

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-077/S-003

Trade Name: Advair Diskus 250/50

Generic Name: fluticasone propionate and salmeterol xinafoate
inhalation powder

Sponsor: GlaxoSmithKline

Approval Date: November 11, 2003

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APPLICATION NUMBER:

NDA 21-077/S-003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-077/S-003

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-077/S-003

GlaxoSmithKline
P. O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Patrick D. Wire, Pharm.D.
Product Director, Respiratory Group

Dear Dr. Wire:

Please refer to your supplemental new drug application dated May 4, 2001, received May 7, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advair Diskus 250/50 (fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder).

We acknowledge receipt of your submissions dated August 31, October 17, and 26, and November 9, 2001, and February 28, March 22, June 20, July 10, October 25, and November 13, 2002, and January 14, May 30, October 10, 2003, November 6, 12, and 17, 2003.

Your submission of May 30, 2003, constituted a complete response to our December 12, 2002, action letter.

This supplemental new drug application provides for the use of Advair Diskus 250/50 (fluticasone propionate and salmeterol xinafoate inhalation powder) for Chronic Obstructive Pulmonary Disease associated with Chronic Bronchitis.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted on November 17, 2003, and text for the patient instruction leaflet submitted on November).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-077/S-003." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated November 17, 2003. These commitments are listed below.

1. Conduct a randomized double-blind parallel-group study to evaluate the effect of Advair 250/50 via Diskus on bone mineral density in subjects with chronic obstructive pulmonary disease. The agreed upon timelines for the submission of the final protocol is April 2004, and the final report is due in December 2007.
2. Conduct a randomized double-blind, parallel-group study to evaluate the effect of Advair 250/50 via Diskus on exacerbations in subjects with chronic obstructive pulmonary disease. The agreed upon timelines for the submission of the final protocol is April 2004, and the final report is due in August 2007.

Submit clinical protocols to your IND for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol," "Postmarketing Study Final Report," or "Postmarketing Study Correspondence."

In addition, we remind you of the following agreements as stated in your submission dated November 17, 2003.

1. Review all new serious unexpected cases (spontaneous cases and attributable clinical trial cases) within 1-2 days of receipt and follow up on the cases for full documentation using targeted questions.
2. Submit a quarterly listing and review of all serious adverse events occurring during clinical trials with Advair.
3. Review all new spontaneous cases describing adverse events of special interest within 1-2 days of receipt and follow up on the cases for full documentation using targeted questions. Adverse events of special interest are (a) decrease bone mineral density, osteoporosis, and fractures (b) cataract and glaucoma, (c) adrenal suppression and (d) lower respiratory tract infections [pneumonia].
4. Maintain monthly listings and review all newly reported adverse events, and perform monthly data mining of your spontaneous adverse event database for adverse events of special interest as listed in item 3 above. Submit the results with quarterly reports.
5. Submit a quarterly cumulative review of all spontaneous adverse event reports, and clinical trial cases of adverse events of special interest as listed in item 3 above.
6. Submit cumulative review of all spontaneous reports describing pneumonia, categorized by patient age, total daily dose and indication at six month intervals.

7. Submit a plan for evaluating the performance of the elements of the risk management plan with details of the timeline and the methodology that will be applied in the plan.
8. Specify a time when you will report back to the Agency to provide data on (a) the extent of high-dose use of Advair Diskus among patients with COPD and (b) the extent of compliance with the risk management plan and complications of product use (through surveys of COPD patients and/or physicians using claims databases).
9. Produce patient and health care provider educational material describing the possible risks of Advair use in COPD patients, such as bone demineralization, glaucoma, and cataract formation. In addition, advise physicians and patients on the appropriate use of Advair Diskus for the treatment of COPD associated with chronic bronchitis.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary & Allergy Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 21-077/S-003

Page 4

Enclosure (Package insert & Patient Instruction leaflet)

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/s/

Badrul Chowdhury
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APPLICATION NUMBER:

NDA 21-077/S-003

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-077/S-003

GlaxoSmithKline
P. O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Patrick D. Wire, Pharm.D.
Product Director, Respiratory Group

Dear Dr. Wire:

Please refer to your supplemental new drug application dated May 4, 2001, received May 5, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder).

We acknowledge receipt of your submissions dated August 31, October 17 and 26, November 9, 2001, and February 28, March 22, June 20, July 10, October 25, and November 13, 2002.

Your submission of July 10, 2002, constituted a complete response to our March 5, 2002, action letter.

This supplemental new drug application proposes for the use of Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) for the long-term twice daily maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, you must address the following deficiencies.

1. Your response does not provide data that more fully delineate the efficacy and safety of Advair 250/50 (see approvable letter March 5, 2002) to support approval for COPD.
2. Efficacy data from study SFCB3024 does not address the efficacy of Advair 250/50 as this study was conducted with Advair 500/50. Additionally, the signal in the data sets provided suggest an increase in lower respiratory tract infections (including pneumonia and viral respiratory infections) with Advair 500/50 compared to its individual components.
3. The safety results from study FLTA30001 do not address the long-term safety of inhaled corticosteroids in the COPD population.
4. The results of the 4-observational studies do not constitute substantial evidence of efficacy or safety, and from a regulatory standpoint, cannot be used as the basis for drug approval. Pharmacoeconomic endpoints such as resource utilization and cost are not regulatory considerations for drug approval in the United States.

5. In order to be approved, you must supply data that more fully define the efficacy (including outcome data) and safety (including impact on bone density) of Advair 250/50 in patients with COPD (see Approvable letter of March 5, 2002).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required. You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 301-827-1084.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Acting Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-077/S-003
NDA 20-833/S-004

GlaxoSmithKline
P.O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Attention: C. Elaine Jones, Ph.D.
Director, Regulatory Affairs

Dear Dr. Jones:

Please refer to your supplemental new drug applications dated May 4, 2001, and May 25, received May 7, 2001, and May 25, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advair Diskus (fluticasone propionate and salmeterol xinofoate inhalation powder), and Flovent Diskus (fluticasone propionate inhalation powder) respectively.

We acknowledge receipt of your submissions dated August 31, October 17, and 26, and November 9, 2001 for Advair Diskus. We also acknowledge receipt of your submissions dated August 10, September 5, and 17, October 17, and 26, November 9, 2001, January 31, and February 12, 2002, for Flovent Diskus. We also acknowledge receipt of your submissions dated February 28, 2002, containing safety updates for the above applications. These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

These supplemental new drug applications propose for the use of Advair Diskus (fluticasone propionate and salmeterol xinofoate inhalation powder), and Flovent Diskus (fluticasone propionate inhalation powder) for the long-term, twice daily, maintenance treatment of chronic obstructive lung disease (COPD) including chronic bronchitis and emphysema.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to address the following.

We do not believe that you have provided substantial data to support a conclusion that these drug products are sufficiently safe and effective for the indication proposed in the COPD population. Given the modest and limited extent of the efficacy findings (including a lack of effect on exacerbation rates), given the known potential for fluticasone to cause adverse systemic effects as demonstrated by spontaneous adverse events reporting and clinical studies, and given the signal in the data sets provided of an increase in upper and lower respiratory infections, we believe that more definitive efficacy and safety data are needed prior to approval. In order to be approved, you must supply data that more fully delineates the safety (including impact on bone density) beyond 6-months and further evidence of efficacy (including outcome data). Data from your current, on-going 3-year trial in COPD, if favorable, may reasonably serve as a substantial portion of these requested data.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are encouraged to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-5584.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Robert Meyer
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-077/S-003

APPROVED LABELING

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PRESCRIBING INFORMATION

1
2 **ADVAIR DISKUS[®] 100/50**

3 (fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

4
5 **ADVAIR DISKUS[®] 250/50**

6 (fluticasone propionate 250 mcg and salmeterol* 50 mcg inhalation powder)

7
8 **ADVAIR DISKUS[®] 500/50**

9 (fluticasone propionate 500 mcg and salmeterol* 50 mcg inhalation powder)

10
11 *As salmeterol xinafoate salt 72.5 mcg, equivalent to salmeterol base 50 mcg

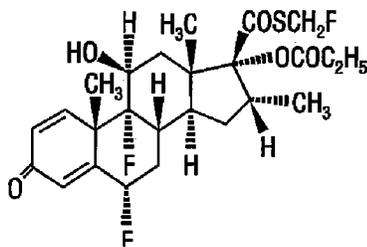
12
13 **For Oral Inhalation Only**

14 **WARNING:** Data from a large placebo-controlled US study that compared the safety of
15 salmeterol (SEREVENT[®] Inhalation Aerosol) or placebo added to usual asthma therapy showed
16 a small but significant increase in asthma-related deaths in patients receiving salmeterol (13
17 deaths out of 13,174 patients treated for 28 weeks) versus those on placebo (4 of 13,179).
18 Subgroup analyses suggest the risk may be greater in African American patients compared to
19 Caucasians (see WARNINGS).

20 **DESCRIPTION**

21 ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are
22 combinations of fluticasone propionate and salmeterol xinafoate.

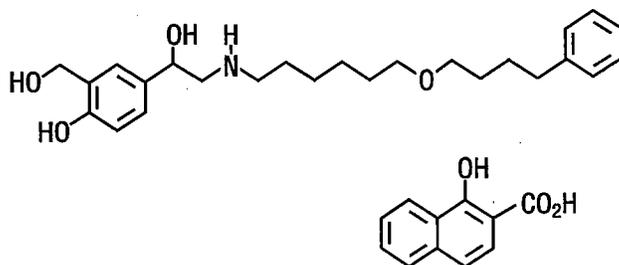
23 One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid having
24 the chemical name *S*-(fluoromethyl) 6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-
25 oxoandrosta-1,4-diene-17 β -carbothioate, 17-propionate and the following chemical structure:
26



27
28
29 Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and
30 the empirical formula is C₂₅H₃₁F₃O₅S. It is practically insoluble in water, freely soluble in
31 dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

32 The other active component of ADVAIR DISKUS is salmeterol xinafoate, a beta₂-adrenergic
33 bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt

34 of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy- α^1 -[[[6-(4-
35 phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-
36 naphthalenecarboxylate, and it has the following chemical structure:



38
39
40 Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8, and the
41 empirical formula is C₂₅H₃₇NO₄•C₁₁H₈O₃. It is freely soluble in methanol; slightly soluble in
42 ethanol, chloroform, and isopropanol; and sparingly soluble in water.

43 ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are
44 specially designed plastic devices containing a double-foil blister strip of a powder formulation
45 of fluticasone propionate and salmeterol xinafoate intended for oral inhalation only. Each blister
46 on the double-foil strip within the device contains 100, 250, or 500 mcg of microfine fluticasone
47 propionate and 72.5 mcg of microfine salmeterol xinafoate salt, equivalent to 50 mcg of
48 salmeterol base, in 12.5 mg of formulation containing lactose (which contains milk proteins).
49 Each blister contains 1 complete dose of both medications. After a blister containing medication
50 is opened by activating the device, the medication is dispersed into the airstream created by the
51 patient inhaling through the mouthpiece.

52 Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg
53 of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS
54 100/50, 250/50, and 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds.
55 In adult patients with obstructive lung disease and severely compromised lung function (mean
56 forced expiratory volume in 1 second [FEV₁] 20% to 30% of predicted), mean peak inspiratory
57 flow (PIF) through a DISKUS[®] inhalation device was 82.4 L/min (range, 46.1 to 115.3 L/min).

58 Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to
59 50 years) patients with asthma inhaling maximally through the DISKUS device show mean PIF
60 of 122.2 L/min (range, 81.6 to 152.1 L/min).

61 The actual amount of drug delivered to the lung will depend on patient factors, such as
62 inspiratory flow profile.

63 CLINICAL PHARMACOLOGY

64 **Mechanism of Action: ADVAIR DISKUS:** Since ADVAIR DISKUS contains both
65 fluticasone propionate and salmeterol, the mechanisms of action described below for the
66 individual components apply to ADVAIR DISKUS. These drugs represent 2 classes of

67 medications (a synthetic corticosteroid and a selective, long-acting beta-adrenergic receptor
68 agonist) that have different effects on clinical and physiological indices.

69 **Fluticasone Propionate:** Fluticasone propionate is a synthetic trifluorinated corticosteroid
70 with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations
71 have established fluticasone propionate as a human glucocorticoid receptor agonist with an
72 affinity 18 times greater than dexamethasone, almost twice that of
73 beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone
74 dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor
75 assay in man are consistent with these results.

76 Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have
77 been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes,
78 macrophages, and neutrophils) and mediator production or secretion (e.g., histamine,
79 eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These
80 anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

81 Inflammation is also a component in the pathogenesis of COPD. In contrast to asthma,
82 however, the predominant inflammatory cells in COPD include neutrophils, CD8+
83 T-lymphocytes, and macrophages. The effects of corticosteroids in the treatment of COPD are
84 not well defined and inhaled corticosteroids and fluticasone propionate when used apart from
85 ADVAIR DISKUS are not indicated for the treatment of COPD.

86 **Salmeterol Xinafoate:** Salmeterol is a long-acting beta₂-adrenergic agonist. In vitro studies
87 and in vivo pharmacologic studies demonstrate that salmeterol is selective for
88 beta₂-adrenoceptors compared with isoproterenol, which has approximately equal agonist
89 activity on beta₁- and beta₂-adrenoceptors. In vitro studies show salmeterol to be at least 50 times
90 more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the
91 predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the
92 predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart
93 comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors
94 has not been established, but they raise the possibility that even highly selective beta₂-agonists
95 may have cardiac effects.

96 The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including salmeterol, are at
97 least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes
98 the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic
99 AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition
100 of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

101 In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast
102 cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung.
103 Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits
104 platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when
105 administered by the inhaled route. In humans, single doses of salmeterol administered via
106 inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

107 **Pharmacokinetics: ADVAIR DISKUS:** Following administration of ADVAIR DISKUS to
108 healthy subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to
109 2 hours and those of salmeterol were achieved in about 5 minutes.

110 In a single-dose crossover study, a higher than recommended dose of ADVAIR DISKUS was
111 administered to 14 healthy subjects. Two (2) inhalations of the following treatments were
112 administered: ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol
113 powder 50 mcg given concurrently, and fluticasone propionate powder 500 mcg alone. Mean
114 peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL,
115 respectively, and of salmeterol averaged 200 and 150 pg/mL, respectively, indicating no
116 significant changes in systemic exposures of fluticasone propionate and salmeterol.

117 In a repeat-dose study, the highest recommended dose of ADVAIR DISKUS was
118 administered to 45 patients with asthma. One (1) inhalation twice daily of the following
119 treatments was administered: ADVAIR DISKUS 500/50, fluticasone propionate powder
120 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder
121 500 mcg alone. Mean peak steady-state plasma concentrations of fluticasone propionate
122 averaged 57, 73, and 70 pg/mL, respectively, indicating no significant changes in systemic
123 exposure of fluticasone propionate. No plasma concentrations of salmeterol were measured in
124 this repeat-dose study.

125 No significant changes in excretion of fluticasone propionate or salmeterol were observed.
126 The terminal half-life of fluticasone propionate averaged 5.33 to 7.65 hours when ADVAIR
127 DISKUS was administered, which is similar to that reported when fluticasone propionate was
128 given concurrently with salmeterol or when fluticasone propionate was given alone (average,
129 5.30 to 6.91 hours). No terminal half-life of salmeterol was reported upon administration of
130 ADVAIR DISKUS or salmeterol given concurrently with fluticasone propionate.

131 **Special Populations:** Formal pharmacokinetic studies using ADVAIR DISKUS have
132 not been conducted to examine gender differences or in special populations, such as elderly
133 patients or patients with hepatic or renal impairment.

134 **Drug Interactions:** In the repeat- and single-dose studies, there was no evidence of
135 significant drug interaction in systemic exposure between fluticasone propionate and salmeterol
136 when given as ADVAIR DISKUS.

137 **Fluticasone Propionate: Absorption:** Fluticasone propionate acts locally in the lung;
138 therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled
139 and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone
140 propionate is negligible (<1%), primarily due to incomplete absorption and presystemic
141 metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered
142 to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate from
143 the DISKUS device in healthy volunteers averages 18%.

144 Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma
145 (N = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone

146 propionate inhalation powder using the DISKUS device. The mean fluticasone propionate
147 plasma concentration was 110 pg/mL.

148 Peak steady-state fluticasone propionate plasma concentrations in subjects with COPD
149 averaged 53 pg/mL (range, 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily
150 (N = 30) via the DISKUS device.

151 **Distribution:** Following intravenous administration, the initial disposition phase for
152 fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding.
153 The volume of distribution averaged 4.2 L/kg.

154 The percentage of fluticasone propionate bound to human plasma proteins averages 91%.
155 Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly
156 bound to human transcortin.

157 **Metabolism:** The total clearance of fluticasone propionate is high (average,
158 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only
159 circulating metabolite detected in man is the 17 β -carboxylic acid derivative of fluticasone
160 propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had
161 less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of
162 human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other
163 metabolites detected in vitro using cultured human hepatoma cells have not been detected in
164 man.

165 **Elimination:** Following intravenous dosing, fluticasone propionate showed
166 polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours.
167 Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the
168 remainder excreted in the feces as parent drug and metabolites.

169 **Special Populations: Hepatic Impairment:** Since fluticasone propionate is
170 predominantly cleared by hepatic metabolism, impairment of liver function may lead to
171 accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease
172 should be closely monitored.

173 **Gender:** Full pharmacokinetic profiles were obtained from 9 female and 16 male
174 patients with asthma given fluticasone propionate inhalation powder 500 mcg twice daily using
175 the DISKUS device and from 14 female and 43 male patients with COPD given 250 or 500 mcg
176 twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

177 **Age:** No relationship between fluticasone propionate systemic exposure and age was
178 observed in 57 patients with COPD (aged 40 to 82 years) given 250 or 500 mcg twice daily.

179 **Other:** Formal pharmacokinetic studies using fluticasone propionate have not been
180 conducted in other special populations.

181 **Drug Interactions:** Fluticasone propionate is a substrate of cytochrome P450 3A4.
182 Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor
183 ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18
184 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was
185 coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate

186 concentrations following fluticasone propionate aqueous nasal spray alone were undetectable
187 (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{max}
188 averaged 11.9 pg/mL [range, 10.8 to 14.1 pg/mL] and $AUC_{(0-\tau)}$ averaged 8.43 pg•hr/mL [range,
189 4.2 to 18.8 pg•hr/mL]). Fluticasone propionate C_{max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range,
190 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively,
191 after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This
192 significant increase in plasma fluticasone propionate exposure resulted in a significant decrease
193 (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

194 Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are
195 coadministered with fluticasone propionate. In a drug interaction study, coadministration of
196 orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted
197 in increased plasma fluticasone propionate exposure and reduced plasma cortisol AUC, but had
198 no effect on urinary excretion of cortisol.

199 In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone
200 propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect
201 fluticasone propionate pharmacokinetics.

202 **Salmeterol Xinafoate:** Salmeterol xinafoate, an ionic salt, dissociates in solution so that the
203 salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed,
204 metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma
205 levels do not predict therapeutic effect.

206 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low
207 or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder
208 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol
209 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7
210 patients with asthma; plasma concentrations were very low, with mean peak concentrations of
211 167 pg/mL at 20 minutes and no accumulation with repeated doses.

212 **Distribution:** The percentage of salmeterol bound to human plasma proteins averages
213 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much
214 higher concentrations than those achieved following therapeutic doses of salmeterol.

215 **Metabolism:** Salmeterol base is extensively metabolized by hydroxylation, with
216 subsequent elimination predominantly in the feces. No significant amount of unchanged
217 salmeterol base was detected in either urine or feces.

218 **Elimination:** In 2 healthy subjects who received 1 mg of radiolabeled salmeterol (as
219 salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was
220 eliminated in urine and feces, respectively; over a period of 7 days. The terminal elimination
221 half-life was about 5.5 hours (1 volunteer only).

222 The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly
223 protein bound (>99%) and has a long elimination half-life of 11 days.

224 **Special Populations: Hepatic Impairment:** Since salmeterol is predominantly
225 cleared by hepatic metabolism, impairment of liver function may lead to accumulation of
226 salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

227 **Other:** Formal pharmacokinetic studies using salmeterol base have not been conducted
228 in other special populations.

229 **Pharmacodynamics: ADVAIR DISKUS:** Since systemic pharmacodynamic effects of
230 salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce
231 measurable effects. Four studies were conducted in healthy subjects: (1) a single-dose crossover
232 study using 2 inhalations of ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg
233 and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg
234 given alone, (2) a cumulative dose study using 50 to 400 mcg of salmeterol powder given alone
235 or as ADVAIR DISKUS 500/50, (3) a repeat-dose study for 11 days using 2 inhalations twice
236 daily of ADVAIR DISKUS 250/50, fluticasone propionate powder 250 mcg, or salmeterol
237 powder 50 mcg, and (4) a single-dose study using 5 inhalations of ADVAIR DISKUS 100/50,
238 fluticasone propionate powder 100 mcg alone, or placebo. In these studies no significant
239 differences were observed in the pharmacodynamic effects of salmeterol (pulse rate, blood
240 pressure, QTc interval, potassium, and glucose) whether the salmeterol was given as ADVAIR
241 DISKUS, concurrently with fluticasone propionate from separate inhalers, or as salmeterol alone.
242 The systemic pharmacodynamic effects of salmeterol were not altered by the presence of
243 fluticasone propionate in ADVAIR DISKUS. The potential effect of salmeterol on the effects of
244 fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis was also evaluated in
245 these studies. No significant differences across treatments were observed in 24-hour urinary
246 cortisol excretion and, where measured, 24-hour plasma cortisol AUC. The systemic
247 pharmacodynamic effects of fluticasone propionate were not altered by the presence of
248 salmeterol in ADVAIR DISKUS in healthy subjects.

249 **Asthma:** In clinical studies with ADVAIR DISKUS in patients with asthma, no
250 significant differences were observed in the systemic pharmacodynamic effects of salmeterol
251 (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was
252 given alone or as ADVAIR DISKUS. In 72 adolescent and adult patients with asthma given
253 either ADVAIR DISKUS 100/50 or ADVAIR DISKUS 250/50, continuous 24-hour
254 electrocardiographic monitoring was performed after the first dose and after 12 weeks of
255 therapy, and no clinically significant dysrhythmias were noted.

256 In a 28-week study in patients with asthma, ADVAIR DISKUS 500/50 twice daily was
257 compared with the concurrent use of salmeterol powder 50 mcg plus fluticasone propionate
258 powder 500 mcg from separate inhalers or fluticasone propionate powder 500 mcg alone. No
259 significant differences across treatments were observed in plasma cortisol AUC after 12 weeks
260 of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

261 In a 12-week study in patients with asthma, ADVAIR DISKUS 250/50 twice daily was
262 compared with fluticasone propionate powder 250 mcg alone, salmeterol powder 50 mcg alone,
263 and placebo. For most patients, the ability to increase cortisol production in response to stress, as

264 assessed by 30-minute cosyntropin stimulation, remained intact with ADVAIR DISKUS. One
265 patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal response (peak serum
266 cortisol <18 mcg/dL) after dosing, compared with 2 patients (6%) who received placebo,
267 2 patients (6%) who received fluticasone propionate 250 mcg, and no patients who received
268 salmeterol.

269 **Chronic Obstructive Pulmonary Disease:** In clinical studies with ADVAIR
270 DISKUS in patients with COPD associated with chronic bronchitis, no significant differences
271 were seen in pulse rate, blood pressure, potassium, and glucose between ADVAIR DISKUS, the
272 individual components of ADVAIR DISKUS, and placebo. In a study of ADVAIR DISKUS
273 250/50, 8 subjects (2 [1.1%] in the group given ADVAIR DISKUS 250/50, 1 [0.5%] in the
274 fluticasone propionate 250 mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the
275 placebo group) had QTc intervals >470 msec at least 1 time during the treatment period. Five (5)
276 of these 8 subjects had a prolonged QTc interval at baseline.

277 In a 24-week study, 130 patients with COPD associated with chronic bronchitis received
278 continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of
279 twice-daily treatment with either ADVAIR DISKUS 500/50, fluticasone propionate powder
280 500 mcg, salmeterol powder 50 mcg, or placebo. No significant differences in ventricular or
281 supraventricular arrhythmias and heart rate were observed among the groups treated with
282 ADVAIR DISKUS 500/50, the individual components, or placebo. One (1) subject in the
283 fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the
284 group given ADVAIR DISKUS 500/50 experienced heart block. There were 3 cases of
285 nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone 500 mcg
286 treatment groups).

287 Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in
288 101 patients with COPD receiving twice-daily ADVAIR DISKUS 250/50, fluticasone propionate
289 powder 250 mcg, salmeterol powder 50 mcg, or placebo. For most patients, the ability to
290 increase cortisol production in response to stress, as assessed by short cosyntropin stimulation,
291 remained intact with ADVAIR DISKUS 250/50. One (1) patient (3%) who received ADVAIR
292 DISKUS 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL
293 assessed by high-performance liquid chromatography) after dosing, compared with 2 patients
294 (9%) who received fluticasone propionate 250 mcg, 2 patients (7%) who received salmeterol
295 50 mcg, and 1 patient (4%) who received placebo following 24 weeks of treatment or early
296 discontinuation from study.

297 **Fluticasone Propionate: Asthma:** In clinical trials with fluticasone propionate inhalation
298 powder using doses up to and including 250 mcg twice daily, occasional abnormal short
299 cosyntropin tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted
300 both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence
301 of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out
302 with the DISKHALER[®] inhalation device in 64 patients with mild, persistent asthma (mean
303 FEV₁ 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo,

304 no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin
305 infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1
306 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing
307 at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had
308 an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or
309 2 years.

310 **Chronic Obstructive Pulmonary Disease:** In a 24-week study, the steady-state
311 fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of
312 patients with COPD associated with chronic bronchitis (N = 86) randomized to twice-daily
313 fluticasone propionate inhalation powder via the DISKUS 500 mcg, fluticasone propionate
314 inhalation powder 250 mcg, or placebo. Serial serum cortisol concentrations were measured
315 across a 12-hour dosing interval following at least 4 weeks of dosing. Serum cortisol
316 concentrations following 250 and 500 mcg twice-daily dosing were 10% and 21% lower than
317 placebo, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

318 **Salmeterol Xinafoate:** Inhaled salmeterol, like other beta-adrenergic agonist drugs, can
319 produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium
320 (see PRECAUTIONS: General). The cardiovascular effects (heart rate, blood pressure)
321 associated with salmeterol occur with similar frequency, and are of similar type and severity, as
322 those noted following albuterol administration.

323 **Asthma:** The effects of rising doses of salmeterol and standard inhaled doses of albuterol
324 were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg
325 administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the
326 same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and
327 adult patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent
328 continuous electrocardiographic monitoring during two 12-hour periods after the first dose and
329 after 1 month of therapy, and no clinically significant dysrhythmias were noted.

330 **Chronic Obstructive Pulmonary Disease:** In 24-week clinical studies in patients
331 with COPD associated with chronic bronchitis, the incidence of clinically significant
332 electrocardiogram (ECG) abnormalities (myocardial ischemia, ventricular hypertrophy, clinically
333 significant conduction abnormalities, clinically significant arrhythmias) was lower for patients
334 who received salmeterol (1%, 9 of 688 patients who received either salmeterol 50 mcg or
335 ADVAIR DISKUS) compared with placebo (3%, 10 of 370 subjects).

336 No significant differences with salmeterol 50 mcg alone or in combination with fluticasone
337 propionate as ADVAIR DISKUS 500/50 was observed on pulse rate and systolic and diastolic
338 blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign
339 measurements after the first dose (N = 183) and after 12 weeks of therapy (N = 149). Median
340 changes from baseline in pulse rate and systolic and diastolic blood pressure were similar to
341 those seen with placebo (see ADVERSE REACTIONS: Chronic Obstructive Pulmonary Disease
342 Associated With Chronic Bronchitis).

343 Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence
344 of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when
345 beta-agonists and methylxanthines are administered concurrently. The clinical significance of
346 these findings is unknown.

347 **CLINICAL TRIALS**

348 **Asthma:** In clinical trials comparing ADVAIR DISKUS with the individual components,
349 improvements in most efficacy endpoints were greater with ADVAIR DISKUS than with the use
350 of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed similar
351 results between ADVAIR DISKUS and the concurrent use of fluticasone propionate plus
352 salmeterol at corresponding doses from separate inhalers.

353 ***Studies Comparing ADVAIR DISKUS to Fluticasone Propionate Alone or***
354 ***Salmeterol Alone:*** Three (3) double-blind, parallel-group clinical trials were conducted with
355 ADVAIR DISKUS in 1,208 adolescent and adult patients (≥ 12 years, baseline FEV₁ 63% to 72%
356 of predicted normal) with asthma that was not optimally controlled on their current therapy. All
357 treatments were inhalation powders, given as 1 inhalation from the DISKUS device twice daily,
358 and other maintenance therapies were discontinued.

359 ***Study 1: Clinical Trial With ADVAIR DISKUS 100/50:*** This placebo-controlled,
360 12-week, US study compared ADVAIR DISKUS 100/50 with its individual components,
361 fluticasone propionate 100 mcg and salmeterol 50 mcg. The study was stratified according to
362 baseline asthma maintenance therapy; patients were using either inhaled corticosteroids
363 (N = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg;
364 fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg)
365 or salmeterol (N = 106). Baseline FEV₁ measurements were similar across treatments: ADVAIR
366 DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and
367 placebo, 2.15 L.

368 Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were
369 utilized for this placebo-controlled study. Worsening asthma was defined as a clinically
370 important decrease in FEV₁ or peak expiratory flow (PEF), increase in use of VENTOLIN®
371 (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency
372 intervention or hospitalization due to asthma, or requirement for asthma medication not allowed
373 by the protocol. As shown in Table 1, statistically significantly fewer patients receiving
374 ADVAIR DISKUS 100/50 were withdrawn due to worsening asthma compared with fluticasone
375 propionate, salmeterol, and placebo.

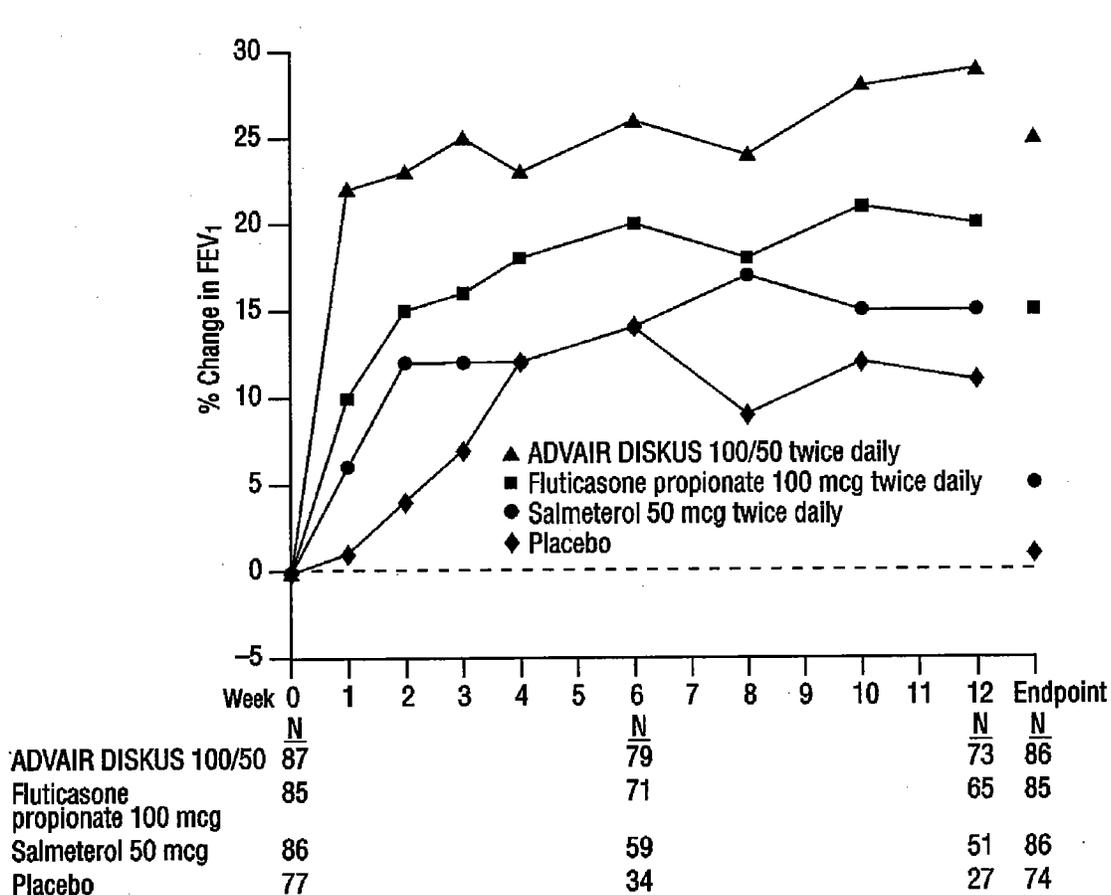
376

377 **Table 1. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously**
 378 **Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**

ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
3%	11%	35%	49%

379
 380 The FEV₁ results are displayed in Figure 1. Because this trial used predetermined criteria for
 381 worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV₁
 382 results at Endpoint (last available FEV₁ result) are also provided. Patients receiving ADVAIR
 383 DISKUS 100/50 had significantly greater improvements in FEV₁ (0.51 L, 25%) compared with
 384 fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L,
 385 1%). These improvements in FEV₁ with ADVAIR DISKUS were achieved regardless of baseline
 386 asthma maintenance therapy (inhaled corticosteroids or salmeterol).

387
 388 **Figure 1. Mean Percent Change From Baseline in FEV₁ in Patients With Asthma**
 389 **Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**



391
 392

393 The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is shown in
 394 Table 2.

395
 396 **Table 2. Peak Expiratory Flow Results for Patients With Asthma Previously Treated**
 397 **With Either Inhaled Corticosteroids or Salmeterol (Study 1)**

Efficacy Variable*	ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
AM PEF (L/min)				
Baseline	393	374	369	382
Change from baseline	53	17	-2	-24
PM PEF (L/min)				
Baseline	418	390	396	398
Change from baseline	35	18	-7	-13

*Change from baseline = change from baseline at Endpoint (last available data).

398
 399 The subjective impact of asthma on patients' perception of health was evaluated through use
 400 of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point
 401 scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR DISKUS
 402 100/50 had clinically meaningful improvements in overall asthma-specific quality of life as
 403 defined by a difference between groups of ≥ 0.5 points in change from baseline AQLQ scores
 404 (difference in AQLQ score of 1.25 compared to placebo).

405 **Study 2: Clinical Trial With ADVAIR DISKUS 250/50:** This placebo-controlled,
 406 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components,
 407 fluticasone propionate 250 mcg and salmeterol 50 mcg in 349 patients with asthma using inhaled
 408 corticosteroids (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to
 409 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100
 410 to 1,600 mcg). Baseline FEV₁ measurements were similar across treatments: ADVAIR DISKUS
 411 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

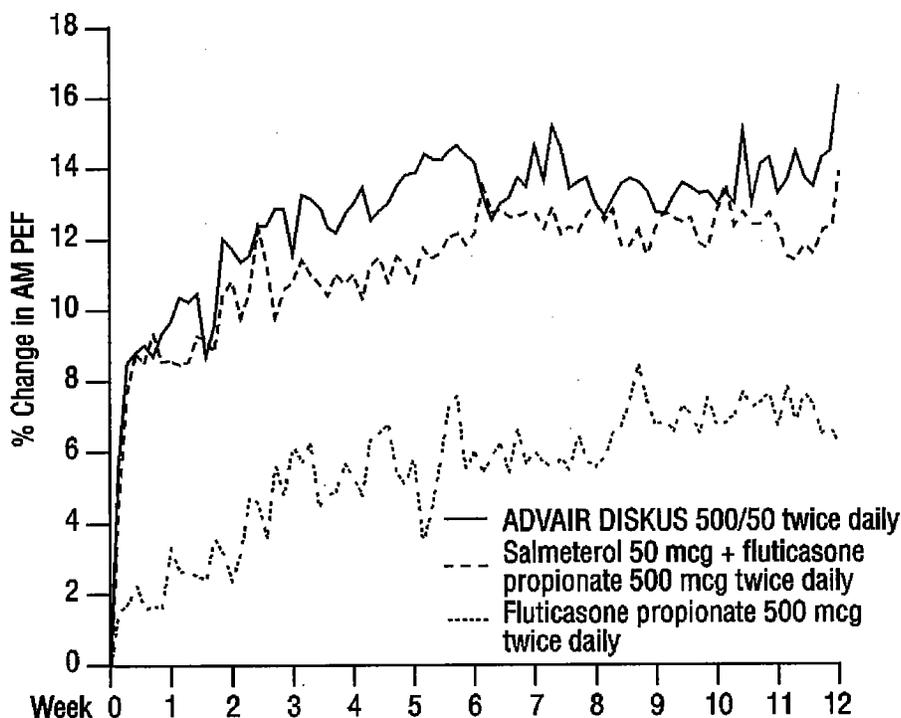
412 Efficacy results in this study were similar to those observed in Study 1. Patients receiving
 413 ADVAIR DISKUS 250/50 had significantly greater improvements in FEV₁ (0.48 L, 23%)
 414 compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and
 415 placebo (decrease of 0.11 L, decrease of 5%). Statistically significantly fewer patients receiving
 416 ADVAIR DISKUS 250/50 were withdrawn from this study for worsening asthma (4%)
 417 compared with fluticasone propionate (22%), salmeterol (38%), and placebo (62%). In addition,
 418 ADVAIR DISKUS 250/50 was superior to fluticasone propionate, salmeterol, and placebo for
 419 improvements in morning and evening PEF. Patients receiving ADVAIR DISKUS 250/50 also
 420 had clinically meaningful improvements in overall asthma-specific quality of life as described in
 421 Study 1 (difference in AQLQ score of 1.29 compared to placebo).

422 **Study 3: Clinical Trial With ADVAIR DISKUS 500/50:** This 28-week, non-US study
423 compared ADVAIR DISKUS 500/50 with fluticasone propionate 500 mcg alone and concurrent
424 therapy (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from separate
425 inhalers) twice daily in 503 patients with asthma using inhaled corticosteroids (daily doses of
426 beclomethasone dipropionate 1,260 to 1,680 mcg; budesonide 1,500 to 2,000 mcg; flunisolide
427 1,500 to 2,000 mcg; or fluticasone propionate inhalation aerosol 660 to 880 mcg [750 to
428 1,000 mcg inhalation powder]). The primary efficacy parameter, morning PEF, was collected
429 daily for the first 12 weeks of the study. The primary purpose of weeks 13 to 28 was to collect
430 safety data.

431 Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50,
432 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. As
433 shown in Figure 2, morning PEF improved significantly with ADVAIR DISKUS 500/50
434 compared with fluticasone propionate 500 mcg over the 12-week treatment period.
435 Improvements in morning PEF observed with ADVAIR DISKUS 500/50 were similar to
436 improvements observed with concurrent therapy.

437

438 **Figure 2. Mean Percent Change From Baseline in Morning Peak Expiratory**
 439 **Flow in Patients With Asthma Previously Treated With Inhaled Corticosteroids**
 440 **(Study 3)**
 441



	Week 0 N	Week 6 N	Week 12 N
ADVAIR DISKUS 500/50	167	159	149
Salmeterol 50 mcg + fluticasone propionate 500 mcg	170	160	147
Fluticasone propionate 500 mcg	164	148	136

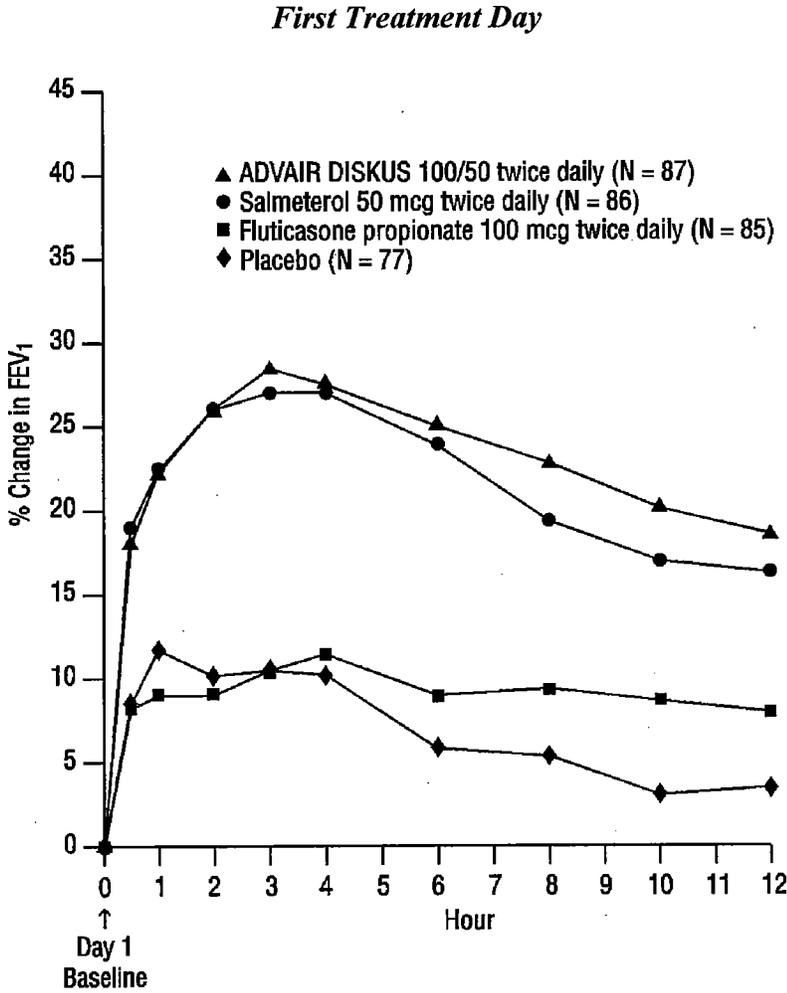
442
 443
 444 **Onset of Action and Progression of Improvement in Asthma Control:** The onset
 445 of action and progression of improvement in asthma control were evaluated in the 2
 446 placebo-controlled US trials. Following the first dose, the median time to onset of clinically
 447 significant bronchodilatation ($\geq 15\%$ improvement in FEV₁) in most patients was seen within 30
 448 to 60 minutes. Maximum improvement in FEV₁ generally occurred within 3 hours, and clinically
 449 significant improvement was maintained for 12 hours (see Figure 3).

450 Following the initial dose, predose FEV₁ relative to Day 1 baseline improved markedly over
 451 the first week of treatment and continued to improve over the 12 weeks of treatment in both
 452 studies.

453 No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR
 454 DISKUS 100/50 (Figures 3 and 4) or ADVAIR DISKUS 250/50 as assessed by FEV₁ following
 455 12 weeks of therapy.
 456

457 **Figure 3. Percent Change in Serial 12-hour FEV₁**
458 **in Patients With Asthma Previously Using Either Inhaled**
459 **Corticosteroids or Salmeterol (Study 1)**

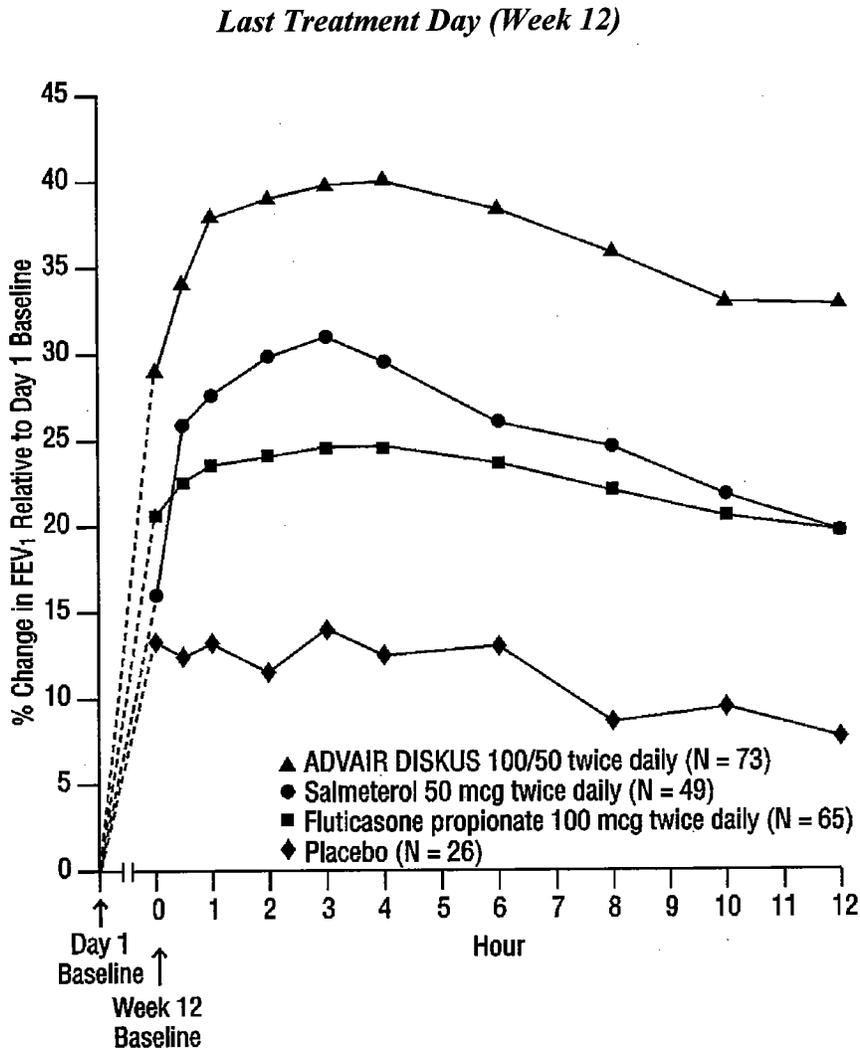
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463
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465 **Figure 4. Percent Change in Serial 12-hour FEV₁**
 466 **in Patients Previously With Asthma Using Either Inhaled**
 467 **Corticosteroids or Salmeterol (Study 1)**

468
 469
 470



471
 472

473 Reduction in asthma symptoms, use of rescue VENTOLIN Inhalation Aerosol, and
 474 improvement in morning and evening PEF also occurred within the first day of treatment with
 475 ADVAIR DISKUS, and continued to improve over the 12 weeks of therapy in both studies.

476 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** In a
 477 clinical trial evaluating twice-daily treatment with ADVAIR DISKUS 250/50 in patients with
 478 COPD associated with chronic bronchitis, improvements in lung function (as defined by predose
 479 and postdose FEV₁) were significantly greater with ADVAIR DISKUS than with fluticasone
 480 propionate 250 mcg, salmeterol 50 mcg, or placebo. The study was a randomized, double-blind,
 481 parallel-group, 24-week trial. All patients had a history of cough productive of sputum that was
 482 not attributable to another disease process on most days for at least 3 months of the year for at

483 least 2 years. Study treatments were inhalation powders given as 1 inhalation from the DISKUS
 484 device twice daily. Maintenance COPD therapies were discontinued, with the exception of
 485 theophylline.

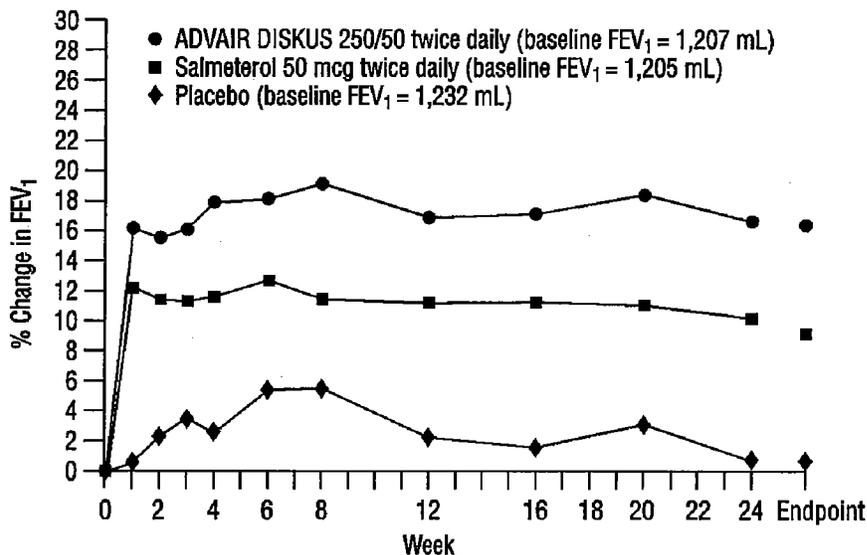
486 Figures 5 and 6 display predose and 2-hour postdose FEV₁ results. To account for patient
 487 withdrawals during the study, FEV₁ at Endpoint (last evaluable FEV₁) was evaluated. Patients
 488 receiving ADVAIR DISKUS 250/50 had significantly greater improvements in predose FEV₁ at
 489 Endpoint (165 mL, 17%) compared with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL,
 490 1%), demonstrating the contribution of fluticasone propionate to the improvement in lung
 491 function with ADVAIR DISKUS (Figure 5). Patients receiving ADVAIR DISKUS 250/50 had
 492 significantly greater improvements in postdose FEV₁ at Endpoint (281 mL, 27%) compared with
 493 fluticasone propionate 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the
 494 contribution of salmeterol to the improvement in lung function with ADVAIR DISKUS
 495 (Figure 6).

496 A similar degree of improvement in lung function was also observed with ADVAIR DISKUS
 497 500/50 twice daily.

498

499 **Figure 5. Predose FEV₁: Mean Percent Change From Baseline in Patients**
 500 **With COPD Associated With Chronic Bronchitis**

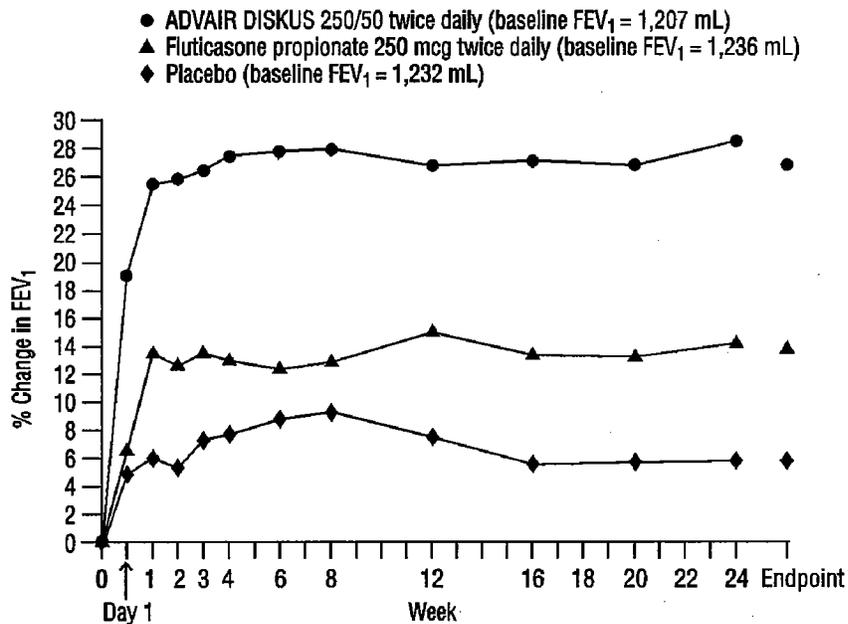
501



	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 250/50	178	144	124	171
Salmeterol 50 mcg	177	135	119	168
Placebo	185	139	125	172

502
 503

504 **Figure 6. Two-Hour Postdose FEV₁: Mean Percent Changes From Baseline**
 505 **Over Time in Patients With COPD Associated With Chronic Bronchitis**
 506



	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 250/50	178	144	117	171
Fluticasone propionate 250 mcg	183	147	130	175
Placebo	185	139	119	172

507
 508
 509 Patients treated with ADVAIR DISKUS 250/50 or ADVAIR DISKUS 500/50 did not have a
 510 significant reduction in chronic bronchitis symptoms (as measured by the Chronic Bronchitis
 511 Symptom Questionnaire) or in COPD exacerbations compared to patients treated with placebo
 512 over the 24 weeks of therapy. The improvement in lung function with ADVAIR DISKUS 500/50
 513 was similar to the improvement seen with ADVAIR DISKUS 250/50. Since there is evidence of
 514 more systemic exposure to fluticasone from this higher dose and no documented advantage for
 515 efficacy, ADVAIR DISKUS 500/50 is not recommended for use in COPD.

516 The benefit of treatment of patients with COPD associated with chronic bronchitis with
 517 ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated.

518 **INDICATIONS AND USAGE**

519 **Asthma:** ADVAIR DISKUS is indicated for the long-term, twice-daily, maintenance treatment
 520 of asthma in patients 12 years of age and older.

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

522 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:**

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

525 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of
 526 COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50,

527 are not recommended (see DOSAGE AND ADMINISTRATION: Chronic Obstructive
528 Pulmonary Disease Associated With Chronic Bronchitis).

529 The benefit of treating patients with COPD associated with chronic bronchitis with ADVAIR
530 DISKUS 250/50 for periods longer than 6 months has not been evaluated. Patients who are
531 treated with ADVAIR DISKUS 250/50 for COPD associated with chronic bronchitis for periods
532 longer than 6 months should be reevaluated periodically to assess the continuing benefits and
533 potential risks of treatment.

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

535 **CONTRAINDICATIONS**

536 ADVAIR DISKUS is contraindicated in the primary treatment of status asthmaticus or other
537 acute episodes of asthma or COPD where intensive measures are required.

