CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021077Orig1s056

Trade Name:	ADVAIR DISKUS
Generic or Proper Name:	fluticasone propionate and salmeterol xinafoate inhalation powder
Sponsor:	GlaxoSmithKline
Approval Date:	December 20, 2017
Indication:	ADVAIR DISKUS is a combination product containing a corticosteroid and a long-acting beta2-adrenergic agonist (LABA) indicated for: • Twice-daily treatment of asthma in patients aged 4 years and older. • Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD).

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21077/S-056 and S-057

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

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

Attention: Kevin C. Fitzgerald, R.Ph.
Senior Director, Global Regulatory Affairs

Dear Mr. Fitzgerald:

Please refer to your Supplemental New Drug Applications (sNDAs) dated October 3, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Advair Diskus (fluticasone propionate/salmeterol xinafoate) Inhalation Powder, 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg.

We acknowledge receipt of your major amendment dated July 13, 2017, which extended the goal date by three months.

These Prior Approval supplemental new drug applications provide for changes to the prescribing information to incorporate the results of the required safety trials with Advair Diskus and revised class labeling for inhaled corticosteroid/long-acting beta agonist combination products, including removal of the Boxed Warning for asthma-related death. These supplements also provide for replacement of the Medication Guide with the Patient Information leaflet and revised labeling in accordance with the Pregnancy and Lactation Labeling Rule (PLLR).

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert, text for the patient information leaflet, and text for the instructions for use, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

FULFULLMENT OF POSTMARKETING COMMITMENT

We have received your submissions dated January 15 and May 19, 2016, containing the final reports for the following postmarketing requirements listed in the April 14, 2011 postapproval postmarketing requirement letter.

1750-1 A randomized, double-blind, 26-week, active controlled clinical trial comparing

Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) and fluticasone propionate inhalation powder to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 11,700 adult and adolescent patients 12 years of age and older with persistent asthma.

Final Protocol Submission: May 2011
Trial Completion: February 2017
Final Report Submission: June 2017

1750-2 A randomized, double-blind, 26-week, active controlled clinical trial comparing Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) and Flovent Diskus (fluticasone propionate inhalation powder) to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 6200 pediatric patients 4 to 11 years of age with persistent asthma.

Final Protocol Submission: May 2011
Trial Completion: February 2017
Final Report Submission: June 2017

We have reviewed your submissions and conclude that the above requirements were fulfilled.

This completes all your postmarketing requirements acknowledged in our April 14, 2011, letter.

REPORTING REQUIREMENTS

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 Carol F. Hill, Senior Regulatory Health Project Manager for Safety, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Sally Seymour, MD
Deputy Director for Safety
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

SALLY M SEYMOUR
12/20/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

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<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ADVAIR DISKUS safely and effectively. See full prescribing information for ADVAIR DISKUS.

ADVAIR DISKUS (fluticasone propionate and salmeterol inhalation powder), for oral inhalation
Initial U.S. Approval: 2000

----------RECENT MAJOR CHANGES----------

Boxed Warning	Removed-12/2017
Indications and Usage, Treatment of Asthma (1.1)	12/2017
Dosage and Administration, Asthma (2.1)	12/2017
Contraindications (4)	12/2017
Warnings and Precautions, Serious Asthma-Related Events – Hospitalizations, Intubations, Death (5.1)	12/2017

---------- INDICATIONS AND USAGE----------

ADVAIR DISKUS is a combination product containing a corticosteroid and a long-acting beta$_2$-adrenergic agonist (LABA) indicated for:

- Twice-daily treatment of asthma in patients aged 4 years and older. (1.1)
- Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). (1.2)

Important limitation of use: Not indicated for relief of acute bronchospasm. (1.1, 1.2)

----------DOSAGE AND ADMINISTRATION----------

- For oral inhalation only. (2)
- Treatment of asthma in patients aged 12 years and older: 1 inhalation of ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR DISKUS 500/50 twice daily. Starting dosage is based on asthma severity. (2.1)
- Treatment of asthma in patients aged 4 to 11 years: 1 inhalation of ADVAIR DISKUS 100/50 twice daily. (2.1)
- Maintenance treatment of COPD: 1 inhalation of ADVAIR DISKUS 250/50 twice daily. (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------

Inhalation powder: Inhaler containing a combination of fluticasone propionate (100, 250, or 500 mcg) and salmeterol (50 mcg) as a powder formulation for oral inhalation. (3)

---------- CONTRAINDICATIONS ----------

- Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone propionate, salmeterol, or any of the excipients. (4)

---------- WARNINGS AND PRECAUTIONS----------

- LABA monotherapy increases the risk of serious asthma-related events. (5.1)
- Do not initiate in acutely deteriorating asthma or COPD. Do not use to treat acute symptoms. (5.2)
- Do not use in combination with an additional medicine containing a LABA because of risk of overdose. (5.3)
- *Candida albicans* infection of the mouth and pharynx may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation to help reduce the risk. (5.4)
- Increased risk of pneumonia in patients with COPD. Monitor patients for signs and symptoms of pneumonia. (5.5)
- Potential worsening of infections (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infections; ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.6)
- Risk of impaired adrenal function when transferring from systemic corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to ADVAIR DISKUS. (5.7)
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue ADVAIR DISKUS slowly. (5.8)
- If paradoxical bronchospasm occurs, discontinue ADVAIR DISKUS and institute alternative therapy. (5.10)
- Use with caution in patients with cardiovascular or central nervous system disorders because of beta-adrenergic stimulation. (5 12)
- Assess for decrease in bone mineral density initially and periodically thereafter. (5.13)
- Monitor growth of pediatric patients. (5.14)
- Close monitoring for glaucoma and cataracts is warranted. (5.15)
- Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. (5.16, 5.18)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.17)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥3%) include:

- Asthma: Upper respiratory tract infection or inflammation, pharyngitis, dysphonia, oral candidiasis, bronchitis, cough, headaches, nausea and vomiting. (6.1)
- COPD: Pneumonia, oral candidiasis, throat irritation, dysphonia, viral respiratory infections, headaches, musculoskeletal pain. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole): Use not recommended. May increase risk of systemic corticosteroid and cardiovascular effects. (7 1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of salmeterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

---------- USE IN SPECIFIC POPULATIONS ----------

Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2017

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- 1.2 Maintenance Treatment of Chronic Obstructive Pulmonary Disease

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Asthma

ADVAIR DISKUS is indicated for the twice-daily treatment of asthma in patients aged 4 years and older. ADVAIR DISKUS should be used for patients not adequately controlled on a long-term asthma control medication such as an inhaled corticosteroid (ICS) or whose disease warrants initiation of treatment with both an ICS and long-acting beta$_2$-adrenergic agonist (LABA).

Important Limitation of Use

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

1.2 Maintenance Treatment of Chronic Obstructive Pulmonary Disease

ADVAIR DISKUS 250/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. ADVAIR DISKUS 250/50 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. ADVAIR DISKUS 250/50 twice daily is the only approved dosage for the treatment of COPD because an efficacy advantage of the higher strength ADVAIR DISKUS 500/50 over ADVAIR DISKUS 250/50 has not been demonstrated.

Important Limitation of Use

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

2 DOSAGE AND ADMINISTRATION

ADVAIR DISKUS should be administered as 1 inhalation twice daily by the orally inhaled route only. After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

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More frequent administration or a greater number of inhalations (more than 1 inhalation twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. Patients using ADVAIR DISKUS should not use additional LABA for any reason. *[See Warnings and Precautions (5.3, 5.12).]*

2.1 Asthma

If asthma symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

Adult and Adolescent Patients Aged 12 Years and Older

For patients aged 12 years and older, the dosage is 1 inhalation twice daily, approximately 12 hours apart.

When choosing the starting dosage strength of ADVAIR DISKUS, consider the patients' disease severity, based on their previous asthma therapy, including the ICS dosage, as well as the patients' current control of asthma symptoms and risk of future exacerbation.

The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily.

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

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

If a previously effective dosage regimen fails to provide adequate improvement in asthma control, the therapeutic regimen should be reevaluated and additional therapeutic options (e.g., replacing the current strength of ADVAIR DISKUS with a higher strength, adding additional ICS, initiating oral corticosteroids) should be considered.

Pediatric Patients Aged 4 to 11 Years

For patients with asthma aged 4 to 11 years who are not controlled on an ICS, the dosage is 1 inhalation of ADVAIR DISKUS 100/50 twice daily, approximately 12 hours apart.

2.2 Chronic Obstructive Pulmonary Disease

The recommended dosage for patients with COPD is 1 inhalation of ADVAIR DISKUS 250/50 twice daily, approximately 12 hours apart.

If shortness of breath occurs in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

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3 DOSAGE FORMS AND STRENGTHS

Inhalation powder: Inhaler containing a foil blister strip of powder formulation for oral inhalation. The strip contains a combination of fluticasone propionate 100, 250, or 500 mcg and salmeterol 50 mcg per blister.

4 CONTRAINDICATIONS

The use of ADVAIR DISKUS is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required *[see Warnings and Precautions (5.2)]*.
- Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone propionate, salmeterol, or any of the excipients *[see Warnings and Precautions (5.11), Adverse Reactions (6.3), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Asthma-Related Events – Hospitalizations, Intubations, Death

Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death *[see Salmeterol Multicenter Asthma Research Trial (SMART)]*. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone *(see Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta$_2$-adrenergic Agonists).*

<u>Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta$_2$-adrenergic Agonists</u>

Four (4) large, 26-week, randomized, double-blind, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared with ICS alone in subjects with asthma. Three (3) trials included adult and adolescent subjects aged 12 years and older: 1 trial compared fluticasone propionate/salmeterol inhalation powder (ADVAIR DISKUS) with fluticasone propionate inhalation powder *[see Clinical Studies (14.1)]*, 1 trial compared mometasone furoate/formoterol with mometasone furoate, and 1 trial compared budesonide/formoterol with budesonide. The fourth trial included pediatric subjects aged 4 to 11 years and compared fluticasone propionate/salmeterol inhalation powder with fluticasone propionate inhalation powder *[see Clinical Studies (14.1)]*. The primary safety endpoint for all 4 trials was serious asthma-related events (hospitalizations, intubations, death). A blinded adjudication committee determined whether events were asthma related.

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The 3 adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk margin of 2.7. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the 3 adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

Table 1. Meta-analysis of Serious Asthma-Related Events in Subjects with Asthma Aged 12 Years and Older

	ICS/LABA (n = 17,537)[a]	**ICS (n = 17,552)[a]**	**ICS/LABA vs. ICS Hazard Ratio (95% CI)[b]**
Serious asthma-related event[c]	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization (≥24-hour stay)	115	105	

ICS = Inhaled Corticosteroid, LABA = Long-acting Beta$_2$-adrenergic Agonist.

[a] Randomized subjects who had taken at least 1 dose of study drug. Planned treatment used for analysis.

[b] Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials.

[c] Number of subjects with event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Subjects can have one or more events, but only the first event was counted for analysis. A single, blinded, independent adjudication committee determined whether events were asthma related.

The pediatric safety trial included 6,208 pediatric subjects aged 4 to 11 years who received ICS/LABA (fluticasone propionate/salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3,107 (0.9%) subjects randomized to ICS/LABA and 21/3,101 (0.7%) subjects randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significantly increased risk of a serious asthma-related event compared with ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27).

Salmeterol Multicenter Asthma Research Trial (SMART)

A 28-week, placebo-controlled, U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol versus 3/13,179 in subjects

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treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

5.2 Deterioration of Disease and Acute Episodes

ADVAIR DISKUS should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. ADVAIR DISKUS has not been studied in subjects with acutely deteriorating asthma or COPD. The initiation of ADVAIR DISKUS in this setting is not appropriate.

Serious acute respiratory events, including fatalities, have been reported when salmeterol, a component of ADVAIR DISKUS, has been initiated in patients with significantly worsening or acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, previous life-threatening acute asthma exacerbations) and in some patients with acutely deteriorating asthma (e.g., patients with significantly increasing symptoms; increasing need for inhaled, short-acting beta$_2$-agonists; decreasing response to usual medications; increasing need for systemic corticosteroids; recent emergency room visits; deteriorating lung function). However, these events have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol contributed to these events.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of ADVAIR DISKUS with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation twice daily of ADVAIR DISKUS.

ADVAIR DISKUS should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ADVAIR DISKUS has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

When beginning treatment with ADVAIR DISKUS, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

5.3 Excessive Use of ADVAIR DISKUS and Use with Other Long-acting Beta$_2$-agonists

ADVAIR DISKUS should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ADVAIR

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DISKUS should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Local Effects of Inhaled Corticosteroids

In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with ADVAIR DISKUS. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with ADVAIR DISKUS continues, but at times therapy with ADVAIR DISKUS may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.5 Pneumonia

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap.

Lower respiratory tract infections, including pneumonia, have been reported in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS. In 2 replicate 1-year trials in 1,579 subjects with COPD, there was a higher incidence of pneumonia reported in subjects receiving ADVAIR DISKUS 250/50 (7%) than in those receiving salmeterol 50 mcg (3%). The incidence of pneumonia in the subjects treated with ADVAIR DISKUS was higher in subjects older than 65 years (9%) compared with the incidence in subjects younger than 65 years (4%). *[See Adverse Reactions (6.2), Use in Specific Populations (8.5).]*

In a 3-year trial in 6,184 subjects with COPD, there was a higher incidence of pneumonia reported in subjects receiving ADVAIR DISKUS 500/50 compared with placebo (16% with ADVAIR DISKUS 500/50, 14% with fluticasone propionate 500 mcg, 11% with salmeterol 50 mcg, and 9% with placebo). Similar to what was seen in the 1-year trials with ADVAIR DISKUS 250/50, the incidence of pneumonia was higher in subjects older than 65 years (18% with ADVAIR DISKUS 500/50 versus 10% with placebo) compared with subjects younger than 65 years (14% with ADVAIR DISKUS 500/50 versus 8% with placebo). *[See Adverse Reactions (6.2), Use in Specific Populations (8.5).]*

5.6 Immunosuppression

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

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patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

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

5.7 Transferring Patients from Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

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

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

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to ADVAIR DISKUS. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with ADVAIR DISKUS. Lung function (mean forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [AM PEF]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to ADVAIR DISKUS may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

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

5.8 Hypercorticism and Adrenal Suppression

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

Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with ADVAIR DISKUS should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, ADVAIR DISKUS should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of asthma symptoms should be considered.

5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with ADVAIR DISKUS is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

5.10 Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medicines, ADVAIR DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ADVAIR DISKUS, it should be treated immediately with an inhaled, short-acting bronchodilator; ADVAIR DISKUS should be discontinued immediately; and alternative therapy should be instituted. Upper airway symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving ADVAIR DISKUS.

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5.11 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of ADVAIR DISKUS. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of powder products containing lactose; therefore, patients with severe milk protein allergy should not use ADVAIR DISKUS *[see Contraindications (4)]*.

5.12 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia *[see Overdosage (10.2)]*. Therefore, ADVAIR DISKUS, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Salmeterol, a component of ADVAIR DISKUS, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.13 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids), should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating ADVAIR DISKUS and periodically thereafter. If significant reductions in BMD are seen and ADVAIR DISKUS is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered.

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2-Year Fluticasone Propionate Trial

A 2-year trial in 160 subjects (females aged 18 to 40 years, males 18 to 50) with asthma receiving chlorofluorocarbon (CFC)-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar regions L1 through L4.

3-Year Bone Mineral Density Trial

Effects of treatment with ADVAIR DISKUS 250/50 or salmeterol 50 mcg on BMD at the L_1-L_4 lumbar spine and total hip were evaluated in 186 subjects with COPD (aged 43 to 87 years) in a 3-year double-blind trial. Of those enrolled, 108 subjects (72 males and 36 females) were followed for the entire 3 years. BMD evaluations were conducted at baseline and at 6-month intervals. Conclusions cannot be drawn from this trial regarding BMD decline in subjects treated with ADVAIR DISKUS versus salmeterol due to the inconsistency of treatment differences across gender and between lumbar spine and total hip.

In this trial there were 7 non-traumatic fractures reported in 5 subjects treated with ADVAIR DISKUS and 1 non-traumatic fracture in 1 subject treated with salmeterol. None of the non-traumatic fractures occurred in the vertebrae, hip, or long bones.

3-Year Survival Trial

Effects of treatment with ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on BMD was evaluated in a subset of 658 subjects (females and males aged 40 to 80 years) with COPD in the 3-year survival trial. BMD evaluations were conducted at baseline and at 48, 108, and 158 weeks. Conclusions cannot be drawn from this trial because of the large number of dropouts (>50%) before the end of the follow-up and the maldistribution of covariates among the treatment groups that can affect BMD.

Fracture risk was estimated for the entire population of subjects with COPD in the survival trial (N = 6,184). The probability of a fracture over 3 years was 6.3% for ADVAIR DISKUS, 5.4% for fluticasone propionate, 5.1% for salmeterol, and 5.1% for placebo.

5.14 Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving ADVAIR DISKUS routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, titrate each patient's dosage to the lowest dosage that effectively controls his/her symptoms *[see Dosage and Administration (2.1), Use in Specific Populations (8.4)]*.

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5.15 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of ICS, including fluticasone propionate, a component of ADVAIR DISKUS. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on development of cataracts or glaucoma was evaluated in a subset of 658 subjects with COPD in the 3-year survival trial. Ophthalmic examinations were conducted at baseline and at 48, 108, and 158 weeks. Conclusions about cataracts cannot be drawn from this trial because the high incidence of cataracts at baseline (61% to 71%) resulted in an inadequate number of subjects treated with ADVAIR DISKUS 500/50 who were eligible and available for evaluation of cataracts at the end of the trial (n = 53). The incidence of newly diagnosed glaucoma was 2% with ADVAIR DISKUS 500/50, 5% with fluticasone propionate, 0% with salmeterol, and 2% with placebo.

5.16 Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled fluticasone propionate, a component of ADVAIR DISKUS, may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other ICS in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established.

5.17 Coexisting Conditions

ADVAIR DISKUS, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.18 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2)]*. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose

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and/or serum potassium were seen infrequently during clinical trials with ADVAIR DISKUS at recommended doses.

6 ADVERSE REACTIONS

Use of LABA may result in the following:

- Serious asthma-related events – hospitalizations, intubations, death *[see Warnings and Precautions (5.1)]*
- Cardiovascular and central nervous system effects *[see Warnings and Precautions (5.12)]*

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.4)]*
- Pneumonia in patients with COPD *[see Warnings and Precautions (5.5)]*
- Immunosuppression *[see Warnings and Precautions (5.6)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*
- Reduction in bone mineral density *[see Warnings and Precautions (5.13)]*
- Growth effects *[see Warnings and Precautions (5.14)]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.15)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Asthma

Adult and Adolescent Subjects Aged 12 Years and Older

The incidence of adverse reactions associated with ADVAIR DISKUS in Table 2 is based upon two 12-week, placebo-controlled, U.S. clinical trials (Trials 1 and 2). A total of 705 adult and adolescent subjects (349 females and 356 males) previously treated with salmeterol or ICS were treated twice daily with ADVAIR DISKUS (100/50- or 250/50-mcg doses), fluticasone propionate inhalation powder (100- or 250-mcg doses), salmeterol inhalation powder 50 mcg, or placebo. The average duration of exposure was 60 to 79 days in the active treatment groups compared with 42 days in the placebo group.

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Table 2. Adverse Reactions with ADVAIR DISKUS with ≥3% Incidence and More Common than Placebo in Adult and Adolescent Subjects 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 and vomiting	4	6	3	4	1	1
Gastrointestinal discomfort and 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

The types of adverse reactions and events reported in Trial 3, a 28-week, non-U.S. clinical trial in 503 subjects previously treated with ICS who were treated twice daily with ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation powder 500 mcg, were similar to those reported in Table 2.

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Additional Adverse Reactions

Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that were reported more frequently by subjects with asthma treated with ADVAIR DISKUS compared with subjects treated with placebo include the following: lymphatic signs and symptoms; muscle injuries; fractures; wounds and lacerations; contusions and hematomas; ear signs and symptoms; nasal signs and symptoms; nasal sinus disorders; keratitis and conjunctivitis; dental discomfort and pain; gastrointestinal signs and symptoms; oral ulcerations; oral discomfort and pain; lower respiratory signs and symptoms; pneumonia; muscle stiffness, tightness, and rigidity; bone and cartilage disorders; sleep disorders; compressed nerve syndromes; viral infections; pain; chest symptoms; fluid retention; bacterial infections; unusual taste; viral skin infections; skin flakiness and acquired ichthyosis; disorders of sweat and sebum.

Pediatric Subjects Aged 4 to 11 Years

The safety data for pediatric subjects aged 4 to 11 years is based upon 1 U.S. trial of 12 weeks' treatment duration. A total of 203 subjects (74 females and 129 males) who were receiving ICS at trial entry were randomized to either ADVAIR DISKUS 100/50 or fluticasone propionate inhalation powder 100 mcg twice daily. Common adverse reactions (≥3% and greater than placebo) seen in the pediatric subjects but not reported in the adult and adolescent clinical trials include: throat irritation and ear, nose, and throat infections.

Laboratory Test Abnormalities

Elevation of hepatic enzymes was reported in ≥1% of subjects in clinical trials. The elevations were transient and did not lead to discontinuation from the trials. In addition, there were no clinically relevant changes noted in glucose or potassium.

6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

Short-term (6 Months to 1 Year) Trials

The short-term safety data are based on exposure to ADVAIR DISKUS 250/50 twice daily in one 6-month and two 1-year clinical trials. In the 6-month trial, a total of 723 adult subjects (266 females and 457 males) were treated twice daily with ADVAIR DISKUS 250/50, fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder, or placebo. The mean age of the subjects was 64, and the majority (93%) was Caucasian. In this trial, 70% of the subjects treated with ADVAIR DISKUS reported an adverse reaction compared with 64% on placebo. The average duration of exposure to ADVAIR DISKUS 250/50 was 141.3 days compared with 131.6 days for placebo. The incidence of adverse reactions in the 6-month trial is shown in Table 3.

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Table 3. Overall Adverse Reactions with ADVAIR DISKUS 250/50 with ≥3% Incidence in Subjects with Chronic Obstructive Pulmonary Disease Associated with Chronic Bronchitis

Adverse Event	ADVAIR DISKUS 250/50 (n = 178) %	Fluticasone Propionate 250 mcg (n = 183) %	Salmeterol 50 mcg (n = 177) %	Placebo (n = 185) %
Ear, nose, 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 and fatigue	3	2	2	3
Musculoskeletal				
Musculoskeletal pain	9	8	12	9
Muscle cramps and spasms	3	3	1	1

In the two 1-year trials, ADVAIR DISKUS 250/50 was compared with salmeterol in 1,579 subjects (863 males and 716 females). The mean age of the subjects was 65 years, and the majority (94%) was Caucasian. To be enrolled, all of the subjects had to have had a COPD exacerbation in the previous 12 months. In this trial, 88% of the subjects treated with ADVAIR DISKUS and 86% of the subjects treated with salmeterol reported an adverse event. The most common events that occurred with a frequency of >5% and more frequently in the subjects treated with ADVAIR DISKUS were nasopharyngitis, upper respiratory tract infection, nasal congestion, back pain, sinusitis, dizziness, nausea, pneumonia, candidiasis, and dysphonia. Overall, 55 (7%) of the subjects treated with ADVAIR DISKUS and 25 (3%) of the subjects treated with salmeterol developed pneumonia.

The incidence of pneumonia was higher in subjects older than 65 years, 9% in the subjects treated with ADVAIR DISKUS compared with 4% in the subjects treated with ADVAIR DISKUS younger than 65 years. In the subjects treated with salmeterol, the incidence of pneumonia was the same (3%) in both age groups. *[See Warnings and Precautions (5.5), Use in Specific Populations (8.5).]*

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Long-term (3 Years) Trial

The safety of ADVAIR DISKUS 500/50 was evaluated in a randomized, double-blind, placebo-controlled, multicenter, international, 3-year trial in 6,184 adult subjects with COPD (4,684 males and 1,500 females). The mean age of the subjects was 65 years, and the majority (82%) was Caucasian. The distribution of adverse events was similar to that seen in the 1-year trials with ADVAIR DISKUS 250/50. In addition, pneumonia was reported in a significantly increased number of subjects treated with ADVAIR DISKUS 500/50 and fluticasone propionate 500 mcg (16% and 14%, respectively) compared with subjects treated with salmeterol 50 mcg or placebo (11% and 9%, respectively). When adjusted for time on treatment, the rates of pneumonia were 84 and 88 events per 1,000 treatment-years in the groups treated with fluticasone propionate 500 mcg and with ADVAIR DISKUS 500/50, respectively, compared with 52 events per 1,000 treatment-years in the salmeterol and placebo groups. Similar to what was seen in the 1-year trials with ADVAIR DISKUS 250/50, the incidence of pneumonia was higher in subjects older than 65 years (18% with ADVAIR DISKUS 500/50 versus 10% with placebo) compared with subjects younger than 65 years (14% with ADVAIR DISKUS 500/50 versus 8% with placebo). *[See Warnings and Precautions (5.5), Use in Specific Populations (8.5).]*

Additional Adverse Reactions

Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that were reported more frequently by subjects with COPD treated with ADVAIR DISKUS compared with subjects treated with placebo include the following: syncope; ear, nose, and throat infections; ear signs and symptoms; laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection; hypothyroidism; dry eyes; eye infections; gastrointestinal signs and symptoms; oral lesions; abnormal liver function tests; bacterial infections; edema and swelling; viral infections.

Laboratory Abnormalities

There were no clinically relevant changes in these trials. Specifically, no increased reporting of neutrophilia or changes in glucose or potassium was noted.

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of any formulation of ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to ADVAIR DISKUS, fluticasone propionate, and/or salmeterol or a combination of these factors.

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Cardiac Disorders

Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular tachycardia), ventricular tachycardia.

Endocrine Disorders

Cushing's syndrome, Cushingoid features, growth velocity reduction in children/adolescents, hypercorticism.

Eye Disorders

Glaucoma.

Gastrointestinal Disorders

Abdominal pain, dyspepsia, xerostomia.

Immune System Disorders

Immediate and delayed hypersensitivity reaction (including very rare anaphylactic reaction). Very rare anaphylactic reaction in patients with severe milk protein allergy.

Infections and Infestations

Esophageal candidiasis.

Metabolic and Nutrition Disorders

Hyperglycemia, weight gain.

Musculoskeletal, Connective Tissue, and Bone Disorders

Arthralgia, cramps, myositis, osteoporosis.

Nervous System Disorders

Paresthesia, restlessness.

Psychiatric Disorders

Agitation, aggression, depression. Behavioral changes, including hyperactivity and irritability, have been reported very rarely and primarily in children.

Reproductive System and Breast Disorders

Dysmenorrhea.

Respiratory, Thoracic, and Mediastinal Disorders

Chest congestion; chest tightness; dyspnea; facial and oropharyngeal edema, immediate bronchospasm; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

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Skin and Subcutaneous Tissue Disorders

Ecchymoses, photodermatitis.

Vascular Disorders

Pallor.

7 DRUG INTERACTIONS

ADVAIR DISKUS has been used concomitantly with other drugs, including short-acting beta$_2$-agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with asthma or COPD without adverse drug reactions *[see Clinical Pharmacology (12.2)]*. No formal drug interaction trials have been performed with ADVAIR DISKUS.

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate and salmeterol, the individual components of ADVAIR DISKUS, are substrates of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with ADVAIR DISKUS is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

Ritonavir

Fluticasone Propionate: A drug interaction trial with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations *[see Clinical Pharmacology (12.3)]*. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.

Ketoconazole

Fluticasone Propionate: Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol area under the curve (AUC), but had no effect on urinary excretion of cortisol.

Salmeterol: In a drug interaction trial in 20 healthy subjects, coadministration of inhaled salmeterol (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased 1.4-fold). Three (3) subjects were withdrawn due to beta$_2$-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

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7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

ADVAIR DISKUS should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol, a component of ADVAIR DISKUS, on the vascular system may be potentiated by these agents.

7.3 Beta-adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, but may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of ADVAIR DISKUS with non–potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of ADVAIR DISKUS or individual monoproducts, fluticasone propionate and salmeterol xinafoate, in pregnant women. There are clinical considerations with the use of ADVAIR DISKUS in pregnant women *(see Clinical Considerations).* In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight and/or skeletal variations, in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a mcg/m^2 basis *(see Data)*. However, fluticasone propionate administered via inhalation to rats decreased fetal body weight, but did not induce teratogenicity at a maternal toxic dose less than the MRHDID on a mcg/m^2 basis *(see Data)*. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. Oral administration of salmeterol to pregnant rabbits caused teratogenicity characteristic of beta-adrenoceptor stimulation at maternal doses approximately 50 times the MRHDID on an AUC basis. These adverse effects generally occurred at large multiples of the MRHDID when salmeterol was administered by the oral route

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to achieve high systemic exposures. No such effects occurred at an oral salmeterol dose approximately 20 times the MRHDID *(see Data)*.

The estimated risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryofetal Risk: In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal adverse outcomes such as pre-eclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control.

Data

Human Data: Fluticasone Propionate: Following inhaled administration, fluticasone propionate was detected in the neonatal cord blood after delivery.

Animal Data: Fluticasone Propionate and Salmeterol: In an embryofetal development study with pregnant rats that received the combination of subcutaneous administration of fluticasone propionate and oral administration of salmeterol at doses of 0/1,000; 30/0; 10/100; 30/1,000; and 100/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) during the period of organogenesis, findings were generally consistent with the individual monoproducts and there was no exacerbation of expected fetal effects. Omphalocele, increased embryofetal deaths, decreased body weight, and skeletal variations were observed in rat fetuses in the presence of maternal toxicity when combining fluticasone propionate at a dose approximately equivalent to the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 100 mcg/kg/day) and salmeterol at a dose approximately 970 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 10,000 mcg/kg/day). The rat no observed adverse effect level (NOAEL) was observed when combining fluticasone propionate at a dose approximately 0.3 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 30 mcg/kg/day) and salmeterol at a dose approximately 100 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 1,000 mcg/kg/day).

In an embryofetal development study with pregnant mice that received the combination of following subcutaneous administration of fluticasone propionate and oral administration of salmeterol at doses of 0/1,400; 40/0; 10/200; 40/1,400; or 150/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) during the period of organogenesis, findings were generally consistent with the individual monoproducts and there was no exacerbation of expected fetal effects. Cleft palate, fetal death, increased implantation loss, and delayed ossification were observed in mouse fetuses when combining fluticasone propionate at a dose approximately 0.7 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 150 mcg/kg/day) and salmeterol at a dose

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approximately 490 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 10,000 mcg/kg/day). No developmental toxicity was observed at combination doses of fluticasone propionate up to approximately 0.2 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 40 mcg/kg) and doses of salmeterol up to approximately 70 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 1,400 mcg/kg).

Fluticasone Propionate: In embryofetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone propionate was teratogenic in both species. Omphalocele, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, at a dose approximately equivalent to the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 100 mcg/kg/day). The rat NOAEL was observed at approximately 0.3 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 30 mcg/kg/day). Cleft palate and fetal skeletal variations were observed in mouse fetuses at a dose approximately 0.2 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.07 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryofetal development study with pregnant rats dosed by the inhalation route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.25 times the MRHDID (on a mcg/m^2 basis with a maternal inhalation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose approximately 0.05 times the MRHDID (on a mcg/m^2 basis with a maternal inhalation dose of 5.5 mcg/kg/day).

In an embryofetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced reductions of fetal body weights, in the presence of maternal toxicity, at doses approximately 0.012 times the MRHDID and higher (on a mcg/m^2 basis with a maternal subcutaneous dose of 0.57 mcg/kg/day). Teratogenicity was evident based upon a finding of cleft palate for 1 fetus at a dose approximately 0.08 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 4 mcg/kg/day). The NOAEL was observed in rabbit fetuses with a dose approximately 0.002 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).

Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

In a pre- and post-natal development study in pregnant rats dosed by the subcutaneous route from late gestation through delivery and lactation (Gestation Day 17 to Postpartum Day 22), fluticasone propionate was not associated with decreases in pup body weight, and had no effects on developmental landmarks, learning, memory, reflexes, or fertility at doses up to 0.5 times the MRHDID (on a mcg/m^2 basis with maternal subcutaneous doses up to 50 mcg/kg/day).

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Salmeterol: In 3 embryofetal development studies, pregnant rabbits received oral administration of salmeterol at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. In pregnant Dutch rabbits administered salmeterol doses approximately 50 times the MRHDID (on an AUC basis at maternal oral doses of 1,000 mcg/kg/day and higher), fetal toxic effects were observed characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at a salmeterol dose approximately 20 times the MRHDID (on an AUC basis at a maternal oral dose of 600 mcg/kg/day). New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at a salmeterol dose approximately 2,000 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 10,000 mcg/kg/day).

In 2 embryofetal development studies, pregnant rats received salmeterol by oral administration at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. Salmeterol produced no maternal toxicity or embryofetal effects at doses up to 973 times the MRHDID (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

In a peri- and post-natal development study in pregnant rats dosed by the oral route from late gestation through delivery and lactation, salmeterol at a dose 973 times the MRHDID (on a mcg/m^2 basis with a maternal oral dose of 10,000 mcg/kg/day) was fetotoxic and decreased the fertility of survivors.

Salmeterol xinafoate crossed the placenta following oral administration to mice and rats.

8.2 Lactation

Risk Summary

There are no available data on the presence of fluticasone propionate or salmeterol in human milk, the effects on the breastfed child, or the effects on milk production. Other corticosteroids have been detected in human milk. However, fluticasone propionate and salmeterol concentrations in plasma after inhaled therapeutic doses are low and therefore concentrations in human breast milk are likely to be correspondingly low *[see Clinical Pharmacology (12.3)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ADVAIR DISKUS and any potential adverse effects on the breastfed child from ADVAIR DISKUS or from the underlying maternal condition.

Data

Animal Data: Subcutaneous administration of tritiated fluticasone propionate at a dose in lactating rats approximately 0.08 times the MRHDID for adults (on a mcg/m^2 basis) resulted in measurable levels in milk. Oral administration of salmeterol at a dose in lactating rats approximately 973 times the MRHDID for adults (on a mcg/m^2 basis) resulted in measurable levels in milk.

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8.4 Pediatric Use

Use of ADVAIR DISKUS 100/50 in patients aged 4 to 11 years is supported by extrapolation of efficacy data from older subjects and by safety and efficacy data from a trial of ADVAIR DISKUS 100/50 in children with asthma aged 4 to 11 years *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.1)]*. The safety and effectiveness of ADVAIR DISKUS in children with asthma younger than 4 years have not been established.

ICS, including fluticasone propionate, a component of ADVAIR DISKUS, may cause a reduction in growth velocity in children and adolescents *[see Warnings and Precautions (5.14)]*. The growth of pediatric patients receiving orally inhaled corticosteroids, including ADVAIR DISKUS, should be monitored.

A 52-week placebo-controlled trial to assess the potential growth effects of fluticasone propionate inhalation powder (FLOVENT ROTADISK) at 50 and 100 mcg twice daily was conducted in the U.S. in 325 prepubescent children (244 males and 81 females) aged 4 to 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and 5.66 cm/year in the 100-mcg group (n = 89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the trial revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the 100-mcg group (n = 79). In children aged 8.5 years, the mean age of children in this trial, the range for expected growth velocity is: boys – 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year. The clinical relevance of these growth data is not certain.

If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, each patient should be titrated to the lowest strength that effectively controls his/her asthma *[see Dosage and Administration (2.1)]*.

8.5 Geriatric Use

Clinical trials of ADVAIR DISKUS for asthma did not include sufficient numbers of subjects aged 65 years and older to determine whether older subjects with asthma respond differently than younger subjects.

Of the total number of subjects in clinical trials receiving ADVAIR DISKUS for COPD, 1,621 were aged 65 years and older and 379 were aged 75 years and older. Subjects with COPD aged

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65 years and older had a higher incidence of serious adverse events compared with subjects younger than 65 years. Although the distribution of adverse events was similar in the 2 age groups, subjects older than 65 years experienced more severe events. In two 1-year trials, the excess risk of pneumonia that was seen in subjects treated with ADVAIR DISKUS compared with those treated with salmeterol was greater in subjects older than 65 years than in subjects younger than 65 years *[see Adverse Reactions (6.2)]*. As with other products containing $beta_2$-agonists, special caution should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by $beta_2$-agonists. Based on available data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR DISKUS in geriatric patients is warranted.

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

8.6 Hepatic Impairment

Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with hepatic impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with renal impairment.

10 OVERDOSAGE

No human overdosage data has been reported for ADVAIR DISKUS.

ADVAIR DISKUS contains both fluticasone propionate and salmeterol; therefore, the risks associated with overdosage for the individual components described below apply to ADVAIR DISKUS. Treatment of overdosage consists of discontinuation of ADVAIR DISKUS together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Fluticasone Propionate

Chronic overdosage of fluticasone propionate may result in signs/symptoms of hypercorticism *[see Warnings and Precautions (5.8)]*. Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate CFC inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at dosages of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy

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volunteers and repeat oral doses up to 20 mg daily for 42 days in subjects were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups.

10.2 Salmeterol

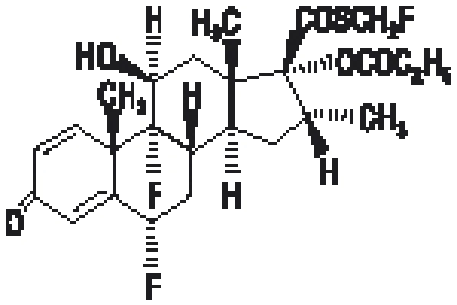
The expected signs and symptoms with overdosage of salmeterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). Overdosage with salmeterol can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias.

As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of salmeterol.

11 DESCRIPTION

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

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



Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

The other active component of ADVAIR DISKUS is salmeterol xinafoate, a beta$_2$-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. It has the chemical name 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino] methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate and the following chemical structure:

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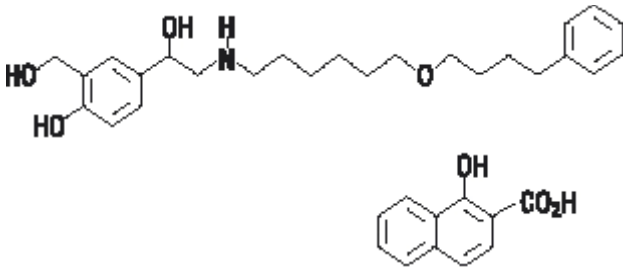

Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is $C_{25}H_{37}NO_4 \bullet C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

ADVAIR DISKUS is a purple plastic inhaler containing a foil blister strip. Each blister on the strip contains a white powder mix of micronized fluticasone propionate (100, 250, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins). After the inhaler is activated, the powder is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds.

In adult subjects with obstructive lung disease and severely compromised lung function (mean FEV_1 20% to 30% of predicted), mean peak inspiratory flow (PIF) through the DISKUS inhaler was 82.4 L/min (range: 46.1 to 115.3 L/min).

Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to 50 years) subjects with asthma inhaling maximally through the DISKUS inhaler show mean PIF of 122.2 L/min (range: 81.6 to 152.1 L/min). Inhalation profiles for pediatric subjects with asthma inhaling maximally through the DISKUS inhaler show a mean PIF of 75.5 L/min (range: 49.0 to 104.8 L/min) for the 4-year-old subject set (N = 20) and 107.3 L/min (range: 82.8 to 125.6 L/min) for the 8-year-old subject set (N = 20).

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ADVAIR DISKUS

ADVAIR DISKUS contains both fluticasone propionate and salmeterol. The mechanisms of action described below for the individual components apply to ADVAIR DISKUS. These drugs

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represent 2 different classes of medications (a synthetic corticosteroid and a LABA) that have different effects on clinical, physiologic, and inflammatory indices.

Fluticasone Propionate

Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone propionate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is 18 times that of dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results. The clinical significance of these findings is unknown.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

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

Salmeterol Xinafoate

Salmeterol is a selective LABA. In vitro studies show salmeterol to be at least 50 times more selective for $beta_2$-adrenoceptors than albuterol. Although $beta_2$-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-adrenoceptors are the predominant receptors in the heart, there are also $beta_2$-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D_2, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor–induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled

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route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

12.2 Pharmacodynamics

ADVAIR DISKUS

Healthy Subjects: Cardiovascular Effects: Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four (4) trials were conducted with healthy adult subjects: (1) a single-dose crossover trial using 2 inhalations of ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and salmeterol inhalation powder 50 mcg given concurrently, or fluticasone propionate inhalation powder 500 mcg given alone, (2) a cumulative-dose trial using 50 to 400 mcg of salmeterol inhalation powder given alone or as ADVAIR DISKUS 500/50, (3) a repeat-dose trial for 11 days using 2 inhalations twice daily of ADVAIR DISKUS 250/50, fluticasone propionate inhalation powder 250 mcg, or salmeterol inhalation powder 50 mcg, and (4) a single-dose trial using 5 inhalations of ADVAIR DISKUS 100/50, fluticasone propionate inhalation powder 100 mcg alone, or placebo. In these trials no significant differences were observed in the pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given as ADVAIR DISKUS, concurrently with fluticasone propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic effects of salmeterol were not altered by the presence of fluticasone propionate in ADVAIR DISKUS. The potential effect of salmeterol on the effects of fluticasone propionate on the HPA axis was also evaluated in these trials.

Hypothalamic-Pituitary-Adrenal Axis Effects: No significant differences across treatments were observed in 24-hour urinary cortisol excretion and, where measured, 24-hour plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone propionate were not altered by the presence of salmeterol in ADVAIR DISKUS in healthy subjects.

