SUMMARY REVIEW OF REGULATORY ACTION

Date:	April 30, 2008
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	21-077, S-029 for Advair Diskus 250/50
Applicant Name:	GlaxoSmithKline
Date of Submission:	October 30, 2007
PDUFA Goal Date:	April 30, 2008
Proprietary Name:	Advair Diskus
Established Name:	Fluticasone propionate and salmeterol
Dosage form:	Oral Inhalation
Strength:	Fluticasone propionate 250 mcg and salmeterol 50 mcg
Proposed Indications:	Chronic Obstructive Pulmonary Disease
Action:	Approval

1. Introduction

GlaxoSmithKline (GSK) submitted a complete response to efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include beta-adrenergic agents, anticholinergic agents, combination products containing beta-adrenergic agents and anticholinergic agents, combination of long-acting beta-adrenergic agents and corticosteroids, and methyxanthines. There is no drug indicated to reduce exacerbations in patients with COPD. Advair Diskus will be first drug to have this indication.

GSK submitted an NDA supplement in October 2006 to support approval of Advair Diskus 500/50 twice daily to increase survival, reduce exacerbations, and improve airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The submission was discussed at a Pulmonary-Allergy Drug Advisory

Committee (PADAC) in May 2007. A not-approval action was taken on the application in August 2007 . Advair Diskus 250/50 was previously approved for maintenance of airflow obstruction in COPD but only in patients with associated chronic bronchitis. In this complete response GSK has , and submitted results from two new studies conducted with Advair 250/50 to support reduction in COPD exacerbation and maintenance of airflow obstruction in COPD including chronic bronchitis and emphysema.

3. Chemistry, Manufacturing, and Controls

Advair Diskus is an approved product and there are no CMC issues.

4. Nonclinical Pharmacology and Toxicology

No new pharmacology and toxicology studies were submitted with this complete response. The pharmacology and toxicology data were reviewed in the original NDA.

5. Clinical Pharmacology and Biopharmaceutics

The general clinical pharmacology and biopharmaceutic considerations for Advair Diskus were addressed in the original NDA. There are no issues with this application.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the pivotal studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Pivotal Advair Diskus clinical studies

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
Submitted with the original application							
SCO 30003	Efficacy and safety (survival, and exacerbation)	156 week	>40	Adv 500/50 Sal 50 FP 500 Pbo	1546 1542 1551 1545	2005	USA, Canada, EU, Asia, S America, S Africa, NZ and Australia
SFCB	Efficacy and safety	52 week	>40	Adv 500/50	358	2000	Canada, EU,

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
3024	(FEV1, and exacerbation)			Sal 50 FP 500 Pbo	372 374 361		S Africa, NZ and Australia
Submitted with complete response							
SCO 40043	Efficacy and safety (FEV1, and exacerbation)	52 week	>40	Adv 250/50 Sal 50	391 385	2006	USA, Canada
SCO 100250	Efficacy and safety (FEV1, and exacerbation)	52 week	>40	Adv 250/50 Sal 50	385 393	2007	USA, Canada
* Adv = Advair Diskus; Sal = Salmeterol; FP: Fluticasone propionate; Pbo = Placebo # Year study subject enrollment ended							

b. Design and conduct of the studies

Studies SCO30003 and SFCB3024:

These studies were submitted with the original application in October 2006 and were the subject of the PADAC meeting in May 2007. My Decisional Review from August 2007 and Memorandum for PADAC from April 2007 discusses these studies and are appended to this review.

Studies SCO40043 and SCO100250:

These were randomized, double-blind, parallel-group in design conducted in patients with COPD with a history of at least one COPD exacerbation in the previous 12 months. The study had a 4-week run-in period when all patients were treated with Advair 250/50 followed by 52-week double-blind treatment period. The primary efficacy variable was annual rate of moderate/severe COPD exacerbations. Other efficacy variables included FEV1, dairy recording of shortness of breath, night time awakening, supplemental albuterol use, and SGRQ. Safety evaluation included recording of adverse events.