538 Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see
539 DESCRIPTION and ADVERSE REACTIONS: Observed During Clinical Practice: *Non-Site*
540 *Specific*).

541 **WARNINGS**

542 DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS
543 STOPPED EARLY SUGGEST THAT SALMETEROL, A COMPONENT OF ADVAIR
544 DISKUS, MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR
545 ASTHMA-RELATED DEATHS. The Salmeterol Multi-center Asthma Research Trial
546 (SMART) enrolled long-acting beta₂-agonist-naïve patients with asthma to assess the safety of
547 salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared to
548 placebo, when added to usual asthma therapy. The primary endpoint was the combined number
549 of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and
550 mechanical ventilation). Other endpoints included combined asthma-related deaths or
551 life-threatening experiences and asthma-related deaths.

552 A planned interim analysis was conducted when approximately half of the intended number of
553 patients had been enrolled (N = 26,353). The analysis showed no significant difference for the
554 primary endpoint for the total population. However, a higher number of asthma-related deaths or
555 life-threatening experiences (36 vs. 23) and a higher number of asthma-related deaths (13 vs. 4)
556 occurred in the patients treated with SEREVENT Inhalation Aerosol. Post hoc subgroup analyses
557 revealed no significant increase in respiratory- or asthma-related episodes, including deaths, in
558 Caucasian patients. In African Americans, the study showed a small, though statistically
559 significantly greater, number of primary events (20 vs. 7), asthma-related deaths or
560 life-threatening experiences (19 vs. 4), and asthma-related deaths (8 vs. 1) in patients taking
561 SEREVENT Inhalation Aerosol compared to those taking placebo. Even though SMART did not
562 reach predetermined stopping criteria for the total population, the study was stopped due to the
563 findings in African American patients and difficulties in enrollment. The data from the SMART
564 study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as
565 fluticasone propionate, a component of ADVAIR DISKUS, provides protection from this risk.

566 Therefore, it is not known whether the findings seen with SEREVENT Inhalation Aerosol would
567 apply to ADVAIR DISKUS.

568 Findings similar to the SMART study findings were reported in a prior 16-week clinical study
569 performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the
570 SNS study, the incidence of asthma-related death was numerically, though not statistically,
571 greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol
572 (180 mcg 4 times daily) added to usual asthma therapy.

573 Given the similar basic mechanisms of action of beta₂-agonists, it is possible that the findings
574 seen in the SMART study may be consistent with a class effect.

575 **1. ADVAIR DISKUS SHOULD NOT BE USED FOR TRANSFERRING PATIENTS**
576 **FROM SYSTEMIC CORTICOSTEROID THERAPY.** Particular care is needed for patients
577 who have been transferred from systemically active corticosteroids to inhaled corticosteroids
578 because deaths due to adrenal insufficiency have occurred in patients with asthma during and
579 after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids.
580 After withdrawal from systemic corticosteroids, a number of months are required for recovery of
581 HPA function.

582 Patients who have been previously maintained on 20 mg or more per day of prednisone (or its
583 equivalent) may be most susceptible, particularly when their systemic corticosteroids have been
584 almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs
585 and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection
586 (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although
587 inhaled corticosteroids may provide control of asthma symptoms during these episodes, in
588 recommended doses they supply less than normal physiological amounts of glucocorticoid
589 systemically and do NOT provide the mineralocorticoid activity that is necessary for coping with
590 these emergencies.

591 During periods of stress or a severe asthma attack, patients who have been withdrawn from
592 systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses)
593 immediately and to contact their physicians for further instruction. These patients should also be
594 instructed to carry a warning card indicating that they may need supplementary systemic
595 corticosteroids during periods of stress or a severe asthma attack.

596 **2. ADVAIR DISKUS SHOULD NOT BE INITIATED IN PATIENTS DURING RAPIDLY**
597 **DETERIORATING OR POTENTIALLY LIFE-THREATENING EPISODES OF**
598 **ASTHMA. Serious acute respiratory events, including fatalities, have been reported both in**
599 **the United States and worldwide when salmeterol, a component of ADVAIR DISKUS, has**
600 **been initiated in patients with significantly worsening or acutely deteriorating asthma. In**
601 **most cases, these have occurred in patients with severe asthma (e.g., patients with a history of**
602 **corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent**
603 **hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients**
604 **in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications;**
605 **increasing need for inhaled, short-acting beta₂-agonists; increasing need for systemic**

606 corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or
607 progressive deterioration in pulmonary function). However, they have occurred in a few patients
608 with less severe asthma as well. It was not possible from these reports to determine whether
609 salmeterol contributed to these events or simply failed to relieve the deteriorating asthma.

610 **3. Drug Interaction With Ritonavir:** A drug interaction study in healthy subjects has shown
611 that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma
612 fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations
613 (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Drug*
614 *Interactions* and PRECAUTIONS: Drug Interactions: *Inhibitors of Cytochrome P450*). During
615 postmarketing use, there have been reports of clinically significant drug interactions in patients
616 receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects
617 including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone
618 propionate and ritonavir is not recommended unless the potential benefit to the patient
619 outweighs the risk of systemic corticosteroid side effects.

620 **4. Do Not Use ADVAIR DISKUS to Treat Acute Symptoms:** An inhaled, short-acting
621 beta₂-agonist, not ADVAIR DISKUS, should be used to relieve acute symptoms of shortness of
622 breath. When prescribing ADVAIR DISKUS, the physician must also provide the patient with an
623 inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of shortness of breath that
624 occurs acutely, despite regular twice-daily (morning and evening) use of ADVAIR DISKUS.

625 When beginning treatment with ADVAIR DISKUS, patients who have been taking oral or
626 inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to
627 discontinue the regular use of these drugs. For patients on ADVAIR DISKUS, inhaled,
628 short-acting beta₂-agonists should only be used for symptomatic relief of acute symptoms of
629 shortness of breath (see PRECAUTIONS: Information for Patients).

630 **5. Watch for Increasing Use of Inhaled, Short-Acting Beta₂-Agonists, Which Is a Marker of**
631 **Deteriorating Asthma:** Asthma may deteriorate acutely over a period of hours or chronically over
632 several days or longer. If the patient's inhaled, short-acting beta₂-agonist becomes less effective,
633 the patient needs more inhalations than usual, or the patient develops a significant decrease in
634 lung function, this may be a marker of destabilization of the disease. In this setting, the patient
635 requires immediate reevaluation with reassessment of the treatment regimen, giving special
636 consideration to the possible need for replacing the current strength of ADVAIR DISKUS with a
637 higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids.
638 Patients should not use more than 1 inhalation twice daily (morning and evening) of ADVAIR
639 DISKUS.

640 **6. Do Not Use an Inhaled, Long-Acting Beta₂-Agonist in Conjunction With ADVAIR DISKUS:**
641 Patients who are receiving ADVAIR DISKUS twice daily should not use additional salmeterol
642 or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of exercise-induced
643 bronchospasm (EIB) or the maintenance treatment of asthma or the maintenance treatment of
644 bronchospasm associated with COPD. Additional benefit would not be gained from using

645 supplemental salmeterol or formoterol for prevention of EIB since ADVAIR DISKUS already
646 contains an inhaled, long-acting beta₂-agonist.

647 7. Do Not Exceed Recommended Dosage: ADVAIR DISKUS should not be used more often or
648 at higher doses than recommended. Fatalities have been reported in association with excessive
649 use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times
650 the recommended dose) have been associated with clinically significant prolongation of the QTc
651 interval, which has the potential for producing ventricular arrhythmias.

652 8. Paradoxical Bronchospasm: As with other inhaled asthma and COPD medications, ADVAIR
653 DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical
654 bronchospasm occurs following dosing with ADVAIR DISKUS, it should be treated
655 immediately with an inhaled, short-acting bronchodilator, ADVAIR DISKUS should be
656 discontinued immediately, and alternative therapy should be instituted.

657 9. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after
658 administration of ADVAIR DISKUS, as demonstrated by cases of urticaria, angioedema, rash,
659 and bronchospasm.

660 10. Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as
661 stridor and choking, have been reported in patients receiving fluticasone propionate and
662 salmeterol, components of ADVAIR DISKUS.

663 11. Cardiovascular Disorders: ADVAIR DISKUS, like all products containing sympathomimetic
664 amines, should be used with caution in patients with cardiovascular disorders, especially
665 coronary insufficiency, cardiac arrhythmias, and hypertension. Salmeterol, a component of
666 ADVAIR DISKUS, can produce a clinically significant cardiovascular effect in some patients as
667 measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon
668 after administration of salmeterol at recommended doses, if they occur, the drug may need to be
669 discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as
670 flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The
671 clinical significance of these findings is unknown.

672 12. Discontinuation of Systemic Corticosteroids: Transfer of patients from systemic
673 corticosteroid therapy to ADVAIR DISKUS may unmask conditions previously suppressed by
674 the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and
675 eosinophilic conditions.

676 13. Immunosuppression: Persons who are using drugs that suppress the immune system are more
677 susceptible to infections than healthy individuals. Chickenpox and measles, for example, can
678 have a more serious or even fatal course in susceptible children or adults using corticosteroids.
679 In such children or adults who have not had these diseases or been properly immunized,
680 particular care should be taken to avoid exposure. How the dose, route, and duration of
681 corticosteroid administration affect the risk of developing a disseminated infection is not known.
682 The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also
683 not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG)
684 may be indicated. If exposed to measles, prophylaxis with pooled intramuscular

685 immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG
686 and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be
687 considered.

688 **PRECAUTIONS**

689 **General: Cardiovascular Effects:** Cardiovascular and central nervous system effects seen
690 with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can
691 occur after use of salmeterol, a component of ADVAIR DISKUS, and may require
692 discontinuation of ADVAIR DISKUS. ADVAIR DISKUS, like all medications containing
693 sympathomimetic amines, should be used with caution in patients with cardiovascular disorders,
694 especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with
695 convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to
696 sympathomimetic amines.

697 As has been described with other beta-adrenergic agonist bronchodilators, clinically
698 significant changes in ECGs have been seen infrequently in individual patients in controlled
699 clinical studies with ADVAIR DISKUS and salmeterol. Clinically significant changes in systolic
700 and/or diastolic blood pressure and pulse rate have been seen infrequently in individual patients
701 in controlled clinical studies with salmeterol, a component of ADVAIR DISKUS.

702 **Metabolic and Other Effects:** Long-term use of orally inhaled corticosteroids may affect
703 normal bone metabolism, resulting in a loss of bone mineral density (BMD). A 2-year study of
704 160 patients (females 18 to 40 and males 18 to 50 years of age) with asthma receiving
705 chlorofluorocarbon-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice
706 daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and
707 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar
708 region L1 through L4. Long-term treatment effects of fluticasone propionate on BMD in the
709 COPD population have not been studied.

710 In patients with major risk factors for decreased bone mineral content, such as tobacco use,
711 advanced age, sedentary lifestyle, poor nutrition, family history of osteoporosis, or chronic use of
712 drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), ADVAIR DISKUS
713 may pose an additional risk. Since patients with COPD often have multiple risk factors for
714 reduced BMD, assessment of BMD is recommended, including prior to instituting ADVAIR
715 DISKUS 250/50 and periodically thereafter. If significant reductions in BMD are seen and
716 ADVAIR DISKUS 250/50 is still considered medically important for that patient's COPD
717 therapy, use of medication to treat or prevent osteoporosis should be strongly considered.
718 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of
719 COPD associated with chronic bronchitis, and higher doses, including ADVAIR DISKUS
720 500/50, are not recommended.

721 Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with
722 asthma and COPD following the long-term administration of inhaled corticosteroids, including

723 fluticasone propionate, a component of ADVAIR DISKUS; therefore, regular eye examinations
724 should be considered.

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

728 Doses of the related beta₂-adrenoceptor agonist albuterol, when administered intravenously,
729 have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic
730 agonist medications may produce significant hypokalemia in some patients, possibly through
731 intracellular shunting, which has the potential to produce adverse cardiovascular effects. The
732 decrease in serum potassium is usually transient, not requiring supplementation.

733 Clinically significant changes in blood glucose and/or serum potassium were seen
734 infrequently during clinical studies with ADVAIR DISKUS at recommended doses.

735 During withdrawal from oral corticosteroids, some patients may experience symptoms of
736 systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and
737 depression, despite maintenance or even improvement of respiratory function.

738 Fluticasone propionate, a component of ADVAIR DISKUS, will often help control asthma
739 symptoms with less suppression of HPA function than therapeutically equivalent oral doses of
740 prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically
741 active at higher doses, the beneficial effects of ADVAIR DISKUS in minimizing HPA
742 dysfunction may be expected only when recommended dosages are not exceeded and individual
743 patients are titrated to the lowest effective dose. A relationship between plasma levels of
744 fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown
745 after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual
746 sensitivity to effects on cortisol production exists, physicians should consider this information
747 when prescribing ADVAIR DISKUS.

748 Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated
749 with ADVAIR DISKUS should be observed carefully for any evidence of systemic
750 corticosteroid effects. Particular care should be taken in observing patients postoperatively or
751 during periods of stress for evidence of inadequate adrenal response.

752 It is possible that systemic corticosteroid effects such as hypercorticism and adrenal
753 suppression (including adrenal crisis) may appear in a small number of patients, particularly
754 when fluticasone propionate is administered at higher than recommended doses over prolonged
755 periods of time. If such effects occur, the dosage of ADVAIR DISKUS should be reduced
756 slowly, consistent with accepted procedures for reducing systemic corticosteroids and for
757 management of asthma symptoms.

758 Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to
759 pediatric patients (see PRECAUTIONS: Pediatric Use). Patients should be maintained on the
760 lowest strength of ADVAIR DISKUS that effectively controls their asthma.

761 The long-term effects of ADVAIR DISKUS in human subjects are not fully known. In
762 particular, the effects resulting from chronic use of fluticasone propionate on developmental or

763 immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients
764 have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or
765 longer. In clinical studies in patients with asthma treated for 2 years with inhaled fluticasone
766 propionate, no apparent differences in the type or severity of adverse reactions were observed
767 after long- versus short-term treatment.

768 In clinical studies with ADVAIR DISKUS, the development of localized infections of the
769 pharynx with *Candida albicans* has occurred. When such an infection develops, it should be
770 treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on
771 treatment with ADVAIR DISKUS, but at times therapy with ADVAIR DISKUS may need to be
772 interrupted.

773 Inhaled corticosteroids should be used with caution, if at all, in patients with active or
774 quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial,
775 viral, or parasitic infections; or ocular herpes simplex.

776 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a
777 component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some
778 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a
779 condition that is often treated with systemic corticosteroid therapy. These events usually, but not
780 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy
781 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions
782 have also been reported with other inhaled corticosteroids in this clinical setting. Physicians
783 should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac
784 complications, and/or neuropathy presenting in their patients. A causal relationship between
785 fluticasone propionate and these underlying conditions has not been established (see ADVERSE
786 REACTIONS: Observed During Clinical Practice: *Eosinophilic Conditions*).

787 **Chronic Obstructive Pulmonary Disease:** ADVAIR DISKUS 250/50 twice daily is the
788 only dosage recommended for the treatment of airflow obstruction in patients with COPD
789 associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50, are not
790 recommended, as no additional improvement in lung function (defined by predose and postdose
791 FEV₁) was observed in clinical trials and higher doses of corticosteroids increase the risk of
792 systemic effects.

793 The benefit of treatment of patients with COPD associated with chronic bronchitis with
794 ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated. Patients
795 who are treated with ADVAIR DISKUS 250/50 for COPD associated with chronic bronchitis
796 for periods longer than 6 months should be reevaluated periodically to assess the continuing
797 benefits and potential risks of treatment.

798 **Information for Patients:** Patients being treated with ADVAIR DISKUS should receive the
799 following information and instructions. This information is intended to aid them in the safe and
800 effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

801 It is important that patients understand how to use the DISKUS inhalation device
802 appropriately and how it should be used in relation to other asthma or COPD medications they
803 are taking. Patients should be given the following information:

- 804 1. Patients should use ADVAIR DISKUS at regular intervals as directed. Results of clinical
805 trials indicate significant improvement may occur within the first 30 minutes of taking the
806 first dose; however, the full benefit may not be achieved until treatment has been
807 administered for 1 week or longer. The patient should not use more than the prescribed
808 dosage but should contact the physician if symptoms do not improve or if the condition
809 worsens.
- 810 2. Most patients are able to taste or feel a dose delivered from ADVAIR DISKUS. However,
811 whether or not patients are able to sense delivery of a dose, you should instruct them not to
812 exceed the recommended dose of 1 inhalation each morning and evening, approximately 12
813 hours apart. You should instruct them to contact you or the pharmacist if they have questions.
- 814 3. The bronchodilation from a single dose of ADVAIR DISKUS may last up to 12 hours or
815 longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not
816 be exceeded. Patients who are receiving ADVAIR DISKUS twice daily should not use
817 salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of
818 EIB or maintenance treatment of asthma or the maintenance treatment of bronchospasm in
819 COPD.
- 820 4. ADVAIR DISKUS is not meant to relieve acute asthma symptoms and extra doses should
821 not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting
822 beta₂-agonist such as albuterol (the physician should provide the patient with such
823 medication and instruct the patient in how it should be used). ADVAIR DISKUS is not
824 meant to relieve acute asthma symptoms or exacerbations of COPD.
- 825 5. Patients should not stop therapy with ADVAIR DISKUS without physician/provider
826 guidance since symptoms may recur after discontinuation.
- 827 6. The physician should be notified immediately if any of the following situations occur, which
828 may be a sign of seriously worsening asthma:
 - 829 • decreasing effectiveness of inhaled, short-acting beta₂-agonists;
 - 830 • need for more inhalations than usual of inhaled, short-acting beta₂-agonists;
 - 831 • significant decrease in lung function as outlined by the physician.
- 832 7. Patients should be cautioned regarding common adverse effects associated with
833 beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 834 8. Patients who are at an increased risk for decreased BMD should be advised that the use of
835 corticosteroids may pose an additional risk and should be told to monitor and, where
836 appropriate, seek treatment for this condition.
- 837 9. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of
838 ADVAIR DISKUS, may increase the risk of some eye problems (cataracts or glaucoma).
839 Regular eye examinations should be considered.

- 840 10. When patients are prescribed ADVAIR DISKUS, other medications for asthma and COPD
841 should be used only as directed by their physicians.
- 842 11. ADVAIR DISKUS should not be used with a spacer device.
- 843 12. Patients who are pregnant or nursing should contact their physicians about the use of
844 ADVAIR DISKUS.
- 845 13. Effective and safe use of ADVAIR DISKUS includes an understanding of the way that it
846 should be used:
- 847 • Never exhale into the DISKUS.
 - 848 • Never attempt to take the DISKUS apart.
 - 849 • Always activate and use the DISKUS in a level, horizontal position.
 - 850 • After inhalation, rinse the mouth with water without swallowing.
 - 851 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
 - 852 • Always keep the DISKUS in a dry place.
 - 853 • Discard **1 month** after removal from the moisture-protective foil overwrap pouch or after
854 all blisters have been used (when the dose indicator reads “0”), whichever comes first.
- 855 14. Patients should be warned to avoid exposure to chickenpox or measles and, if they are
856 exposed, to consult their physicians without delay.
- 857 15. For the proper use of ADVAIR DISKUS and to attain maximum improvement, the patient
858 should read and carefully follow the Patient’s Instructions for Use accompanying the
859 product.

860 **Drug Interactions:** ADVAIR DISKUS has been used concomitantly with other drugs,
861 including short-acting beta₂-agonists, methylxanthines, and intranasal corticosteroids, commonly
862 used in patients with asthma or COPD, without adverse drug reactions. No formal drug
863 interaction studies have been performed with ADVAIR DISKUS.

864 **Short-Acting Beta₂-Agonists:** In clinical trials with patients with asthma, the mean daily
865 need for albuterol by 166 patients using ADVAIR DISKUS was approximately
866 1.3 inhalations/day, and ranged from 0 to 9 inhalations/day. Five percent (5%) of patients using
867 ADVAIR DISKUS in these trials averaged 6 or more inhalations per day over the course of the
868 12-week trials. No increase in frequency of cardiovascular adverse reactions was observed
869 among patients who averaged 6 or more inhalations per day.

870 In a COPD clinical trial, the mean daily need for albuterol for patients using ADVAIR
871 DISKUS 250/50 was 4.1 inhalations/day. Twenty-six percent (26%) of patients using ADVAIR
872 DISKUS 250/50 averaged 6 or more inhalations per day over the course of the 24-week trial. No
873 increase in frequency of cardiovascular adverse reactions was observed among patients who
874 averaged 6 or more inhalations of albuterol per day.

875 **Methylxanthines:** The concurrent use of intravenously or orally administered
876 methylxanthines (e.g., aminophylline, theophylline) by patients receiving ADVAIR DISKUS has
877 not been completely evaluated. In clinical trials with patients with asthma, 39 patients receiving
878 ADVAIR DISKUS 100/50, 250/50, or 500/50 twice daily concurrently with a theophylline
879 product had adverse event rates similar to those in 304 patients receiving ADVAIR DISKUS

880 without theophylline. Similar results were observed in patients receiving salmeterol 50 mcg plus
881 fluticasone propionate 500 mcg twice daily concurrently with a theophylline product (N = 39) or
882 without theophylline (N = 132).

883 In a COPD clinical trial, 17 patients receiving ADVAIR DISKUS 250/50 twice daily
884 concurrently with a theophylline product had adverse event rates similar to those in 161 patients
885 receiving ADVAIR DISKUS without theophylline. Based on the available data, the concomitant
886 administration of methylxanthines with ADVAIR DISKUS did not alter the observed adverse
887 event profile.

888 **Fluticasone Propionate Nasal Spray:** In patients taking ADVAIR DISKUS in clinical
889 trials, no difference in the profile of adverse events or HPA axis effects was noted between
890 patients taking FLONASE[®] (fluticasone propionate) Nasal Spray, 50 mcg concurrently (N = 46)
891 and those who were not (N = 130).

892 **Monoamine Oxidase Inhibitors and Tricyclic Antidepressants:** ADVAIR DISKUS
893 should be administered with extreme caution to patients being treated with monoamine oxidase
894 inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents,
895 because the action of salmeterol, a component of ADVAIR DISKUS, on the vascular system
896 may be potentiated by these agents.

897 **Beta-Adrenergic Receptor Blocking Agents:** Beta-blockers not only block the
898 pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, but
899 may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma
900 should not normally be treated with beta-blockers. However, under certain circumstances, there
901 may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with
902 asthma. In this setting, cardioselective beta-blockers could be considered, although they should
903 be administered with caution.

904 **Diuretics:** The ECG changes and/or hypokalemia that may result from the administration of
905 nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by
906 beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although
907 the clinical significance of these effects is not known, caution is advised in the coadministration
908 of beta-agonists with nonpotassium-sparing diuretics.

909 **Inhibitors of Cytochrome P450:** Fluticasone propionate is a substrate of cytochrome
910 P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy
911 subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can
912 significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced
913 serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics:
914 *Fluticasone Propionate: Drug Interactions*). During postmarketing use, there have been reports
915 of clinically significant drug interactions in patients receiving fluticasone propionate and
916 ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal
917 suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not
918 recommended unless the potential benefit to the patient outweighs the risk of systemic
919 corticosteroid side effects.

920 In a placebo-controlled, crossover study in 8 healthy volunteers, coadministration of a single
921 dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole
922 (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a
923 reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should
924 be exercised when ADVAIR DISKUS is coadministered with ketoconazole and other known
925 potent cytochrome P450 3A4 inhibitors.

926 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone Propionate:**

927 Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to
928 1,000 mcg/kg (approximately 4 times the maximum recommended daily inhalation dose in adults
929 on a mcg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than the
930 maximum recommended daily inhalation dose in adults on a mcg/m² basis) for 104 weeks.

931 Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in
932 vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in
933 vitro or in the mouse micronucleus test.

934 No evidence of impairment of fertility was observed in reproductive studies conducted in
935 male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum
936 recommended daily inhalation dose in adults on a mcg/m² basis). Prostate weight was
937 significantly reduced at a subcutaneous dose of 50 mcg/kg.

938 **Salmeterol:** In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of
939 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose
940 in adults based on comparison of the plasma area under the curves [AUCs]) caused a
941 dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular
942 hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of
943 leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg
944 (approximately 3 times the maximum recommended daily inhalation doses in adults based on
945 comparison of the AUCs).

946 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol
947 caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at
948 doses of 0.68 mg/kg and above (approximately 60 times the maximum recommended daily
949 inhalation dose in adults on a mg/m² basis). No tumors were seen at 0.21 mg/kg (approximately
950 20 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). These
951 findings in rodents are similar to those reported previously for other beta-adrenergic agonist
952 drugs. The relevance of these findings to human use is unknown.

953 Salmeterol produced no detectable or reproducible increases in microbial and mammalian
954 gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo
955 in a rat micronucleus test. No effects on fertility were identified in male and female rats treated
956 with salmeterol at oral doses up to 2 mg/kg (approximately 180 times the maximum
957 recommended daily inhalation dose in adults on a mg/m² basis).

958 **Pregnancy: Teratogenic Effects: ADVAIR DISKUS:** Pregnancy Category C. From the
959 reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using

960 combinations of fluticasone propionate and salmeterol compared to toxicity data from the
961 components administered separately. In mice combining 150 mcg/kg subcutaneously of
962 fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a
963 mcg/m² basis) with 10 mg/kg orally of salmeterol (approximately 450 times the maximum
964 recommended daily inhalation dose in adults on a mg/m² basis) was teratogenic. Cleft palate,
965 fetal death, increased implantation loss and delayed ossification were seen. These observations
966 are characteristic of glucocorticoids. No developmental toxicity was observed at combination
967 doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the maximum
968 recommended daily inhalation dose in adults on a mcg/m² basis) and up to 1.4 mg/kg orally of
969 salmeterol (approximately 65 times the maximum recommended daily inhalation dose in adults
970 on a mg/m² basis). In rats, no teratogenicity was observed at combination doses up to 30 mcg/kg
971 subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation
972 dose in adults on a mcg/m² basis) and up to 1 mg/kg of salmeterol (approximately 90 times the
973 maximum recommended daily inhalation dose in adults on a mg/m² basis). Combining
974 100 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended
975 daily inhalation dose in adults on a mcg/m² basis) with 10 mg/kg orally of salmeterol
976 (approximately 900 times the maximum recommended daily inhalation dose in adults on a
977 mg/m² basis) produced maternal toxicity, decreased placental weight, decreased fetal weight,
978 umbilical hernia, delayed ossification, and changes in the occipital bone. There are no adequate
979 and well-controlled studies with ADVAIR DISKUS in pregnant women. ADVAIR DISKUS
980 should be used during pregnancy only if the potential benefit justifies the potential risk to the
981 fetus.

982 **Fluticasone Propionate:** Pregnancy Category C. Subcutaneous studies in the mouse
983 and rat at 45 and 100 mcg/kg (less than or equivalent to the maximum recommended daily
984 inhalation dose in adults on a mcg/m² basis), respectively, revealed fetal toxicity characteristic of
985 potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft
986 palate, and retarded cranial ossification.

987 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of
988 4 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m²
989 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg
990 (approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m²
991 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this
992 study, consistent with the established low bioavailability following oral administration (see
993 CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Absorption*).

994 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose
995 of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a
996 mcg/m² basis) administration of a subcutaneous or an oral dose of 100 mcg/kg to rats
997 (approximately equivalent to the maximum recommended daily inhalation dose in adults on a
998 mcg/m² basis) and an oral dose of 300 mcg/kg administered to rabbits (approximately 5 times the
999 maximum recommended daily inhalation dose in adults on a mcg/m² basis).

1000 There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate
1001 should be used during pregnancy only if the potential benefit justifies the potential risk to the
1002 fetus.

1003 Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to
1004 physiologic, doses suggests that rodents are more prone to teratogenic effects from
1005 corticosteroids than humans. In addition, because there is a natural increase in corticosteroid
1006 production during pregnancy, most women will require a lower exogenous corticosteroid dose
1007 and many will not need corticosteroid treatment during pregnancy.

1008 **Salmeterol:** Pregnancy Category C. No teratogenic effects occurred in rats at oral doses
1009 up to 2 mg/kg (approximately 180 times the maximum recommended daily inhalation dose in
1010 adults on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and
1011 above (approximately 50 times the maximum recommended daily inhalation dose in adults based
1012 on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting
1013 from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate,
1014 sternal fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones.
1015 No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the
1016 maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

1017 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal
1018 bones was seen at an oral dose of 10 mg/kg (approximately 1,800 times the maximum
1019 recommended daily inhalation dose in adults on a mg/m² basis). Extensive use of other
1020 beta-agonists has provided no evidence that these class effects in animals are relevant to their use
1021 in humans. There are no adequate and well-controlled studies with salmeterol in pregnant
1022 women. Salmeterol should be used during pregnancy only if the potential benefit justifies the
1023 potential risk to the fetus.

1024 Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice
1025 and rats (approximately 450 and 900 times, respectively, the maximum recommended daily
1026 inhalation dose in adults on a mg/m² basis).

1027 **Use in Labor and Delivery:** There are no well-controlled human studies that have
1028 investigated effects of ADVAIR DISKUS on preterm labor or labor at term. Because of the
1029 potential for beta-agonist interference with uterine contractility, use of ADVAIR DISKUS during
1030 labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

1031 **Nursing Mothers:** Plasma levels of salmeterol, a component of ADVAIR DISKUS, after
1032 inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There
1033 are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known
1034 whether fluticasone propionate, a component of ADVAIR DISKUS, is excreted in human breast
1035 milk. However, other corticosteroids have been detected in human milk. Subcutaneous
1036 administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the
1037 maximum recommended daily inhalation dose in adults on a mcg/m² basis) resulted in
1038 measurable radioactivity in milk.

1039 Since there are no data from controlled trials on the use of ADVAIR DISKUS by nursing
1040 mothers, a decision should be made whether to discontinue nursing or to discontinue ADVAIR
1041 DISKUS, taking into account the importance of ADVAIR DISKUS to the mother.

1042 Caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.

1043 **Pediatric Use:** The safety and effectiveness of ADVAIR DISKUS in children with asthma
1044 under 12 years of age have not been established. In one 12-week study, 257 patients 4 to
1045 11 years inadequately controlled using inhaled corticosteroids were randomized to ADVAIR
1046 DISKUS 100/50 or concurrent therapy with fluticasone propionate inhalation powder 100 mcg
1047 plus salmeterol inhalation powder 50 mcg twice daily. The pattern of adverse events reported in
1048 patients 4 to 11 years of age was similar to that seen in patients 12 years of age and older treated
1049 with ADVAIR DISKUS.

1050 Controlled clinical studies have shown that orally inhaled corticosteroids may cause a
1051 reduction in growth velocity in pediatric patients. This effect has been observed in the absence of
1052 laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive
1053 indicator of systemic corticosteroid exposure in pediatric patients than some commonly used
1054 tests of HPA axis function. The long-term effects of this reduction in growth velocity associated
1055 with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The
1056 potential for “catch-up” growth following discontinuation of treatment with orally inhaled
1057 corticosteroids has not been adequately studied.

1058 Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS,
1059 may cause a reduction in growth velocity in children and adolescents (see PRECAUTIONS:
1060 General: *Metabolic and Other Effects*). The growth of pediatric patients receiving orally inhaled
1061 corticosteroids, including ADVAIR DISKUS, should be monitored. If a child or adolescent on
1062 any corticosteroid appears to have growth suppression, the possibility that he/she is particularly
1063 sensitive to this effect of corticosteroids should be considered. The potential growth effects of
1064 prolonged treatment should be weighed against the clinical benefits obtained. To minimize the
1065 systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, each patient
1066 should be titrated to the lowest strength that effectively controls his/her asthma (see DOSAGE
1067 AND ADMINISTRATION: Asthma).

1068 **Geriatric Use:** Of the total number of patients in clinical studies of ADVAIR DISKUS for
1069 asthma, 44 were 65 years of age or older and 3 were 75 years of age or older. Of the total
1070 number of patients in a clinical study of ADVAIR DISKUS 250/50 for COPD, 85 were 65 years
1071 of age or older and 31 were 75 years of age or older. For both diseases, no overall differences in
1072 safety were observed between these patients and younger patients, and other reported clinical
1073 experience, including studies of the individual components, has not identified differences in
1074 responses between the elderly and younger patients, but greater sensitivity of some older
1075 individuals cannot be ruled out. As with other products containing beta₂-agonists, special caution
1076 should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant
1077 cardiovascular disease that could be adversely affected by beta₂-agonists. Based on available

1078 data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR
1079 DISKUS in geriatric patients is warranted.

1080 **ADVERSE REACTIONS**

1081 **Asthma:** The incidence of common adverse events in Table 3 is based upon 2
1082 placebo-controlled, 12-week, US clinical studies (Studies 1 and 2). A total of 705 adolescent and
1083 adult patients (349 females and 356 males) previously treated with salmeterol or inhaled
1084 corticosteroids were treated twice daily with ADVAIR DISKUS (100/50- or 250/50-mcg doses),
1085 fluticasone propionate inhalation powder (100- or 250-mcg doses), salmeterol inhalation powder
1086 50 mcg, or placebo.

1087

1088 **Table 3. Overall Adverse Events With $\geq 3\%$ Incidence in US Controlled Clinical Trials**
 1089 **With ADVAIR DISKUS in Patients With Asthma**

Adverse Event	ADVAIR DISKUS 100/50 (N = 92) %	ADVAIR DISKUS 250/50 (N = 84) %	Fluticasone Propionate 100 mcg (N = 90) %	Fluticasone Propionate 250 mcg (N = 84) %	Salmeterol 50 mcg (N = 180) %	Placebo (N = 175) %
Ear, nose, and throat						
Upper respiratory tract infection	27	21	29	25	19	14
Pharyngitis	13	10	7	12	8	6
Upper respiratory inflammation	7	6	7	8	8	5
Sinusitis	4	5	6	1	3	4
Hoarseness/dysphonia	5	2	2	4	<1	<1
Oral candidiasis	1	4	2	2	0	0
Lower respiratory						
Viral respiratory infections	4	4	4	10	6	3
Bronchitis	2	8	1	2	2	2
Cough	3	6	0	0	3	2
Neurology						
Headaches	12	13	14	8	10	7
Gastrointestinal						
Nausea & vomiting	4	6	3	4	1	1
Gastrointestinal discomfort & pain	4	1	0	2	1	1
Diarrhea	4	2	2	2	1	1
Viral gastrointestinal infections	3	0	3	1	2	2
Non-site specific						
Candidiasis unspecified site	3	0	1	4	0	1
Musculoskeletal						
Musculoskeletal pain	4	2	1	5	3	3
Average duration of exposure (days)	77.3	78.7	72.4	70.1	60.1	42.3

1090
 1091 Table 3 includes all events (whether considered drug-related or nondrug-related by the
 1092 investigator) that occurred at a rate of 3% or greater in either of the groups receiving ADVAIR
 1093 DISKUS and were more common than in the placebo group. In considering these data,

1094 differences in average duration of exposure should be taken into account. Rare cases of
1095 immediate and delayed hypersensitivity reactions, including rash and other rare events of
1096 angioedema and bronchospasm, have been reported.

1097 These adverse reactions were mostly mild to moderate in severity.

1098 Other adverse events that occurred in the groups receiving ADVAIR DISKUS in these studies
1099 with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1100 **Blood and Lymphatic:** Lymphatic signs and symptoms.

1101 **Cardiovascular:** Palpitations.

1102 **Drug Interaction, Overdose, and Trauma:** Muscle injuries, fractures, wounds and
1103 lacerations, contusions and hematomas, burns.

1104 **Ear, Nose, and Throat:** Rhinorrhea/postnasal drip; ear, nose and throat infections; ear
1105 signs and symptoms; nasal signs and symptoms; nasal sinus disorders; rhinitis; sneezing; nasal
1106 irritation; blood in nasal mucosa.

1107 **Eye:** Keratitis and conjunctivitis, viral eye infections, eye redness.

1108 **Gastrointestinal:** Dental discomfort and pain, gastrointestinal signs and symptoms,
1109 gastrointestinal infections, gastroenteritis, gastrointestinal disorders, oral ulcerations, oral
1110 erythema and rashes, constipation, appendicitis, oral discomfort and pain.

1111 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1112 **Lower Respiratory:** Lower respiratory signs and symptoms, pneumonia, lower respiratory
1113 infections.

1114 **Musculoskeletal:** Arthralgia and articular rheumatism; muscle stiffness, tightness, and
1115 rigidity; bone and cartilage disorders.

1116 **Neurology:** Sleep disorders, tremors, hypnagogic effects, compressed nerve syndromes.

1117 **Non-Site Specific:** Allergies and allergic reactions, congestion, viral infections, pain, chest
1118 symptoms, fluid retention, bacterial infections, wheeze and hives, unusual taste.

1119 **Skin:** Viral skin infections, urticaria, skin flakiness and acquired ichthyosis, disorders of
1120 sweat and sebum, sweating.

1121 The incidence of common adverse events reported in Study 3, a 28-week, non-US clinical
1122 study of 503 patients previously treated with inhaled corticosteroids who were treated twice daily
1123 with ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and
1124 salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation
1125 powder 500 mcg was similar to the incidences reported in Table 3.

1126 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** The
1127 incidence of common adverse events in Table 4 is based upon 1 placebo-controlled, 24-week, US
1128 clinical trial in patients with COPD associated with chronic bronchitis. A total of 723 adult
1129 patients (266 females and 457 males) were treated twice daily with ADVAIR DISKUS 250/50,
1130 fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder 50 mcg, or
1131 placebo.

1132

1133 **Table 4. Overall Adverse Events With $\geq 3\%$ Incidence With ADVAIR DISKUS 250/50**
 1134 **in Patients With Chronic Obstructive Pulmonary Disease Associated With Chronic**
 1135 **Bronchitis**

Adverse Event	ADVAIR DISKUS 250/50 (N = 178) %	Fluticasone Propionate 250 mcg (N = 183) %	Salmeterol 50 mcg (N = 177) %	Placebo (N = 185) %
Ear, nose, and throat				
Candidiasis mouth/throat	10	6	3	1
Throat irritation	8	5	4	7
Hoarseness/dysphonia	5	3	<1	0
Sinusitis	3	8	5	3
Lower respiratory				
Viral respiratory infections	6	4	3	3
Neurology				
Headaches	16	11	10	12
Dizziness	4	<1	3	2
Non-site specific				
Fever	4	3	0	3
Malaise & fatigue	3	2	2	3
Musculoskeletal				
Musculoskeletal pain	9	8	12	9
Muscle cramps & spasms	3	3	1	1
Average duration of exposure (days)	141.3	138.5	136.1	131.6

1136
 1137 Table 4 includes all events (whether considered drug-related or nondrug-related by the
 1138 investigator) that occurred at a rate of 3% or greater in the group receiving ADVAIR DISKUS
 1139 250/50 and were more common than in the placebo group.

1140 These adverse reactions were mostly mild to moderate in severity.

1141 Other adverse events that occurred in the groups receiving ADVAIR DISKUS 250/50 with an
 1142 incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1143 **Cardiovascular:** Syncope.

1144 **Drug Interaction, Overdose, and Trauma:** Postoperative complications.

1145 **Ear, Nose, and Throat:** Ear, nose, and throat infections; ear signs and symptoms;
 1146 laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection.

1147 **Endocrine and Metabolic:** Hypothyroidism.

1148 **Eye:** Dry eyes, eye infections.

1149 **Gastrointestinal:** Constipation, gastrointestinal signs and symptoms, oral lesions.

1150 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1151 **Lower Respiratory:** Breathing disorders, lower respiratory signs and symptoms.
1152 **Non-Site Specific:** Bacterial infections, candidiasis unspecified site, edema and swelling,
1153 nonspecific conditions, viral infections.

1154 **Psychiatry:** Situational disorders.

1155 **Observed During Clinical Practice:** In addition to adverse events reported from clinical
1156 trials, the following events have been identified during worldwide use of any formulation of
1157 ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are
1158 reported voluntarily from a population of unknown size, estimates of frequency cannot be made.
1159 These events have been chosen for inclusion due to either their seriousness, frequency of
1160 reporting, or causal connection to ADVAIR DISKUS, fluticasone propionate, and/or salmeterol
1161 or a combination of these factors.

1162 In extensive US and worldwide postmarketing experience with salmeterol, a component of
1163 ADVAIR DISKUS, serious exacerbations of asthma, including some that have been fatal, have
1164 been reported. In most cases, these have occurred in patients with severe asthma and/or in some
1165 patients in whom asthma has been acutely deteriorating (see WARNINGS no. 2), but they have
1166 also occurred in a few patients with less severe asthma. It was not possible from these reports to
1167 determine whether salmeterol contributed to these events or simply failed to relieve the
1168 deteriorating asthma.

1169 **Cardiovascular:** Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular
1170 tachycardia), ventricular tachycardia.

1171 **Ear, Nose, and Throat:** Aphonia, earache, facial and oropharyngeal edema, paranasal sinus
1172 pain, throat soreness.

1173 **Endocrine and Metabolic:** Cushing syndrome, Cushingoid features, growth velocity
1174 reduction in children/adolescents, hypercorticism, hyperglycemia, weight gain, osteoporosis.

1175 **Eye:** Cataracts, glaucoma.

1176 **Gastrointestinal:** Abdominal pain, dyspepsia, xerostomia.

1177 **Musculoskeletal:** Back pain, cramps, muscle spasm, myositis.

1178 **Neurology:** Paresthesia, restlessness.

1179 **Non-Site Specific:** Immediate and delayed hypersensitivity reaction (including very rare
1180 anaphylactic reaction), pallor. Very rare anaphylactic reaction in patients with severe milk
1181 protein allergy.

1182 **Psychiatry:** Agitation, aggression, depression.

1183 **Respiratory:** Chest congestion; chest tightness; dyspnea; immediate bronchospasm;
1184 influenza; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory
1185 symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

1186 **Skin:** Contact dermatitis, contusions, ecchymoses, photodermatitis.

1187 **Urogenital:** Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal
1188 candidiasis, vaginitis, vulvovaginitis.

1189 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a
1190 component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some

1191 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a
1192 condition that is often treated with systemic corticosteroid therapy. These events usually, but not
1193 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy
1194 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions
1195 have also been reported with other inhaled corticosteroids in this clinical setting. While
1196 ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid
1197 therapy, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary
1198 symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal
1199 relationship between fluticasone propionate and these underlying conditions has not been
1200 established (see PRECAUTIONS: General: *Eosinophilic Conditions*).

1201 **OVERDOSAGE**

1202 **ADVAIR DISKUS:** No deaths occurred in rats given combinations of salmeterol and
1203 fluticasone propionate at acute inhalation doses of 3.6 and 1.9 mg/kg, respectively
1204 (approximately 320 and 15 times the maximum recommended daily inhalation dose in adults on
1205 a mg/m² basis).

1206 **Fluticasone Propionate:** Chronic overdosage with fluticasone propionate may result in
1207 signs/symptoms of hypercorticism (see PRECAUTIONS: General: *Metabolic and Other*
1208 *Effects*). Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate
1209 inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate inhalation
1210 aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of
1211 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated.
1212 Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to
1213 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or
1214 moderate severity, and incidences were similar in active and placebo treatment groups. The oral
1215 and subcutaneous median lethal doses in mice and rats were >1,000 mg/kg (>4,300 and >8,700
1216 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m²
1217 basis).

1218 **Salmeterol:** The expected signs and symptoms with overdosage of salmeterol are those of
1219 excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and
1220 symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or
1221 hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache,
1222 tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and
1223 insomnia. Overdosage with salmeterol may be expected to result in exaggeration of the
1224 pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia
1225 and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead
1226 to clinically significant prolongation of the QTc interval, which can produce ventricular
1227 arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

1228 As with all sympathomimetic medications, cardiac arrest and even death may be associated
1229 with abuse of salmeterol.

1230 Treatment consists of discontinuation of salmeterol together with appropriate symptomatic
1231 therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing
1232 in mind that such medication can produce bronchospasm. There is insufficient evidence to
1233 determine if dialysis is beneficial for overdosage of salmeterol. Cardiac monitoring is
1234 recommended in cases of overdosage.

1235 No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg
1236 (approximately 250 times the maximum recommended daily inhalation dose in adults on a
1237 mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 190 times the
1238 maximum recommended daily inhalation dose in adults on a mg/m² basis). By the oral route, no
1239 deaths occurred in mice at 150 mg/kg (approximately 6,500 times the maximum recommended
1240 daily inhalation dose in adults on a mg/m² basis) and in rats at 1,000 mg/kg (approximately
1241 86,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis).

1242 **DOSAGE AND ADMINISTRATION**

1243 ADVAIR DISKUS should be administered by the orally inhaled route only (see PATIENT'S
1244 INSTRUCTIONS FOR USE). After inhalation, the patient should rinse the mouth with water
1245 without swallowing. ADVAIR DISKUS should not be used for transferring patients from
1246 systemic corticosteroid therapy.

1247 **Asthma:** ADVAIR DISKUS is available in 3 strengths, ADVAIR DISKUS 100/50, ADVAIR
1248 DISKUS 250/50, and ADVAIR DISKUS 500/50, containing 100, 250, and 500 mcg of
1249 fluticasone propionate, respectively, and 50 mcg of salmeterol per inhalation.

1250 For patients 12 years of age and older, the dosage is 1 inhalation twice daily (morning and
1251 evening, approximately 12 hours apart).

1252 The recommended starting dosages for ADVAIR DISKUS are based upon patients' current
1253 asthma therapy.

- 1254 • For patients who are not currently on an inhaled corticosteroid, whose disease severity
1255 warrants treatment with 2 maintenance therapies, including patients on non-corticosteroid
1256 maintenance therapy, the recommended starting dosage is ADVAIR DISKUS 100/50 twice
1257 daily.
- 1258 • For patients on an inhaled corticosteroid, Table 5 provides the recommended starting dosage.
1259 The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily.

1260 **For all patients it is desirable to titrate to the lowest effective strength after adequate**
1261 **asthma stability is achieved.**

1262

1263 **Table 5. Recommended Dosages of ADVAIR DISKUS for Patients With Asthma Taking**
 1264 **Inhaled Corticosteroids**

Current Daily Dose of Inhaled Corticosteroid		Recommended Strength and Dosing Schedule of ADVAIR DISKUS
Beclomethasone dipropionate	≤420 mcg	100/50 twice daily
	462-840 mcg	250/50 twice daily
Budesonide	≤400 mcg	100/50 twice daily
	800-1,200 mcg	250/50 twice daily
	1,600 mcg*	500/50 twice daily
Flunisolide	≤1,000 mcg	100/50 twice daily
	1,250-2,000 mcg	250/50 twice daily
Fluticasone propionate inhalation aerosol	≤176 mcg	100/50 twice daily
	440 mcg	250/50 twice daily
	660-880 mcg*	500/50 twice daily
Fluticasone propionate inhalation powder	≤200 mcg	100/50 twice daily
	500 mcg	250/50 twice daily
	1,000 mcg*	500/50 twice daily
Triamcinolone acetonide	≤1,000 mcg	100/50 twice daily
	1,100-1,600 mcg	250/50 twice daily

* ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid therapy.

1265
 1266 ADVAIR DISKUS should be administered twice daily every day. More frequent
 1267 administration (more than twice daily) or a higher number of inhalations (more than 1 inhalation
 1268 twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some
 1269 patients are more likely to experience adverse effects with higher doses of salmeterol. The safety
 1270 and efficacy of ADVAIR DISKUS when administered in excess of recommended doses have not
 1271 been established.

1272 If symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should
 1273 be taken for immediate relief.

1274 Patients who are receiving ADVAIR DISKUS twice daily should not use additional
 1275 salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of EIB,
 1276 or for any other reason.

1277 Improvement in asthma control following inhaled administration of ADVAIR DISKUS can
 1278 occur within 30 minutes of beginning treatment, although maximum benefit may not be
 1279 achieved for 1 week or longer after starting treatment. Individual patients will experience a
 1280 variable time to onset and degree of symptom relief.

1281 For patients who do not respond adequately to the starting dosage after 2 weeks of therapy,
1282 replacing the current strength of ADVAIR DISKUS with a higher strength may provide
1283 additional improvement in asthma control.

1284 If a previously effective dosage regimen of ADVAIR DISKUS fails to provide adequate
1285 improvement in asthma control, the therapeutic regimen should be reevaluated and additional
1286 therapeutic options, e.g., replacing the current strength of ADVAIR DISKUS with a higher
1287 strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be
1288 considered.

1289 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** The
1290 dosage for adults is 1 inhalation (250/50 mcg) twice daily (morning and evening, approximately
1291 12 hours apart).

1292 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of
1293 COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50,
1294 are not recommended, as no additional improvement in lung function was observed in clinical
1295 trials and higher doses of corticosteroids increase the risk of systemic effects.

1296 If shortness of breath occurs in the period between doses, an inhaled, short-acting
1297 beta₂-agonist should be taken for immediate relief.

1298 Patients who are receiving ADVAIR DISKUS twice daily should not use additional
1299 salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for the maintenance
1300 treatment of COPD or for any other reason.

1301 **Geriatric Use:** In studies where geriatric patients (65 years of age or older, see
1302 PRECAUTIONS: Geriatric Use) have been treated with ADVAIR DISKUS, efficacy and safety
1303 did not differ from that in younger patients. Based on available data for ADVAIR DISKUS and
1304 its active components, no dosage adjustment is recommended.

1305 **Directions for Use:** Illustrated Patient's Instructions for Use accompany each package of
1306 ADVAIR DISKUS.

1307 **HOW SUPPLIED**

1308 ADVAIR DISKUS 100/50 is supplied as a disposable, purple device containing 60 blisters.
1309 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective
1310 foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional
1311 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS
1312 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch
1313 (NDC 0173-0695-02).

1314 ADVAIR DISKUS 250/50 is supplied as a disposable, purple device containing 60 blisters.
1315 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective
1316 foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional
1317 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS
1318 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch
1319 (NDC 0173-0696-02).

1320 ADVAIR DISKUS 500/50 is supplied as a disposable, purple device containing 60 blisters.
1321 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective
1322 foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional
1323 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS
1324 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch
1325 (NDC 0173-0697-02).

1326 **Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place**
1327 **away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation**
1328 **device is not reusable. The device should be discarded 1 month after removal from the**
1329 **moisture-protective foil overwrap pouch or after all blisters have been used (when the dose**
1330 **indicator reads “0”), whichever comes first. Do not attempt to take the device apart.**

1331
1332



1333 GlaxoSmithKline
1334 GlaxoSmithKline
1335 Research Triangle Park, NC 27709

1336
1337 ©Year, GlaxoSmithKline. All rights reserved.

1338
1339 Month Year

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1 **Patient's Instructions for Use**

2
3 Product logo
4

5
6 **ADVAIR DISKUS® 100/50**
7 **(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)**

8
9 **ADVAIR DISKUS® 250/50**
10 **(fluticasone propionate 250 mcg and salmeterol* 50 mcg inhalation powder)**

11
12 **ADVAIR DISKUS® 500/50**
13 **(fluticasone propionate 500 mcg and salmeterol* 50 mcg inhalation powder)**

14
15 *** As salmeterol xinafoate salt 72.5 mcg, equivalent to salmeterol base 50 mcg**
16

17 **FOR ORAL INHALATION ONLY**

18
19 (illustration of device with parts labeled:

- 20 Outer Case
- 21 Mouthpiece
- 22 Lever
- 23 Thumbgrip
- 24 Dose Indicator)
- 25
- 26

27 Read this leaflet carefully before you start to take your medicine. It provides a summary of
28 information about your medicine. Keep it for future use. Read the leaflet every time you refill
29 your prescription because there may be new information.
30

31 *For more information ask your doctor or pharmacist.*

32
33 **What Is ADVAIR DISKUS®?**

34 Your doctor has prescribed ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR
35 DISKUS 500/50. The medicine is available in 3 different strengths, and your doctor has chosen
36 the one most suitable for you.

37 Asthma is a long-term condition affecting the lungs. Symptoms of asthma include shortness of
38 breath, wheezing, chest tightness, and cough. Two main causes of asthma symptoms are

39 bronchoconstriction (tightening of the muscles surrounding the airways) and inflammation
40 (swelling and irritation of the airways).

41 Chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis is a
42 long-term, progressively worsening condition that restricts airflow into and out of the lungs. The
43 main cause of COPD is exposure to lung irritants, including tobacco smoke and airborne
44 pollutants, which may lead to bronchoconstriction, inflammation, and lung tissue damage.

45 ADVAIR DISKUS contains 2 medicines, fluticasone propionate (a synthetic corticosteroid) and
46 salmeterol xinafoate (a long-acting bronchodilator), which work in different ways in the lungs to
47 improve lung function and symptoms in patients with asthma. Fluticasone propionate is used to
48 reduce the airway inflammation and salmeterol a long-acting bronchodilator helps prevent and
49 relieve bronchospasm, making it easier to breathe.

50 Fluticasone propionate and salmeterol in ADVAIR DISKUS work together to improve lung
51 function in patients with COPD associated with chronic bronchitis.

