)	<0.001	--	--
SFCA3006 (24 weeks)	Primary	Pre-dose FEV_1; ANCOVA adjusted for Investigator and Baseline FEV_1; average difference at Endpoint.	Placebo	181	--	--	--	--
			SAL 50	160	92 (42, 142)	<0.001	67 (15, 118)	0.012
			FP 500	168	105 (55, 155)	<0.001	54 (3, 106)	0.038
			SFC 50/500	165	159 (109, 209)	<0.001	--	--
Post-Bronchodilator or Post-Dose FEV_1, mL [Treatment Difference (95% CI)]								
SCO30003 (3 years)	Other	Post-bronchodilator FEV_1; repeated measures analysis adjusted for smoking status, age, sex, Baseline FEV_1, BMI, region, visit, Baseline FEV_1 by treatment group and treatment group by visit; average difference over 3 years.	Placebo	1524	--	--	--	--
			SAL 50	1521	42 (26, 58)	<0.001	50 (34, 67)	<0.001
			FP 500	1534	47 (31, 64)	<0.001	44 (28, 61)	<0.001
			SFC 50/500	1533	92 (75, 108)	<0.001	--	--
SFCB3024 (52 weeks)	Other	Post-bronchodilator FEV_1; repeated measures analysis adjusted for smoking status, age, sex, amalgamated center, and Baseline pre-bronchodilator FEV_1; average difference over 52 weeks.	Placebo	361	--	--	--	--
			SAL 50	372	28 (-1, 57)	0.058	48 (19, 77)	0.001
			FP 500	374	46 (17, 75)	0.002	31 (2, 60)	0.039
			SFC 50/500	358	76 (47, 106)	<0.001	--	--
SFCA3006 (24 weeks)	Primary	Post-dose FEV_1; ANCOVA adjusted for Investigator and Baseline FEV_1; average difference at Endpoint.	Placebo	171	--	--	--	--
			SAL 50	158	191 (136, 245)	<0.001	40 (-16, 96)	0.162
			FP 500	161	101 (47, 156)	<0.001	129 (73, 185)	<0.001
			SFC 50/500	157	231 (176, 286)	<0.001	--	--

In Study SFCB3024, a significant improvement in pre-bronchodilator FEV_1 relative to placebo was demonstrated for SFC 50/500 treatment over 52 weeks (average difference 133mL; p<0.001). Significant improvement in pre-bronchodilator FEV_1 was also seen for SFC 50/500 treatment compared with SAL 50 (average difference 73mL; p<0.001) and FP 500 (average difference 95mL; p<0.001). A significant improvement in post-bronchodilator FEV_1 relative to placebo was also demonstrated in Study SFCB3024 for SFC 50/500 over 52 weeks (average difference 76mL; p<0.001). Significant improvement in post-bronchodilator FEV_1 was also seen for SFC 50/500 compared with SAL 50 (average difference 48mL; p=0.001) and FP 500 (average difference 31mL; p=0.039).

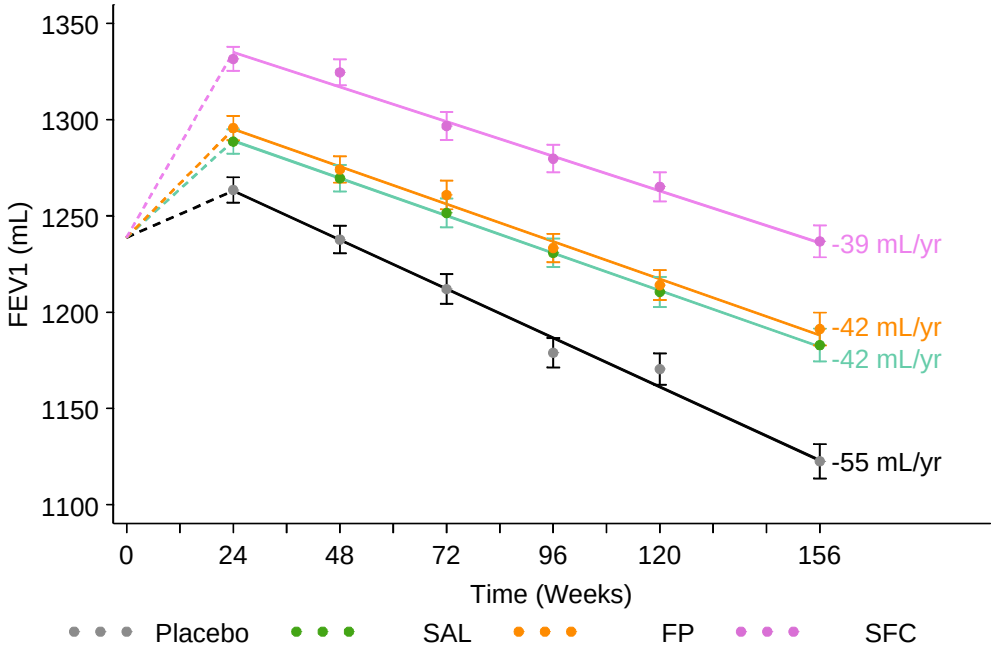
In Study SFCA3006, a significant improvement in pre-dose FEV_1 relative to placebo was demonstrated for SFC 50/500 at Endpoint (average difference 159mL; p<0.001). Significant improvement in pre-dose FEV_1 was also seen for SFC 50/500 compared with SAL 50 (average difference 67mL; p=0.012) and FP 500 (average difference 54mL; p=0.038). A significant improvement in post-dose FEV_1 relative to placebo was also demonstrated in Study SFCA3006 for SFC 50/500 at Endpoint (average difference 231mL; p<0.001). Significant improvement in post-dose FEV_1 was also seen for SFC 50/500 compared with FP 500 (average difference 129mL; p<0.001), but not SAL 50 (average difference 40mL; p=0.162).

In Study SCO30003, a significant improvement in post-bronchodilator FEV_1 compared with placebo was demonstrated for SFC 50/500 over 3 years (average difference 92mL; p<0.001). Significant improvement in post-bronchodilator FEV_1 was also seen for SFC 50/500 compared with SAL 50 (average difference 50mL; p<0.001) and FP 500 (average difference 44mL; p<0.001).

4.4.2. Rate of Decline in FEV_1 in Study SCO30003

In Study SCO30003, a *post hoc* analysis, using a random coefficients model, was performed to investigate the effects of treatment on rate of decline in FEV_1 (Figure 7 and Table 25).

Figure 7 **Rate of Decline (mL/year) in Post-Bronchodilator FEV_1 (ITT Population)**



Note: Random coefficients model adjusted for smoking status, age, sex, baseline FEV_1, region, and time on treatment and random patient effects.
Note: Adjusted means from repeated measures analysis adjusted for smoking status, age, sex, baseline FEV_1, region, visit, baseline FEV_1 by visit and treatment group by visit interaction. Vertical bars represent standard errors

Table 25 **Analysis of Rate of Decline (mL/year) in Post-Bronchodilator FEV_1 - ITT Population SCO30003**

	Placebo (N=1524)	SAL 50 (N=1521)	FP 500 (N=1534)	SFC 50/500 (N=1533)
Number of patients	1261	1334	1356	1392
Baseline Raw mean (SD)	1257 (444)	1231 (431)	1233 (437)	1236 (455)
Adjusted rate of decline (SE)	-55.3 (3.2)	-42.3 (3.1)	-42.3 (3.1)	-39.0 (3.0)
Active treatment minus placebo (SE)		13.0 (4.4)	13.0 (4.4)	16.3 (4.4)
95% CI		4.3, 21.7	4.3, 21.7	7.7, 24.9
p-value		0.003	0.003	<0.001
SFC 50/500 minus components (SE)		3.3 (4.3)	3.3 (4.3)	
95% CI		-5.1, 11.7	-5.1, 11.6	
p-value		0.441	0.445	

Note: Random coefficients model adjusted for smoking status, age, sex, baseline FEV_1, region, and time on treatment and random patient effects.

From 6 months onward, the adjusted rate of decline in FEV_1 was 55mL/year for placebo, 42mL/year for SAL 50, 42mL/year for FP 500 and 39mL/year for SFC 50/500. The 6-month time point was chosen to account for the initial treatment effect. Rate of decline was reduced by all active treatments compared with placebo ($p \leq 0.003$). Compared with placebo, the reduction in decline was 16mL/year (95% CI 8, 25mL) for SFC 50/500, 13mL/year for SAL 50 and 13mL/year for FP 500. There was no difference observed

between SFC 50/500 and either SAL 50 or FP 500. This analysis also confirmed the results seen in the pre-specified analyses, showing that each active treatment had consistently higher mean post-bronchodilator FEV_1 values than placebo and SFC 50/500 had consistently higher values than either SAL 50 or FP 500 at each visit.

5. SAFETY RESULTS

5.1. Extent of Exposure

The mean extent of exposure to study medication in Study SCO30003 was higher in the active treatment groups (120 weeks for SAL 50 and FP 500 and 125 weeks for SFC 50/500) than in the placebo treatment group (111 weeks). These exposure data reflect the different withdrawal rates seen across treatments described in Section 3.1. In Study SFCB3024, mean exposure to study medication was also higher in the active treatment groups (43 weeks for SAL 50 and 44 weeks for FP 500 and SFC 50/500) than in the placebo treatment group (39 weeks). In Study SFCA3006, mean extent of exposure was similar between the treatment groups.

Exposure to study medication for the Safety Population in the 3 pivotal studies in terms of total treatment years of exposure are summarized in Table 26.

Table 26 Summary of Exposure to Study Medication (Safety Population)

	Placebo		SAL 50		FP 500		SFC 50/500	
	N	Exposure	N	Exposure	N	Exposure	N	Exposure
SCO30003	1544	3278	1542	3531	1552	3555	1546	3700
SFCB3024	361	268	372	307	374	315	358	302
SFCA3006	185	64	164	63	173	60	169	64
Combined Total	2090	3610	2078	3901	2099	3930	2073	4066

Note: Exposure = total treatment years of exposure

A summary of the characteristics of the study populations for the 3 pivotal studies is provided in Section 3.

5.2. Adverse Events

As the treatment exposure from Study SCO30003 was approximately 10-fold higher than Studies SFCB3024 and SFCA3006 combined and there were no remarkable differences in adverse event reporting between Study SCO30003 and Studies SFCB3024 and SFCA3006, this Document will only provide AE data from Study SCO30003.

For AEs, in general, as well as for fatal AEs, SAEs, and AEs leading to withdrawal, AEs presented in the following tables were identified based on the number (e.g., ≥5 patients) or incidence (e.g., ≥3% of patients in some cases, and ≥1% of patients in other cases) of patients per treatment group in Study SCO30003 in which AEs were reported.

All AEs presented in the following sections reflect those events reported from patients while receiving double-blind study drug treatment. Since there was a marked difference in exposure to study treatment between the treatment groups in Study SCO30003, AEs are presented both as the number of patients experiencing each event and as the rate of each event per 1000 years of treatment exposure (number of events x 1000/ total treatment exposure) for each treatment group.

5.2.1. Most Common Adverse Events

The numbers (%) of patients in the Safety Population with the most commonly reported AEs that started during treatment in Study SCO30003, as defined by occurring in ≥3% of patients in any active treatment group in any study, along with exposure-adjusted AE data, are summarized in Table 27.

The overall incidence (89-90%) and exposure-adjusted AE rates (2767 - 2982 AEs/1000 treatment years) were similar across the treatment groups.

By far, the most frequent of these AEs was COPD, which was reported in more than half of patients in any treatment group. [Note: Although "COPD" is the preferred term used throughout this Briefing Document, it should be noted that the vast majority (>99%) of events coded to "COPD" were actually exacerbations of already-existing COPD.] The greater number of COPD exacerbations in the placebo group as compared to the active treatment groups reflect the benefit of treating patients with COPD as was discussed in Section 4.2 of this Briefing Document.