COPD exacerbation in these studies was defined as: (1) worsening of two or more of the following major symptoms for at least two consecutive days: dyspnea, sputum volume, and sputum purulence; or, (2) worsening of any one major symptom together with any one of the following minor symptoms for at least two consecutive days: sore throat, colds (nasal discharge and/or nasal congestion), fever without any cause, and increased cough or wheeze. Each COPD exacerbation was defined as a mild exacerbation when it required only a change in bronchodilator, or a moderate/severe exacerbation when it required treatment with antibiotics, parenteral corticosteroids, and/or hospitalization.

There is no generally accepted definition of COPD exacerbations, but it usually includes some combination of symptoms and a change of treatment. The definition used in these

studies is as precise as practicable and generally follows closely the definitions used in the literature.[1]

c. Efficacy findings and conclusions

There are three components of efficacy assessments relevant to this application. These are airflow obstruction, exacerbations, and survival. These three areas are briefly discussed below.

Airflow obstruction

Advair 250/50 is currently approved for maintenance treatment of airflow obstruction in patients with COPD with chronic bronchitis. The approval was based on findings from two 6-month studies (SFCA3006 and SFCA3007, not discussed in this review) that were conducted in patients who had predominantly chronic bronchitis. Of the patients enrolled in those studies 54% had a bronchodilator response of >12% and 200 mL. In those studies the quantitative response showed no advantage of the Advair 500/50 mcg over Adair 250/50, and the current product label specifically states that Advair 500/50 dose is not recommended for use in COPD patients.

One change with this approval will be removal of restriction to patients with chronic bronchitis. The product will now be indicated for both chronic bronchitis and emphysema. This change is supported by results of FEV1 from the four studies (Table 1). None of these studies were restricted to patients with chronic bronchitis. Patients enrolled in these studies had features consistent with chronic bronchitis and emphysema, and increase in FEV1 was seen across the disease spectrum. The labeling will remain restricted to Advair 250/50 because no quantitative advantage of Advair 500/50 over Advair 250/50 was shown.

Exacerbations

Reduction of exacerbation claim for Advair 250/50 is supported by studies SCO40043 and SCO100250. Treatment with Advair 250/50 resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with salmeterol in study SCO40043 (30.5% reduction [95% CI: 17.0, 41.8], $p<0.001$) and in study SCO100250 (30.4% reduction [95% CI: 16.9, 41.7], $p<0.001$). Patients treated with Advair 250/50 also had a significantly lower annual rate of exacerbations requiring treatment with oral corticosteroids compared with patients treated with salmeterol in study SCO40043 (39.7% reduction [95% CI: 22.8, 52.9], $p <0.001$) and in study SCO100250 (34.3% reduction [95% CI: 18.6, 47.0], $p<0.001$).

In studies SCO30003 and SFCB3024 Advair 500/50 also showed lower rate of exacerbations, but by comparing across studies no quantitative advantage was seen for Advair 500/50 over Advair 250/50. Therefore, similar to airflow obstruction, the labeling will be restricted to Advair 250/50 for reduction of exacerbations as well.

[1] Cazzola M, MacNee W, Martizez FJ, et al. ATS/ERS Task Force Report: Outcomes for COPD pharmacological trials, from lung function to biomarkers. Eur Resp J 2008; 31: 416-468.

Survival

Survival was specifically studied in study SCO30003. Survival with Advair 500/50 was not significantly improved compared with placebo or the individual components. All cause mortality rate was 12.6% for Advair 500/50, 15.2% placebo, 13.5% for salmeterol 50 mcg, and 16.0% for fluticasone propionate 500 mcg. Advair will not have a survival benefit claim.

8. Safety

a. Safety database

The safety database for Advair in COPD patients is relatively large. In addition to the previous studies that was the basis of approval of Advair 250/50 for maintenance treatment of airflow obstruction in patients with COPD associated with chronic obstruction, this supplement brings in three one-year studies and one three-year study to the already existing safety database (Table 1).

b. Safety findings and conclusion

The Agency has previously concluded that Advair 250/50 is safe for use in COPD patients as labeled. This overall conclusion is not changed with the findings from the new studies submitted with the NDA supplement and the complete response. One major finding from the new studies is the observation of increased frequency of lower respiratory tract infection, specifically pneumonia, with Advair in COPD patients.