Important Points to Remember About Using ADVAIR DISKUS

52
53 **1. TELL YOUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE if you**
54 **are:**

- 55 • pregnant (or intending to become pregnant);
- 56 • breastfeeding a baby;
- 57 • allergic to ADVAIR DISKUS, any other medicines, or food products;
- 58 • taking a medicine containing ritonavir (commonly used to treat HIV infection or AIDS); or
- 59 • taking other medicines, especially any other orally inhaled bronchodilator or
60 corticosteroids, over-the-counter medicines, and herbal products.

61 In some circumstances, this medicine may not be suitable for you, and your doctor may wish
62 to give you a different medicine.

63 **2. It is important that you inhale each dose as your doctor has advised. The label provided by**
64 **your pharmacist will usually tell you what dose to take and how often. If it doesn't, or if you**
65 **are not sure, ask your doctor or pharmacist. Do not use ADVAIR DISKUS more**
66 **frequently than 2 times daily, morning and evening, approximately 12 hours apart, at**
67 **the recommended dose of 1 inhalation each time.**

68 **3. ADVAIR DISKUS delivers your dose of medicine as a very fine powder that most, but not**
69 **all, patients can taste or feel.** Whether or not you are able to taste or feel your dose of
70 medicine, you should not exceed the recommended dose of 1 inhalation each morning and
71 evening, approximately 12 hours apart. If you are not sure you are receiving your dose of
72 ADVAIR DISKUS, contact your doctor or pharmacist.

73 **4. You may breathe more easily after the first dose of ADVAIR DISKUS; however, it may take**
74 **1 week or longer to achieve maximum benefit. It is IMPORTANT THAT YOU USE**

75 **ADVAIR DISKUS REGULARLY. DO NOT STOP TREATMENT EVEN IF YOU**
76 **ARE FEELING BETTER** unless told to do so by your doctor.

77 5. If you miss a dose, just take your next scheduled dose when it is due. **DO NOT DOUBLE**
78 the dose.

79 6. **DO NOT USE ADVAIR DISKUS TO RELIEVE SUDDEN SYMPTOMS OF**
80 **SHORTNESS OF BREATH** (e.g., sudden severe onset or worsening of wheezing, cough,
81 chest tightness). **An inhaled, short-acting bronchodilator such as albuterol should be**
82 **used to relieve sudden symptoms of shortness of breath.** If you do not have an inhaled,
83 short-acting bronchodilator, contact your doctor to have one prescribed for you. **You should**
84 **continue to take ADVAIR DISKUS as instructed by your doctor.**

85 7. **Tell your doctor immediately if your condition is getting worse, as indicated by any of**
86 **the following situations.**

- 87 • Your inhaled, short-acting bronchodilator becomes less effective.
- 88 • You need more inhalations than usual of your inhaled, short-acting bronchodilator.
- 89 • You have asthma and you have a significant decrease in your peak flow measurement as
90 previously defined by your doctor.

91 8. If you have asthma and your symptoms do not improve after using ADVAIR DISKUS
92 regularly for 2 weeks, tell your doctor.

93 9. **While you are taking ADVAIR DISKUS twice daily, you should not use SEREVENT[®]**
94 **DISKUS[®] (salmeterol xinafoate inhalation powder) or FORADIL[®] AEROLIZER[™]**
95 **(formoterol fumarate inhalation powder) for any reason, including prevention of**
96 **exercise-induced asthma or the maintenance treatment of asthma or COPD.**

97 10. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of
98 ADVAIR DISKUS, may increase the risk of some eye problems (cataracts or glaucoma).
99 Regular eye examinations should be considered.

100 11. If you have COPD, you may be at greater risk of developing bone loss (osteoporosis) and the
101 use of corticosteroids, including ADVAIR DISKUS, may increase your risk. Talk to your
102 doctor about ways to reduce your risk.

103 12. Use other asthma or COPD medicines only as directed by your doctor.

104 13. Do not use ADVAIR DISKUS with a spacer device.

105

106

How to Use Your ADVAIR[™] DISKUS[®]

107 Follow the instructions below. If you have any questions, ask your doctor or pharmacist.

108 When you take the ADVAIR DISKUS out of the box and foil overwrap pouch, write the **“Pouch**
109 **opened”** and **“Use by”** dates on the label in the space provided on the device. **The “Use by”**
110 **date is 1 month from date of opening.**

111 The DISKUS® inhalation device will be in the closed position when the pouch is opened.
112 The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose
113 indicator number will decrease each time you use the DISKUS. After the DISKUS has delivered
114 55 doses (23 doses for the institutional or sample pack), numbers 5 to 0 will appear in **red** to
115 warn you that there are only a few doses left (*see Figure 1*).

116

117

Figure 1

118 Taking a dose of ADVAIR DISKUS requires the following 3 simple steps: Open, Click, Inhale.

119 **1 OPEN:** Hold the DISKUS in one hand and put the thumb of your other hand on the
120 **thumbgrip**. Push your thumb away from you as far as it will go until the mouthpiece appears
121 and snaps into position (*see Figure 2*).

122

123

Figure 2

124 **2 CLICK:** Hold the DISKUS in a level, horizontal position with the mouthpiece towards you.
125 Slide the **lever** away from you as far as it will go until it **clicks** (*see Figure 3*). The DISKUS
126 is now ready to use.

127

128

Figure 3

129 Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a
130 decrease in numbers on the dose counter. **To avoid releasing or wasting doses:**

- 131 • **Do not close the DISKUS.**
- 132 • **Do not tilt the DISKUS.**
- 133 • **Do not play with the lever.**
- 134 • **Do not advance the lever more than once.**

135 **3 INHALE:** Before inhaling your dose of ADVAIR DISKUS, breathe out as far as is
136 comfortable, holding the DISKUS level and away from your mouth (*see Figure 4*).
137 **Remember, never breathe out into the DISKUS mouthpiece.**

138

139

Figure 4

140 Put the mouthpiece to your lips (*see Figure 5*). Breathe in quickly and deeply through the
141 DISKUS, not through your nose.

142

143

Figure 5

144 Remove the DISKUS from your mouth. Hold your breath for about 10 seconds, or for as long as
145 is comfortable. Breathe out slowly.

146 **CLOSE the DISKUS when you are finished taking a dose so that the DISKUS will be ready**
147 **for you to take your next dose.** Put your thumb on the thumbgrip and slide the thumbgrip back
148 towards you as far as it will go (*see Figure 6*). The DISKUS will click shut. The lever will
149 automatically return to its original position. The DISKUS is now ready for you to take your next
150 scheduled dose, due in approximately 12 hours. (Repeat steps 1 through 3.)

151

152

Figure 6

153 REMEMBER:

- 154 • Never exhale into the DISKUS.
- 155 • Never attempt to take the DISKUS apart.
- 156 • Always activate and use the DISKUS in a level, horizontal position.
- 157 • After inhalation, rinse the mouth with water without swallowing.
- 158 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
- 159 • Always keep the DISKUS in a dry place.
- 160 • Never take an extra dose, even if you feel you did not receive a dose.

161

Storing Your ADVAIR DISKUS

162 **Store at controlled room temperature, 20° to 25°C (68° to 77°F) in a dry place away from**
163 **direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation device is not**
164 **reusable. The device should be discarded 1 month after removal from the**
165 **moisture-protective foil overwrap pouch or after all blisters have been used (when the dose**
166 **indicator reads “0”), whichever comes first. Do not attempt to take the device apart.**

167 **REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give**
168 **this medicine to anyone else.**

169

Further Information

170 This leaflet does not contain the complete information about your medication. *If you have any*
171 *questions, or are not sure about something, then you should ask your doctor or pharmacist.*

172 You may want to read this leaflet again. Please **DO NOT THROW IT AWAY** until you have
173 finished your medicine.

174 Your doctor has determined that this product is likely to help your personal health. **USE THIS**
175 **PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR**
176 **DOCTOR.** If you have any questions about alternatives, consult with your doctor.

177 ADVAIR DISKUS and SEREVENT DISKUS are registered trademarks of GlaxoSmithKline.
178 FORADIL AEROLIZER is a trademark of Novartis Pharmaceuticals Corporaion.

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Research Triangle Park, NC 27709

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Month Year

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-077/S-003

MEDICAL REVIEW(s)

DIVISION DIRECTOR'S MEMORANDUM

Date: November 14, 2003

To: NDA 21-077

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Advair Diskus 250/50 (fluticasone 250 mcg and salmeterol 50 mcg inhalation powder)

Applicant: GlaxoSmithKline

Administrative, Introduction, and Regulatory History

GlaxoSmithKline (GSK) submitted a supplemental NDA (21-077/S-03) for Advair Diskus 250/50 and 500/50 as a 505(b)(1) application for long-term maintenance treatment of chronic obstructive pulmonary disease (COPD) that was received by the Agency on May 7, 2001. Later in the month, GSK submitted two other supplemental NDAs for Flovent Diskus 250 and 500 (20-833/SE1-04), and for Serevent Diskus 50 (20-692/SE1-016) for the treatment COPD. The three supplemental NDAs were based on three pivotal studies that were overlapping among the applications (discussed below). The Advair and Flovent supplemental NDAs were discussed at a Pulmonary-Allergy Drugs Advisory Committee (PADAC) on January 17, 2002. The two applications were discussed at the PADAC meeting because inhaled corticosteroids, either alone or in combination products, are not approved for use in COPD in the United States. The PADAC concluded that the data show limited efficacy of Advair Diskus and Flovent Diskus in COPD, but were concerned that long term safety data on the use of inhaled corticosteroids in COPD were lacking. The PADAC voted 6 to 2 in favor of approval of Advair Diskus and 5 to 4 in favor of approval of Flovent Diskus, but recommended that the indication be limited to chronic bronchitic patients that were studied. The Agency took an approvable action on the Advair Diskus and Flovent Diskus applications because of lack of convincing efficacy balanced against safety concerns with the use of inhaled corticosteroid in COPD.

GSK submitted a complete response to the Advair Diskus approvable action on June 20, 2002, which resulted in a second approvable action by the Agency on December 16, 2002, because of the same concerns that were noted in the first action. GSK submitted a second complete response on May 30, 2003, which is the subject of this action. /

For the Advair Diskus, GSK decided to pursue the 250/50 strength and not the 500/50 strength, because the higher strength did not show any efficacy benefit over the lower strength and the higher strength of corticosteroid would be expected to have more safety concerns. GSK has also submitted some additional safety and efficacy data with this submission, and

modified the proposed indication to limit to COPD associated with chronic bronchitis. Based on these changes, the application is now adequate to support approval.

The relevant areas of the original submission and the current submission are briefly summarized in the following sections. These are reviewed in detail in Dr. Gilbert-McClain's excellent medical officer reviews of the previous and current submissions, and in other discipline reviews and summary memoranda of the previous submissions.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

Advair Diskus is an approved and marketed product in the United States. There are no outstanding issues with CMC aspects of the product and with the manufacturing facilities.

Pharmacology and Toxicology

The applicant did not conduct any new preclinical data for this application because Advair Diskus and the two active components of Advair are approved products.

Clinical and Statistical

GSK conducted three studies (FLTA3025, SFCA 3006, and SFCA 3007) to support the approval of Advair Diskus, Flovent Diskus, and Serevent Diskus for the treatment of COPD. Studies 3006 and 3007 were designed to compare the efficacy and safety of Advair Diskus 500/50 (study 3006) and Advair Diskus 250/50 (study 3007) to salmeterol 50 mcg and fluticasone 500 mcg and 250 mcg, respectively. Both studies also had placebo arms for comparison to the fluticasone arms. Study 3025 was designed to compare efficacy and safety of fluticasone 500 mcg and 250 mcg to placebo. These studies were submitted with the original submission, and was reviewed by the Agency and discussed at the PADAC meeting on January 17, 2003.

The three studies were randomized, double-blind, parallel-group, and 24 weeks in duration. Patients enrolled in the studies were adults with a history of COPD with cough productive of sputum on most days for at least 3 months of the year for at least 2 years, and the sputum production was not attributable to any other diseases process. The primary efficacy variables were pre-dose FEV1 and 2-hour post-dose FEV1 to assess the contribution of fluticasone and salmeterol, respectively. In the study that tested Advair 250/50, patients receiving Advair 250/50 had significantly greater improvement in pre-dose FEV1 at endpoint (165 mL, 17%) compared to patients receiving salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL, 1%), demonstrating the contribution of fluticasone in the Advair product. Patients receiving Advair 250/50 also had significantly greater improvement in post-dose FEV1 at endpoint (281 mL, 27%) compared to patients receiving fluticasone 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the contribution of salmeterol in the Advair product. Similar efficacy advantage was also seen at other time points during the study. In the study that tested Advair 500/50, a similar degree of improvement of lung function was observed with Advair 500/50. Patients treated with Advair 250/50 and Advair 500/50 did not have a significant

reduction in chronic bronchitis symptoms (as measured by the Chronic Bronchitis Symptom Questionnaire), or in COPD exacerbations. In the clinical studies, no new safety signals were noted.

Overall, the clinical program supports efficacy of both strengths of Advair products for short-term treatment of airflow obstruction in patients with COPD associated with chronic bronchitis, but incremental benefit with the higher strength product was not noted. Originally GSK applied for approval of both strengths of Advair and asked for an indication supporting long-term maintenance treatment of COPD. However, GSK later withdrew the higher strength and limited the indication to the treatment of airflow obstruction in patients with COPD associated with chronic bronchitis.

One of the lingering concerns with the approval of Advair for use in COPD patients was the question of safety with the use of inhaled fluticasone. To support the safety of inhaled fluticasone and to further bolster efficacy, GSK submitted results of studies comparing Advair to Combivent (Studies SCO 40011 and SCO 40012), and four case-control studies (EPI 40204, EPI 40205, EPI 40206, and EPI 40207) assessing fracture risk associated with use of inhaled corticosteroids in COPD patients. GSK has also submitted review of post-marketing data, including data from countries where Advair or Flovent or both are approved for use in COPD patients. These are reviewed in Dr. Gilbert-McClain's review of the current submission. In addition GSK has submitted extensive risk management plans, plans for continued monitoring of adverse events with special attention to those organ systems that may be attributable to corticosteroids, and two phase 4 commitment studies, one to assess the effect of Advair on bone mineral density, and the other to assess the efficacy of Advair in COPD exacerbation. The new data and the proposed plans are adequate to address the safety concerns of Advair in COPD patients.

The overall efficacy data, safety data, and risk management plans are adequate to support the approval of Advair in patients with COPD associated with chronic bronchitis.

Clinical Pharmacology and Biopharmaceutics

The clinical pharmacokinetics data were reviewed with the original application and also with this submission for labeling purpose. These are no outstanding issues.

Data Quality, Integrity, and Financial Disclosure

No new data are submitted that would warrant a DSI audit. The original application has no issues with data quality and integrity. All studies were conducted in accordance with accepted ethical standards. No financial disclosure issues are present.

Pediatric Consideration

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

Product Name

The proprietary name of Advair is approved and used by GSK for the product line containing salmeterol and fluticasone.

Labeling

GSK submitted a product label containing various new sections relevant to the COPD studies and the COPD indication. The labeling has been extensively reviewed by all relevant disciplines. The Division and GSK have agreed on a final labeling text that adequately reflects the data and the new indication.

Action

The overall clinical data submitted with the original NDA and with the later submissions are sufficient to support efficacy and safety of Advair 250/50 for use in COPD patients. There are no outstanding issues with this application. Therefore, the action on this application will be APPROVAL.

GSK has agreed to conduct two studies post-approval, one study to evaluate the effect of Advair 250/50 on bone mineral density, and another study to evaluate the efficacy of Advair 250/50 on COPD exacerbations.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Badrul Chowdhury
11/14/03 12:21:47 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION: NDA 21-077/SE1-003 TRADE NAME: Advair
 APPLICANT/SPONSOR: GlaxoSmithKline (GSK) USAN NAME: Fluticasone propionate/salmeterol
 MEDICAL OFFICER: Lydia Gilbert-McClain, MD, FCCP xinafoate
 TEAM LEADER: Badrul Chowdhury, MD, PhD CATEGORY: Corticosteroid/Long-acting β_2 -agonist
 PDUFA DUE DATE: 11/30/03 ROUTE: Oral Inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
May 30, 2003	Electronic Submission	Complete response	Complete Response to December 16, 2002 AE letter
October 10, 2003	Electronic submission	Final Safety update	
Miscellaneous	October 3, 2003	ODS consult	Consult from ODS on GSK's risk management plan

RELATED APPLICATIONS

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>
May 4, 2001	Original sNDA 21-077/SE1-03	Submitted for Advair 250/50 and Advair 500/50 COPD indication
June 20, 2002	Complete response to AE letter of March 5, 2002	

REVIEW SUMMARY: This is a complete response to the AE letter of December 16, 2003 for Advair Diskus 250/50 for the COPD indication. With the agreed upon changes in the label the application can be APPROVED for the maintenance treatment of lung function in patients with COPD associated with chronic bronchitis. The sponsor has also submitted a risk management plan which includes a proposal for 2 phase 4 studies to further define the benefit/risk of Advair Diskus 250/50 in the COPD population.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES: SAFE TO PROCEED CLINICAL HOLD
 NDA/SUPPLEMENTS: FILEABLE NOT FILEABLE
 APPROVAL APPROVABLE NOT APPROVABLE
 OTHER ACTION:

EXECUTIVE SUMMARY

I. RECOMMENDATIONS

A. Recommendation on Approvability

This reviewer recommends an APPROVAL action for the Advair Diskus 250/50 product for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis at the recommended dose of one inhalation twice daily. The approval of this application is contingent upon the sponsor's acceptance of the Agency's proposed labeling changes and the institution of the risk management plan and agreements to the phase 4 commitments outlined below.

B. Recommendation on phase 4 studies and Risk Management Steps

Generally, a Risk Management Plan (RMP) and phase 4 commitments are separate elements of the post-approval process. However, GSK's proposed RMP includes a proposal for conducting at 2 studies as phase 4 commitments. In addition to the proposed phase 4 commitments, the RMP includes enhanced post-marketing surveillance, and labeling and educational materials. The risk management plan was reviewed by the Office of Drug Safety (ODS) and the recommendations conveyed to the sponsor are those received from consultation with ODS. The objectives of the risk management plan [see page 12] are appropriate for this indication in the patient population of interest.

As part of a RMP to further define the benefit/risk profile of Advair Diskus 250/50 in patients with COPD, GSK has proposed and should conduct the following studies as phase 4 commitments.

- (1) A randomized double-blind parallel-group 2-year study to evaluate the effect of Advair 250/50 on bone mineral density in patients with COPD.
- (2) A randomized double-blind, parallel-group 52-week study to evaluate the effect of Advair 250/50 on exacerbations in patients with COPD.

Additionally, GSK has proposed enhanced post marketing surveillance activities as part of the RMP [See page 14]. The activities proposed are acceptable and many are expected usual practice in monitoring the safety of marketed drugs.

The office of Drug Safety recommends that:

- GSK should include a component for evaluating the performance of the RMP with details of the timeline and the methodology that will be applied.
- GSK should propose a time to report to the Agency and provide data on: (a) the extent of high-dose use among patients with COPD (specifying the methods and data sources used and (b) Complications of product use (through surveys of COPD patients and/or physicians).

The RMP proposes using labeling and educational interventions to achieve the other stated objectives [i.e. (i) to achieve the use of Advair 250/50 and to minimize the prescribing of the high dose and (ii) to minimize potential risks associated with the disease itself and the use of Advair 250/50 in the COPD population]. The Office of Drug Safety agrees that labeling and educational interventions are appropriate tools to

achieve these objectives. Labeling has been negotiated with the Division to address these issues.

II. BACKGROUND/REGULATORY HISTORY

On May 4, 2001, GlaxoSmithKline (GSK) submitted a supplemental new drug application (sNDA) 21-077/S-003 for Advair Diskus (fluticasone propionate and salmeterol inhalation powder) for the long-term maintenance treatment of chronic obstructive pulmonary disease (COPD). The Development program was designed with the intent of supporting approval of Flovent Diskus, Salmeterol Diskus and Advair Diskus for the long-term maintenance treatment of COPD. The program was comprised of three pivotal studies - FLTA3025, SFCA3006, and SFAC3007. Studies SFCA3006 and 3007 were designed to compare the efficacy and safety of Advair Diskus 500/50 (SFCA3006) and Advair Diskus 250/50 (SFCA3007) to the individual components salmeterol 50 mcg and fluticasone propionate (FP) 500 and 250 mcg and placebo. Study FLTA 3025 was designed to demonstrate efficacy and safety of FP 500 and FP 250 compared to placebo. The three studies were submitted to three separate sNDAs for Advair Diskus (sNDA 21-077/S-03), Flovent Diskus (sNDA20-833/SE1-04) and Serevent Diskus (sNDA20-692/SE1-016).

This drug development program was discussed with the Pulmonary Division at an EOP2 meeting held April 21, 1998. At that meeting, the Division agreed that the design of the phase 3 studies for Advair Diskus would meet the requirements of the combination policy as set forth in 21 CFR 300.50. Additionally, the Division agreed that the primary efficacy endpoints of pre-dose FEV₁ and 2-hour post-dose FEV₁ were acceptable to assess the contribution of FP and salmeterol (SAL) in the combination product. GSK modified an instrument (The Chronic Bronchitis Symptom Questionnaire - CBSQ) previously designed by Thomas Petty¹ to assess symptomatic improvement in COPD and discussed this instrument at the EOP2 meeting. The Division agreed that the revised instrument with some validation efforts made by GSK appeared to be reasonable to use in the clinical program. Another objective of the development program was to assess the effect of Advair Diskus and its individual components compared to placebo on patient-reported outcomes as measured by the Chronic Respiratory Disease Questionnaire (CRDQ). Secondary efficacy assessments in this program also included an assessment of dyspnea as measured by the Baseline/Transition Dyspnea Index (BDI/TDI) as well as COPD exacerbations, nighttime symptoms requiring rescue medication and use of short-acting beta₂-agonists.

At the EOP2 meeting, although the Division stated that the proposed clinical program was acceptable on the surface, there were concerns about the potential systemic effects of fluticasone over time in elderly patients. The Division also cautioned GSK that additional Phase 4 studies might be needed if FP gained a COPD indication but safety issues remained.

Three weeks following the submission of sNDA for Advair Diskus, sNDAs were submitted for Flovent Diskus 500, and 250 and salmeterol Diskus. All three sNDAs contained the same studies. The Division had previously informed the sponsor that the

Advair and Flovent Diskus applications would be taken to the Pulmonary –Allergy Drugs Advisory Committee.

On January 17, 2002, the Advair and FP Diskus applications were discussed at the Advisory Committee meeting. There were several reasons for taking these applications to the Advisory committee. Corticosteroids are commonly used in the treatment of patients with COPD both in the acute exacerbation setting where treatment is mainly systemic and of short duration² and in the maintenance setting where treatment is commonly either inhaled or systemic³. However, the FDA to date has not approved such use. The benefit of long-term maintenance treatment of inhaled corticosteroid (ICS) in COPD remains unproven and the most recent long-term (2 – 3years duration) studies in the literature indicate that the initial improvement in FEV₁ that may be seen with the early use of ICS is not sustained over time and ICS do not affect the rate of decline of lung function in patients with COPD^{4,5,6,7}. Additionally, the potential systemic effects of the long-term use of ICS in an elderly COPD population should be taken into the context of any purported short-term [or long-term] benefit of the drug. Therefore, these two applications – one for a corticosteroid in combination with a long-acting bronchodilator (Advair Diskus), and one for a corticosteroid alone (FP Diskus) represented groundbreaking important issues for the FDA.

At the time of the initial submission of these applications, FP was approved for use in COPD in several developing countries in the West Indies, Africa, South America, and in Pakistan, the Philippines, Romania, Slovakia, Turkey and Yugoslavia, however Advair had not been approved for COPD in any country. Since salmeterol metered-dose inhaler was already approved for COPD in the U.S., the salmeterol Diskus application was not discussed at the Advisory committee and the salmeterol Diskus application was approved in the first approval cycle in 2002.

The Advisory committee members agreed that the data showed limited efficacy of Advair Diskus [and Flovent Diskus] for the treatment of COPD and that long-term safety data were lacking. Nevertheless, the committee voted 6/2 in favor of approval for Advair Diskus 500/50 and 250/50 [and 5/4 in favor of FP Diskus 500 and 250] with recommendations for a revised labeled indication and additional studies possibly as phase 4 commitments. The committee agreed that an indication for the long-term maintenance treatment of COPD was not supported by the data but recommended that an indication be limited to the subpopulation of COPD patients with chronic bronchitis i.e. the subset of patients actually studied in the clinical trials. The committee also recommended that treatment be restricted to no longer than 6 months in duration but did not provide specific recommendations as to how physicians would determine when to discontinue therapy.

On March 5, 2002, the Agency took an APPROVABLE action on Advair Diskus and Flovent Diskus and issued an identical AE letter to both applications. The Division acknowledged that although GSK demonstrated statistically significant improvement in the primary efficacy endpoints (pre-dose FEV₁, and 2-hour post dose FEV₁)) for Advair Diskus (*see Medical Officer Review for details*) in view of the failure to demonstrate a clearly-defined clinical benefit on symptoms, exacerbations, or patient-reported

250/50 dosage strength since the 500/50 strength did not show additional efficacy and the lower dose of corticosteroid would improve the risk/benefit ratio.

On May 30, 2003, GSK submitted a complete response to the Dec 16, 2002 approvable letter for Advair Diskus 250/50.

III. SUMMARY OF THE MAY 30, 2003 COMPLETE RESPONSE

The contents of the sponsor's submission are outlined below followed by this reviewer's comments/review of each item.

CONTENTS OF THE SUBMISSION

The complete response contains the following:

- Clinical studies SCO40011 and SCO40012 comparing Advair 250/50 to Combivent in COPD patients treated for 8 weeks
- Clinical studies SMS40320 and SMS40321 comparing salmeterol to Combivent
- Four case-control studies EPI40204, 40205, 40206 and 40207 assessing fracture risk associated with ICS use among COPD patients
- An examination of GSK spontaneous adverse event data to evaluate a dose response association between FP and adverse events of special interest.
- A risk management plan
- Concept protocols for phase 4 commitments
- Updated proposed labeling
- DRAFT launch materials for illustrative purposes only (Not reviewed)

Efficacy

The sponsor submitted 4 clinical studies in the application in order to address the comment in the approvable letter to "*more fully define the efficacy (including outcome data).*"

Studies SCO40011 and SCO40012

Studies SCO40011 and SCO40012 were randomized controlled studies with 8-week treatment periods in COPD patients randomized to Advair 250/50 BID or Combivent® QID. These studies were initiated in November – December 2001 as development phase 4 studies and were completed in 2003. Patient demographics were typical of COPD subjects with mean age of approximately 65 years, long-standing smoking history (mean ~ 57 years) and about one-third each reported a history of emphysema, chronic bronchitis or both. Specific criteria to define emphysema, or chronic bronchitis were not included in these protocols. Baseline spirometric data were consistent with moderate to severe COPD with a similar degree of reversibility (18 – 19%) between both treatment groups in both studies.

In both studies, the sponsor demonstrated a statistically significant improvement in pre-dose FEV₁ over baseline at endpoint in the Advair 250/50 group compared to Combivent. This finding is not unexpected. The primary endpoint selected provides a unique advantage to Advair given that this endpoint (trough FEV₁) specifically evaluates the contribution of the FP component of the drug product with some

carryover bronchodilator effects of salmeterol. The efficacy of Combivent - a combination product comprised of 2 bronchodilators would be best demonstrated by evaluating the FEV₁ AUC 0-6 hours. This endpoint was assessed as one of the secondary endpoints. Again, with this endpoint, Advair 250/50 showed greater improvement at Week 8 compared to Combivent. Given that the bronchodilator component of Advair is the long-acting β_2 agonist salmeterol – this improvement in FEV₁ compared to the shorter acting bronchodilators (albuterol and ipratropium) is not unexpected. Symptomatic improvement assessed using VAS ratings was reported to be numerically better in the Advair 250/50 group for overall daytime symptoms compared to Combivent. These two studies demonstrate what was seen in the pivotal Advair studies that Advair does improve lung function as assessed by FEV₁.

Studies SMS40320 and SMS40321

The sponsor submitted the results of these two studies SMS 40320 and SMS40321 comparing salmeterol to Combivent, to support the argument that the improvement in symptoms seen in the Advair/Combivent studies was in part due to the FP component of Advair 250/50. It must be kept in mind that these are cross-study comparisons. However, that caveat aside, the improvement in symptoms reported in studies SCO40011 and SCO40012 in the Advair treatment groups was only marginally better than in the Combivent treatment groups.

Both studies SMS 40320 and 40321 were identical in design and compared the efficacy and safety of salmeterol to Combivent in COPD patients over a 4-week treatment period. The primary endpoint was AM pre-dose FEV₁. This primary endpoint could still provide the salmeterol an unfair advantage compared to Combivent. This is because previous studies in the salmeterol database suggest that residual bronchodilation remained in the morning pre-dose FEV₁ from the previous dose of salmeterol. This observation was raised at the EOP2 meeting for Advair and prompted the concern that it may be difficult to show an advantage of fluticasone in the combination product over salmeterol alone – [nevertheless FP was able to show an advantage over salmeterol for the predose FEV₁ endpoint]. In these two studies salmeterol had a statistically significantly greater improvement in AM pre-dose FEV₁ at Week 1 and Week 4 compared to Combivent, but there was no difference in symptomatic improvement among the two treatment groups.

SAFETY

Epidemiology Reports

The sponsor submitted 4 case-controlled studies to assess the risk of non-vertebral fracture associated with ICS use in COPD patients. These studies were all retrospective observational studies and are briefly reviewed here with input from Dr. Ted Guo Biostatistician.

EPI40204: Title: "The use of inhaled corticosteroids and risk of non-vertebral fracture among COPD patients in the UK General Research Practice Database (GRPD): a nested case-control study."

The study was conducted to analyze the association of non-vertebral fracture and exposure to inhaled corticosteroids including FP in a cohort of COPD patients. For the purposes of the study the cases were defined as patients with a first fracture recorded in their medical records and the date the first fracture occurred was defined as the "index date." The controls for each case were selected at a ratio of up to 4: 1 (4 controls to 1 case) on the basis of the absence of any fracture. The number of COPD cases that met all the pre-defined criteria were 2808 and the number of matched controls were 8453. The COPD cases were mainly female (62%) and older (≥ 75 years) and the majority of fractures reported (39.7%) were in the upper limb. The second most common (24%) type of fracture among women and men were in the lower limb. Hip fractures were reported least frequently (16%) in both sexes.

The ICS exposure in the data base was predominantly due to beclomethasone (BDP), and budesonide (BUD) use. The use of fluticasone propionate (FP) was very low among the cases reviewed. Of the total 2808 COPD cases, 2087 reported ICS use and 721 never used corticosteroids. Only 125 cases were FP users.

The results of the analyses showed that use of ICS prior to the index date was associated with a slight increase in the risk of fracture (unadjusted odds ratio 1.12) compared to patients without ICS use. When evaluated according to specific ICS, the positive association with all fractures was limited to the use of BDP or BUD (OR 2.10). There was no increase risk of all fracture associated with FP (OR 0.82).

Reviewer comment

A serious limitation of this study is the low number of FP users in the COPD cohort. Loss of bone density and resultant fractures are associated with the use of ICS^s and of the ICS used by the cohort FP is the most potent. Therefore, if the number of subjects in the FP group were larger one might have seen different results

EPI40205: A case-control study of the exposure-specific incidence of fracture with a focus on fluticasone: Final report.

This was an observational study of the epidemiology of non-vertebral fracture among adults with respiratory disease (i.e. asthma or COPD) to examine the risk associated with exposure to ICS. The dates of observation was from / / and the data source was / / containing information from 25 affiliated health plans located in the U.S. The study subjects were aged 40 years and older with asthma or COPD and had at least 12 months of continuous enrollment to / prior to the date on which asthma or COPD were claimed. The cases were all persons with claims evidence of an incident fracture occurring during the study period. Controls were randomly selected in a ratio of 10 controls per case. The sponsor used analyses of Odds ratios in determining the association between

fracture and exposure. The respiratory cohort was made up of 89,877 patients and of these 36,190 (40%) had a diagnosis of COPD and the rest either had asthma or asthma/COPD.

A total of 1722 non-vertebral fracture cases were identified by claims and of these 26 (1.5%) were hip fractures. Of the 1722 claims of fracture only 280 (16%) patients had used FP within the year prior to the index date while 869 (50%) of patients had used either another ICS (22%) or oral steroids (28%) during that time. The odds ratio [OR] for all users (other ICS, FP and oral steroids) and the odds ratio when separated by groups was less than one suggesting that there was no association between the occurrence of fracture and exposure to corticosteroids.

Reviewer comment

The dose of FP noted in this report was variable from doses as low as (< 168 mcg to > 840 mcg)

EPI40206: "Inhaled corticosteroid use in COPD and the risk of fracture"

The dates of observation for this epidemiological study was January 1, 1988 to December 31, 2001 and the study site was Quebec, Canada. Similar to the other studies this was a case-control study to assess whether long-term inhaled and nasal corticosteroid use increased the risk of fractures among elderly patients with COPD. The patient population consisted of COPD patients aged 65 years and older. The data source was ¹ A case was defined as the first fracture of the hip or upper extremities that required medical attention reported in the [†] The COPD cohort included 100,709 subjects with a mean age of 81 years with 8,044 cases of fracture of the hip or upper extremities and 138,102 age-matched controls.

Of the 8,044 cases 2951 (36%) were fractures of the hip. Of the cases with fractures 55.7% had any use of inhaled corticosteroids during 4 years prior to the index date. Similar to the other observational studies, FP use was low (17%) and the majority of users had used or were using BDP (63%), or BUD (19%). The adjusted odds ratio suggested that there was no association of hip and upper extremity fractures (OR 0.88 – 0.82) except at high doses (> 2000 mcg equivalent of BDP) where the OR was 1.14 suggesting a slight increased risk of fracture.

Reviewer comment

The time period covered includes 8 years where no FP formulations were marketed or approved in the U.S, so it is not unusual that the % of FP use is lower than for other ICS use. Again the low use of FP in the population studied greatly limits the interpretation of these data..

EPI40207 "Assessment of the risk of non-vertebral fractures associated with inhaled corticosteroid use in chronic obstructive pulmonary disease patients in the VA".

The dates of observation were October 1, 1997 – September 30, 2002. A total of 1708 cases in the COPD cohort were identified and were matched to 6817 controls. Of the 1708 cases, 365 (21.4%) had a history of ever use of ICS and 98 (5.7%) were current (last 30 days) or recent (last 90 days) users of ICS. Similar to the other observational studies, the % of cases with FP use was low (9.2%). The analysis suggested that for patients ever exposed to ICS to those never exposed there was no increase in the risk of fractures. However, this association changed depending on the dose of ICS or the time of the exposure with higher doses of ICS and more recent exposure being associated with an increased risk of non-vertebral fracture.

Conclusions

The four epidemiology studies provide limited data on the effect of fluticasone propionate on bone loss in the COPD population. Overall, the results support the known association of bone loss and the use of corticosteroids and that the risk is greater with higher doses of corticosteroids. A full characterization of this risk with the dose of corticosteroid proposed for the COPD population in this application cannot be determined from these studies. However it is reasonable to conclude that the risk of bone loss with Advair 250/50 would be less compared to Advair 500/50 which contains twice the dose of corticosteroid.

Safety Update

On October 10, 2003, GSK submitted a one year safety update that covers the period from September 1, 2002 to August 15, 2003. The safety update was reviewed very briefly since it was submitted only 50 days prior to the end of the review cycle. The safety update provided information from the following studies:

- (1) Six (6) ongoing controlled clinical trials,
- (2) Six (6) non-US Regional studies
- (3) Two (2) completed US Regional (Local) studies – previously submitted in the complete response of May 30, 03
- (4) Post-marketing experience.

There were no ongoing or completed pharmacology studies during the safety update period. The six ongoing controlled clinical trials are shown in the table below copied from the sponsor's submission.

1. To further define the benefit/risk profile of Advair 250/50 in patients with COPD
2. To achieve the use of Advair Diskus at the optimal dose (250/50) one inhalation twice daily) and to minimize the prescribing of high doses of Advair Diskus
3. To minimize potential risks associated with the disease itself and the use of Advair 250/50 in the COPD population

The tools proposed to fulfill these objectives are described below.

Objective # 1: To further define the benefit/risk profile of Advair 250/50 in patients with COPD

GSK's Proposed Tool (s)

1. Concept Protocol SCO40041:

"A randomized double-blind parallel-group clinical trial evaluating the effect of the fluticasone propionate/salmeterol combination product 250/50 BID via DISKUS and ~~on bone mineral density~~ on bone mineral density in subjects with chronic obstructive pulmonary disease (COPD)".

~~[Redacted content]~~

Study Population

~~[Redacted content]~~

~~_____~~

Measurements

~~_____~~

Reviewer comments

~~_____~~

~~_____~~

(As these are concept protocols comments will not be sent to the sponsor until the final protocols are submitted to the IND).

2. Concept protocol

~~_____~~

Objectives

~~_____~~

~~_____~~

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~~_____~~

Study Design

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~~_____~~

Reviewer comment (with input from ODS consultation)

~~_____~~

4. Quarterly listing and review of all serious adverse events occurring during clinical trials with Advair.
5. 6-month summaries and analysis of post-marketing safety via Periodic Update Safety Reports (PSUR)

- Education

Professional and patient education including changes to the product labeling and patient leaflet, promotional and educational materials for both healthcare professionals and patients.

Objective # 3: To minimize potential risks associated with the disease itself and the use of Advair 250/50 in the COPD population

GSK's Proposed Tool

Professional and patient education including changes to the product labeling and patient leaflet, promotional and educational materials for both healthcare professionals and patients

Reviewer's Comments

Several of the recommendations made by ODS have been incorporated in the label (see FDA proposed labeling changes). ODS also recommended that The RMP should include a component for evaluating its performance with details of the timeline and the methodology that will be applied. GSK should report back to the Agency (at an agree upon interval with the review Division) and provide data on:

- 1. The extent of high-dose use among patients with COPD (specifying the methods and data sources used) and*
- 2. The extent of compliance with the RMP and complications of product use (through surveys of COPD patients and/or physicians).*

Commercial Marketing Experience and Foreign Regulatory Action

In the European experience, the fluticasone propionate/salmeterol combination products 100/50, 250/50 and 500/50 were first licensed for the regular treatment of asthma via a Mutual Recognition Procedure (MRP) in December 1998 with Sweden as the Reference Member state (RMS). In September 2001, the Marketing Authorization Holders applied to include COPD as a therapeutic indication for Advair 500/50 twice daily. The application initially received a negative review by the RMS even after the proposed treatment population was restricted to patients with moderate to severe COPD as indicated by an FEV₁ of 50% or less of predicated normal. In April 2002, a referral to the European Agency for the Evaluation of Medicinal Products (EMA) was initiated via the Irish Medicines Board (IMB) for reconsideration of the decision. The IMB believed that a fixed dose combination could represent a convenience and compliance advantage to patients suffering from COPD and that this aspect was not sufficiently taken into consideration when the RMS reached its opinion that the clinical benefit of the combination was marginal and that the efficacy advantage of the combination had not been convincingly demonstrated with respect to that of the separate components. The IMB therefore requested the CPMP (subcommittee of the EMA) to give an opinion on the scope of this application i.e. the indication of treatment of COPD.

Based on re-evaluation, the CPMP considered that overall the balance of risks and benefits was favorable and on January 23, 2003 recommended the granting of the variation of the Marketing Authorizations for the fixed combination medicinal products containing salmeterol and fluticasone propionate for the indication of *"the symptomatic treatment of patients with severe COPD (FEV₁ < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy"*. The final opinion was converted into a decision by the European Commission on May 21, 2003⁹.

An application for Advair Diskus for COPD was submitted to Canada in 2001 and on April 23rd, 2003, Canada granted approval for Advair Diskus 250/50 and 500/50 for the treatment of COPD. The indication reads, *"Advair 250 Diskus and Advair 500 Diskus are indicated for the maintenance treatment of COPD, including emphysema and chronic bronchitis, in patients where the use of a combination product is considered appropriate"*.

As of April 23, 2003 the salmeterol/fluticasone propionate combination product for COPD has been approved in several developing countries such as Argentina, Aruba, Bangladesh, Columbia, Dominican Republic, Ecuador, El Salvador, Guyana, Mexico, Nicaragua, Philippines, Thailand, Trinidad & Tobago, Yugoslavia, Zambia and Zimbabwe.

CONCLUSIONS

The efficacy results of the two clinical studies SCO40011 and SCO40012 demonstrated (as was seen in the pivotal trials) that Advair 250/50 produces a statistically significant improvement in lung function as measured by FEV₁. There was no clinically meaningful improvement in symptoms with Advair Diskus 250/50 a finding that was also noted in the pivotal studies with both Advair 250/50 and Advair Diskus 500/50. The interpretation of the results of the 4 epidemiology studies is very limited and the associated risk of fracture with the dose of ICS (FP 250 mcg BID) in the proposed dose of Advair Diskus 250/50 cannot be fully characterized. However, from these studies and other reports in the literature⁸, it appears that the associated risk with Advair Diskus 250/50 would be less than with Advair 500/50.

Taken together, upon re-evaluation of the data from the pivotal trials, and the efficacy and safety data submitted in this complete response the approval of Advair Diskus 250/50 for a limited indication in a subpopulation of COPD is justifiable. Advair Diskus 250/50 demonstrated significant improvement in lung function (as measured by FEV₁), both in the pivotal trials and in the comparative studies with Combivent. Although the risks associated with long term use of ICS are not well characterized in this population, they are nevertheless monitorable risks and therefore, a limited indication targeted to the subpopulation of COPD patients evaluated in the clinical program –i.e. COPD associated with chronic bronchitis is acceptable.

LABELING

The approval of Advair Diskus 250/50 requires that the language in the label specifically address the following: *(See proposed label for FDA's specific labeling changes)*.

1. That the approval of Advair Diskus 250/50 does NOT endorse the use of inhaled corticosteroids (ICS) apart from this combination product in COPD
2. That the inflammatory process in COPD is different from that seen in asthma
3. That the benefit of inhaled corticosteroids alone for controlling COPD remains unproven.
4. That the use of Advair Diskus 250/50 be restricted to patients with COPD associated with chronic bronchitis.
5. That the indication specifically reflect what was convincingly demonstrated in the pivotal trials –i.e. improvement in lung function as measured by pre- and post-dose FEV₁
6. That Advair Diskus 500/50 is NOT recommended for patients with COPD because no additional improvement in lung function [nor improvement in symptoms or exacerbations] was/were seen with the higher dose . Therefore, if no improvement is seen with Advair Diskus 250/50 the dose should not be increased to 500/50.
7. That neither Advair Diskus 250/50 nor Advair Diskus 500/50 demonstrated improvement in COPD symptoms or exacerbations compared to placebo or the individual components salmeterol or fluticasone propionate.
8. That the higher dose of FP (500) is associated with increased systemic effects as demonstrated by a dose dependent increase in systemic exposure to fluticasone propionate.
9. That the continued benefit of treating patients for longer than 6 months has not been demonstrated.
10. That COPD patients because of underlying factors (smoking, sedentary, poor nutrition) are at increased risk for decrease bone mass and fractures and use of inhaled corticosteroids increase that risk and therefore COPD patients for whom Advair Diskus 250/50 therapy is deemed appropriate should be assessed for bone mineral density and treated appropriately.
11. That COPD patients taking Advair Diskus 250/50 should be monitored for other risks associated with the use of ICS such as cataracts and glaucoma.

With satisfactory resolution of labeling negotiations with GSK, the supplement can be approved.

with COPD and (b) the extent of compliance with the risk management plan and complications of product use (through surveys of COPD patients and/or physicians)

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5. Long-term effect on inhaled budesonide in mild and moderate chronic obstructive pulmonary diseases: a randomized controlled trial. *Jorgen vestbo et.al; The Lancet vol 353 May 29, 1999; 1819 –1823*
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9. The European Agency for the Evaluation of Medicinal Products . Committee for Proprietary Medicinal Products (CPMP). Opinion Following an Article 7 (5) Referral. Salmeterol and Fluticasone propionate. *7 July 2003; CPMP/1327/03*

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/s/

Lydia McClain
11/10/03 08:48:15 AM
MEDICAL OFFICER

Badrul Chowdhury
11/12/03 09:43:51 AM
MEDICAL OFFICER

Medical Officer Review

Division of Pulmonary and Allergy Drug Products (HFD-570)

Application #:	NDA 21-077/003	Category of Drug:	Corticosteroid/Long-Acting β_2 -Agonist
Sponsor:	GlaxoSmithKline	Route of Administration:	Oral Inhalation
Proprietary Name:	Advair™ Diskus @ 250/50	Medical Reviewer:	Lydia I. Gilbert-McClain, MD, FCCP
USAN/Established Name:	Fluticasone propionate/salmeterol xinafoate	PDUFA Date:	January 12, 2003

Submissions Reviewed in This Document

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
June 20, 2002		Complete response	
July 12, 2002		Correspondence	Fax from sponsor, removing Advair 500/50 from the complete response

Related Applications (if applicable)

March 24, 1999		NDA 21-077	Original NDA for Advair™ Diskus approved August 24, 2000 for the long-term maintenance treatment of asthma
May 4, 2001		NDA 21-077/S 003	Supplement for COPD indication

Overview of Document: See executive summary

Outstanding Issues: N/A

Recommended Regulatory Action NAI

NDA/Supplements:

Approval
 xx Approvable
 Not Approvable

EXECUTIVE SUMMARY

GlaxoSmithKline submitted a supplemental new drug application NDA 21-077/S-003, on May 4, 2001 for Advair Diskus 500/50 and Advair Diskus 250/50 for the indication "long-term maintenance treatment of COPD". The sponsor also submitted the sNDA 20-833/S004 for Flovent Diskus 250 and Flovent Diskus 500 on May 25, 2001 for the same indication.

On January 17, 2002, these applications were discussed at a Pulmonary-Allergy Advisory Committee meeting in Gaithersburg, MD. On March 5, 2002 the Agency took an Approvable action on both these applications. In the approvable letter the Agency stated the following:

"We do not believe that you have provided substantial data to support a conclusion that these drug products are sufficiently safe and effective for the indication proposed in the COPD population. Given the modest and limited extent of the efficacy findings (including a lack of effect on exacerbation rates), given the known potential for fluticasone to cause adverse systemic effects as demonstrated by spontaneous adverse events reporting and clinical studies, and given the signal in the data sets provided of an increase in upper and lower respiratory infections, we believe that more definitive efficacy and safety data are needed prior to approval. In order to be approved, you must supply data that more fully delineates the safety (including impact on bone density) beyond 6-months and further evidence of efficacy (including outcome data). Data from your current, on-going 3-year trial in COPD, if favorable, may reasonably serve as a substantial portion of these requested data".

On June 20th, 2002, GlaxoSmithKline submitted a complete response to the approvable letter for Advair Diskus 250/50 and indicated that a response to the approvable letter for Advair Diskus 500/50 would be the subject of a separate submission. However in the sponsor's cover letter dated June 20, 2002, they stated that the complete response was for both Advair 500/50, and Advair 250/50. On July 12, Glaxo clarified that the complete response was only to address the AE action of Advair 250/50.

To address the deficiencies noted in the AE letter, the sponsor submitted data from four sources: 1) Results from a non-US, 1-year safety and efficacy study that compared Advair 500/50 to each of its components in a COPD population, 2) Results of a safety study FLTA30001 that looked at the long-term safety of fluticasone propionate inhalation aerosol in asthmatics, 3) Four observational studies, and 4) Publications from the medical literature.

In general, these data are unconvincing and are largely irrelevant to Advair 250/50. The submission fails to provide the additional evidence of efficacy or long-term safety of Advair 250/50 described in the Approvable letter of March 5, 2002.

RECOMMENDATION

There are insufficient data to adequately define the efficacy and safety of Advair 250/50 in the COPD population and this application should be given an "Approvable" action.

INTRODUCTION

To address the deficiencies mentioned in the AE letter, GSK submitted the following in their complete response:

- A proposal to change the proposed indication which was "for long-term, twice daily maintenance treatment of COPD including chronic bronchitis and emphysema" to "twice daily maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis"
- Clinical data from a non-US study, SFCB3024.
- Study FLTA30001
- Publications
- Cross-reference to the safety update submitted on February 28, 2002 which amended all available safety data up until October 31, 2001.

MEDICAL OFFICER REVIEW AND COMMENTS

SFCB3024

SFCB3024 was a randomized, double-blind, parallel group, placebo-controlled study to compare the efficacy and safety of Advair 500/50 BID with salmeterol 50 mcg BID alone and FP 500 mcg BID alone in the treatment of subjects with COPD for 12 months. The study was a multicenter European study. The primary efficacy variable was pre-dose FEV₁. Secondary variables included the number of moderate and/or severe COPD exacerbations, time to first moderate to severe exacerbation, patient reported outcomes (assessed by the St George's Respiratory Disease Questionnaire [SGRQ]), daily symptom assessments, rescue bronchodilator use, number of study withdrawals, and morning PEFr.

Population

Male and female patients with a diagnosis of COPD as defined by the European Respiratory Society (ERS) were enrolled in this study. Subjects were age 40 –79 years and had a smoking history of ≥ 10 pack-years. Subjects who had stopped smoking 6 months prior to enrollment in the study were defined as ex-smokers. All subjects had to have cough productive of sputum on most days during at least 3 months in 2 consecutive years. Subjects were to have $< 10\%$ reversibility

according to the ERS definition of reversibility, defined as a percentage of the predicted FEV₁ as follows:

$$(\text{reversibility} = \text{post-bronchodilator FEV}_1 - \text{prebronchodilator FEV}_1 \times 100 / \% \text{ predicted FEV}_1)$$

Population Results

Of a total of 1974 patients screened, 1469 were randomized. The population was 99% Caucasian. There were 16 subjects of other races, 15 were Asian and one was black. The mean pack-years smoked among subjects ranged from 41.0 – 44.0 pack years, and between 47% - 53% of the subjects were current smokers. The mean percent predicted pre-bronchodilator FEV₁ ranged from 44.2% to 45%. According to the ERS definition of reversibility $\leq 4\%$ of this population was reversible.

Of the 1469 subjects randomized, 1009 (69%) completed the study and 31% withdrew from the study. The percentage of subjects withdrawing from the study was highest in the placebo group (39%), followed by the SAL group (32%), the FP group (29%) and the Advair group had the lowest percentage of withdrawals (25%).

Efficacy results

The mean change in pre-dose FEV₁ over the 52-week treatment period is summarized in table 1. Compared to its individual components, Advair 500/50 has a modest effect on pre-dose FEV₁ which was statistically significant. The contribution of FP to the combination product is less than 100 mL (73 mL).

Table 1 Mean Change in pre-dose FEV₁

	Placebo	SAL 50	FP 500	Advair 500/50
N	353	361	371	345
Baseline FEV ₁ , L	1.26L	1.24L	1.26L	1.308L
Adjusted mean over weeks 1 –52	1.264 L	1.323 L	1.302L	1.396 L
Active treatment – placebo	-	60 mL	39 mL	133 mL**
95% CI		(32,88)	(11,66)	(105,161)
p-value		<0.001	0.006	<0.001
** This number is inconsistent with the Baseline and adjusted mean values over 1-52 weeks. The difference between Advair and placebo is ~ 84 mL				

Patient-reported outcomes as assessed by the SGRQ did not demonstrate a clinically meaningful improvement (at least a 4-point change) in total score or in any of the individual domains. This was true for subjects treated with Advair 500/50 compared with placebo-treated subjects or for any of the individual components, as shown in table 2 below.

Table 2 – Repeated measures analysis of SGRQ scores over all 52 Weeks (ITT population).

	Advair 500/50 – Placebo	Advair – SAL 50	Advair 500/50 – FP 500
Total	-2.2	-1.1	-1.4
Symptoms	-2.2	-2.1	-1.6
Impact	-2.7	-0.8	-1.5
Activity	-2.3	-1.7	-2.0

Severity of exacerbations were defined by the need for Ventolin use, antibiotics or corticosteroid use, or hospitalization (as was done for the U.S. pivotal studies SFCA3006 and SFCA3007). The mean number of exacerbations (moderate and/or severe) was similar for the Advair group and the individual components (Advair 0.97, SAL 1.04, FP 1.05). The placebo group had a mean number of moderate/severe exacerbations per year of 1.30.

Safety results

With respect to safety, 216 subjects (15%) withdrew due to an adverse event and of these, 84 (6%) subjects withdrew due to a serious adverse event. The percentage of withdrawals due to adverse events was highest in the placebo group (19%). The Advair group had the lowest percentage of withdrawals (13%) due to adverse events. The serious adverse events did not appear to be drug-related in the opinion of this reviewer. Of interest is the number of subjects experiencing adverse events related to the respiratory system. These events are summarized in the table below.

Table 3. Respiratory system events in > 5% ITT population

	Placebo N = 361	SAL 50 N = 372	FP 500 N = 374	Advair 500/50 N = 358	Total N=1465
Any Adverse Event	283 (78%)	295 (79%)	302 (81%)	285 (80%)	1165 (80%)
URTI	43 (12%)	34 (9%)	56 (15%)	44 (12%)	177 (12%)
Lower Respiratory infections	10 (5%)	11 (3%)	27 (7%)	31 (9%)	88 (6%)
Viral respiratory infections	21 (6%)	20(5%)	17 (5%)	29 (8%)	87 (6%)
Cough	21 (6%)	12 (3%)	16 (4%)	14 (4%)	62 (4%)
Pneumonia	8 (2%)	16 (4%)	19 (5%)	17 (5%)	60 (4%)

In percent of subjects and in absolute numbers, there were more subjects with lower respiratory infections, viral respiratory infections, and pneumonia in the Advair 500/50 group compared with the SAL group. Arguably, these AE's should be pooled, and the difference would then constitute a stronger safety signal. The association of LRTI with use of Advair or FP has been observed in other controlled clinical trials, and was an important consideration in asking for additional safety and outcome data.