Oral candidiasis, dysphonia, and pneumonia were reported at a higher rate for the FP 500 and SFC 50/500 groups than for placebo or SAL 50. In general, candidiasis and dysphonia are reflective of the topical effects that are well known with the use of inhaled corticosteroids. Further discussion concerning AEs of pneumonia is presented in Section 5.6.1.

Table 27 Summary of Most Common AEs (Occurring in Greater Than or Equal to 3% of Patients in Any Active Treatment Group) – Study SCO30003

AE Preferred Term	Placebo (N=1544) n (%) [Rate]	SAL 50 (N=1542) n (%) [Rate]	FP 500 (N=1552) n (%) [Rate]	SFC 50/500 (N=1546) n (%) [Rate]
Any Event	1385 (90%) [2981.7]	1381 (90%) [2767.2]	1395 (90%) [2964.8]	1381 (89%) [2868.1]
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]
Bronchitis	91 (6%) [48.5]	97 (6%) [50.1]	102 (7%) [51.2]	121 (8%) [54.3]
Headache	115 (7%) [81.8]	100 (6%) [58.6]	115 (7%) [59.6]	111 (7%) [50.3]
Back pain	94 (6%) [37.5]	97 (6%) [35.1]	96 (6%) [35.2]	96 (6%) [37.0]
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]
Chest pain	59 (4%) [22.9]	72 (5%) [24.1]	72 (5%) [27.0]	93 (6%) [30.8]
Hypertension	77 (5%) [25.3]	92 (6%) [27.5]	89 (6%) [26.2]	82 (5%) [23.0]
Influenza	66 (4%) [31.4]	69 (4%) [26.3]	86 (6%) [28.7]	82 (5%) [28.6]
Oral candidiasis	27 (2%) [11.0]	28 (2%) [9.9]	106 (7%) [45.9]	84 (5%) [36.8]
Bronchitis acute	48 (3%) [26.5]	48 (3%) [20.1]	59 (4%) [29.5]	73 (5%) [31.4]
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]
Diarrhea	50 (3%) [20.1]	66 (4%) [23.5]	65 (4%) [20.0]	68 (4%) [21.1]
Insomnia	62 (4%) [22.6]	50 (3%) [15.3]	61 (4%) [21.1]	56 (4%) [16.8]
Constipation	56 (4%) [18.6]	49 (3%) [17.0]	47 (3%) [17.2]	66 (4%) [23.2]
Arthralgia	51 (3%) [26.2]	46 (3%) [15.3]	49 (3%) [16.6]	63 (4%) [18.1]
Depression	42 (3%) [14.3]	42 (3%) [12.5]	46 (3%) [14.1]	55 (4%) [14.9]
Muscle spasms	35 (2%) [12.8]	37 (2%) [13.0]	46 (3%) [14.3]	66 (4%) [22.2]
Dizziness	43 (3%) [16.8]	40 (3%) [12.7]	42 (3%) [12.9]	56 (4%) [17.3]

AE Preferred Term	Placebo (N=1544) n (%) [Rate]	SAL 50 (N=1542) n (%) [Rate]	FP 500 (N=1552) n (%) [Rate]	SFC 50/500 (N=1546) n (%) [Rate]
Dysphonia	12 (<1%) [3.7]	15 (<1%) [4.8]	52 (3%) [17.4]	67 (4%) [20.8]
Pyrexia	26 (2%) [9.2]	43 (3%) [19.5]	37 (2%) [12.7]	55 (4%) [18.9]
Peripheral Edema	54 (3%) [20.1]	54 (4%) [19.0]	55 (4%) [16.9]	52 (3%) [17.0]
Urinary Tract Infection	55 (4%) [22.0]	45 (3%) [18.1]	61 (4%) [25.6]	49 (3%) [15.9]
Dyspnea Exacerbated	55 (4%) [18.6]	56 (4%) [19.5]	49 (3%) [16.9]	44 (3%) [13.5]
Nausea	49 (3%) [16.8]	52 (3%) [19.8]	57 (4%) [18.3]	43 (3%) [17.8]
Lower Respiratory Tract Infection	46 (3%) [20.1]	46 (3%) [19.0]	43 (3%) [21.4]	53 (3%) [23.2]
Pain in Extremity	52 (3%) [22.0]	36 (2%) [14.4]	35 (2%) [13.8]	47 (3%) [15.1]
Rhinitis	32 (2%) [11.9]	44 (3%) [16.7]	46 (3%) [15.8]	46 (3%) [14.3]
Gastroesophageal Reflux Disease	34 (2%) [11.3]	41 (3%) [13.3]	49 (3%) [14.3]	39 (3%) [10.5]
Respiratory Tract Infection	36 (2%) [14.3]	38 (2%) [19.0]	30 (2%) [13.2]	44 (3%) [17.0]
Abdominal Pain Upper	28 (2%) [10.4]	40 (3%) [13.3]	38 (2%) [11.5]	40 (3%) [13.0]
Cataract	27 (2%) [9.2]	37 (2%) [12.5]	29 (2%) [8.4]	48 (3%) [13.8]
Dyspepsia	24 (2%) [9.2]	32 (2%) [13.0]	36 (2%) [12.9]	39 (3%) [13.0]
Candidiasis	19 (1%) [7.9]	10 (<1%) [4.0]	50 (3%) [21.9]	38 (2%) [16.8]
Anxiety	34 (2%) [11.3]	43 (3%) [13.9]	39 (3%) [11.5]	22 (1%) [6.8]

Note: Rate represents the rate of events per 1000 treatment years, calculated as: events x 1000/total treatment exposure

5.2.2. Drug-Related Adverse Events

The numbers (%) of patients in the Safety Population with the most commonly reported drug-related AEs (as determined by the Investigator) that started during treatment in Study SCO30003, as defined by occurring in ≥1% of patients in any active treatment group in any study, along with exposure-adjusted AE data, are summarized in Table 28.

The overall incidence of drug-related AEs in the SFC 50/500 group (18%) was higher than the incidence in the SAL 50 (12%) and placebo groups (13%) and similar to the FP 500 (19%) group. This pattern was also present when the AE data were adjusted for exposure.

Oral candidiasis and dysphonia were reported at a higher rate for the FP 500 and SFC 50/500 groups than for placebo or SAL 50. In general, candidiasis and dysphonia are reflective of the topical effects that are well known with the use of inhaled corticosteroids.

Table 28 Summary of Most Common Drug-Related AEs (Occurring in Greater Than or Equal to 1% of Patients in Any Active Treatment Group) – Study SCO30003

AE Preferred Term	Placebo (N=1544) n (%) [Rate]	SAL 50 (N=1542) n (%) [Rate]	FP 500 (N=1552) n (%) [Rate]	SFC 50/500 (N=1546) n (%) [Rate]
Any Event	207 (13%) [102.5]	187 (12%) [87.5]	302 (19%) [152.2]	285 (18%) [157.6]
Oral Candidiasis	14 (<1%) [6.7]	21 (1%) [7.6]	85 (5%) [35.2]	65 (4%) [28.4]
Candidiasis	16 (1%) [5.5]	9 (<1%) [3.7]	38 (2%) [15.8]	33 (2%) [14.3]
Oropharyngeal Candidiasis	9 (<1%) [2.7]	9 (<1%) [2.8]	24 (2%) [12.7]	24 (2%) [15.9]
Dysphonia	8 (<1%) [2.4]	11 (<1%) [3.4]	45 (3%) [14.6]	47 (3%) [15.1]
COPD	38 (2%) [15.9]	29 (2%) [11.0]	22 (1%) [7.9]	13 (<1%) [4.3]
Pharyngolaryngeal Pain	7 (<1%) [2.7]	14 (<1%) [5.1]	19 (1%) [6.2]	17 (1%) [5.1]

Note: Rate represents the rate of events per 1000 treatment years, calculated as: events x 1000/total treatment exposure.

5.3. Deaths

The numbers (%) of patients in the Safety Population with the most commonly reported fatal AEs that started during treatment in Study SCO30003, as defined by occurring in ≥5 patients in any active treatment group in any study, along with exposure-adjusted AE data are summarized in Table 29.

In Study SCO30003, a total of 7% of patients in the SFC 50/500 treatment group and 10%, 8%, and 9% in the FP 500, SAL 50, and placebo treatment groups, respectively, experienced fatal AEs during the Treatment Period of the study.

No individual fatal AE was reported in more than 2% of patients in any treatment group. By far, the most frequent of these AEs was COPD (COPD exacerbation). It should be noted, however, that COPD was reported as a fatal AE less frequently in the SFC 50/500 group (6.5 events/1000 treatment years) compared with the other 3 treatment groups (9.1-10.7 events/1000 treatment years).

Table 29 Summary of Most Common Fatal AEs (Occurring in Greater Than or Equal to 5 Patients in Any Active Treatment Group) – Study SCO30003

AE Preferred Term	Placebo (N=1544) n (%) [Rate]	SAL 50 (N=1542) n (%) [Rate]	FP 500 (N=1552) n (%) [Rate]	SFC 50/500 (N=1546) n (%) [Rate]
Any Event	133 (9%) [52.5]	126 (8%) [43.9]	160 (10%) [59.4]	114 (7%) [37.3]
COPD	32 (2%) [9.8]	32 (2%) [9.1]	38 (2%) [10.7]	24 (2%) [6.5]
Respiratory Failure	7 (<1%) [2.1]	12 (<1%) [3.4]	17 (1%) [4.8]	6 (<1%) [1.6]
Acute Respiratory Failure	6 (<1%) [1.8]	3 (<1%) [0.8]	5 (<1%) [1.4]	2 (<1%) [0.5]
Myocardial Infarction	8 (<1%) [2.4]	5 (<1%) [1.4]	6 (<1%) [1.7]	7 (<1%) [1.9]
Cardiac Failure	7 (<1%) [2.1]	7 (<1%) [2.0]	5 (<1%) [1.4]	6 (<1%) [1.6]
Cardiac Arrest	6 (<1%) [1.8]	6 (<1%) [1.7]	5 (<1%) [1.4]	4 (<1%) [1.1]
Acute Myocardial Infarction	6 (<1%) [1.8]	1 (<1%) [0.3]	5 (<1%) [1.4]	2 (<1%) [0.5]
Lung Neoplasm Malignant	6 (<1%) [1.8]	10 (<1%) [2.8]	11 (<1%) [3.1]	11 (<1%) [3.0]
Pneumonia	9 (<1%) [2.7]	10 (<1%) [2.8]	12 (<1%) [3.4]	8 (<1%) [2.2]
Sudden Death	8 (<1%) [2.4]	6 (<1%) [1.7]	4 (<1%) [1.1]	4 (<1%) [1.1]
Cerebrovascular Accident	0 0	1 (<1%) [0.3]	5 (<1%) [1.4]	3 (<1%) [0.8]

Note: Rate represents the rate of events per 1000 treatment years, calculated as: events x 1000/total treatment exposure.

5.4. Serious Adverse Events

The numbers (%) of patients in the Safety Population with the most commonly reported SAEs that started during treatment in Study SCO30003, as defined by occurring in ≥1% of patients in any active treatment group in any study, along with exposure-adjusted AE data, are summarized in Table 30.

In Study SCO30003, a total of 43% of patients in the SFC 50/500 treatment group and 42%, 40%, and 41% in the FP 500, SAL 50, and placebo treatment groups, respectively, experienced SAEs during the Treatment Period of the study.

By far, the most frequent of these SAEs was COPD (COPD exacerbation), which was reported in about one-fifth of patients in each of the treatment groups. It should be noted, however, that COPD was reported as an SAE less frequently in the SFC 50/500 group (135 events/1000 treatment years) compared with the other 3 treatment groups (146-168 events/1000 treatment years).

Pneumonia was reported at a higher rate for the FP 500 and SFC 50/500 groups than for placebo or SAL 50 (further details are provided in Section 5.6.1). Non-specific chest pain was also reported at a slightly higher rate for FP 500 and SFC 50/500 than for placebo but this event was reported at a low incidence (≤1%) across all treatments.