A clear increase in the incidence of pneumonia was seen in patients treated with fluticasone containing products (Advair or fluticasone propionate) in the COPD studies. In the combined analysis of studies SCO40043 and 100250 (the two replicate COPD exacerbations studies with Advair 250/50 compared to salmeterol 50) in a time-to-event analysis the probability (95% CI) of developing pneumonia at week 52 was 8.1 % (6.1, 10.2) with Advair 250/50 compared to 4.3% (2.6, 5.9) with salmeterol. The Kaplan-Meier survival curves from the two studies combined are shown in Figure 1. These results are similar to those seen in the study SCO30003 (the three-year survival study with Advair 500/50). The three-year incidence of pneumonia was 19.6%, 18.3%, 13.3%, and 12.3%, for Advair 500/50, fluticasone propionate 500, salmeterol 50, and placebo, respectively.

Other safety findings from the new studies did not show previously unknown safety signal for Advair. There were a relatively large number of deaths in the COPD program, which is not unexpected given the number of patients studied, the age of the patients, presence of COPD and other concomitant diseases, and in study SCO30003 the primary efficacy variable was death. In the two studies submitted with this complete response (studies SCO40043 and 100250) there were a total of 32 deaths. Review of these case reports did not show any findings suggestive of a safety signal specific for Advair. Of the serious adverse events from these two new studies, most common events were related to the respiratory tract followed by infection. Of the serious infectious events the majority were pneumonia. The common adverse events reported from these two new

studies followed the same pattern and distribution that has been reported in this group of patients in the previous studies.

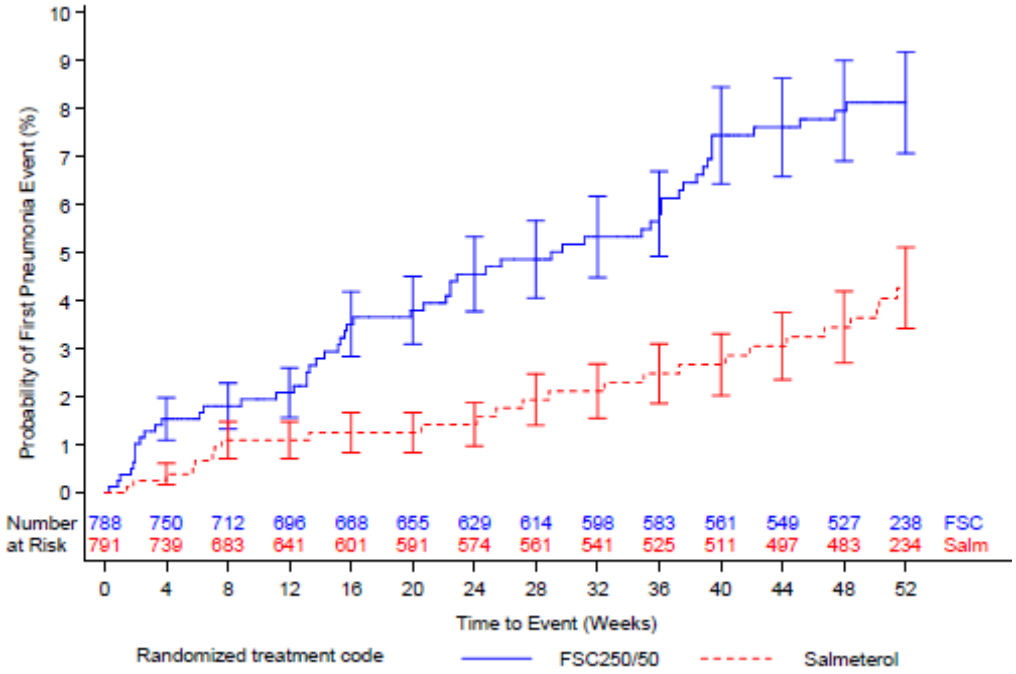


Figure 1. Incidence of pneumonia in combined study populations from studies SCO40043 and SCO100250. (FSC is Advair 250/50, Salm is salmeterol 50). [Figured copied from FDA medical review.