Candidiasis occurred in higher percentage of subjects in the Advair (8%) and FP (7%) compared with the placebo and SAL groups (2%) and was the most common drug-related adverse event.

Twenty-six deaths were reported in this study, 2 during the run-in period. None of the deaths appear to be drug-related. Four of the deaths occurred during treatment with Advair, 10 deaths occurred during treatment with placebo, 5 during treatment with salmeterol, and 5 during treatment with FP.

A total of 6 fractures occurred during the study, 3 were in the Advair group, 2 in the FP group and one in the placebo group. Two subjects sustained a femur fracture after a fall shortly after completing the one year treatment period. One subject was in the Advair group, and the other subject was in the FP 500 group. The other fractures reported were of the rib, arm, tibia, and clavicle.

Reviewer Comments

The patient population in this study was similar to that of the patient population in the US pivotal study SFCA3006 i.e. COPD with chronic bronchitis. Although the sponsor states that the subjects in study SFCB 3024 were non-reversible, it is important to note that reversibility as defined by the ERS allows for subjects who would otherwise be reversible by the ATS definition to be classified as irreversible.

The efficacy findings of this study are not germane to the complete response for Advair 250/50 given that this study evaluated the efficacy of Advair 500/50 and not Advair 250/50. Nevertheless, the efficacy findings of this study are similar to that seen in the US pivotal study SFAC30006. There is a modest effect of Advair 500/50 on FEV₁ that is not supported by demonstrable efficacy in the secondary endpoints. In particular, there is a failure to demonstrate a clinically meaningful improvement in patient-reported outcomes (as assessed by the SGRQ) and there is no clear demonstrable effect on exacerbations. As such, the clinical benefit of the modest FEV₁ improvement seen with Advair, remains unclear.

The higher number of lower respiratory and viral infections, and pneumonias in the Advair 500/50 group compared with placebo and SAL is a safety concern given that these events themselves trigger COPD exacerbations. This observation also brings into question the validity of the purported benefit of Advair on COPD exacerbations reported by the sponsor.

STUDY FLTA30001

"A randomized, double-blind, parallel-group trial to assess the long term safety of fluticasone propionate inhalation aerosol (MDI) 100 mcg BID and 500 mcg BID versus placebo BID in adult subjects with moderate asthma".

This study was a 104-week study in asthmatic adult patients, male ages 18 to 50 years and premenopausal female ages 18 to 40 years. The study was conducted

at 9 outpatient asthma clinics in the U.S. between July 1994 and June 1997. This study report was submitted to IND NDA 20-548 and to sNDA 20-833/S-004 (Flovent Diskus for COPD). One hundred and sixty patients were studied for a 104-week treatment period. Bone mineral density was measured at the lumbar spine, proximal femur and total body. As was pointed out in the review done by Medical Officer Dr. Charles Lee, the lumbar spine was the only area that underwent prospective quality assurance from the osteoporosis central laboratory. Results from the proximal femur and total body bone mineral density were collected for observational purposes only, as there was no prospective quality assurance for these measurements. At week 104, a mean percent increase in bone mineral density was observed in the placebo group (0.20%) and the FP 88 mcg BID group (0.68%). A mean decrease in bone mineral density was observed in the FP 440 mcg BID group (-0.28%)

Reviewer Comment

The findings of this study does not address the long-term safety (specifically effects on bone) of FP in the COPD population. It is important to note that in this study, the lumbar spine was the only body site that underwent prospective quality assurance. From the Lung Health Study II data¹, the femoral neck appears to be a more sensitive area to screen for decreased bone density. After three years of treatment, in the LHS II, a decrease in bone mineral density was noted in patients using 1200 mcg of orally inhaled Triamcinolone per day.

More recently Elliot and colleagues² reported the results of a three-year prospective study of the effects of ICS on bone mineral density in premenopausal asthmatics. A cohort of 109 female asthmatics age 24 –44 years were treated with orally inhaled Triamcinolone 100 mcg/puff (maximum dosage used was 28 puffs/day). Bone density [measured with DEXA] was performed at both the hip and the trochanter. After 3 years, there was a statistically significant decline in bone density at both the hip ($p = 0.01$) and the trochanter ($p = 0.005$). These findings add support to the concern that COPD subjects would suffer greater consequences of the effects of ICS on bone, given these patients would be starting treatment with a lower total bone mass than the average asthmatic patient by virtue of their age, smoking history and other factors leading to an increased risk for osteoporosis.

Observational Studies

The sponsor submitted the following observational studies (epidemiological studies) to support the approval of Advair 250/50.

1. Study EPI40151 – "Survival of COPD patients exposed to inhaled steroids and/or a long-acting beta agonist". This study was a retrospective observational study in two managed care populations that examined the relationship between survival and exposure to inhaled corticosteroids. Subjects were patients who had enrolled in the _____ or

¹ N Engl. J Med 2000; 343: 1902-9

² N Engl. J Med 2001; 345: 941-7

resource utilization and costs are not regulatory considerations for drug approval in the U.S.

Conclusions

The data submitted in the complete response for Advair 250/50 for a COPD indication do not address the issues stated in the approvable action letter of March 5, 2002.

Comments to be sent to the sponsor

1. Your complete response does not provide data that more fully delineate the efficacy and safety of Advair 250/50 (*see approvable letter March 5, 2002*) to support approval for COPD..
2. Efficacy data from study SFCB3024 does not address the efficacy of Advair 250/50 as this study was conducted with Advair 500/50. Additionally, the signal in the data sets provided suggest an increase in lower respiratory tract infections (including pneumonia and viral respiratory infections) with Advair 500/50 compared to its individual components.
3. The safety results from study FLTA30001 do not address the long-term safety of inhaled corticosteroids in the COPD population.
4. The results of the 4 observational studies do not constitute substantial evidence of efficacy or safety, and from a regulatory standpoint, cannot be used as the basis for drug approval. Pharmacoeconomic endpoints such as resource utilization and cost are not regulatory considerations for drug approval in the U.S.
5. In order to be approved, you must supply data that more fully define the efficacy (including outcome data) and safety (including impact on bone density) of Advair 250/50 in patients with COPD. (*see Approvable letter of March 5, 2002*).

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/s/

Lydia McClain
11/19/02 05:21:37 PM
MEDICAL OFFICER

Mary Purucker
11/22/02 12:26:45 PM
MEDICAL OFFICER

Concur. In this CR, the applicant has restricted consideration for a COPD indication to a single product, Advair 250/50. In spite of this, the submission fails to provide convincing evidence of efficacy or long-term safety.

Division Director's Memorandum

Date: Monday, March 04, 2002
NDA: 21-077, efficacy supplement 003 for maintenance treatment of COPD; NDA 20-833, supplement 004
Sponsor: Glaxo Wellcome
Proprietary Name: ADVAIR Diskus (fluticasone propionate/salmeterol xinafoate inhalation powder); Flovent Diskus (fluticasone propionate)

Introduction: These are related efficacy supplements for the maintenance treatment of COPD for Advair 250/50 and 500/50 and Flovent Diskus 250 mcg and 500 mcg. The sponsor, GSK, has conducted three clinical trials to primarily support these two supplements, as well as a third related supplement for Serevent Diskus. The Serevent supplement will be addressed in a separate document.

There has never been an approval of a corticosteroid for the maintenance treatment of Chronic Obstructive Pulmonary Disease (COPD) in the U.S., so would be a unique claim for an inhaled corticosteroid (ICS) and/or a corticosteroid-containing product. The division had extensive discussions with the company on the development of this indication, including the choice of primary endpoints and the need to meet the combination policy for Advair, since COPD is a distinct population for whom ICS have not previously been approved. The choice of endpoints for the fluticasone program and the fluticasone component of the Advair program was change from baseline in "trough" FEV1 (i.e., pre-dose). While the division agreed to this endpoint, we did also state that we would expect to see support from other assessments. GSK utilized numerous secondary endpoints, including the patient reported outcome assessments of Guyatt's CRDQ, Mahler's BDI/TDI and a modified-Petty Chronic Bronchitis Questionnaire.

Administrative: These applications were reviewed separately by two medical officers, but with a common Medical Team Leader. They were presented at the Pulmonary and Allergy Drugs Advisory Committees in January 17th, 2002. The regulatory 10-month due date for the Advair application (21-077) is March 7th 2002. The due date for Flovent (20-833) is March 25th, 2002.

Chemistry/Manufacturing and Controls: No new issues, since this application required no new dosage form for approval.

Pharmacology/Toxicology: No new issues.

Biopharmaceutics: See Dr. Suarez-Sharp's Flovent review for details. The limited biopharmaceutics information for this application was based on showing bioavailability of the fluticasone in the COPD population of interest, as well as establishing dose-proportionality of the dosage strengths. Of note, the 500 mcg Flovent Diskus (not an approved product) is not dose-proportional to the 250 mcg product based on the data provided by the sponsor. The exposure to FP systemically from 2 puffs of the 250 product would be expected to be higher than 1 puff of the 500 mcg product. The latter was used in the clinical trials, but is not approved and was not submitted in this

application. Therefore, given FP's bioavailability arising primarily from the lung, one could reasonably assume that using 2 puffs of the available 250 product likely give comparable efficacy (or better) to the tested 500 mcg product, but would pose potentially more safety issues.

The bioavailability (BA) of FP appears lower in COPD patients than normals (and perhaps lower than asthma patients). Within COPD subjects, current smoking status appears not to effect BA, but patients with poor reversibility – who appeared to benefit less from treatment – had higher bioavailability (and hence more safety concerns).

Clinical / Statistical: See Dr. Lee's primary review of Flovent and Dr. Gilbert-McClain's review of Advair for details, as well as Dr. Purucker's team leader memo. The sponsor conducted three adequate placebo-controlled trials for this program. One study examined Advair 500mcg/50mcg versus its components (fluticasone and salmeterol) and placebo (SCFA3006), another examined Advair 250mcg/50mcg versus its components and placebo (SCFA3007), and the third examined the two doses of fluticasone, 250 and 500 mcg, against placebo. In this way, each dose for each treatment was examined against placebo in 2 different studies. While the primary endpoint was met and replicated for most doses (Flovent 250 mcg did not beat placebo in 2 trials), the effect size was modest and varied from approximately 50 cc to 150 cc. The comparison between Advair and salmeterol showed an effect size of about 68 cc. Clearly, this level of improvement is of questionable value, especially given that the ISOLDE trial (which was submitted by GSK as supportive) and other data suggest no long-term lung function preservation with inhaled corticosteroids. Secondary assessments, while showing statistical superiority at times, rarely showed a clinically meaningful improvement in mean changes between fluticasone and placebo and/or Advair and salmeterol. Thus, the support that fluticasone on its own or added to Serevent in the form of Advair has a significant effectiveness in COPD is rather weak. In the pivotal trials, no differences were seen in exacerbation rates, one of the putative benefits of ICS in COPD, according to the NIH's GOLD guidelines on COPD.

As for safety, the sponsor has shown that these doses of fluticasone (250 mcg BID and 500 mcg BID) are systemically available and active. This raises the concern about osteopenia and ocular effects in this elder, vulnerable population which have not been fully addressed by the sponsor. The sponsor did provide data from an asthma population showing no striking long-term effect on Bone Mineral Density (BMD) of the high dose proposed, but it is not clear that this same lack of worrisome change would be seen in this population. Certainly, the Lung Health Study II – which examined a different moiety (triamcinolone) showed a reduction in BMD over the course of several years therapy. The SAE database in the agency is further replete with systemic adverse events from inhaled fluticasone at the doses proposed, including bone effects. Also worrisome is that there was a numerical excess of AE's either coded as respiratory infections or pneumonias overall in the pivotal trials and the ISOLDE trials. In the latter, these off-set the apparent reduction in exacerbations.

Advisory Committee Recommendations: The advisory committee voted in majority to recommend approval of the COPD applications for both Flovent and Advair. However, it important to stress the following:

- The majority of the committee voted that there were insufficient safety data for Flovent (despite their overall approval recommendation).
- The committee strongly voiced that the population studied should lead to restriction of the labeling to chronic bronchitis patients with significant airflow obstruction (which they termed "Chronic Obstructive Bronchitis")
- The committee strongly voiced that the known safety and efficacy were limited to 6 months, and therefore the product should be labeled for use only for 6 months.

Conclusions: Given the significant outlying safety issues and the relatively modest effects shown to date, I do not believe that either application should be approved, despite the recommendation of the advisory committee. As for the advice of the committee, FDA has many important lessons (e.g., Duract) that labeling to limit the use of a drug to a prespecified period is not adhered to in practice, so the committee's recommendation on the 6-months of therapy could not be practically affected. It must be remembered that since both of these products are approved, physicians who wish to use them in this manner for this disease may do so. However, use in practice is a very different matter from the U.S. FDA granting an indication for a drug as being safe and effective. The sponsor will be asked to better define the long-term safety and/or further support the efficacy of these products.

Robert J. Meyer, MD
Director,
Division of Pulmonary and Allergy Drug Products.

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/s/

Robert Meyer
3/4/02 04:00:36 PM
MEDICAL OFFICER

CLINICAL TEAM LEADER REVIEW MEMORANDUM

Memorandum to: NDA 20-833 SE1-004 and NDA 21-077 SE1-003
Products: Flovent Diskus and Advair Diskus
Proposed Indication: Maintenance Treatment of COPD
Memo date: 22 February 2002
Memo from: Mary Purucker, MD, PhD, Medical Team Leader

This memorandum is to document the secondary review conclusions for the above NDA efficacy supplements for Flovent (fluticasone propionate) Diskus 250 and 500 mcg strengths and Advair Diskus 250/50 and 500/50 mcg strengths. The latter product is a combination of the mono-therapies fluticasone propionate, a corticosteroid, and salmeterol xinafoate, a long-acting β -agonist. The two products are proposed for the long-term, twice-daily, maintenance treatment of COPD, including emphysema and chronic bronchitis, via the orally inhaled route.

The applications were presented to the Pulmonary-Allergy Drug Products Advisory Committee (PADAC) for consideration and comment on 17 January 2002. This memo also serves to document the discussion by the PADAC on the suitability of these products for the proposed indication and their view on the strength of the data submitted by GSK in support of this indication.

Based upon careful review of the applications and advice from the PADAC, it is recommended that the applications not be approved at this time. It is further recommended that an "approvable" action be taken, and the sponsor be informed that additional data should be submitted to support the long-term safety and efficacy of these products in the proposed population under the recommended conditions of use. A full study report from ongoing clinical trial SCO30003, particularly outcome data and bone density information, may serve to fulfill this requirement.

Introduction and Background: These two supplements have separate action dates, but a combined action is being taken to approximately coincide with the PDUFA date for NDA 21-077 SE1-003 for Advair Diskus, which is 4 March 2002. Both products are already approved for the maintenance treatment of asthma as twice daily therapy.

Three separate efficacy supplements were submitted in close temporal proximity in May, 2001 for Diskus[®] products for the indication of COPD. For one of the applications, Serevent Diskus, the active moiety salmeterol xinafoate has been previously approved for COPD as an aerosol formulation in a metered dose inhaler, and was not considered controversial for the indication. However, the drug development program for all three products was based upon the same three clinical trials and was concurrently conducted (see table, below), although

approval of any single product required only two out of the three trials. The novel moiety for COPD is the corticosteroid fluticasone propionate and is shared by Advair® and Flovent®. It is the use of an ICS for chronic management of the signs and symptoms of COPD that lead the Division to seek public comment and advice at the PADAC.

Although not a presently approved indication in the US, inhaled corticosteroids (ICS) are widely used off-label in the treatment of COPD.¹ This observation is reflected in the frequency with which this indication is cited on post-marketing adverse event reports received by the Agency.² Practice parameter guidelines and other publications recommend use of ICS for some sub-populations of COPD patients, but acknowledge that the evidence in support of clinical benefit is limited.³

Clinical Development Program

The clinical development program for Flovent® Diskus and Advair® Diskus for COPD was conducted under INDs 44,090 and 50,703, respectively. The Division worked closely with the sponsor in issues of clinical trial design and endpoints. The primary endpoint for the Flovent program was change in pre-dose FEV₁, which measures the contribution of the fluticasone moiety. The Advair program included co-primary endpoints change in pre-dose FEV₁ and 2-hour post-dose FEV₁, the latter to measure the salmeterol component (see table, next page). The sponsor had been advised that it would be necessary to fulfill of the "combination policy" for drug product approval (21 CFR 300.50) for the new indication.

These endpoints are identical to those used to approve Flovent and Advair Diskus for the asthma indication, however, the sponsor was advised that a "win" on the two physiologic primaries ought to be supported by secondary endpoints to demonstrate that the benefit was robust. As it turned out, generally modest changes in the primary endpoints were observed in the pivotal trials in this program, and the clinical importance of so modest a change did not receive strong support from the secondary endpoints. This was an issue brought before the PADAC (see below).

A separate issue with regard to efficacy was selection of the patient population. In particular, it was agreed that the sponsor could include some representation of COPD patients with reversible airflow obstruction in the clinical trials. The randomization of >50% patients with a mean reversibility of >22% was higher than anticipated. The exclusion of patients who did not have "chronic bronchitis" was also a concern. This issue was brought before the PADAC, who generally agreed that this was a concern. The PADAC advised that restrictive labeling be crafted to indicate the product only for individuals with COPD who had "chronic obstructive bronchitis with reversibility," and that it would not be appropriate for patients with pure "emphysema," as proposed in the sponsor's labeling.

Safety and how to adequately measure it, particularly with regard to systemic corticosteroid effects, was another concern raised by this clinical development program. Relevant safety issues include chronic corticosteroid effects on the HPA-axis and bone, and ocular, dermatologic, and metabolic effects. It is fair to point out that this program was initiated in 1998, nearly 3 years before publication of the results of the Lung Health Study II,⁴ and GSK was not specifically asked to provide serial bone density determination. The potential for chronic ICS treatment to impact bone was not widely appreciated at that time, as was the recognition of systemic corticosteroid effects of ICS in general. Serial DEXA measurements have been required of a subsequent study, SCO30003, initiated in the year 2000.

One important question posed to the PADAC was the adequacy of the safety database submitted by the sponsor. The PADAC was asked to consider our present state of knowledge of the potential of ICS to have systemic effects, the indefinite duration of the therapy, the doses of ICS proposed, and how well the proposed COPD population might tolerate these effects.

Efficacy: The primary data for these supplements is contained in three studies, two of which included both Advair and Flovent arms and one of which included Flovent alone. The three clinical trials were designed to provide comparative data and replication for the three products (including Serevent Diskus) under consideration for the indication of COPD, and are shown in the table, below. There were a number of concerns raised concerning these efficacy results during the primary review of these applications, each of which will be summarized here.

TABLE OF STUDIES

Trial	Design	Treatment Arms	Effect size Δ FEV ₁ ¹	Effect size Δ 2 hr. post-dose FEV ₁ ²	p-value
FLTA3025 (US)	R, DB, AC, 24-wk	FP 500 BID Diskus FP 250 BID Diskus Placebo BID Diskus	50 mL 27 mL -	- - -	P=0.01 P=0.140 -
SCFA3006 (US)	R, DB, AC, 24-wk	Advair 500/50 Diskus FP 500 BID Diskus Sal 50 BID Diskus Placebo BID Diskus	67 mL 113 mL - -	129 - - -	P<0.001 P<0.001 - -
SCFA3007 (US)	R, DB, AC, 24-wk	Advair 250/50 Diskus FP 250 BID Diskus Sal 50 BID Diskus Placebo BID Diskus	69 mL 108 mL - -	124 - - -	P<0.001 P<0.001 - -

¹ Comparison vs. placebo for FP and vs Salmeterol for Advair

² Comparison vs. FP

FP will be discussed first. The FP 250 dose did not achieve statistical significance in two studies

With regard to the FP 500 dose, the overall effect size in FEV₁ is quite small and is between 50

and 113 mL (mean, about 80 mL). This would be about 6.3% change relative to mean baseline FEV₁. Although inferential testing cannot be performed, subgroup analysis showed that the magnitude of this effect size was heavily dependent upon the 55 – 60% of the patients considered “reversible.”

It is difficult to know how or to what to compare this mean effect size of 80 mL, since the indication is somewhat novel. However, some frame of reference is appropriate. Ipratropium (Atrovent® Boehringer-Ingelheim) is indicated for chronic use in COPD, and the mean maximal effect size over a 12-week study was 15%. Using the baseline FEV₁ in this study, that would be about 190 mL. By similar reasoning, a 12-week study of Combivent® (Boehringer-Ingelheim) showed a mean maximal effect size of 25% or about 315 mL. For further perspective, one could use a cross-indication comparison to the effect size seen for asthmatics treated for 12-weeks with FP. In general, the mean effect size ranged from 15% to 30% and generally exceeded 250 mL. Hence, by reasonable comparison, the effect size seen for FP in COPD is small, and needs to be further supported, by other endpoints or by some other means.

The secondary endpoints, which included AM PEF, BDI/TDI (a dyspnea index), the CRDQ (HRQL instrument), COPD exacerbation, rescue bronchodilator use, and nighttime awakenings, failed to provide substantial support of clinically meaningful benefit. Particularly troubling is the COPD exacerbation rate, a clinically important endpoint, and the CRDQ index, which argued that patients did not perceive meaningful benefit.

Durability of response is of concern. There is insufficient evidence to conclude whether the modest benefit of 80 mL or so will be sustained beyond the 24-week study period, or whether chronic treatment with FP will impact on overall rate of decline in FEV₁ or on patient survival. The absence of impact on exacerbation rate, which is an important predictor of functional decline, makes it imperative that this question be answered before this indication can be recommended for approval.

With regard to the efficacy findings of Advair, the considerations are similar. The effect size of Advair over and above that of Salmeterol alone is relatively small, 69 or 67 mL, and not dose-related to the FP. The same considerations needed to justify the clinical importance of an effect size of this magnitude apply as for FP, because the novel moiety that has been added is FP. The same issues regarding the patient population, the general lack of strong support from the secondary endpoints, and the absence of data beyond 24 weeks are again found. Once again we are troubled by the lack of impact on COPD exacerbation rate and PRO (patient reported outcome), as measured by the HRQL instrument.

The PADAC echoed most of these concerns. The issue of patient population has been addressed in the previous section on study design considerations. The Committee expressed skepticism about the value of FEV₁ as the sole endpoint,

particularly given the absence of evidence showing symptomatic benefit. They were also concerned about the durability of the response, and whether therapy with either agent could be recommended beyond 24 weeks. One member specifically asked GSK about their ongoing trial (identified in this document as SCO30003) to answer this question and relate it to the ultimate issue of survival benefit. Committee members were also concerned by the lack of a dose response for FP, and recommended removal for lack of evidence of the statement in the proposed label to increase the dose of either product in the absence of the desired clinical response.

Ultimately, the majority of the PADAC concluded that it would be possible to "label around" these concerns, although the minority remained unconvinced that a practitioner would stop using either product after 24 weeks. "Restrictive labeling" with regard to patient population appropriate for this therapy also met with skepticism, although it was recommended. There was support for completing the ongoing "survival study" SCO30003 as a phase 4 commitment, and incorporating the results into the label (or possibly withdrawing approval, should the evidence show no benefit).

Safety

It should be stressed that once again the novel moiety for treatment of COPD, fluticasone, became the major focus for safety. During program development,

[REDACTED]

It would appear that the sponsor has chosen to fulfill neither of these two options.

Safety data from these applications included adverse event profile, clinical laboratory results including some HPA-axis testing, ECG's, and physical exam with VS and oropharyngeal exam. Conspicuously absent was measurement of bone density or DEXA determinations in the pivotal trials, although limited data sets were included of other studies and populations treated with FP where this information was collected. Sensitive measures of HPA axis function were limited to a single subset in one of the three studies.

In all studies, patients receiving Advair or FP had a higher incidence of AE's than patients assigned to the placebo or Salmeterol comparator arm. Oropharyngeal candidiasis occurred in 12% of FP 500 patients compared to <1% of placebo. Also notable was the more frequently reported occurrence in the FP and Advair groups of dysphonia, throat irritation, and a disturbing composite of URTI, viral respiratory tract infection, and pneumonia. SAE's and dropouts due to pneumonia and COPD exacerbation were also higher in the FP groups, in a

dose-dependent manner. The association of FP with an increased occurrence of pneumonia has been noted in other studies, particularly the ISOLDE study, submitted as supportive in the current package.

HPA-axis studies were comprised of serum cortisol AUC conducted during the 4th week of FLTA3025 on a subset of participants. Samples were drawn concurrent with a PK study intended to capture C_{max} for FP, but nevertheless succeeded in demonstrating a 21% and 11% reduction in 12-hour serum cortisol AUC for FP 500 and FP 250 subjects, respectively, relative to placebo. Other HPA-axis studies included standard dose cosyntropin stimulation testing (250 mcg/dose) of a subset of participants in clinical trials SFCA3006 and SFCA3007. The latter failed to detect any occurrence of adrenal insufficiency, although the test is not adequately sensitive to detect more subtle impacts on the HPA-axis. Examples of adrenal insufficiency occurring during the course of supportive studies were identified by the primary reviewer and more fully described (see review, Dr. Charles Lee).

As stated earlier, the impact of chronic ICS therapy on bone density was not specifically addressed in the three pivotal trials, in part because of their duration. Two of the supportive studies included DEXA scan results from relatively young (18 – 45 years), predominantly male and pre-menopausal female asthmatics. While one study showed a negative impact on hip/trochanter over a 2-year period, the other study was negative. Because of differences in dose, population, site validation issues, and duration of therapy, the single negative result provides little reassurance.

The three pivotal trials were also not designed for or of sufficient duration to detect ocular abnormalities or to screen for dermatologic or metabolic effects of chronic ICS therapy.

In summary, we are left with strong evidence that FP is systemically available in COPD patients in a dose-dependent manner, that FP levels can be directly correlated to an impact on the HPA axis, and that other systemic CS effects are reasonably to be expected. The expected effects would be directed at bone, skin and connective tissue, ocular structures, and metabolic disorders such as diabetes and others. These data are crucial for an accurate and informative label to be constructed. It is also crucial for a proper risk/benefit analysis to be conducted in order to determine the approvability of these drug products for the COPD indication.

The PADAC also focused on the fluticasone moiety as being central to the safety issue for these products. Most members stated that they found the cortisol data concerning, and felt that they had insufficient information about bone, ocular, or long-term safety effects. Several members stated that there was insufficient safety information to approve the drugs beyond 24 weeks. One member pointed out that patients with the best lung function were most likely to receive the

highest systemic dose, and that risk/benefit determination should be performed for each potential patient. There was general agreement that additional safety data beyond what had been submitted in the package would be required, although several PADAC members again stated that it would be possible to "label around" these deficiencies using the known safety profile of FP from other sources while awaiting more definitive data.

Overall Conclusions and Recommendation:

The applications are not recommended for approval at this time, but are approvable pending provision of an adequate response to each of the deficiencies identified below.

GSK has not provided substantial evidence of the efficacy of Flovent Diskus 500 mcg BID and Advair Diskus 500/50 and 250/50 mcg BID in long-term, chronic treatment of COPD, including chronic bronchitis and emphysema.

The crucial efficacy data include evidence of long-term benefit from use of these drug products, including maintenance of the effect size beyond 24 weeks and evidence of improved survival or otherwise superior outcome data. The signal of increased occurrence of pneumonia, upper or lower RTI, or viral infection with FP should not have shown any evidence of worsening. A favorable effect on COPD exacerbation rate would also provide strong support of efficacy.

GSK has not provided adequate assurance of safety of Flovent Diskus 500 mcg BID and Advair Diskus 500/50 and 250/50 mcg BID in the proposed population under the label-recommended conditions of use. Systemic FP levels have been well-documented, as has the PD effect on the HPA axis at steady state. What is needed is a better quantification of other to-be-expected systemic effects, particularly on bone density, over the long-term.

The full study report of ongoing clinical trial SCO30003 may serve as the primary source to provide data to answer these deficiencies.

References:

1. Internal documents, data purchased from IMS health.
2. FDA Adverse Event Database (AERS) search, conducted by Dr. Joyce Weaver of OPDRA.
3. Global Initiative for Chronic Obstructive Lung Disease—Executive Summary, NHLBI/WHO March, 2001—NIH publication No. 2701A.
4. The Lung Health Study Research Group. "Effect of Inhaled Triamcinolone on the Decline in Pulmonary Function in Chronic Obstructive Pulmonary Disease." *New Engl J Med* 2000 Dec 28;343(26):1902-9.

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Addendum to Medical Officer Review

Division of Pulmonary and Allergy Drug Products (HFD-570)

Application #:	NDA 21-077/SE1-003	Category of Drug:	Corticosteroid/Long-Acting β_2 -Agonist
Sponsor:	GlaxoSmithKline	Route of Administration:	Oral Inhalation
Proprietary Name:	Advair™ Diskus @ 250/50 and Advair™ Diskus@ 500/50	Medical Reviewer:	Lydia I. Gilbert-McClain, MD, FCCP
USAN/Established Name:	Fluticasone propionate/salmeterol xinafoate	Review Date:	February 12, 2002

Submissions Reviewed in This Document

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
May 4, 2001	Electronic submission	sNDA/SE1-003	New indication for Advair Diskus -Maintenance treatment for COPD
PDUFA due date: March 7, 2002			

Related Applications (if applicable)

March 24, 1999		NDA 21-077	Original NDA for Advair™ Diskus approved August 24, 2000 for the long-term maintenance treatment of asthma
June 21, 2001		sNDA21-077/SE8-02	Labeling supplement for Advair™ Diskus@
May 25, 2001		sNDA20-833/SE1-04	Efficacy supplement for Flovent @ Diskus@ Indication for COPD
May 25, 2001		sNDA20-692/SE1-016	Efficacy supplement Serevent @ Diskus@ Indication for COPD

Overview of Document: This addendum to the Medical Officer Review presents the Primary Medical Reviewer's recommendation on the approvability of Advair Diskus for COPD. The comments and recommendations from the Pulmonary and Allergy Drug products Advisory Committee meeting held January 17, 2002 were taken into account. This addendum also includes corrections to some errors noted in the original Medical Officer review document. These errors did not have any impact on the safety and efficacy findings presented in the primary review document.

Outstanding Issues: The sponsor needs to supply data that more fully characterize the long-term safety and efficacy [including outcome data] of Advair beyond 6 months. Currently the sponsor is conducting a 3-year international study SFCB30003 and data from this study may serve as a substantial portion of the long-term data needed prior to approval. Labeling review has been deferred in this review cycle.

Recommended Regulatory Action

NDA/Supplements:

Approval
 xx Approvable
 Not Approvable

MEDICAL OFFICER ADDENDUM REVIEW

Executive Summary

Introduction

This addendum to the original Medical Officer review is to finalize recommendations on approvability of Advair Diskus 250/50 and Advair Diskus 500/50 for the indication proposed by the sponsor that is "for the long-term maintenance treatment of COPD (including chronic bronchitis and emphysema)." This addendum also includes an erratum to the original Medical Officer review. The errors noted in the original review did not in any way change the conclusions of efficacy or safety described in the review.

Recommendation on Approvability

From a clinical standpoint, Advair is approvable for use in the COPD population. In order to be approved, the sponsor must supply data that more fully delineate the long-term efficacy [including outcome data] and safety [including the impact on bone density of fluticasone in combination with salmeterol [Advair]] in COPD patients.

Review Summary

Please refer to the original Primary Medical Officer review for details.

Advair Diskus 250/50 and Advair Diskus 500/50 [Advair] both met the efficacy criteria for combination drug products in the primary efficacy endpoints. The efficacy of Advair on airflow limitation [pre-dose and 2 hr-post-dose FEV₁] was essentially identical for both Advair strengths. The contribution of fluticasone propionate [assessed by the pre-dose FEV₁ endpoint] to the combination was 69 ml [model-adjusted] for Advair 250/50 and 67 ml [model-adjusted] for Advair 500/50. Similarly, the overall efficacy of Advair [i.e. Advair vs. placebo] for the pre-dose FEV₁ endpoint was 164 ml for Advair 250/50 and 160 ml for Advair 500/50. In the secondary endpoints including patient-related outcomes and COPD exacerbation rates, Advair did not demonstrate a clear treatment advantage over placebo or the individual components fluticasone propionate, or salmeterol. Overall, the data were not strongly supportive of efficacy in the COPD population. The lack of a treatment advantage in the supportive secondary endpoints of clinical relevance [such as COPD exacerbations, chronic bronchitis symptoms, and patient - reported outcomes] calls into question the clinical relevance of the FEV₁ changes seen in the 6-month study period.

At the Pulmonary and Allergy Drugs Advisory Committee meeting held January 17, 2002, some of the concerns raised by members of the committee were the limited efficacy and the lack of and need for long term safety data. The committee members noted that the duration of the studies in this development program could not address many of the long-term safety issues that would be of relevance to the COPD population taking an inhaled corticosteroid indefinitely.

Although the Advisory committee members agreed that an indication for the long-term maintenance treatment of COPD could not be granted based on these data, they voted 6/2 in favor of approval for Advair with several caveats that they felt could be addressed with adequate labeling. The committee recommended that Advair could be approved for a limited indication for patients with chronic bronchitis [the subpopulation of COPD actually studied in this program]. They recommended that treatment be restricted to no longer than 6 months duration. However, the committee did not provide specific recommendations to guide physicians in determining when to discontinue therapy.

The sponsor is conducting a 3-year international study SFCB30003 with the primary objective of evaluating the survival benefit of Advair Diskus 500/50 compared to FP 500, and salmeterol compared with placebo in patients with COPD. The primary endpoint for this study is all-cause mortality. Secondary endpoints include COPD exacerbations, patient-related outcomes [using the St Georges Respiratory Questionnaire] and COPD-related mortality. Safety evaluations will include bone density measurements by DEXA and ocular exams. Over 5,000 patients will be enrolled in the study [up to 1260 patients in each treatment arm] over 170 study sites. This study will be particularly instrumental in further evaluating the long-term safety and clinical benefit of Advair in the COPD population.

Inhaled corticosteroids are widely used (reportedly up to 40% of patients) in the treatment of COPD. Advair is currently marketed in the U.S. and is approved for the long-term maintenance treatment of asthma. Therefore withholding approval of Advair will not affect its availability or the practice of medicine.

The FD & C act calls for evidence from adequate and well-controlled investigations to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by experts that the drug will have the effects it is purported to have and that the sponsor has included all test reasonably applicable to show the drug is safe under the conditions suggested in the proposed labeling thereof. This reviewer concludes that the sponsor has not provided sufficient evidence to establish the efficacy and safety of Advair for the proposed indication.

Conclusions

- Given the modest and limited extent of the efficacy findings [including a lack of effect on COPD exacerbation rates as well as a lack of a treatment advantage compared with placebo on patient-related outcomes], as well as the lack of long-term safety information, and given the potential for fluticasone propionate to cause systemic effects as demonstrated by spontaneous adverse events reporting and clinical studies, and given the signal in the datasets provided of an increase in upper and lower respiratory infections,

approval of Advair for COPD should be withheld pending additional long-term data in support of its efficacy and safety.

- Data from the ongoing 3-year study SFCB30003 may reasonably serve as a substantial portion of these requested data.

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Labeling Review

Labeling review is deferred at this time.

Erratum to Original Primary Medical Officer Review

1. State of Armamentarium for Indication - page 12
The first line should read "The drugs currently approved for use in COPD are only for the *maintenance treatment of bronchospasm* associated with the disease.
2. Table 2 page 24. "Prior ICS Use". Both studies SFCA3006 and SFCA3007 had identical criterion for high dose steroid use. The correct criterion is listed under SFCA3006.
3. Table 10 page 35. For the non-reversible patients the mean baseline FEV₁ for the FP 500 group is 1114 mL and not 114 mL
4. Table 28 page 50. The text above the table and the data in the table columns labeled "former smokers" and "current smokers" are reversed. The four columns labeled "former smokers" present data for "current smokers" and vice versa.
5. Page 27. "Sample Size and power calculations". Insert "actual estimated" before the words "standard deviation" in the text.
6. Page 46 Table 22. Under "non-reversible population" Advair 250/50 column the mean change should be 126 ml and not 116 ml as shown in the table.
7. Page 52 Table 30. The numbers for the Dyspnea domain in the columns "placebo, SAL 50, FP 250, and Advair Diskus 250/50 should be 2.7, 3.0, 3.8, and 4.1. The uncorrected and corrected table is displayed below.

**Table 30 - Summary of Mean Change from Baseline at Endpoint in CRDQ Domains
[uncorrected]**

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

Corrected Table 30

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

	Placebo	SAL 50	FP 250	Advair Diskus 250/50
Dyspnea Domain [MCIC ≥ 2.5] Mean change	2.7	3.0	3.8	3.9
Fatigue Domain [MCIC ≥ 2.0] Mean Change	1.5	0.9	1.7	2.5
Emotional Function Domain [MCIC ≥ 3.5] Mean Change	1.1	1.4	2.5	2.4
Mastery Domain [MCIC ≥ 2.0] Mean Change	1	0.9	1.8	1.9

The results for Advair 250/50 for the dyspnea domain were not affected by this error.

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Medical Officer Review

Division of Pulmonary and Allergy Drug Products (HFD-570)

Application #:	NDA 21-077/SE1-003	Category of Drug:	Corticosteroid/Long-Acting β_2 -Agonist
Sponsor:	GlaxoWellcome Inc.	Route of Administration:	Oral Inhalation
Proprietary Name:	Advair™ Diskus® 250/50 and Advair™ Diskus® 500/50	Medical Reviewer:	Lydia I. Gilbert-McClain, MD, FCCP
USAN/Established Name:	Fluticasone propionate/salmeterol xinafoate	Review Date:	December 17, 2001

Submissions Reviewed in This Document

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
May 4, 2001	Electronic submission	sNDA/SE1-003	New indication for Advair Diskus -Maintenance treatment for COPD
August 8, 2001	Electronic Submission	Response to FDA questions	
August 31, 2001	Electronic submission	Safety Update	120-day safety update
October 17, 2001	Electronic Submission	Response to FDA Questions	
October 26, 2001	Electronic Submission	Response to FDA Questions	
November 09, 2001	Electronic Submission	Response to FDA Questions	

Related Applications (if applicable)

March 24, 1999		NDA 21-077	Original NDA for Advair™ Diskus approved August 24, 2000 for the long-term maintenance treatment of asthma
June 21, 2001		sNDA21-077/SE8-02	Labeling supplement for Advair™ Diskus®
May 25, 2001		sNDA20-833/SE1-04	Efficacy supplement for Flovent® Diskus® Indication for COPD
May 25, 2001		sNDA20-692/SE1-016	Efficacy supplement Serevent® Diskus® Indication for COPD

Overview of Application: See Executive Summary.

Outstanding Issues:

Recommended Regulatory Action

NDA/Supplements:

Approval
 Approvable
 Not Approvable

Signature: _____ **Date:** _____

Lydia I. Gilbert-McClain, MD, FCCP
Medical Reviewer

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EXECUTIVE SUMMARY

I. RECOMMENDATIONS

A. Recommendation on Approvability

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

B. Recommendation on Phase 4 studies and Risk Management Steps

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

II. SUMMARY OF CLINICAL FINDINGS

A. Overview of clinical program

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

Advair Diskus is the combination product comprised of the two drug substances-salmeterol xinafoate and fluticasone propionate [FP] in a dry powder formulation in the Diskus device. The two active moieties produce different pharmacological actions in the airway. Salmeterol xinafoate is a long-acting beta₂-receptor

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

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

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

The two pivotal studies with Advair Diskus were conducted in male and female subjects 40 years of age and older. Subjects were current or former smokers with a FEV₁ between 40% - 42% of predicted normal, a ratio of FEV₁ to force vital capacity (FEV₁/FVC) of 47% -51% as well as a history of chronic bronchitis. Subjects were stratified by reversibility [reversible vs. non-reversible] based on their response to bronchodilators as defined by the ATS [see pg. 25]. Study SFCA3006 was done with Advair Diskus 500/50 and study SFCA3007 was done with Advair Diskus 250/50. These studies had 4 arms; Advair Diskus 500/50 or 250/50, Flovent® Diskus 500 or 250, Serevent® Diskus 50, and placebo. The contribution of fluticasone and salmeterol in the combination were each assessed using a different primary endpoint. Change from Baseline in pre-dose FEV₁ was the primary endpoint used to evaluate the contribution of fluticasone in the combination by comparing Advair Diskus vs. salmeterol. Change from Baseline in 2-hr post dose FEV₁ was the primary endpoint used to evaluate the contribution of salmeterol in the combination by comparing Advair Diskus vs. fluticasone. The asthma trials with Advair Diskus were similarly designed except

¹ PS Burge et.al Randomized double blind placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* vol 320 13 May 2000; 1297-1303

Pier Luigi Paggiaro et.al. Multicentre randomized placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. *The Lancet* Vol 351 March 14, 1998; 773-779

that FEV₁ AUC over 12 hours was used to assess the salmeterol effect and not 2-hr post-dose FEV₁. At the end of phase 2 meeting for the COPD program, [April 21, 1998] the Division agreed that it was acceptable to use the 2-hr post dose FEV₁ but that the sponsor should collect serial FEV₁ measurements in at least one study to confirm the 12-hour duration of action and the durability of that action over time. Therefore, the sponsor collected serial FEV₁ measurements over 12 hours on Treatment Day 1 and at Week 12 in a subset of patients at 30 sites in study SFCA3006.

A total of 1,414 patients were enrolled in these two pivotal trials. Of these, 347 patients were exposed to Advair Diskus, 356 to Flovent® Diskus, 341 to Serevent® Diskus and 370 to placebo. Of the subjects exposed to Advair Diskus, 169 received Advair Diskus 500/50 mcg bid and 178 received Advair Diskus 250/50 mcg bid. The mean duration of exposure was 141.3 days for Advair Diskus 500/50 mcg bid and 138.6 days for Advair Diskus 250/50 mcg bid.

B. Efficacy

Advair Diskus 500/50 and Advair Diskus 250/50 both met the efficacy criteria for combination drug products as stated in the Code of Federal Regulations. However the efficacy of Advair Diskus was not demonstrated for any of the supportive secondary endpoints relevant to the COPD indication. There was no treatment difference in COPD-related quality of life, the frequency or severity of COPD exacerbations, or in the chronic bronchitis symptom questionnaire. This finding seriously questions the overall clinical significance of the FEV₁ improvements seen in these trials to the COPD population.

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

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

In study SFCA3006 the effect size [Advair vs. placebo] for Advair for the reversible group for the mean change from Baseline in mean morning pre-dose FEV₁ was 192 mL compared to 124 mL for the non-reversible population. Therefore, the reversible population had an effect size that was [numerically] 1.5 times that of the non-reversible population. In study SFCA3007, the effect size for the reversible population was [numerically] more than twice [211 mL] the effect size of the non-reversible population [97 mL] for the mean change from

Baseline in mean morning pre-dose FEV₁. For the mean change from Baseline in post-dose FEV₁ the effect size of the reversible population was [numerically] 1.5 times that of the non-reversible population in both studies.

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

Other secondary endpoints evaluated were AM peak flow, Ventolin use and nighttime awakenings requiring Ventolin use. As expected, the AM peak flow results were concordant with the FEV₁ findings. The results were similar in both studies. In study SFCA3006, the mean change in AM PEF at Endpoint was 31.9 L/min for Advair Diskus 500/50 compared with 12.9 L/min for Flovent® Diskus 500 and 16.8 L/min for Serevent® Diskus. In study SFCA3007, the improvement in AM PEF was 30.6 L/min for Advair 250/50 compared with 11.3 L/min for Flovent® Diskus 250, and 14.7 L/min for Serevent® Diskus. Although there were improvements in Ventolin use and nighttime awakenings, these changes were very small and difficult to put in a clinical perspective. Also, these secondary endpoints and in particular, nighttime awakenings are of more clinical relevance in an asthmatic population.

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

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

C. Safety

The safety profile of beta₂-agonists and corticosteroids is fairly well understood and characterized in the asthma population. However, although salmeterol has been approved for use in patients with COPD, neither fluticasone propionate nor any other corticosteroid has been approved for use in this patient population in the U.S. Although three large multicenter studies conducted outside of the U.S. provide some safety assessment of the use of inhaled corticosteroids for ≥ 6 months in this population the long term safety effects of inhaled corticosteroids in COPD patients is still not fully known.

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

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

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

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

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

serum cortisol levels compared to Treatment Day one levels, but these differences were not clinically significant but tended to suggest [as expected] that with higher doses of inhaled corticosteroids there is some systemic exposure. In study FLTA3025, measurements of serum cortisol AUC at treatment Week 4 showed a dose dependent decrease in serum cortisol in subjects treated with Flovent compared to placebo. Mean cortisol AUC₁₂ was 21% lower than placebo for FP 500 and 10% lower than placebo for FP 250.

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

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

D. Dosing

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

E. Special Population

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

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

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

List of Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
AM	Morning
CRDQ	Chronic respiratory disease questionnaire
ATS	American Thoracic Society
BID/bid/BD	Twice daily
BDI/TDI	Baseline dyspnea index/transitional dyspnea index
CBSQ	Chronic bronchitis symptom questionnaire
CRF	Case report form
DPI	Dry powder inhaler
DSI	Division of Scientific Investigations
FEV ₁	Forced expiratory flow rate in one second
FP	Fluticasone propionate
GI	Gastrointestinal
ICS	Inhaled corticosteroid
ITT	Intent to treat
IRB	Institutional Review Board
ISS	Integrated summary of safety
ISE	Integrated summary of efficacy
L	Liter
L-hours	liter-hours
LLN	Lower limit of normal range
Mcg	microgram
MDI	Metered Dose Inhaler
Mins	Minutes
PEF/PEFR	Peak expiratory Flow [Peak expiratory flow rate]
PFT	Pulmonary function test
PD	Pharmacodynamic
PK	Pharmacokinetic
PM	Evening
PRN/prn	As needed
PVC	Premature ventricular contraction
SAE/SE	Serious adverse event/Serious event
SAL	Salmeterol
ULN	Upper limit of normal

CLINICAL REVIEW

I. INTRODUCTION AND BACKGROUND

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

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

B. State of Armamentarium for Indication

The drugs currently approved for use in COPD are only for the relief of dyspnea associated with the disease. These drugs include short acting and long acting β_2 -agonists such as albuterol, salmeterol, and most recently [September 2001] formoterol. The long and short acting theophylline preparations and the anticholinergic drug ipratropium bromide alone, and in combination with albuterol sulphate [Combivent®] are also approved medications for the relief of bronchospasm associated with COPD. The only therapy to date that has been shown to improve survival in COPD is long term oxygen therapy in hypoxemic patients². Oral and inhaled corticosteroids are used off label for this disease however; the benefit of corticosteroids in the long-term maintenance treatment of COPD in contrast to their value in asthma is unclear. The benefit of a short course of systemic corticosteroids in COPD patients hospitalized with acute exacerbations has been reported in the literature.³

C. Important Milestones in Product Development

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

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

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

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

The Division accepted the sponsor's primary efficacy endpoint - 2-hr post-dose FEV₁ to assess the salmeterol effect in the combination product. However the Division asked the sponsor to confirm the 12-hour duration of action of salmeterol and the durability of that action over time in at least one study. A meeting was held August 4, 2000 to discuss electronic submissions and a pre-NDA meeting was held December 1, 2000 to discuss submission of the sNDAs. The sponsor initially intended to submit a single sNDA containing all of the clinical data for all three products [Advair, salmeterol, and fluticasone propionate] but this was not acceptable to the Agency and the sponsor was asked to submit all of the clinical data to three separate NDAs.

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

D. Other Relevant Information

See "Postmarketing Experience" section on page 15.

E. Important Issues with Pharmacologically Related Agents

N/A

II. Chemistry, Pharmacology/Toxicology, Statistics

Advair Diskus is a combination of fluticasone propionate and salmeterol xinafoate in a Diskus device. Fluticasone propionate is a potent fluorinated glucocorticoid having the chemical name S-fluoromethyl 6 α -methyl-3-oxo-17 α -propionyloxyandrost-1, 4-diene-17 β -carbothioate. Fluticasone propionate is a white to off-white powder with a molecular formula of C₂₄H₃₁F₃O₅S and molecular weight of 500.6. Salmeterol is a long-acting beta₂ adrenergic agonist. The xinafoate salt of salmeterol is used in the combination product and has the chemical name 4-hydroxy- α -1-(((6-(4-phenylbutoxy) hexyl)-amino)methyl)-1,3-benzenedimethanol, 1-hydroxy-2-napthoate. It is a white to off-white powder with

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

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

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

The sponsor is seeking approval of the 2 higher strengths for the long-term maintenance treatment of COPD. The proposed dosage is one inhalation twice daily. Under standardized *in vitro* test conditions, Advair Diskus 250/50 and 500/50 delivers 233 and 465 mcg of fluticasone respectively and 45 mcg of salmeterol base per blister when tested at a flow rate of 60 L/min for 2 seconds. In 9 adult patients with obstructive lung disease and severely compromised lung function [FEV₁ 20% -30% predicted] mean peak inspiratory flow through a Diskus device was 80.0 L/min [range 46.1 to 115.3 L/min].

Pharmacology/toxicology data were not submitted to this sNDA.

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

III. Human Pharmacokinetics and Pharmacodynamics

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

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

IV. Description of Clinical Data and Sources

A. Overall Data

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

- Advair Diskus 250/50 and 500/50 compared with salmeterol 50 to evaluate the contribution of FP to the combination product
- Advair Diskus 250/50 and 500/50 compared with FP Diskus 250 and 500 respectively to evaluate the contribution of salmeterol in the combination.
- Advair Diskus 250/50 and 500/50 versus placebo to evaluate the overall safety and efficacy profile of the combination product.

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

B. Table of Clinical Studies

TABLE 1. PIVOTAL CLINICAL STUDIES

Study #	Location	Study Objective	Treatments Arms/ BID Dosage (mcg)	Primary Endpoints	N Randomized	N Completed
SFCA3006	US	Demonstrate efficacy of the combination product over the individual components and placebo	Advair Diskus 500/50 SAL Diskus 50 FP Diskus 500 Placebo Diskus	Change from Baseline in 2-hr post-dose FEV ₁ [to assess the salmeterol effect in Advair]	691	440
SFCA3007	US	Demonstrate efficacy of the combination product over the individual components and placebo	Advair Diskus 250/50 SAL Diskus 50 FP Diskus 250 Placebo Diskus	Change from Baseline in 2-hr post-dose FEV ₁ [to assess the salmeterol effect in Advair] Change from baseline in AM pre-dose FEV ₁ [to assess the FP effect in Advair]	723	505
FLTA3025	US	Demonstrate efficacy of Flovent Diskus over placebo	FP Diskus 500 , FP Diskus 250 , placebo	Change from baseline in pre-dose FEV ₁	640	414

C. Postmarketing Experience

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

D. Literature Review

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

- (I) Long term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease that continue smoking. *Romain A. Pauwels et.al for the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease [EUROSCOP]. NEJM 1999;340:1948-53*
- (II) Randomised, double-blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary diseases: the ISOLDE trial. PS Burge et.al on behalf of the ISOLDE study investigators. *BMJ Vol 320; 1297-1303*
- (III) Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. Pier Luigi Paggiaro et.al. On behalf of the international COPD study group. *Lancet Vol 351;773-779*
- (IV) Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med. 1987; 106:196-204*
- (V) Standards for the diagnosis and care of patients with chronic obstructive pulmonary diseases. *Am J Respir Crit care Med. 1995; Vol 152 pp s77-s120*

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

V. CLINICAL REVIEW METHODS

A. Conduct of the Review

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

B. Overview of Materials Consulted in the Review

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

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

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

D. Ethical Conduct of Trials

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

E. Evaluation of Financial Disclosure

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

VI. INTEGRATED REVIEW OF EFFICACY

A. Conclusions

Advair Diskus 500/50 and Advair Diskus 250/50 were statistically superior to placebo. For the primary efficacy endpoint "mean change from Baseline in pre-dose FEV₁," both Advair 500/50 and Advair Diskus 250/50 had a statistically significant treatment effect when compared with salmeterol establishing the contribution of fluticasone in the combination product. The model-adjusted treatment effect was 67 mL [$p \leq 0.012$] for Advair Diskus 500/50, and 69 mL [$p = 0.012$] for Advair Diskus 250/50.

For the primary efficacy endpoint "mean change from Baseline in 2-hr post-dose FEV₁," the model adjusted treatment effect of Advair Diskus compared to FP was 129 mL [$p < 0.001$] for Advair Diskus 500/50, and 124 mL [$p < 0.001$] for Advair Diskus 250/50. The comparison of Advair vs. FP establishes the contribution of salmeterol in the combination product.

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

Improvements in AM peak flow (PEF) measurements at Endpoint in patients treated with Advair Diskus were numerically superior to patients treated with SAL, FP, or placebo in both studies and are supportive of the FEV₁ results. This is not an unexpected finding as PEF measurements also assess lung function and would be expected to be similar to FEV₁ measurements. Nighttime

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

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

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

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

In summary Advair Diskus 500/50 and Advair Diskus 250/50 both met the efficacy criteria for combination drug products as stated in the Code of Federal Regulations. However except for dyspnea as evaluated with the BDI/TDI with the 500/50 mcg dose, the efficacy of Advair Diskus was not demonstrated for any of the secondary endpoints relevant to the COPD indication. The patient population studied was not representative of the COPD population at large in that $> 50\%$ of the subjects showed significant reversibility and the study was limited to only patients with confirmed chronic bronchitis. The failure of Advair to demonstrate a treatment effect in the secondary endpoints of relevance to COPD [i.e. exacerbations, CRDQ, CBSQ] calls into question the clinical significance of the FEV₁ findings. Taken together, These data do not appear to be robustly supportive of efficacy in the COPD population.