Subjects with Asthma: Adult and Adolescent Subjects: Cardiovascular Effects: In clinical trials with ADVAIR DISKUS in adult and adolescent subjects aged 12 years and older with asthma, no significant differences were observed in the systemic pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given alone or as ADVAIR DISKUS. In 72 adult and adolescent subjects with asthma given either ADVAIR DISKUS 100/50 or ADVAIR DISKUS 250/50, continuous 24-hour electrocardiographic monitoring was performed after the first dose and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

Hypothalamic-Pituitary-Adrenal Axis Effects: In a 28-week trial in adult and adolescent subjects with asthma, ADVAIR DISKUS 500/50 twice daily was compared with the concurrent use of salmeterol inhalation powder 50 mcg plus fluticasone propionate inhalation powder 500 mcg from separate inhalers or fluticasone propionate inhalation powder 500 mcg

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alone. No significant differences across treatments were observed in serum cortisol AUC after 12 weeks of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

In a 12-week trial in adult and adolescent subjects with asthma, ADVAIR DISKUS 250/50 twice daily was compared with fluticasone propionate inhalation powder 250 mcg alone, salmeterol inhalation powder 50 mcg alone, and placebo. For most subjects, the ability to increase cortisol production in response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with ADVAIR DISKUS. One subject (3%) who received ADVAIR DISKUS 250/50 had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing, compared with 2 subjects (6%) who received placebo, 2 subjects (6%) who received fluticasone propionate 250 mcg, and no subjects who received salmeterol.

In a repeat-dose, 3-way crossover trial, 1 inhalation twice daily of ADVAIR DISKUS 100/50, FLOVENT DISKUS 100 mcg (fluticasone propionate inhalation powder 100 mcg), or placebo was administered to 20 adult and adolescent subjects with asthma. After 28 days of treatment, geometric mean serum cortisol AUC over 12 hours showed no significant difference between ADVAIR DISKUS and FLOVENT DISKUS or between either active treatment and placebo.

Pediatric Subjects: Hypothalamic-Pituitary-Adrenal Axis Effects: In a 12-week trial in subjects with asthma aged 4 to 11 years who were receiving ICS at trial entry, ADVAIR DISKUS 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 mcg administered twice daily via the DISKUS. The values for 24-hour urinary cortisol excretion at trial entry and after 12 weeks of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol excretion was also similar between the 2 groups.

Subjects with Chronic Obstructive Pulmonary Disease: Cardiovascular Effects: In clinical trials with ADVAIR DISKUS in subjects with COPD, no significant differences were seen in pulse rate, blood pressure, potassium, and glucose between ADVAIR DISKUS, the individual components of ADVAIR DISKUS, and placebo. In a trial of ADVAIR DISKUS 250/50, 8 subjects (2 [1.1%] in the group given ADVAIR DISKUS 250/50, 1 [0.5%] in the fluticasone propionate 250-mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the placebo group) had QTc intervals >470 msec at least 1 time during the treatment period. Five (5) of these 8 subjects had a prolonged QTc interval at baseline.

In a 24-week trial, 130 subjects with COPD received continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of twice-daily treatment with either ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg, salmeterol inhalation powder 50 mcg, or placebo. No significant differences in ventricular or supraventricular arrhythmias and heart rate were observed among the groups treated with ADVAIR DISKUS 500/50, the individual components, or placebo. One (1) subject in the fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the group given ADVAIR DISKUS 500/50 experienced heart block. There were 3 cases of

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nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone propionate 500-mcg treatment groups).

In 24-week clinical trials in subjects with COPD, the incidence of clinically significant ECG abnormalities (myocardial ischemia, ventricular hypertrophy, clinically significant conduction abnormalities, clinically significant arrhythmias) was lower for subjects who received salmeterol (1%, 9 of 688 subjects who received either salmeterol 50 mcg or ADVAIR DISKUS) compared with placebo (3%, 10 of 370 subjects).

No significant differences with salmeterol 50 mcg alone or in combination with fluticasone propionate as ADVAIR DISKUS 500/50 were observed on pulse rate and systolic and diastolic blood pressure in a subset of subjects with COPD who underwent 12-hour serial vital sign measurements after the first dose (n = 183) and after 12 weeks of therapy (n = 149). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar to those seen with placebo.

Hypothalamic-Pituitary-Adrenal Axis Effects: Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in 101 subjects with COPD receiving twice-daily ADVAIR DISKUS 250/50, fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder 50 mcg, or placebo. For most subjects, the ability to increase cortisol production in response to stress, as assessed by short cosyntropin stimulation, remained intact with ADVAIR DISKUS 250/50. One (1) subject (3%) who received ADVAIR DISKUS 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by high-performance liquid chromatography) after dosing, compared with 2 subjects (9%) who received fluticasone propionate 250 mcg, 2 subjects (7%) who received salmeterol 50 mcg, and 1 subject (4%) who received placebo following 24 weeks of treatment or early discontinuation from trial.

After 36 weeks of dosing, serum cortisol concentrations in a subset of subjects with COPD (n = 83) were 22% lower in subjects receiving ADVAIR DISKUS 500/50 and 21% lower in subjects receiving fluticasone propionate 500 mcg than in subjects receiving placebo.

Other Fluticasone Propionate Products

Subjects with Asthma: Hypothalamic-Pituitary-Adrenal Axis Effects: In clinical trials with fluticasone propionate inhalation powder using dosages up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted both in subjects receiving fluticasone propionate and in subjects receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year trial carried out with the DISKHALER inhalation device in 64 subjects with mild, persistent asthma (mean FEV_1 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no subject receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1 subject receiving fluticasone propionate (4%) had an abnormal

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response at 1 year; repeat testing at 18 months and 2 years was normal. Another subject receiving fluticasone propionate (5%) had an abnormal response at 2 years. No subject on placebo had an abnormal response at 1 or 2 years.

Subjects with Chronic Obstructive Pulmonary Disease: Hypothalamic-Pituitary-Adrenal Axis Effects: After 4 weeks of dosing, the steady-state fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of subjects with COPD (n = 86) randomized to twice-daily fluticasone propionate inhalation powder via the DISKUS 500 mcg, fluticasone propionate inhalation powder 250 mcg, or placebo. Serial serum cortisol concentrations were measured across a 12-hour dosing interval. Serum cortisol concentrations following 250- and 500-mcg twice-daily dosing were 10% and 21% lower than placebo, respectively, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

Other Salmeterol Xinafoate Products

Subjects with Asthma: Cardiovascular Effects: Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium *[see Warnings and Precautions (5.12, 5.18)]*. The cardiovascular effects (heart rate, blood pressure) associated with salmeterol inhalation aerosol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

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

Concomitant Use of ADVAIR DISKUS with Other Respiratory Medicines

Short-acting Beta$_2$-agonists: In clinical trials in subjects with asthma, the mean daily need for albuterol by 166 adult and adolescent subjects aged 12 years and older using ADVAIR DISKUS was approximately 1.3 inhalations/day and ranged from 0 to 9 inhalations/day. Five percent (5%) of subjects using ADVAIR DISKUS in these trials averaged 6 or more inhalations per day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse events was observed among subjects who averaged 6 or more inhalations per day.

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

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Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by adult and adolescent subjects aged 12 years and older receiving ADVAIR DISKUS has not been completely evaluated. In clinical trials in subjects with asthma, 39 subjects receiving ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR DISKUS 500/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 304 subjects receiving ADVAIR DISKUS without theophylline. Similar results were observed in subjects receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily concurrently with a theophylline product (n = 39) or without theophylline (n = 132).

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

Fluticasone Propionate Nasal Spray: In adult and adolescent subjects aged 12 years and older receiving ADVAIR DISKUS in clinical trials, no difference in the profile of adverse events or HPA axis effects was noted between subjects who were receiving FLONASE (fluticasone propionate) Nasal Spray, 50 mcg concurrently (n = 46) and those who were not (n = 130).

12.3 Pharmacokinetics

Absorption

Fluticasone Propionate: Healthy Subjects: Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Trials using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed.

Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours. In a single-dose crossover trial, a higher-than-recommended dose of ADVAIR DISKUS was administered to 14 healthy adult subjects. Two (2) inhalations of the following treatments were administered: ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and salmeterol inhalation powder 50 mcg given concurrently, and fluticasone propionate inhalation powder 500 mcg alone. Mean peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL, respectively, indicating no significant changes in systemic exposures of fluticasone propionate.

In 15 healthy subjects, systemic exposure to fluticasone propionate from 4 inhalations of ADVAIR HFA 230/21 (fluticasone propionate 230 mcg and salmeterol 21 mcg) Inhalation

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Aerosol (920/84 mcg) and 2 inhalations of ADVAIR DISKUS 500/50 (1,000/100 mcg) was similar between the 2 inhalers (i.e., 799 versus 832 pg•h/mL, respectively), but approximately half the systemic exposure from 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg (880 mcg, AUC = 1,543 pg•h/mL). Similar results were observed for peak fluticasone propionate plasma concentrations (186 and 182 pg/mL from ADVAIR HFA and ADVAIR DISKUS, respectively, and 307 pg/mL from the fluticasone propionate CFC inhalation aerosol). Absolute bioavailability of fluticasone propionate was 5.3% and 5.5% following administration of ADVAIR HFA and ADVAIR DISKUS, respectively.

Subjects with Asthma and COPD: Peak steady-state fluticasone propionate plasma concentrations in adult subjects with asthma (N = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone propionate inhalation powder using the DISKUS inhaler. The mean fluticasone propionate plasma concentration was 110 pg/mL.

Full pharmacokinetic profiles were obtained from 9 female and 16 male subjects with asthma given fluticasone propionate inhalation powder 500 mcg twice daily using the DISKUS inhaler and from 14 female and 43 male subjects with COPD given 250 or 500 mcg twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

Peak steady-state fluticasone propionate plasma concentrations in subjects with COPD averaged 53 pg/mL (range: 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily (n = 30) and 84 pg/mL (range: 24.3 to 197.1 pg/mL) after treatment with 500 mcg twice daily (n = 27) via the fluticasone propionate DISKUS inhaler. In another trial in subjects with COPD, peak steady-state fluticasone propionate plasma concentrations averaged 115 pg/mL (range: 52.6 to 366.0 pg/mL) after treatment with 500 mcg twice daily via the fluticasone propionate DISKUS inhaler (n = 15) and 105 pg/mL (range: 22.5 to 299.0 pg/mL) via ADVAIR DISKUS (n = 24).

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

Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of salmeterol were achieved in about 5 minutes.

In 15 healthy subjects receiving ADVAIR HFA 230/21 Inhalation Aerosol (920/84 mcg) and ADVAIR DISKUS 500/50 (1,000/100 mcg), systemic exposure to salmeterol was higher (317 versus 169 pg•h/mL) and peak salmeterol concentrations were lower (196 versus 223 pg/mL) following ADVAIR HFA compared with ADVAIR DISKUS, although pharmacodynamic results were comparable.

Subjects with Asthma: Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended dosages (50 mcg of salmeterol inhalation powder twice daily). Following chronic administration of an inhaled dose

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of 50 mcg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7 subjects with asthma; plasma concentrations were very low, with mean peak concentrations of 167 pg/mL at 20 minutes and no accumulation with repeated doses.

Distribution

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

The percentage of fluticasone propionate bound to human plasma proteins averages 99%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

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

Metabolism

Fluticasone Propionate: The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for <0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the CYP3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

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

An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to α-hydroxysalmeterol (aliphatic oxidation) by CYP3A4. Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of α-hydroxysalmeterol in vitro.

Elimination

Fluticasone Propionate: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites. Terminal half-life estimates of fluticasone propionate for ADVAIR HFA, ADVAIR DISKUS, and fluticasone propionate CFC inhalation aerosol were similar and averaged 5.6 hours.

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

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days. No terminal half-life estimates were calculated for salmeterol following administration of ADVAIR DISKUS.

Specific Populations

A population pharmacokinetic analysis was performed for fluticasone propionate and salmeterol utilizing data from 9 controlled clinical trials that included 350 subjects with asthma aged 4 to 77 years who received treatment with ADVAIR DISKUS, the combination of HFA-propelled fluticasone propionate and salmeterol inhalation aerosol (ADVAIR HFA), fluticasone propionate inhalation powder (FLOVENT DISKUS), HFA-propelled fluticasone propionate inhalation aerosol (FLOVENT HFA), or CFC-propelled fluticasone propionate inhalation aerosol. The population pharmacokinetic analyses for fluticasone propionate and salmeterol showed no clinically relevant effects of age, gender, race, body weight, body mass index, or percent of predicted FEV_1 on apparent clearance and apparent volume of distribution.

Age: When the population pharmacokinetic analysis for fluticasone propionate was divided into subgroups based on fluticasone propionate strength, formulation, and age (adolescents/adults and children), there were some differences in fluticasone propionate exposure. Higher fluticasone propionate exposure from ADVAIR DISKUS 100/50 compared with FLOVENT DISKUS 100 mcg was observed in adolescents and adults (ratio 1.52 [90% CI: 1.08, 2.13]). However, in clinical trials of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50 and FLOVENT DISKUS 100 mcg in adolescents and adults, no differences in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed. Similar fluticasone propionate exposure was observed from ADVAIR DISKUS 500/50 and FLOVENT DISKUS 500 mcg (ratio 0.83 [90% CI: 0.65, 1.07]) in adolescents and adults.

Steady-state systemic exposure to salmeterol when delivered as ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR HFA 115/21 (fluticasone propionate 115 mcg and salmeterol 21 mcg) Inhalation Aerosol was evaluated in 127 subjects aged 4 to 57 years. The geometric mean AUC was 325 pg•h/mL (90% CI: 309, 341) in adolescents and adults.

The population pharmacokinetic analysis included 160 subjects with asthma aged 4 to 11 years who received ADVAIR DISKUS 100/50 or FLOVENT DISKUS 100 mcg. Higher fluticasone propionate exposure (AUC) was observed in children from ADVAIR DISKUS 100/50 compared with FLOVENT DISKUS 100 mcg (ratio 1.20 [90% CI: 1.06, 1.37]). Higher fluticasone propionate exposure (AUC) from ADVAIR DISKUS 100/50 was observed in children compared with adolescents and adults (ratio 1.63 [90% CI: 1.35, 1.96]). However, in clinical trials of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50 and FLOVENT DISKUS 100 mcg in

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both adolescents and adults and in children, no differences in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed.

Exposure to salmeterol was higher in children compared with adolescents and adults who received ADVAIR DISKUS 100/50 (ratio 1.23 [90% CI: 1.10, 1.38]). However, in clinical trials of up to 12 weeks' duration with ADVAIR DISKUS 100/50 in both adolescents and adults and in children, no differences in systemic effects of $beta_2$-agonist treatment (e.g., cardiovascular effects, tremor) were observed.

Male and Female Patients: The population pharmacokinetic analysis involved 202 males and 148 females with asthma who received fluticasone propionate alone or in combination with salmeterol and showed no gender differences for fluticasone propionate pharmacokinetics.

The population pharmacokinetic analysis involved 76 males and 51 females with asthma who received salmeterol in combination with fluticasone propionate and showed no gender differences for salmeterol pharmacokinetics.

Patients with Hepatic and Renal Impairment: Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with hepatic or renal impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Drug Interaction Studies

In the repeat- and single-dose trials, there was no evidence of significant drug interaction in systemic exposure between fluticasone propionate and salmeterol when given alone or in combination via the DISKUS. The population pharmacokinetic analysis from 9 controlled clinical trials in 350 subjects with asthma showed no significant effects on fluticasone propionate or salmeterol pharmacokinetics following co-administration with $beta_2$-agonists, corticosteroids, antihistamines, or theophyllines.

Inhibitors of Cytochrome P450 3A4: Ritonavir: Fluticasone Propionate: Fluticasone propionate is a substrate of CYP3A4. Coadministration of fluticasone propionate and the strong CYP3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction trial in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{max}) averaged 11.9 pg/mL (range: 10.8 to 14.1 pg/mL) and $AUC_{(0-\tau)}$ averaged 8.43 pg•h/mL (range: 4.2 to 18.8 pg•h/mL). Fluticasone propionate C_{max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range: 110 to 648 pg/mL) and 3,102.6 pg•h/mL (range: 1,207.1 to 5,662.0 pg•h/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray.

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This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Ketoconazole: Fluticasone Propionate: In a placebo-controlled crossover trial in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Salmeterol: In a placebo-controlled, crossover drug interaction trial in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76 [90% CI: 10.66, 23.31]) mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist–mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

Erythromycin: Fluticasone Propionate: In a multiple-dose drug interaction trial, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Salmeterol: In a repeat-dose trial in 13 healthy subjects, concomitant administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol C_{max} at steady state (ratio with and without erythromycin 1.4 [90% CI: 0.96, 2.03], $P = 0.12$), a 3.6-beat/min increase in heart rate ([95% CI: 0.19, 7.03], $P<0.04$), a 5.8-msec increase in QTc interval ([95% CI: -6.14, 17.77], $P = 0.34$), and no change in plasma potassium.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone Propionate

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 5 and 10 times the MRHDID for adults and children, respectively, on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to the MRHDID for adults and children, respectively, on a mcg/m^2 basis) for 104 weeks.

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

Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 0.5 times the MRHDID for adults on a mcg/m^2 basis).

Salmeterol

In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1,400 mcg/kg and above (approximately 20 times the MRHDID for adults and children based on comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at 200 mcg/kg (approximately 3 times the MRHDID for adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 680 mcg/kg and above (approximately 66 and 35 times the MRHDID for adults and children, respectively, on a mcg/m^2 basis). No tumors were seen at 210 mcg/kg (approximately 20 and 10 times the MRHDID for adults and children, respectively, on a mcg/m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test.

Fertility and reproductive performance were unaffected in male and female rats at oral doses up to 2,000 mcg/kg (approximately 195 times the MRHDID for adults on a mcg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

Preclinical

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

14 CLINICAL STUDIES

14.1 Asthma

Adult and Adolescent Subjects Aged 12 Years and Older

In clinical trials comparing ADVAIR DISKUS with its individual components, improvements in most efficacy endpoints were greater with ADVAIR DISKUS than with the use of either

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fluticasone propionate or salmeterol alone. In addition, clinical trials showed similar results between ADVAIR DISKUS and the concurrent use of fluticasone propionate plus salmeterol at corresponding doses from separate inhalers.

Trials Comparing ADVAIR DISKUS with Fluticasone Propionate Alone or Salmeterol Alone: Three (3) double-blind, parallel-group clinical trials were conducted with ADVAIR DISKUS in 1,208 adult and adolescent subjects (aged 12 years and older, baseline FEV_1 63% to 72% of predicted normal) with asthma that was not optimally controlled on their current therapy. All treatments were inhalation powders given as 1 inhalation from the DISKUS inhaler twice daily, and other maintenance therapies were discontinued.

Trial 1: Clinical Trial with ADVAIR DISKUS 100/50: This placebo-controlled, 12-week, U.S. trial compared ADVAIR DISKUS 100/50 with its individual components, fluticasone propionate 100 mcg and salmeterol 50 mcg. The trial was stratified according to baseline asthma maintenance therapy; subjects were using either ICS (n = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg) or salmeterol (n = 106). Baseline FEV_1 measurements were similar across treatments: ADVAIR DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and placebo, 2.15 L.

Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were utilized for this placebo-controlled trial. Worsening asthma was defined as a clinically important decrease in FEV_1 or PEF, increase in use of VENTOLIN (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. As shown in Table 4, statistically significantly fewer subjects receiving ADVAIR DISKUS 100/50 were withdrawn due to worsening asthma compared with fluticasone propionate, salmeterol, and placebo.

Table 4. Percent of Subjects Withdrawn due to Worsening Asthma in Subjects Previously Treated with Either Inhaled Corticosteroids or Salmeterol (Trial 1)

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

The FEV_1 results are displayed in Figure 1. Because this trial used predetermined criteria for worsening asthma, which caused more subjects in the placebo group to be withdrawn, FEV_1 results at Endpoint (last available FEV_1 result) are also provided. Subjects receiving ADVAIR DISKUS 100/50 had significantly greater improvements in FEV_1 (0.51 L, 25%) compared with fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L,

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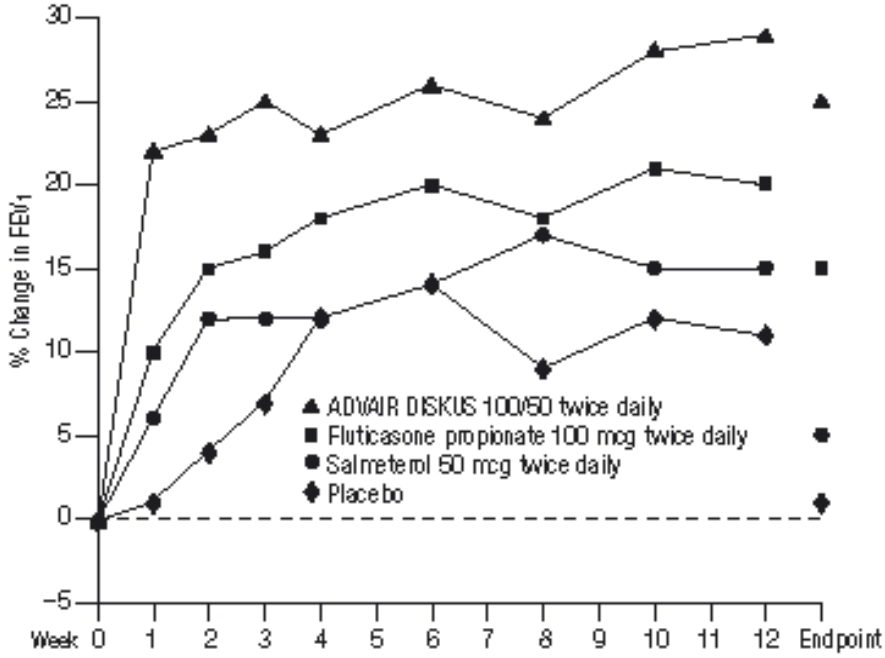
1%). These improvements in FEV_1 with ADVAIR DISKUS were achieved regardless of baseline asthma maintenance therapy (ICS or salmeterol).

Figure 1. Mean Percent Change from Baseline in FEV_1 in Subjects with Asthma Previously Treated with Either Inhaled Corticosteroids or Salmeterol (Trial 1)



	N		N		N	N
ADVAIR DISKUS 100/50	87		79		73	86
Fluticasone propionate 100 mcg	85		71		65	85
Salmeterol 50 mcg	86		59		51	86
Placebo	77		34		27	74

The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is shown in Table 5.

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Table 5. Peak Expiratory Flow Results for Subjects with Asthma Previously Treated with Either Inhaled Corticosteroids or Salmeterol (Trial 1)

Efficacy Variable[a]	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

[a] Change from baseline = change from baseline at Endpoint (last available data).

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

Trial 2: Clinical Trial with ADVAIR DISKUS 250/50: This placebo-controlled, 12-week, U.S. trial compared ADVAIR DISKUS 250/50 with its individual components, fluticasone propionate 250 mcg and salmeterol 50 mcg, in 349 subjects with asthma using ICS (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100 to 1,600 mcg). Baseline FEV_1 measurements were similar across treatments: ADVAIR DISKUS 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

Efficacy results in this trial were similar to those observed in Trial 1. Subjects receiving ADVAIR DISKUS 250/50 had significantly greater improvements in FEV_1 (0.48 L, 23%) compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and placebo (decrease of 0.11 L, decrease of 5%). Statistically significantly fewer subjects receiving ADVAIR DISKUS 250/50 were withdrawn from this trial for worsening asthma (4%) compared with fluticasone propionate (22%), salmeterol (38%), and placebo (62%). In addition, ADVAIR DISKUS 250/50 was superior to fluticasone propionate, salmeterol, and placebo for improvements in morning and evening PEF. Subjects receiving ADVAIR DISKUS 250/50 also had clinically meaningful improvements in overall asthma-specific quality of life as described in Trial 1 (difference in AQLQ score of 1.29 compared with placebo).

Trial 3: Clinical Trial with ADVAIR DISKUS 500/50: This 28-week, non-U.S. trial compared ADVAIR DISKUS 500/50 with fluticasone propionate 500 mcg alone and concurrent

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therapy (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from separate inhalers) twice daily in 503 subjects with asthma using ICS (daily doses of beclomethasone dipropionate 1,260 to 1,680 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; or fluticasone propionate inhalation aerosol 660 to 880 mcg [750 to 1,000 mcg inhalation powder]). The primary efficacy parameter, morning PEF, was collected daily for the first 12 weeks of the trial. The primary purpose of weeks 13 to 28 was to collect safety data.

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

Onset of Action and Progression of Improvement in Asthma Control: The onset of action and progression of improvement in asthma control were evaluated in the 2 placebo-controlled U.S. trials. Following the first dose, the median time to onset of clinically significant bronchodilatation (≥15% improvement in FEV_1) in most subjects was seen within 30 to 60 minutes. Maximum improvement in FEV_1 generally occurred within 3 hours, and clinically significant improvement was maintained for 12 hours (Figure 2). Following the initial dose, predose FEV_1 relative to Day 1 baseline improved markedly over the first week of treatment and continued to improve over the 12 weeks of treatment in both trials. No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR DISKUS 100/50 (Figures 2 and 3) or ADVAIR DISKUS 250/50 as assessed by FEV_1 following 12 weeks of therapy.

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Figure 2. Percent Change in Serial 12-Hour FEV_1 in Subjects with Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Trial 1)

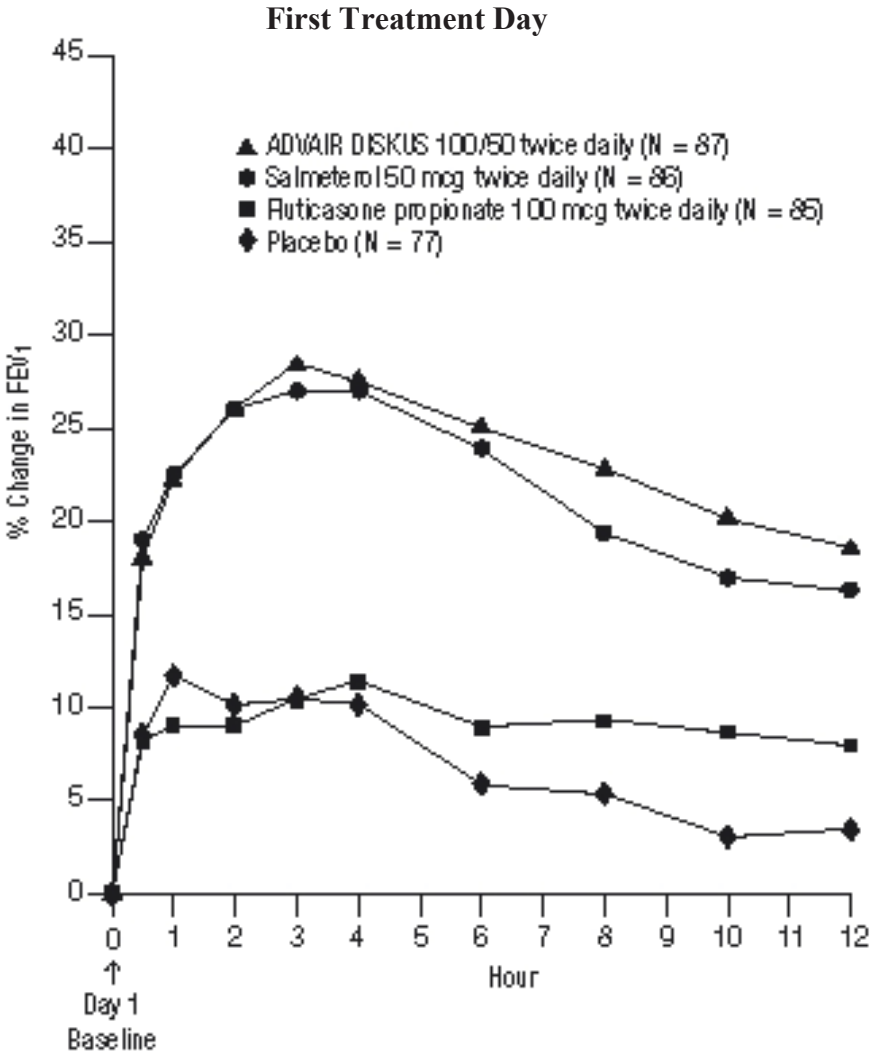

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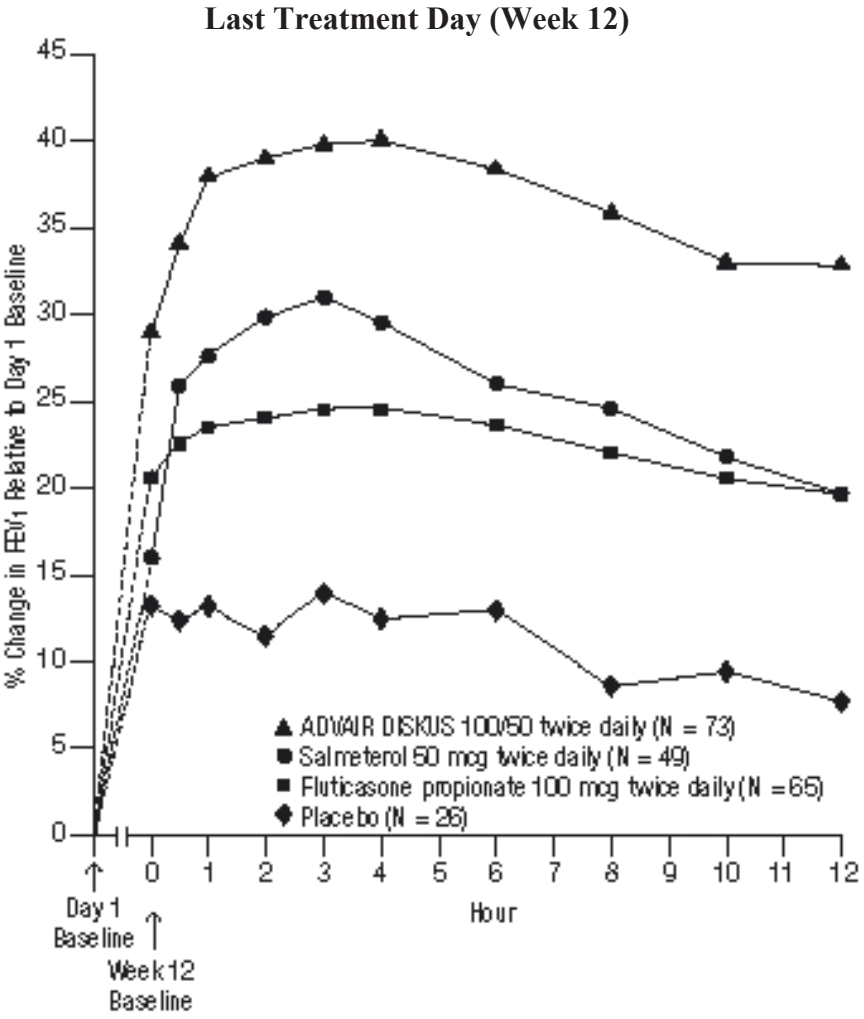
Figure 3. Percent Change in Serial 12-Hour FEV_1 in Subjects with Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Trial 1)



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

Pediatric Subjects

In a 12-week U.S. trial, ADVAIR DISKUS 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 mcg twice daily in 203 children with asthma aged 4 to 11 years. At trial entry, the children were symptomatic on low doses of ICS (beclomethasone dipropionate 252 to 336 mcg/day; budesonide 200 to 400 mcg/day; flunisolide 1,000 mcg/day; triamcinolone acetonide 600 to 1,000 mcg/day; or fluticasone propionate 88 to 250 mcg/day). The primary objective of this trial was to determine the safety of ADVAIR DISKUS 100/50

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compared with fluticasone propionate inhalation powder 100 mcg in this age group; however, the trial also included secondary efficacy measures of pulmonary function. Morning predose FEV_1 was obtained at baseline and Endpoint (last available FEV_1 result) in children aged 6 to 11 years. In subjects receiving ADVAIR DISKUS 100/50, FEV_1 increased from 1.70 L at baseline (n = 79) to 1.88 L at Endpoint (n = 69) compared with an increase from 1.65 L at baseline (n = 83) to 1.77 L at Endpoint (n = 75) in subjects receiving fluticasone propionate 100 mcg.

The findings of this trial, along with extrapolation of efficacy data from subjects aged 12 years and older, support the overall conclusion that ADVAIR DISKUS 100/50 is efficacious in the treatment of asthma in subjects aged 4 to 11 years.

Safety and Efficacy Trials Comparing ADVAIR DISKUS with Fluticasone Propionate

Serious Asthma-Related Events: Two 26-week, randomized, double-blind, parallel-group, active comparator trials were conducted to compare the safety and efficacy of ADVAIR DISKUS with fluticasone propionate inhalation powder in adult and adolescent subjects (Trial 4, NCT01475721) and in pediatric subjects aged 4 to 11 years (Trial 5, NCT01462344). The primary safety objective of both trials was to evaluate whether the addition of salmeterol xinafoate to fluticasone propionate therapy (ADVAIR DISKUS) was non-inferior to ICS fluticasone propionate in terms of the risk of a serious asthma-related event (hospitalization, endotracheal intubation, and death). The trials were designed to rule out pre-defined risk margins for serious asthma-related events of 2.0 for Trial 4 and 2.7 for Trial 5. A blinded adjudication committee determined whether events were asthma related.

Trial 4 enrolled subjects with moderate to severe persistent asthma with a history of asthma-related hospitalization or at least 1 asthma exacerbation in the previous year treated with systemic corticosteroids. A total of 11,679 adult and adolescent subjects [5,834 receiving ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR DISKUS 500/50 and 5,845 receiving fluticasone propionate inhalation powder (100, 250, or 500 mcg)] were included. Trial 5 enrolled subjects with a diagnosis of asthma and a history of at least 1 asthma exacerbation in the previous year treated with systemic corticosteroid. A total of 6,208 subjects aged 4 to 11 years [3,107 receiving ADVAIR DISKUS 100/50 or ADVAIR DISKUS 250/50 and 3,101 receiving fluticasone propionate inhalation powder (100 or 250 mcg)] were included. In both trials, subjects with life-threatening asthma were excluded. In Trials 4 and 5, ADVAIR DISKUS was non-inferior to fluticasone propionate in terms of time to first serious asthma-related events based on the pre-specified risk margins, with estimated hazard ratios of 1.03 (95% CI: 0.64, 1.66) and 1.29 (95% CI: 0.73, 2.27), respectively (Table 6).

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Table 6. Serious Asthma-Related Events in the 26-Week Trials 4 and 5

	Adult and Adolescent Subjects Aged 12 Years and Older (Trial 4)		Pediatric Subjects Aged 4 to 11 Years (Trial 5)	
	ADVAIR DISKUS (n = 5,834)	Fluticasone Propionate Inhalation Powder (n = 5,845)	ADVAIR DISKUS (n = 3,107)	Fluticasone Propionate Inhalation Powder (n = 3,101)
Serious asthma-related event (hospitalization, endotracheal intubation, and death)[a]	34 (0.6%)	33 (0.6%)	27 (0.9%)	21 (0.7%)
Hazard ratio (ADVAIR DISKUS/fluticasone propionate)	1.03 (0.64-1.66)[b]		1.29 (0.73-2.27)[b]	
Asthma-related death	0	0	0	0
Asthma-related intubation (endotracheal)	0	2	0	0
Asthma-related hospitalization (≥24-hour stay)	34	33	27	21

[a] Number of subjects with event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug treatment, whichever date was later. Subjects can have one or more events, but only the first event was counted for analysis. A blinded adjudication committee determined whether events were asthma related.

[b] The hazard ratio for time to first event was based on a Cox proportional hazards model with a single covariate of treatment (ADVAIR DISKUS vs. fluticasone propionate) and baseline hazards stratified by incoming asthma medication/asthma control status. If the resulting upper 95% CI estimate for the relative risk was <2.0 (Trial 4) or <2.7 (Trial 5), then non-inferiority was concluded.

Effect on Exacerbation: Trials 4 and 5 included time to first exacerbation as a secondary endpoint, where exacerbation was defined as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. In Trials 4 and 5, the hazard ratio for the time to first asthma exacerbation for ADVAIR DISKUS relative to fluticasone propionate inhalation powder was 0.79 (95% CI: 0.70, 0.89) and 0.86 (95% CI: 0.73, 1.01), respectively. The difference in exacerbations was primarily driven by a reduction in those requiring systemic corticosteroids only.

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14.2 Chronic Obstructive Pulmonary Disease

The efficacy of ADVAIR DISKUS 250/50 and ADVAIR DISKUS 500/50 in the treatment of subjects with COPD was evaluated in 6 randomized, double-blind, parallel-group clinical trials in adult subjects aged 40 years and older. These trials were primarily designed to evaluate the efficacy of ADVAIR DISKUS on lung function (3 trials), exacerbations (2 trials), and survival (1 trial).

Lung Function

Two (2) of the 3 clinical trials primarily designed to evaluate the efficacy of ADVAIR DISKUS on lung function were conducted in 1,414 subjects with COPD associated with chronic bronchitis. In these 2 trials, all the subjects had a history of cough productive of sputum that was not attributable to another disease process on most days for at least 3 months of the year for at least 2 years. The trials were randomized, double-blind, parallel-group, 24-week treatment duration. One (1) trial evaluated the efficacy of ADVAIR DISKUS 250/50 compared with its components fluticasone propionate 250 mcg and salmeterol 50 mcg and with placebo, and the other trial evaluated the efficacy of ADVAIR DISKUS 500/50 compared with its components fluticasone propionate 500 mcg and salmeterol 50 mcg and with placebo. Trial treatments were inhalation powders given as 1 inhalation from the DISKUS inhaler twice daily. Maintenance COPD therapies were discontinued, with the exception of theophylline. The subjects had a mean pre-bronchodilator FEV_1 of 41% and 20% reversibility at trial entry. Percent reversibility was calculated as 100 times (FEV_1 post-albuterol minus FEV_1 pre-albuterol)/FEV_1 pre-albuterol.

Improvements in lung function (as defined by predose and postdose FEV_1) were significantly greater with ADVAIR DISKUS than with fluticasone propionate, salmeterol, or placebo. The improvement in lung function with ADVAIR DISKUS 500/50 was similar to the improvement seen with ADVAIR DISKUS 250/50.

Figures 4 and 5 display predose and 2-hour postdose, respectively, FEV_1 results for the trial with ADVAIR DISKUS 250/50. To account for subject withdrawals during the trial, FEV_1 at Endpoint (last evaluable FEV_1) was evaluated. Subjects receiving ADVAIR DISKUS 250/50 had significantly greater improvements in predose FEV_1 at Endpoint (165 mL, 17%) compared with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL, 1%), demonstrating the contribution of fluticasone propionate to the improvement in lung function with ADVAIR DISKUS (Figure 4). Subjects receiving ADVAIR DISKUS 250/50 had significantly greater improvements in postdose FEV_1 at Endpoint (281 mL, 27%) compared with fluticasone propionate 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the contribution of salmeterol to the improvement in lung function with ADVAIR DISKUS (Figure 5).

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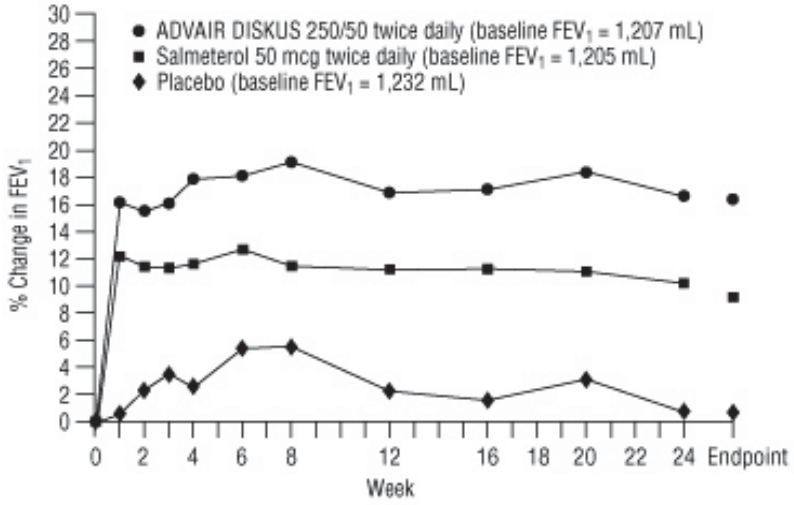
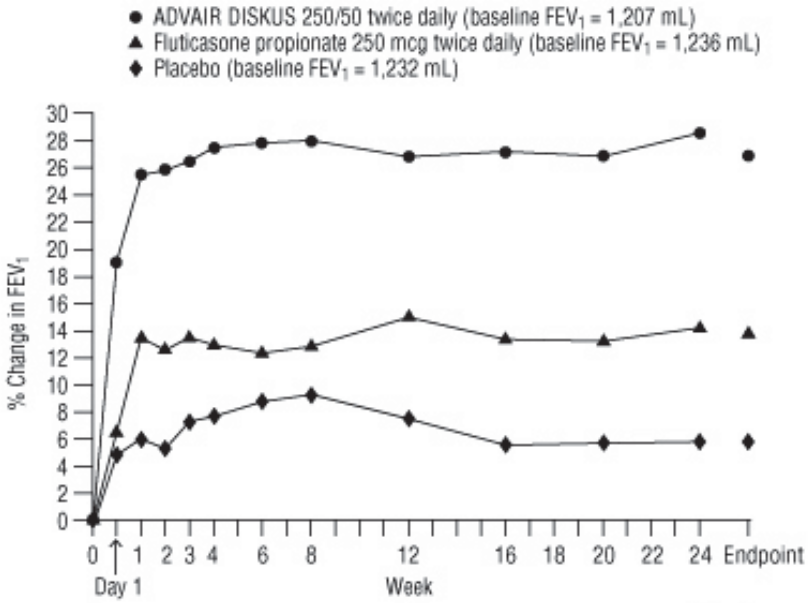
Figure 4. Predose FEV_1: Mean Percent Change from Baseline in Subjects with Chronic Obstructive Pulmonary Disease



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

Figure 5. Two-Hour Postdose FEV_1: Mean Percent Changes from Baseline over Time in Subjects with Chronic Obstructive Pulmonary Disease



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

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The third trial was a 1-year trial that evaluated ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, and placebo in 1,465 subjects. The subjects had an established history of COPD and exacerbations, a pre-bronchodilator FEV_1 <70% of predicted at trial entry, and 8.3% reversibility. The primary endpoint was the comparison of pre-bronchodilator FEV_1 in the groups receiving ADVAIR DISKUS 500/50 or placebo. Subjects treated with ADVAIR DISKUS 500/50 had greater improvements in FEV_1 (113 mL, 10%) compared with fluticasone propionate 500 mcg (7 mL, 2%), salmeterol (15 mL, 2%), and placebo (-60 mL, -3%).