c. REMS/RiskMAP

Advair Diskus currently has a Boxed Warning and a Medication Guide because of risk of asthma related death. The review of this application identified a new safety signal of increased risk of pneumonia in patients with COPD treated with Advair Diskus. The pneumonia safety finding will be included in the Medical Guide. The increased risk of pneumonia is a "new safety information" as defined in section 505-1(a)(2) of FDAAA. In consultation with the Office of New Drugs and Office of Surveillance and Epidemiology (OSE) it was decided that the Medication Guide will now be considered part of a Risk Evaluation and Mitigation Strategy (REMS), as required by the FDAAA. GSK will submit three assessments of the REMS at 18 month, 3 years, and 7 years from approval of this supplement. Information for the assessment of REMS will include at least the following: 1. Survey of patients' understanding of the serious risks of Advair Diskus; 2. Report on periodic assessment of the distribution and dispensing of the Medical Guide; and, 3. Reports on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

9. Advisory Committee Meeting

An advisory committee was not convened for this complete response. An advisory committee meeting was convened for the original application as discussed in the materials appended to this review.

10. Pediatric

COPD is an adult disease, therefore, specific pediatric studies would not be required that relate to this action specific to COPD.

11. Other Relevant Regulatory Issues

a. DSI Audits

No DSI audit was conducted for this complete response. Audit of multiple sites were done in the past for the original application and no major deficiencies were identified. During review of the original NDA supplement and this complete response the clinical team did not identify any irregularities that would raise concerns regarding data integrity. It was noted that the applicant disqualified one center in study SCO40043 and six centers in study SCO100250 due to good clinical practice violation. The descriptions of the reasons for disqualifying these centers are justified. No ethical issues were present. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. Of the 172 clinical centers included in the two new studies, three investigators reported financials interested with a potential conflict. A total of 19 patients were enrolled at the three centers. The number of subjects that these investigators enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that equity interests could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from DDMAC, DSRCS, or from other groups in CDER.

12. Labeling

a. Proprietary Name

There are no issues with the proprietary name as the name Advair Diskus was previously reviewed and found to be acceptable.

b. Physician Labeling

The labeling of Advair Diskus was reviewed in the past with approval of the asthma and COPD indications and various supplements. With this application the existing label has undergone changes to include the new information related to the COPD indication changes, and the format was changed to the new Physician's Labeling Rule (PLR) format. There were some content changes to make the label consistent with the

expectations of the labeling language under the PLR format, and to make the language consistent with some other single ingredient inhaled long-action beta-agonist and inhaled corticosteroid labels that are in PLR format. The label was reviewed by various disciplines of this Division, and by DDMAC, OSE, and SEALD. The Division and the applicant have agreed to the final version of the label.

c. Carton and Immediate Container Labels

Advair is a marketed product and there were no changes to the carton and immediate container labels with this application. These were reviewed previously by various disciplines of this Division, and the current version was found to be acceptable.

d. Patient Labeling and Medication Guide

The Patient Counseling Information was reviewed by various disciplines of this Division, and DSRCS, and found to be acceptable. The existed Medication Guide was modified to include the pneumonia finding as discussed in section 8c above.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has submitted adequate data to support approval of Advair Diskus 250/50 for maintenance treatment of airflow obstruction and to reduce exacerbations in patients with COPD, including chronic bronchitis and/or emphysema. The action on this application will be Approval.

For administrative reasons the application was split into two, one for Advair Diskus 250/50 where the action will be approval (under NDA 21-077, S-029), and the other for Advair Diskus 500/50 where the action will be not approval (under NDA 21-077, [redacted].

[redacted]

b. Risk Benefit Assessment

The overall risk benefit assessment support approval of Advair 250/50 for maintenance treatment of airflow obstruction and to reduce exacerbations in patients with COPD, including chronic bronchitis and/or emphysema. The major risks associated with use of Advair 250/50 in COPD patients is the newly identified finding of pneumonia. There are other risks associated with the use of inhaled fluticasone and salmeterol that are described in the product label. Pneumonia is a serious safety finding, but it is reasonable to expect that health care providers taking care of patients with COPD will be able to readily diagnose pneumonia, differentiate it from a COPD exacerbation, and treat the pneumonia appropriately. The benefits of Advair 250/50 outweigh these risks and justify approval. Relief of airflow obstruction is a clinically meaningful improvement in COPD patients and by itself is not a trivial benefit. COPD exacerbation is a serious morbidity and is a common cause of COPD related hospitalization. Recurrent episodes of COPD exacerbation is associated with further impairment of lung function. At present there are no drugs approved for reduction of COPD exacerbation. Advair 250/50 will be the first product approved for reducing COPD exacerbation and represents a significant advancement in COPD treatment.

c. Post-marketing Risk Management Activities

Advair 250/50 currently has a Medication Guide, which will now be considered part of REMS. Risk management activities will fall under the provision of REMS (discussed in section 8c above).

d. Post-marketing Study Commitments

There will be no post-marketing studies required.