Table 30 Summary of Most Common SAEs (Occurring in Greater Than or Equal to 1% of Patients in Any Active Treatment Group) – Study SCO30003

AE Preferred Term	Placebo (N=1544) n (%) [Rate]	SAL 50 (N=1542) n (%) [Rate]	FP 500 (N=1552) n (%) [Rate]	SFC 50/500 (N=1546) n (%) [Rate]
Any Event	627 (41%) [430.8]	622 (40%) [398.2]	655 (42%) [437.1]	659 (43%) [412.2]
COPD	339 (22%) [167.5]	307 (20%) [145.6]	318 (20%) [150.8]	298 (19%) [134.6]
Respiratory Failure	23 (1%) [7.9]	29 (2%) [8.8]	32 (2%) [10.1]	26 (2%) [7.3]
Pneumothorax	7 (<1%) [3.1]	10 (<1%) [3.1]	8 (<1%) [2.5]	16 (1%) [4.6]
Pneumonia	69 (4%) [23.5]	82 (5%) [24.1]	121 (8%) [41.9]	138 (9%) [47.3]
Lobar Pneumonia	11 (<1%) [4.0]	9 (<1%) [2.5]	23 (1%) [7.0]	15 (<1%) [4.3]
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]
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%) [3.5]
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]

Note: Rate represents the rate of events per 1000 treatment years, calculated as: events x 1000/total treatment exposure.

5.5. Withdrawals Due to Adverse Events

The numbers (%) of patients in the Safety Population with the most commonly reported AEs that started during treatment and led to withdrawal in Study SCO30003, as defined by occurring in ≥5 patients in any active treatment group in any study, along with exposure-adjusted AE data, are summarized in Table 31.

The overall incidence of AEs leading to withdrawal in the SFC 50/500 group (18%) was lower than the incidences in the FP 500 (23%) and placebo (24%) groups and comparable with the incidence in the SAL 50 group (20%). This pattern was also present when the AE data were adjusted for exposure.

Overall adverse event rates were infrequent and similar between treatment groups (eg < 1%). The only exceptions were COPD and pneumonia. By far, COPD was the most frequent of these AEs leading to withdrawal with the SFC 50/500 group with the lowest exposure-adjusted rate (22 events/1000 treatment years) compared with the other 3 treatment groups (32-52 events/1000 treatment years). Pneumonia was reported as an AE leading to withdrawal in 2% of patients in the SFC 50/500 treatment group compared with 1% of patients from the FP 500, SAL 50, and placebo treatment groups. Further discussion concerning AEs of pneumonia is presented in Section 5.6.1

Table 31 Summary of Most Common AEs Leading to Withdrawal (Occurring in Greater Than or Equal to 5 Patients in Any Active Treatment Group) – Study SCO30003

AE Preferred Term	Placebo (N=1544) n (%) [Rate]	SAL 50 (N=1542) n (%) [Rate]	FP 500 (N=1552) n (%) [Rate]	SFC 50/500 (N=1546) n (%) [Rate]
Any Event	367 (24%) [144.3]	315 (20%) [107.3]	356 (23%) [131.1]	272 (18%) [88.4]
COPD	169 (11%) [51.6]	144 (9%) [40.8]	114 (7%) [32.1]	81 (5%) [21.9]
Respiratory Failure	10 (<1%) [3.1]	18 (1%) [5.1]	19 (1%) [5.3]	9 (<1%) [2.4]
Dyspnea Exacerbated	11 (<1%) [3.7]	9 (<1%) [2.5]	7 (<1%) [2.0]	3 (<1%) [0.8]
Dyspnea	7 (<1%) [2.1]	10 (<1%) [2.8]	8 (<1%) [2.3]	4 (<1%) [1.1]
Dysphonia	0 [0]	0 [0]	7 (<1%) [2.0]	12 (<1%) [3.2]
Acute Respiratory Failure	7 (<1%) [2.1]	3 (<1%) [0.8]	5 (<1%) [1.4]	1 (<1%) [0.3]
Cough	3 (<1%) [0.9]	4 (<1%) [1.1]	5 (<1%) [1.4]	3 (<1%) [0.8]
Myocardial Infarction	11 (<1%) [3.4]	11 (<1%) [3.1]	9 (<1%) [2.5]	8 (<1%) [2.2]
Cardiac Failure	10 (<1%) [3.1]	10 (<1%) [2.8]	6 (<1%) [1.7]	8 (<1%) [2.2]
Cardiac Arrest	7 (<1%) [2.1]	7 (<1%) [2.0]	6 (<1%) [1.7]	4 (<1%) [1.1]
Acute Myocardial Infarction	7 (<1%) [2.1]	1 (<1%) [0.3]	6 (<1%) [1.7]	2 (<1%) [0.5]
Pneumonia	17 (1%) [5.2]	21 (1%) [5.9]	23 (1%) [6.5]	26 (2%) [7.0]
Oral Candidiasis	2 (<1%) [0.6]	0 [0]	7 (<1%) [2.0]	3 (<1%) [0.8]
Lung Neoplasm Malignant	6 (<1%) [1.8]	13 (<1%) [3.7]	12 (<1%) [3.4]	11 (<1%) [3.0]
Cerebral Hemorrhage	1 (<1%) [0.3]	0 [0]	5 (<1%) [1.4]	0 [0]
Sudden Death	8 (<1%) [2.4]	6 (<1%) [1.7]	4 (<1%) [1.1]	4 (<1%) [1.1]

Note: Rate represents the rate of events per 1000 treatment years, calculated as: events x 1000/total treatment exposure.

5.6. Adverse Events of Special Interest

AEs of Special Interest in the pivotal clinical studies included the following event categories: Pneumonias, Bone Disorders, Eye Disorders, and HPA Axis Disorders.

5.6.1. Pneumonias

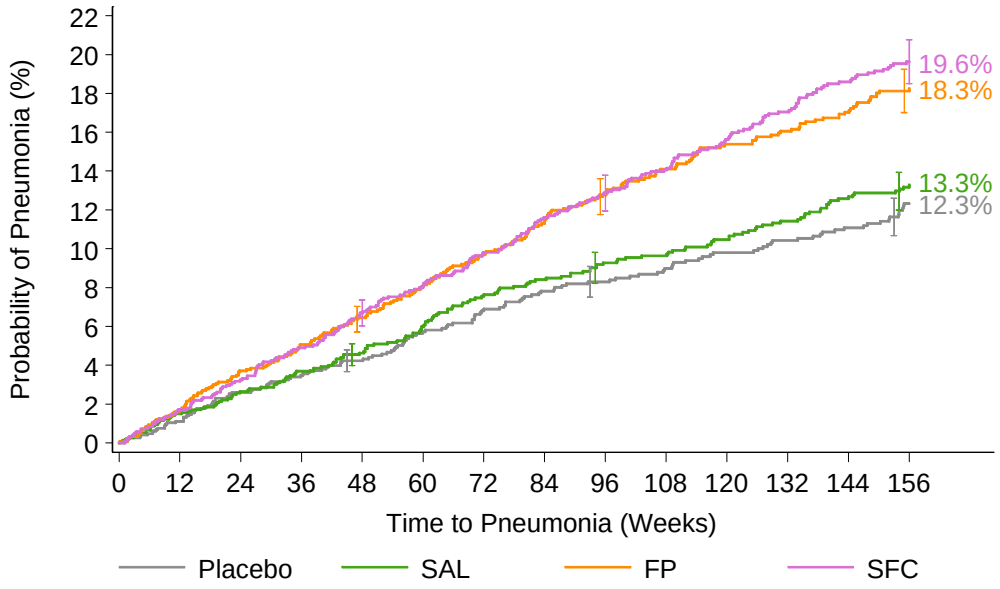
The three pivotal studies did not specify that the diagnosis of pneumonia required a chest x-ray, culture of respiratory secretions, or a complete blood count for confirmation.

In order to further explore the differential reporting of pneumonia in particular, events of physician reported pneumonias coded to the following terms were summarized to allow a more complete summary of all physician reported pneumonias: 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.

In Study SCO30003, there were no reports of opportunistic pneumonia infections (except for one patient in the placebo arm with HIV and pneumocystis jiroveci pneumonia) as evidenced by microbiology and/or clinical response to conventional antibiotics. Review of the SAE narratives in Study SCO30003 suggests that the pathogens recovered in patients receiving SFC 50/500 were consistent with the clinical presentation of those that occur in the community or hospital setting, both in terms of recovered pathogens and response to conventional antibiotics.

The time to the first reported pneumonia AE during treatment in Study SCO30003 is shown in Figure 8. Pneumonia adverse events were reported from patients during the time they were receiving double-blind study drug treatment in Study SCO30003.

Figure 8 **Time to First Reported Pneumonia Special Interest AE – Study SCO30003**



Number at Risk

Placebo	1544	1117	947	587
SAL	1542	1214	1024	645
FP	1552	1189	992	574
SFC	1546	1231	1034	631

Note: Vertical bars represent standard error.

The log-rank analysis of the time to the first reported pneumonia AE is presented in Table 32**.** The hazard ratio for time to the first reported Pneumonia AE for SFC 50/500 vs. placebo was 1.64, which represents a 64% increase in the risk of reporting a Pneumonia AE over 3 years compared with placebo ($p<0.001$). In addition, an increase of 51% in the risk of a reported Pneumonia AE was noted for SFC 50/500 vs. SAL 50 ($p<0.001$), and an increase of 53% was noted for FP 500 vs. placebo ($p<0.001$).

Table 32 Log-rank Analysis of Time to First Reported Pneumonia Special Interest AE (Safety Population) – Study SCO30003

	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	SFC 50/500 (N=1546)
Number of patients with an event	139 (9%)	162 (11%)	224 (14%)	248 (16%)
Probability of event by 156 weeks (%) [a]	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 vs. Placebo				
Hazard ratio		1.088	1.533	1.639
95% CI		0.867, 1.365	1.240, 1.894	1.331, 2.017
p-value		0.465	<0.001	<0.001
SFC 50/500 vs. Components				
Hazard ratio		1.508	1.068	
95% CI		1.237, 1.838	0.891, 1.280	
p-value		<0.001	0.475	

a. Kaplan-Meier estimate

Table 33 provides a summary of the number of patients and the exposure adjusted rate of pneumonia adverse events occurring while on treatment in Study SCO30003.

Table 33 Summary of Pneumonia Adverse Events of Special Interest (Safety Population) – Study SCO30003

	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	SFC 50/500 (N=1546)
Number of Patients	139 (9%)	162 (11%)	224 (14%)	248 (16%)
Rate per 1000 treatment years [1]	52	52	84	88

1. Rate = 1000 x number of pneumonia AE occurrences / treatment exposure in years

The percent of patients with pneumonia adverse events in Study SCO30003 was markedly higher in the SFC 50/500 (16%) and FP 500 (14%) treatment groups than in the SAL 50 (11%) and placebo (9%) groups. A similar pattern was present when the AE data were adjusted for time on study drug: the placebo and SAL 50 treatment groups had similar rates (52 events per 1000 patient years each) while the FP 500 and SFC 50/500 treatment groups had higher rates (84 and 88 events per 1000 patient years, respectively).

Table 34 presents a complete summary of pneumonia SAEs, including CEC adjudicated as deaths due to pneumonia from the Safety Population in Study SCO30003.

Table 34 Summary of Pneumonia Special Interest SAEs Including CEC Adjudicated Deaths Due to Pneumonia (Safety Population) – Study SCO30003

	PLA (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	SFC 50/500 (N=1546)
Pneumonia terms†				
Patients with SAEs*	86 (6%)	99 (6%)	150 (10%)	157 (10%)
Rate (Number of events)	30 (97)	30 (105)	52 (184)	55 (204)
Patients with fatal SAEs*	10	11	15	12
Rate	3.1	3.1	4.2	3.2
CEC primary cause of death (pneumonia)				
ITT Population over 3 years	13	15	21	15
ITT Population on-treatment	7	9	13	8

* All SAE events started during treatment

† Pneumonia terms = 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.