Exacerbations

Two (2) trials were primarily designed to evaluate the effect of ADVAIR DISKUS 250/50 on exacerbations. In these 2 trials, exacerbations were defined as worsening of 2 or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of any 1 major symptom together with any 1 of the following minor symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or wheeze for at least 2 consecutive days. COPD exacerbations were considered of moderate severity if treatment with systemic corticosteroids and/or antibiotics was required and were considered severe if hospitalization was required.

Exacerbations were also evaluated as a secondary outcome in the 1- and 3-year trials with ADVAIR DISKUS 500/50. There was not a symptomatic definition of exacerbation in these 2 trials. Exacerbations were defined in terms of severity requiring treatment with antibiotics and/or systemic corticosteroids (moderately severe) or requiring hospitalization (severe).

The 2 exacerbation trials with ADVAIR DISKUS 250/50 were identical trials designed to evaluate the effect of ADVAIR DISKUS 250/50 and salmeterol 50 mcg, each given twice daily, on exacerbations of COPD over a 12-month period. A total of 1,579 subjects had an established history of COPD (but no other significant respiratory disorders). Subjects had a pre-bronchodilator FEV_1 of 33% of predicted, a mean reversibility of 23% at baseline, and a history of ≥1 COPD exacerbation in the previous year that was moderate or severe. All subjects were treated with ADVAIR DISKUS 250/50 twice daily during a 4-week run-in period prior to being assigned trial treatment with twice-daily ADVAIR DISKUS 250/50 or salmeterol 50 mcg. In both trials, treatment with ADVAIR DISKUS 250/50 resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with salmeterol (30.5% reduction [95% CI: 17.0, 41.8], $P<0.001$) in the first trial and (30.4% reduction [95% CI: 16.9, 41.7], $P<0.001$) in the second trial. Subjects treated with ADVAIR DISKUS 250/50 also had a significantly lower annual rate of exacerbations requiring treatment with oral corticosteroids compared with subjects treated with salmeterol (39.7% reduction [95% CI: 22.8, 52.9], $P<0.001$) in the first trial and (34.3% reduction [95% CI: 18.6, 47.0], $P<0.001$) in the second trial. Secondary endpoints including pulmonary function and symptom scores improved more in subjects treated with ADVAIR DISKUS 250/50 than with salmeterol 50 mcg in both trials.

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Exacerbations were evaluated in the 1- and the 3-year trials with ADVAIR DISKUS 500/50 as 1 of the secondary efficacy endpoints. In the 1-year trial, the group receiving ADVAIR DISKUS 500/50 had a significantly lower rate of moderate and severe exacerbations compared with placebo (25.4% reduction compared with placebo [95% CI: 13.5, 35.7]) but not when compared with its components (7.5% reduction compared with fluticasone propionate [95% CI: -7.3, 20.3] and 7% reduction compared with salmeterol [95% CI: -8.0, 19.9]). In the 3-year trial, the group receiving ADVAIR DISKUS 500/50 had a significantly lower rate of moderate and severe exacerbations compared with each of the other treatment groups (25.1% reduction compared with placebo [95% CI: 18.6, 31.1], 9.0% reduction compared with fluticasone propionate [95% CI: 1.2, 16.2], and 12.2% reduction compared with salmeterol [95% CI: 4.6, 19.2]).

There were no trials conducted to directly compare the efficacy of ADVAIR DISKUS 250/50 with ADVAIR DISKUS 500/50 on exacerbations. Across trials, the reduction in exacerbations seen with ADVAIR DISKUS 500/50 was not greater than the reduction in exacerbations seen with ADVAIR DISKUS 250/50.

Survival

A 3-year multicenter, international trial evaluated the efficacy of ADVAIR DISKUS 500/50 compared with fluticasone propionate 500 mcg, salmeterol 50 mcg, and placebo on survival in 6,112 subjects with COPD. During the trial subjects were permitted usual COPD therapy with the exception of other ICS and long-acting bronchodilators. The subjects were aged 40 to 80 years with an established history of COPD, a pre-bronchodilator FEV_1 <60% of predicted at trial entry, and <10% of predicted reversibility. Each subject who withdrew from double-blind treatment for any reason was followed for the full 3-year trial period to determine survival status. The primary efficacy endpoint was all-cause mortality. Survival with ADVAIR DISKUS 500/50 was not significantly improved compared with placebo or the individual components (all-cause mortality rate 12.6% ADVAIR DISKUS versus 15.2% placebo). The rates for all-cause mortality were 13.5% and 16.0% in the groups treated with salmeterol 50 mcg and fluticasone propionate 500 mcg, respectively. Secondary outcomes, including pulmonary function (post-bronchodilator FEV_1), improved with ADVAIR DISKUS 500/50, salmeterol 50 mcg, and fluticasone propionate 500 mcg compared with placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

ADVAIR DISKUS 100/50 is supplied as a disposable purple plastic inhaler containing a foil blister strip with 60 blisters. The inhaler is packaged in a plastic-coated, moisture-protective foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional pack containing 14 blisters (NDC 0173-0695-04).

ADVAIR DISKUS 250/50 is supplied as a disposable purple plastic inhaler containing a foil blister strip with 60 blisters. The inhaler is packaged in a plastic-coated, moisture-protective foil

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pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional pack containing 14 blisters (NDC 0173-0696-04).

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Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. Keep out of reach of children.

ADVAIR DISKUS should be stored inside the unopened moisture-protective foil pouch and only removed from the pouch immediately before initial use. Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all blisters have been used), whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler apart.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Serious Asthma-Related Events

Inform patients with asthma that LABA when used alone increases the risk of asthma-related hospitalization or asthma-related death. Available data show that when ICS and LABA are used together, such as with ADVAIR DISKUS, there is not a significant increase in the risk of these events.

Not for Acute Symptoms

Inform patients that ADVAIR DISKUS is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

Tell patients they should not stop therapy with ADVAIR DISKUS without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-acting Beta$_2$-agonists

Instruct patients not to use other LABA for asthma and COPD.

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Local Effects

Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, treat it with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with ADVAIR DISKUS, but at times therapy with ADVAIR DISKUS may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.

Pneumonia

Patients with COPD have a higher risk of pneumonia; instruct them to contact their healthcare providers if they develop symptoms of pneumonia.

Immunosuppression

Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Hypercorticism and Adrenal Suppression

Advise patients that ADVAIR DISKUS may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to ADVAIR DISKUS.

Immediate Hypersensitivity Reactions

Advise patients that immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of ADVAIR DISKUS. Patients should discontinue ADVAIR DISKUS if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of powder products containing lactose; therefore, patients with severe milk protein allergy should not take ADVAIR DISKUS.

Reduction in Bone Mineral Density

Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Reduced Growth Velocity

Inform patients that orally inhaled corticosteroids, including fluticasone propionate, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route.

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Ocular Effects

Inform patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.

Risks Associated with Beta-agonist Therapy

Inform patients of adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

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Research Triangle Park, NC 27709

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PATIENT INFORMATION

ADVAIR DISKUS [AD vair DISK us]
(fluticasone propionate and salmeterol inhalation powder)
for oral inhalation

What is ADVAIR DISKUS?

- ADVAIR DISKUS combines the inhaled corticosteroid (ICS) medicine fluticasone propionate and the long-acting beta$_2$-adrenergic agonist (LABA) medicine salmeterol.
  - ICS medicines such as fluticasone propionate help to decrease inflammation in the lungs. Inflammation in the lungs can lead to breathing problems.
  - LABA medicines such as salmeterol help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing, cough, chest tightness, and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe.
- **ADVAIR DISKUS is not used to relieve sudden breathing problems** and will not replace a rescue inhaler.
- It is not known if ADVAIR DISKUS is safe and effective in children younger than 4 years.
- ADVAIR DISKUS is used for asthma and COPD as follows:

  Asthma:
  - ADVAIR DISKUS is a prescription medicine used to control symptoms of asthma and to prevent symptoms such as wheezing in adults and children aged 4 years and older.
  - ADVAIR DISKUS contains salmeterol, the same medicine found in SEREVENT DISKUS (salmeterol xinafoate inhalation powder). LABA medicines such as salmeterol when used alone increase the risk of hospitalizations and death from asthma problems. ADVAIR DISKUS contains an ICS and a LABA. When an ICS and LABA are used together, there is not a significant increased risk in hospitalizations and death from asthma problems.
  - ADVAIR DISKUS is not for adults and children with asthma who are well controlled with an asthma control medicine, such as a low to medium dose of an ICS medicine. ADVAIR DISKUS is for adults and children with asthma who need both an ICS and LABA medicine.

  COPD:

  ADVAIR DISKUS 250/50 is a prescription medicine used to treat COPD. COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both. ADVAIR DISKUS 250/50 is used long term as 1 inhalation 2 times each day to improve symptoms of COPD for better breathing and to reduce the number of flare-ups (the worsening of your COPD symptoms for several days).

Do not use ADVAIR DISKUS:

- to relieve sudden breathing problems.
- as a rescue inhaler.
- if you have a severe allergy to milk proteins. Ask your healthcare provider if you are not sure.
- if you are allergic to fluticasone propionate, salmeterol, or any of the ingredients in ADVAIR DISKUS. See the end of this Patient Information for a complete list of ingredients in ADVAIR DISKUS.

Before using ADVAIR DISKUS, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems.
- have high blood pressure.

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- have seizures.
- have thyroid problems.
- have diabetes.
- have liver problems.
- have weak bones (osteoporosis).
- have an immune system problem.
- have or have had eye problems, such as increased pressure in your eye (glaucoma) or cataracts.
- are allergic to milk proteins.
- have any type of viral, bacterial, or fungal infection.
- are exposed to chickenpox or measles.
- are pregnant or plan to become pregnant. It is not known if ADVAIR DISKUS may harm your unborn baby.
- are breastfeeding. It is not known if the medicines in ADVAIR DISKUS pass into your milk and if they can harm your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ADVAIR DISKUS and certain other medicines may interact with each other. This may cause serious side effects. Especially tell your healthcare provider if you take antifungal or anti-HIV medicines.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use ADVAIR DISKUS?

Read the step-by-step instructions for using ADVAIR DISKUS at the end of this Patient Information.

- **Do not** use ADVAIR DISKUS unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly.
- Children should use ADVAIR DISKUS with an adult's help, as instructed by the child's healthcare provider.
- ADVAIR DISKUS comes in 3 different strengths. Your healthcare provider prescribed the strength that is best for you.
- Use ADVAIR DISKUS exactly as your healthcare provider tells you to use it. **Do not** use ADVAIR DISKUS more often than prescribed.
- Use 1 inhalation of ADVAIR DISKUS 2 times each day. Use ADVAIR DISKUS at the same time each day, about 12 hours apart.
- If you miss a dose of ADVAIR DISKUS, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at 1 time.
- If you take too much ADVAIR DISKUS, call your healthcare provider or go to the nearest hospital emergency room right away if you have any unusual symptoms, such as worsening shortness of breath, chest pain, increased heart rate, or shakiness.
- **Do not use other medicines that contain a LABA for any reason.** Ask your healthcare provider or pharmacist if any of your other medicines are LABA medicines.
- **Do not** stop using ADVAIR DISKUS, even if you are feeling better, unless your healthcare provider tells you to.
- **ADVAIR DISKUS does not relieve sudden breathing problems.** Always have a rescue inhaler with you to treat sudden symptoms. If you do not have a rescue inhaler, call your healthcare provider to have one prescribed for you.
- Rinse your mouth with water **without swallowing** after each dose of ADVAIR DISKUS. This will help lessen the chance of getting a yeast infection (thrush) in your mouth and throat.

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- Call your healthcare provider or get medical care right away if:
  - your breathing problems get worse.
  - you need to use your rescue inhaler more often than usual.
  - your rescue inhaler does not work as well to relieve your symptoms.
  - you need to use 4 or more inhalations of your rescue inhaler in 24 hours for 2 or more days in a row.
  - you use 1 whole canister of your rescue inhaler in 8 weeks.
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
  - you have asthma and your symptoms do not improve after using ADVAIR DISKUS regularly for 1 week.

What are the possible side effects of ADVAIR DISKUS?

ADVAIR DISKUS can cause serious side effects, including:

- **fungal infection in your mouth or throat (thrush).** Rinse your mouth with water **without swallowing** after using ADVAIR DISKUS to help reduce your chance of getting thrush.
- **pneumonia.** People with COPD have a higher chance of getting pneumonia. ADVAIR DISKUS may increase the chance of you getting pneumonia. Call your healthcare provider right away if you have any of the following symptoms:
  - increase in mucus (sputum) production
  - change in mucus color
  - fever
  - chills
  - increased cough
  - increased breathing problems
- **weakened immune system and increased chance of getting infections (immunosuppression).**
- **reduced adrenal function (adrenal insufficiency).** Adrenal insufficiency is a condition where the adrenal glands do not make enough steroid hormones. This can happen when you stop taking oral corticosteroid medicines (such as prednisone) and start taking a medicine containing an inhaled steroid (such as ADVAIR DISKUS). During this transition period, when your body is under stress such as from fever, trauma (such as a car accident), infection, surgery, or worse COPD symptoms, adrenal insufficiency can get worse and may cause death.

  Symptoms of adrenal insufficiency include:
  - feeling tired
  - lack of energy
  - weakness
  - nausea and vomiting
  - low blood pressure (hypotension)
- **sudden breathing problems immediately after inhaling your medicine.** If you have sudden breathing problems immediately after inhaling your medicine, stop using ADVAIR DISKUS and call your healthcare provider right away.
- **serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - swelling of your face, mouth, and tongue
  - breathing problems
- **effects on heart.**
  - increased blood pressure
  - a fast or irregular heartbeat
  - chest pain
- **effects on nervous system.**
  - tremor
  - nervousness
- **bone thinning or weakness (osteoporosis).**
- **slowed growth in children.** Your child's growth should be checked regularly by the healthcare provider while using

ADVAIR DISKUS.

- **eye problems including glaucoma and cataracts.** You should have regular eye exams while using ADVAIR DISKUS.
- **changes in laboratory blood levels (sugar, potassium, certain types of white blood cells).**

Common side effects of ADVAIR DISKUS include:

Asthma:

- upper respiratory tract infection
- throat irritation
- hoarseness and voice changes
- thrush in your mouth or throat. Rinse your mouth with water without swallowing after use to help prevent this.
- bronchitis
- cough
- headache
- nausea and vomiting

In children with asthma, infections in the ear, nose, and throat are common.

COPD:

- thrush in your mouth or throat. Rinse your mouth with water without swallowing after use to help prevent this.
- throat irritation
- hoarseness and voice changes
- viral respiratory infections
- headache
- muscle and bone pain

These are not all the possible side effects of ADVAIR DISKUS.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ADVAIR DISKUS?

- Store ADVAIR DISKUS at room temperature between 68°F and 77°F (20°C and 25°C). Keep in a dry place away from heat and sunlight.
- Store ADVAIR DISKUS in the unopened foil pouch and only open when ready for use.
- Safely throw away ADVAIR DISKUS in the trash 1 month after you open the foil pouch or when the counter reads **0**, whichever comes first.

Keep ADVAIR DISKUS and all medicines out of the reach of children.

General information about the safe and effective use of ADVAIR DISKUS.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ADVAIR DISKUS for a condition for which it was not prescribed. Do not give ADVAIR DISKUS to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about ADVAIR DISKUS that was written for health professionals.

What are the ingredients in ADVAIR DISKUS?

Active ingredients: fluticasone propionate, salmeterol xinafoate

Inactive ingredient: lactose monohydrate (contains milk proteins)

For more information about ADVAIR DISKUS, call 1-888-825-5249 or visit our website at www.advair.com.

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ADD:xPIL

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: December 2017

Reference ID: 4198047

INSTRUCTIONS FOR USE

ADVAIR DISKUS [AD vair DISK us]
(fluticasone propionate and salmeterol inhalation powder)

for oral inhalation

Read this Instructions for Use before you start using ADVAIR DISKUS and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

Your ADVAIR DISKUS inhaler

Figure A

Important information about your ADVAIR DISKUS inhaler:

- **ADVAIR DISKUS is for oral inhalation use only.**
- Take ADVAIR DISKUS out of the foil pouch just before you use it for the first time. Safely throw away the pouch. The DISKUS will be in the closed position.
- Write the date you opened the foil pouch in the first blank line on the label. **See Figure A.**
- Write the "use by" date in the second blank line on the label. **See Figure A.** That date is 1 month after the date you wrote in the first line.
- The counter should read **60**. If you have a sample (with "Sample" on the back label) or institutional (with "INSTITUTIONAL PACK" on the back label) pack, the counter should read **14**.

How to use your ADVAIR DISKUS inhaler
Follow these steps every time you use ADVAIR DISKUS.

Step 1. Open your ADVAIR DISKUS.

- Hold the DISKUS in your left hand and place the thumb of your right hand in the thumb grip. Push the thumb grip away from you as far as it will go until the mouthpiece shows and snaps into place. **See Figure B**.

Step 2. Slide the lever until you hear it click.

- **Hold the DISKUS in a level, flat position** with the mouthpiece towards you. Slide the lever away from the mouthpiece as far as it will go until it **clicks**. **See Figure C.**

Figure B

Figure C

- The number on the counter will count down by 1. The DISKUS is now ready to use.

Follow the instructions below so you will not accidentally waste a dose:

- **Do not** close the DISKUS.
- **Do not** tilt the DISKUS.
- **Do not** move the lever on the DISKUS.

Step 3. Inhale your medicine.

- Before you breathe in your dose from the DISKUS, breathe out (exhale) as long as you can while you hold the DISKUS level and away from your mouth. **See Figure D.** Do not breathe into the mouthpiece.
- Put the mouthpiece to your lips. **See Figure E.** Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.

Figure D

Figure E

- Remove the DISKUS from your mouth **and hold your breath for about 10 seconds,** or for as long as is comfortable for you.
- **Breathe out slowly as long as you can. See Figure D.**
- The DISKUS delivers your dose of medicine as a very fine powder that you may or may not taste or feel. **Do not** take an extra dose from the DISKUS even if you do not taste or feel the medicine.

Step 4. Close the DISKUS.

- Place your thumb in the thumb grip and slide it back towards you as far as it will go. **See Figure F.** Make sure the DISKUS clicks shut and you cannot see the mouthpiece.

Figure F

- The DISKUS is now ready for you to take your next scheduled dose in about 12 hours. **When you are ready to take your next dose, repeat Steps 1 through 4.**

Step 5. Rinse your mouth.

- **Rinse your mouth with water after breathing in the medicine.** Spit out the water. Do not swallow it. **See Figure G.**

Figure G

When should you get a refill?

The counter on top of the DISKUS shows you how many doses are left. After you have taken **55** doses (**9** doses from the sample or institutional pack), the numbers **5** to **0** will show in red. **See Figure H.** These numbers warn you there are only a few doses left and are a reminder to get a refill.

Figure H

For correct use of the DISKUS, remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. Do not swallow the water.
- **Do not** take an extra dose, even if you did not taste or feel the powder.
- **Do not** take the DISKUS apart.
- **Do not** wash the DISKUS.
- Always keep the DISKUS in a dry place.
- **Do not** use the DISKUS with a spacer device.

For more information about ADVAIR DISKUS or how to use your inhaler, call 1-888-825-5249 or visit our website at www.advair.com.

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This Instructions for Use has been approved by the U.S. Food and Drug Administration Revised: December 2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021077Orig1s056

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sally Seymour, MD Deputy Director for Safety, DPARP
Subject	Cross Discipline Team Leader Review Division Director Summary Review
NDA/BLA # and Supplement #	NDA# 21077, S-56 (Advair Adult/Adolescent PMR) NDA# 21077, S-57 (Advair Pediatric PMR) NDA# 21929, S-42 (Symbicort) NDA# 22518, S-22 (Dulera) NDA# 21254, S-27 (Advair HFA) NDA# 204275, S-15 (Breo Ellipta) NDA# 208799, S-2 (AirDuo)
Applicant	GlaxoSmithKline (GSK) – Advair, Breo AstraZeneca (AZ) - Symbicort Merck - Dulera Teva - AirDuo
Date of Submission	October 3, 2016 – NDA# 21077, S-56 and S-57 February 28, 2017 – NDA# 21929, S-42 July 14, 2017 - NDA# 21254, S-27 July 31, 2017 - NDA# 22518, S-022 August 3, 2017 - NDA# 204275, S-15 November 3, 2017 - NDA# 208799, S-2
PDUFA Goal Date	NDA# 21077, S-56 and 57 - August 3, 2017 - extended November 3, 2017 NDA# 21929, S-42 - December 28, 2017 NDA# 22518, S-22 – May 31, 2018 NDA# 21254, S-27 – January 14, 2018 NDA# 204275, S-15 – February 3, 2018 NDA# 208799, S-2 - May 3, 2018
Proprietary Name	Advair Diskus, Symbicort Inhalation Aerosol, Dulera Inhalation Aerosol, Advair HFA, Breo Ellipta, AirDuo
Established or Proper Name	fluticasone propionate/salmeterol; budesonide/formoterol; mometasone/formoterol; fluticasone propionate/salmeterol; fluticasone furoate/vilanterol
Dosage Form(s)	Dry powder inhaler and metered dose inhaler
Applicant Proposed Indication(s)/Population(s)	No new indication; addition of results of ICS/LABA safety trial
Action	Approval
Approved/Recommended Indication(s)/Population(s) (if applicable)	Addition of results of ICS/LABA safety trials, meta-analysis and removal of Boxed Warning

Reference ID: 4198161

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	**Robert Lim, MD** **- August 11, 2017 (Advair Diskus)** **- September 13, 2017 (Symbicort)** **- December 14, 2017 (Dulera)**
Statistical Review	**Changming (Sherman) Xia, PhD** **- June 26, 2017 (Advair Diskus)** **- September 28, 2017 (Symbicort)** **- December 19, 2017 (Dulera)** **Robert Abugov, PhD** **- August 9, 2017 (Symbicort)** **- September 27, 2017 (Dulera)** **Shanti Gomatam, PhD, August 14, 2017 (Advair Diskus)**
Pharmacology/Toxicology	**Tim Robison, PhD June 2, 2017 (Advair Diskus)**
OPDP	**Taylor Burnett, November 3, 2017**
OSI	
CDTL Review	
OSE/DEPI	**Veronica Sansing-Foster, PhD, MS** **- November 8, 2017** **- November 29, 2017**
OSE/DMEPA	
Patient Labeling	**Sharon Williams, MSN, BSN, RN, November 3, 2017**

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Reference ID: 4198161

1. Introduction

This is a Division Summary for a group of supplements submitted for inhaled corticosteroid/ long-acting beta agonist (ICS/LABA) products [Advair Diskus, Symbicort, Dulera, Advair HFA, Breo Ellipta, AirDuo] to update the product labels with results of completed large safety trials, a meta-analysis of the combined trials, and removal of the Boxed Warning for asthma-related death from ICS/LABA product labeling. In 2010, FDA required 5 large safety trials evaluating the safety of LABA on background ICS. Four of the trials were completed and one was terminated. Results of all the trials (completed and terminated) have been submitted and reviewed. Four supplements [Advair Diskus (adults and pediatric trial), Dulera, Symbicort] were submitted with clinical data to include the results of the completed clinical trials in product labeling. As described in this memo, based upon the review of the results of the completed trials, FDA decided to remove the Boxed Warning for asthma-related death from the ICS/LABA product labels. Therefore, we requested that all ICS/LABA sponsors amend supplements or submit a labeling supplement to remove the Boxed Warning. Three new labeling supplements were submitted based upon this request [AirDuo, Breo Ellipta, Advair HFA].

The FDA mandated ICS/LABA safety trials were designed at the same time, with similar trial design and shared adjudication, steering, and data monitoring committees (adult and adolescent trials) with the intent of combining the results when the trials were completed. The individual trial results were reviewed together and combined by the FDA, and support class ICS/LABA labeling changes. This memo covers all 7 of the ICS/LABA supplements for the 6 affected products. The formoterol trial was terminated and was reviewed separately.

2. Background

There have been longstanding safety concerns regarding LABAs and an increased risk of severe asthma exacerbation leading to hospitalizations and asthma-related deaths.[1] These concerns were based upon results from the Salmeterol Nationwide Surveillance (SNS) Study[2] and the Salmeterol Multicenter Asthma Research Trial (SMART)[3]. SNS compared salmeterol twice daily to salbutamol (albuterol) four times a day and showed a non-statistically significant (p=0.105) but 3 fold increase in respiratory and asthma related death in patients taking salmeterol (0.07%) versus scheduled salbutamol (0.02%). In 1996, SMART was initiated at the Agency's request following approval of salmeterol due to safety concerns raised by the SNS study, as well as reports of serious asthma exacerbations and deaths after its approval.

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[1]FDA Drug Safety Communication: Drug labels now contain updated recommendations on the appropriate use of long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs), June 2, 2010. Available at: http://www fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm; accessed July 7, 2017.
[2] Castle W, Fuller R, et al. BMJ 1993; 306: 1034-7.
[3] Nelson HS, Weiss ST, et al. Chest 2006; 129: 15-26.

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SMART was a 28-week, randomized, double-blind study that enrolled patients 12 years of age and older with asthma not currently using a LABA. These patients were randomized to salmeterol (Serevent Inhalation Aerosol) or placebo twice daily added to usual asthma therapy. Patients were not required to be on background ICS. SMART was prematurely halted in 2003 after a planned interim analysis suggested that salmeterol may be associated with an increased risk of serious asthma exacerbations including asthma-related death (relative risk 4.37 [CI 1.25, 15.34]). Results of SMART and other available data led to the addition of a Boxed Warning on LABA and ICS/LABA products.

LABA safety in asthma was discussed at a December 2008 FDA Advisory Committee (AC), during which FDA presented the results of a meta-analysis that suggested an age-related trend of increased asthma hospitalizations in pediatric patients. During the AC meeting, the committee stressed the need for more safety data, especially in the pediatric population where the data were very limited. In February 2010, to further evaluate the safety of LABA, the Agency required safety trials be conducted in adults and children with the LABA products that were approved for the treatment of asthma to further evaluate the safety concerns of this drug class in the asthmatic population.[4] The design of the LABA safety trials was discussed at a March 2010 AC meeting. In April 2011, the Agency announced the basic design (randomized, double-blind, controlled clinical trials comparing the addition of LABAs to inhaled corticosteroids versus inhaled corticosteroids alone).[5] The following is a list of the PMRs required and the final report submission dates.

- 1750-1 [Advair Diskus]
  A randomized, double-blind, 26-week, active-controlled clinical trial comparing Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) and fluticasone propionate inhalation powder to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 11,700 adult and adolescent patients 12 years of age and older with persistent asthma.
  - Final report submitted – January 15, 2016
  - Supplement submitted – October 3, 2016
- 1750-2 [Advair Diskus]
  A randomized, double-blind, 26-week, active-controlled clinical trial comparing Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) and Flovent Diskus (fluticasone propionate inhalation powder) to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 6200 pediatric patients 4 to 11 years of age with persistent asthma.
  - Final report submitted – May 19, 2016

[4] FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs), February 18, 2010. Available at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm; accessed July 7, 2017

[5] FDA Drug Safety Communication: FDA requires post-market safety trials for Long-Acting Beta-Agonists, April 15, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm251512.htm; accessed July 7, 2017.

Reference ID: 4198161

  - Supplement submitted – October 3, 2016

- 1749-1 [Symbicort]
  A randomized, double-blind, 26-week, active-controlled clinical trial comparing Symbicort (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol with budesonide HFA to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 11,700 adult and adolescent patients 12 years of age and older with persistent asthma.

  - Final report submitted – May 10, 2016
  - Supplement submitted – February 28, 2017

- 1751-1 [Dulera]
  A randomized, double-blind, 26-week, active-controlled clinical trial comparing Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol and mometasone furoate to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 11,700 adult and adolescent patients 12 years of age and older with persistent asthma.

  - Final report submitted – July 13, 2017
  - Supplement submitted - July 31, 2017

- 1752-2 [Foradil]
  A randomized, double-blind, 26-week, active-controlled clinical trial comparing Foradil Aerolizer (formoterol fumarate inhalation powder) and fluticasone propionate with fluticasone propionate to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 11,700 adult and adolescent patients 12 years of age and older with persistent asthma.

  - Final report submitted – September 29, 2016

Additional Relevant Regulatory History

There is an extensive regulatory history of the background and interactions to discuss the design of the ICS/LABA safety trials as described in my review dated January 7, 2013. There is also extensive regulatory history regarding the conduct of the Foradil (formoterol) LABA safety trial that is discussed in the clinical review dated October 20, 2017 for NDA# 20831.

As the ICS/LABA safety trials were completed and submitted to the FDA, several key meetings/events are important to note.

- April 25, 2017 – DPARP briefed Dr. Woodcock on the preliminary findings from the ICS/LABA safety trials and discussed removal of the Boxed Warning from the ICS/LABA safety products. Agreement was reached that if FDA verified the findings; removal of the BW from the ICS/LABA products was supported. FDA could also work towards an expedited action by foregoing an Advisory Committee meeting because of the consistent results.

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- May 22, 2017 – DPARP met with members of OSE/DEPI, OB/DBVII, OPT, and DPMH to discuss the results of the ICS/LABA safety trials and the preliminary plan for removal of Boxed Warning. Agreement was reached and a path forward was planned.
- June 15, 2017 – DPARP held a teleconference with GSK, AZ, Merck to discuss the publically available results from the LABA safety studies. The Advair Diskus and Symbicort trials had been published and Merck had issued a press release with the top line results for the Dulera trial.[6,7,8,9] During the tcon, DPARP noted that if the results are verified by FDA, removal of the Box Warning from the ICS/LABA products would be supported and an AC meeting would not be necessary. DPARP requested submission of a new labeling supplement or an amendment to an existing sNDA that provides for removal of the Boxed Warning for asthma-related deaths from the label. The submission should include justification for removal of the BW and take into account the publically available results from the completed LABA safety studies. The sponsors were encouraged to work together with regard to ICS/LABA class labeling.
- October 20, 2017 – Teleconference with TEVA requesting submission of a supplement for AirDuo with removal of the Boxed Warning based upon the ICS/LABA safety trials.

3. Product Quality

Product quality data were not required or submitted for these supplements.

4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology input was required for the Advair Diskus supplements and proposed changes to include Pregnancy and Lactation Labeling Rule (PLLR) labeling. Agreement was reached on the PLLR labeling for Advair Diskus.

5. Clinical Pharmacology

Clinical pharmacology data were not required or submitted for these supplements.

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[6] Stempel DA, Raphiou IH, Kral KM, et al. N Engl J Med 2016; 374:1822-1830.
[7] Stempel DA, Szefler SJ, Pedersen SR, et al. N Engl J Med 2016; 375: 840-849.
[8] Peters SP, Bleecker ER, Canonica GW, et al. N Engl J Med 2016; 375; 850-860.
[9] May 22, 2017 - Merck Press Release [http://www.mrknewsroom.com/news/company-statements/merck-announces-top-line-results-long-term-laba-safety-study-dulera-mometaso]

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6. Clinical Microbiology

Clinical microbiology data were not required or submitted for these supplements.

7. Clinical/Statistical-Efficacy

The study design and efficacy results will be reviewed in this section. The safety findings and meta-analysis will be covered in Section 8.

Study Design and Conduct
The trials were randomized double-blind, active controlled, parallel group 26-weeks duration in patients with asthma. There were 4 trials in adults and adolescents 12 years of age and older comparing ICS/LABA to ICS. Trials were required for each of the following products:

- Advair Diskus (fluticasone propionate/salmeterol)
- Dulera (mometasone furoate/formoterol)
- Foradil (formoterol) and fluticasone propionate
- Symbicort (budesonide/formoterol)

There was also a similarly designed trial in pediatric patients 4 to 11 years of age with Advair Diskus. Since the pediatric trial was similar in design, it will not be described separately, but important differences compared to the adult/adolescent trials will be noted.

Objective
The primary objective of the trials was to evaluate whether the addition of LABA to ICS therapy is non-inferior to ICS therapy in terms of serious asthma related events (asthma-related hospitalizations, endotracheal intubations, and death). A secondary objective (efficacy) was to evaluate whether ICS/LABA is superior to ICS therapy in terms of severe asthma exacerbations. Table 1 provides a summary of the ICS/LABA Safety Trials.

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Table 1 Summary of ICS/LABA Safety Trials

Study (study dates)	Objective	Design	Population	Treatment arms (BID)	Primary endpoints
SAS115359 Advair Diskus Nov 2011-June 2015	Safety/ efficacy	R, DB, AC, MC, PG	Asthma patients ≥12 years	FP 100mcg FP/S 100/50mcg FP 250mcg FP/S 250/50mcg FP 500mcg FP/S 500/50mcg	Safety: serious asthma outcomes Efficacy: exacerbation
SAS1153598 Advair Diskus Nov 2011-Nov 2015	Safety/ efficacy	R, DB, AC, MC, PG	Asthma patients 4-11 years	FP 100mcg FP/S 100/50mcg FP 250mcg FP/S 250/50mcg	Safety: serious asthma outcomes Efficacy: exacerbation
P202MK0887A Dulera Jan 2012-Nov 2016	Safety/ efficacy	R, DB, AC, MC, PG	Asthma patients ≥12 years	Mom 200mcg Mom/F 200/10mcg Mom 400mcg Mom/F 400/10mcg	Safety: serious asthma outcomes Efficacy: exacerbation
D5896C00027 Symbicort Dec 2011-Oct 2015	Safety/ efficacy	R, DB, AC, MC, PG	Asthma patients ≥12 years	Bud 160mcg Bud/F 160/9 mcg Bud 320mcg Bud/F 320/9 mcg	Safety: serious asthma outcomes Efficacy: exacerbation

R=randomized, DB=double-blind, AC=active controlled, PC=placebo controlled, MC=multicenter, PG=parallel group
FP=fluticasone propionate, FP/S=FP/salmeterol xinafoate
Bud = budesonide, Bud/F = Bud/formoterol
Mom = mometasone, Mom/F = Mom/formoterol

Study Population

Eligible patients had a diagnosis of persistent asthma as defined by national and international guidelines (e.g., GINA 2009 and NAEPP 2007) for at least 1-year prior to enrollment. Patients had to have at least one asthma exacerbation requiring treatment with a systemic corticosteroid or hospitalization between 30 days and 12 months prior to randomization and a PEF ≥ 50% of predicted. Patients were eligible if the severity of their asthma warranted treatment with ICS/LABA as determined by baseline asthma therapy, Asthma Control Questionnaire (ACQ-6) score, and investigator clinical judgement as listed below.

- ICS or ICS with one or more adjunctive therapies [e.g., LABA, leukotriene (LTRA) receptor antagonist] for at least 4-weeks prior to randomization. At visit 1, patients maintained on a stable high dose ICS with or without adjunctive therapies must have had an ACQ-6 score <1.5 (i.e., controlled).
- LTRA or theophylline as monotherapy at a stable dose for at least 4-week prior to randomization. These patients were only eligible if ACQ-6 scores were ≥1.5 (i.e., not well controlled) and if in the investigator's clinical judgment, the patient's asthma severity would justify treatment with ICS or ICS+LABA.
- Daily rescue medication in the 4-week prior to randomization. These patients were only eligible if ACQ-6 scores were ≥1.5 (i.e., not well controlled) and if in the investigator's clinical judgment, the patient's asthma severity would justify treatment with ICS or ICS+LABA.

Patients with the following were excluded: a history of life-threatening asthma requiring intubation and/or associated with hypercapnea requiring non-invasive ventilator support;

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asthma exacerbation within 4 weeks of randomization or more than 4 separate exacerbations in the 12 months prior to randomization; more than 2 asthma hospitalizations in the 12 months prior to randomization; or unstable asthma within 7 days of randomization. Also patients with COPD or a history of smoking > 10 pack years were excluded.

For the pediatric trial, children with persistent asthma who had a history of asthma exacerbation in the past year were eligible for the study. Asthma therapy, the Childhood Asthma Control Test (C-ACT) and exacerbations were used to determined eligibility as shown Table 2. Similar to the adult trials, children with history of life-threatening asthma, unstable asthma, on high dose ICS or ICS/LABA, or recent exacerbation within 4 weeks were excluded.

Table 2 Eligibility Criteria in Pediatric ICS/LABA Safety Trial

Prior Asthma Therapy	Childhood Asthma Control Test score at Visit 1	One exacerbation in previous year	Two or more exacerbations in previous year
SABA, LTRA, theophylline or cromolyn	≥20	Not eligible	Not eligible
	≤19	Not eligible	Eligible
Low-dose ICS monotherapy	≥20	Not eligible	Eligible
	≤19	Eligible	Eligible
Low-dose ICS and one or more adjunctive therapy	≥20	Eligible	Eligible
	≤19	Eligible	Eligible
Medium-dose ICS monotherapy	≥20	Eligible	Eligible
	≤19	Eligible	Eligible
Medium-dose ICS and one or more adjunctive therapy	≥20	Eligible	Not eligible
	≤19	Not eligible	Not eligible

Source: SAS115358 Protocol, Table 1

Patients with life-threatening asthma, recent instability or multiple exacerbations were excluded. While these patients would be at high risk for the events of interest - serious asthma outcomes, enrollment of these patients raised ethical concerns because of the potential for randomization to step down in therapy from ICS/LABA to ICS. Exclusion of these patients will impact the ability to generalize safety conclusions to these patients.[10]

Once eligibility was determined, patients were discontinued from current asthma medication and randomized. Patients were randomized 1:1 to blinded therapy and stratified to ICS dose based on prior asthma medications and ACQ-6 score. Refer to Dr. Lim's reviews for details of the stratification strategy. As noted in the introduction, the Foradil trial is not included in this review, but it had important differences worth noting. Because Foradil is a single ingredient LABA product, it was administered with an ICS in a separate inhaler, i.e. it was not a fixed dose combination ICS/LABA treatment. The ICS (fluticasone) arm was open-label and the LABA treatment was blinded.

[10] Martinez FD. N Engl J Med 2016; 374:1887-1888.

Reference ID: 4198161

Patients were allowed use of rescue medication and other medications with the exception of prohibited medications, such as Xolair and/or other monoclonal antibodies or investigational drugs. Following the randomization visit (visit 2), patients were seen in clinic at days 30, 90, and 182 (visits 3, 4, and 5). During months without a clinic visit, patients were contacted by phone.

Primary Safety Endpoint

The primary safety endpoint was serious asthma-related events defined as a composite of asthma-related hospitalizations (≥ 24 hours), asthma-related intubations, or asthma-related deaths over the 26-week treatment period. Asthma-relatedness for these events was determined by a shared, independent, blinded adjudication committee for the adult/adolescent trials. The following were the members of the joint adjudication committee: (b) (6) (b) (6) (b) (6). The pediatric trial had a separate independent, blinded adjudication committee. The following were members of the pediatric adjudication committee: (b) (6) (b) (6) (b) (6)

All potential hospitalizations and deaths were sent to the adjudication committee for adjudication to determine asthma causality. Hospitalizations were screened by an adjudication committee member to determine whether full adjudication should be performed. All deaths and intubations were completely adjudicated. Patients who discontinued study medication were to be followed through the 6 month treatment period for assessment of the primary outcome of interest – hospitalization, intubation, and death.

Secondary safety endpoints included the individual components of the composite: asthma-related hospitalizations, asthma-related intubations, asthma-related deaths, and withdrawals due to exacerbations. Given the size and objective of the trial, only SAEs and AEs leading to discontinuation were collected and recorded.

Primary Efficacy Endpoint

The primary efficacy endpoint was severe exacerbation. This was defined as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an inpatient hospitalization or emergency department visit (> 24 hours) due to asthma that required systemic corticosteroids. A single depo-injectable dose of corticosteroids was considered equivalent to a three day course. The definition used for exacerbation is consistent with other asthma programs and consistent with the ATS/ERS definition of severe asthma exacerbation.[11] Other efficacy endpoints included rescue medication use, unscheduled healthcare utilization, and ACQ-6 score. For the efficacy endpoint of exacerbations, the time to first asthma exacerbation between treatment groups was compared using a Cox proportional hazards regression model.

Sample size

[11] Reddel HK, Taylor DR, Bateman ED, et al. Am J Respir Crit Care Med 2009; 180: 59-99.

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The planned sample size of 11,700 for each of the adult and adolescent trials was based on an assumed rate of serious asthma-related events of 0.0075 per 26-weeks, a one-sided alpha=0.025, a power of 90%, and a non-inferiority margin of relative risk equal to 2. It was estimated the sample size would result in approximately 87 patients experiencing a serious asthma-related event. Ten percent of the population was to be adolescents 12-18 years of age. For the pediatric trial, similar assumptions were used and a sample size of 6200 patients was estimated to observe 43 patients experiencing a serious asthma-related event with a non-inferiority margin of relative risk equal to 2.7.