DIVISION DIRECTOR DECISIONAL REVIEW

Date: August 7, 2007

To: NDA 21-077, S029

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy products, CDER, FDA

Product: Advair Diskus 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder)

Applicant: GlaxoSmithKline

Administrative and Introduction

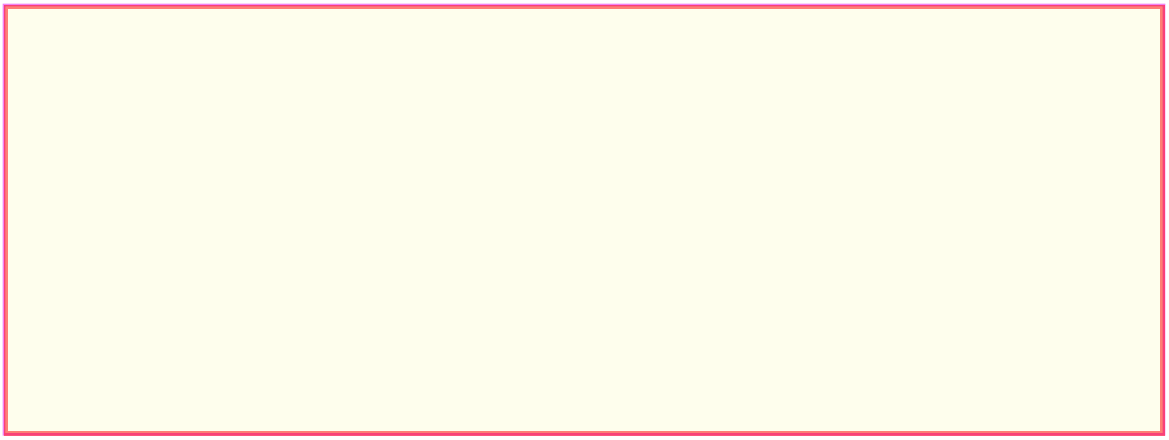
GlaxoSmithKline (GSK) submitted a supplemental new drug application (NDA 21-077, S029) on October 6, 2006 (received on October 10, 2006, CDER stamp date) to add a COPD indication for Advair Diskus 500/50. The proposed indication includes increased survival, reduction of exacerbation, and improvement of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. The PDUFA due date for this application is August 10, 2007. The action on this application will be Not Approvable. This document briefly describes the basis of this action. For details the reader is referred to Dr. Gilbert-McClain's Clinical Team Leader summary review. This application was the subject of a Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting held on May 1, 2007. My memorandum for the PADAC meeting is appended to this document. Dr. Gilbert-McClain's summary review and my memorandum for the PADAC meeting describe the clinical program that GSK submitted with this application. The clinical program is not further reviewed in this document.