Rate = event per thousand treatment years

Pneumonia SAEs were reported in 86 patients (6%) in the placebo group, 99 patients (6%) in the SAL 50 group, 150 patients (10%) in the FP 500 group and 157 patients (10%) in the SFC 50/500 group. Fatal pneumonia events that started during treatment were reported in 10 patients in the placebo group, 11 patients in the SAL 50 group, 15 patients in the FP 500 group and 12 patients in the SFC 50/500 group. Assignment of primary cause of death was determined by the CEC. The number of ITT Population deaths attributable to pneumonias, as adjudicated by the CEC, was 13 patients in the placebo group, 15 patients in the SAL 50 group, 21 patients in the FP 500 group and 15 patients in the SFC 50/500 group. The number of on-treatment deaths attributable to pneumonias, as adjudicated by the CEC, was 7 in the placebo group, 9 in the SAL 50 group, 13 in the FP 500 group, and 8 in the SFC 50/500 group. Treatment with SFC50/500 in COPD did not appear to increase the risk of dying from pneumonia.

The overall number of patients with pneumonia adverse events in Study SFCB3024 was 5% in all active treatment groups (SFC 50/500, FP 500, and SAL 50) and 2% in the placebo group. The times to the first reported Pneumonia AE in SFCB3024 were similar for SFC 50/500, FP 500, and SAL 50 with respect to placebo, and the effects of SFC 50/500 and FP 500, with respect to one another, were also similar.

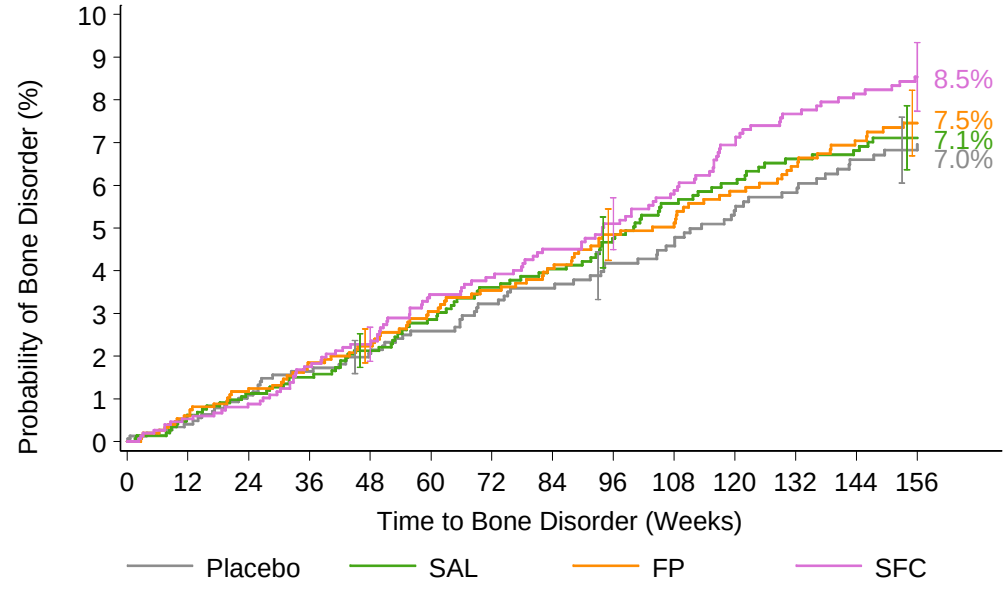
In Study SFCA3006, there were too few events for analysis of time to first pneumonia AE (1 event for placebo, 3 events for FP 500, and 2 events for SFC 50/500).

5.6.2. Bone Disorders

Bone disorders (which included all types of fractures, and reports of osteoporosis, bone density decreased, osteopenia, osteonecrosis and osteosclerosis) were reported from patients during the time they were receiving double-blind study drug treatment in Study SCO30003.

The time to the first reported bone disorder AE during treatment in Study SCO30003 is shown in Figure 9.

Figure 9 Time to First Reported Bone Disorder Adverse Event – Study SCO30003



Number at Risk

Placebo	1544	1138	976	603
SAL	1542	1229	1058	673
FP	1552	1232	1065	633
SFC	1546	1277	1109	702

Note: Vertical bars represent standard error.

Although the SFC 50/500 line appears to separate from the other treatments, the difference was small and not statistically significantly different (Table 35) compared with placebo. In addition, the FP 500 alone treatment group was similar to placebo.

Table 35 Log-rank Analysis of Time to First Reported Bone Disorder AE (Safety Population) – Study SCO30003

	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	SFC 50/500 (N=1546)
Number of patients with an event	77 (5%)	85 (6%)	90 (6%)	105 (7%)
Probability of event by 156 weeks (%) [a]	7.0	7.1	7.5	8.5
95% CI	5.4, 8.5	5.6, 8.6	5.9, 9.0	7.0, 10.1
Active treatment vs. Placebo				
Hazard ratio		1.024	1.083	1.218
95% CI		0.752, 1.393	0.799, 1.468	0.908, 1.634
p-value		0.882	0.607	0.188
SFC 50/500 vs. Components				
Hazard ratio		1.189	1.124	
95% CI		0.893, 1.582	0.848, 1.489	
p-value		0.235	0.415	

a. Kaplan-Meier estimate

Table 36 summarizes the number of patients and the rate of bone disorder adverse events reported from patients during the time they were receiving double-blind study drug treatment in Study SCO30003. The number of patients reporting each individual AE included within the category of bone disorders was low.

Table 36 Summary of Bone Disorder Adverse Events of Special Interest (Safety Population) – Study SCO30003

	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	SFC 50/500 (N=1546)
Number of Patients	77 (5%)	85 (6%)	90 (6%)	105 (7%)
Rate per 1000 treatment years [1]	28	29	29	32

1. Rate = 1000 x number of bone disorder AE occurrences / treatment exposure in years

The overall incidence of Bone Disorder Special Interest AEs in Study SFCB3024 was 1%, 2%, and 1% in the active treatment groups SFC 50/500, FP 500, and SAL 50, respectively and 2% in the placebo group.

The times to the first bone disorder event in Study SFCB3024 were similar for SFC 50/500, FP 500, and SAL 50 with respect to placebo, and the effects of SFC 50/50 and FP 500, with respect to one another, were also similar.

In Study SFCA3006, there were too few events for analysis of time to first Bone Disorders event (2 events for placebo, 1 event for SAL 50, 1 event for FP 500, and 3 events for SFC 50/500).

5.6.2.1. Fracture Reporting

In Study SCO30003, additional information was captured prospectively to enable summary of location of each fracture and whether or not traumatic (the Investigator assessed whether the fracture was traumatic or non-traumatic). A non-traumatic bone fracture was defined as a fracture caused by a fall from less than a standing height.

Table 37 summarizes the number of patients and the rate of bone fracture adverse events reported from patients during the time they were receiving double-blind study drug treatment in Study SCO30003. The number of patients reporting bone fracture AEs was low and similar across treatment groups.

Table 37 Summary of Bone Fracture Occurrence Rates During Treatment – (Safety Population) SCO30003

	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	SFC 50/500 (N=1546)
Number of Patients	57 (4%)	61 (4%)	65 (4%)	78 (5%)
Rate per 1000 treatment years [1]	19	20	20	22

1. Rate = 1000 x number of bone fracture occurrences / treatment exposure in years

Table 38 summarizes patients with bone fractures that started during treatment during Study SCO30003. There were no remarkable differences between treatments in the incidence of traumatic or non-traumatic fractures as related to the location of fractures reported.

Table 38 Summary of Patients with Bone Fractures that Occurred During Treatment – Study SCO30003

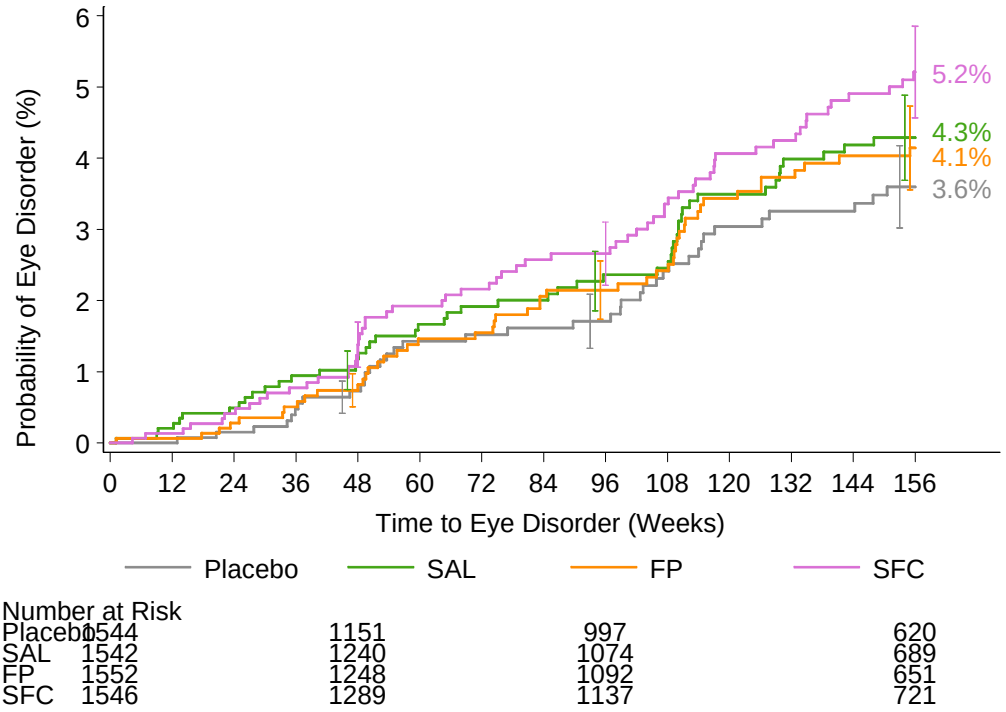
	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1522)	SFC 50/500 (N=1546)
All Patients with a bone fracture	57 (3.7%)	61 (4.0%)	65 (4.2%)	78 (5.0%)
Patients with a non-traumatic bone fracture	20 (1.3%)	29 (1.9%)	21 (1.4%)	21 (1.4%)
Hip	0	2 (0.1%)	2 (0.1%)	0
Wrist	2 (0.1%)	2 (0.1%)	0	1 (0.1%)
Spine	7 (0.5%)	12 (0.8%)	7 (0.5%)	7 (0.5%)
Rib	6 (0.4%)	8 (0.5%)	4 (0.3%)	3 (0.2%)
Other	5 (0.3%)	7 (0.5%)	9 (0.6%)	10 (0.6%)
Patients with a traumatic bone fracture	39 (2.5%)	37 (2.4%)	45 (2.9%)	58 (3.8%)
Hip	5 (0.3%)	6 (0.4%)	8 (0.5%)	7 (0.5%)
Wrist	5 (0.3%)	2 (0.1%)	11 (0.7%)	3 (0.2%)
Spine	1 (0.1%)	4 (0.3%)	2 (0.1%)	5 (0.3%)
Rib	9 (0.6%)	8 (0.5%)	10 (0.6%)	15 (1.0%)
Other	21 (1.4%)	17 (1.1%)	17 (1.1%)	30 (1.9%)

5.6.3. Eye Disorders Special Interest Adverse Events

Eye disorder adverse events (which included all types of cataract, all types of glaucoma, increased intraocular pressure and ocular hypertension) were reported from patients during the time they were receiving double-blind study drug treatment in Study SCO30003.

The time to the first reported eye disorder AE during treatment in Study SCO30003 is shown in Figure 10.

Figure 10 **Time to First Reported Eye Disorder Adverse Event – Study SCO30003**



Number at Risk

Placebo	1544	1151	997	620
SAL	1542	1240	1074	689
FP	1552	1248	1092	651
SFC	1546	1289	1137	721

Note: Vertical bars represent standard error.

Although the SFC 50/500 line appears to separate from the other treatments, the difference was small and not statistically significantly different (Table 39) compared with placebo. In addition, the FP 500 alone treatment group was similar to placebo.