Analysis populations
The primary analysis population was the Intent-to-Treat (ITT) population, which includes all patients randomized. Adverse events that occurred within the 6-month trial period or a 7-day follow-up period after study drug discontinuation, whichever was later were included in the analyses. This is also considered the "on study" analysis. A second analysis population, the modified-ITT (mITT) population, consisted of all randomized patients and AEs that occurred while on study treatment and 7-days after study drug was stopped. This is considered the "on treatment" analysis.

Primary Analysis - Safety
The primary safety endpoint is the number of patients experiencing the composite endpoint of serious asthma outcomes over the 26-week study period. The "on study" dataset was specified for the primary analysis. Analysis of the "on treatment" dataset was a sensitivity analysis.

The time to first event was analyzed using a Cox proportional hazards model, with adjustments that varied across sponsors. The resulting upper bound of the two-sided 95% CI of the hazard ratio was to be used to assess statistical non-inferiority. If the upper-limit of the estimated hazard ratio was <2.0 for the adult/adolescent trials, then non-inferiority was demonstrated. If the upper-limit of the estimated hazard ratio was <2.7 for the pediatric trial, then non-inferiority was demonstrated. The different doses of ICS/LABA groups were pooled as were the ICS groups. An interim analysis was conducted when half of the expected number of patients who experienced a primary event was observed.

Oversight
Each of the adult/adolescent trials, had a trial specific Data Monitoring Committee. The adult/adolescent trials also shared an independent Joint Oversight Steering Committee (JOSC) and a shared independent Joint Data Monitoring Committee (JDMC). The JOSC provided guidance on trial conduct and monitored enrollment and event rates in order to recommend changes in trial conduct or sample size. The JDMC monitored asthma-related deaths and intubations to determine if a formal interim analysis of asthma related deaths across the trials was necessary. The pediatric trial had a Pediatric Steering Committee, Pediatric Adjudication Committee, and a Data Monitoring Committee.

Population and Disposition
Across the trials, ninety-nine percent of patients completed the trial and assessments for primary endpoint and over 80% of patients completed study treatment. The main reason for

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discontinuation of study treatment was patient decision. Less than 2% of patients withdrew from the trials.

The mean age in the adult/adolescent trials ranged from 43 to 45 years. Approximately 10% of the patients were adolescents 12-17 years of age. Racial and ethnicity distribution varied between trials and depending on the trial, there were 6 to 15% black or African American patients enrolled. In the pediatric trial, the mean age was 7.6 years with 36% of patients 4-6 years of age and 64% of patients 7-11 years of age. Seventeen percent of pediatric patients were African American.

Efficacy Results – Exacerbations
Table 3 shows the results for the primary efficacy endpoint of asthma exacerbations. Exacerbations are based upon the on-treatment analysis set since exacerbations were not collected after discontinuation of study medication. Results of these trials show that adult/adolescent patients treated with ICS/LABA had a reduction in exacerbation compared to patients treated with ICS.

Table 3 Efficacy Asthma Exacerbations

	Advair (fluticasone/ salmeterol)		**Advair (fluticasone/ salmeterol) Pediatric**		**Symbicort (budesonide/ formoterol)**		**Dulera (mometasone/ formoterol)**	
	FP/Salm	FP	FP/Salm	FP	Bud/Form	Bud	Mom/Form	Mom
N	5834	5845	3107	3101	5486	5487	5868	5861
Number of patients experiencing exacerbation	480 (8)	597 (10)	265 (9)	309 (10)	539 (9)	633 (11)	708 (12)	779 (13)
Hazard Ratio (95% CI)	0.79 (0.70, 0.89)†		0.86 (0.73, 1.01)†		0.84 (0.75, 0.94)§		0.89 (0.80, 0.98)‡	

† Age as a covariate; § Treatment and asthma treatment/control status at randomization; ‡ Treatment and ICS dose level covariates
FP=fluticasone propionate, FP/S=FP/salmeterol xinafoate; Bud = budesonide, Bud/F = Bud/formoterol; Mom = mometasone, Mom/F = Mom/formoterol

The majority of the exacerbation events were those events that required use of systemic corticosteroids, so the results are driven by this component. There were few exacerbations requiring hospitalizations and ED visits. Results for the adolescent (12-17 years of age) subgroup were generally consistent with the overall population. While the results for the pediatric trial are not statistically significant, the results are numerically favorable and overall consistent with the findings from the adult/adolescent trials.

Currently, the ICS/LABA products do not have a claim for a reduction in asthma exacerbations. Unlike the primary safety outcome, these exacerbations were not adjudicated, but the definition utilized in these trials is an established/accepted definition. The data from the individual trials support claims for a reduction in asthma exacerbations for each of the products – Advair Diskus, Symbicort, and Dulera. This is an important clinically meaningful benefit for these products. During the review, there was discussion of whether these data supported an indication for a reduction in asthma exacerbations for Advair Diskus, Symbicort, and Dulera. An indication for reduction in exacerbations would imply that ICS/LABA

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reduced all exacerbations, including hospitalizations. The data from these trials do not show that ICS/LABA decrease asthma hospitalizations compared to ICS. In fact, as discussed in the following section, the adjudicated asthma hospitalizations were numerically higher in the ICS/LABA group compared to the ICS group in each of the trials. So while the reduction in exacerbations that required systemic corticosteroids is an important benefit, an indication for reduction in asthma exacerbations is not supported and would be an overstatement of the benefit of ICS/LABA.

8. Safety

Results for the primary safety endpoint and meta-analysis are discussed in this section. For the primary composite safety outcome of adjudicated serious asthma-related events, the results from each of the individual trials are shown in the table below. The primary analysis of the safety outcome was an "on study" analysis i.e. patients were followed and events were included even after study medication discontinuation through the end of the trial.

Table 4 Primary Safety Outcome – Adjudicated Asthma-related Hospitalizations, Intubation, Death

	Advair (fluticasone/ salmeterol)		**Advair (fluticasone/ salmeterol) Pediatric**		**Symbicort (budesonide/ formoterol)**		**Dulera (mometasone/ formoterol)**	
	FFP/Salm	FP	FFP/Salm	FP	Bud/Form	Bud	Mom/Form	Mom
N	5834	5845	3107	3101	5486	5487	5868	5861
Serious asthma outcomes†	34 (0.6)	33 (0.6)	27 (0.9)	21 (0.7)	43 (0.7)	40 (0.7)	39 (0.7)	32 (0.5)
Hazard Ratio (95% CI)	**1.03§ (0.6, 1.7)**		**1.29§ (0.7, 2.3)**		**1.07‡ (0.7, 1.7)**		**1.22* (0.8, 1.9)**	
Deaths	0	0	0	0	2 (<1%)	0	0	0
Intubation	0	2 (<1%)	0	0	1 (<1%)	0	0	0
Hospitalizations	34 (0.6)	33 (0.6)	27 (0.9)	21 (0.7)	42 (0.7)	40 (0.7)	39 (0.7)	32 (0.5)

FP=fluticasone propionate, FP/S=FP/salmeterol xinafoate; Bud = budesonide, Bud/F = Bud/formoterol; Mom = mometasone, Mom/F = Mom/formoterol

† Number of patients with events that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug treatment, whichever date was later. Patients can have one or more events, but only the first event was counted for analysis.

§The hazard ratio for time to first event was based on a Cox proportional hazards model with a single covariate of treatment and baseline hazards stratified by incoming asthma medication/asthma control status.

‡The hazard ratio for time to first event was based on a non-stratified Cox proportional hazards model with covariates of treatment and ICS dose level, as randomized.

* The hazard ratio for time to first event was based on a non-stratified Cox proportional hazards model with covariates of treatment and ICS dose level, as treated.

Source: FDA Statistician - Changming (Sherman) Xia, PhD

Each of the clinical trials excluded the pre-specified non-inferiority (NI) margin. There were few events of deaths and intubations. This may be in part because patients with life-threatening or unstable asthma or recent history of asthma hospitalization were excluded. In terms of the hospitalizations, there was a consistent (albeit small) numerical trend of a greater number of hospitalizations in the ICS/LABA treatment group compared to the ICS group.

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Subgroup analysis for race, age, and gender were generally consistent. Sensitivity analyses for the "on treatment" dataset also consistently excluded the pre-specified NI margin with the exception of the Dulera trial. For the "on treatment" dataset (data censored 7 days after last dose of study medication), there were 38 events in the Mom/F group and 25 events in the Mom group with HR 1.5 (95% CI: 0.9, 2.5). This difference was due to an additional 7 events in the Mom group after study drug discontinuation but while still on study.

While the clinical trial with Foradil was terminated early, the results from the terminated trial are of interest for completeness. In the Foradil trial, there were 411 patients in the formoterol/FP group and 409 patients in the FP group. Overall, there were 3 serious asthma related events in each treatment group, all of which were hospitalizations. There were no intubations or deaths.

Meta-Analysis Methods

As planned when these trials were conceived, a meta-analysis was performed. Although the plan was to combine the results of all the trials, because Novartis terminated the trial with Foradil, results from this trial were not included. While patients were given the option to complete the Foradil trial, patients may have decided to discontinue study medication and withdraw consent, knowing that the trial was being terminated. Compared to the other safety trials, only 80% of patients completed the Foradil trial and 11% of patients withdrew consent. In addition, the Foradil trial is different in that the ICS/LABA was not administered in fixed combination and this could have impacted the compliance with ICS and LABA. We also did not include the dedicated pediatric trial with Advair Diskus in the meta-analysis given the younger age group.

Thus, the meta-analysis was based on patient-level data from the 3 completed adult/adolescent trials with Advair Diskus, Symbicort, and Dulera. The primary meta-analysis endpoint was the composite of adjudicated asthma-related death, asthma-related intubation, and asthma-related hospitalization. The primary analysis population consisted of all randomized patients who received at least one dose of study treatment in the three trials listed above. The primary analysis method estimated the hazard ratio of time to the first primary composite event associated with LABA plus ICS vs. ICS alone through a Cox proportional hazards model with baseline hazards stratified by trial and a single covariate for planned treatment (LABA plus ICS vs. ICS alone). If a patient had multiple events in the composite, only the first event was used for analysis. Analyses were based on randomized treatment, regardless of the actual treatment received.

Meta-Analysis Results

The combined dataset used for the meta-analysis contained 35,089 patients who were randomized and received at least one dose of study medication. The analysis included events that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug treatment, whichever date was later, i.e. "on study" analysis. Results are shown in Table 5.

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Table 5 Meta-Analysis of Serious Asthma-Related Events from 3 Completed ICS/LABA Safety Trials in Patients with Asthma Aged 12 Years and Older [a]

	ICS/LABA N= 17,537[b]	ICS N= 17,552[b]	ICS/LABA vs. ICS Hazard Ratio (95% CI)[c]
Serious Asthma-related event [d]	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation	1	2	
Asthma-related hospitalization	115	105	

[a] Includes data from the adult/adolescent safety trials with Advair Diskus, Dulera, and Symbicort
[b] Randomized patients who had taken at least 1 dose of study drug. Planned treatment used for analysis.
[c] Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials.
[d] Number of patients with event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Patients can have one or more events, but only the first event was counted for analysis. A single, blinded, independent adjudication committee determined whether events were asthma related.

Source: FDA Statistician - Changming (Sherman) Xia, PhD

For serious asthma outcomes in the meta-analysis, the Mantel-Haenszel risk difference was 0.0006 [95% CI: -0.0010, 0.0023] (6 events per 10,000 patients treated for 6 months [95% CI: -10, 23]). The number needed to harm (NNH) was 1582 patients treated for 6 months. The on-treatment sensitivity analysis for the primary endpoint, which truncated data 7 days after the last exposure to treatment, resulted in an estimated hazard ratio of 1.25 [95% CI: 0.95, 1.65].

Subgroup analyses were performed by gender, age, race, region, ICS dose level, baseline ACQ score, and past hospitalization history. Subgroup analysis results were generally consistent with the overall population. The estimated HRs for LABA plus ICS in some subgroups of special interest are as follows: patients 12 to 17 years of age, HR 0.93 [95% CI 0.36, 2.40] and black patients in the USA region, HR 0.95 [95% CI: 0.48, 1.90].

The figure below shows the results of the individual trials as well as the meta-analysis for the primary safety composite outcome. The results of the meta-analysis provide greater precision of the risk of serious asthma outcomes for ICS/LABA compared to ICS and show that there is not a significant increase in serious asthma outcomes with ICS/LABA compared to ICS.

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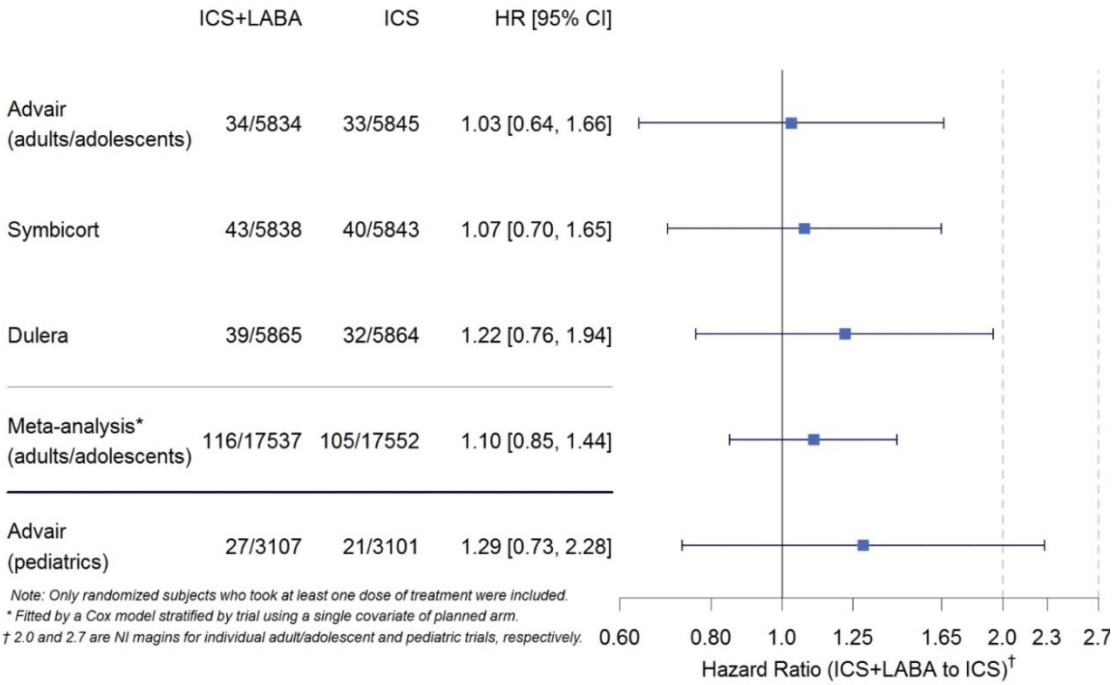
Figure 1

Serious Asthma Outcomes (hospitalizations, intubations, death)
for Individual ICS/LABA Safety Trials and Meta-analysis of Adult/Adolescent Trials



Source: FDA Statistician - Changming (Sherman) Xia, PhD

As with any trial, these safety trials cannot answer all the questions regarding LABA safety, so some uncertainties remain. We cannot conclude that ICS mitigate the risk of LABA or that there is no increase in risk with ICS/LABA combination compared to ICS. These trials were not designed to answer these questions. Patients with life-threatening or unstable asthma were excluded due to safety and ethical concerns, and so we cannot conclude whether the results can be generalized to these patients. Going into the trials, it was clear the individual trials were not powered to make conclusions regarding death, but the plan was that the combined data from the trials would provide some information about intubations and death. The extremely low number of deaths and intubations limits conclusions on these endpoints, but the low event rate is also reassuring. Given the consistent findings across the trials, the data generated from these large safety trials are appropriate to not only describe in the Advair, Dulera, and Symbicort product labeling, but the data also support broader class labeling changes.

As described in the Background section, all LABA products, including ICS/LABA products have a Boxed Warning for Asthma-Related Death. The Boxed Warning for asthma-related death describes results of SMART and also includes the following statements/recommendations:

- Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

- Physicians should only prescribe ICS/LABA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA.
- Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ICS/LABA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.
- Do not use ICS/LABA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

The results of these large ICS/LABA safety trials clearly support modification of the BW. The bigger question was whether the results of these trials support removal of the BW altogether. In considering whether removal of the BW is appropriate, it is helpful to consider regulatory precedent as removal of a BW is not common. The following are a few examples of removal of a BW.

- Removal of BW for serious mental side effects from varenicline product labeling following review of a large outcome trial that did not demonstrate increased risk of neuropsychiatric events.[12]
- Removal of the BW for liver injury from ambrisentan based upon review of available clinical trial data.[13]
- Removal of BW for HPA axis suppression when patients were switched from systemic corticosteroids to ICS on ICS product labeling.[14] Removal of the BW was based upon the change in standard of care for asthma treatment over time, such that systemic corticosteroid use was not standard of care and thus, the BW was no longer relevant.

The BW was added to LABA product labels primarily based upon results from the SNS Study and SMART, but these large trials were conducted at a time when patients on LABAs were not necessarily on ICS therapy, which is now considered standard of care for asthma. Given the consistent results of the ICS/LABA safety trials that show when ICS and LABA are used in fixed dose combination, there is not a significant increase in serious asthma outcomes compared to ICS, FDA determined the data from the ICS/LABA safety trials supported removal of the BW for asthma related death from the ICS/LABA products. Based upon internal discussions, we also decided that an Advisory Committee (AC) meeting was not necessary, given the results of the trials were consistent and considerable time and resources are needed to hold an AC meeting and this would delay removal of the BW. This decision was discussed at the Center level as noted in the Background section.

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[12] FDA Drug Safety Communication: FDA revises description of mental health side effects of the stop-smoking medicines Chantix (varencicline) and Zyban (bupropion) to reflect clinical trial findings – December 12, 2016; Available at: https://www fda.gov/Drugs/DrugSafety/ucm532221 htm; accessed on December 14, 2017

[13] FDA Drug Safety Communication: Liver injury warning to be removed from Letairis (ambrisentan) tablets – March 4, 2011; Available at https://www.fda.gov/Drugs/DrugSafety/ucm245852.htm; accessed on December 14, 2017.

[14] Drugs at FDA – Flovent Diskus November 1, 2002, Approval Letter Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020833; accessed on December 14, 2017.

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While the BW is removed, a Warning will remain on the ICS/LABA product labeling. The remaining Warning will emphasize the risk of LABA monotherapy (without ICS) and to describe available data from the ICS/LABA safety trials and the FDA meta-analysis. Language regarding stepping down asthma therapy by discontinuing the LABA has been removed. The overall message is that there is not a significant increase in serious asthma events with ICS/LABA products.

FDA was aware of the controversy of requiring these trials and understood significant resources were necessary to conduct trials of this scope and size. Overall, these large safety trials have provided a significant contribution to the debate about the safety of LABAs and the data generated support important changes to the product labeling of ICS/LABA products.

9. Advisory Committee Meeting

An Advisory Committee meeting was not required for these supplements. At the time the trials were designed, the plan was to combine the results of the completed trials to evaluate rare events and discuss the results at an Advisory Committee. As the results of the trials were consistent and confirmed, FDA made the decision that an AC meeting was not necessary and would require consider time to prepare for and plan. FDA opted to forego an AC meeting in order to move forward expeditiously with removal of the Boxed Warning from ICS/LABA products.

10. Pediatrics

Pediatric patients are of particular concern with the LABA safety issue given the findings from a meta-analysis conducted by the FDA in 2011 showed an age related trend with younger patients at higher risk as shown in

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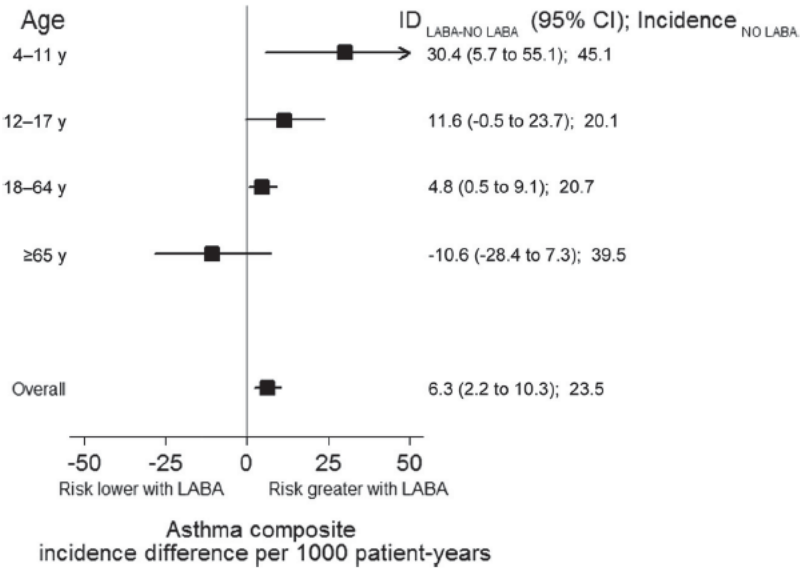
Figure 2.[15]

Figure 2 FDA Meta-Analysis from 2011 - Risk Difference for LABA by Age for asthma composite (asthma-related death, asthma-related intubation, asthma related hospitalization)



Source: McMahon AW, Levenson MS, et al. Pediatrics 2011; 125(5): e1147-54.

Because of this concern, a dedicated pediatric trial was required with Advair Diskus, which was the only ICS/LABA product approved in children younger than 12 years of age at the time the trials were required. In addition, Sponsors were encouraged to ensure representation of adolescents 12-18 years of age (10% of the overall population) in the adult and adolescent trials.

The pediatric trial with Advair Diskus in children 4-11 years of age was designed to rule out a hazard ratio NI margin of 2.7. The estimated HR and 95% confidence interval 1.29 [95% CI 0.73, 2.27] successfully ruled out the pre-specified NI margin. For adolescents, the meta-analysis of the 3 recently completed ICS/LABA safety trials did not suggest an age related

[15] McMahon AW, Levenson MS, et al. Pediatrics 2011; 125(5): e1147-54.

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trend compared to adults with an estimated HR 0.93 [95% CI 0.36, 2.40] for ICS/LABA in adolescents 12 to 17 years of age.

The risk difference (RD) for serious asthma outcomes in the pediatric trial was 1.9 [95% CI: -2.4, 6.3] patients with an event per 1000 patients treated for 6 months or 3.8 patients with an event per 1000 patients treated for a year. These results are much lower compared to the incidence difference estimated for children 4 to 11 years of age in the 2011 FDA meta-analysis (Figure 2). Overall, the pediatric and adolescent data from the ICS/LABA safety trials are reassuring.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues. Financial disclosures were included with the supplements and were reviewed by Dr. Robert Lim. An OSI audit was not conducted for any of the trials because of the large number of study sites; therefore, an individual site would not have an influence on trial results.

12. Labeling

The following is a high-level summary of labeling changes provided for in the ICS/LABA class labeling supplements.

All ICS/LABA products

- The Boxed Warning was removed from all the ICS/LABA products.
- The Warning was revised to emphasize the risk of LABA monotherapy (without ICS) and to describe available data from the ICS/LABA safety trials. Results of the FDA meta-analysis are described in the revised Warning. The template Warning language is shown below.

5.1 Serious Asthma-Related Events – Hospitalizations, Intubations and Death

Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death [see *Salmeterol Multicenter Asthma Research Trial (SMART)*]. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. (b) (4). When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared to ICS alone (see *Serious Asthma-Related Events with ICS/LABA*).

Serious Asthma-Related Events with ICS/LABA

Four large, 26-week, randomized, (b) (4) active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared to ICS alone in patients with asthma. Three

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trials included adult and adolescent patients aged ≥12 years: one trial compared [redacted] (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) The primary safety endpoint for all four trials was serious asthma-related events (hospitalizations, intubations and death). A blinded adjudication committee determined whether events were asthma-related.

The three adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk of 2.7. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the three adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

Table 1 Meta-analysis of Serious Asthma-Related Events in Patients with Asthma Aged 12 Years and Older

	ICS/LABA (N =17,537)[1]	ICS (N =17,552)[1]	ICS/LABA vs ICS Hazard ratio (95% CI)[2]
Serious asthma-related event[3]	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization (≥24-hour stay)	115	105	

ICS = Inhaled Corticosteroid, LABA = Long-acting Beta$_2$-adrenergic Agonist

1. Randomized patients who had taken at least 1 dose of study drug. Planned treatment used for analysis.
2. Estimated using a Cox proportional hazards model of time to first event with baseline hazards stratified by each of the 3 trials.
3. Number of patients with event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Patients can have one or more events, but only the first event was counted for analysis. A single, blinded, independent adjudication committee determined whether events were asthma-related.

The pediatric safety trial included 6208 pediatric patients 4 to 11 years of age who received ICS/LABA (fluticasone propionate /salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3107 (0.9%) patients randomized to ICS/LABA and 21/3101 (0.7%) patients randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significantly increased risk of a serious asthma-related event compared to ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27).

Salmeterol Multicenter Asthma Research Trial (SMART)

A 28-week, placebo-controlled U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; relative risk: 4.37 [95% CI 1.25, 15.34]). Use

of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

Formoterol Monotherapy Studies [Included only in ICS/LABA products containing formoterol] Clinical studies with formoterol used as monotherapy suggested a higher incidence of serious asthma exacerbation in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the difference in serious asthma exacerbations between treatment groups.

- The Patient Counseling Information (Section 17) was modified to reflect the revised Warning.
- The Medication Guide was replaced with a Patient Information leaflet with updated language to reflect the revised Warning.

Advair Diskus, Dulera, Symbicort

- For those products which were the subject of ICS/LABA safety trials, the Clinical Studies section (14) was updated with the results of the individual ICS/LABA safety trial. The new language included a description of the clinical trial and a table with the results of the primary safety endpoint, including individual components (hospitalization, intubation, death) of the composite. In addition, a brief paragraph describing the efficacy exacerbation endpoint with the results was also included.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

The recommended regulatory action is approval of all the supplements discussed in this review. These supplements provide for ICS/LABA class labeling changes to remove the Boxed Warning for asthma related death and incorporate the results of the recently completed ICS/LABA safety trials and meta-analysis in ICS/LABA product labeling. The Advair Diskus, Dulera, and Symbicort supplements also provide for a description of the completed ICS/LABA safety trial in the Clinical Studies section of the label. This description includes the efficacy results which show a reduction in asthma exacerbations that require systemic corticosteroids.

- Risk Benefit Assessment

Results from the large ICS/LABA safety trials provide for a more favorable benefit risk assessment for ICS/LABA products. Overall, these large safety trials have provided a significant contribution to our knowledge of not only the safety of ICS/LABA, but also the benefit of ICS/LABA. The trials provided evidence for additional benefit of reduction in asthma exacerbations requiring corticosteroid use for Advair Diskus, Dulera, and Symbicort. Results for the primary safety outcome from these trial show that ICS/LABA combination products do not have a significant risk of serious asthma outcomes compared to ICS. The safety data provide sufficient evidence to support removal of the Boxed Warning from the ICS/LABA combination products.

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- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

A REMS is not recommended for this application.

- Recommendation for other Postmarketing Requirements and Commitments

No additional postmarketing requirements and/or commitments are proposed. These supplements fulfill the FDAAA PMRs requirements listed below.

- 1750-1 [Advair Diskus]
  A randomized, double-blind, 26-week, active-controlled clinical trial comparing Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) and fluticasone propionate inhalation powder to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 11,700 adult and adolescent patients 12 years of age and older with persistent asthma.

- 1750-2 [Advair Diskus]
  A randomized, double-blind, 26-week, active-controlled clinical trial comparing Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) and Flovent Diskus (fluticasone propionate inhalation powder) to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 6200 pediatric patients 4 to 11 years of age with persistent asthma.

- 1751-1 [Dulera]
  A randomized, double-blind, 26-week, active-controlled clinical trial comparing Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol and mometasone furoate to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 11,700 adult and adolescent patients 12 years of age and older with persistent asthma.

- 1749-1 [Symbicort]
  A randomized, double-blind, 26-week, active-controlled clinical trial comparing Symbicort (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol with budesonide HFA to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 11,700 adult and adolescent patients 12 years of age and older with persistent asthma.

Reference ID: 4198161

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/s/

SALLY M SEYMOUR
12/20/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021077Orig1s056

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	21077 S-056/057
Priority or Standard	Standard
Submit Date(s)	10/03/2016
Received Date(s)	10/03/2016
PDUFA Goal Date	11/03/2017
Division / Office	DPARP
Reviewer Name(s)	Robert H. Lim
Review Completion Date	08/11/2017
Established Name	Fluticasone/Salmeterol
(Proposed) Trade Name	Advair Diskus
Therapeutic Class	ICS/LABA
Applicant	GlaxoSmithKline
Formulation(s)	Dry powder
Dosing Regimen	One click BID
Indication(s)	Asthma and COPD
Intended Population(s)	≥4 years (asthma) Adult (COPD)

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended regulatory action for this Advair Diskus supplemental NDA (sNDA) for asthma is Approval, contingent upon reaching agreement with GlaxoSmithKline (GSK) on the labeling. The sNDA provides for modification of the labeling to include the results from the two completed large safety trials evaluating serious asthma-related outcomes and asthma exacerbations with Advair Diskus. The demonstration of non-inferiority of Advair to the monocomponent fluticasone in terms of serious asthma-related outcomes in two similarly designed post-marketing required studies supports inclusion of such data in the label. Demonstration, in these same trials, of a decrease in exacerbations with Advair versus fluticasone alone also warrants inclusion in the label.

Given the results of the completed long acting beta-agonist (LABA) safety trials, removal of the Boxed Warning from inhaled corticosteroid (ICS)/LABA products is planned, contingent upon FDA confirming results of the completed ICS/LABA safety trials with Advair, Symbicort, and Dulera. GSK submitted revised labeling on July 14, 2017, with removal of the Boxed Warning. The PDUFA clock has been extended. At the time of finalization of this review, the agreed upon labeling is pending.

1.2 Risk Benefit Assessment

Safety:
There have been longstanding safety concerns regarding LABAs and an increased risk of serious asthma-related events (e.g., hospitalizations, intubations, and deaths). As a result of these concerns, a boxed warning (BW) was added to all LABA containing products. To address this concern for serious asthma-related events, the Agency required safety studies be conducted with LABA products approved for asthma on background ICS in adults and children. This requirement was announced in February of 2010, and in April 2011 the basic design (randomized, double-blind, controlled clinical trials comparing the addition of LABAs to inhaled corticosteroids versus inhaled corticosteroids alone) of the trials was announced. Five studies in total were required: [GlaxoSmithKline: Advair Diskus (adult and pediatric studies}, AstraZeneca: Symbicort, Merck: Dulera, and Novartis: Foradil]. These studies were designed similarly with shared adjudication, data monitoring, and oversight committees with the idea of combining the data when completed to evaluate rare events of death and intubation. The post-marketing required (PMR) studies required for GSK were as follows:

- 1750-1:

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A randomized, double-blind, 26-week, active-controlled clinical trial comparing Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) and fluticasone propionate inhalation powder to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 11,700 adult and adolescent patients 12 years of age and older with persistent asthma.

- 1750-2:
  A randomized, double-blind, 26-week, active-controlled clinical trial comparing Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) and Flovent Diskus (fluticasone propionate inhalation powder) to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 6200 pediatric patients 4 to 11 years of age with persistent asthma.

This sNDA incorporates the results of these two PMR studies in the Advair Diskus product labeling. In this sNDA the sponsor has submitted data from two 26-week, randomized, double-blind, active controlled trials in pediatric (4 to 11 years old) and adolescent/adult (≥12 years) asthma patients with a history of exacerbation. These studies, SAS115358 and SAS115359, respectively, compared Advair Diskus [fluticasone/salmeterol (FSC)] to fluticasone (FP) alone in terms of serious asthma-related outcomes. The pediatric study (SAS115358) addressed PMR 1750-2 and included approximately 6200 patients. The adolescent/adult study (SAS115359) addressed PMR 1750-1 and included approximately 11,700 patients. The primary endpoint of both studies was time to serious asthma-related events defined as the composite of asthma-related hospitalizations, deaths, and intubations. Asthma-relatedness was adjudicated by an independent Joint Adjudication Committee (JAC).

For both studies a pre-defined non-inferiority (NI) margin for the hazard ratio for time to event was agreed upon between the Agency and the Sponsor. For the pediatric study (SAS115358) the NI margin was 2.7 and for the adolescent/adult study (SAS115359), the NI margin was 2.0. Results from both studies demonstrated that the upper limits of the 95% confidence intervals (CI) were less than the pre-specified NI margins. For the pediatric study, the hazard ratio (HR) was 1.29 (95%CI 0.7, 2.3) and for the adolescent/adult study the HR was 1.03 (95%CI 0.6, 1.7). There were no asthma-related deaths in either study and these results were driven by asthma-related hospitalizations. Multiple subgroup analyses were performed (e.g., age, race, sex, exacerbation history, asthma control, etc) and results of these analyses were generally consistent with the overall population, though 95%CI were wider.

Efficacy

Advair Diskus is currently approved for the treatment of asthma. However, there is no label claim for exacerbation reduction. In this sNDA the sponsor has submitted data

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from two 26-week, randomized, double-blind, active controlled trials in pediatric (4 to 11 years old) and adolescent/adult (≥12 years) asthma patients with a history of exacerbation. These studies, SAS 115358 and 115359, respectively, compared Advair Diskus [fluticasone/salmeterol (FSC)] to fluticasone (FP) alone in terms of exacerbation. In the adolescent/adult study (SAS115359), exacerbation was defined as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. In the pediatric study, exacerbation was defined as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days. The pediatric study (SAS115358) included approximately 6200 patients and the adolescent/adult study (SAS115359) approximately 11,700 patients. While FP does not carry an exacerbation reduction indication or claim, it is approved for the treatment of asthma. As such, demonstration that FSC treatment resulted in reduced exacerbations compared to FP treatment would support the addition of exacerbation data to section 14 of the label. In the adolescent/adult study, FSC treated patients demonstrated a reduction in exacerbation compared to FP treated patients, which was statistically significant [hazard ratio 0.79 (95%CI 0.7, 0.9)]. In the pediatric study, a similar trend was observed, though results failed to exclude 1 in the 95% confidence interval [hazard ratio 0.86 (95% CI0.7, 1.0)]. These results demonstrate that FSC use does result in exacerbation reduction compared to FP use and are supportive of adding the exacerbation results to section 14 of the label.

Benefit/Risk and Labeling
Based on the results of these trials, Advair shows a reduction in exacerbations (systemic corticosteroids use), which is an important efficacy finding. Safety was the primary objective of these trials and FSC demonstrated non-inferiority to FP based on the pre-specified NI-margins. This demonstrates that that the addition of salmeterol to FP does not result in a significantly higher risk of serious asthma-related events. Overall, the data are reassuring and important for patients and healthcare providers. Preliminary results from the other PMR LABA safety studies demonstrate similar results, i.e., upper-limit of the 95%CI is less than the pre-specified NI-margin. When these results are confirmed by FDA analysis, these data taken together would support class labeling changes.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

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1.4 Recommendations for Postmarket Requirements and Commitments

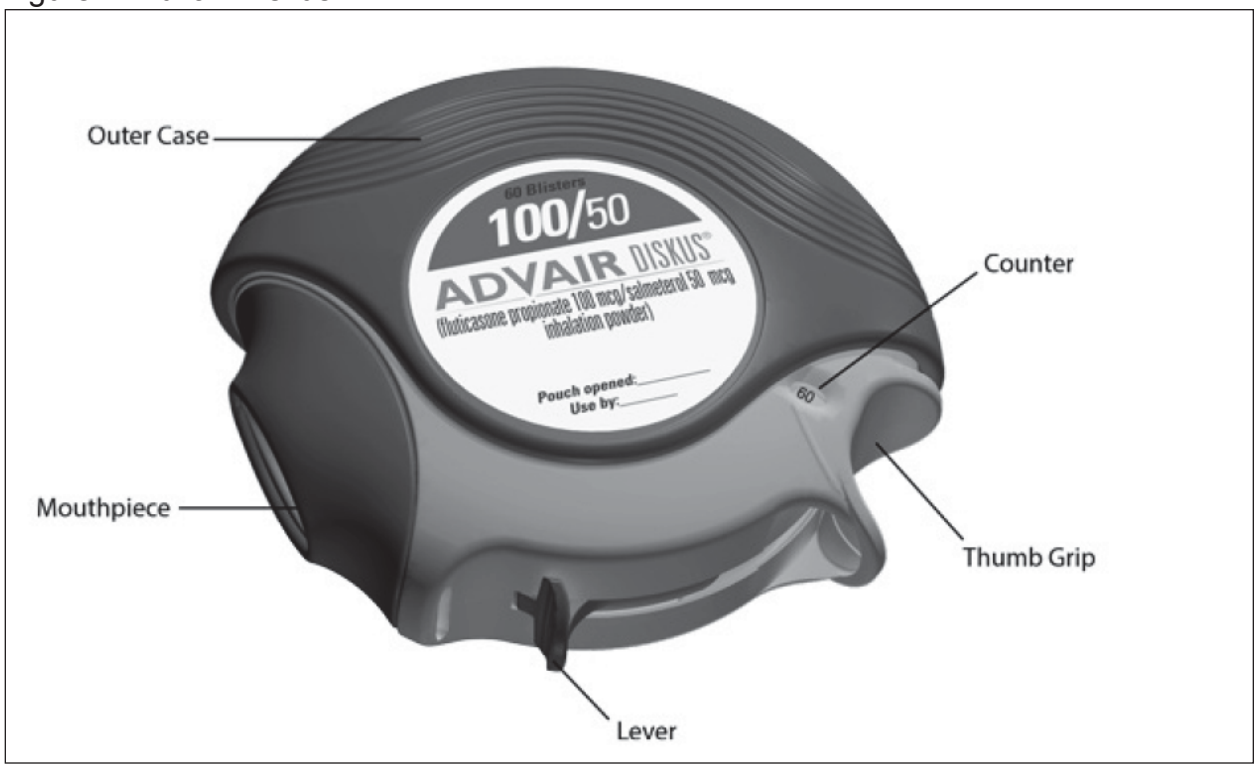
The studies submitted in this sNDA were post-marketing required safety trials under FDAAA. PMRs 1750-1 and 1750-2 can be considered fulfilled. There are no recommendations for additional PMR or PMC.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed product is a fixed-dose long-acting beta agonist (LABA) and inhaled corticosteroid (ICS) combination dry powder delivered via the Diskus device. The fixed dose combination (FDC) contains salmeterol xinafoate as the LABA and fluticasone propionate as the ICS. The dry powder is packaged in foil blister strips which are contained within the Diskus device. Figure 1 depicts the Advair Diskus at the 100/50mcg strength.

Figure 1. Advair Diskus



Source: approved Advair Diskus label

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Approved Asthma Therapies

Drug Class	Generic Name	Brand Name
Inhaled corticosteroids	Fluticasone furoate DPI	Arnuity Ellipta
	Beclomethasone dipropionate HFA	QVAR
	Budesonide DPI and respules	Pulmicort
	Fluticasone propionate HFA and Diskus	Flovent
	Mometasone DPI and HFA	Asmanex
	Ciclesonide HFA	Alvesco
Long-acting beta-agonists	Formoterol fumarate capsule	Foradil
	Salmeterol Diskus	Serevent
Combination inhaled corticosteroid/long-acting beta-agonist (ICS/LABA)	Budesonide/Formoterol HFA	Symbicort
	Fluticasone/Salmeterol HFA and Diskus	Advair
	Fluticasone/Salmeterol inhalation powder	AirDuo
	Mometasone/Formoterol HFA	Dulera
	Fluticasone furoate/Vilanterol	Breo Ellipta
Anticholinergics	Tiotropium	Spiriva Respimat
Immunomodulators	Omalizumab (Anti-IgE mAb)	Xolair
	Mepolizumab (Anti-IL5 mAb)	Nucala
	Reslizumab (Anti-IL5 mAb)	Cinqair
Leukotriene modifiers	Montelukast	Singulair
	Zafirlukast	Accolate
	Zileuton	Zyflo
Xanthines	Theophylline	multiple
Abbreviations: DPI=dry powder inhaler, HFA=hydrofluoroalkane, mAb=monoclonal antibody		

2.3 Availability of Proposed Active Ingredient in the United States

Salmeterol xinafoate is currently available in combination with fluticasone propionate under the tradename Advair Diskus and Advair HFA inhalation solution for the treatment of asthma and COPD. It is also available as a single ingredient under the tradename Serevent for the treatment of asthma and COPD.

Fluticasone propionate is currently available in combination with salmeterol xinafoate under the tradename Advair Diskus and Advair HFA inhalation aerosol. It is also available a single ingredient under the tradename Flovent Diskus and Flovent HFA inhalation aerosol for the treatment of asthma. It is also available as a nasal spray for the treatment of allergic rhinitis under the tradename Flonase.

2.4 Important Safety Issues With Consideration to Related Drugs

ICS safety concerns:
As evidenced by ICS/LABA development programs in COPD, the use of ICS in COPD has been associated with an increased risk of pneumonia and

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lower respiratory tract infections in an ICS-dose-dependent manner.