Basis of the Action

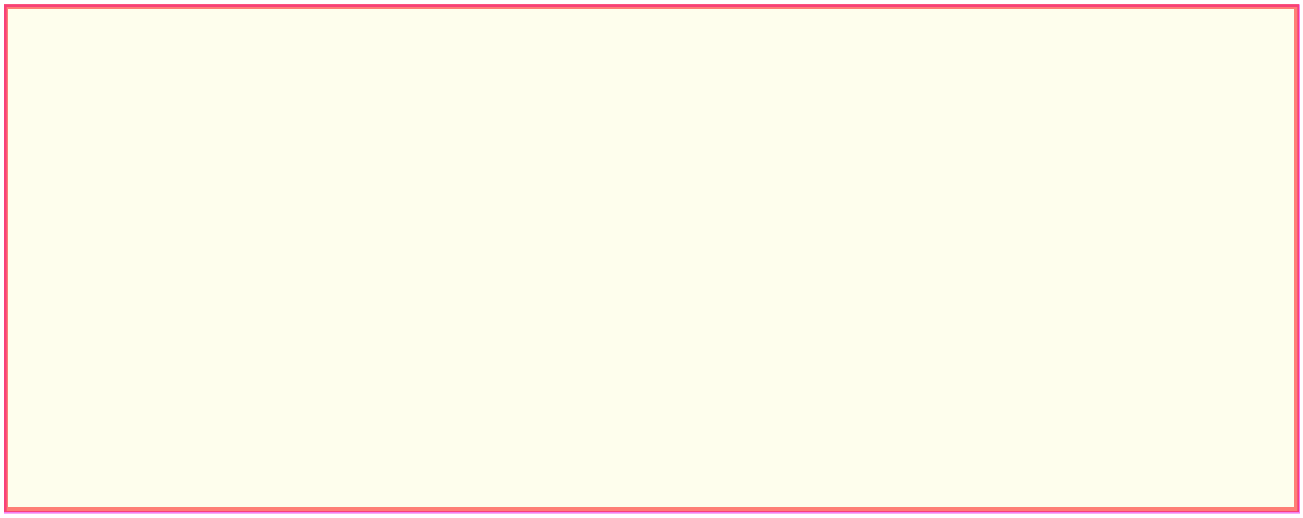
Three dosage strengths of Advair Diskus are currently marketed in the United States; these are Advair 100/50, Advair 250/50, and Advair 500/50, containing 100 mcg, 250 mcg, and 500 mcg, of fluticasone propionate, respectively, and each with 50 mcg of salmeterol. In the United States, Advair is currently approved for use in patients with asthma and in patients with COPD. All three dosage strengths are indicated as maintenance treatment of asthma. Only one dosage strength, Advair 250/50, has a COPD indication. The indication is for maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis. Advair 500/50 is not recommended for use in COPD because the pivotal studies that formed the basis of approval of Advair 250/50 showed no additional benefit with the higher dose, and the higher corticosteroid dose could have the potential for additional adverse effects in susceptible patients.

The proposed indication for increased survival and reduction of exacerbations are novel for a COPD drug in the United States. The current COPD indication is restricted to

patients with chronic bronchitis, while the new claim would add patients with emphysema as well. Further, the application is for Advair 500/50, which is currently not approved for use in COPD.



At the PADAC meeting held on May 1, 2007, the focus of the discussion was around the increased survival claim, reduction of exacerbation claim, and the safety concerns of pneumonia and other respiratory tract infections. The majority of the PADAC voting members concluded that the data did not provide substantial convincing evidence that Advair 500/50 increased survival in COPD patients (9 voted No, 2 voted Yes, none abstained from voting). Some PADAC members commented on the observation that the mortality data seemed to suggest that salmeterol alone was showing the positive signal in favor of survival, whereas fluticasone seemed to be detrimental. On the issue of reduction on exacerbation, the unanimous conclusion was that the submitted data did provided substantial convincing evidence that Advair 500/50 provided decrease in COPD exacerbation (11 voted Yes, 0 voted No, none abstained from voting). There was also unanimous conclusion that the findings of pneumonia and respiratory infections seen in the studies are of concern and further studies are warranted to address this safety signal.