Table 39 **Log-rank Analysis of Time to First Reported Eye Disorder AE - (Safety Population) Study SCO30003**

	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	SFC 50/500 (N=1546)
Number of patients with an event	38 (2%)	50 (3%)	48 (3%)	63 (4%)
Probability of event by 156 weeks (%) [a]	3.6	4.3	4.1	5.2
95% CI	2.5, 4.7	3.1, 5.5	3.0, 5.3	3.9, 6.5
Active treatment vs. Placebo				
Hazard ratio		1.228	1.156	1.462
95% CI		0.806, 1.873	0.755, 1.769	0.978, 2.187
p-value		0.338	0.505	0.063
SFC 50/500 vs. Components				
Hazard ratio		1.202	1.263	
95% CI		0.830, 1.743	0.868, 1.839	
p-value		0.330	0.221	

a. Kaplan-Meier estimate

Table 40 summarizes the number of patients and the rate of eye disorder adverse events reported from patients during the time they were receiving double-blind study drug treatment in Study SCO30003. The incidence of AEs of eye disorders was low across treatment groups (2% to 4%).

Table 40 Summary of Eye Disorder Adverse Events of Special Interest (Safety Population) – Study SCO30003

	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	SFC 50/500 (N=1546)
Number of Patients	38 (2%)	50 (3%)	48 (3%)	63 (4%)
Rate per 1000 treatment years [1]	14	18	16	19

1. Rate = 1000 x number of eye disorder AE occurrences / treatment exposure in years

In Studies SFCB3024 and SFCA3006, there were too few events for analysis of time to the first Eye Disorder event (Study SFCB3024: 1 event for placebo, 4 events for SAL 50, 2 events for FP 500, and 1 event for SFC 50/500); Study SFCA3006: 2 events for placebo, 2 events for FP 500, and 1 event for SFC 50/500).

5.6.4. HPA Axis Disorders Special Interest AEs

HPA Axis disorders were reported in too few patients overall and in too few patients in any 1 treatment group in any study to justify analyses of the type described in this section for the Special Interest AE groups of Pneumonias, Bone Disorders, and Eye Disorders.

Number of patients reporting HPA Axis disorder adverse events:

- Study SCO30003: 2 each in the placebo and FP 500 groups
- Study SFCB3024: 1 each in the SAL 50, FP 500, and SFC 50/500 groups
- Study SFCA3006: no patients

5.7. Cardiac Adverse Events

Patients with COPD are commonly at increased risk of cardiovascular problems and there have been suggestions that β-adrenergic stimulation may increase the risk of tachyarrhythmia. Adverse event reporting from Study SCO30003 showed no evidence of a higher rate of cardiac adverse events for SFC 50/500, SAL 50 or FP 500 (87, 114 and 102 events per 1000 treatment years, respectively) compared with placebo (113 events per 1000 treatment years).

Table 41 Summary of Cardiac Adverse Events (Safety Population) – Study SCO30003

	Placebo (N=1544)	SAL 50 (N=1542)	FP 500 (N=1552)	SFC 50/500 (N=1546)
Number of Patients	247 (16%)	243 (16%)	244 (16%)	217 (14%)
Rate per 1000 treatment years [1]	113	114	102	87

1. Rate = 1000 x number of cardiac AE occurrences / treatment exposure in years

Notably, the incidence of deaths due to cardiovascular causes was numerically higher for placebo than for any of the active treatments (Table 14).

5.8. Prospective Assessments of Safety

More detailed safety information concerning potential effects of long-term ICS use on bone mineral density (at the total hip and lumbar spine) and ophthalmic disorders (for cataracts and glaucoma) were prospectively assessed in a subset of patients (n=658) from 88 US sites, which represented approximately half of all US patients participating in the SCO30003 study. All patients from this subset participated in annual assessments of bone mineral density and slit lamp eye examinations. In a further subset of these patients, HPA-axis effects were assessed by serial serum cortisol measurements collected at 9 months post-randomization.

The following additional prospective safety assessments were conducted in Studies SFCB3024 and SFCA3006:

- Morning serum cortisol measurements (Studies SFCB3024 and SFCA3006), urine cortisol measurements (Study SFCB3024), and cosyntropin stimulation testing (Study SFCA3006)
- Cardiovascular assessments of ECGs (Studies SFCB3024 and SFCA3006), holters (Study SFCA3006), and vital signs (Studies SFCB3024 and SFCA3006)
- Laboratory data (Studies SFCB3024 and SFCA3006) and bruise counts of >5cm in diameter on the volar surface of each forearm (Study SFCB3024)

5.8.1. Bone Mineral Density

Bone mineral density (BMD) was prospectively collected only in Study SCO30003. BMD was measured in the Ophthalmic and Skeletal Safety Population, a subset of the Safety Population (658 patients in the US).

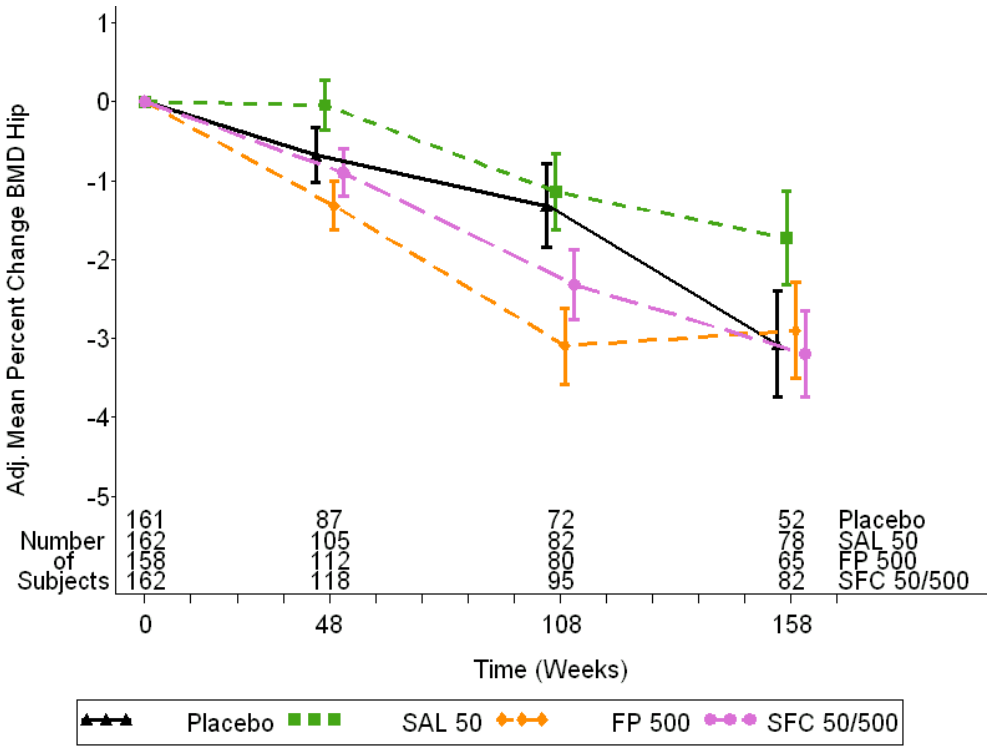
BMD was measured using dual energy x-ray absorptiometry (DEXA). The DEXA measurements of the total hip and the L1 through L4 regions of the spine were completed at Visits 2 (Baseline), 6 (48 weeks), 11 (108 weeks), and 16 (156 weeks).

5.8.1.1. DEXA Measurements of the Total Hip

Baseline mean BMD values were higher in the SAL 50 group (0.893g/cm^2) and the SFC 50/500 group (0.905g/cm^2) than in the placebo group (0.854g/cm^2) or FP 500 group (0.853g/cm^2).

Adjusted mean percent changes from baseline in BMD at the total hip are shown in Figure 11. There was a decrease in BMD over the course of the study in each treatment group.

Figure 11 **Adjusted Mean Percent Change in BMD at the Total Hip over Time - Repeated Measures Analysis (Ophthalmic and Skeletal Safety Population) Study SCO30003**



Note: Vertical bars represent standard errors
Note: Repeated measures analysis adjusted for smoking status, age, sex, BMI, log baseline BMD, BMD therapy, visit, log baseline BMD by visit and treatment by visit

As shown in Table 42, repeated measures analyses of percent change in BMD at the total hip showed no difference between any active treatment and placebo overall or at Week 158 (Year 3).

Table 42 Repeated Measures Analysis of Percent Change in Bone Mineral Density at the Total Hip at Week 158 – (Ophthalmic and Skeletal Safety Population) Study SCO30003

Week 158	Placebo N=164	SAL 50 N=166	FP 500 N=163	SFC 50/500 N=165
Number of Patients	52	78	65	82
Baseline Raw Geometric Mean (g/cm^2)	0.878	0.908	0.850	0.899
Adjusted % Change from Baseline[a]	-3.1%	-1.7%	-2.9%	-3.2%
Active Treatment vs. Placebo				
Difference in % Change[b]		1.39	0.17	-0.13
95% CI		(-0.42, 3.23)	(-1.65, 2.03)	(-1.88, 1.65)
p-value		0.134	0.853	0.885
SFC 50/500 vs. Component				
Difference in % Change[b]		-1.50	-0.30	
95% CI		(-3.08, 0.11)	(-1.96, 1.38)	
p-value		0.068	0.721	

Note: Repeated measures analysis adjusted for smoking status, age, sex, BMI, log baseline BMD, BMD therapy, visit, log baseline BMD by visit and treatment by visit.
a. Percent change calculated as (ratio to baseline - 1) x 100
b. Percent change calculated as (ratio to placebo - 1) x 100

No differences between active treatments and placebo were observed at Week 48 or Week 108 with the exception of a difference between FP 500 and placebo in favor of placebo at Week 108 (difference -1.81%; 95% CI -3.20, -0.39%; p=0.013). No such difference was apparent at the subsequent assessment (Week 158).

An ANCOVA analysis performed for each visit separately showed similar results to the repeated measures analyses. No significant differences were observed between active treatments and placebo except for the difference between FP 500 and placebo, in favor of placebo at Week 108 (difference -1.91%; 95% CI -3.32%, -0.48%; p=0.009). At Week 158, differences in percent change vs. placebo were 1.95% (95% CI -0.03%, 3.97%; p=0.054) for SAL 50, 0.83% (95% CI -1.20%, 2.90%; p=0.425) for FP 500, and 0.28% (95% CI -1.70%, 2.29%; p=0.783) for SFC 50/500.

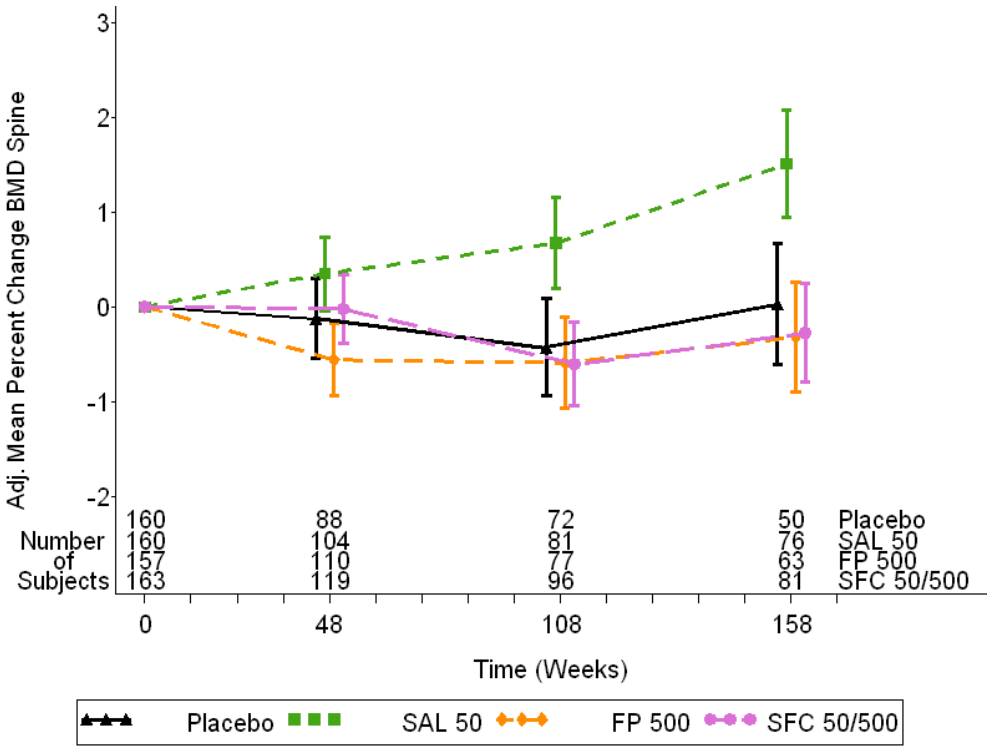
The absolute change in BMD at the total hip was analyzed with a repeated measures analysis. Overall and at Week 158, no significant differences were observed between active treatments and placebo. Results of the repeated measures analysis of the absolute change at Weeks 48 and 108 also showed no difference between active treatments and placebo with the exception of the difference between FP 500 and placebo at Week 108 (difference -0.0144; 95% CI -0.0259, -0.0029; p=0.015).