LABA safety concerns:
There have been longstanding safety concerns regarding LABAs and an increased risk of severe asthma exacerbation leading to hospitalizations and asthma-related deaths.[1] These concerns initially stemmed from results from two studies from the scientific literature. The first of these studies, the Salmeterol Nationwide Surveillance (SNS) Study, [2] was published in 1993. This study compared salmeterol twice daily to salbutamol (albuterol) four times a day and showed a non-statistically significant (p=0.105) but 3 fold increase in respiratory and asthma related death in patients taking salmeterol (0.07%) versus scheduled salbutamol (0.02%). In 1996, the second study was initiated at the Agency's request following approval of salmeterol due to safety concerns raised by the SNS study, as well as reports of serious asthma exacerbations and deaths after its approval. This study, the Salmeterol Multicenter Asthma Research Trial (SMART) [3], was a 28-week, randomized, double-blind study that enrolled patients 12 years of age and older with asthma not currently using a LABA. These patients were randomized to salmeterol (Serevent Inhalation Aerosol) or placebo twice daily added to usual asthma therapy. SMART was prematurely halted in 2003 after a planned interim analysis suggested that salmeterol may be associated with an increased risk of serious asthma exacerbations including asthma-related death (relative risk 4.37 [CI 1.25, 15.34]). GSK submitted preliminary summary results of the SMART to the Agency in February 2003, which led to labeling changes, including the addition of a boxed warning cautioning the use of salmeterol in patients with asthma. SMART results were discussed at the July 2005 PADAC meeting.[4]

LABA safety in asthma was further discussed at the November 2007, December 2008, and March 2010 AC meetings. At the 2007 meeting, the Agency recommended that the safety of salmeterol be revisited, which the AC agreed with. At the December 2008 meeting the safety issue was revisited and included discussion of the safety and risk-benefit assessment of LABAs for the entire asthma population (adults and pediatrics). At the December meeting, the committee stressed the need for more safety data, especially in the pediatric population where the data were very limited. To this end, the Agency proposed that additional safety studies be conducted in adults and children with the LABA products that were approved for the treatment of asthma to further evaluate the safety concerns of this drug class in the asthmatic population. This requirement was

[1]FDA Drug Safety Communication: Drug labels now contain updated recommendations on the appropriate use of long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs), June 2, 2010. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm; accessed July 7, 2017.
[2] Castle W, Fuller R, et al. BMJ 1993: 306: 1034-7.
[3] Nelson HS, Weiss ST, et al. Chest 2006; 129: 15-26.
[4] July 13-14, 2005, FDA PADAC Mtg [http://www.fda.gov/ohrms/dockets/ac/cder05.html#PulmonaryAllergy]

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announced in February of 2010[5].The design of LABA safety trials meant to address the PAC safety concerns was then discussed at the March 2010 AC meeting. As a result of this AC and ongoing discussions, in April 2011[6] the Agency announced which manufacturers would be required to conduct these studies and their basic design (randomized, double-blind, controlled clinical trials comparing the addition of LABAs to inhaled corticosteroids versus inhaled corticosteroids alone). The trials included in this submission were performed in response to this requirement.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In addition to the regulatory activity described in section 2.4, there were additional regulatory interactions specific to this sNDA. Relevant interactions are summarized as follows:

- April 14, 2011 - PMR for Advair LABA safety studies issued
  - 1750-1:
    A randomized, double-blind, 26-week, active-controlled clinical trial comparing Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) and fluticasone propionate inhalation powder to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 11,700 adult and adolescent patients 12 years of age and older with persistent asthma.

  - 1750-2:
    A randomized, double-blind, 26-week, active-controlled clinical trial comparing Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) and Flovent Diskus (fluticasone propionate inhalation powder) to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 6200 pediatric patients 4 to 11 years of age with persistent asthma.

- June 7, 2016 – PreNDA comments
  - Changes to the box warning and class labeling are not anticipated until data from all LABA safety studies has been reviewed.
  - Need for specific risk management plan is not anticipated

- June 15, 2017 – Teleconference with ICS/LABA sponsors

[5] FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs), February 18, 2010. Available at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm; accessed July 7, 2017

[6] FDA Drug Safety Communication: FDA requires post-market safety trials for Long-Acting Beta-Agonists, April 15, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm251512.htm; accessed July 7, 2017.

    - Provided that the publically available results from the LABA safety studies are confirmed by the FDA, removal of the Box Warning from the LABA containing asthma products may be warranted.
    - Sponsors should submit a new sNDA or an amendment to an existing sNDA that removes the Box Warning for asthma-related deaths from the label. The submission should include justification for removal and take into account the publically available results from the completed LABA safety studies. This submission should be received by July 14, 2015. This may constitute a major amendment for those sponsors with an sNDA currently under review.
    - The sponsors were encouraged to work together with regard to ICS/LABA class labeling.
- July 19, 2017 – Letter to sponsor
    - PDUFA date extended to November 3, 2017 due to submission of major amendment on July 13, 2017.

2.6 Other Relevant Background Information

none

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was appropriately indexed and complete to permit review. DSI audits were not requested.

3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices (GCP) is located in each clinical study report. There was one clinical site with conduct substandard to GCP which raised concerns for data integrity. This site, 205463, randomized 109 patients. No serious asthma outcomes were reported from this site. Analyses of the primary safety and efficacy endpoints were conducted removing sites 205463 and the results were unchanged.

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3.3 Financial Disclosures

See appendix 9.4 Clinical Investigator Financial Disclosure Review Template for financial disclosures

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new information was submitted

4.2 Clinical Microbiology

No new information was submitted

4.3 Preclinical Pharmacology/Toxicology

No new information was submitted

4.4 Clinical Pharmacology

No new information was submitted

4.4.1 Mechanism of Action

4.4.2 Pharmacodynamics

4.4.3 Pharmacokinetics

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5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study (study dates)	**Objective**	**Design**	**Population**	**Treatment arms**	**Primary endpoints**
SAS115359 Adolescent/Adult Study (11/18/11-6/23/15)	Safety/efficacy	R, DB, AC, MC, PG	Asthma patients ≥12 years	FP 100mcg FSC 100/50mcg FP 250mcg FSC 250/50mcg FP 500mcg FSC 500/50mcg	Efficacy: exacerbation Safety: serious asthma outcomes
SAS1153598 Pediatric Study (11/17/11- 11/3/15)	Safety/efficacy	R, DB, AC, MC, PG	Asthma patients 4-11 years	FP 100mcg FSC 100/50mcg FP 250mcg FSC 250/50mcg	Efficacy: exacerbation Safety: serious asthma outcomes

R=randomized, DB=double-blind, AC=active controlled, PC=placebo controlled, MC=multicenter, PG= parallel groups, FP=fluticasone propionate, FCS=FP/salmeterol xinafoate

5.2 Review Strategy

This clinical review focuses on the PMR studies in adolescent/adult (SAS115359) and pediatric (SAS115358) patients. The efficacy data regarding exacerbation are presented in 6 Review of Efficacy. Safety data is presented in 7 Review of Safety. For these analyses (efficacy and safety) no pooling of data between studies were performed. The individual study protocols are reviewed in 5.3 Discussion of Individual Studies/Clinical Trials.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Adolescent/Adult Study (SAS115359)

Administrative Information

- **Study title**: a Safety and Efficacy Study of Inhaled Fluticasone Propionate/Salmeterol Combination (FSC) versus Inhaled Fluticasone Propionate (FP) in the Treatment of Adolescent and Adult Patients with Asthma
- **Study dates:** November 18, 2011 – June 23, 2015
- **Study sites:** multinational
- **Study report date:** December 7, 2015

Objectives/Rationale

- Primary: To evaluate whether the addition of LABA to ICS therapy (FSC) is

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non-inferior to ICS therapy alone (FP) in terms of serious asthma related events (asthma-related hospitalizations, endotracheal intubations, and death).

- Secondary: To evaluate whether the addition of LABA to ICS therapy (FSC) is superior to ICS therapy alone (FP) in terms of severe asthma exacerbations

Study Design and Conduct

Overview

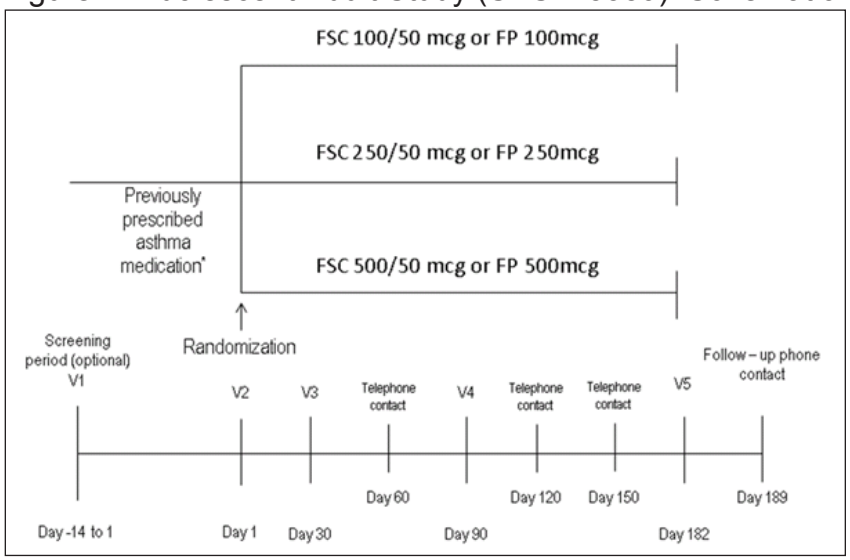
This was a global, randomized double-blind, active controlled, parallel group 26-week trial in asthma patients ≥12 years of age who require controller medication. This was one of the trials initiated in response to the April 2011[7] announcement that manufacturers of LABA would be required to conduct randomized, double-blind, controlled clinical trials comparing the addition of LABAs to inhaled corticosteroids versus inhaled corticosteroids alone. Once eligibility was determined at visit 1, patients were discontinued from current asthma medication and randomized. Patients were stratified based on prior asthma medications and Asthma Control Questionnaire (ACQ-6) score. The treatment arms were as follows:

- FP 100mcg BID
- FCS 100/50mcg BID
- FP 250mcg BID
- FSC 250/50mcg BID
- FP 500mcg BID
- FSC 500/50mcg BID

Following visit 2, patients were seen in clinic at days 30, 90, and 182 (visits 3, 4, and 5). During months without a clinic visit, patients were contacted by phone. The trial schematic is summarized in Figure 2 and the assessment schedule in Table 2.

[7]FDA Drug Safety Communication: FDA requires post-market safety trials for Long-Acting Beta-Agonists, April 15, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm251512.htm; accessed July 7, 2017.

Figure 2. Adolescent/Adult Study (SAS115359). Schematic



Source: protocol SAS115359; figure 11.2; pg 62

Table 2. Adolescent/Adult Study (SAS115359). Assessment schedule

Visit Number	1 Screening[a]	2 Randomization	3		4			5	E/W	F/U
Scheduled Phone Call				1		2	3			4
Treatment Day		Day 1	30	60	90	120	150	182		189
Informed Consent and Assent (if applicable)	x									
Demographics	x									
Medical and asthma history	x									
Smoking history	x									
Current Asthma therapy	x									
Asthma exacerbation history	x	x								
Concomitant medication assessment	x	x	x		x			x	x	x[b]
Assess inclusion/exclusion criteria	x	x								
Urine pregnancy test[c]		x						x	x	
Asthma Control Questionnaire	x		x		x			x	x	
Physical Exam[d]	x	x								
In clinic peak expiratory flow (PEF) – (pre-bronchodilator/pre-dose)	x									
Vital signs[e]	x	x	x		x			x	x	
Pharmacogenetic sample collection[f]		x								
Subject IVRS compliance and data review (assessment of unstable asthma criteria)			x	x	x	x	x	x	x	
Asthma-related unscheduled healthcare utilization			x	x	x	x	x	x	x	
AE and SAE assessments[g]		x	x	x	x	x	x	x	x	x
Assess for withdrawal criteria			x	x	x	x	x	x	x	
Dispense diary card		x	x		x					
Collect diary card			x		x			x	x	
Train subjects' on use of daily IVRS		x								
Train and assess subjects' ability to use DISKUS/ACCUHALER inhaler		x	x		x					
Dispense albuterol/salbutamol at Visit 1 and/or 2 and as needed at other visits[h]	x	x	x		x					
Collect dispensed albuterol/salbutamol as needed			x		x			x	x	
Dispense double-blind study drug. Assess ability to use study drug.		x	x		x					
Collect double-blind study drug			x		x			x	x	
Assess study treatment compliance			x	x	x	x	x	x	x	
Register Visit in IVRS (or eCRF)[i]	x	x	x		x			x	x	
Register scheduled telephone call in electronic data capture system (eCRF)				x		x	x			x

a. It is permissible for Visit 1 and Visit 2 to occur on the same day, if Visit 1 and Visit 2 do not occur on the same day the maximum allowed time between Visit 1 and Visit 2 is 15 days.
b. Only required for subjects reporting an AE(s)
c. For females of childbearing potential only. Female subjects who begin menses subsequent to receiving randomized study treatment should have a pregnancy test at their next scheduled in-clinic visit.
d. A complete physical exam should be performed prior to randomization. See SPM for a more detailed description of the elements of the physical examination. The physical exam can be performed at Visit 1 or Visit 2.
e. Height, weight, blood pressure, temperature and heart rate. Vital signs can be collected at Visit 1 or Visit 2 and at Visits 3, 4, 5 and/or Early Withdrawal.
f. Pharmacogenetic sample collection will be collected by buccal swab. Collection is preferred at Visit 2 but can occur at any clinic visit during the study after PGx informed consent has been signed and subject has been randomized.
g. Adverse events that result in withdrawal from study treatment and Serious Adverse Events must be collected from the start of study treatment (Visit 2) until the follow-up phone contact. However, any serious adverse events assessed as related to study participation or related to a GSK concomitant medication will be recorded from the time of consent.
h. Albuterol/salbutamol to be used and dispensed on an as-needed basis. Usage must be recorded daily by subjects through daily IVRS (puffs per day of MDI)
i. Whether or not V1 and V2 occur on the same day, V1 must be completed in IVRS (to obtain screening number) but V2 can be completed in IVRS or eCRF (to obtain allocation number for randomized subjects). All further visits can be registered in either system

Source: protocol SAS115359; table 2; pg 31-32

This study did not include evaluation of FEV1, a parameter typically assessed in asthma trials. As FSC and FP have already demonstrated a bronchodilator effect, inclusion of an FEV1 assessment is not required in terms of efficacy. However, assessment of FEV1 may have been helpful in terms of assessing treatment compliance.

During this trial patients were allowed used of rescue medication and other medications with the exception of the prohibited medications, such as Xolair and/or other monoclonal

Reference ID: 4138257

antibodies or investigational drugs. Only serious adverse events (SAE) and non-serious adverse events (AE) leading to discontinuation were collected, as per previous agreement with the Division.

Trial Population
The trial consisted of approximately 11,700 randomized persistent asthma patients.

Key Inclusion Criteria
1. All patients (or patient's legal guardian) signed an informed consent.
2. All patients had a diagnosis of persistent asthma as defined by national and international guidelines (e.g., GINA 2009 and NAEPP 2007) for at least 1-year prior to enrollment.
3. Male or female patients, 12 years of age or older
4. Peak Expiratory Flow (PEF) of ≥50% of predicted normal.
5. Current asthma therapy must have included the following:
   - ICS or ICS with one or more adjunctive therapies [e.g., LABA, leukotriene (LTRA) receptor antagonist, or theophylline] for at 4-weeks prior to randomization. At visit 1, patients maintained of a stable high dose ICS or stable high dose ICS with one or more adjunctive therapies must have had an ACQ-6 score <1.5 (i.e., controlled) at visit 1.
   - LTRA or theophylline as monotherapy at a stable dose for at least 4-week prior to randomization. These patients were only eligible if ACQ-6 scores were ≥1.5 (i.e., not well controlled) and if in the investigator's clinical judgment, the patient's asthma severity would justify treatment with ICS or ICS+LABA.
   - Daily rescue medication in the 4-week prior to randomization. These patients were only eligible if ACQ-6 scores were ≥1.5 (i.e., not well controlled) and if in the investigator's clinical judgment, the patient's asthma severity would justify treatment with ICS or ICS+LABA.
6. Patients have had at least one asthma exacerbation requiring treatment with a systemic steroid between 30-days and 12-months prior to randomization OR an asthma related hospitalization (inpatient stay of >24 hours) between 30 days and 12 months prior to randomization.

Key Exclusion Criteria
1. History of life threatening asthma defined as an asthma episode that required intubation and/or was associated with hypercapnea requiring non-invasive ventilator support.
2. History of COPD
3. Concurrent respiratory disease or respiratory infection
4. History of smoking >10 pack years
5. Exercised induced asthma
6. Unstable asthma within 7-days of randomization defined as follows:
   - Asthma symptoms that persisted throughout the day on 2 consecutive days
   - Nighttime awakening due to asthma ≥3 times

Reference ID: 4138257

- Albuterol/salbutamol (or equivalent) use for the acute worsening of asthma symptoms >8 puffs a day over 2 consecutive days or ≥25 puffs in one day
- Asthma symptoms so severe that the patient was limited in their ability to perform normal daily activity on any 1 day

7. Asthma exacerbation within 4-weeks of randomization or more than 4 separate exacerbations in the 12 months preceding randomization.
8. More than 2 asthma hospitalizations (>24 hour inpatient stay) in the 12-months preceding randomization.
9. Use of investigational medications
10. Participation in a concurrent LABA safety study
11. Use of monoclonal antibody 6-month prior to randomization.
12. Use of restricted medications.
13. Use of potent CYP4503A inhibitor within 4-weeks of randomization
14. A child who has been placed under the control or protection of an agency, organization, institution, or entity by the courts, government or a government body.

This study excluded those patients with life-threatening asthma. These patients would likely be at the highest risk for the types of serious asthma outcomes this study is trying to capture. Exclusion of these patients may hamper the ability to generalize safety conclusions to that population. However, inclusion of such patients would have been ethically problematic, as per protocol, patients on ICS/LABA at baseline could have been randomized to FP alone or FSC. De-escalating therapy in a patient with life-threatening asthma for approximately half a year would have placed those patients at increased risk for a poor clinical outcome.

Withdrawal from study treatment criteria:

1. A patient requires additional asthma medication over and above asthma medication allowed by the protocol to maintain long-term asthma control.
2. A patient has 2 asthma-related exacerbations treated with systemic corticosteroids within a 13-week period (during the double-blind treatment period) or 3 total exacerbations treated with systemic corticosteroids during the 26-week treatment period.
3. A patient requires endotracheal intubation for asthma.
4. A patient has an adverse event that would, in the investigator's judgment, make continued participation an unacceptable risk.
5. A patient becomes pregnant
6. A patient whose exacerbation is not responding to therapy in the judgment of the investigator or is not responding to 14 days of treatment with a systemic corticosteroid.
7. In the opinion of the investigator, a patient is judged to be significantly noncompliant with the requirements of the protocol.
8. The treatment blind is broken for a patient.

Reference ID: 4138257

Patients who prematurely discontinued study medication continued to be followed for the 26-week treatment period via monthly telephone calls.

Treatments

Treatment groups:

1. FP 100mcg BID
2. FCS 100/50mcg BID
3. FP 250mcg BID
4. FSC 250/50mcg BID
5. FP 500mcg BID
6. FSC 500/50mcg BID

Eligible patients were randomized 1:1 for FP versus FSC and stratified by current asthma medication and ACQ-6 score as summarized in the Table 3.

Table 3. Adolescent/Adult Study (SAS115359). Treatment Assignment

Randomization Strata	ACQ-6 Score and Current Asthma Medication	Randomization Assignment
A	**ACQ-6 <1.5*** on low dose ICS or on low dose ICS and one or more adjunctive therapy (LABA, LTRA, theophylline)	FSC 100/50 or FP 100
B	**ACQ-6 <1.5*** on medium dose ICS or on medium dose ICS and one or more adjunctive therapy (LABA, LTRA, theophylline)	FSC 250/50 or FP 250
C	**ACQ-6 <1.5*** on high dose ICS or high dose ICS and one or more adjunctive therapy (LABA, LTRA, theophylline)	FSC 500/50 or FP 500
D	**ACQ-6 ≥1.5*** on daily rescue medication or LTRA monotherapy or daily theophylline**	FSC 100/50 or FP 100
E	**ACQ-6 ≥1.5*** on low dose ICS or on low dose ICS and one or more adjunctive therapy (LABA, LTRA, theophylline)	FSC 250/50 or FP 250
F	**ACQ-6 ≥1.5*** on medium dose ICS or medium dose ICS and one or more adjunctive therapy (LABA, LTRA, theophylline)	FSC 500/50 or FP 500

*For the purpose of this protocol ACQ-6<1.5 = controlled status; ACQ-6≥1.5 = not well controlled asthma
**For subjects entering on daily rescue medication or LTRA monotherapy or theophylline, must be using daily rescue medication or LTRA monotherapy or daily theophylline for at least 4-weeks prior to randomization with no other controller.

Source: protocol SAS115359; table 1; pg 27

This treatment assignment approach allows for step-up therapy as per GINA and NAEPP guidelines in those patients who were not well controlled on their current medications. However, it does not appear that repeated assessments are performed to determine if further step-up (or step-down) is necessary.

Concomitant/Restricted Medication

The following medications were prohibited for the duration of the treatment period:

- Inhaled corticosteroids, other than study drug. Intranasal and dermatological corticosteroids were permitted
- LABA (other than study drug) or an extended release SABA.
- Anticholinergics (including intranasal). Short-term use of an anticholinergic for an acute asthma event is acceptable.
- Leukotriene modifiers (e.g., zileuton). Short-term use of leukotriene receptor antagonists (e.g. montelukast, zafirlukast, or pranlukast) for acute asthma events is acceptable.
- Xanthines (e.g., theophylline). Short-term use of xanthines for acute asthma events is acceptable
- Prescription or over the counter medications that would significantly interact with beta-agonists or inhaled corticosteroids.
- Beta-blockers including ophthalmic preparations within 1-day of randomization and throughout the treatment period.

Patients may receive immunotherapy for the treatment of allergies provided they are on stable regimen for at least 4-weeks prior to randomization and use a stable dose throughout the double-blind treatment period. Short and long-acting antihistamines were allowed for the treatment of allergic symptoms.

Endpoints

Safety:

The primary objective of this trial was to evaluate the safety of FSC versus FP. To that end, the primary safety endpoint of this study was number of patients experiencing a serious asthma-related event. This was defined as a composite of asthma-related hospitalizations, asthma-related intubations, or asthma-related deaths over the 26-week treatment period. Asthma-relatedness for these events was determined by an independent adjudication committee.

Secondary safety endpoints included the individual components of the composite: asthma-related hospitalizations, asthma-related intubations, asthma-related deaths, and withdrawals due to exacerbations.

Given the size and objective of the trial, only SAEs and AEs leading to discontinuation were collected and recorded in the CRF.

Efficacy:

The primary efficacy endpoint for this trial was exacerbation. This was defined as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. Note that a single depo-injectable dose of corticosteroids was considered equivalent to a three day course. The definition used for exacerbation is typical for a phase 3 asthma program. The secondary efficacy endpoint for this study was rescue medication use.

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Compliance
Compliance was monitored through the dose counter read-out during clinic visit and telephone contact.

Ethics:
This trial was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (2008), and ICH guidelines.

Statistical Analysis
Sample size
The sample size of 11,664 was based on an assumed rate of serious asthma-related events of 0.0075 per 26-weeks, a one-sided alpha=0.025, a power of 90%, and a non-inferiority margin of relative risk equal to 2. This sample size would result in approximately 87 patients experiencing as serious asthma-related event.

Analysis populations
This trial has two analysis populations. The primary analysis population is the Intent-to-Treat (ITT) population, which will include all patients randomized who received at least one dose of study drug. Adverse events that occur within 6-month trial period and a 7-day follow-up period were included in the analyses. The second analysis population, the modified-ITT (mITT), also consisted of all randomized patients who received at least one dose study drug, but included on those AEs that occurred while on study treatment and 7-days after study drug was stopped.

Primary Analysis
The primary safety endpoint is the number of subjects experiencing the composite endpoint of serious asthma outcomes over the 26-week study period. The time to first event as part of the composite endpoint was analyzed using a Cox proportional hazards regression model, adjusting for asthma medication/asthma control and randomization stratum. The resulting upper bound of the two-sided 95% CI of the hazard ratio was to be used to assess statistical non-inferiority of FSC to FP. If the upper-limit of the estimated hazard ratio was <2.0, then the Applicant concluded that non-inferiority was achieved. Note that in this analysis, the three FSC dose groups were pooled, as were the 3 FP dose groups.

The primary efficacy endpoint is asthma exacerbations. Time to first asthma exacerbation was to be compared between treatment groups.

Protocol Amendments
There were 4 protocol amendments submitted since the initial submission of this protocol (September 2011). The first was submitted in May of 2012 and removed the inclusion of 12 to <18 year old patients from French sites. The second amendment, submitted in November of 2013, eliminated a table that listed which doses of various

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ICS corresponded to low, medium, and high dose ICS. This was removed due to differences in labeled ICS dose based on country specific labeling, which was causing confusion for some investigators. Amendments 3 and 4, submitted in February 2014 and May 2014, corrected typographical errors and updated contact information. None of these amendments affected the interpretation of the safety or efficacy data.

5.3.2 Pediatric Study (SAS115358)

Administrative Information

- **Study title**: A 6-month safety and benefit study of inhaled fluticasone propionate/salmeterol combination (FSC) versus inhaled fluticasone propionate (FP) in the treatment of patients 4-11 years of age with persistent asthma
- **Study dates:** November 17, 2011-November 3, 2015
- **Study sites:** multinational
- **Study report date:** May 2, 2016

Objectives/Rationale

- Primary: To evaluate whether the addition of LABA to ICS therapy (FSC) is non-inferior to ICS therapy alone (FP) in terms of serious asthma related events (asthma-related hospitalizations, endotracheal intubations, and death).
- Secondary: To evaluate whether the addition of LABA to ICS therapy (FSC) is superior to ICS therapy alone (FP) in terms of severe asthma exacerbations

Study Design and Conduct

Overview

This was a global, randomized double-blind, active controlled, parallel group 26-week trials in asthma patients 4-11 years of age with persistent asthma. This was one of the trials initiated in response to the April 2011[8] announcement that manufacturers of LABA would be required to conduct randomized, double-blind, controlled clinical trials comparing the addition of LABAs to inhaled corticosteroids versus inhaled corticosteroids alone. Once eligibility was determined at visit 1, patients were discontinued from current asthma medication and randomized. Patients were stratified based on prior asthma medications and Asthma Control Questionnaire (ACQ-6) score. The treatment arms were as follows:

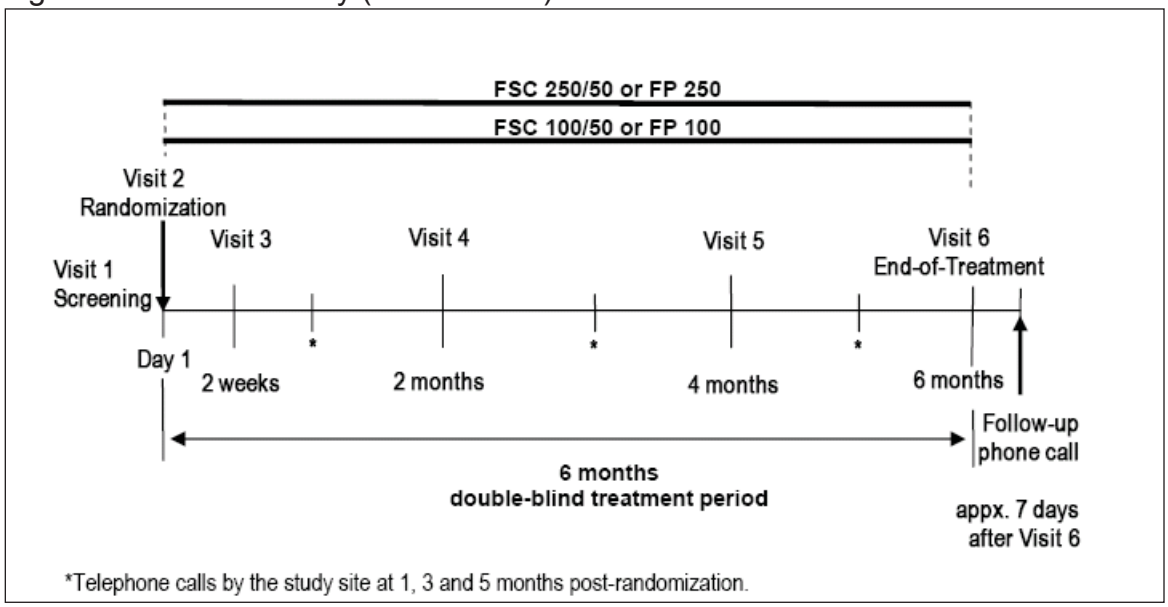
- FP 100mcg BID

[8]FDA Drug Safety Communication: FDA requires post-market safety trials for Long-Acting Beta-Agonists, April 15, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm251512.htm; accessed July 7, 2017.

- FCS 100/50mcg BID
- FP 250mcg BID
- FSC 250/50mcg BID

Following visit 2, patients were seen in clinic at days 30, 90, and 182 (visits 3, 4, and 5). During months without a clinic visit, patients were contacted by phone. The trial schematic and assessment schedule are summarized in Figure 2 and Table 4.

Figure 3. Pediatric Study (SAS115358). Assessment schedule



Source: SAS115358 CSR; figure 1; pg 16

Table 4. Pediatric Study (SAS115358). Assessment schedule

Visit Number	1 Screening	2[2] Randomization	3		4		5		6	EW	FU[9]
Randomized Treatment Duration (in months unless otherwise specified)[1]		Day 1	2 weeks	1	2	3	4	5	6		
Telephone call[3]				x		x		x			x
Informed Consent/Assent (study-specific and PGx[4])	x										
Physical exam[5]	x										
Collect demographics and contact information	x										
Medical history and asthma/asthma exacerbation history	x										
Concomitant medication (including asthma medication) assessment	x	x	x		x		x		x	x	
Assess inclusion/exclusion criteria	x	x									
Urine pregnancy test for all female subjects of childbearing potential		x							x	x	
Train subject/caregiver on use of daily IVRS		x									
IVRS compliance and data review			x		x		x		x	x	
Vital signs (blood pressure and pulse)	x										
Height and weight[6]		x	x		x		x		x	x	
PGx sampling		x[7]								x[8]	
AE/SAE assessment (according to Section 6.2.7)	x	x	x	x	x	x	x	x	x	x	x
Potential study endpoint assessment (Section 6.2.4)			x	x	x	x	x	x	x	x	x
Childhood Asthma Control Test	x				x		x		x	x	
Assess for asthma exacerbation, worsening asthma, and withdrawal criteria			x	x	x	x	x	x	x	x	x[10]
Unscheduled asthma-related healthcare utilization			x	x	x	x	x	x	x	x	
Dispense DISKUS study drug		x			x		x				
Dispense albuterol/salbutamol at Visit 1 and prn at other visits	x	x	x		x		x				
Assess ability to use study drug		x	x		x		x				
Collect DISKUS study drug					x		x		x	x	
Collect albuterol/salbutamol as needed		x	x		x		x		x	x	
Assess study drug compliance			x		x		x		x	x	

1. Refer to the SPM for visit windows
2. Visit 2 (randomization) can occur on the same day of or up to 15 days after Visit 1 (screening). Subjects are expected to continue their current asthma medication(s) until randomization.
3. Subjects to be contacted by the study site via telephone between study visits at 1, 3, and 5 months post-randomization to monitor asthma status and query for asthma outcomes of interest/potential study endpoint (Section 6.2.4).
4. PGx consent may be obtained at any visit (at or after Visit 1)
5. Results are recorded in source documents only.
6. Height measurements should be made using a stadiometer (recommended) or other appropriate method for measuring standing height in children. The method used must be documented and consistent throughout the study.
7. PGx sample may be obtained at any visit from randomized subjects who have signed PGx consent/assent.
8. Collect PGx sample at EW if PGx consent is signed and the sample is not already collected.
9. Follow-up phone call occurs approximately 7 days after Visit 6/EW.
10. Withdrawal criteria are not assessed during the follow-up telephone call.

EW: Early Withdrawal
FU: Follow-Up
PGx: Pharmacogenetic
prn: Pro Re Nata, as needed

Source: SAS115358 protocol; table 3; pp31-32

As with the adolescent/adult study (SAS115359), this study did not include evaluation of FEV1, a parameter typically assessed in asthma trials. As FSC and FP have already demonstrated a bronchodilator effect, inclusion of an FEV1 assessment is not required in terms of efficacy. However, assessment of FEV1 may have been helpful in terms of assessing treatment compliance.

During this trial patients were allowed used of rescue medication and other medications with the exception of the prohibited medications, such as Xolair and/or other monoclonal antibodies or investigational drugs. Only serious adverse events (SAE) and non-serious adverse events (AE) leading to discontinuation were collected, as per previous agreement with the Division.

Reference ID: 4138257

Trial Population
The trial consisted of approximately 6200 randomized asthma patients who required ICS or ICS+LABA maintenance treatment.

Key Inclusion Criteria
1. All patients' guardians signed an informed consent and the patients give assent where possible.
2. All patients had a diagnosis of asthma as defined by national and international guidelines (e.g., GINA 2009 and NAEPP 2007) for at least 6-months prior to visit 1
3. Male or female patients, 4-11 years of age.
4. Patients have had at least one asthma exacerbation requiring treatment with a systemic steroid between 30-days and 12-months prior to visit 1.
5. Stable asthma therapy for the 4-weeks prior to Visit 1 and patients must meet one of the following pre-study asthma medication, impairment domain (Childhood Asthma Control Test, C-ACT) and risk domain (asthma exacerbations) criteria to be eligible for enrollment.
   - Patients on SABA alone, LTRA, theophylline, or cromolyn as monotherapy with Childhood Asthma Control Test score ≤19 at Visit 1 and have had 2 or more asthma exacerbations in the previous year, or
   - Patients on low-dose ICS monotherapy with Childhood Asthma Control Test score ≥20 at Visit 1 and have had 2 or more asthma exacerbations in the previous year, or
   - Patients on low-dose ICS monotherapy with Childhood Asthma Control Test score ≤19 at Visit 1 and have had at least 1 asthma exacerbation in the previous year, or
   - Patients on low-dose ICS and one or more adjunctive therapy (LABA, LTRA, or theophylline) with Childhood Asthma Control Test score ≥20 at Visit 1 and have had at least 1 asthma exacerbation in the previous year, or
   - Patients on low-dose ICS and one or more adjunctive therapy (LABA, LTRA, or theophylline) with Childhood Asthma Control Test score ≤19 at Visit 1 and have had at least 1 asthma exacerbation in the previous year, or
   - Patients on medium-dose ICS monotherapy with Childhood Asthma Control Test score ≥20 at Visit 1 and have had at least 1 asthma exacerbation in the previous year, or
   - Patients on medium-dose ICS monotherapy with Childhood Asthma Control Test score ≤19 at Visit 1 and have had at least 1 asthma exacerbation in the previous year, or
   - Patients on medium-dose ICS and one or more adjunctive therapy (LABA, LTRA, or theophylline) with Childhood Asthma Control Test score ≥20 at Visit 1 and have had only 1 asthma exacerbation in the previous year.

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Table 5. Pediatric Study (SAS115358). Summary of medication and C-ACT based inclusion criteria

Prior Asthma Therapy	Childhood Asthma Control Test score at Visit 1	One exacerbation in previous year	Two or more exacerbations in previous year
SABA, LTRA, theophylline or cromolyn	≥20	Not eligible	Not eligible
	≤19	Not eligible	Eligible
Low-dose ICS monotherapy	≥20	Not eligible	Eligible
	≤19	Eligible	Eligible
Low-dose ICS and one or more adjunctive therapy	≥20	Eligible	Eligible
	≤19	Eligible	Eligible
Medium-dose ICS monotherapy	≥20	Eligible	Eligible
	≤19	Eligible	Eligible
Medium-dose ICS and one or more adjunctive therapy	≥20	Eligible	Not eligible
	≤19	Not eligible	Not eligible

Source: SAS115358 protocol; table 1; pg 22
Note that an C-ACT score of ≤19 is considered not well controlled (NAEPP).

Key Exclusion Criteria

1. History of life threatening asthma defined as an asthma episode that required intubation, hypercapnea requiring non-invasive ventilator support, respiratory arrest, hypoxic seizures, or asthma related syncopal episode(s).
2. Concurrent respiratory disease or respiratory infection
3. Exercised induced asthma
4. Unstable asthma at Visit 1 defined as follows:
   - Daily use of >4 puffs of albuterol/salbutamol (other than pre-exercise), ≥8 puffs for 2 or more consecutive 24-hour periods in the 7-days preceding Visit 1
   - ≥2 nighttime awakenings due to asthma symptoms in the 7-days preceding Visit 1
   - Investigator discretion
5. Patients currently receiving high-dose ICS or ICS/LABA to treat asthma symptoms
6. Asthma exacerbation within 4-weeks of Visit 1 or more than 4 separate exacerbations in the last 12 months prior to Visit 1. This includes exacerbations due to poor compliance. Each exacerbation must be separated by >7-days from discontinuation of oral steroids to be considered an individual event.
7. More than 2 asthma hospitalizations (>24 hour inpatient stay) in the 12-months prior to visit 1 or an hospitalization for asthma within 4-weeks of Visit 1. To considered separate hospitalizations, events must be separated by >7-days.
8. Use of investigational medications
9. Use of restricted medications.

10. Use of potent CYP4503A inhibitor within 4-weeks of Visit 1
11. A child who has been placed under the control or protection of an agency, organization, institution, or entity by the courts, government or a government body.

For reasons similar to the adolescent/adult study, the pediatric study excluded those patients with life-threatening asthma. These patients would likely be at the highest risk for the types of serious asthma-related events this study is trying to capture. Exclusion of these patients may hamper the ability to generalize safety conclusions to that population.

Withdrawal from study treatment criteria:
1. A patient requires additional asthma medication over and above asthma medication allowed by the protocol to maintain long-term asthma control.
2. A patient ≥2 episodes of treatment for protocol defined asthma exacerbations during the entire study (withdrawn upon 3rd exacerbation)
3. A patient requires endotracheal intubation for asthma.
4. A patient has an adverse event that would, in the investigator's judgement, make continued participation an unacceptable risk.
5. A patient becomes pregnant
6. A patient whose exacerbation is not responding to therapy in the judgment of the investigator or is not responding to 14 days of treatment with a systemic corticosteroid.
7. In the opinion of the investigator, a patient is judged to be significantly noncompliant with the requirements of the protocol.
8. The treatment blind is broken for a patient.

Patients who prematurely discontinued study medication continued to be followed for the 26-week treatment period for the primary safety outcome. During this time patients were contacted via monthly telephone calls.

The inclusion/exclusion and withdrawal criteria are reasonable and generally consistent with the adult study.

Treatments
Treatment groups:
1. FP 100mcg BID
2. FCS 100/50mcg BID
3. FP 250mcg BID
4. FSC 250/50mcg BID

As compared to the adult study FSC 500/50 and FP 500 arms were not included due to patient age. FSC 250/50 and FP 250 treatment arms were included, though neither are approved for use in patients <12 years of age. However, use of such doses are consistent with national and international treatment guidelines (e.g., NAEPP and GINA).

Reference ID: 4138257

Patients were assigned to study treatment group based on baseline medication, C-ACT score, and exacerbation history. Treatment assignment strategy is summarized in Table 6.

Table 6. Pediatric Study (SAS115358). Treatment assignment strategy

Prior Asthma Therapy	Childhood Asthma Control Test score at Visit 1*	One exacerbation in previous year	Two or more exacerbations in previous year†	Randomization Group
SABA, LTRA, theophylline or cromolyn	≥20	Not eligible	Not eligible	Not eligible
	≤19	Not eligible	FSC 100/50 or FP 100	a
Low-dose ICS monotherapy	≥20	Not eligible	FSC 100/50 or FP 100	c
	≤19	FSC 250/50 or FP 250	FSC 250/50 or FP 250	b
Low-dose ICS and one or more adjunctive therapy	≥20		FSC 250/50 or FP 250	d
		FSC 100/50 or FP 100		f
	≤19	FSC 250/50 or FP 250	FSC 250/50 or FP 250	d
Medium-dose ICS monotherapy	≥20		FSC 250/50 or FP 250	e
		FSC 100/50 or FP 100		f
	≤19	FSC 250/50 or FP 250	FSC 250/50 or FP 250	e
Medium-dose ICS and one or more adjunctive therapy	≥20	FSC 250/50 or FP 250	Not eligible	g
	≤19	Not eligible	Not eligible	Not eligible

FP = fluticasone propionate FSC = FP/salmeterol combination; ICS = Inhaled corticosteroid; LABA =long acting beta$_2$-agonist; LTRA = leukotriene receptor antagonist

*Control defined by Childhood Asthma Control Test - **Controlled** defined as Childhood Asthma Control Test score ≥20;

†Subjects with more than 4 separate exacerbations in the last 12 months from Visit 1 are not eligible for randomization.

Source: SAS115358 protocol; table 2; pg27

This treatment assignment approach allows for step-up therapy as per GINA and NAEPP guidelines in those patients who are not well controlled on their current medications. However, it does not appear that repeated assessments are performed to determine if further step-up (or step-down) is necessary. As such, it is possible that some patients may be over (or under) treated.