DIVISION DIRECTOR MEMORANDUM

Date: April 4, 2007

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

To: Members, Pulmonary-Allergy Drugs Advisory Committee

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

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

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

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

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

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

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

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

Study SCO30003

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

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

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

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

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

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

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

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

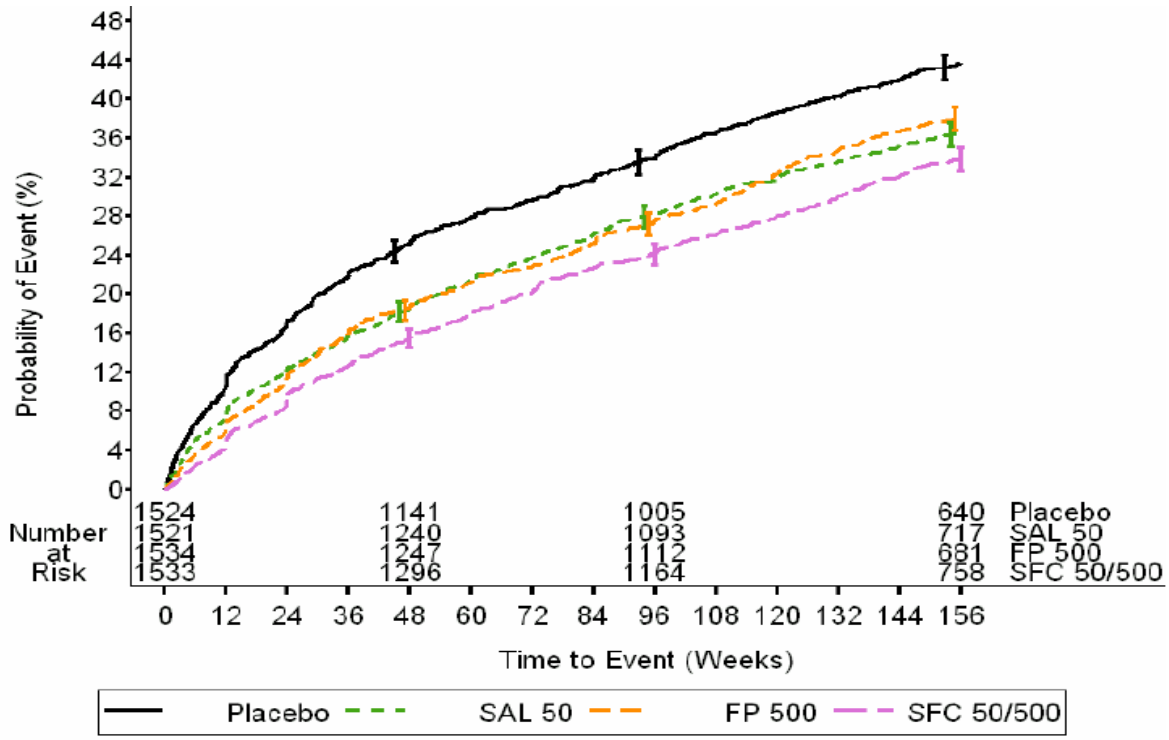


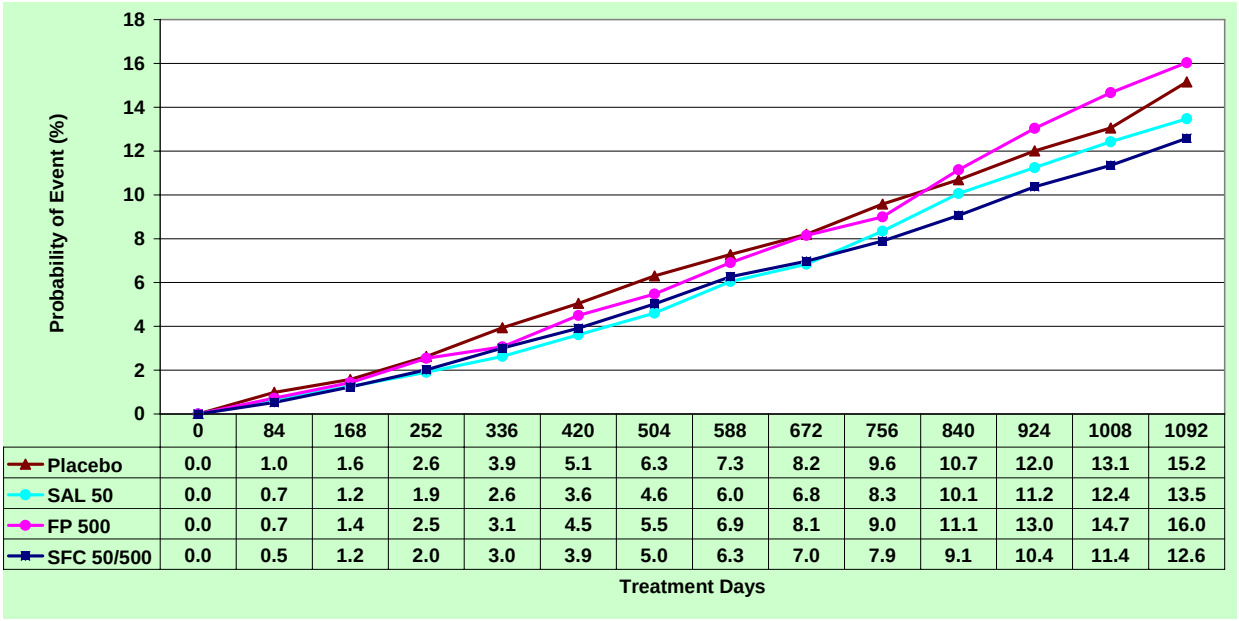
Figure 1. Time to study drug discontinuation – cumulative incidence curve (MITT), [Study SCO30003]