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

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

C. DETAILED REVIEW OF CLINICAL TRIALS

The three trials for the COPD indication are:

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

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

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

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

TRIAL DESIGN of STUDIES SFCA3006 AND SFCA 3007

OBJECTIVES

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

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

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

SFCA3006

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

SFCA3007

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

Patients were followed every week for the first 4 weeks, every 2 weeks through Treatment Week 8, and then at 4-week intervals for the remainder of the treatment period. Subjects who developed an exacerbation of COPD after randomization were treated with antibiotic therapy as an outpatient for up to two exacerbations but were withdrawn from the study if a third exacerbation occurred, or if they required hospitalization to treat an exacerbation.

Reviewer Comment: The sponsor did not define COPD exacerbation per se but defined the severity of an exacerbation based on the treatment the subject received. [See pg.26]

PATIENT POPULATION

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

Inclusion Criteria

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

- Female subjects had to be of non-child-bearing potential or if of childbearing potential must have a negative serum pregnancy test and must use an approved contraceptive, undergo female sterilization, or their male partner must have undergone sterilization.
- Subjects had to have a current or prior history of ≥ 20 pack-years of cigarette smoking. Subjects who were ex-smokers must have discontinued smoking for at least 6 months prior to Screening.
- Subjects must have a history of cough productive of sputum on most days for at least 3 months of the year for at least 2 years, that was not attributable to another disease process.
- Subjects had to have a baseline FEV₁ of $< 65\%$ predicted normal but > 0.70 L OR FEV₁ ≤ 0.70 L AND $>40\%$ but still $< 65\%$ of predicted normal value [according to Crapo et al.]⁵ AND FEV₁/FVC ratio of $\leq 70\%$.
- Subjects also had to achieve a score of ≥ 2 on the Modified Medical Research Council Dyspnea Scale [MMRCD] (see Appendix on pg. 83) at screening
- Subjects had to have a score of ≥ 4 [out of possible 16] on the Chronic Bronchitis Symptoms Questionnaire [CBSQ] (see Appendix on pg. 75 for CBSQ) at Treatment Day 1 to qualify for the study.
- Subjects could be on inhaled corticosteroids not exceeding the doses outlined in Table 2, below.

Exclusion Criteria

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

- A diagnosis of asthma as defined by the ATS⁶

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

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

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

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

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

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

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

STUDY PROCEDURE

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

Reversible: Subjects that demonstrated a bronchodilator response (post albuterol) of ≥200 mL AND 12% improvement in FEV₁ over Baseline.

Non reversible: Subjects that demonstrated a bronchodilator response (post albuterol) of <200 mL or < 12% improvement in FEV₁ over Baseline.

Note: Bronchodilator response = percent improvement over Baseline, calculated as follows:

$$(post-bronchodilator FEV_1 - pre-bronchodilator FEV_1) / pre-bronchodilator FEV_1 \times 100$$

In the data analysis, the sponsor also defined a **poorly reversible population** that they have indicated as applicable to the rest of the world (ROW). The **poorly reversible population** was defined as subjects that demonstrated an increase in percent predicted FEV₁ of < 10% after 4 puffs of albuterol inhalation aerosol at Screening.

Reviewer's Comment: When reversibility is defined as a function of percent-predicted FEV₁ some patients defined as Reversible by ATS criteria could be defined as "Poorly Reversible" leading to potential misunderstanding of the degree of individual patient responsiveness to bronchodilators (see examples in the table below). Because this definition of reversibility is seldom used in this country, details of this population will not be discussed in this review.

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

Subject #	% Predicted FEV ₁ [Pre]	FEV ₁ [Pre]	FEV ₁ [Post]	% Predicted FEV ₁ [Post]	Reversibility [% change in FEV ₁ and Absolute mL]	Reversibility [Change in % predicted]
9029	20.1	0.71	1.01	28.61	42.3% , 300mL	8.5%
9254	39.8	1.44	1.74	48.1	20.8% , 300 mL	8.3%
9532	61.6	2.04	2.30	69.4	12.7% , 260mL	7.8%
9729	38.2	1.48	1.78	46.0	20.3% , 300mL	7.7%

Withdrawal Criteria

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

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

Exacerbations of COPD

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

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

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

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

STATISTICAL AND ANALYTICAL PLAN

EFFICACY

Primary Efficacy Endpoints

The mean change from Baseline at Endpoint in the Pre-dose FEV₁ and 2 hr-post-dose FEV₁ were the primary efficacy analyses. The pre-dose FEV₁ was the primary endpoint used to evaluate the effect of FP in the combination product, while the 2 hr-post-dose FEV₁ was the endpoint used to evaluate the effect of SAL in the combination product. The comparison was made between Advair Diskus [500/50 and 250/50] and SAL 50 to evaluate the effect of FP. The comparison was made between Advair Diskus 500/50 and FP 500 in study SFCA3006 and between Advair Diskus 250/50 and FP 250 in study SFCA3007 to evaluate the effect of SAL.

Baseline FEV₁ was the pre-dose FEV₁ at Treatment Day 1. The endpoint value for FEV₁ measurements was the last on-treatment measurement recorded excluding data from discontinuation visits for each subject.

Sample size and power calculations

The standard deviation of the change from pre-dose Treatment Day 1 Baseline in pre-dose FEV₁ at each treatment visit was assumed to be 0.28 L. Using a two sample t-test with an α of 0.05 a sample size of 175 patients per treatment arm would provide $\geq 91\%$ power to detect a difference of 0.1 L for any pairwise treatment comparisons. A total of 692 subjects in 65 centers were randomized to study SFCA3006 and 723 subjects in 76 centers were randomized to study SFCA3007. The sponsor indicated that the standard deviation of change from Baseline at Endpoint in pre-dose FEV₁ ranged from 220 mL to 239 mL for the ITT population for study SFCA3006 and ranged from 204 mL to 277 mL for study SFCA3007. For post-dose FEV₁ the standard deviation of change from Baseline at Endpoint ranged from 134 mL to 212 mL for the ITT population for study SFCA3006 and ranged from 211 mL to 313 mL for study SFCA3007. Therefore, the studies were adequately powered to show a 100 mL difference for both pre-dose and post-dose FEV₁ for the ITT population.

Secondary Efficacy Endpoints

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

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

Chronic Bronchitis Symptom Questionnaire [CBSQ]

The CBSQ combined selected questions from the Petty Subject Evaluation Questionnaire and the Revised Global Petty Questionnaire for Ease of Cough and Sputum Clearance⁷. The CBSQ evaluated the COPD symptoms of cough frequency and severity, chest discomfort, and sputum production on a scale of 0-4 where a rating of 0 reflected no symptoms (see Appendix On pg. 75). Subjects had to have a score of ≥ 4 out of possible 16 at Treatment Day 1 to qualify for the study. The test was given at every study visit as well as the discontinuation visit where possible. Individual scores were added to provide a Global Assessment Score (GAS). The minimal clinically important change (MCIC) for the CBSQ was determined to be a change from baseline of 1.4 in the CBSQ GAS. The MCIC was determined by matching changes from Baseline in the CBSQ GAS with a separate measure of change in chronic bronchitis symptoms called the Global Rate of Change [GRC]. The GRC was a 2-part question asked by the

⁷ Petty TL. The national mucolytic study: results of a randomized, double blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. *Chest* 1990;97:75-83
Rubin Bk, Ramirez O, Ohar JA. Iodinated glycerol has no effect on pulmonary function, symptom score, or sputum properties in patients with stable chronic bronchitis. *Chest* 1996;109:348-52

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

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

Baseline/Transition Dyspnea Index (BDI/TDI)

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

Health Outcomes

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

item was considered to be clinically meaningful based on published literature⁸. Therefore, for this study, an improvement of at least 10 in the Overall score was considered an overall improvement in COPD-specific quality of life. For treatment group comparisons, a difference of at least 10 in the Overall score in the mean change from Baseline at Endpoint between treatment groups was considered clinically meaningful. A reduced ITT population was used for the analysis of the CDRQ data. Subjects were excluded from the analyses based on their scores as follows:

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

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

SAFETY

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

EFFICACY RESULTS

RESULTS STUDY SFCA3006

Patient Disposition

A total of 1,352 patients were screened, and 691 patients were randomized. Of the 1,352 subjects screened, 661 failed screening. The most common reason for screening failure was not meeting the entrance criteria of disease severity [i.e. an FEV₁/FVC of $\leq 70\%$ and Baseline FEV₁ of $\leq 65\%$ predicted but $>0.70L$].

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

Of the 674 subjects analyzed in the ITT population, 165 were in the Advair Diskus 500/50 group, 160 in the salmeterol group, 168 were in the Flovent

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

⁹ Investigator 1403: Jay Grossman, M.D., Vivra Research

Diskus 500 group, and 181 were in the placebo group. Two hundred and thirty-four (234) of the 674 subjects withdrew from the study prior to completion and 440 (65%) completed the study.

Table -4. Patient Disposition ITT Population SFCA 3006

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

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

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

Medication Compliance

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

Demographics

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

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

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

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

The screening spirometry results were consistent with airflow obstruction with FEV₁% predicted ranging from 40.25% to 41.48% across treatment groups. The FEV₁/FVC x100 ratio ranged from 47.64% to 49.41%. The FEV₁ % predicted and the FEV₁/FVC ratio were similar for the reversible and the non-reversible population. The table below summarizes the screening spirometry results for the overall ITT population and the reversible and non-reversible population. The bronchodilator response ranged from 19.23% to 21.18% across treatment groups. The reversible subjects had a bronchodilator response ranging from 28.05% to 31.56%, while the non-reversible population had a bronchodilator response ranging from 8.04% to 10.28%. Screening spirometry and bronchodilator response data were similar between the former smokers and current smokers. Table 6 summarizes the spirometry and bronchodilator response results.

Table 6 - Spirometry and Bronchodilator Response Results SFCA 3006

	Placebo	SAL 50	FP 500	Advair 500/50
ITT Population				
Randomized n	181	160	168	165
Mean FEV ₁ [mL]	1282	1192	1174	1254
FEV ₁ % predicted	41.48	40.25	41.40	40.85
FEV ₁ /FVC x 100	49.02	48.58	47.64	49.41
Bronchodilator response [%]	19.33	21.18	19.23	20.58
Reversible Population				
Randomized n	101	82	90	88
Mean FEV ₁ [mL]	1322	1250	1228	1366
FEV ₁ % predicted	40.85	39.12	40.82	41.25
FEV ₁ /FVC x 100	48.91	48.32	47.74	50.20
Bronchodilator response [%]	28.05	31.55	28.56	31.56
Non-Reversible Population				
Randomized n	80	78	78	77
Mean FEV ₁ [mL]	1230	1132	1114	1129
FEV ₁ % predicted	42.29	41.44	42.09	40.40
FEV ₁ /FVC x 100	49.17	48.45	47.52	48.51
Bronchodilator response [%]	8.33	10.28	8.46	8.04

Reviewer's Comments:

There are a number of concerns regarding the patient population enrolled in this study and hence whether it is appropriate to generalize the results of this trial to the COPD population as a whole. The proportion of patients enrolled in the study with reversibility (54%) is much higher than the approximately 30% reported in the population of COPD patients at large¹⁰. Secondly, all patients had to have a diagnosis of chronic bronchitis to be enrolled in the study. While chronic bronchitis and emphysema can occur together, the study entry criteria specifically eliminated those COPD patients with relatively "pure" emphysema. The diagnosis of emphysema was captured by patient self-reporting without pre-defined objective criteria.

EFFICACY RESULTS SFCA3006

Primary Efficacy Results

Change from baseline in mean morning pre-dose FEV₁ at endpoint

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

¹⁰ Standards for the Diagnosis and Care of Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* Vol 152. Pp. S77-S120, 1995

Table 7 Mean Change [mL] from Baseline in Pre-Dose FEV₁ SFCA3006

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

a $p \leq 0.028$ vs. placebo

b $p \leq 0.016$ vs. SAL

c $p \leq 0.038$ vs. FP500

For the ITT population, mean improvement in pre-dose FEV₁ at Endpoint was 156 mL (14.5% change) for Advair Diskus 500/50, and 107 mL (10.0% change) for SAL 50 representing a mean difference of 49 mL [$p \leq 0.028$]. The model-adjusted mean difference was 67 mL [$p \leq 0.012$].

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

Table 8 summarizes the actual change from Baseline in Pre-Dose FEV₁ across multiple timepoints for each treatment group. Over the 24 weeks of treatment, mean changes from Baseline in AM pre-dose FEV₁ ranged from 159 mL to 192 mL for the Advair Diskus 500/50 group, 110 mL to 134 mL for the SAL 50 group, 69 mL to 131 mL for the FP 500 group and 18 mL to 28 mL for the placebo group.

Table 8 - Summary of Pre-Dose FEV₁ [mL] Across Multiple Timepoints SFCA3006
[Data Table 7.3 SFCA3006.pdf] (All timepoints not shown)

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

Advair Diskus 500/50 had numerically greater improvements in Pre-dose FEV₁ at all timepoints throughout the study compared to its individual components and placebo, although Endpoint was selected *a priori* to assess the contribution of fluticasone to the combination.

Mean Change From Baseline at Endpoint in 2-hr Post-Dose FEV₁

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

Table 9 - Mean Change (mL) from Baseline in 2-Hour Post-Dose FEV₁ ITT Population SFCA 3006

	Placebo N= 181	SAL 50 N=160	FP 500 N=168	Advair Diskus 500/50 N=165
Baseline N	181	159	166	163
Baseline mean FEV ₁ [mL] (SD)	1282 [491]	1192 [441]	1174 [445]	1254 [546]
Endpoint n	171	158	160	156
Mean 2-hour Post-Dose FEV ₁ at Endpoint [mL] (SD)	1324 [504]	1429 [532]	1327 [501]	1515 [616]
Mean change from Baseline in morning 2-hour post-dose FEV ₁ [mL] [SD]	28 [231]	233 ^a [283]	138 ^{a,b} [231]	261 ^{a,c} [261]
Percent change	3.7%	21.6%	13.1%	24.2%

a p<0.024 vs. placebo

b p<0.043 vs. SAL 50

c p<0.001 vs. FP 500

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

There was a greater increase in the 2-hr post-dose FEV₁ at Endpoint in the Advair 500/50 treatment group (261 mL) compared with the FP 500 treatment group (138 mL). The mean treatment difference is 123 mL [$p \leq 0.024$]. The model-adjusted mean treatment difference was 129 mL. The mean treatment difference between Advair 500/50 and placebo for the reversible and the non-reversible population was 290 mL and 167 mL respectively. Numerically, these results demonstrate an effect size for the reversible population that was 1.5 times the treatment effect for the non-reversible population. No inferential statistics on the subgroup analyses were performed.

Table 10 - Mean Change from Baseline in Post-Dose FEV₁ Reversible and Non-Reversible Population SFCA3006

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

Onset of Effect and Duration of Effect

Onset, offset, and duration of effect were defined based on the serial FEV₁ measurements collected on Treatment Day 1, and at Treatment Week 12. Onset of effect was defined as the time point within 4 hours post-dose at which the increase of FEV₁ achieved 100 mL or greater above Day 1 Baseline. The duration of effect was defined as the difference between time of onset to time of offset of effect. The time to offset was defined as the time point post dose at which a given subject's FEV₁ dropped below the 100 mL improvement threshold for two consecutive timepoints. Most patients in the Advair Diskus and salmeterol groups [$\geq 87\%$] achieved ≥ 100 mL improvement in FEV₁ over Baseline within 4 hours on Treatment Day 1 and Treatment Week 12 compared to 61.1% and 67.7% of subjects in the FP 500 group and 49.5% and 61.5% of subjects in the placebo group on Treatment Day 1, and Treatment Week 12 respectively.

Reviewer's comment. In previous COPD studies with salmeterol MDI an improvement of 12% in FEV₁ was used to define onset of effect and not an absolute increase of 100 ml as is being used here. The onset of effect of Advair is driven by the salmeterol component. The Baseline mean FEV₁ for the SAL 50 group was 1192 ml and for Advair 500/50 was 1254. Therefore, an increase of

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

Reviewer Comment:

The sponsor explained that since 12% of the mean Baseline FEV₁ for all treatment groups was less than 200 mL the greater of a mean 12% increase and a mean increase of 200 mL is 200 mL for every treatment group. From data submitted via Facsimile on December 12, 2001, the sponsor showed that at 0.5 hrs, 38% of subjects in the Advair group reached or exceeded the threshold of at least 12% and at least 200 mL above the subject's pre-dose value on Treatment Day 1. The mean time to reach an increase of at least 12% and at least 200 mL above the subject's pre-dose value on Treatment Day 1 was 2.01 hrs for the Advair group, 1.74 hrs for the salmeterol group and 3.96 hours for the placebo group. The percentage of subjects reaching that threshold was 74% in the Advair group, 67% in the salmeterol group and 26% in the placebo group.

Secondary Efficacy Measures SFCA3006

Diary Data

AM PEF

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

Table 11 - AM PEF Results SFCA3006

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

*Baseline for AM PEF is the average of the values between Screening and Day 1.

**Overall = the entire treatment period.

Ventolin® Use

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

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

Nighttime Awakenings /Night Requiring Ventolin

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

Chronic Bronchitis Questionnaire [CBSQ GAS]

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

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

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

Baseline Dyspnea Index/Transitional Dyspnea Index [BDI/TDI]

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

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

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

Exacerbations of COPD

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

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

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

Reviewer comment: Most published definitions of COPD exacerbations encompass some combination of three clinical findings: worsening dyspnea, increase in sputum purulence, and increase in sputum volume. A severity scale for acute exacerbations developed by Anthonisen and colleagues is based on these findings as well as others.¹¹

¹¹ Severity of COPD exacerbations: Type 1 (severe) – Increased dyspnea, sputum volume, and sputum purulence (ii) Type 2 (moderate) – Two of these three symptoms are present (iii) Type 3 (mild) – One of these three symptoms are present in addition to at least one of the following findings: upper respiratory infection within the past 5 days; fever without other cause; increased wheezing; increased cough; or increase in respiratory rate or heart rate by 20% as compared with baseline. *Anthonisen et.al Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Int Med; 1987 106: 196-204*

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

Table 14 - Incidence of COPD exacerbations. ITT Population SFCA3006

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

Subgroup analysis in Current smokers and Former smokers

Summary statistics showed that the combination group had similar results for the primary efficacy endpoints regardless of smoking status. For the primary endpoint mean change in pre-dose FEV₁ at Endpoint, the mean treatment difference between Advair and SAL was 47 mL in former smokers compared with 52 mL in current smokers. For the primary endpoint change in 2-hr post-dose FEV₁ at Endpoint the mean treatment difference between Advair and FP was 117 mL in former smokers and 132 mL in current smokers. These results are displayed in the table below.

Table 15 - Summary of Results Displayed by Smoking Status

Efficacy Variable	Former Smokers				Current Smokers			
	Placebo N=84	SAL 50 N=86	FP 500 N=91	Advair 500/50 N=81	Placebo N=97	SAL 50 N=74	FP 500 N=77	Advair 500/50 N=76
Pre-Dose FEV₁ (mL) Change from Baseline								
Mean change at Endpoint	16	132	139	179	- 21	78	73	130
Post-Dose FEV₁ (mL) Change from Baseline								
Mean Change at Endpoint	45	243	140	257	15	221	134	266
Transition Dyspnea Index (TDI)								
Mean at Endpoint	-0.1	1.0	1.3	1.9	0.7	0.9	1.3	2.2

HEALTH OUTCOMES RESULTS

COPD-related Quality of Life assessed by the CRDQ

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

Results

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

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

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

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

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

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

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

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

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

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

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

RESULTS STUDY SFCA3007

Patient Disposition

A total of 1,489 patients were screened, and 723 patients were randomized and 766 failed screening. The most common reason for screening failure [516 subjects (67%)] was not meeting the entrance criteria of an FEV₁/FVC of $\leq 70\%$ and Baseline FEV₁, of $\leq 65\%$ predicted but >0.70 L. Of the 723 subjects randomized 178 were in the Advair Diskus 250/50 group, 177 in the salmeterol group, 183 were in the fluticasone Diskus 250 group, and 185 were in the placebo group. Two hundred and eighteen subjects [30%] withdrew from the study prior to completion and 505 (70%) completed the study.

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

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

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

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

Medication Compliance

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

Demographics

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

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

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

	Placebo N = 185	SAL 50 N= 177 ^a	FP 250 N= 183	Advair Diskus 250/50 N =178
Age (yrs)				
Mean	64.8	64.2	63.3	63.4
Range	40-81	42-87	40-84	40-87
Gender				
Male	126 (68%)	102 (58%)	121 (66%)	108 (59%)
Female	59 (32%)	75 (42%)	62 (34%)	70 (41%)
Race				
Caucasian	173 (94%)	165 (93%)	167 (91%)	170 (95%)
Black	6 (3%)	7 (4%)	9 (5%)	5 (3%)
Asian/Other	6 (3%)	5 (3%)	7 (4%)	3 (2%)
Median Duration of COPD (yrs)	6.00	6.00	6.00	6.00
Emphysema				
Yes	126 [68]	142 [80]	132 [72]	137 [77]
No	59 [32]	35 [20]	51 [28]	41 [23]
Inhaled steroids at screening				
No	130 (70%)	142 (80%)	132 (74%)	137 (77%)
Yes	55 (30%)	35 (20%)	51 (26%)	41 (23%)
Former Smoker	98 (53%)	87 (49%)	95 (52%)	101 (57%)
Current Smoker	87 (47%)	90 (51%)	88 (48%)	77 (43%)
*MMRC Dyspnea Score				
2	118 (64%)	120 (68%)	116 (63%)	109 (61%)
3	58 (31%)	49 (28%)	63 (34%)	63 (35%)
4	9 (5%)	8 (4%)	2 (3%)	6 (4%)
^a Total number in SAL 50 group 176 [79 non-reversible, 97 reversible] per sponsor's submission 10/17/2001 <i>response.pdf</i> pg. 13 making total subjects in ITT population 722 and not 723				
*Two subjects in the FP 250 group had missing data				

The screening spirometry results for the ITT population were consistent with moderate airflow obstruction with FEV₁% predicted ranging from 41.37% to 42.05% across treatment groups. The FEV₁/FVC x100 ratio ranged from 49.48% to 51.29%. The spirometry results for the reversible and the non-reversible population were also consistent with moderate airflow obstruction with FEV₁ % predicted ranging from 40.37% to 42.67 % for the reversible population and 41.19% and 42% for the non-reversible population. The bronchodilator response for the ITT population ranged from 19.53% to 21.31% across treatment groups. The reversible subjects had a bronchodilator response ranging from 29.88% to 30.87%, while the non-reversible population had a bronchodilator response ranging from 7.93% -8.58%. The table below summarizes the screening

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

Table 21 - Screening Spirometry and Bronchodilator Response SFCA3007

	Placebo	SAL	FP 250	Advair 250/50
	ITT Population			
Randomized n	185	177	183	178
Mean FEV ₁ [mL]	1289	1245	1313	1252
FEV ₁ % predicted	42.05	41.94	41.96	41.37
FEV ₁ /FVC x100	49.63	50.83	51.29	49.48
Bronchodilator response [%]	20.24	21.31	19.53	20.14
	Reversible Population			
Randomized n	102	97	100	99
Mean FEV ₁ [mL]	1313	1235	1359	1286
FEV ₁ % predicted	42.67	40.37	42.59	40.87
FEV ₁ /FVC x100	51.01	50.81	52.16	49.56
Bronchodilator response [%]	29.72	30.87	28.93	29.88
	Non-reversible Population			
Randomized n	83	79	83	79
Mean FEV ₁ [mL]	1259	1245	1256	1208
FEV ₁ % predicted	41.29	43.64	41.19	42.00
FEV ₁ /FVC x100	47.94	50.69	50.19	49.37
Bronchodilator response [%]	8.58	9.56	8.19	7.93

EFFICACY RESULTS SFCA3007

Primary Efficacy Results

Change from baseline in mean morning pre-dose FEV₁ at endpoint

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

Table 22 - Mean Change [mL] from Baseline in Pre-Dose FEV₁, SFCA3007

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

a p≤0.005 vs. placebo

b p=0.012 vs. SAL 50

For the ITT population, mean improvement in AM pre-dose FEV₁ at Endpoint in the Advair Diskus 250/50 group was 165 mL compared with 91mL in the SAL 50 group [p = 0.012]. The model-adjusted mean difference was, 69 mL[p=0.012].

For the primary endpoint "mean change from Baseline in pre-dose FEV₁", the mean treatment difference between Advair 250/50 and placebo was 211 mL for the reversible population and 97 mL for the non-reversible population. Numerically, this is equivalent to a treatment difference in the reversible population that was twice the treatment effect seen in the non-reversible population. Inferential statistics were not done on these subgroups.

Over the 24 weeks of treatment, mean changes from Baseline in AM pre-dose FEV₁ ranged from 153 mL to 189 mL [15.8% to 19.2%] for the Advair Diskus 250/50 group, 102 mL to 129 mL [9.2% to 12.8%] for the SAL 50 group, 83 mL to 118 mL [7.3% to 11.3%] for the FP 250 group and 3 mL to 49 mL [0.5% to 5.6%] for the placebo group. Similar to study SFCA3006, Advair Diskus 250/50 had numerically greater improvements in AM Pre-dose FEV₁ at all timepoints throughout the study compared to its individual components and placebo.

Mean Change from Baseline in 2-hour Post-Dose FEV₁

The comparison of interest is Advair 250/50 vs. FP 250. There was a statistically significant greater increase in the 2-hr post-dose FEV₁ at Endpoint in the Advair 250/50 treatment group [281 mL, 27.0%] compared with FP 250 [147 mL, 13.8%], placebo [58 mL, 5.9%], and SAL 50 [200 mL, 19.0%] p≤0.007. The results are displayed in the table below.

Table 23 - Mean change [mL] from Baseline in 2-hour Post-Dose FEV₁ ITT Population- Study SFCA3007 [Data from Tables 7.4-7.5 SFCA3007.pdf]

	Placebo N=185	SAL 50 N=177	FP 250 N=183	Advair Diskus 250/50 N=178
Baseline n	185	177	166	163
Mean FEV ₁ [mL]	1232	1205	1236	1207
Endpoint n	172	168	175	171
Mean 2-hour post-dose FEV ₁ at Endpoint [mL]	1298	1413	1389	1490
Mean change from Baseline in morning 2-hour post-dose FEV ₁ [mL]	58	200	147	281

The mean change in post-dose FEV₁ for the Advair 250/50 group compared with placebo was numerically greater [282 mL] in the reversible population compared with the non-reversible population [150 mL]. Again no inferential analyses were conducted in these subgroups.

Table 24 - Summary of mean Change [mL] in Post-Dose FEV₁

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

SECONDARY EFFICACY MEASURES

Diary Data

AM PEF

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

Table 25 - AM PEF Results SFCA3007

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

Ventolin Use

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

Nighttime Awakenings/Night Requiring Ventolin

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

Chronic Bronchitis Symptoms Questionnaire

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

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

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

Baseline/Transition Dyspnea Index (BDI/TDI)

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

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

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

Exacerbations of COPD

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

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

Subgroup Analysis by Smoking Status

For the primary endpoint change from Baseline in pre-dose FEV₁ current smokers had a numerically greater mean treatment effect [107 ml] compared with former smokers [31 m] for the comparison Advair 250/50 vs. SAL. For the primary endpoint change from Baseline in 2-hr post-dose FEV₁, former smokers had a numerically similar effect [138 ml] compared with current smokers [124 ml] for the comparison Advair 250/50 vs. FP 250. No inferential analyses for these subgroups were done. The primary efficacy results by smoking status are displayed in the table.

Table 28 - Summary of Efficacy Results Displayed by Smoking Status

Efficacy Variable	Former Smokers				Current Smokers			
	Placebo N=87	SAL N=90	FP 250 N=88	Advair 250/50 N=77	Placebo N=98	SAL N=87	FP250 N=95	Advair 250/50 N=101
Pre-Dose FEV₁ (mL) Change from Baseline								
Mean change at Endpoint	4	96	80	127	-3	86	136	193
2-Hr Post-Dose FEV₁ (mL) Change from Baseline								
Mean Change at Endpoint	52	222	115	253	64	177	176	301
Transition Dyspnea Index (TDI)								
Mean at Endpoint	1.1	1.7	1.6	1.6	0.9	1.5	1.8	1.8

HEALTH OUTCOMES RESULTS

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

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

Timepoint	Placebo		SAL 50		FP 250		Advair Diskus 250/50	
Day1								
N	180		173		177		175	
Mean [SD]	84.8 [17.8]		86.3 [18]		85.5 [17.4]		84.1 [17.6]	
Endpoint								
N	177		170		170		169	
Mean [SD]	89.6 [24.9]		93.0 [21.3]		96.4 [20.3]		93.9	
Mean Change	5.0		6.4		10.4		10	
Week 2								
N	161		158		161		162	
Mean change from Baseline	3.8		6.2		5.2		7.5	
Week 4								
N	148		158		155		162	
Mean change from Baseline	7.5		6.2		9.2		7.5	
Week 8								
N	138		136		142		145	
Mean change from Baseline	9.4		7.7		10.1		11.2	
Week 24								
N	116		113		122		119	
Mean change from Baseline	9.4		10.3		13.6		13.3	
	Current Smokers				Former Smokers			
	Placebo	SAL	FP 250	Advair 250/50	Placebo	SAL	FP 250	Advair 250/50
	N=83	N=87	N=84	N=76	N=98	N=86	N=94	N=99
	Mean Change in Overall CRDQ Score							
Mean change at Endpoint	5.2	6.6	9.5	11.2	4.9	6.3	11.1	9.1

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

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

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

EFFICACY CONCLUSIONS

Summary

Advair Diskus 500/50 mcg and Advair Diskus 250/50 mcg both met the established efficacy criteria for combination drug products as stated in the Code of Federal Regulations. However except for dyspnea as evaluated with the BDI/TDI with the 500/50 mcg dose, the efficacy of Advair Diskus was not demonstrated for any of the secondary endpoints relevant to the COPD indication. The patient population studied was not representative of the COPD population at large in that > 50% of the subjects showed significant reversibility and the study was limited to only patients with confirmed chronic bronchitis. The failure to demonstrate efficacy with the secondary endpoints of relevance to COPD [i.e. exacerbations, CRDQ, CBSQ] calls into question the clinical significance of the FEV₁ findings. Taken together the efficacy data do not appear to support broad-based efficacy conclusions in the proposed population. The efficacy conclusions are outlined below in bulleted text.

Both Advair Diskus 500/50 mcg and Advair Diskus 250/50 mcg bid showed statistically significant effect compared to placebo for each of the primary endpoints "mean change from Baseline in pre-dose FEV₁ and 2-hr post-dose FEV₁". Compared to their individual components FP 500 mcg and 250 mcg and SAL 50 mcg, Advair Diskus 500/50 and Advair Diskus 250/50 had a statistically significant treatment effect. This finding established from a regulatory standpoint the efficacy requirement for Advair as a combination drug product in that both components contributed to the effect of the combination.

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

- Advair Diskus 500/50 and 250/50 did not have a clinically meaningful change compared with placebo or any of its components in the chronic bronchitis questionnaire
- Both studies failed in their quality of life objective. Compared to placebo or their individual components, neither Advair Diskus 500/50 nor Advair Diskus 250/50 had a clinically meaningful change in COPD-related quality of life as assessed by the CRDQ.
- In the assessment of dyspnea using the BDI/TDI, using a score of ≥ 1.0 as clinically meaningful Advair 500/50 had a meaningful improvement in dyspnea compared with placebo and salmeterol, but Advair 250/50 did not.
- Treatment with Advair 500/50 and Advair 250/50 did not result in a significant decrease in the frequency or severity of COPD exacerbations nor the time to COPD exacerbations.
- The percentage of withdrawals due to COPD exacerbations was similar for Advair Diskus and placebo in both studies.
- Changes in nighttime awakenings requiring Ventolin use were numerically small and of questionable clinical value in assessing effect of therapy for the COPD population.
- Inferential analyses in former smokers and current smokers were not conducted but the results seen for Advair Diskus in the overall ITT population did not appear to be affected by smoking status.
- In study SFCA3006 74% of subjects on Advair 500/50 mcg bid achieved a 12% increase in FEV₁ and at least 200 mL improvement above pre-dose FEV₁ values on Treatment Day 1.

VII. INTEGRATED REVIEW OF SAFETY

A. CONCLUSIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In several supportive studies there has been substantial evidence of systemic exposure. For example in an open-label 4-way crossover study [FLTA1003] in which normal subjects received single doses of 1000 mcg of Flovent Diskus via four different dosage strengths, the mean 24-hour urinary cortisol excretion was decreased by 42% to 62% compared to baseline in all treatment groups. In pivotal study FLTA3025 serum cortisol AUC₁₂ measured at Week 4 was reduced in subjects in the FP 250 and FP 500 groups compared with subjects in the placebo group. A dose response effect was noted with the FP 500 and FP 250 groups having mean cortisol AUC₁₂ values that were 21% and 10% lower than placebo respectively.

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

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

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

B. PATIENT EXPOSURE AND DEMOGRAPHICS

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

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

¹² The ISOLDE [Inhaled steroids in obstructive lung disease] trial was a 3-year Non-U.S. multicenter, double blind, placebo-controlled, parallel group study of the efficacy and tolerability of long-term FP 500 mcg BID in COPD.

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

C. METHODS AND SPECIFIC FINDINGS OF SAFETY REVIEW

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

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

SAFETY RESULTS SFCA3006

Extent of Exposure

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

Adverse Events Incidence

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

Table 31 - Adverse Events more Frequent than Placebo and Occurring ≥ 3% SFC3006
 [data table 9.2 SFC3006.pdf]

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

Deaths and Serious Adverse Events

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

Serious AEs

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

Table 32. Serious Adverse Events SFCA3006

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

a Also reported atrial flutter

b Also reported COPD exacerbation.

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

Adverse Events leading to withdrawal

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

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

Placebo

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

SAL 50

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

FP 500

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

Advair Diskus 500/50

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

Drug-related Events

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

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

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

Cardiovascular Safety

Adverse Events

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

ECGs

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

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

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

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

QTc Intervals

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

Holter Monitoring

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

Vital Signs (pulse, blood pressure)

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

Clinical Laboratory Results

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

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

Few subjects ($\leq 2\%$ in each treatment group) had hematology parameters that were outside sponsor-defined threshold values. Of these subjects, 2 in the Advair Diskus group had eosinophils values above the sponsor-defined threshold [$>20\%$] and 3 had WBC counts above the sponsor-defined threshold [$>16 \times 10^3/\mu\text{L}$]. No patients in the Advair Diskus 500/50 or FP 500 treatment groups had lymphocyte or monocyte counts outside of the sponsor-defined threshold [$>60\%$ for lymphocytes and $> 15\%$ for monocytes]. In clinical chemistry parameters, less than 1% of subjects had values outside of the sponsor-defined threshold values for LFTs, calcium, creatinine, phosphorous and potassium. A higher percentage of subjects [$\leq 4\%$] had values outside the sponsor-defined threshold value for glucose. Seven (4%) subjects in the Advair Diskus 500/50 group, 6 (4%) subjects in the FP 500 group and 5 (3%) subjects in the placebo and SAL groups had glucose levels greater than the threshold value. The sponsor's pre-defined threshold for high and low values is significantly different from what would prompt treatment and/or medical evaluation in clinical practice [see table 33 below]. For example, with the sponsor's threshold limits, patients with fasting glucose values of ≥ 120 mg/dL but ≤ 175 mg/dL would not be outside the threshold for high glucose. However, a fasting glucose value of ≥ 120 mg/dL in the clinical setting would prompt an evaluation for diabetes. Similarly a potassium of <3.5 or >5.5 meq/L would be addressed in clinical practice. However, the sponsor's threshold for a low potassium is <3.0 mEq/l.

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

Analyte	Units	Sponsor-defined threshold values		Lab reference range		Range in traditional units
		Low	High	Low	High	
ALT	U/L		>120		>35 U/L	
AST	U/L		>120		>36 U/L	
Alkaline phosphatase	U/L		>300		>115 U/L	
Bilirubin	mg/dl		≥ 2	<3 ($\mu\text{mol/L}$)	>21 ($\mu\text{mol/L}$)	0.3 –1.0 mg/dL
Calcium	mg/dl	<8	>12	<2.1 (nmol/L)	>2.57 (nmol/L)	9 –10.5 mg/dL
Creatinine	mg/dl		>2	<40 ($\mu\text{mol/L}$)	>110 ($\mu\text{mol/L}$)	<1.5 mg/dL
Glucose	mg/dl	<55	>175	<3.9 (mmol/L)	6.7 (mmol/L)	70 –120 mg/dL
WBC		$2.8 \times 10^3/\mu\text{L}$	$16 \times 10^3/\mu\text{L}$			
Potassium	mEq/l	<3.0	>6.0	3.4 (mmol/l)	5.4 (mmol/L)	Same as mEq/L
Eosinophils	%		>20		6.8%	
Lymphocytes	%		≥ 60	15.4%	48.5%	
Monocytes	%		>15	2.6%	10.1%	

Cosyntropin Stimulation Testing

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

Table 34 - ACTH Stimulation Testing Results SFCA3006

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

Normal pre-stimulation plasma cortisol > 4 mcg/dL

Normal post-stimulation cortisol > 14.5 mcg/dL

Endpoint: Week 24, or discontinuation

The mean basal and post-ACTH stimulation plasma cortisol levels were comparable among treatment groups on Treatment Day 1 and at Endpoint. The post-stimulation cortisols for the FP 500 and the Advair Diskus 500/50 treatment groups at Endpoint were slightly lower compared with post-stimulation cortisols on Day 1. The overall results are not suggestive of clinically significant adrenal suppression.

Reviewer Comment: There are discrepancies in the subject numbers in several of the data tables with the cortisol results. Most of these discrepancies are small and is not expected to affect the overall results. However, the sponsor has been asked to clarify these discrepancies and submit corrected data tables.

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

Table 35. Subjects with Abnormal ACTH stimulation results SFCA3006

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

SAFETY RESULTS SFCA 3007

Extent of Exposure

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

Adverse Events Incidence

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

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

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

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

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

Deaths and Serious Adverse Events

There were no deaths during the study.

Serious Adverse Events

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

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

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

Table 37 - Serious Adverse Events SFCA 3007

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

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

Adverse Events leading to withdrawal

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

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

Drug-related Events

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

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

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

Cardiovascular Safety

Adverse Events

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

ECGs

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

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

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

QTc Intervals

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

Vital Signs (pulse, blood pressure)

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

Clinical Laboratory Results

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

Cosyntropin Stimulation Testing

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

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

Table 38 ACTH Stimulation Testing Results SFCA3007

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

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

120-Safety Update

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

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

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

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

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

VIII. Dosing, Regimen, and Administration Issues

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

IX. Use in Special Populations

A. Gender Effects

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

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

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

C. Pediatric Program

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

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

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

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

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

X. Conclusions and Recommendations

A. Conclusions

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

- The improvement in lung function (FEV₁) seen in the clinical trials was not accompanied by improvements in clinically relevant endpoints such as reduction in the frequency or severity of COPD exacerbations, or symptom scores,
- Advair did not demonstrate a treatment advantage for COPD-related quality of life
- There was a clinically meaningful change in the TDI at Endpoint with Advair 500/50 compared to placebo and salmeterol but not with FP.
- The patient population studied did not represent the general COPD population as a whole. Over 50% of the patients had significant reversibility compared with up to 30% in the COPD population and all patients in these studies had chronic bronchitis. This brings into question the efficacy of this therapy in COPD patients whose clinical presentation is predominately emphysema without associated chronic bronchitis.
- There was a relatively high incidence of oral candidiasis in the FP and Advair groups and respiratory infections tended to be higher in the FP and Advair groups compared to placebo and SAL.
- The sponsor's threshold for laboratory values were very liberal making it difficult to evaluate the true incidence of hyperglycemia and hypokalemia in the pivotal studies.
- Monitoring for decreased bone mineral density and ocular pressure disorders and cataracts was not done in these studies.

B. Recommendations

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

XI. Appendix

**Appears This Way
On Original**

Chronic Bronchitis Symptoms Questionnaire (CBSQ)

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

***Appears This Way
On Original***

Cough Frequency

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

Cough Severity

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

Sputum Release

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

Chest Discomfort

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

Baseline/Transition Dyspnea Index

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

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

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

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

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

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

Transition Dyspnea Index

Change in Functional Impairment		
____-3	<i>Major Deterioration</i>	Formerly working and has had to stop working and has completely abandoned some of usual activities due to shortness of breath.
____-2	<i>Moderate Deterioration</i>	Formerly working and has had to stop working or has completely abandoned some of usual activities due to shortness of breath.
____-1	<i>Minor Deterioration</i>	Has changed to a lighter job and/or has reduced activities in number or duration due to shortness of breath. Any deterioration less than preceding categories.
____0	<i>No Change</i>	No change in functional status due to shortness of breath.
____+1	<i>Minor Improvement</i>	Able to return to work at reduced pace or has resumed some customary activities with more vigor than previously due to improvement in shortness of breath.
____+2	<i>Moderate Improvement</i>	Able to return to work at nearly usual pace and/or able to return to most activities with moderate restriction only.
____+3	<i>Major Improvement</i>	Able to return to work at former pace and able to return to full activities with only mild restriction due to improvement of shortness of breath.
____Z	<i>Further Impairment for Reasons Other than Shortness of Breath</i>	Subject has stopped working, reduced work, or has given up or reduced other activities for other reasons. For example, other medical problems, being "laid off" from work, etc.

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

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

The Chronic Respiratory Disease Questionnaire

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

Appendix: Summary of the Chronic Respiratory Disease Questionnaire

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

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

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

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

[Record additional items]

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

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

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

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

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

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

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

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

[List item on response sheet.]

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

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

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

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

This process continues until the subject's degree of dyspnoea on all five of his or her most important activities has been determined. The remainder of the questionnaire asks 15 standard questions, which are identical for each subject. The wording is deliberately repetitious, experience having taught us that the repetition ensures subjects' understanding. Re-

sponse options are consistently presented as seven point scales. An example of the way the questions are structured follows.

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

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

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

- 6 How often during the past 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath?
- 7 What about fatigue? How tired have you felt over the last 2 weeks?
- 8 How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing?
- 9 In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness?
- 10 How much energy have you had in the last 2 weeks?
- 11 In general, how much of the time did you feel upset, worried, or depressed during the last 2 weeks?
- 12 How often during the last 2 weeks did you feel you had complete control of your breathing problems with shortness of breath and tiredness?
- 13 How much of the time during the last 2 weeks did you feel relaxed and free of tension?
- 14 How often during the last 2 weeks have you felt low in energy?
- 15 In general, how often during the last 2 weeks have you felt discouraged or down in the dumps?
- 16 How often during the last 2 weeks have you felt worn out or sluggish?
- 17 How happy, satisfied, or pleased have you been with your personal life during the last 2 weeks?
- 18 How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath?
- 19 In general, how often during the last 2 weeks have you felt restless, irritable, or uptight?

Modified Medical Research Council Dyspnea Scale

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

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this page is the manifestation of the electronic signature.**

/s/

Lydia McClain
1/9/02 09:04:16 AM
MEDICAL OFFICER

In this Review Recommendations on Approval and comments to
the sponsor are withheld pending the PADAC meeting
January 17, 2002. An addendum/update to this Review
will be written following the PADAC meeting.

Mary Purucker
1/9/02 10:30:47 AM
MEDICAL OFFICER
Concur. Final action pending 17 Jan 2001 Advisory Committee
Meeting.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-077/S-003

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW		1. ORGANIZATION HFD-820/570	2. NDA NUMBER 21-077
3. NAME AND ADDRESS OF APPLICANT (City and State) Glaxo Wellcome Inc. Research Triangle Park, NC 27709		4. AF NUMBER	
6. NAME OF DRUG Advair Diskus	7. NONPROPRIETARY NAME fluticasone propionate/salmeterol xinafoate inhalation powder		5. SUPPLEMENT (S) NUMBER(S) DATES(S) SE1-003 5/4/2001
8. SUPPLEMENT PROVIDES FOR: Efficacy supplement for long term, maintenance treatment of COPD, including chronic bronchitis and emphysema.		9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY glucocorticoid/beta- adrenergic agonist	11. HOW DISPENSED RX <input checked="" type="checkbox"/> OTC <input type="checkbox"/> • SPECIAL DRUG PRODUCT YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>		12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) inhalation aerosol	14. POTENCY 100/50 mcg, 250/50 mcg, and 500/50 mcg per blister (fluticasone/salmeterol		
15. CHEMICAL NAME AND STRUCTURE see USAN		16. RECORDS AND REPORTS CURRENT YES <input type="checkbox"/> NO <input type="checkbox"/> REVIEWED YES <input type="checkbox"/> NO <input type="checkbox"/>	
17. COMMENTS CC: Orig. NDA #21-077 HFD-570/Div. File HFD-570/ACSchroeder/11-28-01 HFD-570/GPoochikian HFD-570/CSO LJafari HFD-570/Gilbert-McClain R/D Init. by: _____ F/T by: ACSchroeder/11-28-01 doc # N21077R1_S03.doc			
18. CONCLUSIONS AND RECOMMENDATIONS This supplement may be approved from a CMC standpoint. The project manager should check to be sure that the only changes in the labeling are those indicated by the applicant. The medical officer should evaluate changes in the <i>Description</i> section of the package insert, and in the patient's package insert.			
19. REVIEWER			
NAME Alan C. Schroeder, Ph.D.		SIGNATURE	DATE COMPLETED November 28, 2001
DISTRIBUTION	ORIGINAL JACKET	DIVISION FILE	REVIEWER CSO SUP. CHEMIST

2 Page(s) Withheld

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Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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this page is the manifestation of the electronic signature.**

/s/

Alan Schroeder
11/29/01 11:19:13 AM
CHEMIST

Guiragos Poochikian
11/30/01 01:15:55 PM
CHEMIST

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21077/000	Priority: 4S	Org Code: 570
Stamp: 25-MAR-1999 Regulatory Due: 25-AUG-2000	Action Goal:	District Goal: 26-JUN-2000
Applicant: GLAXO WELLCOME	Brand Name: ADVAIR	
5 MOORE DR	DISKUS(SALMETEROL/FLUTICASON	
RESEARCH TRIANGLE PARK, NC 27	E PRO	
	Established Name:	
	Generic Name: SALMETEROL/FLUTICASONE	
	PROPIONATE INHALA	
	Dosage Form: AER (AEROSOL)	
	Strength: 50 UG/100, 250, 500 UG	
FDA Contacts: P. JANI (HFD-240)	301-827-7248	, Project Manager
D. KOBLE (HFD-170)	301-827-7428	, Review Chemist
G. POOCHIKIAN (HFD-570)	301-827-1050	, Team Leader

Overall Recommendation:

ACCEPTABLE on 05-MAY-2000 by EGASM
ACCEPTABLE on 24-JAN-2000 by EGASM

Establishment: 9610411	DMF No:
GLAXO OPERATIONS UK LTD	AADA No:
WARE, HERTFORDSHIRE, UK	

Profile: ADM	OAI Status: NONE
Last Milestone: OC RECOMMENDATION	
Milestone Date: 05-MAY-2000	
Decision: ACCEPTABLE	
Reason: DISTRICT RECOMMENDATION	
Profile: CRU	OAI Status: NONE
Last Milestone: OC RECOMMENDATION	
Milestone Date: 05-MAY-2000	
Decision: ACCEPTABLE	
Reason: DISTRICT RECOMMENDATION	

Responsibilities: FINISHED DOSAGE
MANUFACTURER

Establishment: 9611205	DMF No:
GLAXO WELLCOME	AADA No:
2262	
JURONG, , SN	

Profile: CSN	OAI Status: NONE
Last Milestone: OC RECOMMENDATION	Responsibilities: DRUG SUBSTANCE
Milestone Date: 04-MAY-2000	MANUFACTURER
Decision: ACCEPTABLE	
Reason: BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: 9610421
GLAXO WELLCOME LTD
DL128DT
BARNARD CASTLE, , UK

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-MAY-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE STABILITY
TESTER

Establishment: 9610414
GLAXO WELLCOME OPERATIONS
DA1 5AH
DARTFORD, KENT, UK

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-MAY-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE RELEASE
TESTER

Establishment: 9617236
GLAXO WELLCOME SPAIN SA
28760
TRES CANTOS, MADRID, SP

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-MAY-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE STABILITY
TESTER

Establishment: 9610419
GLAXOCHEM LTD
COBDEN STREET
MONTROSE ANGUS, , UK DD108EA

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-MAY-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE
MANUFACTURER

Establishment: 9610436

DMF No:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-MAY-2000
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW

Responsibilities: _____

Establishment: 9611905
LABORATOIRES GLAXO
27000
EVREUX, CEDEX, FR

DMF No:
AADA No:

Profile: CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-MAY-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: _____

Establishment: _____

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-MAY-2000
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW

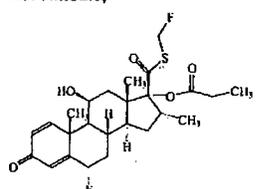
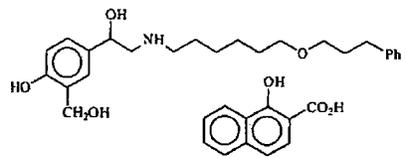
Responsibilities: _____

Establishment: _____

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-MAY-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: _____

CHEMIST'S REVIEW #2		1. ORGANIZATION HFD-570 DPADP (HFD-820)	2. NDA NUMBER 21-077
3. NAME AND ADDRESS OF APPLICANT (City and State) GlaxoSmithKline (GSK) Research Triangle Park, NC 27709		4. AF NUMBER	5. SUPPLEMENT(S) NUMBER SE1-003
			DATE 04-May-2001
6. NAME OF DRUG Advair® Diskus®		7. NONPROPRIETARY NAME fluticasone propionate/salmeterol xinafoate inhalation powder	
8. SUPPLEMENT PROVIDS FOR: Efficacy supplement for long term, maintenance treatment of COPD, including chronic bronchitis and emphysema.			9. AMENDMENT(S), REPORT(S), ETC. SE1-003 AZ* 30-May-2003 *Subject of this review.
		11. HOW DISPENSED RX <input checked="" type="checkbox"/> OTC <input type="checkbox"/>	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) inhalation powders		14. POTENCY 100/50 mcg (per blister), 250/50 mcg, and 500/50 mcg (fluticasone/salmeterol)	
15. CHEMICAL NAME AND STRUCTURE S-(Fluoromethyl)6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-propionyloxyandrost-1,4-diene-17-carbothioate;			16. RECORDS AND REPORTS CURRENT YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> REVIEWED YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
 <p>(±)-4-hydroxy-α¹-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate (salt)</p> 			
17. COMMENTS: The 30-May-2003 amendment does not contain any CMC information. The submission contains a revised package insert, however the changes reflected there were already found acceptable by Dr. A. Schroeder in his 29-Nov-2001 review. cc: Orig. NDA #21-077 HFD-570/div. Files HFD-570/CBertha 8/26/03 HFD-570/GPoochikian HFD-570/LJafari R/D Init. by: _____ F/T by: C. Bertha/8/26/03 doc # 03-05-30.rev.doc			
18. CONCLUSIONS AND RECOMMENDATIONS: The supplemental application is still recommended for approval (AP) , from a CMC perspective.			
19. REVIEWER NAME Craig M. Bertha, Ph.D.		20. SIGNATURE	21. DATE COMPLETED 8/26/03

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Craig Bertha
8/26/03 10:44:49 AM
CHEMIST

no CMC, labeling revisions already reviewed by Dr. Schroeder
in 30-Nov-2001 review

Guiragos Poochikian
8/26/03 02:14:33 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-077/S-003

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

Date

NDA #

1. 21-077 (SE1/S003)
2. 20-833 (SE1/S004)
3. 20-692 (SE1/S016)

Applicant

Name of Drug

Indication

Document Reviewed

Statistical Reviewer

Medical Input

Key Words

GlaxoSmithKline

1. Advair™ Diskus® (Fluticasone propionate/salmeterol inhalation powder) 250/50 mcg and 500/50 mcg
2. Flovent® Diskus® (Fluticasone propionate inhalation powder) 500 mcg and 250 mcg
3. Serevent® Diskus® (salmeterol xinafoate inhalation powder) 50 mcg

Treatment of patients with chronic obstructive pulmonary disease (COPD)

Item 10: Statistical, V. Placebo Controlled Study Reports:
Indication—COPD

1. V. B. Study SFCA3006 dated 5/4/2001:
\\cdsesub1\nda21077\S_003\2001-05-04\clinstat\copd\sfca3006\sfca3006.pdf
 - SFCA3006 Data dated 5/4/2001:
\\CDSESUB1\N21077\S_003\2001-05-04\crt\datasets\Sfca3006\PFT.xpt
2. V. C. Study SFCA3007 dated 5/4/2001:
\\CDSESUB1\N21077\S_003\2001-05-04\clinstat\copd\sfca3007.pdf
 - SFCA3007 Data dated 5/4/2001:
\\CDSESUB1\N21077\S_003\2001-05-04\crt\datasets\SFCA3007\PFT.xpt
3. V. A. Study FLTA3025 dated 5/4/2001:
\\CDSESUB1\N21077\S_003\2001-05-04\clinstat\copd\flta3025.pdf
 - FLTA3025 Data dated 5/4/2001:
\\crt\datasets\flta3025\pft.xpt

Ted J. Guo, Ph.D., Div II/OEB, HFD-715

Lydia I Gilbert McClain, MD,
Eugene Sullivan, MD,
Charles Lee, MD,
Division of Pulmonary Drug Products (ODE II, HFD-570)

NDA, Clinical Studies

Summary

The evaluation of Studies SFCA3006, SFCA3007, and FLTA3025 based on the primary efficacy variables: A.M. pre-dosing and 2-hour post dosing FEV₁ changes from baseline measured at the 24th week concludes:

- Serevent[®] Diskus[®]: SAL50 proved to be statistically superior to placebo in Studies SFCA3006 and SFCA3007.
- Flovent[®] Diskus[®]: FP500 demonstrated statistical superiority to placebo in Studies SFCA3006 and FLTA3025.
- FP250 showed statistical superiority to placebo in Studies SFCA3007, but failed to do so in Study FLTA3025.
- The simultaneous comparisons between SFC50/500 to its two components, FP500 and SAL50, showed that SFC50/500 was statistically superior to both, indicating that significant contributions of FP500 and SAL50 to the combination, SFC50/500 has been demonstrated in one study.
- The simultaneous comparisons between SFC50/250 to its two components, FP250 and SAL50, showed that SFC50/250 was statistically superior to both, indicating that significant contributions of FP250 and SAL50 to the combination, SFC50/250 has been demonstrated in one study.
- Although perhaps not important with respect to the combination drug policy, SFC50/250 and SFC50/500 were shown superior to placebo in Studies SFCA3007 and SFCA3006, respectively.