5.8.1.2. DEXA Measurements of the Lumbar Spine

Baseline mean BMD values for the lumbar spine were higher in the SAL 50 group (1.042g/cm^2) and the SFC 50/500 group (1.034g/cm^2) than in the placebo group (1.003g/cm^2) or FP 500 group (0.991g/cm^2).

Adjusted mean percent changes from baseline in BMD at the lumbar spine are shown in Figure 12.

Figure 12 **Adjusted Mean Percent Change in BMD at the Lumbar Spine over Time - Repeated Measures Analysis (Ophthalmic and Skeletal Safety Population) Study SCO30003**



Note: Vertical bars represent standard errors

As shown in Table 43, repeated measures analysis of percent change in BMD at the lumbar spine showed no difference between any active treatment and placebo, overall or at Week 158, although there was a trend for higher BMD values with SAL 50 than with placebo.

Table 43 Repeated Measures Analysis of Percent Change in Bone Mineral Density at the Lumbar Spine at Week 158 – (Ophthalmic and Skeletal Safety Population) Study SCO30003

Week 158	Placebo N=164	SAL 50 N=166	FP 500 N=163	SFC 50/500 N=165
Number of Patients	50	76	63	81
Baseline Raw Geometric Mean (g/cm^2)	1.008	1.058	0.974	1.014
Adjusted % Change from Baseline[a]	0.0	1.5%	-0.3%	-0.3%
Active Treatment vs. Placebo				
Difference in % Change[b]		1.48	-0.35	-0.31
95% CI		(-0.20, 3.19)	(-2.04, 1.36)	(-1.92, 1.34)
p-value		0.084	0.685	0.711
SFC 50/500 vs. Components				
Difference in % Change[b]		-1.76	0.04	
95% CI		(-3.22, -0.28)	(-1.49, 1.61)	
p-value		0.020	0.954	

Note: Repeated measures analysis adjusted for smoking status, age, sex, BMI, log baseline BMD, BMD therapy, visit, log baseline BMD by visit and treatment by visit.

a. Percent change calculated as (ratio to baseline - 1) x 100

b. Percent change calculated as (ratio to placebo - 1) x 100

No differences between active treatments and placebo were observed at Weeks 48 or 108.

An ANCOVA analysis performed for each visit separately showed similar results to the repeated measures analyses. No significant differences were observed between active treatments and placebo. At Week 158, differences in percent change vs. placebo were 1.56% (95% CI -0.27%, 3.42%) for SAL 50, -0.31% (95% CI -2.17%, 1.58%) for FP 500, and -0.50% (95% CI -2.30%, 1.34%) for SFC 50/500.

The absolute change in BMD at the lumbar spine was analyzed with a repeated measures analysis. Overall and at Week 158, no differences were observed between active treatments and placebo. Results of the repeated measure analysis of the absolute change at Weeks 48 and 108 also showed no difference between active treatments and placebo. These results were supported by an ANCOVA analysis for each visit separately.

5.8.2. Ophthalmic Examinations

Ophthalmic examinations were prospectively performed only in Study SCO30003.

Ophthalmic examinations were conducted in the Ophthalmic and Skeletal Safety Population of Study SCO30003 at Visit 2 (Baseline), Visit 6 (Week 48), Visit 11 (Week 108), and Visit 16 (Follow-up) by board-certified optometrists or opthalmologists using established methodology. Irregular findings (i.e., presence of cataracts and/or glaucoma) were identified and monitored. If necessary, examinations were repeated to confirm an abnormality. To maintain consistency, the same examiner was to perform each patient's initial and follow-up examinations.

Family history of cataracts and/or glaucoma in parents and/or siblings of patients undergoing ophthalmic examinations was also recorded.

5.8.2.1. Cataracts

On ophthalmic examination, the majority of patients (≥61%) had cataracts present prior to randomization. Of those that did not, few developed cataracts over the course of the study and the rate was lower for SFC 50/500, SAL 50 and FP 500 (94, 65 and 72 events per 1000 treatment years, respectively) than for placebo (108 events per 1000 treatment years) Table 44.

Table 44 Summary of Ocular Assessments: Cataracts (Ophthalmic and Skeletal Safety Population) – Study SCO30003

	Placebo N=164	SAL 50 N=166	FP 500 N=163	SFC 50/500 N=165
Cataracts Present Prior to Randomization	105 (64%)	118 (71%)	105 (64%)	101 (61%)
Developed Cataracts? [a] N Yes No	 47 10 (21%) 37 (79%)	 41 6 (15%) 35 (85%)	 47 8 (17%) 39 (83%)	 53 14 (26%) 39 (74%)
Number of Patients Developing Cataracts per 1000 Treatment Years [b]	108	65	72	94

a. Includes patients without cataracts prior to randomization and with at least one post-randomization assessment.
b. Rate = 1000 x number of patients developing cataracts / treatment exposure (years) for patients without cataracts prior to randomization and with at least 1 post-randomization assessment.

5.8.2.2. Glaucoma

As shown in Table 45, on ophthalmic examination, few patients (≤8%) had glaucoma prior to randomization and only 11 patients were noted as developing glaucoma during the study: 2 patients (2%) in the placebo group, none in the SAL 50 group, 6 patients (5%) in the FP 500 group and 3 patients (2%) in the SFC 50/500 group.

Table 45 Summary of Ocular Assessments: Glaucoma - (Ophthalmic and Skeletal Safety Population) Study SCO30003

	Placebo N=164	SAL 50 N=166	FP 500 N=163	SFC 50/500 N=165
Glaucoma Present Prior to Randomization	9 (5%)	9 (5%)	8 (5%)	14 (8%)
Developed Glaucoma? [a] N Yes No	 125 2 (2%) 123 (98%)	 139 0 139 (100%)	 130 6 (5%) 124 (95%)	 131 3 (2%) 128 (98%)
Number of Patients Developing Glaucoma per 1000 Treatment Years [b]	7	0	20	9

a. Includes patients without glaucoma prior to randomization and with at least 1 post-randomization assessment.
b. Rate = 1000 x number of patients developing glaucoma / treatment exposure (years) for patients without glaucoma prior to randomization and with at least 1 post-randomization assessment.

5.8.3. HPA Axis

Serum or urinary samples to evaluate the effects on the HPA axis were collected at selected centers from Studies SCO30003 (12-hour serial serum cortisol at Week 36), SFCB3024 (fasted morning serum cortisol and 24-hour urinary cortisol at Baseline, Week 24, Week 52, and at follow-up if abnormal at Week 52), and SFCA3006 (morning plasma cortisol concentration and short cosyntropin stimulation testing at Day 1 and Week 24 or Early Discontinuation Visit).

Treatment with SFC 50/500 resulted in an approximately 20% reduction in 12-hour serial serum cortisol AUC (Study SCO30003) and 24-hour urinary cortisol (Study SFCB3024) compared with placebo.

Table 46 presents the statistical comparisons between treatments of serum cortisol exposure (AUC_{12}) in patients from the pharmacokinetic safety sub-study population in Study SCO30003.

Table 46 Serum Cortisol AUC_{12} Between Treatment Statistical Comparison (Log-transformed) – (Pharmacokinetics Population) Study SCO30003

	Placebo (n=20)	SAL 50 (n=24)	FP 500 (n=15)	SFC 50/500 (n=24)
AUC_{12} (nmol*hr/L)[a] (95% CI)	3408 (3048, 4067)	3423 (3162, 3888)	2679 (2387, 3893)	2672 (2378, 3357)
Active Treatment vs. Placebo: Hazard Ratio[b] (95% CI)		1 (0.769, 1.31)	0.786 (0.58, 1.07)	0.784 (0.594, 1.04)
SFC 50/500 vs. Component: Hazard Ratio[b] (95% CI)		0.781 (0.603, 1.01)	0.997 (0.741, 1.34)	

a. Geometric least squares mean from ANOVA.
b. Geometric least squares mean ratio from ANOVA.

In Study SCO30003, geometric mean serum cortisol exposure (AUC_{12}) values following SFC 50/500 and FP 500 were 2672 nmol*hr/L and 2679 nmol*hr/L, respectively. Cortisol AUC_{12} values following both treatments were on average 22% lower than placebo, but not statistically different from placebo. The geometric mean ratio vs. placebo was 0.78 (95% CI: 0.59, 1.04) for SFC 50/500 and 0.79 (95% CI: 0.58, 1.07) for FP 500. The difference between SFC 50/500 and FP 500 was also not significant: the geometric mean ratio of SFC 50/500 vs. FP 500 was 0.997 (95% CI: 0.74, 1.34).

As shown in Table 47, the single point cortisol estimate, cortisol C_{min}, showed similar results as did measurement of FP systemic exposure also obtained at this time.

Table 47 Cortisol C_{min} Between Treatment Statistical Comparison (Log-transformed) – (Pharmacokinetics Population) Study SCO30003

	Placebo (n=20)	SAL 50 (n=24)	FP 500 (n=15)	SFC 50/500 (n=24)
Cmin (nmol/L)[a] (95% CI)	152 (134, 220)	135 (122, 172)	117 (97.2, 181)	112 (102, 159)
Active Treatment vs. Placebo: Hazard Ratio[b] (95% CI)		0.883 (0.623, 1.25)	0.768 (0.518, 1.14)	0.732 (0.515, 1.04)
SFC 50/500 vs. Component: Hazard Ratio[b] (95% CI)		0.829 (0.592, 1.16)	0.953 0.650, 1.40)	

a. Geometric mean and 95% CU.
b. Geometric least squares mean ratio from ANOVA.

In Study SFCB3024, significant differences from placebo in urinary cortisol were observed in both the FP 500 and SFC 50/500 groups (ratio 0.78 to 0.80; p<0.001) at Week 24, and these difference were maintained at Week 52 (ratio 0.78 to 0.79; p<0.001). The SFC 50/500 group was also significantly different from SAL 50 at Weeks 24 and 52 (ratio 0.77 to 0.79; p<0.001).

Although these results suggest that SFC 50/500 may affect basal function of the HPA-axis, the results of the cosyntropin stimulation test in Study SFCA3006 (Table 48) suggest that SFC 50/500-treated patients are still able to respond to stress-induced events.

Table 48 Number of Patients with Abnormalities in Short ACTH Stimulation Test Results - Patients with Both Day 1 and Endpoint Assessments - ITT Population Study SFCA3006

	Day 1				Endpoint			
	Placebo n=34	SAL50 n=36	FP500 n=33	SFC 50/500 n=34	Placebo n=34	SAL50 n=36	FP500 n=33	SFC 50/500 n=34
n with AM cortisol <4mcg/dL	0	1	0	1	0	0	1	0
n with post-stim change <5.6mcg/dL	3	4	2	4	1	5	5	5
n with post-stim change <14.5mcg/dL	0	2	0	1	0	1	1	1
n with post-stim change <5.6mcg/dL and post-stim cortisol <14.5mcg/dL	0	1	0	1	0	1	0	0

Note: Endpoint is either Week 24 or patient discontinuation

In Study SFCA3006, the incidence of abnormal cosyntropin stimulation values at Endpoint was similar for the patients not taking FP (placebo and SAL 50 treatment groups) compared with those patients taking FP (FP 500 and SFC 50/500 treatment groups).