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

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

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

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



	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092
Placebo	0.0	1.0	1.6	2.6	3.9	5.1	6.3	7.3	8.2	9.6	10.7	12.0	13.1	15.2
SAL 50	0.0	0.7	1.2	1.9	2.6	3.6	4.6	6.0	6.8	8.3	10.1	11.2	12.4	13.5
FP 500	0.0	0.7	1.4	2.5	3.1	4.5	5.5	6.9	8.1	9.0	11.1	13.0	14.7	16.0
SFC 50/500	0.0	0.5	1.2	2.0	3.0	3.9	5.0	6.3	7.0	7.9	9.1	10.4	11.4	12.6

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

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

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

Table 3. Survival data analyses, [Study SCO30003]

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

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

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

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

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

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

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

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

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

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

Study SFCB3024

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

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

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

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

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

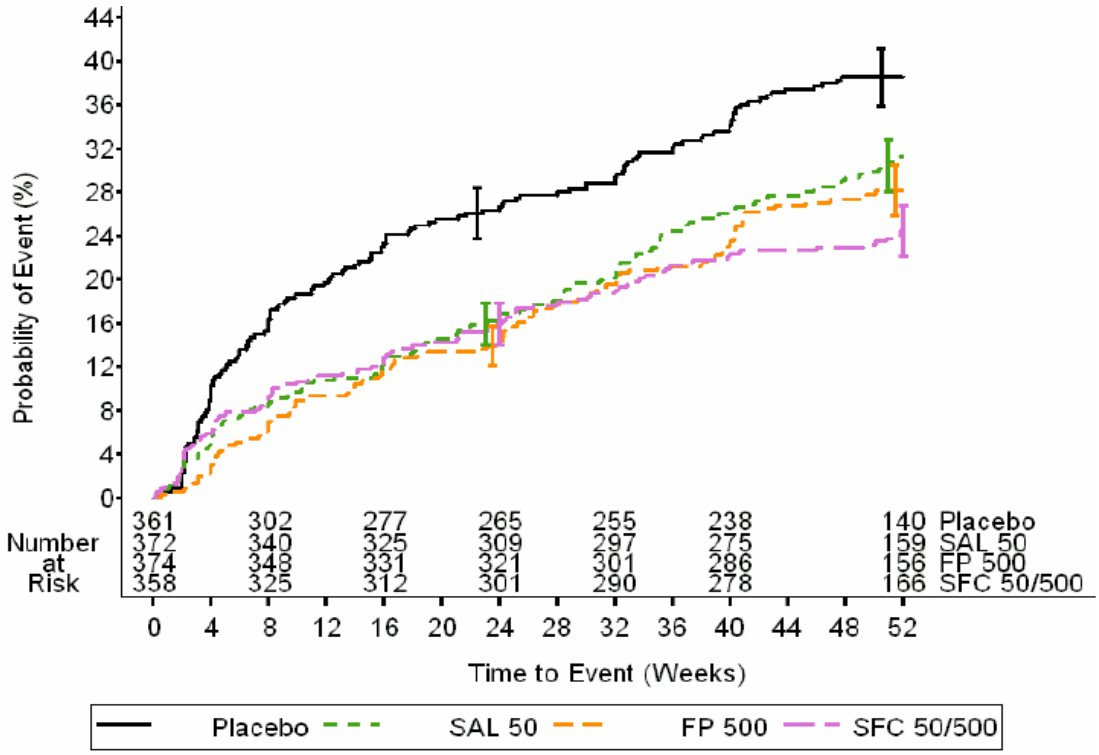


Figure 3. Time to study drug discontinuation – cumulative incidence curve (ITT), [Study SFCB3024]

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

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

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

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

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

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

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

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

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

Key issues

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

Increased survival

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

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

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

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

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

Reduction in exacerbations

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

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

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

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

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

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

Safety

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

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

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

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

Questions

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

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

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

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

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

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

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

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

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/s/

Badrul Chowdhury
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