This reviewer has utilized a conservative Bonferroni adjustment in studies SFCA3006 and SFCA3006 to adjust for the three possible supplemental NDA approvals that the comparisons might support (i.e., Serevent compared to placebo, Flovent compared to placebo, and the simultaneous comparison of Advair and its components). The statistical necessity for this adjustment is still a matter of policy deliberation, but the conclusions in this application do not rest on the outcome of this discussion.

In conclusion, the efficacy of SFC50/500, SFC50/250, SAL50, and FP500 was supported by the sponsor's data. However, the effectiveness of FP250 remains in question based on these three studies.

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Introduction

Advair Diskus®, 250/50 mcg and 500/50 mcg; Flovent Diskus®, 250 mcg and 500 mcg; and Serevent Diskus® 50 mcg are indicated for patients with chronic obstructive pulmonary disease (COPD). All are currently approved for asthma. No corticosteroid is currently approved for COPD. To support the efficacy claim for COPD for the above drugs, the sponsor, GlaxoSmithKline submitted the following placebo-controlled clinical studies (Table 1).

Table 1. Placebo-Controlled Studies Reviewed

Drug		Clinical Study No.	Type
Advair™ Diskus®	Fluticasone propionate/salmeterol inhalation powder, 250/50 mcg (SFC50/250) and 500/50 mcg (SFC50/500)	Studies SFCA3006, SFCA3007, and FLTA3025	Phase III
Flovent® Diskus™	Fluticasone propionate inhalation powder, 250 mcg (FP250) and 500 mcg (FP500)	Studies SFCA3006, SFCA3007, and FLTA3025	Phase III
Serevent® Diskus™	Salmeterol xinafoate inhalation powder, 50 mcg (SAL50)	Studies SFCA3006, SFCA3007, and FLTA3025	Phase III

For the approval of the three above drugs, the sponsor submitted three NDAs, each included three identical studies: SFCA3006, SFCA3007, and FLTA3025. The sponsor compared:

- In SFCA3006: SFC50/500, FP500, SAL50, and placebo
- In SFCA3007: SFC50/250, FP250, SAL50, and placebo
- In FLTA3025: FP500, FP250 and placebo

The three studies had similar designs. They were 24-week, double blind, placebo-controlled, parallel-group, multi-center studies. Patients satisfying the entrance criteria started a 2-week single blind run-in period when placebo was administered via Diskus®. Patients who met the randomization criteria were randomized to the pre-specified treatments. Clinic visits (also called sessions) were scheduled weekly for the first four weeks and biweekly thereafter for a total of 24 weeks. In Studies SFCA3006 and SFCA3007, the sponsor's final efficacy assessment was based on the endpoint (at week 24) analysis of the A.M. pre-dosing and 2-hour post dosing FEV₁ changes from baseline. Last available observations were carried forward to fill in missing observations. In Study FLTA3025, only A.M. pre-dosing FEV₁ changes from baseline was analyzed for the primary efficacy assessment.

This reviewer reanalyzed the sponsor's efficacy data, mainly focusing on the evaluation of the primary efficacy claim as specified in the protocol. Computer codes used to reanalyze the data are included in the Appendix for reference purposes. This reviewer's information inquiry to the sponsor and the sponsor's response are also included in the Appendix.

Note that the NDA was submitted 5/4/2001. During the review, this reviewer discovered that the sponsor failed to provide adequate explanations for the data it submitted. This problem became an obstacle for data reanalysis and evaluation. Upon request of this reviewer, the sponsor responded on 10/17/2001 and adequately addressed this reviewer's concern. In the response, the sponsor provided sufficient explanations for the data (See p. 49, Sponsor's Response to Statistical Questions).

This reviewer reviewed the sponsor's evidence presented in studies SFCA3006, SFCA3007, and FLTA3025 in NDA 21-077. These studies are identical in the other NDA submissions: 20-833 and 20-692.

Evaluation of sponsor's subgroup analyses based on patient status of poor reversibility can be found in the Appendix. The statistical significance based on the subgroup analysis may be underpowered, therefore, should be interpreted with caution.

This reviewer used liters as the measurement unit in reporting analysis results whereas the sponsor used milliliters.

Evaluation of Study SFCA3006

Characteristics of Study SFCA3006

Study SFCA3006 was a 24-week, double blind, placebo-controlled, parallel-group, multi-center study. The objective of the study was to assess the effectiveness of the Diskus[®] formulations of salmeterol 50mcg BID and fluticasone propionate 500mcg BID individually and in combination compared with placebo in COPD patients (p.3, sfca3006.pdf). Patients satisfying the entrance criteria started a 2-week single blind run-in period when placebo was administered via Diskus[®]. Patients who met the randomization criteria were randomized to one of the above treatments. Clinic visits (also called sessions) were scheduled weekly for the first four weeks and biweekly thereafter for a total of 24 weeks (p.5, response.pdf).

Efficacy was assessed by FEV₁ at A.M. pre-dosing and 2-hour post dosing. The primary efficacy variable was the "mean change from baseline in A.M. pre-dose and 2-hr post dose FEV₁," according to the sponsor. The primary (efficacy) analysis was based on FEV₁ data collected at the endpoint—the "last post baseline assessment excluding discontinuation."

Note that some tests (statistical comparisons) used the A.M. pre-dosing FEV₁ while others used the 2-hour post dosing FEV₁. The endpoint was "the last on-treatment assessment within one day of treatment cessation excluding data from the discontinuation visit (p.5, response.pdf)." Furthermore, patients had visits not within the protocol-specific window (say, 22 or 27 weeks) were included in the endpoint analysis (p.5, response.pdf).

Table 2 highlights the characteristics of this study.

Table 2. Characteristics of Study SFCA3006

Study	General Feature	Specific Characteristics
Protocol SFCA3006	24-week study	The study began with a 2-week placebo run-in period followed by a 24-week treatment period: 9/24/1998–5/5/2000.
	Randomized	
	Double-blind	
	Parallel-group	<ul style="list-style-type: none"> • Diskus[®] formulation of salmeterol 50mcg BID (denoted as SAL50) • Diskus[®] formulation of fluticasone propionate 500mcg BID (denoted as FP500) • Combination of salmeterol 50 mcg and fluticasone propionate 500 mcg, BID (denoted as SFC50/500) • Placebo
	Multi-center	64 centers
	Primary efficacy variable: Change from baseline in FEV ₁	Change from baseline in A.M. pre-dosing and 2-hr post dosing FEV ₁ at endpoint

Analysis of Patient Disposition and Accountability

For all efficacy analyses, the sponsor excluded Investigator (center) 1403 because “there was reason to believe the integrity of the data from subjects enrolled at this site may have been compromised (p.92, sfca3006.pdf).”

Patients were identified as reversible or non-reversible based on response to albuterol during the run-in period using ATS rules. Table 3 describes these rules.

Table 3. Determination of Reversibility (Study SFCA3006)

ATS rules for reversibility	%Change from A.M. pre-dosing of albuterol in FEV ₁ >12	%Change from A.M. pre-dosing of albuterol in FEV ₁ <12
Bronchodilator response ≥200mL	Reversible	Non-reversible
Bronchodilator response <200mL	Non-reversible	Non-reversible

Source: p.97, sfca3006.pdf

Patients were also classified as poorly reversible if they demonstrated a percent increase in percent-predicted FEV₁ of less than 10 after 4 puffs of albuterol inhalation at run-in period (p.77, sfca3006.pdf). The determinations for poor reversibility were done only on patients not in center 1403 (p.100, sfca3006.pdf). This rule, different from the ATS rule, is called the ERS rule.

Therefore, the ITT patients included both reversible and non-reversible patients, as well as poorly reversible and non-poorly reversible patients, depending on patient definitions. All ITT patients (excluding center #1403), who had available data, were included in the study population and efficacy analyses (p.95, sfca3006.pdf). Patients who had no baseline values or who had baseline values alone were excluded from the endpoint analysis.

Table 4 shows the number of ITT and completed patients reported in the NDA. This reviewer recalculated the numbers based on the submitted data (pft.xpt). The discrepancy shown is not considered important to the review.

Table 4. ITT Patients Excluding Center 1403 (Study SFCA3006)

	Placebo	SAL50	FP500	SFC50/500
ITT patients	181 (181)	160 (160)	168 (168)	165 (164)
Completed patients	112 (112)	115 (115)	100 (100)	113 (113)

Source: p.93, sfca3006.pdf. The numbers in parentheses are based on the submitted data; the SAS code can be found at SAS Code 1, Appendix

The sponsor pointed out that there were cases where some patients had only baseline values, while some with endpoint FEV₁ values had no baseline values during the trial-data-collection process (p.95, sfca3006.pdf). This reviewer also found cases in which the time was reported as invalid numbers. Moreover, some patients were classified as reversible and non-reversible at the same time. Taken all these facts into consideration, a data set with records considered creditable by this reviewer was created for this review. This way, the number of patients can be counted consistently across patient visits, and trust-worthy analyses can be achieved. To further observe the above cases, please see, in the Appendix, Data Examination: Study SFCA3006.

The following table shows the number of patients by treatment at baseline visit, based on this reviewer's analysis data. Note that, after excluding inconsistent and untrustworthy data records, there are fewer patients (643) in the reviewer's analysis data set than there are all randomized patients shown in Table 4. The exclusion of 16 patients (belonging to Center #1403) from the reviewer's analysis is in accordance with the sponsor's exclusion criteria in their analysis.

Table 5. Number of ITT Patients (Study SFCA3006)

Treatment				Total
PLACEBO	FP500	SAL50	SFC50/50	
No.	No.	No.	No.	No.
171	159	157	156	643

Source: Reviewer's analysis data set, S06rec. The SAS code can be found at SAS Code 2, Appendix

Table 6 shows the number of patients under definitions for reversibility and poor reversibility. Because of invalid classification, 1 patient had no identifiable status for reversibility, based on the ERS rule.

Table 6. ITT Patients Excluding Center 1403 (Study SFCA3006)

	Poorly Reversible Patient			Total
	NA	N	Y	
	No.	No.	No.	No.
Reversible patient/excl ctr 1403				
No	0	0	298	298
Yes	1	172	172	345
Total	1	172	470	643

Source: Reviewer's analysis data set, S06rec. The SAS code can be found at SAS Code 3, Appendix.

In the trial, on average, about 32% of the patients withdrew before reaching the 24th week. According to the sponsor, the endpoint analysis was done using the last available observations.

Table 7. Numbers and Percentages of Patients by Treatment and Status of Completeness (Study SFCA3006)

	Treatment								Total	
	PLACEBO		FP500		SAL50		SFC50/50		No.	%
	No.	%	No.	%	No.	%	No.	%		
Complete										
No	59	34.50	59	37.11	42	26.75	44	28.21	204	31.73
Yes	112	65.50	100	62.89	115	73.25	112	71.79	439	68.27
Total	171	100.00	159	100.00	157	100.00	156	100.00	643	100.00

Source: Reviewer's analysis data set, S06rec. The SAS code can be found at SAS Code 4, Appendix.

Table 8. Statistical Comparisons among Treatments (Study SFCA3006)

LS Mean (mL)	SFC50/500	FP500	SAL50	Placebo
SFC50/500 156 261		2-hr post dosing: $\Delta=261-138=123$ $P<0.001$	A.M. pre-dosing: $\Delta=156-107=49$ $P=0.012$	A.M. pre-dosing: $\Delta=156-(-4)=160$ $P<0.001$ 2-hr post dosing: $\Delta=261-28=233$ $P<0.001$
FP500 109 138				A.M. pre-dosing: $\Delta=109-(-4)=113$ $P<0.001$
SAL50 107 233				2-hr post dosing: $\Delta=233-28=205$ $P<0.001$
Placebo -4 28				

Source: NDA, p.107-p.112, sfca3006.pdf

The above table appears to indicate that SFC50/500 is more effective than its components: FP500 and SAL50 at 2-hr post dosing and A.M. pre-dosing, respectively. SFC50/500 also proves to be statistically superior to placebo. Sponsor's efficacy summary can be found in section 7.1, Efficacy Results (p.107-p.112, sfca3006.pdf), section 7.4, Efficacy Summary (p.152, sfca3006.pdf), and section 7.5, Efficacy Conclusions (p.158, sfca3006.pdf).

This reviewer reanalyzed the sponsor's data. The results of this reviewer's analysis can be found in the following tables: Table 9, Table 10, and Table 11. In the analysis (ANCOVA, including terms for treatment, center, and baseline FEV₁ as the covariate), Bonferroni's method was used to adjust for multiple comparisons. Table 9 shows the least-square (LS) means in FEV₁ changes from baseline. The SFC50/500 group had the greatest FEV₁ changes of all groups while the placebo group had the lowest.

Table 9. LS Means for Change in FEV₁ from Baseline at Endpoint (Study SFCA3006)

Treatment	LS Mean (Pre-dosing)	LS Mean (2-hour post dosing)
PLACEBO	0.00503753	0.04545894
FP500	0.11031039	0.14849693
SAL50	0.09439149	0.23401629
SFC50/500	0.16391829	0.27609990

Source: Reviewer's analysis data set, S06rec. The SAS code can be found at SAS Code 5, Appendix.

The ANOVA tables (Table 10 and Table 11) summarize three tests of interest. Multiple comparisons were adjusted using Bonferroni's method at the 0.0167 (=0.05/3) significance level for each test. This adjustment was chosen because this study can lead to three approvals. The test results in Table 10 and Table 11 are shown to be statistically significant. These findings are consistent with the sponsor's.

Table 10. ANOVA: Change in Pre-Dosing FEV₁ from Baseline at Endpoint (Study SFCA3006)

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
FP500 VS PLACEBO	1	0.88475328	0.88475328	17.03	<0.0001
SAL50 VS PLACEBO	1	0.63328584	0.63328584	12.19	0.0005
SFC50/500 VS SAL50	1	0.36286465	0.36286465	6.99	0.0084

Source: Reviewer's analysis data set, S06rec. The SAS code can be found at SAS Code 5, Appendix.

As stated in the Introduction, this reviewer uses liters as the measurement unit in reporting analysis results.

Table 11. ANOVA: Change in 2-Hour Post Dosing FEV₁ from Baseline at Endpoint (Study SFCA3006)

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
FP500 VS PLACEBO	1	0.84758654	0.84758654	13.77	0.0002
SAL50 VS PLACEBO	1	2.82006478	2.82006478	45.80	<.0001
SFC50/500 VS FP500	1	1.23674940	1.23674940	20.09	<.0001

Source: Reviewer's analysis data set, S06rec. The SAS code can be found at SAS Code 5, Appendix.

Reviewer's Conclusion

Based on the analyses of SFCA3006 data, this reviewer concludes:

- SAL50 and FP500, the two components of SFC50/500, proved to be statistically superior to placebo.
- The combination, SFC50/500 proved to be statistically superior to its components, FP500 and SAL50, indicating that the contributions of SAL50 and FP500 to the combination were adequately demonstrated in this study.

This reviewer's conclusions are consistent with the sponsor's.

Evaluation of Study SFCA3007

Characteristics of Study SFCA3007

Study SFCA3007 was a 24-week, double blind, placebo-controlled, parallel-group, multi-center study. The objective of the study was to assess the effectiveness of the Diskus® formulations of salmeterol 50mcg BID and fluticasone propionate 250mcg BID individually and in combination compared with placebo in COPD patients (p.3, sfca3007.pdf).

Table 12 highlights the characteristics of this study. Note that Study SFCA3007 had the same design as SFCA3006. Details regarding design are omitted in this session. The source of Table 12 comes from p.3, sfca3007.pdf.

Table 12. Characteristics of Study SFCA3007

Study	General Feature	Specific Characteristics
Protocol SFCA3007	24-week study	The study began with a 2-week placebo run-in period followed by a 24-week treatment period.
	Randomized	
	Double-blind	
	Parallel-group	<ul style="list-style-type: none"> • Diskus® formulation of salmeterol 50mcg BID (denoted as SAL50) • Diskus® formulation of fluticasone propionate 250mcg BID (denoted as FP250) • Combination of salmeterol 50 mcg and fluticasone propionate 250 mcg, BID (denoted as SFC50/250) • Placebo
	Multi-center	75 centers
	Primary efficacy variable: Change from baseline in FEV ₁	Change from baseline in A.M. pre-dosing and 2-hr post dosing FEV ₁ at endpoint

Analysis of Patient Disposition and Accountability

Patients were identified as reversible or non-reversible based on response to albuterol during the run-in period using ATS rules (p.85, sfca3007.pdf). Please see Table 3 in the review section for SFCA3006. Patients were also classified as poorly reversible, using the same definition as that for SFCA3006 (p.67, sfca3007.pdf). The ITT patients included both reversible and non-reversible patients, as well as poorly reversible and non-poorly reversible patients, depending on the definitions.

All ITT patients, who had available data, were included in the study population and efficacy analyses (p.83, sfca3007.pdf). Patients who had no baseline values or who had baseline values alone were excluded from the endpoint analysis.

Table 13 shows the number of ITT and completed patients reported in the NDA. This reviewer recalculated the numbers based on the submitted data (pft.xpt). There is no discrepancy in the number of patients with valid treatment codes. There is one patient without a treatment code.

Table 13. ITT Patients (Study SFCA3007)

	Placebo	SAL50	FP250	SFC50/250
ITT patients	185 (185)	177 (177)	183 (183)	178 (178)
Completed patients	126 (126)	121 (121)	133 (133)	125 (125)

Source: p.81, sfca3007.pdf. The numbers in parentheses are based on the submitted data; the SAS code can be found at SAS Code 6, Appendix

The sponsor pointed out that there were cases where some patients had only baseline values, while some with endpoint FEV₁ values had no baseline values during the trial-data-collection process (p.83, sfca3007.pdf). This reviewer also found cases in which the time was reported as invalid numbers. Moreover, some patients were classified as reversible and non-reversible at the same time. Taken all these facts into consideration, a data set with records considered creditable by this reviewer was created for this review. This way, the number of patients can be counted consistently across patient visits, and trust-worthy analyses can be achieved. To further observe the above cases, please see, in the Appendix, Data Examination: Study SFCA3007.

The following table shows the number of patients by treatment at baseline visit, based on this reviewer's analysis data. Note that, after excluding inconsistent and untrustworthy data records, there are fewer patients (678) in the reviewer's analysis data set than there are all randomized patients shown in Table 13.

Table 14. Number of ITT Patients (Study SFCA3007)

Treatment				Total
PLACEBO	FP250	SAL50	SFC50/250	
No.	No.	No.	No.	No.
170	173	168	167	678

Source: Reviewer's analysis data set, S07rec. The SAS code can be found at SAS Code 7, Appendix

Table 15 shows the number of patients under definitions for reversibility and poor reversibility. Because of invalid classification, 1 patient had no identifiable status for reversibility—this patient was not classified either by ATS or ERS rules.

Table 15. ITT Patients Excluding Center 1403 (Study SFCA3007)

	Poorly reversible patient			Total
	NA	N	Y	
	No.	No.	No.	No.
Reversible patient				
No	0	0	302	302
Yes	0	224	151	375
NA	1	0	0	1
Total	1	224	453	678

Source: Reviewer's analysis data set, S07rec. The SAS code can be found at SAS Code 8, Appendix.

In the trial, on average, about 27% of the patients withdrew before reaching the 24th week. According to the sponsor, the endpoint analysis was done using the last available observations.

Table 16. Numbers and Percentages of Patients by Treatment and Status of Completeness (Study SFCA3007)

	Treatment								Total	
	PLACEBO		FP250		SAL50		SFC50/250			
	No.	%	No.	%	No.	%	No.	%	No.	%
Complete										
No	46	27.06	42	24.28	47	27.98	46	27.54	181	26.70
Yes	124	72.94	131	75.72	121	72.02	121	72.46	497	73.30
Total	170	100.00	173	100.00	168	100.00	167	100.00	678	100.00

Source: Reviewer's analysis data set, S07rec. The SAS code can be found at SAS Code 9, Appendix.

Evaluation of Primary Efficacy Analysis

The sponsor based its primary efficacy analysis on patients who were randomized and had taken at least one dose of study medication (p.76, sfca3007.pdf). Patients were excluded if they had treatment-day-one data alone or their treatment-day-one data were missing (p.76, sfca3007.pdf).

The primary efficacy variable was the change from baseline in A.M. pre-dosing and 2-hour post dosing FEV₁ at endpoint. The sponsor defined the endpoint as the final evaluable measurement for the patient. In particular, for patients who completed the study at Week 24, it was the final on-treatment measurement. For those who withdrew, it was the last evaluable measurement taken before the withdrawal. The endpoint analysis used the last valid FEV₁ measurement during the treatment period for all patients (p.81 and p.107, sfca3007.pdf).

The following points summarize the statistical comparisons (Quoted and modified from p.71, sfca3007.pdf, also Protocol p.7132, sfca3007.pdf).

- SFC50/250 vs. SAL50: A.M. pre-dosing FEV₁ (to evaluate the contribution of FP250 to the combination product)
- FP250 vs. placebo: A.M. pre-dosing FEV₁ (to examine efficacy of the individual component)
- SFC50/250 vs. FP250: 2-hour post dosing FEV₁ (to evaluate the contribution of SAL50 to the combination product)
- SAL50 vs. placebo: 2-hour post dosing FEV₁ (to examine efficacy of the individual component)

The baseline was the A.M. pre-dosing FEV₁ at treatment-day one. The sponsor applied the analysis of covariance (ANCOVA) with baseline FEV₁ as the covariate. The ANCOVA model also included terms of treatment and investigator (center) (p.71, sfca3007.pdf).

Table 17 highlights the sponsor's statistical analyses. The explanation of this table is the same as that for Table 8.

Table 17. Statistical Comparisons among Treatments (Study SFCA3007)

LS Mean (mL)	SFC50/250	FP250	SAL50	Placebo
SFC50/250 165 281		2-hr post dosing: $\Delta=281-147=134$ $P<0.001$	A.M. pre-dosing: $\Delta=165-91=74$ $P=0.012$	A.M. pre-dosing: $\Delta=165-1=164$ $P<0.001$ 2-hr post dosing: $\Delta=281-58=223$ $P<0.001$
FP250 109 147				A.M. pre-dosing: $\Delta=109-1=108$ $P<0.001$
SAL50 91 200				2-hr post dosing: $\Delta=200-58=142$ $P<0.001$
Placebo 1 58				

Source: NDA, p.96, sfca3007.pdf

The above table appears to indicate that SFC50/250 is more effective than its components: FP250 and SAL50 at 2-hr post dosing and A.M. pre-dosing, respectively. SFC50/250 also proves to be statistically superior to placebo. Sponsor's efficacy summary can be found on section 7.1, Efficacy Results (p.96-p.101, sfca3007.pdf) and section 7.3, Efficacy Summary (p.136, sfca3007.pdf).

This reviewer reanalyzed the sponsor's data. The results of this reviewer's analysis can be found in Table 18, Table 19, and Table 20. In the analysis (ANCOVA, including terms for treatment, center, and baseline FEV₁ as the covariate), Bonferroni's method was used to adjust for multiple comparisons. Table 18 shows the least-square (LS) means in FEV₁ changes from baseline. The SFC50/250 group had the greatest FEV₁ changes of all groups while placebo group had the lowest.

Table 18. LS Means for Change in FEV₁ from Baseline at Endpoint (Study SFCA3007)

Treatment	LS Mean (Pre-dosing)	LS Mean (2-hour post dosing)
PLACEBO	-0.00344447	0.05968568
FP250	0.10824114	0.14900469
SAL50	0.08880820	0.19964938
SFC50/250	0.15823705	0.27458291

Source: Reviewer's analysis data set, S07rec. The SAS code can be found at SAS Code 10, Appendix.

The ANOVA tables (Table 19 and Table 20) summarize three tests of interest. Multiple comparisons were adjusted using Bonferroni's method at the 0.0167 (=0.05/3) significance level for each test. The test results in both tables are shown to be statistically significant. These findings are consistent with the sponsor's.

Table 19. ANOVA: Change in Pre-Dosing FEV₁ from Baseline at Endpoint (Study SFCA3007)

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
FP250 VS PLACEBO	1	1.02511563	1.02511563	16.62	<.0001
SAL50 VS PLACEBO	1	0.68904409	0.68904409	11.17	0.0009
SFC50/250 VS SAL50	1	0.38750707	0.38750707	6.28	0.0125

Source: Reviewer's analysis data set, S07rec. The SAS code can be found at SAS Code 10, Appendix.

Table 20. ANOVA: Change in 2-Hour Post Dosing FEV₁ from Baseline at Endpoint (Study SFCA3007)

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
FP250 VS PLACEBO	1	0.65564117	0.65564117	9.68	0.0020
SAL50 VS PLACEBO	1	1.58606105	1.58606105	23.40	<.0001
SFC50/250 VS FP250	1	1.28502046	1.28502046	18.96	<.0001

Source: Reviewer's analysis data set, S07rec. The SAS code can be found at SAS Code 10, Appendix.

Reviewer's Conclusion

Based on the analyses of SFCA3007 data, this reviewer concludes:

- SAL50 and FP250, the two components of SFC50/250, prove to be statistically superior to placebo.
- The combination, SFC50/250 proves to be statistically superior to its components, FP250 and SAL50, indicating that the contributions of SAL50 and FP250 to the combination were adequately demonstrated in this study.

This reviewer's conclusions are consistent with the sponsor's.

Evaluation of Study FLTA3025

Characteristics of Study FLTA3025

Study FLTA3025 was a 24-week, double blind, placebo- controlled, parallel-group, multi-center study. The objective of the study was to assess the effectiveness of the Diskus® formulations of fluticasone propionate 500 mcg BID and 250 mcg BID, compared with placebo, in COPD patients (p.3, Flta3025.pdf).

Table 21 highlights the characteristics of this study. Note that Study FLTA3025 had the same design as SFCA3006. Details regarding design are omitted in this session. The source of Table 21 comes from p.3, Flta3025.pdf.

Table 21. Characteristics of Study FLTA3025

Study	General Feature	Specific Characteristics
Protocol FLTA3025	24-week study	The study began with a 2-week placebo run-in period followed by a 24-week treatment period.
	Randomized	
	Double-blind	
	Parallel-group	<ul style="list-style-type: none"> • Diskus® formulation of fluticasone propionate 500 mcg BID (denoted as FP500) • Diskus® formulation of fluticasone propionate 250 mcg BID (denoted as FP250) • Placebo
	Multi-center	55 centers
	Primary efficacy variable: Change from baseline in FEV ₁	Change from baseline in A.M. pre-dosing FEV ₁ at endpoint

Source: NDA p.7, Flta3025.pdf

Analysis of Patient Disposition and Accountability

Patients were identified as reversible or non-reversible based on response to albuterol during the run-in period using ATS rules (p.79, Flta3025.pdf). For definition, please see Table 3 in the review section for SFCA3006. Patients were also classified as poorly reversible, using the same definition as that for SFCA3006 (p.62, Flta3025.pdf). The ITT patients included both reversible and non-reversible patients, as well as poorly reversible and non-poorly reversible patients, depending on the definitions.

All ITT patients, who had available data, were included in the study population and efficacy analyses. Patients who had no baseline values or who had baseline values alone were excluded from the endpoint analysis.

Table 22 shows the number of ITT and completed patients reported in the NDA. This reviewer recalculated the numbers based on the submitted data (pft.xpt). There are some discrepancies in the number of patients.

Table 22. ITT Patients (Study FLTA3025)

	Placebo	FP250	FP500
ITT patients	206 (205)	216 (216)	218 (218)
Completed patients	127(125)	140 (139)	147 (146)

Source: p.75, Flta3025.pdf. The numbers in parentheses are based on the submitted data; the SAS code can be found at SAS Code 11, Appendix

The sponsor pointed out that there were cases where some patients had only baseline values, while some with endpoint FEV₁ values had no baseline values during the trial-data-collection process (p.77, Flta3025.pdf). This reviewer also found cases in which the time was reported as invalid numbers. Moreover, some patients were classified as reversible and non-reversible at the same time. Taken all these facts into consideration, a data set with records considered creditable by this reviewer was created for this review. This way, the number of patients can be counted consistently across patient visits, and trust-worthy analyses can be achieved. To further observe the above cases, please see, in the Appendix, Data Examination: Study FLTA3025.

The following table shows the number of patients by treatment at baseline visit, based on this reviewer's analysis data. Note that, after excluding inconsistent and untrustworthy data records, there are fewer patients (620) in the reviewer's analysis data set than there are all randomized patients shown in Table 22.

Table 23. Number of ITT Patients (Study FLTA3025)

	Treatment			Total
	PLACEBO	FP250	FP500	
	No.	No.	No.	No.
Total	199	211	210	620

Source: Reviewer's analysis data set, S25rec. The SAS code can be found at SAS Code 12, Appendix

The following Table 24 shows the number of patients under definitions for reversibility and poor reversibility. Because of invalid classification, a total of five patients had no identifiable status for reversibility, among whom four patients could not be classified as reversible or non-reversible by ATS rules and five could not be determined as poorly reversible or non-poorly reversible by the ERS rule.

Table 24. ITT Patients Excluding Center 1403 (Study FLTA3025)

	Poorly reversible patient			Total
	NA	N	Y	
	No.	No.	No.	No.
Reversible patient				
No	0	0	254	254
Yes	1	216	145	362
NA	4	0	0	4
Total	5	216	399	620

Source: Reviewer's analysis data set, S25rec. The SAS code can be found at SAS Code 13, Appendix.

In the trial, on average, about 34% of the patients withdrew before reaching the 24th week. According to the sponsor, the endpoint analysis was done using the last available observations.

Table 25. Numbers and Percentages of Patients by Treatment and Status of Completeness (Study FLTA3025)

	Treatment						Total	
	PLACEBO		FP250		FP500		No.	%
	No.	%	No.	%	No.	%		
Complete								
No	74	37.19	72	34.12	64	30.48	210	33.87
Yes	125	62.81	139	65.88	146	69.52	410	66.13
Total	199	100.00	211	100.00	210	100.00	620	100.00

Source: Reviewer's analysis data set, S25rec. The SAS code can be found at SAS Code 14, Appendix.

Evaluation of Primary Efficacy Analysis

The sponsor based its primary efficacy analysis on patients who were randomized and had taken at least one dose of study medication. Patients were excluded if they had treatment-day-one data alone or their treatment-day-one data were missing.

The primary efficacy variable was the change from baseline in A.M. pre-dosing FEV₁ at endpoint. The sponsor defined the endpoint as the final evaluable measurement for the patient. In particular, for patients who completed the study at Week 24, it was the final on-treatment measurement. For those who withdrew, it was the last evaluable measurement taken before the withdrawal. The endpoint analysis used the last valid FEV₁ measurement during the treatment period for all patients (p.77, Flta3025.pdf).

The following points summarize the statistical comparisons (Quoted and modified from p.66, Flta3025.pdf). "The primary comparison was between the two dose levels of FP Diskus® (250mcg BID and 500mcg BID) and placebo."

The baseline was the A.M. pre-dosing FEV₁ at treatment-day one. The sponsor applied the analysis of covariance (ANCOVA) with baseline FEV₁ as the covariate. The ANCOVA model also included terms of treatment and investigator (center) (p.5301, Flta3025.pdf).

Table 26 highlights the sponsor's statistical analyses. Explanation of this table is the same as that for Table 8 (SFCA3006).

Table 26. Statistical Comparisons among Treatments (Study FLTA3025)

LS Mean (mL)	FP500	FP250	Placebo
FP500 61			A.M. pre-dosing: Δ=61-11=50 P<0.01
FP250 38			A.M. pre-dosing: Δ=38-11=27 P>0.05
Placebo 11			

Source: NDA, p.91, Flta3025.pdf

The above table appears to indicate that PF500 is more effective than placebo (P<0.01). The difference between FP250 and placebo is not statistically significant. No comparison was made between FP500 and FP250 (p.91, Flta3025.pdf).

This reviewer reanalyzed the sponsor's data. The results of this reviewer's analysis can be found in Table 27 and Table 28. In the analysis (ANCOVA, including terms for treatment, center, and baseline FEV₁ as the covariate), Dunnett's method was used to adjust for multiple comparisons. Table 27 shows the least-square (LS) means in FEV₁ changes from baseline.

Table 27. LS Means for Change in Pre-Dosing FEV₁ from Baseline at Endpoint (Study FLTA3025)

Treatment	LS Mean (Pre-dosing)
PLACEBO	0.00695199
FP250	0.03905509
FP500	0.06363387

Source: Reviewer's analysis data set, S25rec. The SAS code can be found at SAS Code 15, Appendix.

Table 28 shows that FP500 was statistically superior to placebo, while the superiority for FP250 to placebo was not shown in this reviewer's analysis.

Table 28. ANOVA: Change in Pre-Dosing FEV₁ from Baseline at Endpoint (Study FLTA3025)

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
FP500 VS PLACEBO	1	0.32141527	0.32141527	6.63	0.0103
FP250 VS PLACEBO	1	0.10389072	0.10389072	2.14	0.1437

Source: Reviewer's analysis data set, S25rec. The SAS code can be found at SAS Code 15, Appendix.

Table 29 shows 95% simultaneous confidence intervals for the difference in FEV₁ change from baseline at the endpoint between the active treatments and placebo. The Dunnett's adjustment for multiple comparisons was used. The results are consistent with those described in Table 28 above.

Table 29. Confidence Intervals for Difference in FEV₁ Change from Baseline at Endpoint (FLTA3025)

Treatment Comparison	LS Mean	LS Mean Diff	LowerCL	UpperCL
FP250 - PLACEBO	0.0321	0.0391 - 0.0070	-0.0165	0.0807
FP500 - PLACEBO	0.0567	0.0636 - 0.0070	0.0079	0.1055

Reviewer's Conclusion

FP500 proved to be statistically superior to placebo, while the statistical superiority of FP250 to placebo was not supported by the sponsor's data. This reviewer's conclusion is consistent with the sponsor's.

Conclusions

The evaluation of Studies SFCA3006, SFCA3007, and FLTA3025 based on the primary efficacy variables: A.M. pre-dosing and 2-hour post dosing FEV₁ changes from baseline measured at the 24th week concludes:

- Serevent[®] Diskus[®]: SAL50 proved to be statistically superior to placebo in Studies SFCA3006 and SFCA3007.
- Flovent[®] Diskus[®]: FP500 demonstrated statistical superiority to placebo in Studies SFCA3006 and FLTA3025.
- FP250 showed statistical superiority to placebo in Studies SFCA3007, but failed to do so in Study FLTA3025.
- The simultaneous comparisons between SFC50/500 to its two components, FP500 and SAL50, showed that SFC50/500 was statistically superior to both, indicating that significant contributions of FP500 and SAL50 to the combination, SFC50/500 has been demonstrated in one study.
- The simultaneous comparisons between SFC50/250 to its two components, FP250 and SAL50, showed that SFC50/250 was statistically superior to both, indicating that significant contributions of FP250 and SAL50 to the combination, SFC50/250 has been demonstrated in one study.
- Although perhaps not important with respect to the combination drug policy, SFC50/250 and SFC50/500 were shown superior to placebo in Studies SFCA3007 and SFCA3006, respectively.

This reviewer has utilized a conservative Bonferroni adjustment in studies SFCA3006 and SFCA3006 to adjust for the three possible supplemental NDA approvals that the comparisons might support (i.e., Serevent compared to placebo, Flovent compared to placebo, and the simultaneous comparison of Advair and its components). The statistical necessity for this adjustment is still a matter of policy deliberation, but the conclusions in this application do not rest on the outcome of this discussion.

In conclusion, the efficacy of SFC50/500, SFC50/250, SAL50, and FP500 was supported by the sponsor's data. However, the effectiveness of FP250 remains in question based on these three studies.

Appendix

Data Examination: Study SFCA3006

Valid time should be either 0 or 2. The following patient records had invalid time of PFT.

Table 30. Invalid Time (Study SFCA3006)

Center	Treatment	Patient	Weeks on study	Visit	Time
X	SFC50/500	9709	13	09	-0.50
	FP500	11338	0	BASELINE	-0.50
	SAL50	11335	0	BASELINE	-0.50

Source Code:

```
ods listing close;
ods html path='c:\windows\temp\'
      body='h.htm';
proc sql noprint;
  create table wrongTime
  as select center, treat, patient, weeksstd, visit, time
  from nd4d.pft06a
  where time not in (0,2) and visit^='13';
proc print data=_last_ label noobs;
title; footnote;
run;
ods html close;
ods listing;
```

The following patient records had missing baseline values.

Table 31. Missing Baseline Values (Study SFCA3006)

Center	Treatment	Patient	Weeks on study	Visit	Time	FEV1: Baseline
/	FP500	10931	12	FINAL	0.00	.
	FP500	10931	12	FINAL	2.00	.
	SFC50/500	10932	24	FINAL	0.00	.
	SFC50/500	10932	24	FINAL	2.00	.

Source Code:

```
ods listing close;
ods html path='c:\windows\temp\'
      body='h.htm';
proc sql noprint;
  create table nobaseline
  as select center, treat, patient, weeksstd, visit, time, fevbase
  from nd4d.pft06a
  where visit='99' and
  patient not in (select distinct patient from nd4d.pft06a
  where visit='02');
```

```
proc print data=_last_ label noobs;
title; footnote;
run;
ods html close;
ods listing;
```

The following patient records had missing endpoint values. This means that the LOCF did not or could not apply to these patients.

Table 32. Missing Endpoint Values (Study SFCA3006)

Center	Treatment	Patient	Weeks on study	Visit	Time	FEV1
	PLACEBO	8949	0	BASELINE	0.00	1.460
	PLACEBO	8949	0	BASELINE	2.00	1.440
	SAL50	8927	0	BASELINE	0.00	0.570
	SAL50	8927	0	BASELINE	2.00	0.700
	PLACEBO	9099	0	BASELINE	0.00	1.020
	PLACEBO	9099	0	BASELINE	2.00	0.950
	PLACEBO	15544	0	BASELINE	0.00	1.420
	PLACEBO	15544	0	BASELINE	2.00	1.620
	FP500	15533	0	BASELINE	0.00	0.810
	FP500	15533	0	BASELINE	2.00	0.850
	SFC50/500	15768	0	BASELINE	0.00	1.810
	SFC50/500	15768	0	BASELINE	2.00	2.030
	PLACEBO	9251	0	BASELINE	0.00	0.600
	PLACEBO	9251	0	BASELINE	2.00	0.620
	PLACEBO	9289	0	BASELINE	0.00	0.650
	SFC50/500	9385	0	BASELINE	0.00	1.350
	SFC50/500	9385	0	BASELINE	2.00	1.380
	PLACEBO	9494	0	BASELINE	0.00	1.850
	PLACEBO	9793	0	BASELINE	0.00	0.640
	PLACEBO	9793	0	BASELINE	2.00	0.720
	FP500	9781	0	BASELINE	0.00	0.680
	FP500	9781	0	BASELINE	2.00	0.640
	FP500	9760	0	BASELINE	0.00	0.970
	FP500	9760	0	BASELINE	2.00	0.860
	FP500	9836	0	BASELINE	0.00	0.550
	FP500	9836	0	BASELINE	2.00	0.580
	PLACEBO	9893	0	BASELINE	0.00	0.690
	PLACEBO	9893	0	BASELINE	2.00	0.590

Center	Treatment	Patient	Weeks on study	Visit	Time	FEV1
	SFC50/500	9888	0	BASELINE	0.00	1.340
	SFC50/500	9888	0	BASELINE	2.00	1.440
	FP500	10087	0	BASELINE	0.00	0.870
	FP500	10087	0	BASELINE	2.00	0.850
	SFC50/500	10082	0	BASELINE	0.00	0.680
	SFC50/500	10082	0	BASELINE	2.00	1.020
	SFC50/500	10355	0	BASELINE	0.00	1.650
	SFC50/500	10355	0	BASELINE	2.00	2.030
	FP500	10377	0	BASELINE	0.00	0.890
	FP500	10377	0	BASELINE	2.00	1.040
	PLACEBO	10628	0	BASELINE	0.00	0.690
	PLACEBO	10628	0	BASELINE	2.00	0.690
	FP500	10835	0	BASELINE	0.00	0.880
	FP500	10835	0	BASELINE	2.00	0.960
	SFC50/500	15919	0	BASELINE	0.00	0.990
	SFC50/500	15919	0	BASELINE	2.00	1.070
	PLACEBO	11283	0	BASELINE	0.00	1.370
	PLACEBO	11283	0	BASELINE	2.00	1.340
	SFC50/500	11378	0	BASELINE	0.00	0.720
	SFC50/500	11378	0	BASELINE	2.00	0.880

Source Code.

```
ods listing close;
ods html path='c:\windows\temp\'
      body='h.htm';
proc sql noprint;
  create table noendpoint
  as select center,treat,patient,weeksstd,visit,time,fev
  from nd4d.pft06a
  where visit='02' and
  patient not in (select distinct patient from nd4d.pft06a
  where visit='99');
proc print data=_last_ label noobs;
title; footnote;
run;
ods html close;
ods listing;
```

Data Examination: Study SFCA3007

Valid time should be either 0 or 2. The following patient records had invalid time of PFT.

Table 33. Invalid Time (Study SFCA3007)

Center	Treatment	Patient	Weeks on study	Visit	Time
	SFC50/250	12406	24	WEEK 24	.
	SFC50/250	12406	24	WEEK 24	.
	SFC50/250	12406	24	FINAL	.
	SFC50/250	12406	24	FINAL	.
	SFC50/250	16629	25	WEEK 24	.
	SFC50/250	16629	25	FINAL	.
	PLACEBO	16682	24	WEEK 24	.
	PLACEBO	16682	24	FINAL	.
	FP250	13527	24	WEEK 24	.
	FP250	13527	24	WEEK 24	.
	FP250	13527	24	FINAL	.
	FP250	13527	24	FINAL	.
	SFC50/250	13777	25	WEEK 24	.
	SFC50/250	13777	25	FINAL	.
	PLACEBO	13931	25	WEEK 24	.
	PLACEBO	13931	25	FINAL	.
	SFC50/250	14135	25	WEEK 24	.
	SFC50/250	14135	25	FINAL	.
	FP250	14453	23	WEEK 24	.
	FP250	14453	23	WEEK 24	.
	FP250	14453	23	FINAL	.
	FP250	14453	23	FINAL	.

Source Code:

```
ods listing close;
ods html path='c:\windows\temp\'
      body='h.htm';
proc sql noprint;
  create table wrongTime
  as select center, treat, patient, weeksstd, visit, time
  from nd4d.pft07a
  where time not in (0,2) and visit^='13';
proc print data=_last_ label noobs;
title; footnote;
```

run;
ods html close;
ods listing;

The following patient records had missing endpoint values. This means that the LOCF did not or could not apply to these patients.

Table 34. Missing Endpoint Values (Study SFCA3007)

Center	Treatment	Patient	Weeks on study	Visit	Time	FEV1
	PLACEBO	15035	0	BASELINE	0.00	0.910
	PLACEBO	15035	0	BASELINE	2.00	1.290
	PLACEBO	15037	0	BASELINE	0.00	0.960
	PLACEBO	15037	0	BASELINE	2.00	1.070
	FP250	15042	0	BASELINE	0.00	0.990
	FP250	15042	0	BASELINE	2.00	1.160
	FP250	14032	0	BASELINE	0.00	1.770
	FP250	14032	0	BASELINE	2.00	2.030
	SFC50/250	14728	0	BASELINE	0.00	0.830
	SFC50/250	14728	0	BASELINE	2.00	0.780
	SAL50	15079	0	BASELINE	0.00	1.810
	SAL50	15079	0	BASELINE	2.00	1.580
	PLACEBO	12041	0	BASELINE	0.00	1.730
	PLACEBO	12041	0	BASELINE	2.00	1.740
	PLACEBO	12055	0	BASELINE	0.00	0.630
	PLACEBO	12055	0	BASELINE	2.00	0.660
	SAL50	12232	0	BASELINE	0.00	1.420
	SAL50	12232	0	BASELINE	2.00	1.820
	SAL50	15129	0	BASELINE	0.00	1.110
	SAL50	15129	0	BASELINE	2.00	1.330
	PLACEBO	12381	0	BASELINE	0.00	1.300
	PLACEBO	12381	0	BASELINE	2.00	1.210
	PLACEBO	12393	0	BASELINE	0.00	0.780
	PLACEBO	12393	0	BASELINE	2.00	0.720
	SFC50/250	12385	0	BASELINE	0.00	1.300
	SFC50/250	12385	0	BASELINE	2.00	1.550
	SAL50	12540	0	BASELINE	0.00	0.910
	SAL50	12540	0	BASELINE	2.00	0.960

Center	Treatment	Patient	Weeks on study	Visit	Time	FEV1
	SFC50/250	12544	0	BASELINE	0.00	0.580
	SFC50/250	12544	0	BASELINE	2.00	0.750
	PLACEBO	17381	0	BASELINE	0.00	0.540
	PLACEBO	17381	0	BASELINE	2.00	0.550
	PLACEBO	17280	0	BASELINE	0.00	1.360
	PLACEBO	17280	0	BASELINE	2.00	1.240
	SAL50	17282	0	BASELINE	0.00	1.220
	SAL50	17282	0	BASELINE	2.00	1.350
		12741		BASELINE	0.00	0.490
	SAL50	12800	0	BASELINE	0.00	0.500
	SAL50	12800	0	BASELINE	2.00	0.840
	PLACEBO	16589	0	BASELINE	0.00	2.390
	PLACEBO	16589	0	BASELINE	2.00	2.440
	FP250	16638	0	BASELINE	0.00	2.120
	FP250	16638	0	BASELINE	2.00	2.000
	SAL50	16635	0	BASELINE	0.00	0.750
	SAL50	16635	0	BASELINE	2.00	0.700
	SAL50	16642	0	BASELINE	0.00	1.190
	SAL50	16642	0	BASELINE	2.00	1.180
	SFC50/250	13138	0	BASELINE	0.00	0.990
	SFC50/250	13138	0	BASELINE	2.00	1.110
	SAL50	13227	0	BASELINE	0.00	0.730
	SAL50	13227	0	BASELINE	2.00	0.930
	FP250	13335	0	BASELINE	0.00	0.650
	SFC50/250	16699	0	BASELINE	0.00	1.080
	SFC50/250	16699	0	BASELINE	2.00	1.230
	SFC50/250	13741	0	BASELINE	0.00	1.780
	SFC50/250	13741	0	BASELINE	2.00	1.440
	FP250	13836	0	BASELINE	0.00	1.000
	FP250	13836	0	BASELINE	2.00	1.110
	PLACEBO	14077	0	BASELINE	0.00	0.960
	PLACEBO	14077	0	BASELINE	2.00	1.250
	FP250	14145	0	BASELINE	0.00	0.880

Center	Treatment	Patient	Weeks on study	Visit	Time	FEV1
	FP250	14145	0	BASELINE	2.00	0.750
	SFC50/250	14828	0	BASELINE	0.00	1.460
	PLACEBO	14228	0	BASELINE	0.00	1.030
	PLACEBO	14228	0	BASELINE	2.00	0.970
	PLACEBO	14381	0	BASELINE	0.00	1.170
	PLACEBO	14381	0	BASELINE	2.00	1.360
	PLACEBO	14386	0	BASELINE	0.00	0.960
	PLACEBO	14386	0	BASELINE	2.00	0.820
	FP250	14484	0	BASELINE	0.00	1.010
	FP250	14484	0	BASELINE	2.00	1.030
	FP250	14538	0	BASELINE	0.00	0.470
	FP250	14538	0	BASELINE	2.00	0.500

Source Code:

```
ods listing close;
ods html path='c:\windows\temp\'
      body='h.htm';
proc sql noprint;
  create table noendpoint
  as select center,treat,patient,weeksstd,visit,time,fev
  from nd4d.pft07a
  where visit='02' and
  patient not in (select distinct patient from nd4d.pft07a
  where visit='99');
proc print data=_last_ label noobs;
title; footnote;
run;
ods html close;
ods listing;
```

Data Examination: Study FLTA3025

The following patient records had missing endpoint values. This means that the LOCF did not or could not apply to these patients.

Table 35. Missing Endpoint Values (Study FLTA3025)

Center	Treatment	Patient	Visit	FEV1
	FP250	37276	BASELINE	1.420
	FP500	36223	BASELINE	1.400
	FP500	36225	BASELINE	2.340
	FP500	36431	BASELINE	1.230
	PLACEBO	36521	BASELINE	1.130
	FP500	36824	BASELINE	2.130
	FP250	36875	BASELINE	2.730
	FP250	38726	BASELINE	1.250
	FP500	37031	BASELINE	1.000
	PLACEBO	37073	BASELINE	0.560
	FP500	37529	BASELINE	0.850
	PLACEBO	37737	BASELINE	0.740
	FP500	37723	BASELINE	0.770
	PLACEBO	37171	BASELINE	0.780
	PLACEBO	38485	BASELINE	1.210
	FP250	38475	BASELINE	0.570
	FP500	38473	BASELINE	1.550

Source Code:

```
ods listing close;
ods html path='c:\windows\temp\'
      body='h.htm';
proc sql noprint;
  create table noendpoint
  as select center,treat,patient,visit,fev
  from nd4d.pft25a
  where visit='02' and
  patient not in (select distinct patient from nd4d.pft25a
  where visit='99');
proc print data=_last_ label noobs;
title; footnote;
run;
ods html close;
ods listing;
```

14 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

Withheld Track Number: Statistical-21-073

5003

Notes on Major Events During the Review

The electronic version of the original NDA was submitted by the sponsor to the Agency's Electronic Document Room (EDR) dated 5/4/2001.

This reviewer encountered difficulties in statistical evaluation using sponsor's data. Because of inadequate explanation of the data, this reviewer was not able to gather information and perform confirmatory analyses on efficacy and safety. This reviewer prepared a written information inquiry combining with other inquiries from the reviewing medical reviewers and communicated to the sponsor following a teleconference with the sponsor dated 9/10/2001 (See p.47, This Reviewer's Information Inquiry Regarding Data).

The sponsor responded to the above information inquiry on 10/17/2001 (See p.49, Sponsor's Response to Statistical Questions). The sponsor provided overall acceptable answers to this reviewer's questions and provided generally adequate explanations of the data. Consequently, this reviewer was able to verify the sponsor's statistical findings.

This Reviewer's Information Inquiry Regarding Data

The questions listed here are related to the data submission. They are not necessary in the order of importance to this statistical reviewer. These questions are raised regarding data sets in Study SFCA3006. Similar questions would apply to the data sets for SFCA3007, FLTA3025. To better understand the sponsor's statistical analysis, this reviewer requests the following clarifications.

1. There is not a variable for the week or visit number. A variable, SESS appears to serve as an indicator for visit. How was the variable SESS defined and what does SESS=2.9 mean? If the primary efficacy evaluation was based on FEV₁ measurements at Week 24, how do you handle the patients last measured earlier or later than 24 weeks in your data presentation and analysis (e.g., 22 weeks or 27 weeks)?
2. The variable, PGMPOP labeled "PR/excl. invid. 1403?" is used to define poor reversibility based on ERS definition. How do you explain missing values (e.g., see patient 15482)?
3. There is not a variable for reversibility based on ATS definition in PFT.XPT. Can this variable, if any, be found in other data sets submitted? If not, supply a new data set with ATS reversibility indicators along with the formulas from which the indicators were calculated.
4. In August 10, 2001 response to the Agency, the sponsor explained the definitions for reversibility and poor reversibility with an example. When was the reversibility of a patient determined? If it was determined in the screening period, what does "baseline" mean in the definition? In addition, which data set should we use to recalculate it, assuming the pre-baseline data were not in PFT.XPT.
5. In the definitions for reversibility, 12% and 10% are used as cutoff points for the specified increase. What happens when the increase is actually negative? Do the definitions still apply?
6. Two data sets, PFT.XPT and PFTS.XPT were described as for pulmonary function test. How do they differ? Which one was used in the primary analysis?
7. Protocol-violation data. The following snapshot shows part of a data set merging PROTVAR.SD2 and PROVARTX.SD2. I wonder whether the violation codes and violation names are related or

Sponsor's Response to Statistical Questions

The following is a portion of sponsor's response to statistical questions raised by this reviewer during the review.