5.8.4. Cardiovascular Assessments

Vital signs were collected in Studies SFCB3024 and SFCA3006. No clinically significant effects were observed on vital signs (heart rate and blood pressure in both studies and serial pulse rate and blood pressure in Study SFCA3006) following 1 to 52 weeks of exposure to any treatment in Study SFCB3024 or following 1 to 24 weeks of exposure to any treatment in Study SFCA3006.

ECG measurements were performed in all patients in Studies SFCB3024 and SFCA3006 and 24-hour Holters were performed in a subset of patients (158 patients at 18 sites) in SFCA3006. The incidence of clinically significant ECG abnormalities was comparable among the treatment groups in Studies SFCB3024 and SFCA3006. No treatment-related QTc, cardiac rate, and ventricular or supra-ventricular rhythm abnormalities were observed. The Holter data from SFCA3006 showed that the incidence of ventricular ectopic (VE) events and changes in ECG rates were similar across treatment groups at Screening and at Week 4 in Study SFCA3006. Only 5 patients experienced significant changes from their Screening Holter at Week 4 (1 patient in the placebo group, 1 patient in the SAL 50 group, 2 patients in the FP 500 group, and 1 patient in the SFC 50/500 group). Specifically, there was no increase in incidence of QTc prolongation or arrythmias in the salmeterol-containing treatment groups.

5.8.5. Clinical Laboratory Evaluation and Other Physical Findings

Samples for clinical laboratory evaluations were collected in Studies SFCB3024 and SFCA3006. Laboratory results were analyzed via two different methods: shift analysis relative to the normal range and sponsor pre-defined threshold laboratory values.

Based on shifts with respect to the normal reference range for hematology and clinical chemistry analytes, no trends suggesting an effect of SFC 50/500 or its individual components (SAL 50 and FP 500) on the occurrence of laboratory values outside the normal reference range were observed in either study.

In general, ≤2% of patients in each treatment group had hematology or clinical values that were of potential clinical concern at each time point and at any time during Studies SFCA3006 or SFCB3024 according to pre-defined Sponsor threshold ranges. Exceptions were noted for a few hematology analytes and clinical chemistry analytes; however none of these shifts occurred consistently over time or were associated with a particular active treatment.

Bruise counts were prospectively collected in Study SFCB3024. At each clinic visit, the number of bruises of >5cm in diameter on the volar surface of each forearm was counted and was found to be low (≤3% of patients per treatment group). There were no significant differences between any of the active treatment groups and placebo for bruise count at any time point during the treatment period ($p \geq 0.194$).

6. DISCUSSION OF BENEFIT/RISK

The goals of therapy for patients with COPD include symptom management, prevention of disease progression and reduction of mortality [Global Initiative for Chronic Obstructive Lung Disease, 2006]. The demonstrated benefits of currently available therapies have been significant, but limited and no recently approved treatments have received claims for COPD other than for the relief of airflow obstruction. Bronchodilators, such as beta-agonists and anticholinergics, offer relief from symptoms of breathlessness, and ICS (with or without LABA) can reduce the frequency of exacerbations. However, no treatment (other than smoking cessation) has been shown to have an important impact on disease progression. In addition, no non-surgical interventions, other than smoking cessation and long-term oxygen therapy (LTOT) in those with hypoxemia, have been shown to impact mortality in patients with COPD [Anthonisen, 2005; Crockett, 2001]. Thus, reduction of mortality is one of the greatest unmet needs in the management of COPD. The current Submission demonstrates that SFC 50/500 not only reduces exacerbations but also has an impact on mortality.

6.1. Assessment of Benefits

Mortality: The primary objective of Study SCO30003 was to demonstrate a significant reduction in all-cause mortality in patients with COPD treated with SFC 50/500 compared with placebo, when added to their usual COPD therapy. SFC 50/500 reduced the risk of dying at any time within 3 years from any cause by 17.5% compared with placebo (95% CI: 0%, 32%; p=0.052; adjusted for interim analyses) or an absolute risk reduction of 2.6%.

Our confidence in the treatment effect was confirmed by a supporting log rank analysis stratified by smoking status, country, and participation in the Ophthalmic and Skeletal Safety sub-study, and by an analysis using a Cox proportional hazards model adjusted for smoking status, age, sex, region, Baseline FEV_1, and BMI.

While the primary outcome of Study SCO30003 was all-cause mortality to eliminate bias in the classification of deaths, it was also important to determine if treatment had an effect on COPD-related mortality. In Study SCO30003 there was a 22% reduction in the risk of dying from a COPD-related cause at any time within 3 years for SFC 50/500 compared with placebo. Similarly, there was a clear trend for a reduction in the risk of dying while still on study treatment (or within 14 days of stopping treatment) for SFC 50/500 (a 23% reduction in the risk of dying on study treatment compared with placebo) despite the issue of non-random discontinuation described above (i.e., patients with more profound symptoms of COPD were more likely to discontinue study treatment).

The mechanism by which SFC reduces mortality is not clear and was not specifically addressed in Study SCO30003 (TORCH). The CEC was established to accurately define the cause of death. This process revealed that non-pulmonary (particularly cardiovascular) as well as pulmonary mortality was reduced and the overall mortality benefit was greater than provided by either of the component treatments delivered as monotherapy. Important factors which led to lower death rates may include any or all of

the following: reduced exacerbations (which have been linked with mortality in those with severe COPD), reduced systemic inflammation, and an improvement in activity and general health status.

As discussed above, a 17.5% relative reduction in the risk of dying at any time over 3 years represents a substantial impact, but the true effect may be even larger. The primary analysis of all-cause mortality at 3 years was on an intent-to-treat basis. Many patients withdrew prior to the study end and, having withdrawn, were free to take any medication including ICS or LABA. Irrespective of the medication taken after withdrawal, survival data from all 6112 patients were included. Forty-four percent of the placebo group withdrew before the study end; 25% within the first year. Therefore, it is very likely that a high proportion of placebo patients who withdrew early would have taken active medication such as ADVAIR, an inhaled corticosteroid, or a long-acting beta-agonist. Since a greater proportion of placebo patients withdrew prematurely, this would bias the study toward reducing both the magnitude of the observed treatment effect and the statistical power of the analysis. This is an inevitable bias in such a long study, given the progressive nature of COPD and the recognised benefits and widespread use of ICS and LABA.

Despite these confounding factors, the achievement of a 17.5% reduction in the risk of dying for any reason at any time within 3 years for SFC 50/500 compared with placebo is highly clinically important. It is comparable in magnitude to the 16% reduction reported with statin treatment in patients with coronary heart disease from a pooled analysis of 17 studies [Wilt, 2004]. Moreover, in terms of existing interventions for COPD, it is similar to the mortality benefit observed over 14.5 years following an intensive smoking-cessation program in patients with airflow obstruction [Anthonisen, 2005]. The impact on mortality observed with long-term oxygen therapy (LTOT) have shown a larger impact on mortality in those with advanced COPD and severe hypoxaemia (NNT: 5 patients for 5 years) but there was no mortality benefit observed in those with mild or moderate hypoxaemia [Crockett, 2001].

Study SCO30003 is the first study of its kind to show a mortality benefit for any pharmacological treatment for COPD. Given the conservative design of the study, the results provide compelling evidence that SFC 50/500 demonstrated a clinically meaningful reduction in all-cause mortality compared with placebo. The absolute reduction in risk between SFC 50/500 and placebo (2.6%) corresponds to the prevention of one death for every 39 patients treated for 3 years.

Exacerbations: In Study SCO30003, the rate of moderate and severe exacerbations was statistically significantly reduced by 25% in the SFC 50/500 treatment group compared with placebo ($p<0.001$), a number needed to treat of four to prevent one exacerbation in 1 year. These data were supported by a statistically significant 32% reduction in the rate of moderate and severe exacerbations in the SFC 50/500 treatment group compared with placebo in Study SFCB3024 ($p<0.001$).

The rate of exacerbations requiring treatment with systemic corticosteroids was 43% lower in the SFC 50/500 treatment group compared with placebo ($p<0.001$); a number needed to treat of 3 to prevent one exacerbation requiring treatment with systemic

corticosteroids in 1 year. A result of similar magnitude (45%) was observed in Study SFCB3024 ($p<0.001$).

The rate of exacerbations requiring hospitalization, with its significant associated costs, was 17% lower with SFC 50/500 than with placebo ($p=0.028$); a number needed to treat of 32 to prevent one hospitalization in 1 year.

Health status: The beneficial effects on health-related quality of life, as assessed by the SGRQ total score (in Studies SCO30003 and SFCB3024) or the CRQ overall score (in Study SFCA3006), were observed for the SFC 50/500 treatment group compared with placebo (Section 2.3.3). These findings, although not meeting the pre-specified MID criteria, demonstrated strong trends for improvement in health status in patients with COPD treated with SFC 50/500.

In the SCO30003 study, the well recognized progressive nature of COPD is clearly demonstrated with the steady deterioration in health status after the first 6-12 months of the 3-year study Figure 6. It is notable that after 3 years, the SFC 50/500 group, even though showing evidence of a year-on-year decline in health status still had an overall SGRQ score that had not yet returned to baseline. This may reflect an impact on the disease, which is likely to be important to the patient. A 4-unit decrease from baseline in SGRQ total score is generally taken to represent a clinically relevant change [Jones, 2002] and a greater proportion of SFC 50/500-treated patients experienced a clinically relevant improvement and/or avoided a clinically relevant deterioration in SGRQ total score after 3 years than those who received placebo (odds ratio: 1.86; 95% CI: 1.58, 2.18; $p<0.001$).

Lung function: SFC 50/500 also significantly improved lung function in patients with COPD compared with placebo as well as compared with SAL 50 and FP 500 across all three studies. In addition, by the end of the 3-year treatment period from Study SCO30003, the SFC 50/500 treatment group showed a minimal change in post-bronchodilator FEV_1 (-7mL) compared to larger deteriorations in the placebo (-127mL) and individual component treatment groups (-61mL to -62mL). Therefore, the results from Study SCO30003 provide clear evidence that treatment with SFC 50/500 maintains lung function for up to 3 years, a clinically important finding in the long-term management of COPD.

Also of relevance is the *post hoc* analysis of the rate of decline in FEV_1 in Study SCO30003 (Section 4.4.2). In healthy individuals over the age of 40, one would expect to see a small yearly FEV_1 decline of around 30mL/year [Fletcher, 1977]. The rate of decline from 6 months onwards in FEV_1 in the placebo treatment group in Study SCO30003 was 55mL/year, an accelerated rate that was not unexpected in this population of COPD patients, 43% of whom continued to smoke. However, the rate of decline in FEV_1 in patients in the SFC 50/500 treatment group was 39mL/year, a rate that was statistically significantly lower than placebo. The clinical relevance of this effect on FEV_1 decline is not clear, but suggests that SFC 50/500 may contribute to impeding the progression of the disease.

6.2. Assessment of Risks

There are considerable safety data available for salmeterol and fluticasone propionate as monotherapies and for SFC 50/500 from previous clinical development activity and post-marketing surveillance. Based on the safety data available in this application, in general, the adverse event profile is consistent with the current label with the exception of pneumonia. The data identified candidiasis and dysphonia, which are well recognized AEs associated with ICS arising from local deposition of corticosteroid in the mouth and upper airway, as adverse reactions (i.e. some basis for a causal relationship). The examination of these data also indicated that pneumonia occurred at a higher incidence in patients receiving inhaled SFC and FP. In addition to pneumonia, particular attention has been paid to the development of bone disorders, eye disorders, and HPA-axis disorders, since these events are thought to be related to the administration of corticosteroids.