Concomitant/Restricted Medication
The following medications were prohibited for the duration of the treatment period:

Restricted medications

- Asthma medications other than study drug (DISKUS and rescue albuterol/salbutamol) such as: ICSs (other than study drug) (e.g.,

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budesonide, beclomethasone dipropionate, mometasone furoate, ciclesonide)
- LABA (other than study drug) or an extended release SABA
- LTRA (montelukast), theophylline, cromolyn, or other non-ICS/OCS asthma controller medications
- Prescription or over the counter medications that would significantly interact with beta-agonists or ICSs
- Potent Cytochrome P450 3A4 (CYP3A4) inhibitors within 4 weeks of Visit 1 and during the study (e.g., ritonavir, ketoconazole, itraconazole)
- Anticholinergics (including intranasal)
- Anti-IgE (e.g., Xolair [omalizumab])
- Other immunomodulators

Patients could remain on immunotherapy provided that they were on a stable regimen for at least 4-weeks prior to Visit 1 and planned to maintain that regimen for 6 months. Patients were also allowed topical and/or nasal corticosteroids, short-acting and long-acting antihistamines, and decongestants.

Endpoints

Safety:

The primary safety objective was the same as in the adult study. To that end, the primary safety endpoint of this study was number of patients experiencing a serious asthma-related events defined as in the adult study.

Secondary safety endpoints included the individual components of the composite: asthma-related hospitalizations, asthma-related intubations, asthma-related deaths, and withdrawals due to exacerbations.

As with adult study, given the size and objective of the trial, only SAEs and AEs leading to discontinuation were collected and recorded in the CRF. All hospitalizations were reviewed by an independent adjudication committee to determine if the events are asthma-related.

Efficacy:

The primary efficacy endpoint for this trial was exacerbation. This was defined as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days. The definition used for exacerbation is essentially the same as in the adult study and is typical for a phase 3 asthma program. The secondary efficacy endpoints for this study were rescue free days and asthma control days. A rescue free day was defined as a day without rescue medication use. Asthma controls days were defined as days without rescue medications, nighttime awakenings due to asthma, asthma exacerbation, missed work (caregiver) or daycare/school.

Compliance

Compliance was monitored through the dose counter read-out during clinic visit and telephone contact.

Ethics:
This trial was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (2008), and ICH guidelines.

Statistical Analysis
Sample size
Based on an assumed rate of serious asthma outcomes of 0.007 per 26-months, a one-sided alpha=0.025, a power of 90%, and a non-inferiority margin of relative risk equal to 2.675; the Applicant pre-specified a sample size of n=6202.

Analysis populations
As in the adult study, this trial had two analysis populations. The primary analysis population was the Intent-to-Treat (ITT) population, which included all patients randomized who received at least one dose of study drug. Adverse events that occur within 6-month trial period and a 7-day follow-up period were included in the analyses. The second analysis population, the modified-ITT (mITT), consisted of all randomized patients who received at least one dose of study drug and AEs that occurred while on study treatment and 7-days after study drug was stopped.

Primary Analysis
The primary safety endpoint was the number of subjects experiencing the composite endpoint of serious asthma outcomes over the 6-month study period. The time to first event as part of the composite endpoint will be analyzed using a Cox proportional hazards regression model, adjusting for asthma treatment/asthma control randomization stratum. The resulting upper bound of the two-sided 95% CI of the hazard ratio will be used to assess statistical non-inferiority of FSC to FP. If the upper-limit of the estimated hazard ratio was <2.675 then the Applicant concluded that non-inferiority was achieved. Note that in this analysis, the two FSC dose groups were pooled, as were the two FP dose groups.

The primary efficacy endpoint for each subgroup is asthma exacerbations. Time to first asthma exacerbation will be compared between treatment groups using a Cox proportional hazards regression model. This analysis will only be performed within each subgroup and not for the overall population.

Protocol Amendments
There were no protocol amendments.

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6 Review of Efficacy

Efficacy Summary

Advair Diskus is currently approved for the treatment of asthma. However, there is no label claim for exacerbation reduction. In this sNDA the sponsor has submitted data from two 26-week, randomized, double-blind, active controlled trials in pediatric (4 to 11 years old) and adolescent/adult (≥12 years) asthma patients with a history of exacerbation. These studies, SAS 115358 and 115359, respectively, compared Advair Diskus [fluticasone/salmeterol (FSC)] to fluticasone (FP) alone in terms of exacerbation. In the adolescent/adult study (SAS115359), exacerbation was defined as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. In the pediatric study, exacerbation was defined as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days. The pediatric study (SAS115358) included approximately 6200 patients and the adolescent/adult study (SAS115359) approximately 11,700 patients. While FP does not carry an exacerbation reduction indication or claim, it is approved for the treatment of asthma. As such, demonstration that FSC treatment resulted in reduced exacerbations compared to FP treatment would support the addition of exacerbation data to section 14 of the label. In the adolescent/adult study, FSC treated patients demonstrated a reduction in exacerbation compared to FP treated patients, which was statistically significant [hazard ratio 0.79 (95%CI 0.7, 0.9)]. In the pediatric study, a similar trend was observed, though results failed to exclude 1 in the 95% confidence interval [hazard ratio 0.86 (95% CI0.7, 1.0)]. These results demonstrate that FSC use does result in exacerbation reduction compared to FP use and are supportive of adding the exacerbation results to section 14 of the label.

6.1 Indication

The FP/salmeterol combination (FSC) is approved for the treatment of asthma and COPD. The dry powder formulation (Advair Diskus) is approved for asthma down to the age of 4 years at 100/50mcg twice daily in the 4-11 year old population and at 100/50mcg, 250/50mcg, and 500/50 twice daily for the ≥12 year old population. The HFA formulation (Advair HFA) is approved for asthma in the ≥12 year old population at a dose of 45/21 mcg to 230/21 mcg two inhalations twice daily.

FP is approved for the maintenance treatment of asthma. As the dry powder formulation (Flovent Diskus), it is approved down to the age of 4 years at 50 and 100mcg twice daily in the 4-11 year old population and at 100, 250, and 500mcg twice daily for the ≥12 year old population. The HFA formulation (Flovent HFA) is indicated for the same population. In the 4-11 year old population, it is approved at 88mcg twice daily, and in the ≥12 year old population at 88-440mcg twice daily.

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Neither FSC nor FP have an asthma exacerbation claim.

6.1.1 Methods

Study SAS115359 and SAS115358 were submitted by the Applicant to address the PMR issued for the Advair products. The design and conduct of these trials are outlined in detail in 5.3 Discussion of Individual Studies/Clinical Trials. Briefly, study SAS115359 was a 26-week, randomized, double-blind, active controlled trial in patients ≥12 years of age (adolescents/adults) with persistent asthma. Study SAS115358 was similar in design, except included pediatric patients 4 to 11 years of age. The primary safety endpoint for both was number of patients experiencing a serious asthma-related events, which were defined as a composite of asthma-related hospitalizations, asthma-related intubations, or asthma-related deaths. These events were independently adjudicated for asthma-relatedness. The primary efficacy endpoint for both was exacerbation.

6.1.2 Demographics

In the adult/adolescent study (SAS115359), the mean age was 43 years, with the majority of patients between the ages of 18-64 years. Patients had carried an asthma diagnosis on average for 17 years and the majority had not had an asthma-related hospitalization in the previous year. Demographic and baseline characteristics were similar between treatment groups. These data are summarized in Table 7 and Table 8.

Table 7. Adolescent/Adult Study (SAS115359). Demographics

	FSC (N=5834)	FP (N=5845)	Total (N=11679)
Age (yrs)			
Mean	43.4	43.4	43.4
Median	45.0	45.0	45.0
Min	12	12	12
Max	91	87	91
Age Group, n (%)			
12-17 years	615 (11)	615 (11)	1230 (11)
18-64 years	4576 (78)	4605 (79)	9181 (79)
>64 years	643 (11)	625 (11)	1268 (11)
Sex, n (%)			
Male	1983 (34)	1947 (33)	3930 (34)
Female	3851 (66)	3898 (67)	7749 (66)
Ethnicity, n (%)			
Hispanic or Latino	1013 (17)	989 (17)	2002 (17)
Not Hispanic or Latino	4821 (83)	4856 (83)	9677 (83)
Race, n (%)			
White	4374 (75)	4409 (75)	8783 (75)
Black	870 (15)	856 (15)	1726 (15)
Other racial group	590 (10)	580 (10)	1170 (10)

Source: SAS115359 CSR; table 3, pg 47

Table 8. Adolescent/Adult Study (SAS115359). Baseline characteristics

	FSC (N=5834)	FP (N=5845)	Total (N=11679)
Asthma Duration (yrs)			
Mean	16.9	16.7	16.8
Median	13.0	12.0	12.0
Number of Asthma-Related Hospitalizations in Past 12 months, n (%)			
0	4944 (85)	4976 (85)	9920 (85)
1	837 (14)	800 (14)	1637 (14)
2	53 (<1)	69 (1)	122 (1)
Number of Exacerbations Requiring Systemic Corticosteroids in Past 12 months, n (%)			
0	50 (<1)	46 (<1)	96 (<1)
1	4778 (82)	4795 (82)	9573 (82)
2	775 (13)	740 (13)	1515 (13)
>2	231 (4)	264 (5)	495 (4)
Smoking Status, n (%)			
Current smoker	291 (5)	288 (5)	579 (5)
Former smoker	876 (15)	896 (15)	1772 (15)
Non-smoker	4667 (80)	4660 (80)	9327 (80)
Missing	0	1 (<1)	1 (<1)
Number of Pack-Years			
n	1166	1181	2347
Mean	4.1	4.0	4.1
Median	3.5	3.5	3.5

Source: SAS115359 CSR; table 4; pg49

In the pediatric study (SAS115358), the mean age was 8 years, with the majority of patients between the ages of 7-11 years. Patients had carried an asthma diagnosis on average for 4 years and the majority had not had an asthma-related hospitalization in the previous year. Demographic and baseline characteristics were similar between treatment groups. These data are summarized in Table 9 and Table 10.

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Table 9. Pediatric Study (SAS115358). Demographics

	FSC (N=3107)	FP (N=3101)	Total (N=6208)
Age (yrs)			
Mean	7.6	7.6	7.6
Median	8.0	8.0	8.0
Min	4	4	4
Max	12	11	12
Age Group, n (%)			
4-6 years	1096 (35)	1114 (36)	2210 (36)
7-11 years	2011 (65)	1987 (64)	3998 (64)
Sex, n (%)			
Male	1920 (62)	1874 (60)	3794 (61)
Female	1187 (38)	1227 (40)	2414 (39)
Ethnicity, n (%)			
Hispanic or Latino	910 (29)	868 (28)	1778 (29)
Not Hispanic or Latino	2197 (71)	2233 (72)	4430 (71)
Race, n (%)			
White	1998 (64)	2032 (66)	4030 (65)
Black	539 (17)	511 (16)	1050 (17)
Other racial groups	570 (18)	558 (18)	1128 (18)

Source: SAS115358 CSR; table 5; pg46

Table 10. Pediatric Study (SAS115358). Baseline characteristics

	FSC (N=3107)	FP (N=3101)	Total (N=6208)
Asthma Duration (yrs)			
Mean	4.0	4.0	4.0
Median	4.0	4.0	4.0
Number of Exacerbations in Past 12 months Requiring Hospitalization, n (%)			
0	2663 (86)	2679 (86)	5342 (86)
1	394 (13)	370 (12)	764 (12)
2	50 (2)	52 (2)	102 (2)
>2	0	0	0
Number of Exacerbations in Past 12 Months Requiring Oral/Systemic Corticosteroids and/or Antibiotics, n (%)			
0	138 (4)	132 (4)	270 (4)
1	1935 (62)	1956 (63)	3891 (63)
2	834 (27)	818 (26)	1652 (27)
>2	200 (6)	195 (6)	395 (6)
Number of Exacerbations in the 12 Months Preceding Screening			
Mean	1.4	1.4	1.4
SD	0.71	0.68	0.70
Median	1.0	1.0	1.0

Source: SAS115358 CSR; table 6; pg47

For both these trials, given the inclusion criteria, the patient demographics, and baseline characteristics, the studied population included those patients who would be among those at risk for serious asthma-related events and would typically be treated with ICS or ICS/LABA. However, as noted in an editorial following publication of the adolescent/adult study, these studies excluded those with life threatening asthma[9], as well as those patients with >2 asthma hospitalizations in the previous 12 months. As these patients were not included, one cannot definitively generalize results from these studies to that specific population. Additionally, exclusion of such patients may also have resulted in fewer serious asthma-related events. However, exclusion of such patients was unavoidable given that in both studies, patients could have been randomized step down medication to FP only, if they were previously on ICS/LABA. De-escalating therapy in such patients would have exposed them to additional risk.

4.1.3 Subject Disposition

In adolescent/adult (SAS115359) and pediatric (SAS115358) studies, 11,751 and 6,250 patients were randomized to receive study drug, respectively. Of these, 11,679 and 6208 actually received at least one dose of study drug. This population was considered

9 Martinez, FD. NEJM 2016; 374:1887-1888

by the sponsor to be the Intent-to-Treat (ITT) population for the purposes of both safety and efficacy analyses. It is uncertain why a handful of randomized patients did not receive study medication; however, as these patients were evenly distributed across the treatment groups in both studies and given the size of the studies, it is unlikely that this would affect results or interpretation. Of the ITT populations in studies SAS115359 and SAS115358, 83% and 88% completed treatment. This is within the range typically observed in longer asthma studies. In both studies, the most common reason for withdrawal of study treatment was "withdrawal by subject," followed by "protocol deviation," adverse events, exacerbation (pre-specified definition). These results are summarized in Table 11

Table 11. Patient Disposition

	Adolescent/Adult (SAS115359)			Pediatrics (SAS115358)		
	FSC N=5834	FP N=5845	Total N=11679	FSC N=3107	FP N=3101	Total N=6208
Completed Study, n (%)						
n	5823	5831	11654	3105	3099	6204
Completed Treatment	4887 (84)	4778 (82)	9665 (83)	2724 (88)	2751 (89)	5475 (88)
Withdrawn from Treatment	936 (16)	1053 (18)	1989 (17)	381 (12)	348 (11)	729 (12)
Withdrawn from Study, n (%)						
n	11	14	25	2	2	4
Completed Treatment	0	1 (7)	1 (4)	0	0	0
Withdrawn from Treatment	11 (100)	13 (93)	24 (96)	2 (100)	2 (100)	4 (100)
Reason for Withdrawal from Study Treatment, n (%)						
n	947	1066	2013	383	350	733
Adverse event	102 (11)	96 (9)	198 (10)	24 (6)	23 (7)	47 (6)
Asthma exacerbation	66 (7)	84 (8)	150 (7)	34 (9)	35 (10)	69 (9)
Lack of efficacy	21 (2)	50 (5)	71 (4)	5 (1)	6 (2)	11 (2)
Lost to follow-up	48 (5)	37 (3)	85 (4)	7 (2)	7 (2)	14 (2)
Protocol deviation	130 (14)	147 (14)	277 (14)	68 (18)	53 (15)	121 (17)
Withdrawal by subject	580 (61)	652 (61)	1232 (61)	245 (64)	226 (65)	471 (64)
Reason for Withdrawal from the Study, n (%)						
n	11	14	25	2	2	4
Death	3 (27)	6 (43)	9 (36)	0	0	0
Lost to follow-up	0	0	0	1 (50)	0	1 (25)
Withdrawal by subject	8 (73)	8 (57)	16 (64)	1 (50)	2 (100)	3 (75)

Source:
SAS115359 CSR; table 2; pg 45
SAS115358 CSR; table 4; pg44

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The majority of patients withdrew from treatment due to "withdrawal by subject." On review of line listings, there is no further explanation as to why the patient chose to withdraw. However, this reason for withdrawal was evenly distributed between FSC and FP treatment groups and would not likely have affected interpretation.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint of both studies was time to first asthma exacerbation (FSC versus FP). In both studies, an exacerbation was defined as a deterioration of asthma requiring the use of systemic steroids for at least 3 days. The primary endpoint is appropriate for the desired claim and the exacerbation definition consistent with that used that used in other asthma programs.

In both studies more FP patients experienced exacerbations compared to FSC patients. The hazard ratio (HR) point estimate for time to first exacerbation in both studies was <1, however, only in the adult/adolescent study did the 95% confidence interval exclude 1. These results are summarized in Table 12.

Table 12. Time to first asthma exacerbation

	Adolescent/Adult (SAS115359)		Pediatric (SAS115358)	
	FSC (N=5834)	FP (N=5845)	FSC (N=3107)	FP (N=3101)
Number of Patients	5834	5845	3107	3101
Number of Patients with Event	480 (8)	597 (10)	265 (9)	309 (10)
Hazard Ratio	0.79		0.86	
95% CI	(0.7, 0.9)		(0.7, 1.0)	

Source: Calculated by FDA efficacy statistical reviewer

These data demonstrate that FSC treatment confers a statistically significant exacerbation benefit to adolescents/adults compared to FP and suggest a similar, though not statistically significant, effect in the pediatric population. However, the numerical magnitude of the benefit, especially in the pediatric age group was modest. While the magnitude was modest, the comparison was to FP, which is known to be effective in asthma, though without an exacerbation claim.

In addition to calculating hazard ratios, risk differences (RD) and number needed to treat (NNT) were calculated. Based on sponsor calculated age-adjusted mean exacerbation rate (per 6 months), in the adolescent/adult study, the risk difference was 0.027 and the NNT to prevent 1 exacerbation in 6-months was 37 patients. For the pediatric study, the RD was 0.02 and the NNT to prevent 1 exacerbation in 6-months was 50 patients.

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For both studies, the majority of patients who had an exacerbation, had only one and the vast majority did not result in hospitalization. While overall number of patients with exacerbations was higher in FP versus FSC groups, the number of patients with exacerbations leading to hospitalization was slightly numerically higher in FSC groups versus FP. This may suggest that while FSC may reduce exacerbation compared to FP, this effect is driven by non-severe exacerbations. Alternatively, this may be a chance observation related to the small number of exacerbations leading to hospitalization. These results are summarized in Table 13.

Table 13. Summary of asthma exacerbation

		Adolescent/Adult (SAS115359)		Pediatric (SAS115358)	
		FSC (N=5834)	FP (N=5845)	FSC (N=3107)	FP (N=3101)
Number of Subjects Experiencing at Least One Asthma Exacerbation, n (%)[1]		480 (8)	597 (10)	265 (9)	309 (10)
Number of Asthma Exacerbations		540	673	304	362
Exacerbation Frequency Category, n (%)[1]	0	5354 (92)	5248 (90)	2842 (91)	2792 (90)
	1	423 (7)	525 (9)	233 (7)	263 (8)
	2	54 (<1)	69 (1)	26 (<1)	39 (<1)
	3	3 (<1)	2 (<1)	5 (<1)	7 (<1)
	4	0	1 (<1)	1 (<1)	0
Was the Subject Hospitalized for the Exacerbation?, n (%)[2]	Yes	28 (5)	25 (4)	23 (8)	17 (5)
	No	512 (95)	648 (96)	281 (92)	345 (95)
Did the Subject Visit the Emergency Room or Other Equivalent Facility[2]	Yes	108 (20)	123 (18)	78 (26)	83 (23)
	No	432 (80)	550 (82)	226 (74)	279 (77)

[1]Percentages calculated on number of patients
[2]Percentages calculated on number of events
Source:
SAS115359 CSR; table 23; pp 82-83
SAS115358 CSR; table 25; pp 80-81

6.1.5 Analysis of Secondary Endpoints(s)

In contrast to the primary efficacy endpoint, secondary endpoints between the adolescent/adult (SAS115359) and pediatric (SAS115358) study differed.

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The secondary endpoint for the adolescent/adult study (SAS115359) was rescue medication use. Use of rescue medication (albuterol/salbutamol) was reduced in FSC and FP over the 6-month treatment period at 0.95 puffs/24 hours and 1.14 puff/24 hours, respectively (calculated by FDA efficacy statistical reviewer). The difference was small at -0.19 puffs/24hours (95%CI -0.24, -0.14).

The secondary endpoints for the pediatric study (SAS115358) were rescue free days and asthma control days. Rescue-free days were those days without use of albuterol/salbutamol use. Asthma control days were those days without rescue medication use, night-time awakenings, asthma exacerbation, missed work/school/daycare, and when coughing from asthma score was ≤1 and wheezing score = 0.

The percentage of rescue-free days over the 6-month treatment period was similar between treatment groups at 83% and 82% for the FSC and FP groups, respectively. The percentage of asthma control days was also similar between treatment groups at 74.3% and 73.1%, respectively.

Results for the secondary endpoints for both studies did not strongly suggestive a treatment benefit for either product over the other. This was in distinction to the primary endpoint of exacerbation. This is somewhat surprising as one would assume that rescue medication use would be higher for the group in which more exacerbations occurred. However, this lack of difference may be indicative of the relatively modest magnitude of the exacerbation effect and/or that the bulk of the benefit in terms of rescue medication use was due to the FP.

6.1.6 Other Endpoints

Both studies also included several other exploratory endpoints (e.g., symptom free days, night-time symptoms, etc). Similar to the secondary endpoints, results were largely similar between treatment groups in the overall population.

6.1.7 Subpopulations

In both studies, sub-group analyses were also performed based on age, race, ethnicity, and US versus outside US (OUS). In both studies, results among these subgroups were fairly consistent with the overall population. Results, as calculated by the FDA statistical reviewer, are summarized in Figure 4 and Figure 5.

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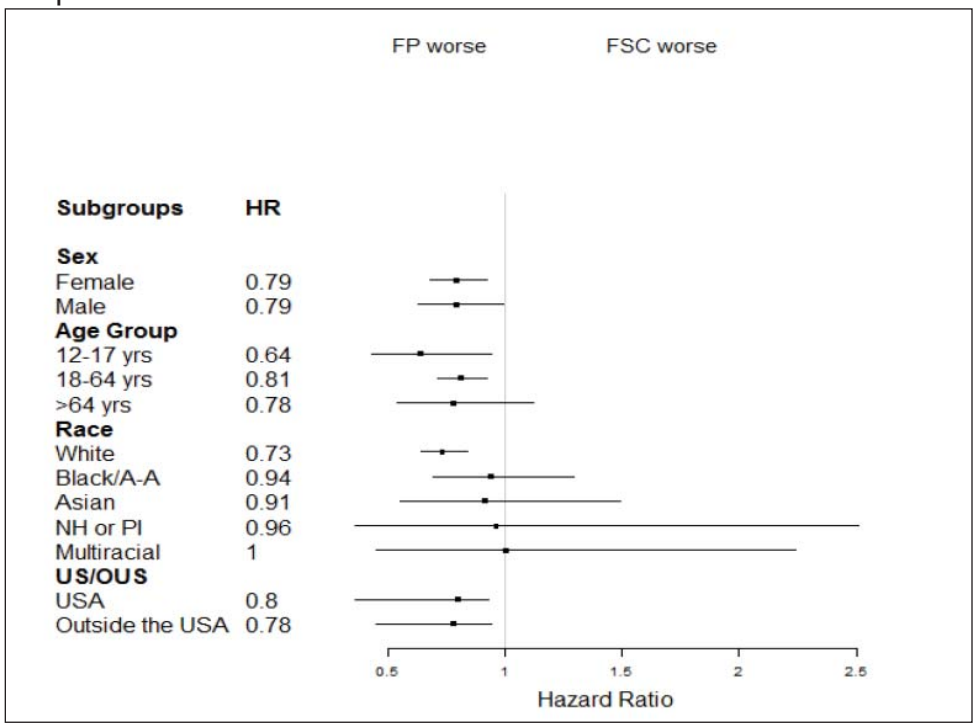
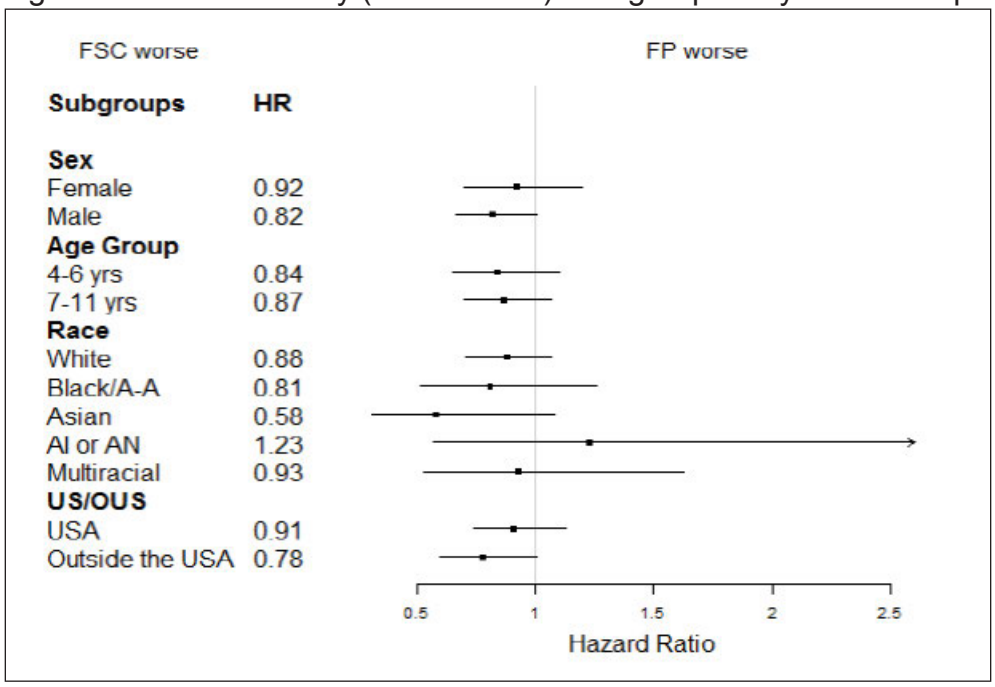
Figure 4. Adolescent/Adult Study (SAS115359). Subgroup analyses for the primary endpoint



Source: calculated by FDA efficacy statistical reviewer

Figure 5. Pediatric Study (SAS115358). Subgroup analyses for the primary endpoint



Source: calculated by FDA efficacy statistical reviewer

Additionally, when comparing FSC dose to corresponding FP dose for both studies, point estimates were numerically similar to the overall populations, though the 95% CI were wider.

Given concerns with exacerbation and the African-American population, subgroup analysis was specifically performed by the FDA efficacy statistical reviewer for Blacks from U.S. study sites. These results were consistent with the overall population for the primary endpoint. In the pediatric study (SAS115358) the HR was 1.08 (0.75, 1.54) and in the adolescent/adult study (SAS115359), the HR was 0.71 (0.44, 1.15).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dosing in the indicated population has already been determined and no dose-ranging was performed.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No formal analysis of persistence or tolerance was performed.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

There have been longstanding safety concerns regarding LABAs and an increased risk of serious asthma-related events (e.g., hospitalizations, intubations, and deaths). As a result of these concerns, a boxed warning (BW) was added to all LABA containing products. To address this concern for serious asthma-related events, the Agency required safety studies be conducted with LABA products approved for asthma on background ICS in adults and children. This requirement was announced in February of 2010, and in April 2011 the basic design (randomized, double-blind, controlled clinical trials comparing the addition of LABAs to inhaled corticosteroids versus inhaled corticosteroids alone) of the trials was announced. Five studies in total were required: [GlaxoSmithKline: Advair Diskus (adult and pediatric studies), AstraZeneca: Symbicort, Merck: Dulera, and Novartis: Foradil]. These studies were designed similarly with shared adjudication, data monitoring, and oversight committees with the idea of combining the data when completed to evaluate rare events of death and intubation. The post-marketing required (PMR) studies required for GSK were as follows:

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- 1750-1:
  A randomized, double-blind, 26-week, active-controlled clinical trial comparing Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) and fluticasone propionate inhalation powder to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 11,700 adult and adolescent patients 12 years of age and older with persistent asthma.

- 1750-2:
  A randomized, double-blind, 26-week, active-controlled clinical trial comparing Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) and Flovent Diskus (fluticasone propionate inhalation powder) to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 6200 pediatric patients 4 to 11 years of age with persistent asthma.

This sNDA incorporates the results of these two PMR studies in the Advair Diskus product labeling. In this sNDA the sponsor has submitted data from two 26-week, randomized, double-blind, active controlled trials in pediatric (4 to 11 years old) and adolescent/adult (≥12 years) asthma patients with a history of exacerbation. These studies, SAS115358 and SAS115359, respectively, compared Advair Diskus [fluticasone/salmeterol (FSC)] to fluticasone (FP) alone in terms of serious asthma-related outcomes. The pediatric study (SAS115358) addressed PMR 1750-2 and included approximately 6200 patients. The adolescent/adult study (SAS115359) addressed PMR 1750-1 and included approximately 11,700 patients. The primary endpoint of both studies was time to serious asthma-related events defined as the composite of asthma-related hospitalizations, deaths, and intubations. Asthma-relatedness was adjudicated by an independent Joint Adjudication Committee (JAC).

For both studies a pre-defined non-inferiority (NI) margin for the hazard ratio for time to event was agreed upon between the Agency and the Sponsor. For the pediatric study (SAS115358) the NI margin was 2.7 and for the adolescent/adult study (SAS115359), the NI margin was 2.0. Results from both studies demonstrated that the upper limits of the 95% confidence intervals (CI) were less than the pre-specified NI margins. For the pediatric study, the hazard ratio (HR) was 1.29 (95%CI 0.7, 2.3) and for the adolescent/adult study the HR was 1.03 (95%CI 0.6, 1.7). There were no asthma-related deaths in either study and these results were driven by asthma-related hospitalizations. Multiple subgroup analyses were performed (e.g., age, race, sex, exacerbation history, asthma control, etc) and results of these analyses were generally consistent with the overall population, though 95%CI were wider.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

While efficacy in asthma has been established for both FP and FSC, there has been a long standing history of safety concerns with LABA use in asthma. These concerns reach back decades and stem from both the scientific literature and FDA analyses. These concerns have resulted in multiple advisory committee meetings as well as a Boxed Warning for all LABA containing medications. Due to these persistent safety concerns, the FDA issued a post-marketing requirement (PMR) that the manufacturers of LABAs conduct the following:

> *"A randomized, double-blind, 26-week, active controlled clinical trial comparing (LABA/ICS) and ICS to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 11,700 adult and adolescent patients 12 years of age and older with persistent asthma."*

Four clinical trials were to be conducted in patients 12 years of age and older for a total of 46,800 patients across trials. Each trial was to evaluate one of the following LABA-containing drugs: 1) Symbicort (budesonide and formoterol); 2) Advair Diskus (FP/Salm); 3) Dulera (mometasone and formoterol); and 4) Foradil (formoterol and fluticasone).

One clinical trial was to be conducted in pediatric patients aged 4 to 11 years with Advair Diskus and was to include 6,200 patients. Patients in all trials were to be treated for six months. The primary endpoint was to be a composite of serious asthma-related events: asthma-related death, intubation, or hospitalization. The pediatric trial was also to assess other relevant quality of life endpoints such as days of school missed and emergency room visits because of asthma related illness.

Each of these trials was individually powered for the primary safety endpoint of serious asthma-related events. However, for asthma related deaths, these four trials were meant to be pooled for a meta-analysis. Based on historical data, each of the adolescent/adults studies were expected to have 87 serious asthma-related events with a total of 28 asthma-related deaths across the 4 studies.

The adolescent/adult (SAS115359) and pediatric (SAS115358) studies were designed to address the PMR and evaluate safety of Advair Diskus in the ≥12 year old and 4 to 11 year old population, respectively.

7.1.2 Categorization of Adverse Events

In both studies, adverse events (AE) were defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which

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does not necessarily have to have a causal relationship with treatment. Given the size and intent of these studies, both studies only reported serious AE (SAE) and AEs leading to discontinuation. AEs were reported using the MedDRA 18.1 dictionary.

Safety analyses in terms of AEs were performed on the modified-intent-to-treat population which consisted of all randomized patients who received at least one dose of study drug and had events which occurred within 7-days following last treatment period (i.e., treatment emergent AEs).

As part of the primary safety endpoint, all deaths, endotracheal intubations, and/or hospitalizations were adjudicated to determine relatedness to asthma. Adjudication of these events was performed by the Joint Adjudication Committee (JAC). The JAC consisted of 3 external physicians with at least one member from the U.S. and one from a non-U.S. country. All were experts in both respiratory diseases and conduct on clinical trials. This primary safety analysis was performed on the intent to treat population which consisted of all randomized patients who received at least one dose of study drug and had events that occurred within 7-days after last treatment or 6-months after initial treatment, whichever was longer.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

There was no pooling of safety data from the adolescent/adult (SAS115358) and pediatric (SAS115359) studies.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The exposure in the adolescent/adult and pediatric studies was consistent with previous agreements with the Agency and the sponsor. In the adolescent/adult study (SAS115359), the mean exposure was approximately 163-165 days (median 183 days). The majority of patients were exposed for >6months. In the pediatric study (SAS115358), the mean exposure was approximately 170-171 days, with the majority of patients also exposed for over 6 months. Across both trials, compliance as measured by dose-counters was approximately 88-90%. Overall the exposure is adequate to assess the safety of FSC and FP. Compliance was also adequate, however, as it was based purely on dose-counters, there may some degree of over-estimation of compliance.

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7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Both studies SAS115359 and SAS115358 were designed to address specific safety concerns related to serious asthma related outcomes (asthma related deaths, hospitalizations, and intubations) associated with LABA use in asthma.

7.3 Major Safety Results

7.3.1 Primary Safety Endpoint

The pre-specified primary safety endpoint of both the adolescent/adult (SAS115359) and pediatric (SAS115358) studies was the time to the composite endpoint of serious asthma-related events defined as asthma related deaths, intubations, and hospitalizations. Asthma relatedness was adjudicated by the JAC. For the adolescent/adult and pediatric study, if the upper-limit of the 95% confidence interval for the hazard ratio (HR) of FSC:FP was less than 2.0 and 2.675, respectively, non-inferiority was to be concluded. This pre-specified non-inferiority margin was agreed upon between GSK (and other LABA sponsors) and the Agency. In the adolescent/adult and pediatric studies, the number of events was on par with what was expected with 67 and 43 total events, respectively. The point estimates for the HRs were 1.03 (95%CI 0.64, 1.7) and 1.23 (95% CI 0.72, 2.3), respectively. For both studies, the results were within the non-inferiority margins of 2.0 and 2.7 for the adolescent/adult and pediatric studies, respectively. These results are summarized in Table 14.

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Table 14. Serious Asthma Outcomes – Time to Event Analysis

		Adolescent/Adult (SAS115359)		Pediatric (SAS115358)	
		FSC (N=5834)	FP (N=5845)	FSC (N=3107)	FP (N=3101)
Beginning of Period	Number of Patients	5834	5845	3107	3101
End of Period	Number of Patients with Event	34 (0.6)	33 (0.6)	27 (0.9)	21 (0.7)
	Number of Patients Censored	5800 (99.4)	5812 (99.4)	3080 (99.1)	3080 (99.3)
	Probability of Having Event, (%)	0.006	0.006	0.011	0.008
	95% CI*	(0.004, 0.008)	(0.004, 0.008)	(0.004, 0.017)	(0.004, 0.011)
FSC/FP	Hazard Ratio	1.029		1.285	
	95% CI	(0.638, 1.662)		(0.726, 2.272)	
	p-value	0.003		0.006	

*calculated on log scale of the survival function
Source: Calculated by FDA safety statistical reviewer

These results indicate that the addition of salmeterol to FP does not result in excessive risk of serious asthma-related events, as the pre-specified NI margins were met. Risk differences (RD) and number needed to harm (NNH) were also calculated by the FDA safety statistical reviewer. In the adolescent/adult study the RD was 0.018% (95% CI -0.26%, 0.29%) and NNH was 5493. That is to say, FSC treatment resulted in 0.018 excess serious asthma-related events per 100 patients compared to FP treatment and that 5493 patients would have to be treated with FSC for 26-weeks (6-months) to have one additional serious asthma-related event. For the pediatric study, the RD was 0.19% (95% CI -0.24%, 0.63%) and NNH was 521. For both studies, the NNH was much larger than the number needed to treat to prevent one exacerbation in a 6-month period (37 and 50 patients in the adolescent/adult and pediatric studies, respectively) which is supportive of a positive risk benefit profile (see section 6 Review of Efficacy.

When examining serious asthma-related events by its constituent parts, the vast majority of events were due to asthma-related hospitalizations. There were only two patients with asthma-related intubations and no asthma-related deaths. As there were no asthma-related deaths, no conclusions or inferences can be made with respect to risk of asthma-related deaths for FSC compared to FP. While it is not unexpected that a single study would lack a sufficient number of asthma-related deaths to make any conclusions, it is worth noting that when the PMR studies were designed, based on historical data, it was expected that there would be approximately 7 deaths in each of the adolescent/adult studies. This would have resulted in 28 deaths across the four adolescent/adult LABA safety studies which would have been sufficient to address the safety concern regarding asthma-related death and LABA. This dearth of deaths may be related to the exclusion of patients with life threatening asthma (i.e., the patients most likely to have an asthma-related death); an exclusion that was unavoidable given

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that patients in this trial could have been stepped down to ICS treatment alone. It is also possible that expected deaths were overestimated. The expected asthma-related death was based on a meta-analysis performed by the FDA. In that meta-analysis all asthma-related deaths were in Serevent (salmeterol) patients, with none having occurred in patients on ICS/LABA. As such, it is possible that the asthma-related death rate used to calculate the goal sample size the studies was an overestimate.

With regard to the asthma-related hospitalizations, based on review of the narratives, they were consistent with clinical exacerbations. It should be noted that asthma-related hospitalizations did not correspond 1:1 with the hospitalizations related to the pre-specified exacerbation definition. However, there was considerable overlap and results for adjudicated asthma-related hospitalizations were generally consistent with the pre-defined exacerbations leading to hospitalization. For non-overlapping events, the primary reason appeared to be that the adjudication committee did not conclude that the hospitalization event was asthma-related, but rather was due to a separate medical issue. For adjudicated asthma-related hospitalizations, the results showed slightly more events numerically in the FSC group versus the FP group, similar to the protocol defined exacerbations leading to hospitalization. This is not necessarily surprising given the overlap in these different but related events. Serious asthma-related events broken down by component are summarized in Table 15.

Table 15. Serious asthma-related Events

	Adolescent/Adult (SAS115359)		Pediatric (SAS115358)	
	FSC (N=5834)	FP (N=5845)	FSC (N=3107)	FP (N=3101)
Subjects Experiencing an Event in the Composite Safety Endpoint, n (%)	34 (<1)	33 (<1)	27 (<1)	21 (<1)
Asthma-Related Deaths, n (%)	0	0	0	0
Subjects Experiencing at Least One Asthma-Related Intubation, n (%)	0	2 (<1)	0	0
Subjects Experiencing at Least One Asthma-Related Hospitalization, n (%)	34 (<1)	33 (<1)	27 (<1)	21 (<1)

Source: FDA safety statistical review tables 6 and 17

The results for the primary safety endpoint of serious asthma-related outcomes are consistent with those recently made available in the public domain for Symbicort (budesonide/formoterol)[10] and Dulera (mometasone/formoterol)[11], in that the

[10] Peters SP, Bleecker ER, Canonica GW. Serious Asthma Events with Budesonide plus Formoterol vs. Budesonide Alone. NEJM 2016; 375:850-60.
[11] http://www.mrknewsroom.com/news/company-statements/merck-announces-top-line-results-long-term-laba-safety-study-dulera-mometaso

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prespecified NI-margins were met and the vast majority of the serious asthma-related outcomes were due to hospitalization. Asthma-related deaths were also not common in these studies. The Dulera and Symbicort LABA safety studies added two asthma-related deaths and 1 asthma related intubation, all in the Symbicort study.

Analysis of the Advair results by subgroup was also performed, which included age, race, ethnicity, baseline LABA use, exacerbation history, baseline asthma control, randomized FSC/FP dose. Results were generally consistent with the overall population with the percentage of patients experiencing a serious asthma events being similar between FSC and FP groups, though confidence intervals were wider. However, given the relatively smaller sub-group sizes with respect to overall population size, definitive conclusions cannot be made.

Because for LABA and salmeterol, a component of Advair, safety in African Americans and pediatrics are of particular concern, the data for these populations are discussed below. FDA statisticians performed subgroup analysis in those populations for both trials. For African Americans, these analyses demonstrated that the hazard ratio (HR) point estimate for African Americans was lower compared to whites and the overall population in the adolescent/adult study (SAS115359). In the pediatric study (SAS115358), the HR point estimates were numerically higher in African Americans versus whites (2.1 vs. 0.87). However, the total number of events in the pediatric and adolescent/adult African American population was small and the 95% CIs were wide. As such, definitive conclusions cannot be made. However, concern regarding use of LABA in African Americans was primarily driven by SMART, which showed a signal in this patient population. The results of these two trials are reassuring in that the data do not show a signal or a concerning trend. These results are summarized in Table 16.

Table 16. Serious asthma-related events by race

	Overall		White		African American*	
Adolescent/Adult (SAS115359)	**FSC n=5845**	**FP n=5834**	**FSC n=4374**	**FP n=4409**	**FSC n=573**	**FP n=573**
Patient with events	34 (0.6)	33 (0.6)	21 (0.5)	23 (0.5)	5 (0.9)	7 (1.2)
Hazard ratio		1.03		0.92		0.69
(95%CI)		(0.64, 1.66)		(0.51, 1.67)		(0.22, 2.18)
Pediatric (SAS115358)	**FSC n=3107**	**FP n=3101**	**FSC n=1998**	**FP n=2032**	**FSC n=326**	**FP n=315**
Patients with event	27 (0.87)	21 (0.68)	11 (0.55)	12 (0.64)	4 (1.23)	2 (0.63)
Hazard ratio		1.29		0.87		2.1
(95%CI)		(0.73, 2.27)		(0.39, 1.94)		(0.39, 11.5)

*Black/African American patients at U.S. clinical sites
Source: calculated by FDA safety statistical reviewer

With regard to the pediatric population, for patients 4-11 years in age, the pediatric study (SAS115358), as previously discussed met the NI-margin for the prespecified

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safety endpoint. Subgroup analyses for the 4-6 and 7-11 year old age group were consistent with the overall population. These results are summarized in Table 17.