2. The following comments pertain to the statistical portions of your submissions with regard to study SFCA3006, SFCA3007, and FLTA3025.

a. There is not a variable for the week or visit number. A variable, SESS, appears to serve as an indicator for visit. How was the variable SESS defined and what does SESS=2.9 mean? If the primary efficacy evaluation was based on FEV1 measurements at Week 24, how do you handle the patients last measured earlier or later than 24 weeks in your data presentation and analysis (e.g. 22 weeks or 27 weeks)?

The variable SESS does in fact correspond to the visits and to the treatment weeks where each visit should have taken place according to the protocol as detailed in the following table.

SESS	1.0	2.0	3.0	4.0	5.0	6.0	7.0
Visit	Screening	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6
SESS	8.0	9.0	10.0	11.0	12.0	13.0	2.9
Visit	Week 8	Week 12	Week 16	Week 20	Week 24	Discontinuation*	Endpoint

a for patients withdrawing prematurely from the trials

SESS numbers with non-zero digits after the decimal such as 2.1 and 2.2 denote data from unscheduled visits taking place between scheduled visits, in this case SESS=2.0 and 3.0. The exception is SESS=2.9. SESS=2.9 was a special designation used in the intermediate analysis data sets to denote Endpoint, the last on-treatment assessment within one day of treatment cessation excluding data from the discontinuation visit for all but the CRDQ. Since the CRDQ was not administered between Weeks 8 and 24, CRDQ assessments from the Discontinuation visit were allowed in the calculation of Endpoint. Endpoint was the primary timepoint for the primary (FEV1) and key secondary measures (CBSQ, TDI, and CRDQ). This number (2.9) for Endpoint was chosen to facilitate the ordering of results in the statistical tables.

Data from measurements obtained in situations where patients attended visits not strictly within the protocol specified window in which the visit was to occur were classified and included with whatever visit procedures were followed at the site. So for example, if a patient actually completed the Week 24 visit procedures during the 22nd or 27th week on treatment, that data would be labeled as SESS=12.0 and included in the Week 24 analysis.

b. The variable, PGMPOP, labeled .PR/excl. invid 1403. is used to define poor reversibility based on ERS definition. How do you explain missing values (e.g., see patient 15482)?

The computer code that generated the variable PGMPOP only assigned 1.s and 0.s if the poorly reversible indicator variable, PRPOP, had a value of 1 since the programs that

generated the statistical analyses and tables only subset where the relevant indicator variable equals 1. Hence, each subgroup population has a unique indicator variable. PGMPOP values of 0 indicate poorly reversible patients from investigator site 1403, since these are the only subjects with PRPOP values of 1 who are excluded from the PR/excl. invid 1403 population. It should be noted that PGMPOP was only used in the analysis of SFCA3006 since investigator site 1403 only participated in this study. In summary, PGMPOP was left missing for patients who were non-poorly reversible. In the case of patient 15482, the change in percent of predicted in response to VENTOLIN was greater than 10% at screening, hence this subject was non-poorly reversible and their PGMPOP value was left missing.

c. There is not a variable for reversibility based on ATS definition in PFT.XPT. Can this variable, if any, be found in other data sets submitted? If not, supply a new data set with ATS reversibility indicators along with the formula from which the indicators were calculated.

The TMT data set in the ISE portion of the submission contains an indicator variable named NREVGPOP that takes the value 1 to indicate patients who were non-reversible at screening according to the ATS definition and not from investigator site 1403. Similarly, there is also an indicator variable named REVGPOP which takes the value 1 to indicate patients who were reversible at screening according to the ATS definition and not from investigator site 1403. This data set also contains a variable, PTID, that can be used to subset the data from each individual study as well as the patient number variable, SUBJECT, that can be used to merge the data set with any other.

A decision prior to unblinding of the clinical trials was made to utilize the actual bronchodilator response calculated from the screening pulmonary function testing data rather than the sometimes inconsistent investigator assigned values to determine reversibility subgroup populations for the analyses and TMT intermediate data set in the ISE. Use of the actual reversibility was judged to be more relevant than the investigator assigned reversibility used for stratification to allow for an accurate assessment of treatment effects in both reversible and non-reversible subgroup populations.

Discrepancies were observed for 78 out of 2054 patients in the three pivotal studies between the investigator determined reversibility value and the actual result.

Additionally, six subjects from all three pivotal studies (1 in SFCA3007 and 5 in FLTA3025) were missing either a pre- or post VENTOLIN value in the screening pulmonary function testing data set, PFTSCRN, which caused missing values of the reversibility indicator variables for these patients.

d. In your August 10, 2001 response, you explained the definitions for reversibility and poor reversibility with an example. When was the reversibility of a patient determined? If it was determined in the screening period, what does .baseline. mean in the definition? In addition, which data set should we use to recalculate it, assuming the pre-baseline data were not in PFT.XPT.

Reversibility was determined at the screening visit. .Baseline. in the August 10, 2001 response refers to the pre-VENTOLIN value obtained at screening. The values needed to calculate the bronchodilator response are contained in the PFTSCRN data set. The variable containing screening assessment values of FEV1 is named FEV, and the pre- and post-VENTOLIN FEV1 values are delineated by OCC1 values of 1 and 2, respectively. The variable PCRVS contains the numerical result of the bronchodilator response calculation.

e. In the definitions for reversibility, 12% and 10% are used as cutoff points for the specified increase. What happens when the increase is actually negative? Do the definitions still apply?

Correct, the same definitions still apply. A negative increase of any size would be considered non-reversibility.

f. Two data sets, PFT.XPT and PFTS.XPT were described for pulmonary function test. How do they differ? Which one was used in the primary analysis?

PFT is the intermediate analysis data set while PFTS is the raw data set. PFT, the intermediate data set, was used to perform the primary statistical analyses.

(1) Protocol-violation data. The following snapshot shows part of a data set merging PROTVAR.SD2 and PROVARTX.SD2. Are the violation codes and protocol variation text related?

No, the protocol violation codes and protocol variation text are not intended to be related. The variables INVAR and EXVAR in data set PROTVAR captured the inclusion and exclusion criteria codes that were violated. The investigator was also given the option of writing comments in a section labeled "other" on the case report form, and the data set PROVARTX captured these comments.

Please explain, modify and insert adequate indicators (variables) so that data subsetting and stratifications can be done easily. If LOCF for FEV1 is used, it is recommended to add an indicator to signify whether the FEV1 value was an actual observation or a value carried over from a previous visit. It is not necessary to put all variables in a single data set. It is even more desirable to put them into different data sets with patient number as the key for future merging.

LOCF was used for FEV1, but only to calculate Endpoint. Endpoint values are denoted in the intermediate analysis data sets by SESS values of 2.9. All other values are actual observations. For example, in cases where a patient completed the trial and has a Week 24 value, this value with SESS=12.0 is duplicated as the Endpoint value corresponding with SESS=2.9.

Additional indicator variables not contained in the individual study TMT intermediate data sets are contained in the ISE and ISS TMT intermediate data sets. These data sets contain a variable, either PTID or STUDYNO, that can be used to subset the data from each individual study as well as the patient number variable, SUBJECT, that can be used to merge the data sets with any other.

Signoff Page

Reviewer:
Concur:

Ted Guo, Ph.D.
James Gebert, Ph.D.

CC:
Archival
NDA 21-077
NDA 20-833
NDA 20-692

HFD-570/Division file
HFD-570/LMcClain
HFD-570/ESullivan
HFD-570/CLec

HFD-715/Division file
HFD-715/JGebert
HFD-715/SWilson
HFD-715/TGuo

HFD-700/Canello

TG/Nda210772083320692.doc

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ted Guo
12/20/01 09:01:21 AM
BIOMETRICS

James Gebert
12/20/01 11:07:46 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-077/S-003

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE

Patent Information

**Item 13 of sNDA 21-077
Pursuant to 21 C.F.R. § 314.53**

**for
ADVAIR™ DISKUS® Inhalation Powder
for**

Chronic Obstructive Pulmonary Disease (COPD)

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: ADVAIR™ Diskus®

Active Ingredient: fluticasone propionate/salmeterol xinafoate

Strengths: fluticasone propionate 100mcg/salmeterol xinafoate 50mcg
fluticasone propionate 250mcg/salmeterol xinafoate 50mcg
fluticasone propionate 500mcg/salmeterol xinafoate 50mcg

Dosage Form: inhalation powder

Route of Administration: oral inhalation

Please list the following patents in the U.S. Department of Health and Human Services "Orange Book" of Approved Drug Products.

	US Patent Number	Expiration Date	Form of Patent Claims
1	4,335,121	14 November, 2003	Drug Substance Drug Product
2	4,992,474	12 February, 2008	Drug Substance Drug Product Method of Use
3	5,126,375	12 February, 2008	Drug Substance Drug Product
4	5,225,445	12 February, 2008	Method of Use
5	5,270,305	7 September, 2010	Drug Substance Drug Product Method of Use
6	5,290,815	1 March, 2011	Method of Use

The undersigned declares the following:

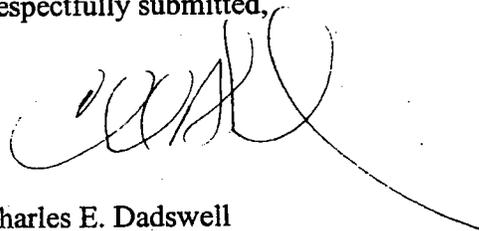
- 1) All of the above patents are owned by Glaxo Group Limited.

- 2) The United States Agent for Glaxo Group Limited is SmithKline Beecham Corporation doing business as GlaxoSmithKline.
- 3) The above Patents (4,335,121; 4,992,474; 5,126,375, 5,225,445, 5,270,305 and 5,290,815) are required to be the subject of a submission of information pursuant to 21 C.F.R. §314.53(b).
- 4) The above Patents (4,335,121; 4,992,474; 5,126,375, 5,225,445, 5,270,305 and 5,290,815) cover the Drug Substance, Drug Product and/or Method of Use of ADVAIR™ DISKUS®.

Please address all communications regarding the patent property of this NDA to:

David J. Levy
Vice President, Intellectual Property Counsel
GlaxoSmithKline
Corporate Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
919/ 483-2723

Respectfully submitted,



Date: 2 April, 2001

Charles E. Dadswell
Assistant Intellectual Property Counsel
GlaxoSmithKline
Registered Patent Attorney
Registration No. 35,851
919/483-6983

Addendum:

Patents 4,992,474; 5,225,445; 5,270,305; and 5,290,815 contain "method of use" claims. For purposes of inclusion of patent information in the *Orange Book*, "method of use" is defined as:

US Patent Number	Method of Use Description
4,992,474	Use in patients with reversible airway obstruction
5,225,445	Use in patients with reversible airway obstruction
5,270,305	Treatment of respiratory disorders
5,290,815	Treatment of inflammation, allergy and allergic reaction

Signed



Sara A. Nelson
Associate Director, Regulatory Affairs
Glaxo Wellcome Inc.

EXCLUSIVITY SUMMARY for NDA # 21-077 SUPPL #SE1-003

Trade Name Advair Diskus 250/50 _____ Generic Name
fluticasone propionate and salmeterol xinafoate inhalation powder

Applicant Name GlaxiSmithKline (GSK)

HFD-570

Approval Date 11-14-03

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/___/ NO / X /

b) Is it an effectiveness supplement? YES / X / NO / ___ /

If yes, what type(SE1, SE2, etc.)? SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / X / NO / ___ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / X / NO / ___ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years. Please refer to the original submission dated May 4, 2001.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /_X_/ NO /___/

If yes, NDA # 21-077 _____ Drug Name Advair
Diskus for asthma.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug

under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

/___/

YES /_X_/

NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/

NO /_X_/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # SFCA3006

Investigation #2, Study # SFCA3007

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1 , Study # SFCA3006

Investigation # 2 , Study # SFCA3007

Investigation # 3 , Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the

conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 50,703 _____ YES / X / ! NO / ___ / Explain:

Investigation #2
IND # 50,703 _____ YES / X / ! NO / ___ / Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!	
YES / ___ / Explain _____	!	NO / ___ / Explain _____
_____	!	_____
_____	!	_____

Investigation #2

YES /___/ Explain _____

NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

Ladan Jafari

Signature of Preparer

Date 11-12-03

Title:

Signature of Office or Division Director

Date

cc:
Archival NDA
HFD- /Division File

HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

NDA 21-077

ADVAIR™ DISKUS®
(fluticasone propionate/salmeterol inhalation powder)
100/50mcg, 250/50mcg, 500/50mcg

Supplemental New Drug Application:
Treatment of Chronic Obstructive Pulmonary Disease

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Charles E. Mueller
Head, North American Clinical Compliance
World Wide Compliance

20 FEB 2001

Date

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: October 3, 2003

THROUGH: Office of Drug Safety:

Mark Avigan, M.D., C.M., Acting Director
Division of Drug Risk Evaluation, HFD-430

Toni Piazza-Hepp, Pharm.D., Acting Director
Division of Surveillance, Research and Communication Support, HFD-410

Jerry Phillips, R.Ph., Acting Director
Division of Medication Errors and Technical Support, HFD-420

FROM: ODS Advair Risk Management Plan Review Team*

TO: Badrul Chowdhury, M.D., Director
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Review of GlaxoSmithKline Risk Management Program (PID # D030422)
Drug—Fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation
powder (Advair Diskus NDA 21-077/S-003)

EXECUTIVE SUMMARY

GlaxoSmithKline (GSK) submitted a Risk Management Plan to address safety concerns with the use of inhaled corticosteroids (ICS) in COPD patients. The Division of Pulmonary and Allergy Drug Products (DPADP) has concerns about possible systemic effects of ICS in COPD patients, including bone effects, ocular effects, hypothalamic-pituitary-adrenal (HPA) axis suppression, and increased respiratory infections. Additionally, trials have established benefit from the use of Advair only in the subset of COPD patients with chronic bronchitis. Even among the subset of patients with chronic bronchitis, no additional benefit was seen in clinical trials with the use of Advair 500/50 (fluticasone 500 mcg and salmeterol 50 mcg per each inhalation) as compared to Advair 250/50 (fluticasone 250 mcg and salmeterol 50 mcg). Use of Advair 500/50 in these patients would be expected to result in additional risk from the increased steroid exposure without expectation of additional benefit. Specifically, DPADP stated that the Risk Management Program (RMP) should be targeted to achieve:

* List of participating team members located at end of document

- use of Advair 250/50 and not Advair 500/50 in the patient population with chronic bronchitis;
- assessment of loss of bone mass with the use of Advair;
- use of Advair in the subset of COPD patients most likely to benefit from the use of the product; that is, the subset of patients with chronic bronchitis.

The proposed RMP was designed to address these safety concerns.

On 8/13/2003, a "black-box" warning was added to the labeling of Advair to warn healthcare practitioners about the results of the Salmeterol Multi-center Asthma Research Trial (SMART). SMART, a large placebo-controlled safety study, was stopped early because interim results showed worse asthma-related outcomes in the salmeterol group compared to the placebo group. The risk management plan for Advair Diskus does not address the safety issues raised by SMART.

The product Warning for Advair Diskus states the following about the SMART study:

"...Post hoc subgroup analyses revealed no significant increase in respiratory-or asthma-related episodes, including deaths, in Caucasian patients. In African-Americans, the study showed a small, though statistically significantly greater, number of primary events (20 vs. 7), asthma-related deaths or life-threatening experiences (19 vs. 4), and asthma-related deaths (8 vs. 1) in patients taking SEREVENT inhalation aerosol compared to those taking placebo."

The labeling goes on to say that the data from SMART are not adequate to determine whether concurrent use of inhaled corticosteroids such as fluticasone propionate, a component of Advair Diskus, provides protection from this risk. Therefore, the risk to African-American subjects from the combination of fluticasone and salmeterol remains undefined. It is recommended that an approach to assessing the risk from exposure to the combination product in African-American subjects be considered.

The Risk Management Plan submitted by GSK for Advair Diskus includes components of a pharmacovigilance plan and an RMP. The pharmacovigilance plan is intended to better characterize the various risks from the use of Advair in COPD patients. The RMP is intended to manage the risk, largely through risk communication, even though the risk has not yet been fully characterized. In our review, we address both the pharmacovigilance plan and the RMP.

The objectives of the Risk Management Plan and the proposed tools to achieve the objectives are:

1. To further define the benefit/risk profile of Advair 250/50 in patients with COPD (tools—Phase 4 studies and enhanced postmarketing surveillance activities);
2. To achieve the use of Advair 250/50 (as opposed to the higher dose), and to minimize the prescribing of high doses of Advair (tools—professional and patient education); and

3. To minimize potential risks associated with the disease itself and the use of Advair 250/50 in the COPD patient population (tools—professional and patient education).

Defining the Benefit/risk Profile of Advair 250/50 in Patients with COPD

The enhanced pharmacovigilance plan proposes Phase 4 studies and enhanced pharmacovigilance activities to further define the benefit/risk profile of Advair 250/50 in patients with COPD. The Phase 4 studies include:

- a 2-year study to assess the effects of Advair 250/50 versus salmeterol on bone mineral density; and
- a 52-week study comparing the annual rate of COPD exacerbations in patients randomized to Advair 250/50 or salmeterol.

Details about the proposed studies are provided below.

The enhanced pharmacovigilance plan appears to be limited in its ability to address specific factors that affect the benefit/risk profile of Advair 250/50 in patients with COPD.

The 2-year study to assess the effects of Advair 250/50 on bone mineralization may be too short to gain sufficient information on outcomes that may take many years to manifest.

The proposed enhanced postmarketing activities may help identify and assess additional risks and risk factors for adverse events. However, if these activities are intended as a method of evaluating the performance of the risk management program, it is not an ideal method of analysis because the reporting of adverse events is affected by many factors.

Additional comments regarding the proposed enhanced pharmacovigilance plan can be found in Table 1 and Attachments 1 and 2.

Minimizing Risks from COPD and from the Use of Advair in COPD Patients

The RMP proposes using labeling and educational interventions to achieve the other stated objectives (to achieve the use of Advair 250/50, to minimize the prescribing of high doses of Advair, and to minimize potential risks associated with the disease itself and the use of Advair 250/50 in the COPD patient population). Labeling and educational interventions are appropriate tools to achieve these objectives. Patient educational materials should be written at a 6th to 8th grade reading comprehension level, and the material should be non-promotional. The important risk information should be highlighted and not downplayed by potential benefits and artwork. Additional comments regarding the proposed patient education materials can be found in Table 2 and Attachment 3.

We have additional comments regarding specific information to be included in the educational material to achieve the stated objective of minimizing potential risks

associated with the disease itself and the use of Advair 250/50 in COPD patients. These additional comments can be found in Table 2 and Attachment 4.

No approach to managing risk to African-Americans can be recommended until the risk is better defined.

Evaluation of the Program

The Sponsor did not include an evaluative component to measure the success of the labeling and educational interventions in achieving the stated objectives. The RMP should include a plan for evaluating the performance of these elements of the program, with details of the timeline and the methodology that will be applied. GSK should report back to the agency (at an interval agreed upon with the review division) and provide data on:

1. the extent of high-dose use among patients with COPD (specifying the methods and data sources used); and
2. the extent of compliance with the RMP and complications of product use (through surveys of COPD patients and/or physicians).

INTRODUCTION/ BACKGROUND

In this review we evaluated the RMP submitted by GSK for Advair Diskus for the treatment of chronic obstructive pulmonary disease (COPD). Additionally, we evaluated the risks addressed in the RMP to the known safety concerns associated with the use of Advair.

Advair Diskus Information and Regulatory History

Advair is a combination inhalation product containing a corticosteroid, fluticasone propionate, and a long-acting beta₂-agonist, salmeterol, in a powder formulation contained in a blister strip. Advair is available with 3 different strengths of fluticasone, 100, 250, and 500 mcg. Each of the 3 strengths of fluticasone is accompanied by 50 mcg of salmeterol in each blister. Advair was approved 8/24/2000 for the long-term, twice-daily, maintenance treatment of asthma in patients 12 years of age and older.

GlaxoSmithKline (GSK) submitted a supplemental new drug application (sNDA) to the FDA on 5/4/2001 seeking approval of Advair in the treatment of chronic obstructive pulmonary disease. Noteworthy events for the sNDA are presented below.

- 1/17/2002—The application was the subject of a meeting of the Pulmonary and Allergy Advisory Committee (PADAC). PADAC recommended approval of Advair with specific labeling and Phase IV commitments.
- 3/5/2002—The FDA issued an approvable letter for the application.
- 6/20/2002—GSK submitted additional data for Advair 250/50 and withdrew the request for approval of Advair 500/50 for the treatment of COPD (no additional benefit was observed in clinical trials with the use of Advair 500/50 as compared to Advair 250/50).

- 12/12/2002—The FDA issued a second approvable letter for the application. The approvable letter proposed that GSK obtain additional data.
- 1/23/2003—SMART study halted.
- 3/25/2003—The FDA and GSK met to discuss the application; GSK committed to submitting:
 - case-control studies assessing the risk of fracture associated with the use of inhaled corticosteroids (ICS) among patients with COPD;
 - an Advair 250/50 vs. Combivent clinical (efficacy and safety) study in patients with COPD;
 - an analysis of GSK's spontaneously reported adverse event data for Advair by dose; and
 - a Risk Management Plan.
- 5/30/2003—GSK submitted a complete response to the approvable letter of 12/12/2002; the complete response included an RMP. The Division of Pulmonary and Allergy Drug Products (DPADP) consulted ODS 7/14/03 to review the RMP.

Relevant product labeling

The draft labeling proposed by GSK can be accessed through the electronic document room at \\Cdsub1\N21077\S_003\2003-05-30\labeling. DPADP has advised ODS that extensive changes to the proposed labeling are likely.

Safety Issues

1. DPADP has concerns about the systemic effects of ICS in COPD patients, including bone effects, ocular effects, HPA suppression, and increased respiratory infections. COPD patients often have decreased baseline bone mass due to their underlying disease and associated conditions; for example, smoking, poor nutrition, and sedentary lifestyle. Because COPD patients tend to be elderly, frequently have a history of cigarette smoking, and often have used systemic corticosteroids, they may be at increased risk for ocular disorders, including cataracts. Likewise, COPD patients are at increased risk for respiratory infections.

Additionally, trials have established benefit from the use of Advair only in the subset of COPD patients with chronic bronchitis; that is, patients experiencing cough and sputum production for at least 3 months in each of 2 consecutive years. If exposed to Advair, those patients with COPD, but not chronic bronchitis, would be exposed to the risks of the product without expectation of benefit. Even among the subset of patients with chronic bronchitis, no additional benefit was seen in clinical trials with the use of Advair 500/50 as compared to Advair 250/50. Use of Advair 500/50 in these patients would be expected to result in additional risk from the increased steroid exposure without expectation of additional benefit.

Specifically, DPADP stated that the RMP should be targeted to achieve:

- use of Advair 250/50 and not Advair 500/50 in the patient population with chronic bronchitis;

- assessment of loss of bone mass with the use of Advair;
- use of Advair in the subset of COPD patients most likely to benefit from the use of the product; that is, the subset of patients with chronic bronchitis.

The proposed RMP addresses these safety concerns.

2. On 8/13/2003, a "black-box" warning was added to the labeling of Advair to warn healthcare practitioners about the results of the Salmeterol Multi-center Asthma Research Trial (SMART). SMART, a large placebo-controlled safety study, was stopped early because interim results showed worse asthma-related outcomes in the salmeterol group compared to the placebo group. The interim analysis did not show a statistically significant result for the primary endpoint - a combination of respiratory-related deaths or intubations (or ventilatory failure). There was a trend, however, towards increases in asthma deaths and serious asthma episodes when all patients in the study were considered, though again this did not reach statistical significance. A further analysis of the data from the study suggested that the risk might be greater in African-American patients.

The risk management plan for Advair Diskus does not address the increased risk of death in African-Americans who were exposed to salmeterol in SMART.

GSK's PROPOSED RISK MANAGEMENT PROGRAM

Goals, Objectives, and Tools

The overall goals of the RMP are not clearly stated in the GSK submission however they do clearly state their objectives and the tools they plan to implement to achieve those objectives.

The objectives of the RMP and the tools designed to achieve the objectives are listed below.

Objective 1. To further define the benefit/risk profile of Advair 250/50 in patients with COPD.

- Additional (Phase 4) studies
 - ~~_____~~
 - a 2-year study to assess the effects of Advair 250/50 on bone mineral density
 - a 52-week study comparing the annual rate of COPD exacerbations in patients randomized to Advair 250/50 or salmeterol
- Enhanced postmarketing surveillance activities

- review of all new spontaneous cases describing adverse events of special interest within 1-2 days of receipt and follow up on the cases for full documentation using targeted questions
- review of all new serious unexpected cases (spontaneous cases and attributable clinical trial cases) within 1-2 days of receipt and follow up on the cases for full documentation using targeted questions
- monthly listing and review of all newly reported adverse events of interest and data mining of GSK's adverse event database for the events of interest
- quarterly listing and review of all serious adverse events occurring during clinical trials with Advair
- 6-month summaries and analysis of post-marketing safety via Periodic Safety Update Reports (PSUR)

Objective 2. To achieve the use of Advair 250/50 and to minimize the prescribing of high doses of Advair.

- Professional and patient education, including changes to the product labeling and patient leaflet, promotional and educational materials for both healthcare professionals and patients.

Objective 3. To minimize potential risks associated with the disease itself and the use of Advair 250/50 in the COPD patient population.

- Professional and patient education, including changes to the product labeling and patient leaflet, promotional and educational materials for both healthcare professionals and patients.

The objectives and tools include components of a pharmacovigilance plan and a risk management program (RMP). The tools proposed under Objective 1, epidemiologic studies and enhanced surveillance fall under the pharmacovigilance plan. These are intended to better characterize the risk from the use of Advair in COPD patients. The educational strategy under Objectives 2 and 3 fall under the RMP. This is intended to manage the risk, largely through risk communication, even though the risk has not yet been fully characterized.

In our review, we address both the pharmacovigilance plan and the RMP.

THE ADVAIR PHARMACOVIGILANCE and RMP and ODS COMMENTS/ SUMMARY

The ODS comments are summarized in the tables below:

Table 1. Pharmacovigilance Plan; and

Table 2. Risk Management Program.

Additional details of the pharmacovigilance plan and the RMP can be found as attachments to this document:

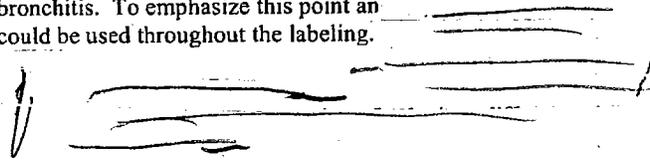
Table 1. Pharmacovigilance Plan		
GSK-Proposed Objective	GSK-Proposed Tool	Office of Drug Safety Comments / Discussion Points
		<ul style="list-style-type: none"> 1
	<p>- 2-year study to assess the effects of Advair 250/50 on bone mineral density:</p> <ul style="list-style-type: none"> _____ 	<ul style="list-style-type: none"> A two-year study may be too short to determine risk for a disease that may take several years of exposure before any discernible effects are seen. _____
	<ul style="list-style-type: none"> _____ <p>- 52-week study comparing the annual rate of COPD exacerbations in</p>	<ul style="list-style-type: none"> The investigators should include a plan to evaluate any increased risk to African-Americans. The protocol does not justify or explain the need for a run-in period of _____ for Advair. Unless specified by spirometry, the protocol does not specify that

Table 1. Pharmacovigilance Plan		
GSK-Proposed Objective	GSK-Proposed Tool	Office of Drug Safety Comments / Discussion Points
	<p>patients randomized to Advair 250/50 or salmeterol:</p> <ul style="list-style-type: none"> • subjects with diagnoses of COPD and documented COPD exacerbations will begin a run-in period at study centers with Advair Diskus 250/50mcg BID. • This will be followed by randomization to a 52-week double blind treatment period with Advair Diskus 250/50mcg BID or to salmeterol 50 mcg BID via Diskus. • Pulmonary function testing will be performed <p>and 52 weeks of treatment.</p> <ul style="list-style-type: none"> • The investigators list inclusion criteria and exclusion criteria as study participation eligibility. 	<p>only individuals having COPD associated with chronic bronchitis are indicated to receive Advair.</p> <ul style="list-style-type: none"> • _____ • _____ • _____
	<p>b. Enhanced postmarketing surveillance activities:</p> <ul style="list-style-type: none"> - review of all new spontaneous cases describing adverse events of special interest within 1-2 days of receipt and follow up on the 	<ul style="list-style-type: none"> • We support these activities. Most of these activities are expected usual practice in monitoring the safety of marketed drugs. • We encourage reporting of potential and actual medication errors.

Table 1. Pharmacovigilance Plan		
GSK-Proposed Objective	GSK-Proposed Tool	Office of Drug Safety Comments / Discussion Points
	<p>cases for full documentation using targeted questions</p> <p>-review of all new serious unexpected cases (spontaneous cases and attributable clinical trial cases) within 1-2 days of receipt and follow up on the cases for full documentation using targeted questions</p> <p>- monthly listing and review of all newly reported adverse events of interest and monthly datamining of GSK's adverse event database for the events of interest</p> <p>- quarterly listing and review of all serious adverse events occurring during clinical trials with Advair</p> <p>- 6-month summaries and analysis of post-marketing safety via Periodic Update Safety Reports (PSUR)</p>	

Table 2. Risk Management Program		
GSK-Proposed RMP Objective	GSK-Proposed RMP Tool	Office of Drug Safety Comments / Discussion Points
2. To achieve the use of Advair 250/50 and to minimize the prescribing of high doses of Advair	Professional and patient education, including changes to the product labeling and patient leaflet, promotional and educational materials for both healthcare professionals and patients.	<ul style="list-style-type: none"> Ensuring that patients take only 2 inhalations per day—AM and PM. This could be placed on the package and in the patient package insert (or if applicable, Medication Guide). An acceptable level of prescribing of high doses should be specified. The RMP can then be evaluated as to whether prescribers attained the acceptable level of prescribing. When measuring the level of

Table 2. Risk Management Program		
GSK-Proposed RMP Objective	GSK-Proposed RMP Tool	Office of Drug Safety Comments / Discussion Points
		<p>permits the distinction between asthma and COPD patient groups as much as possible. A protocol specifying the source of data and its reliability would be necessary for evaluation.</p> <ul style="list-style-type: none"> • The <i>Patient's Instruction for Use</i> Leaflet should be revised to include more complete patient information (and retitled <i>Patient Information</i>), with the instructions for use appended. We recommend following the Medication Guide format and content (21CFR 208) as a guideline for the appropriate information to include. As the <i>Patient Information</i> Leaflet is developed, it should also be written at a 6th to 8th grade reading comprehension level in order to reach a broad range of patients including those with low literacy. It is likely that all patients will receive this information as Advair is packaged in unit-of-use packaging. • The Patient Brochure should be non-promotional and contain language that is consistent with the language in the Patient Information Leaflet and be written at a 6th to 8th grade reading comprehension level. The important risk information should be highlighted and not downplayed by potential benefits and artwork. • The Patient Information Leaflet should contain a warning that states doses higher than Advair Diskus 250/50 twice daily should not be used for treatment of COPD. • _____ • _____ • _____
3. To minimize potential risks associated with the disease itself and the use of Advair 250/50 in the COPD patient population	Professional and patient education, including changes to the product labeling and patient leaflet, promotional and educational materials for both healthcare professionals and patients.	<p>ODS recommends additional measures:</p> <ul style="list-style-type: none"> • Patient education could include lifestyle information important to the management of COPD: <ul style="list-style-type: none"> • Patients who use tobacco should be encouraged to stop smoking and should be recommended to initiate smoking cessation programs. • Patients should be encouraged to engage in physical exercise on a frequent basis. • _____ • Patients should be recommended to receive bone density scans on a regular basis. Since most COPD patients are middle-aged or elderly, this would be consistent with recommendations for the adult white female population. • Patients should be encouraged to have regular eye examinations and to protect their eyes from ultraviolet radiation while outdoors by wearing UV-blocking sunglasses. Patients should be instructed that long-term steroid use increases the risk of cataracts. • The RMP should include a component for evaluating its performance.

Table 2. Risk Management Program		
GSK-Proposed RMP Objective	GSK-Proposed RMP Tool	Office of Drug Safety Comments / Discussion Points
Additional ODS-Proposed RMP Objective	ODS-Proposed RMP Element	Office of Drug Safety Comments / Discussion Points
4. Ensuring that Advair Diskus 250/50 is prescribed for patients with COPD-associated chronic bronchitis.	Professional education, including changes to the product labeling, promotional and educational materials for healthcare professionals.	<ul style="list-style-type: none"> The doctor should be provided with criteria for prescribing this drug, i.e., airflow obstruction, chronic bronchitis, and COPD. The product labeling should emphasize this point throughout by referring to the indication as not just COPD but as COPD associated with chronic bronchitis. To emphasize this point an _____ could be used throughout the labeling. 

CONCLUSION

Risk management planning encompasses all efforts by a sponsor to minimize the risk from its product's use and may include product labeling, risk assessment, pharmacovigilance, and special studies or interventions. For most products, traditional risk management planning consists of professional product labeling (i.e., the package insert or PI) and postmarketing surveillance. However, the PI alone is not always sufficient to minimize a product's risks. In these cases, FDA proposes that sponsors submit an RMP, a strategic safety program designed to decrease product risk by using one or more interventions or tools beyond the package insert. Examples of the intervention tools include (1) specialized educational materials for health care practitioners or patients, (2) processes or forms to increase compliance with reduced-risk prescribing and use, and (3) systems that modify conventional prescribing, dispensing, and use of the product to minimize specific risks.

DPADP asked that the RMP be targeted to achieve the following:

- use of Advair 250/50 and not Advair 500/50 in the patient population with chronic bronchitis;
- assessment of loss of bone mass with the use of Advair; and
- use of Advair in the subset of COPD patients most likely to benefit from the use of the product; that is, the subset of patients with chronic bronchitis.

We evaluated the RMP for these goals. Additionally, we believe the results of SMART should be considered in the design and evaluation of the RMP.

The Risk Management Plan submitted by GSK for Advair Diskus includes components of a pharmacovigilance plan and a risk management program (RMP). The pharmacovigilance plan is intended to better characterize the risk from the use of Advair in COPD patients. The RMP is intended to manage the risk, largely through risk communication, even though the risk has not yet been fully characterized.

The objectives of the Risk Management Plan and the proposed tools to achieve the objectives are:

1. To further define the benefit/risk profile of Advair 250/50 in patients with COPD (tools—Phase 4 studies and enhanced postmarketing surveillance activities);
2. To achieve the use of Advair 250/50 and to minimize the prescribing of high doses of Advair (tools—professional and patient education); and
3. To minimize potential risks associated with the disease itself and the use of Advair 250/50 in the COPD patient population (tools—professional and patient education).

Defining the Benefit/risk Profile of Advair 250/50 in Patients with COPD

The enhanced pharmacovigilance plan proposes Phase 4 studies and enhanced pharmacovigilance activities. The Phase 4 studies include:

- ~~_____~~
- a 2-year study to assess the effects of Advair 250/50 ~~on~~ on bone mineral density; and
- a 52-week study comparing the annual rate of COPD exacerbations in patients randomized to Advair 250/50 or salmeterol.

The enhanced pharmacovigilance plan appears to be limited in its ability to address specific factors that affect the benefit/risk profile of Advair 250/50 in patients with COPD.

As a separate matter, in the development of an RMP, the results of the Salmeterol Multicenter Research Trial (SMART) should be considered. The risk to African-American subjects from the combination of fluticasone and salmeterol remains undefined. It is recommended that an approach to assessing the risk from exposure to the combination product in African-American subjects be considered.

Minimizing Risks from COPD and from the Use of Advair in COPD Patients

The RMP proposes using labeling and educational interventions to achieve the other stated objectives (to achieve the use of Advair 250/50 and to minimize the prescribing of high doses of Advair; and to minimize potential risks associated with the disease itself and the use of Advair 250/50 in the COPD patient population). Labeling and educational interventions are appropriate tools to achieve these objectives. Patient educational materials should be revised for reading comprehension and to highlight the important risk information as detailed in Table 2 and Attachments 3 and 4.

No approach to managing risk to African-Americans can be recommended until the risk to African-Americans is better defined.

Evaluation of the Program

The Sponsor did not include an evaluative component to measure the success of the labeling and educational interventions in achieving the stated objectives. The RMP should include a plan for evaluating the performance of these elements of the program,

with details of the timeline and the methodology that will be applied. GSK should report back to the agency (at an agreed upon interval with the review division) and provide data on:

1. the extent of high-dose use among patients with COPD (specifying the methods and data sources used); and
2. the extent of compliance with the RMP and complications of product use (through surveys of COPD patients and/or physicians).

ODS Advair Risk Management Plan Review Team

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Attachment 1. EVALUATION OF PROPOSED PHASE 4 STUDIES: Detailed comments

The following contains a critique of proposed Epidemiology Studies in 5.3.1:

Throughout this and other sections of this submission, little attention is given to the indication of Advair Diskus for COPD with associated chronic bronchitis. Rather, COPD is referred to as the indication. To ensure understanding that the drug is only indicated for individuals having COPD with associated chronic bronchitis. ~~_____~~

GlaxoSmithKline proposes to conduct an epidemiology study (Section 5.3.1) and clinical studies (Section 5.3.2) as part of a risk management plan. Technically, such studies should be considered part of risk assessment, not risk management. However, for completeness, the proposed studies are critiqued in the following section.

Critique of Concept Protocols for Epidemiology and Clinical Studies concerning Safety of Advair Diskus

General Comments:

None of the studies mention or address safety concerns that were found in the Salmeterol Multi-center Asthma Research Trial (SMART). In this trial, a statistically significant increase in the number of asthma-related deaths and life-threatening experiences in African-Americans exposed to salmeterol resulted in early termination of the study. The results should be acknowledged and taken into account in the design of studies involving salmeterol, which is a component of Advair Diskus. Special surveillance and monitoring of bronchospasm episodes, syncopal episodes, ventricular arrhythmias, sudden deaths, and other potentially relevant outcomes in African-Americans are indicated. In view of the SMART results, the ethics of conducting studies in which only the safety of the fluticasone propionate component of Advair Diskus is assessed is questionable.

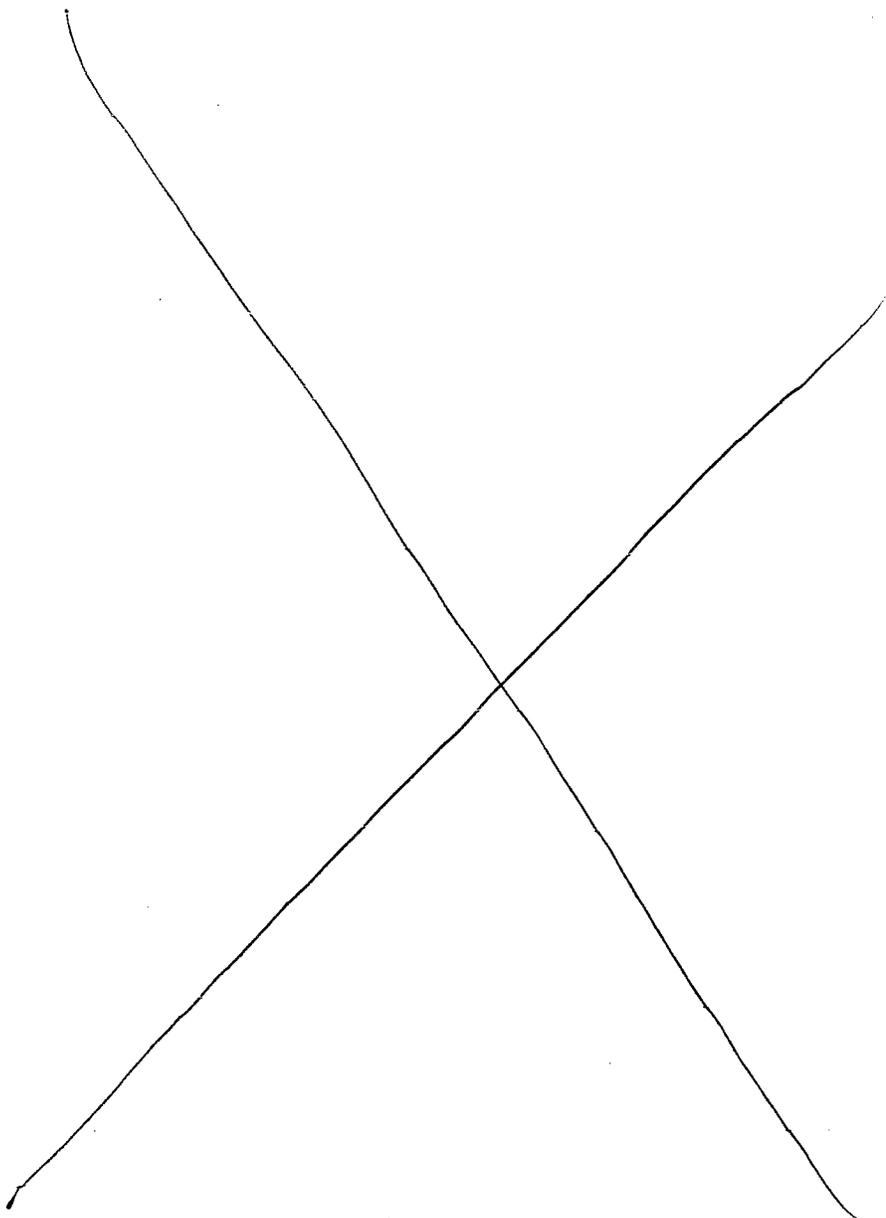
A. ~~_____~~

Study Design:

Critique:

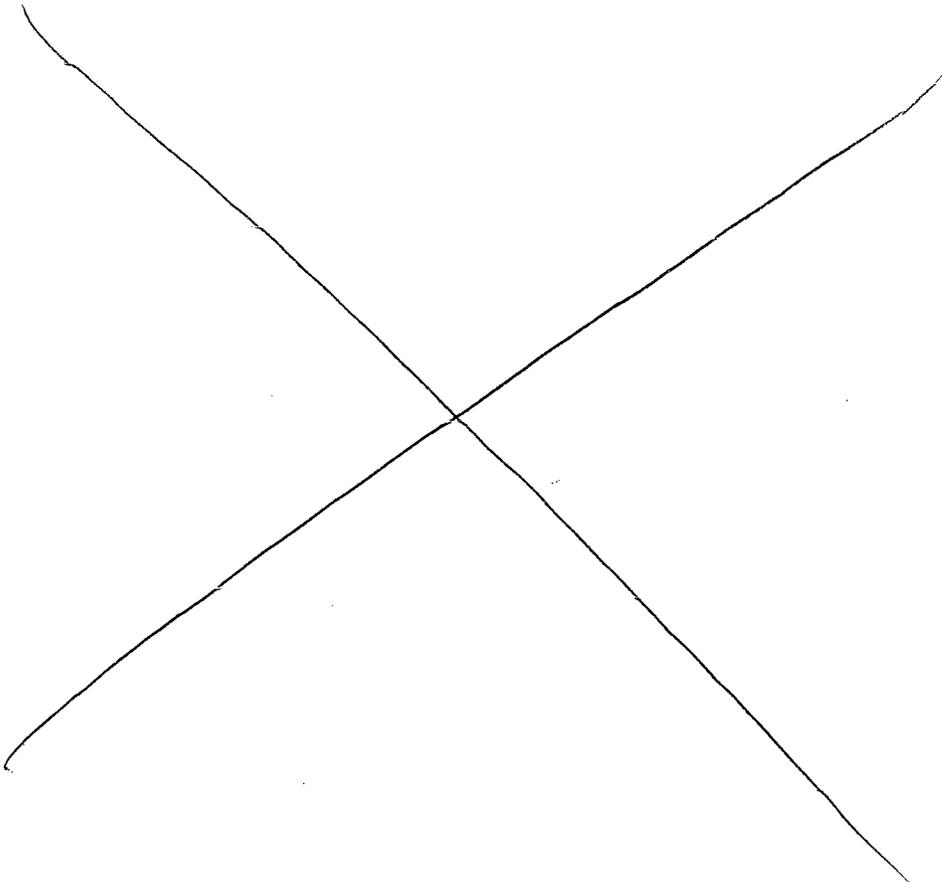
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**B. Concept Protocol RM2003/00255/00, SCO40043
Randomized Trial Comparing COPD Exacerbation Rates for Advair Diskus vs.
Salmeterol Diskus**

Study Design:

subjects with diagnoses of COPD and documented COPD exacerbations will begin a run-in period at / study centers with Advair Diskus 250/50mcg BID. This will be followed by randomization to a 52-week double blind treatment period with Advair Diskus 250/50mcg BID or to salmeterol 50 mcg BID via Diskus. Pulmonary function testing will be performed at clinic visits

Unless specified by spirometry, the protocol does not specify that only individuals having COPD associated with chronic bronchitis are indicated to receive Advair Diskus.

[Redacted text block]

[Redacted text block]

[Redacted text block]

D. Surveillance Methods

In addition to the other concept protocols to further assess risk, the sponsor has also included additional surveillance methods to assist in better understanding the risk. These include analyzing the background incidence of osteoporosis, fractures, cataract and pneumonia in a cohort of COPD patients

[Redacted text block]

Attachment 2.
EVALUATION OF ENHANCED POSTMARKETING SURVEILLANCE
ACTIVITIES

GSK proposes enhanced postmarketing surveillance activities, including:

- review of all new spontaneous cases describing adverse events of special interest within 1-2 days of receipt and follow up on the cases for full documentation using targeted questions;
- review of all new serious unexpected cases (spontaneous cases and attributable clinical trial cases) within 1-2 days of receipt and follow up on the cases for full documentation using targeted questions;
- monthly listing and review of all newly reported adverse events of interest and monthly data mining of GSK's adverse event database for the events of interest;
- quarterly listing and review of all serious adverse events occurring during clinical trials with Advair; and
- 6-month summaries and analysis of post-marketing safety via PSUR.

These postmarketing activities are appropriate to help identify and assess additional risks and risk factors for adverse events. However, if these activities are intended as a method of evaluating the risk management program, it is not an ideal method of analysis because the reporting of adverse events is affected by many factors.

We support GSK's commitment to obtaining full documentation for spontaneously reported adverse events and attributable clinical trial cases, and for periodically reviewing their adverse event database for potential safety signals. However, rather than proposing *enhanced* postmarketing surveillance activities, most of the postmarketing surveillance activities in the submission describe *expected usual* practice in monitoring the safety of marketed drugs. GSK does not explain in the submission how these activities differ from their usual postmarketing surveillance activities. The postmarketing surveillance activities in the submission describe the timely and complete documentation of reported cases of adverse events, periodic data mining of the adverse event database, periodic review of newly reported adverse events of interest, and preparation of PSUR. Except for the expedited review of events within 1-2 days of receipt, we do not view these activities as enhanced postmarketing surveillance activities.

In addition to the postmarketing surveillance activities described in the submission, we encourage reporting of potential and actual / ——— /

Attachment 3.

EVALUATION OF PATIENT EDUCATION

- The *Patient's Instruction for Use* Leaflet should be revised to include more complete patient information (and perhaps retitled *Patient Information*), with the instructions for use appended. We recommend following the Medication Guide format and content (21CFR 208) as a guideline for the appropriate information to include. As the *Patient Information* Leaflet is developed, it should also be written at a 6th to 8th grade reading comprehension level in order to reach a broad range of patients including those with low literacy. It is likely that all patients will receive this information as Advair is packaged in unit-of-use packaging.
- The *Patient Brochure* ~~_____~~ The *Patient Brochure* should be non-promotional and contain language that is consistent with the language in the *Patient Information* Leaflet and be written at a 6th to 8th grade reading comprehension level. The important risk information should be highlighted and not downplayed by potential benefits and artwork.
- The Patient package insert warns "to tell your doctor immediately if your asthma or COPD is getting worse, as indicated by any of the following situations..." the second bullet states "You need more inhalation than usual of your inhaled, short-acting bronchodilator..." ~~_____~~
- ~~_____~~
- ~~_____~~

Attachment 4.
ADDITIONAL COMMENTS on the RMP

The risk management plan for Advair Diskus does not address the increased risk of death in African-Americans who were exposed to salmeterol in SMART. An essential component of the risk management plan for Advair Diskus should be monitoring use of the drug by race. The risk to African-American subjects from the combination of fluticasone and salmeterol remains undefined. It is recommended that an approach to assessing the risk from exposure to the combination product, especially in African-American subjects, be considered.

The first paragraph of 3.1.1 states that dose and duration of oral corticosteroid use are associated with an increased risk of osteoporosis and fractures and that "current evidence from observational studies suggests that the long-term use of high dose inhaled corticosteroids is associated with a slight increase in risk of fracture." The submission briefly describes two studies that found small increases in the risk of fracture with inhaled corticosteroid use. One study had an average length of follow-up of only 1.7 years per person. In the other study, a small group using the highest dose produced an increased risk, however, the assessment of dose using claims data is very imprecise and often leads to misclassification which could bias any findings toward the null hypothesis.

With regard to the risk management strategy proposed, rather than to "minimize" the prescribing of high doses of Advair Diskus in the COPD patient population, an acceptable level of prescribing of high doses should be specified (e.g., 0%, 2%, etc.). By specifying an acceptable level to be attained, the risk management program can then be evaluated as to whether it attained the acceptable level of prescribing. Prescribing can be measured, as described in the submission, by examining pharmaceutical marketing or patient-level drug utilization data. Given the use of Advair Diskus by patients with asthma as well as with COPD, it is important to choose a data source that permits the distinction between these two patient groups as much as possible. A protocol specifying the source of data and its reliability would be necessary for evaluation.

The submission continues to explain that COPD patients are at higher risk for osteoporosis and fracture compared with age-matched controls due to their higher prevalence of many risk factors—cigarette smoking, poor nutrition, lower levels of physical activity, multiple comorbid conditions, and higher rates of oral corticosteroid use.

Because corticosteroids have been found to increase the risk of various problems, including adrenal suppression, osteoporosis, and cataracts, (and also hyperglycemia, steroid myopathy, psychiatric problems, and possibly gastrointestinal bleeding), and because inhaled corticosteroids would be expected to have similar (albeit lessened) pharmacological activity as the oral forms, the same reactions are possible in users of inhaled corticosteroids. The lifetime risk of osteoporosis and other disorders of interest associated with the use of inhaled corticosteroids is not currently known. A calculation

of the lifetime risk of osteoporosis would take into account that persons with COPD are already at risk of osteoporosis due to a number of factors. Concentrating only on the risk associated with inhaled corticosteroids (which is yet to be defined and may be relatively small compared with other risks) would miss the opportunity to favorably affect the health of patients with COPD who use inhaled corticosteroids. Consequently, GSK should consider the following points in assisting physicians and patients manage the risks of disorders prevalent in COPD patients associated with steroid use:

- 1) Individual analysis of risk to benefit in African-Americans and follow-up if prescription is deemed necessary.
- 2) Ensuring that only Advair Diskus 250/50 is prescribed for COPD treatment.
- 3) Ensuring that Advair Diskus 250/50 is prescribed for patients with COPD associated chronic bronchitis. The doctor should be provided with criteria for prescribing this drug, i.e., airflow obstruction, chronic bronchitis, and COPD. The product labeling should emphasize this point throughout by referring to the indication as not just COPD but as COPD associated with chronic bronchitis. To emphasize this point an _____ could be used throughout the labeling.
- 4) Ensuring that patients take only 2 inhalations per day—AM and PM. This could be placed on the package and in the patient package insert (or if applicable, Medication Guide) with a warning that failure to follow these recommendations could result in bone _____ problems.
- 5) Patients who use tobacco should be strongly encouraged to stop smoking and should be recommended to initiate smoking cessation programs. Health professionals and the patient package insert should state that smoking and steroid use increase the risk of bone thinning that can result in fractures and bone deformities.
- 6) Patients should be strongly encouraged to engage in walking or other physical exercise on a daily or frequent basis since exercise maintains bone and muscle mass.
- 7) Patients should be recommended to receive bone density scans on a regular basis. Since most COPD patients are middle-aged or elderly, this would not be inconsistent with recommendations for the adult white female population.
- 8) _____
_____ good nutrition aid immune system function.
- 9) Patients should be encouraged to have regular eye examinations and to protect their eyes from ultraviolet radiation while outdoors by wearing UV-blocking sunglasses. Patients should be instructed that long-term steroid use increases the risk of cataracts.
- 10) Physicians or health providers should review all medications with patients on a regular basis to identify other steroids and those that affect calcium metabolism.

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/s/

Joyce Weaver
10/6/03 08:01:18 AM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
10/7/03 12:41:15 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
10/7/03 04:18:30 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
10/7/03 04:33:38 PM
DRUG SAFETY OFFICE REVIEWER
Acceptable from the Division of Medication Errors and Technical
Support perspective

NDA 21-077/S-003 (Advair Diskus)
NDA 20-833/S-004 (Flovent Diskus)
Sponsor: GlaxoSmithKline
Indication: COPD
Date of Telecon: March 5, 2002

GlaxoSmithKline (GSK) Representative:

Elaine Jones, Ph.D., Director, Regulatory Affairs

Division of Pulmonary & Allergy Drug Products (DPADP):

Lydia Gilbert-McClain, M.D., Medical Reviewer
Ladan Jafari, Regulatory Project Manager
Charles Lee, M.D., Medical Reviewer
Robert Meyer, M.D., Director
Mary Purucker, M.D., Medical Team Leader

Background: The Division requested this meeting to inform GSK about the action taken for Advair and Flovent applications submitted for COPD indication.