Pneumonia: An unexpected finding of Study SCO30003 was the increase in reports of pneumonia in patients receiving ICS compared with the non-ICS-containing arms. Pneumonia is common in patients with COPD and anything that contributes to respiratory compromise can be potentially life-threatening. The rate of pneumonia was 52 per 1000 treatment-years in the placebo group in Study SCO30003 indicating that it was a common event in COPD patients. A total of 976 pneumonia events were reported in Study SCO30003 reported by a total of 13% of patients in the Safety Population. Exacerbations were more common in patients with moderate- severe COPD, with 13,389 moderate or severe exacerbations being reported by a total of 69% of patients in the ITT population. Study SCO30003 showed that while there is an increase in the rate of reporting of pneumonia in the SFC and FP-treated groups, there is a substantial reduction of exacerbations in these groups.

The increased incidence of pneumonia in SFC 50/500- and FP 500-treated patients is the most relevant and potentially significant event when assessing the benefit/risk profile of SFC 50/500. Specific analysis of pneumonias in Study SCO30003 showed that overall incidences and exposure-adjusted rates of pneumonia AEs were notably higher in the SFC 50/500 and FP 500 groups compared with the SAL 50 and placebo groups. Furthermore, there was a 64% increase in the risk of reporting a pneumonia over 3 years in SFC 50/500-treated patients compared with placebo-treated patients. In addition, an increase of 51% in the risk of reporting pneumonia was noted for SFC 50/500 vs. SAL 50 ($p<0.001$), and an increase of 53% was noted for FP 500 vs. placebo.

To investigate possible risk factors for pneumonia, all AEs of physician-reported pneumonia in SCO30003 were summarised by subgroups based on age, sex, smoking status, ethnic origin, BMI, baseline FEV_1, and region. The subgroup analyses indicate that more severe disease (FEV_1 <30% predicted), male gender, older age and lower BMI ($<25 kg/m^2$) are associated with a higher risk of pneumonia across all treatment groups. There was no evidence that current smokers were at greater risk compared with former smokers. In addition, the review of data did not show a consistent pattern in risk factors specific to the ICS-containing groups compared with the non-ICS containing groups. Although older patients with more severe disease were generally more prone to pneumonia (whether receiving FP or not), these patients also derived considerable benefit from SFC 50/500 in terms of reduction in mortality.

The mechanism/pathogenesis of increased pneumonia with inhaled corticosteroids is unclear. It is generally recognized that exacerbations of COPD are associated with infection. Thus, there is an apparent paradox whereby SFC 50/500 reduces the incidence of one infective complication of COPD (i.e. exacerbation) yet potentially increasing another (i.e. pneumonia). A recent report demonstrated that use of ICS is associated with increased colonization of Gram-negative organisms in the upper airways of patients with asthma; the increase in colonization was unrelated to disease severity [Talay, 2007]. However, increase in colonization with gram-negative bacilli was related to disease severity in COPD patients [Mobbs, 1999]. Although not previously reported in patients with COPD, colonization with potentially pathogenic organisms might be enhanced by ICS in these patients as well. Such patients with moderate, severe disease might be at greater risk of aspirating these organisms and hence are more prone to pneumonia. On the other hand, prolonged treatment with systemic corticosteroids is recognized to increase the incidence of opportunistic infections, which are felt to be the result of immunosuppression, and frequently are fatal. This appeared not to be the case with inhaled corticosteroids, as shown by the data from SCO30003.

Review of the SAE narratives in Study SCO30003 suggests that the pneumonias reported with SFC 50/500 are consistent with the clinical presentation of those that occur in the community or hospital setting, both in terms of recovered pathogens and response to conventional antibiotics. For patients in whom pathogens were recovered there was no indication that the pneumonias seen in the SFC 50/500 treatment group were unusual with respect to clinical presentation or etiological organism, and there has been no indication of unusual pneumonias from the clinical study program for SFC 50/500 or FP 500 or from the 29.8 million patient-years of exposure within clinical practice.

Most importantly, treatment with SFC 50/500 in COPD did not appear to increase the risk of dying from pneumonia. In Study SCO30003, the number of on-treatment deaths attributable to pneumonias, as adjudicated by the CEC, was 7 in the placebo group, 9 in the SAL 50 group, 13 in the FP 500 group, and 8 in the SFC 50/500 group.

Bone Disorders: There was no statistically significant difference for any active treatment compared with placebo in the time to the first reported bone disorder or bone fracture AE. The number of patients reporting each individual AE included within the category of bone disorders or bone fracture AEs was low. These data do not indicate clinically relevant differences with SFC 50/500 on bone. This conclusion is further supported by detailed serial BMD examinations of the hip and lumbar spine from a subset of patients in Study SCO30003 (N=658). Analyses revealed no significant difference in the rate of bone loss between any active treatment and placebo.

Eye Disorders: With regard to impact on the eye, there was no statistically significant difference for any active treatment compared with placebo in the time to the first reported eye disorder AE. The incidence of AEs of eye disorders was low across treatment groups. These data do not indicate clinically relevant differences with SFC 50/500 on the eye. This conclusion is further supported by detailed ophthalmic examinations performed in a subset of patients from Study SCO30003 that demonstrated no evidence for a difference between active treatments and placebo in the number of patients who developed cataracts or glaucoma during the study.

HPA Axis Disorders: Treatment with SFC 50/500 resulted in an approximately 20% reduction in 12-hour serial serum cortisol AUC (Study SCO30003) and 24-hour urinary cortisol (Study SFCB3024) compared with placebo, as measured in a subset of patients. Although these results suggest that SFC 50/500 may affect basal function of the HPA axis, the results of the cosyntropin stimulation test in Study SFCA3006 suggest that SFC 50/500-treated patients are still able to respond to stress-induced events.

Cardiovascular Assessments: No evidence was observed for a higher rate of cardiac AEs with SFC 50/500 in Study SCO30003. Notably, the incidence of deaths due to cardiovascular causes in Study SCO30003 was numerically higher for placebo than for any of the active treatments. This was further supported by cardiac monitoring (ECG and Holter) conducted in Studies SFCB3024 and SFCA3006 which showed no evidence of an increased risk of cardiac events with SFC 50/500 therapy.

Additional Safety Assessments: No clinically significant effects were observed in any treatment group on clinical laboratory parameters following 52 weeks of exposure (Study SFCB3024) or following 24 weeks of exposure (Study SFCA3006). Prospective assessment of bruising on the volar surface of the forearm (Study SFCB3024) was low and demonstrated no significant differences between any of the active treatment groups and placebo.

6.3. Conclusion

Results from Studies SCO30003, SFCB3024, and SFCA3006 support the use of SFC 50/500 in patients with COPD with the goal of reducing mortality, reducing exacerbations, and maintaining lung function. COPD, which is increasing in prevalence, is characterized by distressing symptoms as well as early death; a treatment that addresses both of these unmet needs is of great importance.

The increased incidence of pneumonia in SFC 50/500- and FP 500-treated patients is the most relevant and potentially serious event when assessing the benefit/risk profile of SFC 50/500. However, from the SAE narratives in Study SCO30003, it appears that the character of the pneumonias reported with SFC 50/500 are consistent with the clinical presentation of those cases that occur in the community or hospital setting, both in terms of recovered pathogens and response to conventional antibiotics.

There is no clear mechanism as to why patients receiving inhaled corticosteroids are at increased risk of pneumonia. Of critical importance is the issue of whether the increased risk of pneumonia outweighs the benefits of SFC 50/500. The benefits in terms of reduction in all-cause mortality, reduced exacerbations and improved pulmonary function are outlined above and do not appear to be outweighed by the increased reporting of pneumonia. There was no observed increase in pneumonia-associated mortality with SFC 50/500 treatment. This may be because exacerbations and pneumonias have similar presentations and is therefore treated early in their course.

Taking into consideration the positive effects of SFC 50/500 on mortality, exacerbations, quality of life and lung function, as well as the absence of clinically demonstrable effects on bone and eye, when weighed against the potential risks of pneumonia and the well-

known effects of ICS (e.g., oral candidiasis, dysphonia, and HPA-axis), the benefit-risk profile is considered to be favorable.

7. APPROPRIATE USE OF ADVAIR DISKUS IN THE MANAGEMENT OF COPD

7.1. Proposed Label

The wording in the proposed label is supported by the results of this clinical program and amends the current indication, dosage, and administration sections of the ADVAIR DISKUS prescribing information as described below.

7.1.1. Indication

The proposed indication for **ADVAIR DISKUS** for COPD is as follows:

"ADVAIR DISKUS 500/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema, and to increase survival and reduce exacerbations in patients with forced expiratory volume in 1 second (FEV_1) <60% of predicted *[see Clinical Studies (14.2)]*.

ADVAIR DISKUS 250/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with COPD.

ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm."

7.1.2. Dosage and Administration

The proposed dosage and administration for **ADVAIR DISKUS** for COPD is as follows:

"The dosage for patients with COPD is 1 inhalation of ADVAIR DISKUS 500/50 twice daily (morning and evening, approximately 12 hours apart). An alternative dose for some patients is 1 inhalation of ADVAIR DISKUS 250/50 twice daily, but the effect of this lower dose on reducing COPD exacerbations and increasing survival has not been studied.

If shortness of breath occurs in the period between doses, an inhaled, short-acting $beta_2$-agonist should be taken for immediate relief."

7.1.3. ADVAIR DISKUS in Relation to Pneumonia

Amendments to the current wording in the US prescribing information for **ADVAIR DISKUS** in relation to pneumonia are outlined below.

Current wording:

PRECAUTIONS

General: *Metabolic and Other Effects:*

Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS.

Revised wording:

Warnings and Precautions and Adverse Reactions in the Highlights section:

- Risks ass ociated with corticosteroid therapy include hypothalamic-pituitary-adrenal axis effects, pneumonia, and effects on the immune system, growth velocity, bone metabolism, and the eye. (5.7)
- Most common adverse reactions (incidence >1%) are candidiasis, contusion, dysphonia, pneumonia, and throat irritation (6.1, 6.2)

Section 5.7 Risks Associated With Corticosteroid Therapy

Pneumonia: Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS. In a 3-year study of 6,184 patients with COPD, there was a greater incidence of pneumonia in patients receiving ADVAIR DISKUS 50/500 compared with placebo (16% on ADVAIR DISKUS 50/500, 14% on fluticasone propionate 500 mcg, 11% on salmeterol 50 mcg, and 9% on placebo). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap.

Section 6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

Adverse Reactions With ADVAIR DISKUS in Patients With Chronic Obstructive Pulmonary Disease

	ADVAIR DISKUS 50/250 n = 178	ADVAIR DISKUS 50/500 n = 2,073	Fluticasone Propionate 250 mcg n = 183	Fluticasone Propionate 500 mcg n = 2,099	Salmeterol 50 mcg n = 2,255	Placebo n = 2,275
Adverse Reaction	%	%	%	%	%	%
Pneumonia	0*	13	1*	12	8	7
Candidiasis	11	9	9	11	3	3
Dysphonia	11	7	8	8	4	5
Contusion	1	2	1	2	1	1
Average duration of exposure (treatment years)	69	4,066	69	3,929	3,968	3,676

*In the two 6-month studies, pneumonia was considered to be a COPD exacerbation and therefore was not captured as an adverse reaction. Caution should be used when interpreting the incidence of pneumonia in the data for ADVAIR DISKUS 250/50 and fluticasone propionate 250 mcg.

Section 17 Patient Counselling Information has been updated to include the following information concerning pneumonias:

17.4 Risks Associated With Corticosteroid Therapy

Patients with COPD have a higher risk of pneumonia and should be instructed to contact their healthcare provider if they develop symptoms of pneumonia.

Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk.

Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); regular eye examinations should be considered.

In addition, a second bullet has been proposed for addition to the Medication Guide.

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?”
- Patients with COPD may have a higher chance of pneumonia. Call you healthcare provider if you notice any of the following symptoms: increase in sputum production, change in sputum color, fever, chills, increased cough, increased breathing problems.

8. REFERENCES

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