Table 17. Pediatric study (SAS115358) subgroup analysis of serious asthma-related event by age.

	Overall		Age 4-6		Age 7-11	
SAS115358 (Pediatric)	**FSC n=3107**	**FP n=3101**	**FSC n=1096**	**FP n=1114**	**FSC n=2010**	**FP n=1987**
Patient with events	27 (0.87)	21 (0.68)	11 (1.00)	10 (0.90)	16 (0.80)	11 (0.55)
Hazard ratio		1.23		1.14		1.46
(95%CI)		(0.73, 2.27)		(0.48,2.69)		(0.68,3.16)

Source: calculated by FDA safety statistical reviewer

For the subgroup of 12-17 year old patients in the adolescent/adult study (SAS115359), the number of events was small and the HR was 1.38 with a wide 95% CI (0.23, 8.27). Subgroup analyses across the 12-17, 18-64, and >64 year old age group for the adolescent/adult study (SAS115359) are summarized in Table 18.

Table 18. Adolescent/Adult Study (SAS115359) subgroup analysis of serious asthma-related event by age

	Overall		Age 12-17		Age 18-64		Age >64	
SAS115359 (adolescent/adult)	**FSC n=5845**	**FP n=5834**	**FSC n=615**	**FP n=615**	**FSC n=4576**	**FP n=4605**	**FSC n=643**	**FP n=625**
Patient with events	34 (0.6)	33 (0.6)	3 (0.49)	2 (0.33)	28 (0.61)	28 (0.61)	3 (0.47)	3 (0.48)
Hazard ratio		1.03		1.38		1.00		0.97
(95%CI)		(0.64, 1.66)		(0.23,8.27)		(0.59,1.70)		(0.20,4.78)

Source: calculated by FDA safety statistical reviewer

Overall, with regard to the pediatric population, for the 12-17 year olds, only 5 events were observed. Therefore, results in the 12-17 year old age lack the precision to evaluate the risk of FSC. For the 4-11 year old population, the pediatric study excluded the pre-specified NI margin demonstrating that the addition of salmeterol to FP does not result in a significantly higher risk of serious asthma related events in 4-11 year old patients. However, one cannot conclude that there is no increase in risk of serious asthma outcomes when salmeterol is added to FP in the pediatric population.

When subgroup analyses were performed based on gender, in both studies, the HR point estimates were numerically higher in females versus males. In the adolescent/adult study HR point estimates for males and females were 0.46 and 1.41, respectively; however, 95% CI were overlapping and did not exclude 1. In the pediatric study, for females, the HR was 3.13 with a 95% CI that excluded 1 (1.01, 9.70) compared to 0.86 (0.43, 1.72) in males. These results may suggest that for serious asthma-related events, the risk of FSC compared to FP may be more pronounced for females, however, given that this was a *post-hoc* analysis, definitive conclusions cannot

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be made. In addition, a similar trend was not observed in the other LABA safety trials and the impact of gender will be explored in the planned meta-analysis. These results are summarized in Table 19.

Table 19. Subgroup analysis by gender

	Overall		Male		Female	
SAS115359 (adolescent/adult)	**FSC n=5845**	**FP n=5834**	**FSC n=1983**	**FP n=1947**	**FSC n=3851**	**FP n=3898**
Patient with events	34 (0.6)	33 (0.6)	6 (0.30)	13 (0.67)	28 (0.73)	20 (0.51)
Hazard ratio		1.03		0.46		1.41
(95%CI)		(0.64, 1.66)		(0.17, 1.20)		(0.80,2.51)
SAS115358 (pediatric)	**FSC n=3107**	**FP n=3101**	**FSC n=1920**	**FP n=1874**	**FSC n=1187**	**FP n=1227**
Patients with event	27 (0.87)	21 (0.68)	15 (0.78)	17 (0.91)	12 (1.01)	4 (0.33)
Hazard ratio		1.23		0.86		3.13
(95% CI)		(0.73, 2.27)		(0.43,1.72)		(1.01,9.70)

Source: calculated by FDA safety statistical reviewer

Overall, the results for the primary safety endpoint demonstrate that FSC treatment is non-inferior to FP based on the pre-specified NI-margins indicating that the addition of salmeterol to FP does not result in excessive risk of serious asthma-related events. With regard to asthma-related deaths, as none were observed in either study, definitive conclusions cannot be made with regard to risk of asthma-related death of FSC versus FP. However, based on the lack of asthma-related deaths, the estimated overall risk of asthma-related death in patients taking FSC or FP is low and no higher than approximately 3/18,000, which is reassuring.

7.3.2 Deaths

There were nine deaths in the adolescent/adult study. None were adjudicated as asthma-related by the JAC. In the FSC group there were three deaths (heroin overdose, cerebrovascular accident, and hepatic metastatic carcinoma). There were 6 deaths in the FP group (acute aortic dissection, sudden cardiac death, cerebrovascular accident x2, gastroenteritis, and severe sepsis).

There were no deaths in the pediatric study.

7.3.3 Serious Adverse Events

In the adolescent/adults study (SAS115359), serious adverse events (SAE) occurred in 2% of patients across treatment groups. The most numerically common SAE by far was asthma, with similar absolute numbers and percentages across treatment groups. Overall the report SAEs are fairly typical of what would be expected in an asthma population with this age distribution. SAEs are summarized in Table 20.

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Table 20. Adolescent/Adult Study (SAS115359). Serious adverse events that occurred in ≥2 patients in any group

	FSC (N=5834)	FP (N=5845)
Any Event, n (%)	134 (2)	125 (2)
Respiratory, Thoracic and Mediastinal Disorders	33 (<1)	38 (<1)
Asthma	30 (<1)	28 (<1)
Dyspnea	1 (<1)	5 (<1)
Status asthmaticus	0	2 (<1)
Infections and Infestations	29 (<1)	25 (<1)
Pneumonia	8 (<1)	8 (<1)
Gastroenteritis	1 (<1)	2 (<1)
Influenza	0	3 (<1)
Pyelonephritis	3 (<1)	0
Dengue fever	2 (<1)	0
Typhoid fever	2 (<1)	0
Nervous System Disorders	13 (<1)	10 (<1)
Cerebrovascular accident	4 (<1)	3 (<1)
Transient ischemic attack	2 (<1)	2 (<1)
Injury, Poisoning and Procedural Complications	15 (<1)	7 (<1)
Lower limb fracture	2 (<1)	0
Meniscus injury	2 (<1)	0
Cardiac Disorders	10 (<1)	8 (<1)
Atrial fibrillation	3 (<1)	0
Cardiac failure congestive	1 (<1)	2 (<1)
Angina pectoris	0	2 (<1)
Angina unstable	2 (<1)	0
Gastrointestinal Disorders	10 (<1)	7 (<1)
Gastroesophageal reflux disease	2 (<1)	1 (<1)
Gastritis	0	2 (<1)
Musculoskeletal and Connective Tissue	7 (<1)	4 (<1)
Back pain	2 (<1)	1 (<1)
Intervertebral disc protrusion	2 (<1)	0
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	4 (<1)	7(<1)
Psychiatric Disorders	5 (<1)	6 (<1)
Suicidal ideation	1 (<1)	2 (<1)
Depression	0	2 (<1)
Stress	2 (<1)	0
Pregnancy, Puerperium and Perinatal	2(<1)	7 (<1)
Abortion spontaneous	1 (<1)	4 (<1)
General Disorders and Administration Site	2 (<1)	6 (<1)

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Chest pain	2 (<1)	4 (<1)
Hepatobiliary Disorders	1 (<1)	5 (<1)
Cholelithiasis	1 (<1)	2 (<1)
Metabolism and Nutrition Disorders	6 (<1)	0
Diabetes mellitus	3 (<1)	0
Hypokalemia	2 (<1)	0
Renal and Urinary Disorders	3 (<1)	2 (<1)
Nephrolithiasis	2 (<1)	0
Reproductive System and Breast Disorders	2 (<1)	3 (<1)
Vascular Disorders	3 (<1)	2 (<1)
Hypertension	2 (<1)	0
Blood and Lymphatic System Disorders	3 (<1)	1 (<1)
Anemia	3 (<1)	1 (<1)
Immune System Disorders	2 (<1)	2 (<1)
Skin and Subcutaneous Tissue Disorders	2 (<1)	1 (<1)

Source: SAS115359 CSR; table 19; pp74-75

In the pediatric study (SAS115358) serious adverse events (SAE) occurred in 2% of patients across treatment groups. The most numerically common SAE by far was asthma, and, in contrast to the adolescent/adult study, was numerically more frequent in FSC (n=23) versus FP (n=13) groups, though similar by percentage (<1%). It is worth noting that this is consistent with the protocol defined exacerbations leading to hospitalization (efficacy endpoint) and hospitalizations adjudicated as asthma-related (safety endpoint), both of which were also numerically more common in FSC versus FP groups, though similar in terms of percentages. This consistency across the efficacy endpoint, safety endpoint, and SAEs is likely due to the fact, that, although captured differently, all essentially describe the same outcome: asthma exacerbations associated with hospitalizations. As such, these events are not independent of each other. The small numerical differences is likely reflective of the relatively small number of overall events. Overall the report SAEs are typical of what would be expected in a pediatric asthma population. SAEs are summarized in Table 21.

Table 21. Pediatric Study (SAS115358). Serious adverse events that occurred in ≥2 patients in any group

	FSC (N=3107)	FP (N=3101)
Any Event, n (%)	56 (2)	54 (2)
Infections and infestations	24 (<1)	27 (<1)
Pneumonia	11 (<1)	8 (<1)
Bronchitis	3 (<1)	2 (<1)
Urinary tract infection	1 (<1)	2 (<1)
Gastroenteritis	0	2 (<1)
Tonsillitis	0	2 (<1)
Respiratory, thoracic and mediastinal	24 (<1)	14 (<1)
Asthma	23 (<1)	13 (<1)
Injury, poisoning and procedural	8 (<1)	3 (<1)
Concussion	1 (<1)	2 (<1)
Gastrointestinal disorders	3 (<1)	4 (<1)
Abdominal pain	0	2 (<1)
Immune system disorders	0	3 (<1)
Renal and urinary disorders	2 (<1)	1 (<1)

Source: SAS115358 CSR; table 22; pg72

Overall, the SAE data from both studies do not reveal new safety concerns regarding FSC or FP.

7.3.4 Dropouts and/or Discontinuations

Overall, adverse events leading to treatment withdrawal was not common in either study (~1-3% overall). In both studies, the system organ class (SOC) with the most AEs leading to treatment withdrawal was respiratory thoracic and mediastinal. The most common AE leading to discontinuation was the preferred term asthma. This is unsurprising given the characteristics of the studied populations and as withdrawal criteria included criteria such as need for additional asthma medication above that allowed by the protocol, occurrence of 2 asthma exacerbations requiring systemic steroids within a 13-week period, and occurrence of an exacerbation unresponsive to therapy. All patients who withdrew from treatment continued to be followed for the primary safety endpoint. Adverse events leading to treatment withdrawal for the studies are summarized in Table 22 and Table 23.

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Table 22. Adolescent/Adult study (SAS115359). Adverse events leading to treatment withdrawal

	FSC (N=5834)	FP (N=5845)
Any Event, n (%)	165 (3)	180 (3)
Respiratory, Thoracic and Mediastinal Disorders	87 (1)	114 (2)
Asthma	54 (<1)	84 (1)
Dysphonia	13 (<1)	8 (<1)
Cough	6 (<1)	8 (<1)
Dyspnea	6 (<1)	6 (<1)
Oropharyngeal pain	5 (<1)	3 (<1)
Throat irritation	2 (<1)	2 (<1)
Wheezing	1 (<1)	2 (<1)
Bronchospasm	2 (<1)	0
Rhinorrhea	2 (<1)	0
Infections and Infestations	26 (<1)	20 (<1)
Upper respiratory tract infection	4 (<1)	2 (<1)
Bronchitis	3 (<1)	2 (<1)
Oral candidiasis	3 (<1)	1 (<1)
Pneumonia	2 (<1)	2 (<1)
Candida infection	2 (<1)	1 (<1)
Lower respiratory tract infection	2 (<1)	0
Viral upper respiratory tract infection	0	2 (<1)
Nervous System Disorders	16 (<1)	10 (<1)
Headache	6 (<1)	3 (<1)
Dizziness	3 (<1)	1 (<1)
Cerebrovascular accident	1 (<1)	2 (<1)
Tremor	2 (<1)	1 (<1)
General Disorders and Administration Site Conditions	8 (<1)	10 (<1)
Chest pain	3 (<1)	4 (<1)
Chest discomfort	3 (<1)	1 (<1)
Gastrointestinal Disorders	9 (<1)	6 (<1)
Nausea	2 (<1)	1 (<1)
Tongue eruption	2 (<1)	0
Cardiac Disorders	10 (<1)	3 (<1)
Tachycardia	3 (<1)	1 (<1)
Skin and Subcutaneous Tissue Disorders	5 (<1)	6 (<1)
Urticaria	2 (<1)	2 (<1)
Rash	2 (<1)	1 (<1)
Angioedema	0	2 (<1)
Immune System Disorders	4 (<1)	4 (<1)
Anaphylactic reaction	1 (<1)	2 (<1)
Hypersensitivity	2 (<1)	1 (<1)
Psychiatric Disorders	2 (<1)	6 (<1)

Suicidal ideation	0	2 (<1)
Injury, Poisoning and Procedural Complications	4 (<1)	1 (<1)
Lower limb fracture	2 (<1)	0
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	3 (<1)	2 (<1)
Vascular Disorders	2 (<1)	3 (<1)
Hypertension	2 (<1)	1 (<1)
Musculoskeletal and Connective Tissue Disorders	3 (<1)	1 (<1)
Pregnancy, Puerperium and Perinatal Conditions	1 (<1)	2 (<1)
Investigations	0	2 (<1)

Source: study SAS115359 CSR; table 21; pp 78-79

Table 23. Pediatric study (SAS115358). Adverse events leading to treatment withdrawal

	FSC (N=3107)	FP (N=3101)
Any Event, n (%)	58(<1)	58 (1)
Respiratory, Thoracic and Mediastinal Disorders	38 (<1)	42 (<1)
Asthma	35 (<1)	35 (<1)
Cough	2 (<1)	2 (<1)
Infections and Infestations	16 (<1)	8 (<1)
Pneumonia	8 (<1)	4 (<1)
Bronchitis	2 (<1)	1 (<1)
Upper respiratory tract infection	2 (<1)	0
Nervous System Disorders	5 (<1)	3 (<1)
Headache	2 (<1)	2 (<1)
Tremor	2 (<1)	0
Psychiatric Disorders	4 (<1)	1 (<1)
Insomnia	2 (<1)	0
Skin And Subcutaneous Tissue Disorders	1 (<1)	3 (<1)

Source: derived from data in SAS SAS115358 CSR; tables 6.22 and 6.23;pp384-386

7.3.5 Significant Adverse Events

See section 7.3.1.

7.3.6 Submission Specific Primary Safety Concerns

See section 7.3.1.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Neither the adolescent/adult (SAS115358) nor the pediatric (SAS115359) study collected on all adverse events. As discussed earlier, due the objectives and nature of the studies, only data on SAE and AEs leading to discontinuation were collected.

7.4.2 Laboratory Findings

Clinical labs were not collected as part of the protocols.

7.4.3 Vital Signs

Overall, there were no clinically important differences in mean height, weight or BMI at any time point in this study.

7.4.4 Electrocardiograms (ECGs)

Not performed.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Based on sub-group analysis by FSC and FP dose, clear dose-dependency was not demonstrated (see section 7.3.1)

7.5.2 Time Dependency for Adverse Events

Analyses were not specifically performed regarding time dependency for adverse events.

7.5.3 Drug-Demographic Interactions

See section 7.3.1 and sections 8 and 12 of the approved label

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7.5.4 Drug-Disease Interactions

See section 7.3.1 and sections 8 and 12 of the approved label

7.5.5 Drug-Drug Interactions

Drug-drug interaction information is included in section 7 and 12, of the approved label.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

None

7.6.2 Human Reproduction and Pregnancy Data

See section 8 of the approved label

7.6.3 Pediatrics and Assessment of Effects on Growth

See section 8 of the approved label

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

None

7.7 Additional Submissions / Safety Issues

The sponsor also submitted a meta-analysis of clinical studies completed between January 2008 and December 2014. This meta-analysis included studies that were randomized, double-blind, repeat dose, parallel group or crossover, included ADVAIR and FP arms regardless of formulation, and were funded by GSK. The objective was to compare serious asthma outcomes between ADVAIR and FP treatment groups, where serious asthma outcomes were defined as asthma-related hospitalization, intubation, or death. This included 9 studies with treatment lengths ranging from 5-52 weeks and samples sizes ranging from 7-310 asthma patients. This analysis included a total of 1137 ADVAIR patients and 1165 FP patients. In this analysis, 8 patients from the ADVAIR group experienced a serious asthma outcome compared to 1 in the FP group. This resulted in a common odds ratio of 8.2 (95%CI 1.1, 367.3). Results from this retrospective meta-analysis suggest an increased risk of serious asthma-relate events for FSC compared to FP, in contrast to the prospective adolescent/adult and pediatric studies. However, as this was a retrospective analysis with data collected in a post-hoc

manner in a relatively small number of patients, especially in comparison to the adolescent/adult (SAS115359) and pediatric (SAS115358) studies. Moreover the adolescent/adult (SAS115359) and pediatric (SAS115358) studies were specifically designed and powered to prospectively evaluate for the risk of serious asthma-related events in FSC versus FP treated patients. As such, concerns raised by the meta-analysis are fully addressed by studies SAS115359 and SAS115358.

8 Postmarket Experience

Advair was originally approved on August 24, 2000. Aside from the LABA safety concerns which were addressed in this application, there have been no postmarketing reports which would affect the risk/benefit of this product.

Reference ID: 4138257

9 Appendices

9.1 Literature Review/References

1. Castle W, Fuller R, Palmer J. Serevent Nationwide Surveillance Study: Comparison of Salmeterol with Salbutamol in Asthmatic Patients Who Require Regular Bronchodilator Treatment. BMJ 1993; 306 (6884): 1034-1037.
2. Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial: A Comparison of Usual Pharmacotherapy for Asthma or Usual Pharmacotherapy plus Salmeterol. Chest 2006; 129: 15-26.
3. Martinez, FD. Safety of Fluticasone plus Salmeterol in Asthma — Reassuring Data, but No Final Answer. NEJM 2016; 374:1887-1888
4. Peters SP, Bleecker ER, Canonica GW. Serious Asthma Events with Budesonide plus Formoterol vs. Budesonide Alone. NEJM 2016; 375:850-860.
5. FDA Drug Safety Communication: Drug labels now contain updated recommendations on the appropriate use of long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs), June 2, 2010. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm; accessed July 7, 2017.
6. July 13-14, 2005, FDA PADAC Mtg [http://www.fda.gov/ohrms/dockets/ac/cder05.html#PulmonaryAllergy]
7. FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs), February 18, 2010. Available at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm; accessed July 7, 2017
8. FDA Drug Safety Communication: FDA requires post-market safety trials for Long-Acting Beta-Agonists, April 15, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm251512.htm; accessed July 7, 2017.
9. FDA Drug Safety Communication: FDA requires post-market safety trials for Long-Acting Beta-Agonists, April 15, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm251512.htm; accessed July 7, 2017.
10. FDA Drug Safety Communication: FDA requires post-market safety trials for Long-Acting Beta-Agonists, April 15, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm251512.htm; accessed July 7, 2017.

9.2 Labeling Recommendations

The results of the two completed Advair trials will be added to the Advair Diskus product labeling. The results will be described in Section 14 and also noted in the existing Warning for serious asthma outcomes. During the review period, it was noted that inclusion of the results of these trials in the Advair product label was inconsistent with the Boxed Warning and Warning for serious asthma outcomes. For example, because the Boxed Warning is primarily based upon SMART which emphasizes asthma related death with single ingredient LABA use, the results of these trials with ICS/LABA are reassuring and there were no deaths. The results also showed a benefit in asthma exacerbations requiring oral corticosteroid use. In addition, during the review period, the results for the other LABA safety trials with Symbicort and Dulera became available. Because the other completed LABA safety trials met the primary objective, the Division revisited the approach to class labeling for the ICS/LABA products. The Division determined that if the results of the LABA safety trials were confirmed by FDA, the results from these trials supported removal of the Boxed Warning for asthma related death from the ICS/LABA products. There was no need for an Advisory Committee to discuss the results. The sponsors of ICS/LABA products who conducted LABA safety trials were contacted with this recommendation and were asked to submit labeling supplements or amended labeling for existing supplements. GSK has submitted revised labeling and the PDUFA clock will be extended. At the time of finalization of this review, labeling negotiations are ongoing.

9.3 Advisory Committee Meeting

At the time the LABA safety PMR was issued, the Division had planned to have an Advisory Committee meeting to discuss the results of these studies individually and in aggregate, as well as the impact of these results on the asthma-related death BW and class labeling for LABA containing products. However, given the submitted results from the Advair LABA safety studies reviewed in this document, preliminary review of the submitted data from the Symbicort LABA safety study, and the publically available results for the Symbicort and Dulera LABA safety studies, results across all completed LABA PMR studies appears consistent and all studies met the pre-specified non-inferiority margin for the primary safety endpoint of serious asthma-related events. Provided that the sponsors' analyses for serious asthma-related outcomes are confirmed by the Division, AC discussion is not required for removal to the BW for LABA/ICS products. Thus, no advisory meeting will be held for this specific application or the LABA safety studies in aggregate prior to removal of the BW.

9.4 Clinical Investigator Financial Disclosure Review Template

Clinical Investigator Financial Disclosure

Reference ID: 4138257

Review Template

Application Number: 021077

Submission Date(s): 10/03/16

Applicant: GlaxoSmithKline

Product: Advair Diskus

Reviewer: Robert Lim

Date of Review: 08/11/17

Covered Clinical Study (Name and/or Number): SAS 115358 and SAS115359

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 5317		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 18		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 16 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 2		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) (582)		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

From trials SAS115358 and SAS115359, GSK certified the absence of financial arrangement for 5299 primary and sub-investigators. There were 16 investigators with significant payments of other sorts and 2 with significant equity interest. These significant payments of other sorts and equity interests were determined to not have significant impact upon the conduct of this clinical trial, given that the study was randomized, double-blinded, active-controlled trial, with objective safety and exacerbation related endpoints, and since each investigator was only responsible for enrolling a small number of patients to this multi-center trial relative to the total number of patients enrolled. Moreover, for the primary endpoint of serious asthma-related events, these events were adjudicated by an independent adjudication committee.

Reference ID: 4138257

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/s/

ROBERT H LIM
08/11/2017

SALLY M SEYMOUR
08/11/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021077Orig1s056

PRODUCT QUALITY REVIEW(S)

CHEMIST'S REVIEW *Review #1*	1. ORGANIZATION BRANCH 1/DPMA1/OLDP/OPQ	2. NDA NUMBER **021077**
3. NAME AND ADDRESS OF APPLICANT *(City and State)* GlaxoSmithKline Intellectual Property Ltd. England 980 Great West Road Brentford, Middlesex UK TW8 9GS Tel: 1-888-825-5249; Fax: +1 919-315-0033 E-mail Address: mary.v.sides@gsk.com **Name and Title of Applicant's Responsible Official** Kevin C. Fitzgerald, Senior Director, Global Regulatory Affairs Tel: 1 919-483-5727, Fax: 1 919-315-0033 E-mail: kevin.c.fitzgerald@gsk.com		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S) **S-056; SE; SDN 2766** **S-057; SE; SDN 2767** Letter Date: 10/3/16 Stamp Date: 10/3/16 **S-056; SDN 2853** Letter Date: 7/13/16 Stamp Date: 7/13/16 **Due Date: 8/3/17**
6. NAME OF DRUG ADVAIR DISKUS®	7. NONPROPRIETARY NAME fluticasone propionate/salmeterol	
8. SUPPLEMENT PROVIDES FOR: Labeling changes based on Studies SAS115359 (AUSTRI) and SAS115358 (VESTRI).		
9. PHARMACOLOGICAL CATEGORY Treatment of asthma in patients aged 4 years and older. Treatment of COPD.	10. HOW DISPENSED RX x_OTC ___	11. RELATED IND/NDA/DMF
12. DOSAGE FORM(S) Inhaler	13. POTENCY 100/50 mcg, 250/50 mcg, 500/50 mcg	
14. CHEMICAL NAME AND STRUCTURE **Fluticasone propionate**: Chemical name: S-(fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate **Salmeterol xinafoate:** Chemical name: 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3 benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate Refer to page 2 of this review.		15. RECORDS AND REPORTS CURRENT YES__NO__ REVIEWED YES__NO__
16. COMMENTS: Sections 11 (**DESCRIPTION**) and 16 (**HOW SUPPLIED/STORAGE AND HANDLING)** were reviewed.		
17. CONCLUSIONS AND RECOMMENDATIONS The labeling revision is acceptable from CMC standpoint.		
18. REVIEWER NAME Chong-Ho Kim, Ph.D.	SIGNATURE	DATE COMPLETED July 21, 2017

Background:

The purpose of this supplemental application is to share with the Division the results of the two post-marketing safety studies (SAS115358 and SAS115359) and to propose the inclusion of the safety and efficacy data in the labeling for ADVAIR DISKUS. This supplement also provides for revised labeling in accordance with 21CFR 201.57(c)(9)(i) through (iii), in compliance with the December 4, 2014 Final Rule describing requirements for the Pregnancy and Lactation section of the labeling.

Review:

1.14 Labeling

1.14.1 Draft Labeling

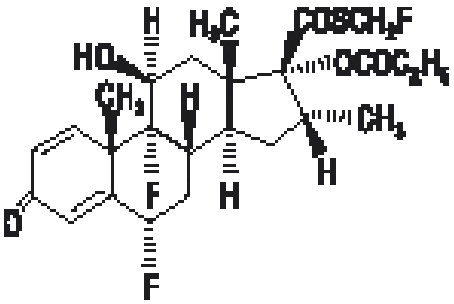
1.14.1.2 Draft Labeling Text - Clean

There are no changes in:

11 DESCRIPTION

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

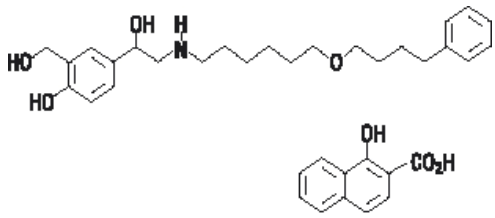
One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid having the chemical name *S*-(fluoromethyl) 6α, 9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

The other active component of ADVAIR DISKUS is salmeterol xinafoate, a beta$_2$-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. It has the chemical

name 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]
methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate and the following chemical structure:



Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is $C_{25}H_{37}NO_4 \bullet C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

ADVAIR DISKUS is a purple plastic inhaler containing a foil blister strip. Each blister on the strip contains a white powder mix of micronized fluticasone propionate (100, 250, or 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins). After the inhaler is activated, the powder is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized *in vitro* test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds.

In adult subjects with obstructive lung disease and severely compromised lung function (mean FEV_1 20% to 30% of predicted), mean peak inspiratory flow (PIF) through the DISKUS® inhaler was 82.4 L/min (range: 46.1 to 115.3 L/min).

Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to 50 years) subjects with asthma inhaling maximally through the DISKUS inhaler show mean PIF of 122.2 L/min (range: 81.6 to 152.1 L/min). Inhalation profiles for pediatric subjects with asthma inhaling maximally through the DISKUS inhaler show a mean PIF of 75.5 L/min (range: 49.0 to 104.8 L/min) for the 4-year-old subject set (N = 20) and 107.3 L/min (range: 82.8 to 125.6 L/min) for the 8-year-old subject set (N = 20).

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

16 HOW SUPPLIED /STORAGE AND HANDLING

ADVAIR DISKUS 100/50 is supplied as a disposable purple plastic inhaler containing a foil blister strip with 60 blisters. The inhaler is packaged in a plastic-coated, moisture-protective foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional pack containing 14 blisters (NDC 0173-0695-04).

ADVAIR DISKUS 250/50 is supplied as a disposable purple plastic inhaler containing a foil blister strip with 60 blisters. The inhaler is packaged in a plastic-coated, moisture-protective foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional pack containing 14 blisters (NDC 0173-0696-04).

ADVAIR DISKUS 500/50 is supplied as a disposable purple plastic inhaler containing a foil blister strip with 60 blisters. The inhaler is packaged in a plastic-coated, moisture-protective foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional pack containing 14 blisters (NDC 0173-0697-04).

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. Keep out of reach of children.

ADVAIR DISKUS should be stored inside the unopened moisture-protective foil pouch and only removed from the pouch immediately before initial use. Discard ADVAIR DISKUS 1 month after opening the foil pouch or when the counter reads "0" (after all blisters have been used), whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler apart.

Amendment dated July 13, 2017 (SDN 2853)

The purpose of this submission is to replace the draft labeling in S056 with draft labeling incorporating revisions discussed at the June 15, 2017 teleconference with the Division and described in the June 16, 2017 Information Request. This amendment contains the following:

- Draft labeling (Annotated, Proposed, and Clean) within m1.14.1
- Justification for removal of Boxed Warning within m1.11.3
- The Division also requested submission minutes for all Joint Adjudication Committee and Joint Oversight Steering Committee meetings and teleconferences. The information is included in m5.3.5.1.

GSK has proposed revisions to the Indications Section (1.1) of the label for ADVAIR DISKUS. As described in m1.11.3, the data from the completed safety studies showed no increased risk associated with LABA use compared to ICS alone; therefore, the asthma indication has been revised to the wording approved for ICS/LABA products prior to the addition of the LABA safety warning. Additionally, the proposed indication is consistent with the recently approved SPIRIVA RESPIMAT (tiotropium bromide) inhalation spray asthma indication. Lastly, the information concerning appropriate patients to treat and dose based on prior therapy and disease severity is included in Section 2, which is consistent with the recently approved DULERA (mometasone furoate and formoterol fumarate dihydrate) inhalation aerosol label.

1.14. Labeling

1.14.1. Draft Labeling

1.14.1.2. Annotated Draft Labeling Text

Evaluation: *Acceptable*
There are no changes made for "DESCRIPTION" and "HOW SUPPLIED/STORAGE AND HANDLING" Sections.

CONCLUSION AND RECOMMENDATION

Sections 11 (**DESCRIPTION**) and 16 (**HOW SUPPLIED/STORAGE AND HANDLING)** were reviewed.

The labeling revision is acceptable from CMC standpoint.

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/s/

CHONG HO KIM
07/23/2017

RAMESH RAGHAVACHARI
07/25/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021077Orig1s056

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION - ADDENDUM

Application number:	21077
Supporting document/s:	SDN #2766 and 2767 (Supplements #056 and 057)
Applicant's letter date:	October 3, 2016
CDER stamp date:	October 3, 2016
Product:	ADVAIR DISKUS® (fluticasone propionate and salmeterol xinafoate inhalation powder)
Indication:	Asthma and COPD
Applicant:	GlaxoSmithKline
Review Division:	Pulmonary, Allergy, and Rheumatology Products
Reviewer//Team Leader:	Timothy W. Robison, Ph.D., D.A.B.T.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Nina Ton

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 21077 are owned by GSK or are data for which GSK has obtained a written right of reference. Any information or data necessary for approval of NDA 21077 that GSK does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 21077.

Reference ID: 4135017

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1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS 3
1.3 RECOMMENDATIONS 3

Reference ID: 4135017

1 Executive Summary

1.1 Introduction

This is an Addendum to the review dated June 2, 2016. The principal change was to add the statement "Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits" to the *Animal Data* in Section 8.1. This statement is present in the labels for FLOVENT DISKUS and FLOVENT HFA, which have undergone PLLR conversion. The Sponsor inadvertently left this statement out of the current label under review. In addition, there were some minor editorial changes in the label.

1.2 Brief Discussion of Nonclinical Findings

There are complete nonclinical programs for monoproducts, fluticasone propionate and salmeterol xinafoate, as well as the combination of the two drugs. No new nonclinical pharmacology or toxicology studies were submitted in support of this supplement.

1.3 Recommendations

1.3.1 Approvability

The present nonclinical review was limited to the PLLR conversion of the product label.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

This is an Addendum to the review dated June 2, 2016. The nonclinical review of the proposed product labels was limited to Sections 8.1 (Pregnancy), 8.2 (Lactation), and 13 (Nonclinical Toxicology). Additions are shown as underlined text and deletions are shown as strikethrough ~~text~~.

8 USE IN SPECIFIC POPULATIONS

8.1 PREGNANCY

Risk Summary

There are no randomized clinical studies of ADVAIR DISKUS or individual monoproducts, fluticasone propionate and salmeterol xinafoate in pregnant women. There are clinical considerations with the use of ADVAIR DISKUS in pregnant women *[see Clinical Considerations].* In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight and/or skeletal variations, in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a mcg/m^2 basis *[see* (b) (4) *Data]*. However, fluticasone propionate administered via inhalation to rats decreased fetal body weight, but did not induce teratogenicity at a maternal toxic dose less than the MRHDID on a mcg/m^2 basis *[see* (b) (4) *Data]*. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. Oral administration of salmeterol

Reference ID: 4135017

to pregnant rabbits caused teratogenicity characteristic of beta-adrenoceptor stimulation at maternal doses approximately (b) (4) times the MRHDID on an AUC basis. These adverse effects generally occurred at large multiples of the MRHDID when salmeterol was administered by the oral route to achieve high systemic exposures. No such effects occurred at an oral salmeterol dose approximately 20 times the MRHDID *[see Data]*. (b) (4) (b) (4) The estimated risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryofetal Risk: In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal adverse outcomes such as pre-eclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control.

Data

(b) (4)

approximately 100 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 1000 mcg/kg/day).

In an embryo/fetal development study with pregnant mice that received the combination of ~~Following~~ subcutaneous administration of fluticasone propionate and oral administration of salmeterol at doses of 0/1400, 40/0, 10/200, 40/1400, or 150/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) [redacted] (b) (4) during the period of organogenesis, findings were generally consistent with the individual monoproducts and there was no exacerbation of expected fetal effects [redacted] (b) (4) Cleft palate, fetal death, increased implantation loss, and delayed ossification were observed in mouse fetuses when combining fluticasone propionate at a dose approximately 0.7 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 150 mcg/kg/day) and salmeterol at a dose approximately 490 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 10,000 mcg/kg/day). [redacted] (b) (4) No developmental toxicity was observed at combination doses of fluticasone propionate up to approximately [redacted] (b) (4) 0.2 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 40 mcg/kg) and doses of salmeterol up to approximately [redacted] (b) (4) 70 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of [redacted] (b) (4) mcg/kg).

Fluticasone Propionate: In embryofetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone propionate was teratogenic in both species. Omphalocele, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, at a dose approximately equivalent to the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 100 mcg/kg/day). The rat NOAEL was observed at approximately 0.3 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 30 mcg/kg/day). Cleft palate and fetal skeletal variations were observed in mouse fetuses at a dose approximately 0.2 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.07 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryofetal development study with pregnant rats dosed by the inhalation route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.25 times the MRHDID (on a mcg/m^2 basis with a maternal inhalation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose approximately 0.05 times the MRHDID (on a mcg/m^2 basis with a maternal inhalation dose of 5.5 mcg/kg/day).

In an embryofetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced

Reference ID: 4135017

reductions of fetal body weights, in the presence of maternal toxicity, at doses approximately 0.012 times the MRHDID and higher (on a mcg/m^2 basis with a maternal subcutaneous dose of 0.57 mcg/kg/day). Teratogenicity was evident based upon a finding of cleft palate for 1 fetus at a dose approximately 0.08 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 4 mcg/kg/day). The NOAEL was observed in rabbit fetuses with a dose approximately 0.002 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).

Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

In a pre- and post-natal development study in pregnant rats dosed by the subcutaneous route from late gestation through delivery and lactation (Gestation Day 17 to Postpartum Day 22), fluticasone propionate was not associated with decreases in pup body weight, and had no effects on developmental landmarks, learning, memory, reflexes, or fertility at doses up to 0.5 times the MRHDID (on a mcg/m^2 basis with maternal subcutaneous doses up to 50 mcg/kg/day).

Salmeterol: In three embryo/fetal development studies, pregnant rabbits received oral administration of salmeterol at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. In pregnant Dutch rabbits administered salmeterol doses approximately 50 times the MRHDID (on an AUC basis at maternal oral doses of 1000 mcg/kg/day and higher), fetal toxic effects were observed characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. (b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted] No such effects occurred at a salmeterol dose approximately (b) (4) times the MRHDID (on an AUC basis at a maternal oral dose of 600 mcg/kg/day). New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at a salmeterol dose approximately 2000 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 10,000 mcg/kg/day). (b) (4) [redacted] (b) (4) [redacted]

In two embryo/fetal development studies, pregnant rats received salmeterol by oral administration at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. Salmeterol produced no maternal toxicity or embryo/fetal effects at doses up to 973 times the MRHDID (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

In a peri- and post-natal development study in pregnant rats dosed by the oral route from late gestation through delivery and lactation, salmeterol at a dose 973 times the

MRHDID (on a mcg/m^2 basis with a maternal oral dose of 10,000 mcg/kg/day) was fetotoxic and decreased the fertility of survivors.

Salmeterol xinafoate crossed the placenta following oral administration to mice and rats.

(b) (4)

8.2 Lactation

Risk Summary

There are no available data on the presence of fluticasone propionate or salmeterol in human milk, the effects on the breastfed child, or the effects on milk production. Other corticosteroids have been detected in human milk. However, fluticasone propionate and salmeterol concentrations in plasma after inhaled therapeutic doses are low and therefore concentrations in human breast milk are likely to be correspondingly low *[see Clinical Pharmacology (12.3)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ADVAIR DISKUS and any potential adverse effects on the breastfed child from ADVAIR DISKUS or from the underlying maternal condition.

Data

Animal Data: Subcutaneous administration of tritiated fluticasone propionate at a dose in lactating rats approximately 0.08 times the MRHDID for adults (on a mcg/m^2 basis) resulted in measurable levels in milk. Oral administration of salmeterol at dose in lactating rats (b) (4) approximately 973 times the MRHDID for adults (on a mcg/m^2 basis) (b) (4) resulted in measurable levels in milk.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone Propionate

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 5 and 10 times the MRHDID for adults and children, respectively, on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to the MRHDID for adults and children, respectively, on a mcg/m^2 basis) for 104 weeks.

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

Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 0.5 times the MRHDID for adults on a mcg/m^2 basis).

Salmeterol

In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of (b) (4) mcg/kg and above (approximately 20 times the MRHDID for adults and children based on comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at (b) (4) 200 mcg/kg (approximately 3 times the MRHDID for adults and children based on com arison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of (b) (4) 680 mcg/kg and above (approximately 66 and (b) (4) 35 times the MRHDID for adults and children, respectively, on a mcg/m^2 basis). No t ors were seen at (b) (4) 210 mcg/kg (approximately 20 and (b) (4) 10 times the MRHDID for adults and children, respectively, on a mcg/m^2 basis). The findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test.

Fertility and reproductive performance were unaffected in male and female rats at oral doses up to 2000 mcg/kg (approximately 195 times the MRHDID for adults on a mcg/m^2 basis).

Reference ID: 4135017

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/s/

TIMOTHY W ROBISON
08/04/2017
Addendum to Review dated June 2, 2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	21077
Supporting document/s:	SDN #2766 and 2767 (Supplements #056 and 057)
Applicant's letter date:	October 3, 2016
CDER stamp date:	October 3, 2016
Product:	ADVAIR DISKUS® (fluticasone propionate and salmeterol xinafoate inhalation powder)
Indication:	Asthma and COPD
Applicant:	GlaxoSmithKline
Review Division:	Pulmonary, Allergy, and Rheumatology Products
Reviewer//Team Leader:	Timothy W. Robison, Ph.D., D.A.B.T.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Nina Ton

Template Version: September 1, 2010

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Reference ID: 4106908

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1 Executive Summary

1.1 Introduction

The Sponsor provided revised product labeling to comply with the Pregnancy and Lactation Labeling Rule as part of the present supplement that contained two postmarketing clinical studies.

1.2 Brief Discussion of Nonclinical Findings

There are complete nonclinical programs for monoproducts, fluticasone propionate and salmeterol xinafoate, as well as the combination of the two drugs. No new nonclinical pharmacology or toxicology studies were submitted in support of this supplement.

1.3 Recommendations

1.3.1 Approvability

The present nonclinical review was limited to the PLLR conversion of the product label.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The nonclinical review of the proposed product labels was limited to Sections 8.1 (Pregnancy), 8.2 (Lactation), and 13 (Nonclinical Toxicology). Additions are shown as underlined text and deletions are shown as strikethrough ~~text~~.

8 USE IN SPECIFIC POPULATIONS

8.1 PREGNANCY

Risk Summary

There are no randomized clinical studies of ADVAIR DISKUS or individual monoproducts, fluticasone propionate and salmeterol xinafoate in pregnant women. There are clinical considerations with the use of ADVAIR DISKUS in pregnant women *[see Clinical Considerations].* In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight and/or skeletal variations, in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a mcg/m^2 basis *[see* (b) (4) *Data]*. However, fluticasone propionate administered via inhalation to rats decreased fetal body weight, but did not induce teratogenicity at a maternal toxic dose less than the MRHDID on a mcg/m^2 basis *[see* (b) (4) *Data]*. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. Oral administration of salmeterol to pregnant rabbits caused teratogenicity characteristic of beta-adrenoceptor stimulation at maternal doses approximately (b) (4) times the MRHDID on an AUC basis. These adverse effects generally occurred at large multiples of the MRHDID when salmeterol was administered by the oral route to achieve high systemic exposures. No such effects occurred at an oral salmeterol dose approximately 20 times the MRHDID *[see Data].* (b) (4)

(b) (4)

(b) (4) The estimated risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryofetal Risk: In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal adverse outcomes such as pre-eclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control.