- The Division informed GSK that we have decided to take an approvable action on these applications and that we do not believe any labeling should be communicated at this point until the deficiencies are further resolved. The deficiencies as outlined in the approvable letter are printed in *Italics* below.

We do not believe that you have provided substantial data to support a conclusion that these drug products are sufficiently safe and effective for the indication proposed in the COPD population. Given the modest and limited extent of the efficacy findings (including a lack of effect on exacerbation rates), given the known potential for fluticasone to cause adverse systemic effects as demonstrated by spontaneous adverse events reporting and clinical studies, and given the signal in the data sets provided of an increase in upper and lower respiratory infections, we believe that more definitive efficacy and safety data are needed prior to approval. In order to be approved, you must supply data that more fully delineates the safety (including impact on bone density) beyond 6-months and further evidence of efficacy (including outcome data). Data from your current, on-going 3-year trial in COPD, if favorable, may reasonably serve as a substantial portion of these requested data.

- The Division informed GSK that we have consulted with Drs. Jenkins and Kweder prior to making a final decision on these applications. We consulted the above individuals, particularly because our conclusions differ from those received in the votes taken by the Advisory Committee (though we did not feel our actions were inconsistent with much of the Advisory Committee's advice).

NDA 21-077/S-003 (Advair Diskus)
NDA 20-833/S-004 (Flovent Diskus)
Sponsor: GlaxoSmithKline
Indication: COPD
Date of Telecon: March 5, 2002
Page 3

Initialed by: Meyer/3-12-02

Filename: COPD Action Tcon.doc

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/s/

Ladan Jafari
3/12/02 03:54:16 PM

NDA :21-077/S-003 & 20-833/S-004

Drugs: Advair & Flovent

Applicant: GlaxoSmithKline (GSK)

Indication: COPD

Meeting Date: April 9,2002

IMTS: 8469

GSK Representatives:

Kourtney Davis, Ph.D., Associate Director, Worldwide Epidemiology

Patrick Darken, Ph.D., Principal Statistician

Andy Gustafson, Ph.D., Vice President, Regulatory Affairs

Michele Hardy, Group Director, Strategic Product Labeling

Elaine Jones, Ph.D., Senior Director, Regulatory Affairs

Kate Knobil, M.D., Senior Director, Respiratory Clinical Development & Medical Affairs

Cal McNeill, M.D., Director, Global Clinical Safety & Pharmacovigilance

Kathy Rickard, M.D., Vice President, Respiratory Clinical Development & Medical Affairs

David Wheadon, M.D., Senior Vice President, Regulatory Affairs

Patrick Wire, Pharm.D., Director, Respiratory Clinical Development & Medical Affairs

Division of Pulmonary & Allergy Drug Products (DPADP):

Emmanuel Fadiran, Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader

James Gebert, Ph.D., Biometrics Team Leader

Lydia Gilbert McClain, M.D., Medical Reviewer

Ladan Jafari, Regulatory Project Manager

Kofi Kumi, Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer

Charles Lee, M.D., Medical Reviewer

Mary Purucker, M.D., Ph.D., Medical Team Leader

Robert Meyer, M.D., Director

Sandra Suarez, Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer

Feng Zhou, M.S., Biometrics Reviewer

Background: GSK submitted a meeting request to further discuss the Division's rationale for taking an approvable action on the Flovent and Advair applications for the COPD indication. In addition, GSK wanted to discuss the path forward with these applications. GSK submitted a briefing package to the Division dated March 22, 2002, which contained additional summary efficacy information regarding Flovent and Advair Diskus for the COPD indication, details on the status of the on-going 3-year mortality reduction study of Advair and Flovent Diskus, proposed revised labeling, and proposed Phase 4 commitments.

NDA :21-077/S-003 & 20-833/S-004

Drugs: Advair & Flovent

Applicant: GlaxoSmithKline (GSK)

Indication: COPD

Meeting Date: April 9, 2002

IMTS: 8469

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- The Division did not agree with the above proposals.

the Division pointed out that there did not seem to be a manner in which, based on the data available, individual patients and/or doctors could decide if the patient was receiving benefit. Given its stated concerns, the

- GSK inquired as to how they could address the balance of safety and efficacy.
- The Division indicated that examination of bone mineral density in the population that is currently being studied in the 3-year trial should provide useful additional information. Even if there are no more evidence of efficacy resulting from this trial, but solely a better understanding of the effects on bone, we could possibly label the drug based on the new findings.
 - GSK indicated that they have long-term data from the use of fluticasone CFC MDI, which has the higher bioavailability than the Diskus, and their data shows that there are fewer fractures in the fluticasone group than the placebo. GSK also indicated that they have many years of patient exposure to fluticasone and if they could provide those data to the Division.
- The Division indicated that the COPD population, is a more fragile population starting off with lower bone density (as shown by GSK's own enrollment data in the 3-year trial) and that the proposed doses for COPD are high. The Division also indicated that it is difficult to take the absence of a clear signal from post-marketing data as confirming a lack of a problem because of the known profound underreporting and the lack of detail in most individual reports.
 - GSK suggested that they only pursue the Advair 250/50 at this time with labeling modifications and/or Phase 4 commitments, and asked if the Division found that proposal acceptable.
- The Division stated that we discussed the entire decision internally at the ODE and OND level prior to taking action on these applications,
 - little marginal benefit was shown for the 500/50 dose. However, we again decided that we needed a better elucidation of the benefit/risk ratio before we can approve Advair or Flovent for this indication.

NDA :21-077/S-003 & 20-833/S-004

Drugs: Advair & Flovent

Applicant: GlaxoSmithKline (GSK)

Indication: COPD

Meeting Date: April 9,2002

IMTS: 8469

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- GSK indicated that they have data on the primary efficacy end point, but do not know if they would ever show significance with secondary end points with this disease.
- The Division suggested that a mortality rate decrease would be convincing, if found in the current 3-year study. The Division stated that the proposed changes to the indication section as outlined in the briefing document appears to be in line with what would be necessary when these products are approved, and that we might be willing to consider the Advair 250/50 with additional systemic and respiratory safety data.

~~.....~~
information from the advisory committee, we make the final decision based on all the information that was provided to us, including agency experiences with labeling and risk-management.

Action: GSK indicated that they would still like to pursue the Advair 250/50 application with a tighter indication and plan to have additional discussions with the Agency regarding this proposal.

NDA :21-077/S-003 & 20-833/S-004
Drugs: Advair & Flovent
Applicant: GlaxoSmithKline (GSK)
Indication: COPD
Meeting Date: April 9,2002
IMTS: 8469
Page 5

Initialed by: Lee/4-18-02
Gilbert-McClain/4-18-02
Purucker/4-18-02
Meyer/4-18-02

Filename: GSK April COPD mtg

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/s/

Ladan Jafari
4/22/02 10:08:13 AM

NDA 21-077/S-003
NDA 20-692/S-016
NDA 20-833/S-004
Date of Telecon: September 28, 2001
IMTS: 7611

GlaxoSmithKline Representatives:

Tushar Shah, VP, Respiratory Clinical Development
Colin Reisner, Director, Respiratory Clinical Development
Don Horstman, Clinical Respiratory
Patrick Wire, Clinical Respiratory
Michael Watkins, Clinical Respiratory
Julie Yates, Clinical Respiratory
Tracy Fischer, Clinical Respiratory
Bob Kunka, Section Head, Clinical Pharmacology
Patrick Darken, Sr. Statistician
Shu-Yen Ho, Manager, Statistics
Michael Golden, Associate Director, CMC Regulatory
Elaine Jones, Director, Regulatory Affairs
Betsy Waldheim, Director, Regulatory Affairs

Division of Pulmonary & Allergy Drug Products (DPADP)

Lydia Gilbert-McClain, Clinical Reviewer
Eugene Sullivan, Clinical Reviewer
Charles Lee, Clinical Reviewer
Mary Purucker, Clinical Team Leader
Badrul Chowdhury, Clinical Team Leader
Robert Meyer, Director
Marianne Mann, Deputy Director
James Gebert, Biometrics Team Leader
Craig Ostroff, Regulatory Project Manager
Ladan Jafari, Regulatory Project Manager

Background: The Division requested this telecon to discuss the upcoming advisory committee meeting and to request for additional information regarding the supplemental applications (Flovent, Serevent, and Advair), which are under review for COPD indication.

NDA 21-077/S-003

NDA 20-692/S-016

NDA 20-833/S-004

Date of Telecon: September 28, 2001

IMTS: 7611

Page 2

- The Division informed GlaxoSmithKline that we plan to take the Flovent and Advair supplemental applications indicated for COPD to the advisory committee meeting, and indicated that we do not believe that the Serevent COPD supplement offers a unique question for discussion at the advisory committee meeting. The Division stated that we would be discussing the efficacy as well as safety concerns with the use of corticosteroids (e.g., bone effect). The Division indicated that Kimberly Topper is the executive secretary for the Advisors and Consultant Staff and she should be contacted for any further questions. The Division asked that GlaxoSmithKline keep the Pulmonary Division informed of any discussions they may have with Ms. Topper. The Division provided the following timelines to GlaxoSmithKline.

Advisory Committee meeting date: January 17 and 18, 2002

Submission of non-releasable background: Due by November 6, 2001

Submission of releasable background: Due by December 14, 2001

The discretion as to whether the data is releasable or non-releasable is at GlaxoSmithKline's discretion.

FDA's background: Due by December 17, 2001

The Federal Register notice will be submitted around November 1, 2001.

- The Division asked if GlaxoSmithKline was planning to submit any CMC information for the 500 mcg device. This Device was used in study 3025. The Division expressed concerns that we need information about the dose proportionality of 250 to 500 mcg device.
 - GlaxoSmithKline stated that they had submitted clinical pharmacology study to show dose proportionality between the 250 and 500 mcg device. This information was submitted as part of the supplemental NDA, identified as Item 6 in the submission. GlaxoSmithKline stated that they plan to submit full CMC data on the 500 mcg device, after approval of the NDA. Due to transfer of some of the manufacturing obligations from _____ / they believe there would be a delay in the submission of full CMC data. They plan to submit the information to the Division by May 2002.
- The Division also requested for additional information with regard to studies FLTA3025, SFCA 3006, and SFCA3007. The following request as well as additional statistical questions were then faxed to GlaxoSmithKline on October 1, 2001.

NDA 21-077/S-003

NDA 20-692/S-016

NDA 20-833/S-004

Date of Telecon: September 28, 2001

IMTS: 7611

Page 3

1. *The following comments pertain to the clinical portions of your applications.*

For FLTA3025, SFCA3006, and SFCA3007.

Provide a subgroup analysis of the non-reversible group, for all treatment arms including all randomized non-reversible patients

- *ATS definition, FEV1 increase <200 mL, or <12% improvement in FEV1 over baseline*
- *Assignment was stratified based on this definition of reversibility*

For the following:

- Demographic and Baseline characteristics*
 - *Gender, age, race, MMRC dyspnea score, inhaled steroids at screen, duration of COPD, emphysema, smoking status, pack-years smoked [as presented in clinstat\copd\flta3025.pdf, page 78]*
 - *Mean screening spirometry [as presented in clinstat\copd\flta3025.pdf, page 79]*
- Primary efficacy endpoint:*
 - *Mean change in FEV1 from baseline to study endpoint [as presented in clinstat\copd\flta3025.pdf, page 91]*
- The following secondary efficacy measures:*
 - *CBSQ, Global Assessment Score, mean change from baseline at endpoint [as presented in clinstat\copd\flta3025.pdf, page 93]*
 - *Incidence of COPD exacerbations of any severity [as presented in clinstat\copd\flta3025.pdf, page 96]*
 - *Number of puffs of Ventolin used per day, mean change from baseline at endpoint (Overall) [as presented in clinstat\copd\flta3025.pdf, page 98].*

The Division gave the example of looking at COPD versus asthma, the change in FEV1 over baseline, as defined by ATS.

Action: GlaxoSmithKline agreed to provide the requested information to the Division as soon as possible.

NDA 21-077/S-003
NDA 20-692/S-016
NDA 20-833/S-004
Date of Telecon: September 28, 2001
IMTS: 7611
Page 4

cc:

HFD-570/Div.files
HFD-570/Gilbert-McClain
HFD-570/Sullivan
HFD-570/Chowdhury
HFD-570/Purucker
HFD-570/Lee
HFD-570/Gebert
HFD-570/Guo
HFD-570/Ostroff
HFD-570/Jafari

Initialed by: Gilbert-McClain/10-15-01
Purucker/10-15-01
Lee/10-15-01
Meyer/10-23-01

Filename: COPDtelecon

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/s/

Ladan Jafari
12/3/01 10:29:29 AM
CSO

Memorandum of Telephone Facsimile Correspondence

Date: April 9, 2001

To: Sara Nelson
Regulatory Affairs

Fax: (919) 680-0955

From: Parinda Jani
Project Manager

Subject: **INDs:** 43,097; 44,090; 50,703
NDA: 20-692, 20-833, 21-077
December 1, 2000/Meeting

Reference is made to the meeting held between representatives of your company and this Division on December 1, 2000. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-1064.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

INDs 43,097, 44,090, 50,703
NDAs 20-236, 20-833, 21-077
Pre sNDA meeting/December 1, 2000
Page 2

Meeting Date: December 1, 2000

Location: Conference Room "K"

Sponsor: Glaxo Wellcome, Inc.

INDs: 43,097; 44,090; 50,703

NDAs: 20-692, 20-833, 21-077

Products: Serevent Diskus (salmeterol xinafoate inhalation powder), Flovent Diskus (fluticasone propionate inhalation powder) and Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder)

Type of Meeting: Pre sNDAs meeting

Time: 2.00 – 3:30 PM

IMTS #: 5588

FDA Attendees:

Young-Moon Choi, Ph.D.

James Gebert, Ph.D.

Lydia Gilbert-McClain, M.D.

Parinda Jani

Susan Johnson, Pharm.D., Ph.D.

Marianne Mann, M.D.

Robert Meyer, M.D.

Mary Purucker, M.D.

Curtis Rosebraugh, M.D.

Steve Wilson, Ph.D.

Biopharm

Biometrics Reviewer

Medical Officer

Project Manager

Medical Reviewer

Deputy Division Director

Division Director, DPADP

Medical Team Leader

Medical officer

Biometrics, Team Leader

Glaxo Attendees:

Patrick Darken, Ph.D.

Tracy Fischer, Pharm.D.

Tom Gerding

Shu-Yen Ho, Ph.D.

Don Horstman, Ph.D.

Bob Kunka, Ph.D.

Sara Nelson

Colin Reisner, M.D.

Senior Statistician

Clinical Research Scientist

Group Director, US Regulatory Affairs

Assistant Director, Biostatistics

Clinical Research Program Head, Clinical Development (COPD)

Clinical Pharmacokinetics

Associate Director, Regulatory Affairs (COPD)

Principal Clinical Research Program Head

Background: See the submissions dated April 4, 2000 (questions 1 – 11) and November 6, 2000 (questions 12 – 18). This meeting was originally scheduled for June 12, 2000; however, it was rescheduled per request of GW in order to be able to present the data from the pivotal studies.

The following issues were discussed.

1. **A single sNDA to cover all three products**

The clinical program consists of three pivotal studies, a combination of which will be used to support COPD indication for one or more of the three products

studies have significant overlap in the products they support, GW proposes to submit a single sNDA containing all of the clinical data for all three products. The full sNDA would be submitted to only one NDA and just a cover letter and labeling would be submitted to the other two NDAs. Does the Division concur?

The Division stated that separate supplements should be submitted for each NDA. GW could cross-reference pertinent data as appropriate. For the Flovent NDA, GW should also submit the _____

2. _____
_____ / Does the Division
concur?

Post-meeting follow-up: _____

3. _____
_____ / Does
the Division concur?

4. **Clinical Pharmacology and Human Pharmacokinetics and Bioavailability**

Since formal PK/PD studies and asthma studies with PK/PD information have been previously submitted to the Advair and Flovent NDAs. GW will not be resubmitting these reports to the COPD sNDA. Instead, GW will submit relevant PK/PD information from these reports with appropriate cross-references and compare these data with the subset of the COPD patients from whom the PK/PD information is collected. Does the Division concur?

The Division stated that the proposed approach is acceptable.

5. **Full study reports without appendices for non-pivotal clinical studies**

GW proposes that the sNDA consist of the full reports for the three pivotal studies identified earlier. These would be fully integrated clinical/statistical study reports

will all relevant appendices (CVs, protocols, sample case report forms, random codes, data listings, etc.) However, COPD studies that are not intended as primary support for the indication or ongoing COPD studies would be provided as full clinical/statistical reports that will contain tabular displays of data and narrative summaries of any serious adverse events, but would not include appendices. Does the Division concur?

The Division stated that the proposed approach is acceptable.

6. Multiple comparisons

All treatment comparisons would be replicated in the three pivotal studies.

See the revision of this question item # 16 and 17.

7. Organization of ISE and ISS

The ISE would contain a discussion of the results of the pivotal studies individually followed by an integrated discussion of the results of these studies by product. The ISS would include an integration of complete safety data from the pivotal clinical studies and a summary of SAEs from other COPD studies. In addition, both ISS and ISE would present data by subsets such as reversibility (using <12% of absolute as the cutoff), smoking status, previous steroid use, gender, age, and race. These subset analyses would not be presented in the individual reports. Does the Division concur?

The Division stated that the proposal to include subset analyses in the ISE and ISS is acceptable. However, the purpose of linking the long-term safety data from the Flovent NDA to the COPD population in the ISS is unclear.

In response, GW stated that it would be done primarily through a comparison of drug plasma levels and cortisol level between the populations and would be detailed in Item 6 of the submission and summarized in the ISS.

8.

The Division stated that data that relate the long-term safety in asthmatics to the COPD population, or data which otherwise characterize long term safety in COPD patients are necessary in this application. The data set should be complete at the time of submission. The Division asked when the data would be available and what safety assessments were performed in this study.

GW responded that the final study report would be available by October 1, 2001. Full study report for the 3-year study (ISOLDE) will be included in the sNDA.

The Division stated that it would consider the extent of safety data that would be included in the sNDA and will get back to GW about the proposal.

9. Foreign marketing experience

GW will provide only the list of countries and labeling for only those countries which have a COPD indication.

The Division stated that submitting labeling only from the countries that has the COPD indication for these products is acceptable.

10. Request for full pediatric waiver

Since COPD is primarily a disease of older adults, and is seen very rarely in young patients, GW is planning to request a waiver from the pediatric studies requirements. Does the Division concur?

The Division stated that the decision regarding a waiver under pediatric rule is made at the time of approval. At this time we expect to be able to grant a waiver, but a definitive response will be given at the time of approval.

11. Electronic components of the application

GW is evaluating the feasibility of submitting all or part of the COPD sNDA in accordance with the current guidance document for the electronic submissions. GW is requesting a separate meeting to discuss the electronic submission.

The electronic submission questions were answered at the August 4, 2000, meeting

12. **The requirements of the combination policy, Advair Diskus for COPD**

The results from trials SFCA3006 and SFCA3007 demonstrate that each component in ADVAIR for both doses contributed to the pulmonary function produced by the combination. There were no differences seen in the safety profile of the combination compared to the individual components administered alone. These data demonstrate that the two dosage strengths of Advair Diskus (250/50 and 500/50) are safe and effective for long-term, twice-daily administration for the maintenance treatment of COPD, including chronic bronchitis and emphysema, and would satisfy the requirements of the combination policy. Does the Division concur?

13. **Serevent Diskus for COPD**

Serevent Diskus administered alone demonstrated superiority to placebo for the maintenance treatment of airway obstruction associated with COPD. These data demonstrate that Serevent Diskus is safe and effective for long-term, twice-daily administration for the maintenance treatment of COPD, including chronic bronchitis and emphysema. Does the Division concur?

14. **Flovent Diskus for COPD**

Flovent Diskus 250 and 500 mcg strengths administered alone demonstrated superiority to placebo for the maintenance treatment of airway obstruction associated with COPD. These data demonstrate that Flovent Diskus is safe and effective for long-term, twice-daily administration for the maintenance treatment of COPD, including chronic bronchitis and emphysema. Does the Division concur?

Response for # 12, 13, and 14: The Division stated that the designs of the trials outlined are consistent with the discussion at the end-of-phase 2 meeting. However, there are concerns about the benefits of the use of steroid alone for the treatment of COPD. The information related to the long-term safety of these products in the COPD population, particularly Flovent should be included in the submission.

15. **Subgroup analysis**

Previously, GW had proposed to provide subgroup analyses in the ISE consisting of FEV1, CBSQ, BDI/TDI, CRDQ, and frequency and time of exacerbation from subgroup analyses.

Does the Division concur?

16. **Multiplicity**

For the Flovent study there was not a *priori* multiplicity strategy in place for the secondary measures. However, for the two other pivotal studies, the protocols were amended before the studies were unblinded to use a gate keeping strategy whereby a significant result for the primary endpoint is necessary as a prerequisite for inferential testing of the key secondary measures in a confirmatory way. Given statistical significance for the primary endpoint, then the Hochberg method is used to control multiplicity for the three key secondary measures (TDI, CRDQ, and CBSQ) for each treatment comparison. IN this way, type I error rate for each treatment comparison is controlled at the 0.05 level across the primary and the three key secondary measures in studies SFCA 3006 and SFCA 3007, and for the primary measure in study FLTA3025.]

The Division questioned how the statistical data would relate to the clinical relevance.

GW responded that a statistically significant result would be placed in the context of a clinically meaningful conclusion after all data had been reviewed in totality.

17. **Use of results from other efficacy measures**

~~_____~~, statistical explanatory analyses will be performed as specified in the protocols and the data analysis plans.

~~_____~~ Consistent patterns in the results from these explanatory analyses will be important for strengthening the findings for the primary and key secondary measures: they can also provide useful information in their own right for understanding the drug effects.

INDs 43,097, 44,090, 50,703
NDAs 20-236, 20-833, 21-077
Pre sNDA meeting/December 1, 2000

GW should give consideration to handling of the high dropout rate in the clinical trials and account for the missing data.

18. Priority review

GW is requesting that the supplemental application get priority review designation. Currently, only oral and inhaled bronchodilators are approved for the maintenance management of COPD. This program would be the first to demonstrate utility of a regularly administered anti-inflammatory agent for the maintenance treatment of COPD. Furthermore, this program would demonstrate that the regular administration of the combination of salmeterol and fluticasone provides additional benefit in the management of patients with COPD over the individual components from an overall efficacy perspective without compromising safety. GW feels that a priority review would be appropriate in light of the severity of this disorder and the limited therapeutic options currently approved for its management.

The Division stated that the preliminary data presented did not warrant a priority review for the sNDA, however, the decision would be made at the time the sNDA is submitted. The Division is very much concerned about the benefit/risk of administering a steroid on regular basis in this patient population. The discussion of the use of these products in COPD population will likely be undertaken with the advisory committee.

Parinda Jani
Project Manager

/s/

Parinda Jani

4/12/01 12:25:03 PM

Jafari, Ladan

From: patrick.d.wire@gsk.com
Sent: Wednesday, November 12, 2003 10:08 AM
To: JAFARIL@cder.fda.gov
Subject: Advair final label and post marketing commitments

Ladan,

Reference is made to the email containing the ADVAIR DISKUS prescribing information from the Division received on November 10th, 2003 and to the FAX of post-marketing commitments received on November 6th, 2003. Further reference is made to the FAX sent to the Division on November 7th, 2003 with the proposed changes to the post-marketing commitments.

GSK have accepted all changes to the label except where clarifications were required in a couple of areas.

In the revision of the ritonavir drug interaction section (line 194-297) the Agency has included arithmetic mean values for AUC and geometric mean values for Cmax. We have changed the AUC values to reflect the geometric means to be consistent with Cmax and the other pharmacokinetic values provided in the label.

In the revision of the cosyntropin stimulation section (line 310-319) the Agency had changed the number of salmeterol subjects reporting an abnormality based on page 166 of SFCA3007.pdf. This information was updated in correspondence that was sent to the Division on October 26th, 2001. The corrected information is provided on page 34 (Table 9.17 Page 3 of 3) of that correspondence. We have changed the value for salmeterol to reflect the corrected data.

No substantial revisions were made to the comments on the Patient Instruction Leaflet; however, some minor editorial changes were made and therefore we have provided a revised version.

Please find attached the following files:

Filename	Contents
proposed.doc	This file contains the prescribing information for ADVAIR DISKUS using the Division email of November 10th, 2003 as a base with all revisions marked.
instructions.doc	This file contains the patient information leaflet for ADVAIR DISKUS using the Division email of November 10th, 2003 as a base with all revisions marked
clean.doc	This file contains the prescribing information for ADVAIR DISKUS with all revisions incorporated.
instructions-clean.doc	This file contains the patient information leaflet for ADVAIR DISKUS with all revisions incorporated.

The following is our current understanding of the post-marketing commitments in which we have agreed:

11/12/2003

Regulatory Affairs
Advair COPD and Flovent
919-483-7650

**Appears This Way
On Original**

Post Marketing Study Commitments:

1. Conduct a randomized double-blind parallel-group clinical trial evaluating the effect of Advair 250/50 via Diskus on bone mineral density in subjects with chronic obstructive pulmonary disease (COPD).
2. Conduct a randomized double-blind, parallel-group study to evaluate the effect of Advair 250/50 via Diskus on exacerbations in subjects with COPD.

Agreements

1. Review all new spontaneous cases describing adverse events of special interest within 1-2 days of receipt and follow up on the cases for full documentation using targeted questions.
2. Review all new serious unexpected cases (spontaneous cases and attributable clinical trial cases) within 1-2 days of receipt and follow up on the cases for full documentation using targeted questions.
3. Maintain monthly listings and review of all newly reported adverse events of interest and monthly data mining of GSK's spontaneous adverse event database for adverse events of special interest – namely (a) decrease bone mineral density, osteoporosis, and fractures (b) cataract and glaucoma, (c) adrenal suppression (d) lower respiratory tract infections {pneumonia}
- / Submit a quarterly listing and review of all serious adverse events occurring during clinical trials with Advair.
5. Submit a quarterly cumulative review of all spontaneous reports and serious clinical trial cases of adverse events of special interest – namely (a) decrease bone mineral density, osteoporosis, and fractures (b) cataract and glaucoma, (c) adrenal suppression (d) lower respiratory tract infections {pneumonia}
6. Submit cumulative review of all spontaneous reports describing pneumonia, categorized by patient age, total daily dose and indication at six month intervals.
7. Submit a plan for evaluating the performance of the elements of the program with details of the timeline and the methodology that will be applied in the risk management plan.
8. Specify a time when you will report back to the Agency to provide data on (a) the extent of high-dose use of Advair Diskus among patients with COPD and (b) the extent of compliance with the risk management plan and complications of product use (through claims databases).
9. Produce educational materials for both physicians and patients which will advise of the risk that COPD patients have for bone demineralization, glaucoma or cataracts and the increase in risk associated with inhaled corticosteroid use. In addition we will advise physicians and patients on the appropriate dose of Advair Diskus for the treatment of COPD associated with Chronic Bronchitis.

We would like to thank the Division for working with GSK on the final label for Advair Diskus. I will also make a full electronic submission of this information that will include the files in a pdf format. Please let me know if you have any questions regarding this submission.

Patrick D. Wire

11/12/2003

GlaxoSmithKline**FACSIMILE**

DATE NOVEMBER 7, 2003 **TOTAL PAGES** 2

To Ms. Ladan Jafari **FAX** 301 827-1271
 Food and Drug Administration **PHONE** 301 827-1084

FROM Mr. Patrick D. Wire, Pharm.D. **FAX** 919-315-0033
PHONE 919-483-7650

Re: **NDA 21-077/S-003; ADVAIR DISKUS® (fluticasone propionate/salmeterol inhalation powder) 100/50 mcg, 250/50 mcg and 500/50 mcg**
Response to FDA Request/Comment: Other- Post-marketing commitments

Ms. Jafari,

Reference is made to your FAX dated November 6th, 2003 containing the post-marketing commitments and agreements. As requested the following are the timelines for the two studies that were requested.

	Final protocol	Study start	Final report
BMD study:	1Q04	2Q04	3Q07
Exacerbation study:	1Q04	2Q04	2Q07

We also agree to the eight agreements that were listed in the November 6th, 2003 FAX and look forward to further discussions with the Division on these post-marketing commitments. We have the following clarification to offer and have added an additional agreement per my conversation with Ms. Sandy Barnes on November 7th, 2003.

The information contained in these documents is confidential and may also be privileged and is intended for the exclusive use of the addressee designated above. If you are not the addressee any disclosures, reproduction, distribution, or any other dissemination or use of this communication is strictly prohibited. If you have received this transmission in error please contact us immediately by telephone so that we can arrange for its return.

GlaxoSmithKline
 Five Moore Drive
 PO Box 13398
 Research Triangle Park, NC
 27708-3398

U. S. Regulatory Affairs
 Phone 919-483-2100

~~(1) decrease in bone mineral density, osteoporosis, and fractures (b) cataract and glaucoma, (c) adrenal suppression (d) lower respiratory tract infections [pneumonia] and submit with quarterly reports.~~

We would propose that the data mining would only occur in the [spontaneous] adverse event database. So we would propose the following alternative wording:

Maintain monthly listing and review of all newly reported adverse events of interest and monthly data mining of GSK's spontaneous adverse event database for adverse events of special interest- namely (a) decrease in bone mineral density, osteoporosis, and fractures (b) cataract and glaucoma, (c) adrenal suppression (d) lower respiratory tract infections [pneumonia] and submit with quarterly reports.

Agreement #8

Specify a time when you will report back to the Agency to provide data on (a) the extent of high-dose use of Advair Diskus among patients with COPD and (b) the extent of compliance with the risk management plan and complications of product use (through surveys of COPD patients and/or physicians).

We agree that we will provide data on the use of high dose Advair Diskus among patients with COPD, and the compliance of the risk management plan and complication of product use. After approval, we would welcome the opportunity to discuss with the Agency the most appropriate methodology to accomplish the collection of this data, however we would like to suggest that claims databases would be a more appropriate way to accomplish collection of this data, as historically they have proven to be more accurate.

Additional Agreement

As specified in our proposed Risk Management Plan, we will commit to produce educational materials for both physicians and patients which will advise of the risk that COPD patients have for bone demineralization, glaucoma or cataracts and the increase in risk associated with inhaled corticosteroid use. In addition we will advise physicians and patients on the appropriate dose of Advair Diskus for the treatment of COPD associated with Chronic Bronchitis.

Please call me if you have any questions on this submission (919) 483-7650.

Dear Dr. Wire:

We are reviewing your supplemental new drug application for Advair Diskus for COPD. Please respond to the following Post marketing study commitments and agreements by COB Friday, November 7, 2003, and propose a timeline listing dates for submission of protocol, study start date, and date for submission of final report for each of these Post marketing study commitments. You must commit to conducting the following two Post marketing study commitments and agree that as part of your risk management plan, you will follow enhanced post-marketing surveillance activities to include labeling and educational materials.

Post marketing study commitments:

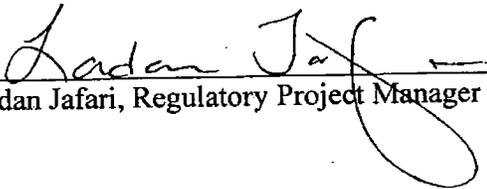
1. Conduct a randomized double-blind parallel-group clinical trial evaluating the effect of Advair 250/50 via Diskus on bone mineral density in subjects with chronic obstructive pulmonary disease (COPD).
2. Conduct a randomized double-blind, parallel-group study to evaluate the effect of Advair 250/50 via Diskus on exacerbations in subjects with COPD.

Agreements

1. Review all new spontaneous cases describing adverse events of special interest within 1-2 days of receipt and follow up on the cases for full documentation using targeted questions.
2. Review all new serious unexpected cases (spontaneous cases and attributable clinical trial cases) within 1-2 days of receipt and follow up on the cases for full documentation using targeted questions.
3. Maintain monthly listings and review of all newly reported adverse events of interest and monthly data mining of GSK's adverse event database for adverse events of special interest – namely (a) decrease bone mineral density, osteoporosis, and fractures (b) cataract and glaucoma, (c) adrenal suppression (d) lower respiratory tract infections [pneumonia] and submit with quarterly reports.
4. Submit a quarterly listing and review of all serious adverse events occurring during clinical trials with Advair
5. Submit a quarterly cumulative review of all spontaneous reports and serious clinical trial cases of adverse events of special interest - namely (a) decrease bone mineral density, osteoporosis, and fractures (b) cataract and glaucoma, (c) adrenal suppression (d) lower respiratory tract infections [pneumonia] categorized by patient age, total daily dose, indication and duration of treatment.

6. Submit cumulative review of all spontaneous reports describing pneumonia, categorized by patient age, total daily dose and indication at six month intervals.
7. Submit a plan for evaluating the performance of the elements of the program with details of the timeline and the methodology that will be applied in the risk management plan.
8. Specify a time when you will report back to the Agency to provide data on (a) the extent of high-dose use of Advair Diskus among patients with COPD and (b) the extent of compliance with the risk management plan and complications of product use (through surveys of COPD patients and/or physicians).

If you have any questions, I may be reached at 301-827-1084.


Ladan Jafari, Regulatory Project Manager

NDA 21-077/S-003

Page 3

Initialed by: Barnes/11-6-03
Gilbert-McClain/11-6-03

Filename: Advair COPD Phase4 commitments



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-077/S-003

GlaxoSmithKline
P. O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Patrick D. Wire, Pharm.D.
Product Director, Respiratory Group

Dear Dr. Wire:

We acknowledge receipt on July 12, 2002, of your June July 10, 2002, resubmission to your supplemental new drug application for Advair Diskus (fluticasone propionate/salmeterol xinafoate inhalation powder).

We consider this a complete, class 2 response to our March 2, 2002, action letter. Therefore, the user fee goal date is January 12, 2003.

If you have any question, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Sandra L. Barnes
Chief, Project Management Staff
Division of Pulmonary & Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ladan Jafari
7/22/02 04:23:03 PM
Signed for Sandy Barnes.



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

DATE: December 19, 2001

FROM: Robert J. Meyer, MD, 
Director, Division of Pulmonary and Allergy Drug Products, FDA

TO: Members, Pulmonary and Allergy Drugs Advisory Committee (PADAC)

SUBJECT: Overview of the FDA background information on the supplemental NDA applications for Advair Diskus and Flovent Diskus for the treatment of COPD

This memorandum serves as an introduction to the FDA background materials for the upcoming (January 17th, 2001) meeting of the PADAC to discuss the supplemental NDAs from GlaxoSmithKline (GSK) seeking an approval for Advair Diskus (fluticasone propionate/salmeterol xinafoate dry powder inhaler) and Flovent Diskus (fluticasone propionate dry powder inhaler) for the treatment of Chronic Obstructive Pulmonary Disease.

In introducing these materials, there are a number of important points to be made.

First, the background materials from FDA represent the findings and opinions of the primary medical reviewers of each application, based on their reviews of the respective submissions from GSK. As such, these documents contain statements of the reviewer's findings, conclusions and other statements that stem from their reviews and interpretations of the data presented. It must be emphasized that these documents represent the review teams' preliminary findings, and that no regulatory decision on the status of either of these applications has been made. Indeed, an important piece of our thinking on these applications will be a full consideration of whatever advice the PADAC provides on these important issues.

Secondly, it is well understood by the Division of Pulmonary and Allergy Drug Products that it is common in the practice of medicine for inhaled corticosteroids to be used in the treatment of COPD. We are also well aware that there are documents that recommend the use of long-term inhaled corticosteroids in certain sub-populations of COPD (albeit based on a level of evidence acknowledged to be less than "substantial").¹ However, using an approved drug off label in the best judgement of a practicing physician and their individual patients, is quite different from the U.S. Food and Drug Administration approving the drug for that specific use. Under the Food, Drug and Cosmetics Act (FD&C Act), the FDA approves

¹ Global Initiative for Chronic Obstructive Lung Disease – Executive Summary, NHLBI / WHO March, 2001 – NIH publication No. 2701A

drugs based on "substantial evidence" of safety and effectiveness. This is, necessarily, a different evidentiary standard than choosing to use a drug in practice. To date, the FDA has NOT included COPD in the indication for any inhaled corticosteroid-containing product, so this is a watershed question to the committee. A recommendation for approval by the committee needs to take into account the FD&C Act's evidentiary standard and needs to fully take into account the overall risk/benefit ratio for these drugs in question. I would add that a very real part of this risk/benefit consideration relates to the safety of inhaled corticosteroids in this primarily elder population. There has, in recent years, been rising evidence that long-term inhaled corticosteroids have systemic effects (e.g., adrenal suppression, growth inhibition, cataracts, decreased bone density). Indeed, important adverse systemic effects have been seen in previous trials in the COPD population.² Any evidence of efficacy must be weighed, then, against the known and potential safety issues that would result from these drugs being chronically administered to a population that largely is middle-age or older (and for females, largely post-menopausal).

Lastly, it must be emphasized that we are discussing two different applications during the meeting on the 17th. While the data are linked due to a number of shared studies supporting each application, any recommendation on the approval of ADVAIR and/or Flovent for the treatment of COPD must be given on its own merits, considering the particulars of their respective databases. A recommendation, positive or negative, by the committee for one agent should not be regarded as being synonymous with a recommendation for the other.

Beyond the overall examination of the safety and efficacy data for each drug product, some critical issues for you to consider as you read the Agency's and Sponsor's background materials include whether each drug should be broadly indicated or should be restricted in any indication to a specific subpopulation of COPD and the issue of what might be the most appropriate dose or doses (since each application examined more than 1 dose).

We look forward to a very interesting meeting and thank you in advance for your time and efforts in this critical meeting.

² Lung Health Study; N Engl J Med 2000 Dec 28;343(26):1902-9

**Notice of Public Meeting, FDA, Pulmonary-
Allergy Drugs Advisory Committee**

**see: Federal Register/Vol. 66/No.
249/Friday, December 28, 2001/Notices**

Dear Dr. Jones:

We are reviewing your submission dated May 4, 2001, and have several questions. Please provide the requested information as soon as possible to assist us in our review.

The protocols define a reversible and non-reversible population for the US ITT population and define a poorly-reversible population for the non-US ITT population. The protocol provides definitions for these populations, however, the data results are confusing and we need further clarification on these populations. Examples are taken from Protocol SFCA 3006 but similar concerns apply to protocols SFCA 3007 and FLTA3025.

Protocol SFCA 3006 describes assignment to study drug based on stratification according to the subjects' response to reversibility testing with Ventolin; i.e., Reversible (≥ 200 mL and $\geq 12\%$ improvement in FEV₁ over baseline) or non-reversible (< 200 mL or $< 12\%$ improvement in FEV₁ over baseline for the US Intent-to-Treat Population).

The protocol also defines a poorly-reversible population [For the non-US population] as subjects that demonstrated an increase in percent predicted FEV₁ of $< 10\%$ after reversibility testing with Ventolin.

Based on the above, we have the following questions.

1. Is the poorly-reversible population a subset of the population enrolled in the study or an entirely different population?
2. If the poorly-reversible population is a subset of the study population from which subjects were stratified as reversible and non-reversible, then please explain the following:

The table on page 97 of the submission (sourced from data table 6.9 and 6.10) shows for the ITT population (excluding investigator 1403)

Total subjects = 674

Total reversible subjects = 361

Total non-reversible subjects = 313

The table on page 100 (sourced from table 6.15 and 6.12) summarizes the subject accountability for the poorly-reversible population. The total number of subjects in that table = 492

- a. Since the non-reversible subjects have FEV₁ $< 12\%$, and the poorly-reversible subjects have FEV₁ $< 10\%$, explain why the poorly-reversible population has a larger (n = 492) than the non-reversible population (n = 361)
- b. Explain the bronchodilator response results for the study population (ITT) outlined on page 97 and the poorly-reversible population outlined on page 104. These results are confusing. For instance, for the ITT population (page 97) results for the placebo group non-reversible subjects (n=80, response = 8.33%), for the

poorly-reversible population (page 104) results for the placebo group $n = 136$, response = 5.12%). Similarly, subjects in all the active treatment groups in the poorly-reversible population have larger N_s than non-reversible population, yet the bronchodilator response for the non-reversible population ($FEV_1 < 12\%$) is almost twice that of the poorly-reversible population ($FEV_1 < 10\%$).

3. Explain the meaning of the Acronym ROW mentioned on page 57.

If you have any questions, please contact Mrs. Gretchen Trout, Project Manager, at 301-827-1058.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Gretchen Trout
8/1/01 11:05:51 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 1, 2001

To: Ms. Betsy Waldheim	From: Ladan Jafari
Company: GlaxoSmithkline	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5756	Fax number: 301-827-1271
Phone number: 919-483-5319	Phone number: 301-827-5584
Subject: Clinical and Statistical comments for SNDA 20-833, 20-692, and 21-077	

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES NO

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NDA 20-833/S-004
NDA 20-692/S-016
NDA 21-077/S-003

We are reviewing your supplemental applications for Advair Diskus, Serevent Diskus, and Flovent Diskus for COPD indication, and have the following questions.

1. The following comments pertain to the clinical portions of your applications.

For FLTA3025, SFCA3006, and SFCA3007.

Provide a subgroup analysis of the non-reversible group, for all treatment arms including all randomized non-reversible patients

- ATS definition, FEV1 increase <200 mL, or <12% improvement in FEV1 over baseline
- Assignment was stratified based on this definition of reversibility

For the following:

- a. Demographic and Baseline characteristics
 - Gender, age, race, MMRC dyspnea score, inhaled steroids at screen, duration of COPD, emphysema, smoking status, pack-years smoked [as presented in `clinstat\copd\flta3025.pdf`, page 78]
 - Mean screening spirometry [as presented in `clinstat\copd\flta3025.pdf`, page 79]
- b. Primary efficacy endpoint:
 - Mean change in FEV1 from baseline to study endpoint [as presented in `clinstat\copd\flta3025.pdf`, page 91]
- c. The following secondary efficacy measures:
 - CBSQ, Global Assessment Score, mean change from baseline at endpoint [as presented in `clinstat\copd\flta3025.pdf`, page 93]
 - Incidence of COPD exacerbations of any severity [as presented in `clinstat\copd\flta3025.pdf`, page 96]
 - Number of puffs of Ventolin used per day, mean change from baseline at endpoint (Overall) [as presented in `clinstat\copd\flta3025.pdf`, page 98].

NDA 20-20-833/S-004

NDA 20-692/S-016

NDA 21-077/S-003

Page 2

2. The following comments pertain to the statistical portions of your submissions with regard to study SFCA3006, SFCA 3007, and FLTA3025.
 - a. There is not a variable for the week or visit number. A variable, SESS appears to serve as an indicator for visit. How was the variable SESS defined and what does SESS=2.9 mean? If the primary efficacy evaluation was based on FEV₁ measurements at Week 24, how do you handle the patients last measured earlier or later than 24 weeks in your data presentation and analysis (e.g., 22 weeks or 27 weeks)?
 - b. The variable, PGMPOP labeled "PR/excl. invid. 1403?" is used to define poor reversibility based on ERS definition. How do you explain missing values (e.g., see patient 15482)?
 - c. There is not a variable for reversibility based on ATS definition in PFT.XPT. Can this variable, if any, be found in other data sets submitted? If not, supply a new data set with ATS reversibility indicators along with the formulas from which the indicators were calculated.
 - d. In your August 10, 2001, response, you explained the definitions for reversibility and poor reversibility with an example. When was the reversibility of a patient determined? If it was determined in the screening period, what does "baseline" mean in the definition? In addition, which data set should we use to recalculate it, assuming the pre-baseline data were not in PFT.XPT.
 - e. In the definitions for reversibility, 12% and 10% are used as cutoff points for the specified increase. What happens when the increase is actually negative? Do the definitions still apply?
 - f. Two data sets, PFT.XPT and PFTS.XPT were described for pulmonary function test. How do they differ? Which one was used in the primary analysis?

- (1) Protocol-violation data. The following snapshot shows part of a data set merging PROTVAR.SD2 and PROVARTX.SD2. Are the violation codes and protocol variation text related?

PATIENT	Were there any protocol violations?	Occurrence level	Protocol variation text
10086		1	
10233	N	1	TREATMENT DISKUS DISPENSED DURING RUN IN PHASE(#1260)
10281		1	PATIENT WAS PUT ON FLUTICASONE FOR ADVERSE EVENT
10433	N	1	WEEK 20 24 PATIENT RECEIVED INCORRECT PACK TREATMENT NUMBER
10531	N	1	NO VARIATIONS
10540	N	1	01 EXCL
10889	N	1	PROHIBITED MEDICATION
10944		1	PATIENT ONLY WASHED OFF 4 1/2 WEEKS FROM PREDNISON
11103		1	PT WAS RANDOMIZED AS REVERSIBLE IN ERROR
11287	N	1	PT WAS GIVEN TREATMENT PACK #1638 INSTEAD OF SINGLE BLIND
11377	N	1	TX DAY 1 PREDOSE PULSE NOT OBTAINED, PREDOSE PULSE NOT OBTAIN
11393	N	1	POST 2 HOUR SPIROMETRY NOT PERFORMED IN ERROR
11549	N	1	PATIENT USING BECONASE AQ NASAL SINCE 01/MAY/99. ENROLLED DUE
15824	N	1	PATIENT TOOK PREDNISON WITHIN THE 6 WEEKS PRIOR TO STUDY ENTY
15825	N	1	PATIENT TOOK CELEXA, AN ANTI DEPRESSANT STARTING 10/15/99 AND
15919	N	1	DISCOVERED DURING THE STUDY PT. HAD SUSPECTED ALCOHOL ABUSE
8937		1	NONE
9327		1	ON JUNE 18,1999 PT. RECEIVED WRONG STUDY MEDICATION PACK THIS
9330		1	POST STIM CORTISOL SAMPLE DRAWN AFTER ADMINISTRATION OF STUDY
9331		1	POST STIM CORTISOL SAMPLE DRAWN AFTER ADMINISTRATION OF STUDY
9332		1	POST STIM CORTISOL SAMPLE DRAWN AFTER ADMINISTRATION OF STUDY
9629	N	1	POST STIM CORTISOL SAMPLE DRAWN AFTER ADMINISTRATION OF STUDY
9977	N	1	TV 6 POST DOSE VITALS AND SPIROMETRY PERFORMED 1 HOUR LATE
9978		1	PATIENT TOOK PROHIBITED CONMED DUE WORSENING COPD(WEATHER
		1	INCORRECT STUDY MED PACK DISPENSED. PT RECEIVED 5 DOSES

Please explain, modify and insert adequate indicators (variables) so that data subsetting and stratifications can be done easily. If LOCF for FEV₁ is used, it is recommended to add an indicator to signify whether the FEV₁ value was an actual observation or a value carried over from a previous visit. It is not necessary to put all variables in a single data set. It is even more desirable to put them into different data sets with patient number as the key for future merging.

NDA 20-20-833/S-004

NDA 20-692/S-016

NDA 21-077/S-003

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cc:

HFD-570/Divfiles

HFD-570/Lee

HFD-570/McClain

HFD-570/Sullivan

HFD-570/Chowdhury

HFD-570/Guo

HFD-570/Gebert

HFD-570/Jafari

Initialed by: Barnes10-1-01
Lee/10-1-01
McClain/10-1-01
Purucker10-1-01
Gebert/10-1-01

Filename:COPDIR

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this page is the manifestation of the electronic signature.**

/s/

Ladan Jafari
10/2/01 08:41:25 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 18, 2001

TO: Ladan Jafari, CSO, Regulatory Project Manager
Charles E. Lee, M.D., Clinical Reviewer
Division of Pulmonary & Allergy Drug Products, HFD-570

THROUGH: John Martin, M.D., Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

FROM: H. W. Ju, M.D., GCP1 Reviewer

SUBJECT: Evaluation of Clinical Inspections

NDA: #20-833

APPLICANT: Glaxo Wellcome, Inc.

DRUG: Flovent[®] Diskus[®] fluticasone propionate inhalation powder

INDICATION: Treatment of COPD

CONSULTATION REQUEST DATE: August 1, 2001

ACTION GOAL DATE: December 14, 2001

PDUFA DATE: March 25, 2002

I. BACKGROUND: Goals of inspections are as follows:

Goals of inspections are to verify the efficacy and safety endpoints generated by 2 studies.

The primary efficacy measure is the spirometric assessment of pulmonary function with the morning pre-dose FEV1. Protocol SFCA 3007 also measure the 2-hour post-dose FEV1

Safety is assessed by examining adverse events, ECGs, routine lab tests, oropharyngeal examinations, and vital signs. Cosyntropin stimulation testing was performed in certain selected sites.

The Medical Officer of the review division selected certain FEV1 values for verification.

II. RESULTS (by protocol/site):

NAME	CITY	STATE	ASSIGNED DATE	ACTION DATE	CLASSIFICATION
Elias	LaJolla	CA	22-Aug-01	12-Dec-01	VAI
Tashkin	Los Angeles	CA	22-May-01	12-Dec-01	VAI

A. Protocol #SFCA3007

Site #0010 Darlene J. Elias, M.D. LaJolla, CA

There were no limitations to this inspection. A total of 33 patients were screened and signed the informed consent. 28 of 33 received the study drug. Twenty-one patients completed the study and seven dropped out of the study due to adverse events. Fifteen of 28 subjects' records were reviewed. The investigator's source documents were adequate in terms of their organization, condition, completeness, and legibility. Data of FEV1 from Table 3 were verified with the source document during the audit. The FEV1 data for subjects #12387, 12392, 12401, 12403, and 12410 were identical with the data provided in the assignment. Thirteen of fifteen subjects indicate that the spirometry measurements of 2 hours post dose FEV were performed 4 minutes to 18 minutes earlier than was specified in the protocol. This observation was discussed with the medical officer of the review division. The data appear acceptable.

B. Protocol #FLTA3025

Site #0049 Donald P. Tashkin, M.D.

There were no limitations to this inspection. A total of 29 subjects were enrolled in the study and 10 subjects completed study. Each subject completed and dated the consent form. The subjects' CRFs were compared to source documents such as pulmonary function reports, laboratory reports, diaries, EKG strips, physical exam records, study visit records, health questionnaires, and drug dispensing records. The tabulation provided by the medical officer of FDA reviewing division was also compared with the source data. No discrepancy was noted. However, the protocol was not always followed in that the screening visit spirometry was not always performed 30 minutes following self-administration of Ventolin. This question was discussed with the medical officer of the reviewing division. The data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Data generated by the two clinical investigators for the above studies appear acceptable for consideration in the drug application. No follow-up actions are scheduled at this time


H. W. Jr., M.D.
Medical Officer
Good Clinical Practice Branch 1

CONCURRENCE:

Supervisory comments


John Martin, M.D., Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

Page 3 Summary NDA #21-340

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HFD-46/GCP1 Branch Chief

HFD-46/GCPB Files #10502 (Elias), #00753 (Tashkin)

HFD-46/47/Reading File

File: O:/JU/SummaryFlovent.doc

April 16, 2001



Mellon Bank
Food and Drug Administration
27th Floor (FDA 360909)
Three Mellon Bank Center
Pittsburgh, PA 15259-0001

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709
Tel. 919 483 2100
www.gsk.com

**Re: NDA 21-077; ADVAIR™ DISKUS® (fluticasone propionate/salmeterol inhalation powder)
100/50 mcg, 250/50 mcg and 500/50 mcg
User Fee: With Clinical Data
User Fee: —**

Please find enclosed Glaxo Wellcome check number 1777571 in the amount of \$154,823.00. This payment is 100% of the application fee for the supplemental New Drug Application: Treatment of Chronic Obstructive Pulmonary Disease (COPD). This application will be submitted to the Division of Pulmonary and Allergy Drug Products, Center for Drug Evaluation and Research, FDA.

Please find below requested information regarding this application.

Type of Application	New Drug Application with Clinical Data	
	New Drug Application without Clinical Data	
	Supplemental New Drug Application with Clinical Data	X

Should you have any questions, please contact E. Allen Jones at (919) 483-9122.

Sincerely,

Sara A. Nelson
Associate Director
Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

3. PRODUCT NAME

ADVAIR DISKUS (fluticasone propionate/salmeterol inhalation powder), 100/50mcg, 250/50mcg, 500/50mcg)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? **Yes**
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

- THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
 THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____
(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(919) 483-2100

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

NDA 21-077

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)
- THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
- THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)
- FOR BIOLOGICAL PRODUCTS ONLY**
- WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
- AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY
- BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92
- A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE. (See item 7, reverse side before checking box.)
- THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, drug, and Cosmetic Act (See item 7, reverse side before checking box.)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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Sara A. Nelson
Sara A. Nelson

TITLE

Associate Director, Regulatory Affairs

DATE

April 16, 2001

FOOD AND DRUG ADMINISTRATION
 P.O. BOX 360909
 PITTSBURGH PA 15259-0001



P.O. BOX 13358
 RESEARCH TRIANGLE PARK, N.C. 27709

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CHECK NUMBER
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 ONLY \$154,823.00

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to order FOOD AND DRUG ADMINISTRATION
 P.O. BOX 360909
 PITTSBURGH PA 15259-0001

Robert Astumian
 Authorized Signature

⑆ 1777571 ⑆ ⑆ 053107633 ⑆ 010459 002194 ⑆