Data

(b) (4)

In an embryo/fetal development study with pregnant mice that received the combination of ~~Following~~ subcutaneous administration of fluticasone propionate and oral administration of salmeterol at doses of 0/1400, 40/0, 10/200, 40/1400, or 150/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) (b) (4) (b) (4) during the period of organogenesis, findings were generally consistent with the individual

monoproducts and there was no exacerbation of expected fetal effects [redacted] (b) (4) Cleft palate, fetal death, increased implantation loss, and delayed ossification were observed in mouse fetuses when combining fluticasone propionate at a dose approximately 0.7 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 150 mcg/kg/day) and salmeterol at a dose approximately 490 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 10,000 mcg/kg/day). [redacted] (b) (4) No developmental toxicity [redacted] (b) (4) nate up to approximately [redacted] (b) (4) 0.2 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 40 mcg/kg) and doses of salmeterol up to approximately [redacted] (b) (4) 70 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of [redacted] (b) (4) mcg/kg).

Fluticasone Propionate: In embryofetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone propionate was teratogenic in both species. Omphalocele, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, at a dose approximately equivalent to the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 100 mcg/kg/day). The rat NOAEL was observed at approximately 0.3 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 30 mcg/kg/day). Cleft palate and fetal skeletal variations were observed in mouse fetuses at a dose approximately 0.2 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.07 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryofetal development study with pregnant rats dosed by the inhalation route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.25 times the MRHDID (on a mcg/m^2 basis with a maternal inhalation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose approximately 0.05 times the MRHDID (on a mcg/m^2 basis with a maternal inhalation dose of 5.5 mcg/kg/day).

In an embryofetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced reductions of fetal body weights, in the presence of maternal toxicity, at doses approximately 0.012 times the MRHDID and higher (on a mcg/m^2 basis with a maternal subcutaneous dose of 0.57 mcg/kg/day). Teratogenicity was evident based upon a finding of cleft palate for 1 fetus at a dose approximately 0.08 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 4 mcg/kg/day). The NOAEL was observed in rabbit fetuses with a dose approximately 0.002 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).

[redacted] (b) (4)

and had no effects on developmental landmarks, learning, memory, reflexes, or fertility at doses up to 0.5 times the MRHDID (on a mcg/m^2 basis with maternal subcutaneous doses up to 50 mcg/kg/day).

Salmeterol: In three embryo/fetal development studies, pregnant rabbits received oral administration of salmeterol at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. In pregnant Dutch rabbits administered salmeterol doses approximately 50 times the MRHDID (on an AUC basis at maternal oral doses of 1000 mcg/kg/day and higher), fetal toxic effects were observed characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. (b) (4) (b) (4) (b) (4) No such effects occurred at a salmeterol dose approximately (b) (4) times the MRHDID (on an AUC basis at a maternal oral dose of 600 mcg/kg/day). New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at a salmeterol dose approximately 2000 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 10,000 mcg/kg/day). (b) (4) (b) (4)

In two embryo/fetal development studies, pregnant rats received salmeterol by oral administration at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. Salmeterol produced no maternal toxicity or embryo/fetal effects at doses up to 973 times the MRHDID (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

In a peri- and post-natal development study in pregnant rats dosed by the oral route from late gestation through delivery and lactation, salmeterol at a dose 973 times the MRHDID (on mcg/m^2 basis with a maternal oral dose of 10,000 mcg/kg/day) was fetotoxic and decreased the fertility of survivors.

Salmeterol xinafoate crossed the placenta following oral administration to mice and rats.

(b) (4)

8.2 Lactation

Risk Summary

There are no available data on the presence of fluticasone propionate or salmeterol in human milk, the effects on the breastfed child, or the effects on milk production. Other corticosteroids have been detected in human milk. However, fluticasone propionate and salmeterol concentrations in plasma after inhaled therapeutic doses are low and therefore concentrations in human breast milk are likely to be correspondingly low *[see Clinical Pharmacology (12.3)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ADVAIR DISKUS and any potential adverse effects on the breastfed child from ADVAIR DISKUS or from the underlying maternal condition.

Data

Animal Data: Subcutaneous administration of tritiated fluticasone propionate at a dose in lactating rats approximately 0.08 times the MRHDID for adults (on a mcg/m^2 basis) resulted in measurable levels in milk. Oral administration of salmeterol at dose in lactating rats (b) (4) approximately 973 times the MRHDID ~~for adults~~ (on a mcg/m^2 basis) (b) (4) resulted in measurable levels in milk.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone Propionate

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 5 and 10 times the MRHDID for adults and children, respectively, on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to the MRHDID for adults and children, respectively, on a mcg/m^2 basis) for 104 weeks.

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

Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 0.5 times the MRHDID for adults on a mcg/m^2 basis).

Salmeterol

In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of (b) (4) mg/kg and above (approximately 20 times the MRHDID for adults and children based on comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at (b) (4) 200 mcg/kg (approximately 3 times the MRHDID for adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas

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and ovarian cysts at doses of [(b)(4)]380 mcg/kg and above (approximately 66 and [(b)(4)]35 times the MRHDID for adults and children, respectively, on a mcg/m^2 basis). No tumors were seen at [(b)(4)]210 mcg/kg (approximately 20 and [(b)(4)]10 times the MRHDID for adults and children, respectively, on a mcg/m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test.

Fertility and reproductive performance were unaffected in male and female rats at oral doses up to 2000 mcg/kg (approximately 195 times the MRHDID for adults on a mcg/m^2 basis).

2 Drug Information

2.1 Drug

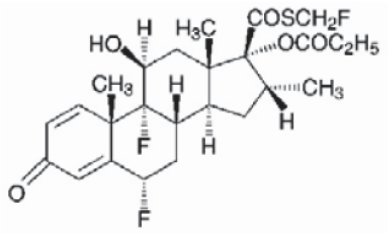
Advair Diskus® is a combination of fluticasone propionate and salmeterol xinafoate.

Generic Name: Fluticasone propionate

Chemical Name: S-(fluoromethyl)6(alpha),9-difluoro-11(beta)-17-dihydroxy-16(alpha)-methyl-3-oxoandrosta-1,4-diene-17(beta)-carbothioate, 17-propionate

Molecular Formula/Molecular Weight: $C_{25}H_{31}F_3O_5S$ / 500.6 g/mole

Structure:



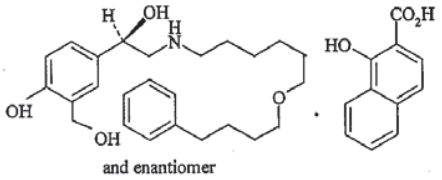
Pharmacologic class: Corticosteroid

Generic Name: Salmeterol xinafoate

Chemical Name: 4-hydroxy-α'-[[[6-4-phenylbutoxyl)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-napthelene carboxylate

Molecular Formula/Molecular Weight: $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$ / 603.8 g/mole

Structure:



Pharmacologic Class: Long acting β_2-adrenergic agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

ADVAIR HFA (NDA 21254)
FLOVENT DISKUS (NDA 20833)
FLOVENT HFA (NDA 21433)

2.6 Proposed Clinical Population and Dosing Regimen

ADVAIR DISKUS is a combination product containing a corticosteroid and a LABA indicated for:

- Treatment of asthma in patients aged 4 years and older
- Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD)

Important limitation:

- Not indicated for relief of acute bronchospasm

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For oral inhalation only.

- Treatment of asthma in patients aged 12 years and older: 1 inhalation of ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR DISKUS 500/50 twice daily. Starting dosage is based on asthma severity.
- Treatment of asthma in patients aged 4 to 11 years: 1 inhalation of ADVAIR DISKUS 100/50 twice daily.
- Maintenance treatment of COPD: 1 inhalation of ADVAIR DISKUS 250/50 twice daily.

2.7 Regulatory Background

Advair Diskus® was approved on August 24, 2000.

3 Studies Submitted

3.1 Studies Reviewed

No new nonclinical pharmacology or toxicology studies were submitted as part of this supplement.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

1. Pharmacology and Toxicology Review of NDA 20833 dated December 9, 1998
2. Pharmacology and Toxicology Review of NDA 21433 dated December 20, 2002
3. Pharmacology and Toxicology Review of NDA 21077 dated January 24, 2000
4. Pharmacology and Toxicology Reviews of NDAs 20844 and 21433 dated July 21, 2016 and September 9, 2016

11 Integrated Summary and Safety Evaluation

The Sponsor provided revised product labeling to comply with the Pregnancy and Lactation Labeling Rule as part of the present supplement that contained two postmarketing clinical studies. There are complete nonclinical programs for monoproducts, fluticasone propionate and salmeterol xinafoate, as well as the combination of the two drugs. No new nonclinical pharmacology or toxicology studies were submitted in support of this supplement. The present nonclinical review was limited to the PLLR conversion of the product label.

Labeling in Sections 8.1 and 8.2 was revised to be consistent with current practices for compliance with the PLLR. There were some minor revisions in Section 13.1. All nonclinical doses for fluticasone propionate and salmeterol xinafoate in Sections 8.1, 8.2, and 13.1 were revised to a mcg/kg/day basis rather than mcg/kg/day for fluticasone propionate and mg/kg/day for salmeterol xinafoate. Dose ratios were expressed on a mcg/m^2, which has no impact; however, it should be noted that clinical doses of fluticasone propionate and salmeterol xinafoate in the product label have always been expressed on a mcg/day basis. Labeling for fluticasone propionate in Sections 8.1, 8.2

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and 13.1 was matched to Labeling Supplements #31 and #32 for Flovent Diskus (NDA 20833) approved on July 28, 2016 and October 5, 2016, respectively.

Labeling Review:
The nonclinical review of the proposed product labels was limited to Sections 8.1 (Pregnancy), 8.2 (Lactation), and 13 (Nonclinical Toxicology). Additions are shown as underlined text and deletions are shown as strikethrough ~~text~~.

Reference ID: 4106908

8 USE IN SPECIFIC POPULATIONS

8.1 PREGNANCY

Current Label	Sponsor's Recommended Changes	Reviewer's Recommended Changes
Teratogenic Effects Pregnancy Category C. There are no adequate and well-controlled trials with ADVAIR DISKUS in pregnant women. Corticosteroids and beta2-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal reproduction studies are not always predictive of human response, ADVAIR DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking ADVAIR DISKUS.	Risk Summary There are no randomized clinical studies of ADVAIR DISKUS (b) (4) (b) (4) There are clinical considerations with the use of ADVAIR DISKUS in pregnant women *[see Clinical Considerations]*. In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight and/or skeletal variations, in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a (b) (4) /m^2 basis *[see* (b) (4) *Dat* However, fluticasone propionate administered via inhalation to rats decreased fetal body weight, but did not induce teratogenicity at a maternal toxic dose less than the MRHDID on a (b) (4) /m^2 basis *[see* (b) (4) *Data]*. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. (b) (4) (b) (4)	Risk Summary There are no randomized clinical studies of ADVAIR DISKUS or individual monoproducts, fluticasone propionate and salmeterol xinafoate in pregnant women. There are clinical considerations with the use of ADVAIR DISKUS in pregnant women *[see Clinical Considerations]*. In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight and/or skeletal variations, in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a mcg/m^2 basis *[see* (b) (4) *Data]*. However, fluticasone propionate administered via inhalation to rats decreased fetal body weight, but did not induce teratogenicity at a maternal toxic dose less than the MRHDID on a mcg/m^2 basis *[see* (b) (4) *Data]*. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. Oral administration of salmeterol to pregnant rabbits caused teratogenicity characteristic of beta-adrenoceptor stimulation at maternal doses approximately (b) (4) times the MRHDID on an AUC basis. These adverse effects generally occurred at large multiples of the MRHDID when salmeterol was administered by the oral route to achieve high systemic exposures. No such effects occurred at an oral salmeterol dose approximately 20 times the MRHDID *[see Data]*. (b) (4)

	In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Clinical Considerations *Disease-Associated Maternal and/or Embryofetal Risk:* In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal adverse outcomes such as pre-eclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control. Data	(b) (4) (b) (4) The estimated risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Clinical Considerations *Disease-Associated Maternal and/or Embryofetal Risk:* In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal adverse outcomes such as pre-eclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control. Data
Fluticasone Propionate and Salmeterol: In the mouse reproduction assay, fluticasone propionate by the subcutaneous route at a dose approximately 3/5 the maximum recommended human daily inhalation dose (MRHDID) (on a mg/m^2 basis at a maternal subcutaneous dose of 150 mcg/kg/day) combined with oral salmeterol at a dose approximately 410 times the MRHDID (on a mg/m^2 basis at a	(b) (4)	(b) (4)

maternal oral dose of 10 mg/kg/day) produced cleft palate, fetal death, increased implantation loss, and delayed ossification. These observations are characteristic of glucocorticoids. No developmental toxicity was observed at combination doses of fluticasone propionate subcutaneously up to approximately 1/6 the MRHDID (on a mg/m^2 basis at a maternal subcutaneous dose of 40 mcg/kg/day) and doses of salmeterol up to approximately 55 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 1.4 mg/kg/day). In rats, combining fluticasone propionate subcutaneously at a dose equivalent to the MRHDID (on a mg/m^2 basis at a maternal subcutaneous dose of 100 mcg/kg/day) and a dose of salmeterol at approximately 810 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 10 mg/kg/day) produced decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone. No such effects were seen when combining fluticasone propionate subcutaneously at a dose less than the MRHDID (on a mg/m^2 basis at a maternal subcutaneous dose of 30 mcg/kg/day) and an oral dose of salmeterol at approximately 80 times the MRHDID (on a mg/ m^2 basis at a maternal oral dose of 1 mg/kg/day).	(b) (4) [redacted]	(b) (4) [redacted]
	(b) (4) [redacted]	In an embryo/fetal development study with pregnant mice that received the combination of ~~Following~~ subcutaneous

	(b) (4)	administration of fluticasone propionate and oral administration of salmeterol at doses of 0/1400, 40/0, 10/200, 40/1400, or 150/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) (b) (4) (b) (4) during the period of organogenesis, findings were generally consistent with the individual monoproducts and there was no exacerbation of expected fetal effects (b) (4) (b) (4) Cleft palate, fetal death, increased implantation loss, and delayed ossification were observed in mouse fetuses when combining fluticasone propionate at a dose approximately 0.7 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 150 mcg/kg/day) and salmeterol at a dose approximately 490 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 10,000 mcg/kg/day). (b) (4) (b) (4) (b) (4) No developmental toxicity was observed at combination doses of fluticasone propionate up to approximately (b) (4) 0.2 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 40 mcg/kg) and doses of salmeterol up to approximately (b) (4) 70 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of (b) (4) mcg/kg).
Fluticasone Propionate: Mice and rats at fluticasone propionate doses less than or equivalent to the MRHDID (on a mg/m^2 basis at a maternal subcutaneous dose of 45 and 100 mcg/kg/day,	*Fluticasone Propionate:* In embryofetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone	*Fluticasone Propionate:* In embryofetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone

respectively) showed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification. No teratogenicity was seen in rats at doses approximately equivalent to the MRHDID (on a mg/m^2 basis at maternal inhaled doses up to 68.7 mcg/kg/day). In rabbits, fetal weight reduction and cleft palate were observed at a fluticasone propionate dose less than the MRHDID (on a mg/m^2 basis at a maternal subcutaneous dose of 4 mcg/kg/day). However, no teratogenic effects were reported at fluticasone propionate doses up to approximately 5 times the MRHDID (on a mg/m^2 basis at a maternal oral dose up to 300 mcg/kg/day). No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration *[see Clinical Pharmacology (12.3)]*. Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.	propionate was teratogenic in both species. Omphalocele, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, at a dose approximately equivalent to the MRHDID (on a (b) (4)/m^2 basis with a maternal subcutaneous dose of 100 mcg/kg/day). The rat NOAEL was observed at approximately 0.3 times the MRHDID (on a (b) (4)/m^2 basis with a maternal bcutaneous dose of 30 mcg/kg/day). Cleft palate and fetal skeletal variations were observed in mouse fetuses at a dose approximately 0.2 times the MRHDID (on a (b) (4)/m^2 basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.07 times the MRHDID (on a (b) (4)m^2 basis with a maternal subcutaneous dose of 15 mcg/kg/day). In an embryofetal development study with pregnant rats dosed by the inhalation route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.25 times the MRHDID (on a (b) (4)/m^2 basis with a maternal inh ation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose approximately 0.05 times the MRHDID (on a (b) (4)m^2 basis with a maternal inhalation dose of 5.5 mcg/kg/day). In an embryofetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced reductions of fetal body weights, in the presence of maternal toxicity, at doses approximately	propionate was teratogenic in both species. Omphalocele, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, at a dose approximately equivalent to the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 100 mcg/kg/day). The rat NOAEL was observed at approximately 0.3 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 30 mcg/kg/day). Cleft palate and fetal skeletal variations were observed in mouse fetuses at a dose approximately 0.2 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.07 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 15 mcg/kg/day). In an embryofetal development study with pregnant rats dosed by the inhalation route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.25 times the MRHDID (on a mcg/m^2 basis with a maternal inhalation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose approximately 0.05 times the MRHDID (on a mcg/m^2 basis with a maternal inhalation dose of 5.5 mcg/kg/day). In an embryofetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced reductions of fetal body weights, in the presence of maternal toxicity, at doses approximately

	(b) (4)	0.012 times the MRHDID and higher (on a mcg/m^2 basis with a maternal subcutaneous dose of 0.57 mcg/kg/day). Teratogenicity was evident based upon a finding of cleft palate for 1 fetus at a dose approximately 0.08 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 4 mcg/kg/day). The NOAEL was observed in rabbit fetuses with a dose approximately 0.002 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).
		(b) (4)
Salmeterol: No teratogenic effects occurred in rats at salmeterol doses approximately 160 times the MRHDID (on a mg/m^2 basis at maternal oral doses up to 2 mg/kg/day). In pregnant Dutch rabbits administered salmeterol doses approximately 50 times the MRHDID (on an AUC basis at maternal oral doses of 1 mg/kg/day and higher), fetal toxic effects were observed characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at a salmeterol dose approximately 20 times the MRHDID (on an AUC basis at a		*Salmeterol:* In three embryo/fetal development studies, pregnant rabbits received oral administration of salmeterol at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. In pregnant Dutch rabbits administered salmeterol doses approximately 50 times the MRHDID (on an AUC basis at maternal oral doses of 1000 mcg/kg/day and higher), fetal toxic effects were observed characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. (b) (4) (b) (4)

maternal oral dose of 0.6 mg/kg/day). New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at a salmeterol dose approximately 1,600 times the MRHDID on a mg/ m^2 basis at a maternal oral dose of 10 mg/kg/day. Salmeterol xinafoate crossed the placenta following oral administration to mice and rats. Nonteratogenic Effects Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.	(b) (4)	(b) (4) (b) (4) such effects occurred at a salmeterol dose approximately (b) (4) times the MRHDID (on an AUC basis at a maternal oral dose of 600 mcg/kg/day). New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at a salmeterol dose approximately 2000 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 10,000 mcg/kg/day). (b) (4) (b) (4) (b) (4) In two embryo/fetal development studies, pregnant rats received salmeterol by oral administration at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. Salmeterol produced no maternal toxicity or embryo/fetal effects at doses up to 973 times the MRHDID (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day). In a peri- and post-natal development study in pregnant rats dosed by the oral route from late gestation through delivery and lactation, salmeterol at a dose 973 times the MRHDID (on mcg/m^2 basis with a maternal oral dose of 10,000 mcg/kg/day) was fetotoxic and decreased the fertility of survivors. Salmeterol xinafoate crossed the

		placenta following oral administration to mice and rats.
		(b) (4)

8.2 Lactation

Current Label	Sponsor's Recommended Changes	Reviewer's Recommended Changes
Plasma levels of salmeterol, a component of ADVAIR DISKUS, after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known whether fluticasone propionate, a component of ADVAIR DISKUS, is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of tritiated fluticasone propionate resulted in measurable radioactivity in milk. Since there are no data from controlled trials on the use of ADVAIR DISKUS by nursing mothers, caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.	Risk Summary There are no available data on the presence of fluticasone propionate or salmeterol in human milk, the effects on the breastfed child, or the effects on milk production. Other corticosteroids have been detected in human milk. However, fluticasone propionate and salmeterol concentrations in plasma after inhaled therapeutic doses are low and therefore concentrations in human breast milk are likely to be correspondingly low *[see Clinical Pharmacology (12.3)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ADVAIR DISKUS and any potential adverse effects on the breastfed child from ADVAIR DISKUS or from the underlying maternal condition. Data *Animal Data:* Subcutaneous administration of tritiated fluticasone propionate at a dose in lactating rats approximately 0.08 times the MRHDID for adults (on a (b) (4)/m^2 basis) resulted in measu ble levels in milk. Oral administration of salmeterol (b) (4) (b) (4) levels in milk.	Risk Summary There are no available data on the presence of fluticasone propionate or salmeterol in human milk, the effects on the breastfed child, or the effects on milk production. Other corticosteroids have been detected in human milk. However, fluticasone propionate and salmeterol concentrations in plasma after inhaled therapeutic doses are low and therefore concentrations in human breast milk are likely to be correspondingly low *[see Clinical Pharmacology (12.3)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ADVAIR DISKUS and any potential adverse effects on the breastfed child from ADVAIR DISKUS or from the underlying maternal condition. Data *Animal Data:* Subcutaneous administration of tritiated fluticasone propionate at a dose in lactating rats approximately 0.08 times the MRHDID for adults (on a (b) (4)m^2 basis) resulted in measurable levels in milk. Oral administration of salmeterol at dose in lactating rats (b) (4) approximately 973 times the MRHDID ~~for adults~~ (on a (b) (4)/m^2 basis) (b) (4) resulted in measurable levels in milk.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Current Label	Sponsor's Recommended Changes	Reviewer's Recommended Changes
Fluticasone Propionate Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 4 and 10 times the MRHDID for adults and children, respectively, on a mg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to the MRHDID for adults and children, respectively, on a mg/ m^2 basis) for 104 weeks. Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the in vivo mouse micronucleus test. No evidence of impairment of fertility was observed in rats at subcutaneous doses up to 50 mcg/kg (less than the MRHDID on a mg/ m^2 basis). Prostate weight was significantly reduced.	Fluticasone Propionate Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 5 and 10 times the MRHDID for adults and children, respectively, on a (b) (4)/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to the MRHDID for adults and children, respectively, on a (b) (4)/m^2 basis) for 104 weeks. Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the in vivo mouse micronucleus test. Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 0.5 times the MRHDID for adults on a (b) (4)/m^2 basis).	Fluticasone Propionate Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 5 and 10 times the MRHDID for adults and children, respectively, on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to the MRHDID for adults and children, respectively, on a mcg/m^2 basis) for 104 weeks. Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the in vivo mouse micronucleus test. Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 0.5 times the MRHDID for adults on a mcg/m^2 basis).
Salmeterol In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 20 times the MRHDID for adults and children based on comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at 0.2 mg/kg (approximately 3 times the MRHDID for adults and children based on comparison of the AUCs).	Salmeterol In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of (b) (4)/kg and above (approxima 20 times the MRHDID for adults and children based on comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at (b) (4)/kg (approximately 3 tim the MRHDID for adults and children based on comparison of the AUCs).	Salmeterol In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of (b) (6) mg/kg and above (approximately 20 times the MRHDID for adults and children based on comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at (b) (4) 200 mcg/kg (approximately 3 times the MRHDID for adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 and 25 times the MRHDID for adults and children, respectively, on a mg/ m^2 basis). No tumors were seen at 0.21 mg/kg (approximately 15 and 8 times the MRHDID for adults and children, respectively, on a mg/ m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown. Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 160 (b)(4) times the MRHDID for adults on a mg/ m^2 basis).	In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of (b)(4)/kg and above (approximately 66 and (b)(4) times the MRHDID for adults and children, respectively, on a (b)(4)/m^2 basis). No tumors were seen at (b)(4)/kg (approximately 20 an (b)(4) mes the MRHDID for adults and children, respectively, on a (b)(4)/m^2 basis). These findings in dents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown. Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. Fertility and reproductive performance were unaffected in male and female rats at oral doses up to (b)(4)/kg (approximately 195 times the MRHDID for adults on a (b)(4)/m^2 basis).	In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of (b)(4)680 mcg/kg and above (approximately 66 and (b)(4) 35 times the MRHDID for adults and children, respectively, on a mcg/m^2 basis). No tumors were seen at (b)(4)210 mcg/kg (approximately 20 and (b)(4)10 times the MRHDID for adults and children, respectively, on a mcg/m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown. Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. Fertility and reproductive performance were unaffected in male and female rats at oral doses up to 2000 mcg/kg (approximately 195 times the MRHDID for adults on a mcg/m^2 basis).

Table 1 Calculations of animal to human exposure margins for fluticasone propionate

Drug:	**Fluticasone propionate**							
			# daily					
	age	mcg/dose	doses	mcg/day	kg	mcg/kg	factor	mcg/m²
Pediatric				0	18	0.0190	25	0.48
Adult	>12	500	2	1000	60	16.6667	37	616.67
			conv.		Dose Ratio		Rounded Dose Ratio	
	route	mg/kg/d	factor	mg/m²	Adults	Children	Adults	Children
Carcinogenicity:								
mouse	Oral	1000	3	3000	4.86	6315.79	5	6300
rat	INH	57	6	342	0.55	720.00	1/2	720
Reproduction and Fertility:								
rat	SC	50	6	300	0.49	N/A	1/2	N/A
Teratogenicity:								
mouse	SC	10	3	30	0.05	N/A	1/21	N/A
mouse	SC	15	3	45	0.07	N/A	1/14	N/A
mouse	SC	40	3	120	0.19	N/A	1/5	N/A
mouse	SC	45	3	135	0.22	N/A	1/5	N/A
mouse	SC	150	3	450	0.73	N/A	1/1	N/A
mouse			3	0	---	N/A	---	N/A
rat	SC	10	6	60	0.10	N/A	1/10	N/A
rat	SC	30	6	180	0.29	N/A	1/3	N/A
rat	SC	50	6	300	0.49	N/A	1/2	N/A
rat	SC	100	6	600	0.97	N/A	1/1	N/A
rat	INH	5.5	6	33	0.05	N/A	1/19	N/A
rat	INH	25.7	6	154.2	0.25	N/A	1/4	N/A
rabbit	SC	0.08	12	0.96	0.00	N/A	1/642	N/A
rabbit	SC	0.57	12	6.84	0.01	N/A	1/90	N/A
rabbit	SC	4	12	48	0.08		1/13	
mouse			3	0	---	N/A	---	N/A

Conversion, Correction, and Rounding Factors:

Human Age (yr)	Weight (kg)	Factor (kg/m²)	Species	Factor (kg/m²)	Exposure greater than x-times human	Round to nearest
0	3	25	dog	20	1	1
1	10	25	guinea pig	8	10	5
2	12	25	hamster	4	100	10
4	16	25	monkey	12	1000	100
6	20	25	mouse	3	10000	1000
12	50	37	rabbit	12		
			rat	6		

Reference ID: 4106908

Table 2 Calculations of animal to human exposure margins for salmeterol

Reference ID: 4106908

Drug:	**Salmeterol**							
			# daily					
	age	mcg/dose	doses	mcg/day	kg	mcg/kg	factor	mg/m²
Pediatric		50	2	100	20	5.0000	25	125.00
Adult	>12	50	2	100	60	1.6667	37	61.67

			conv.		Dose Ratio		Rounded Dose Ratio	
	route	mg/kg/d	factor	mg/m²	Adults	Children	Adults	Children
Carcinogenicity:								
mouse	oral	1400	3	4200	68.11	33.60	70	35
rat	oral	210	6	1260	20.43	10.08	20	10
rat	oral	680	6	4080	66.16	32.64	65	35
Reproduction and Fertility:								
rat	oral	2000	6	12000	194.59	N/A	190	N/A
Teratogenicity:								
mouse	oral	200	3	600	9.73	N/A	10	N/A
mouse	oral	1400	3	4200	68.11	N/A	70	N/A
mouse	oral	10000	3	30000	486.49	N/A	490	N/A
rat	oral	100	6	600	9.73	N/A	10	N/A
rat	oral	1000	6	6000	97.30	N/A	95	N/A
rat	oral	10000	6	60000	972.97	N/A	970	N/A
rat	oral	100	6	600	9.73	N/A	10	N/A
rat	oral	150	6	900	14.59	N/A	15	N/A
rat	oral	500	6	3000	48.65	N/A	50	N/A
rat	oral	1000	6	6000	97.30	N/A	95	N/A
rat	oral	2000	6	12000	194.59	N/A	190	N/A
rat	oral	10000	6	60000	972.97	N/A	970	N/A
rabbit	oral	100	12	1200	19.46	N/A	20	N/A
rabbit	oral	300	12	3600	58.38	N/A	60	N/A
rabbit	oral	600	12	7200	116.76	N/A	120	N/A
rabbit	oral	1000	12	12000	194.59	N/A	190	N/A
rabbit	oral	3000	12	36000	583.78	N/A	580	N/A
rabbit	oral	10000	12	1E+05	1945.95	N/A	1900	N/A

Conversion, Correction, and Rounding Factors:

Human Age (yr)	Weight (kg)	Factor (kg/m²)	Species	Factor (kg/m²)	Exposure greater than x-times human	Round to nearest
0	3	25	dog	20	1	1
1	10	25	guinea pig	8	10	5
2	12	25	hamster	4	100	10
4	16	25	monkey	12	1000	100
6	20	25	mouse	3	10000	1000
12	50	37	rabbit	12		
			rat	6		

Reference ID: 4106908

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/s/

TIMOTHY W ROBISON
06/02/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021077Orig1s056

STATISTICAL REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

STATISTICAL REVIEW

META-ANALYSIS OF CLINICAL STUDIES

NDA Numbers:	21077 S56/S57, 22518 S22, 21929 S42, 21254 S27, 204275 S15, 208799 S2
Drug Names:	Advair Diskus (fluticasone/salmeterol), Dulera (mometasone/formoterol), Symbicort (budesonide/formoterol), Advair HFA (fluticasone/salmeterol), Breo Ellipta (fluticasone/vilanterol), AirDuo (fluticasone/salmeterol)
Proposed Indications:	Treatment of Asthma
Applicants:	GlaxoSmithKline, Merck, [redacted] (b) (4) (b) (4).
Biometrics Division:	Division of Biometrics VII
Statistical Reviewers:	Changming (Sherman) Xia, Ph.D., Mathematical Statistician
Concurring Reviewers:	Eugenio Andraca-Carrera, Ph.D., Team Leader Mat Soukup, Ph.D., Deputy Division Director
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Medical Officer: Robert Lim Medical Team Leader: Sally Seymour
Project Manager:	Carol Hill
Keywords:	Meta-Analysis, asthma; safety assessment; long acting beta2-agonist (LABA), inhaled corticosteroid (ICS); serious asthma adverse events

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

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1. Executive Summary

1.1 Background

A meta-analysis conducted by the FDA (Levenson 2008[1]) showed that Long-Acting Beta-Agonists (LABAs) were associated with an increased risk of asthma-related adverse events relative to non-LABA treatments as measured by the composite endpoint consisting of asthma-related death, asthma-related intubation, and asthma-related hospitalization, with an estimated risk difference (RD) of 2.80 (95% CI: [1.11, 4.49]) per 1000 subjects. This 2008 meta-analysis found no difference in risk between LABA used in combination with inhaled corticosteroids (ICS) relative to ICS alone (RD: 0.25; 95% CI: [-1.69, 2.18] per 1000 subjects). A limitation of this 2008 meta-analysis was that the trials included were generally not designed to evaluate the meta-analysis composite endpoint.

On April 14, 2011, FDA issued a post-marketing requirement (PMR) to all manufacturers of LABA products indicated for the treatment of asthma to conduct controlled trials to assess the safety of LABAs plus ICS. Each sponsor was to carry out an individual non-inferiority trial of LABA+ICS against an ICS-alone control arm in a population of adults and adolescents 12 years of age and older.

This is a statistical review to describe the results of a meta-analysis of serious asthma adverse events (the composite of asthma-related death, intubations, and hospitalizations) associated with products containing LABAs used in combination with ICS for the treatment of asthma compared to treatment with ICS alone. This meta-analysis was conducted by the FDA review team based on subject-level data from 3 randomized clinical trials for Symbicort, Advair Diskus, and Dulera, in adults and adolescent subjects that were designed to address the 2011 PMR. These three trials were completed and reviewed individually between 2016 and 2017. Subgroup analyses in subjects of age younger than 18 included the results of a fourth trial, conducted to evaluate the safety of Advair Diskus in pediatric subjects aged 4 to 11.

1.2 Conclusions and Recommendations

This primary meta-analysis included 17,537 subjects randomized to LABA + ICS and 17,552 subjects randomized to ICS in the three adult and adolescent trials for Symbicort, Advair Diskus, and Dulera that were designed to address the 2011 PMR. Table 1 shows that 116 subjects randomized to LABA + ICS and 105 subjects randomized to ICS alone experienced the primary composite of serious asthma adverse events (asthma-related hospitalizations, intubations and deaths) during the 26-week trial period in these trials. Most of these events were asthma-related hospitalizations. Only 3 asthma-related intubations (2 on ICS, 1 on Symbicort) and 2 asthma-related deaths (both on Symbicort) were observed in these trials. This meta-analysis found no statistically significant difference in the risk of the composite endpoint associated with LABA plus ICS when compared to ICS alone: the estimated meta-analysis HR was 1.10 with a 95% CI of [0.85, 1.44].

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The population of subjects younger than 18 was a subgroup of special interest in this meta-analysis. An Advair pediatric-only trial was combined with subjects under the age of 18 in the other 3 adult/adolescent trials for this analysis. The estimated meta-analysis HR for the risk of the asthma composite endpoint associated with LABA + ICS in this subgroup was 1.22 with a 95% CI of [0.75, 2.00]. The upper 95% CI was lower than the pre-specified NI margins of 2.0 (for individual adult/adolescent trials) and 2.7 (for the pediatric trial), showing no excessive risk associated with LABA plus ICS compared to ICS alone during the 26 weeks of study period for subjects younger than 18 years of age.

Table 1. Meta-Analysis of Serious Asthma Adverse Events in Adult/Adolescent Population (3 Trials)

	LABA + ICS	ICS	Total
N	17537	17552	35089
Composite Event (%)	116 (0.66%)	105 (0.59%)	221 (0.63%)
HR [95% CI] (LABA+ICS to ICS)	**1.10 [0.85, 1.44]**		

2. Introduction

2.1 Overview and Regulatory Background

Dr. Mark Levenson conducted a meta-analysis in 2008 to compare the risk of serious asthma related events associated with the use of LABA relative to non-LABA controls. The meta-analysis suggested a possible increased risk in the composite endpoint of asthma-related death, asthma-related intubation, and asthma-related hospitalization associated with the use of LABAs compared to non-LABAs: risk difference (RD) 2.80 (95% CI: 1.11, 4.49) per 1000 subjects. When comparing the combination of LABAs plus ICS to ICS alone, the meta-analysis found a small, non-statistically significant difference in risk: RD 0.25 (95% CI: -1.69, 2.18) per 1000 subjects. These results were presented at a joint meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee in December 2008. The Office of New Drugs and the Office of Surveillance and Epidemiology presented recommendations for post-marketing safety clinical trials to further examine this issue at a joint meeting of the Pulmonary-Allergy Drugs Advisory and Drug Safety and Risk Management Advisory Committees in March 2010. In April 2011, a post-marketing requirement (PMR) was issued to all manufacturers of LABA products with an indication of maintenance treatment of asthma to conduct controlled trials to assess the safety of LABA plus ICS versus ICS alone. The language in the PMR is quoted below:

> *To further evaluate the safety of Long-Acting Beta-Agonists (LABAs) when used in combination with inhaled corticosteroids for the treatment of asthma, the U.S. Food and Drug Administration (FDA) is requiring the manufacturers of LABAs to conduct five*

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randomized, double-blind, controlled clinical trials comparing the addition of LABAs to inhaled corticosteroids versus inhaled corticosteroids alone.

Four clinical trials will be conducted in adult and adolescent patients 12 years of age and older. The adult and adolescent trials will include 11,700 patients in each trial for a total of 46,800 patients. Each trial will evaluate one of the following LABA-containing drugs: 1) Symbicort (budesonide and formoterol); 2) Advair Diskus (fluticasone and salmeterol); 3) Dulera (mometasone and formoterol); and 4) Foradil (formoterol). The Foradil trial will also include treatment with fluticasone, which will be provided in a separate inhaler.

One clinical trial will be conducted in pediatric patients aged 4 to 11 years with Advair Diskus. The pediatric trial will include 6,200 patients. Patients in all trials will be treated for six months, and the primary endpoint will be a composite of serious asthma outcomes: asthma-related death, intubation, or hospitalization. The pediatric trial will also assess other relevant quality of life endpoints such as days of school missed and emergency room visits because of asthma related illness.

The sponsors of Symbicort (AstraZeneca), Advair Diskus (GSK), and Dulera (Merck) have completed the clinical trials requested in this PMR. The results of these trials were submitted to NDA 21929 (Symbicort) on 2/28/2017, NDA 21077 (Advair Diskus) on 10/3/2016, and NDA 22518 (Dulera) on 7/13/2017. Statistical reviews of each of these trials have been completed and uploaded to DARRTS[a] by Dr. Changming Xia. In September 2017, the FDA review team drafted a Statistical Analysis Plan (SAP) for a meta-analysis of the three clinical trials in adult and adolescent subjects for these products which were conducted to fulfill the PMR.

Novartis initiated trial FOR258D2416 in 2013 to address the 2011 PMR to evaluate the safety of Foradil in adult and adolescent subjects. The trial was terminated early in 2015 and the product was withdrawn from the market for business reasons. At the time the trial was terminated, a total of 825 subjects had been enrolled. Trial FOR258D2416 was different from the trials for Advair, Symbicort, and Dulera in at least the following ways:

1. Subjects were given the option to continue for the remainder of the trial and continue study visits as planned at the time of trial termination. It is possible that subjects who decided to continue in the trial may have been different from subjects who discontinued in terms of both efficacy and safety.
2. Foradil is a single ingredient LABA that was administered with a separate ICS. Even though the two products were meant to be administered together, it is possible that some subjects used the individual products alone. Note that Symbicort, Advair, and Dulera include ICS and LABA in the same inhaler.

Because of the reasons listed above, the results from the safety trial for Foradil may be difficult to interpret, and therefore this trial was not included in the present meta-analysis.

[a] Dates when the individual statistical reviews were signed into DARRTS were: 9/28/2017 (NDA 21929), 6/27/2017 (NDA 21077), 12/19/2017 (NDA 22518).

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In addition, GSK conducted a randomized pediatric trial (VESTRI) to evaluate the safety of Advair Diskus in subjects aged 4 to 11. This meta-analysis combined data from the VESTRI trial with data from the three adult/adolescent trials (age 12 to 17) to conduct subgroup analyses in the combined pool of pediatric and adolescent subjects of age younger than 18. A statistical review of the VESTRI trial was conducted separately of the adult trials and was uploaded to DARRTS in 2017.

2.2 Data Sources

This meta-analysis was conducted based on subject-level data and study reports submitted to the Agency by the sponsors to document the results of the following three adult and adolescent trials designed and conducted to fulfill the 2011 PMR:

1. Advair Diskus (NDA 21077 S056): Trial SAS115359 (AUSTRI).
2. Symbicort (NDA 21929 S042): Trial D5896C00027.
3. Dulera (NDA 22518 S022): Trial P202 (SPIRO).

Subgroup analyses in pediatric and adolescent subjects (age < 18) were conducted based on corresponding data from the above three trials and data from the pediatric-only trial:

4. Advair Diskus (NDA 21077 S057): Trial SAS115358 (VESTRI).

The individual trial protocols, statistical analysis plans, and study reports for these trials are available under each of the NDA submissions listed above. The individual designs of these trials have been reviewed separately for each NDA application and will not be further discussed in this document.

A Joint Oversight Steering Committee (JOSC) was established to oversee and provide guidance regarding the conduct of these studies. All hospitalizations, endotracheal intubations, and deaths were adjudicated by an independent Joint Adjudication Committee (JAC). A Joint Data Monitoring Committee (JDMC) monitored accumulating asthma-related deaths and endotracheal intubations across these three studies. The charters for these joint committees were submitted as part of the NDA applications listed above.

3. Statistical Methodology

3.1 Objectives

The purpose of this meta-analysis is to provide a more precise estimate of the risk of serious asthma adverse events associated with the combination products containing LABA plus ICS than is possible for any one of the individual trials alone. The following objectives were pre-specified in the meta-analysis SAP authored by the FDA review team:

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1. Examine if the combination products containing LABA plus ICS are associated with increased risk of the composite endpoint of asthma-related death, asthma-related intubation, and asthma-related hospitalization, relative to treatment with ICS alone.
2. Examine if the combination products containing LABA plus ICS are associated with increased risk of the composite endpoint of asthma-related death and asthma-related intubation.
3. Examine if the combination products containing LABA plus ICS are associated with increased risk of each of the following individual endpoints: asthma-related death, asthma-related intubation, and asthma-related hospitalization.

Estimated parameters and 95% confidence intervals will be reported but no hypotheses will be formally tested.

3.2 Endpoints

The primary meta-analysis endpoint is the composite of adjudicated asthma-related death, asthma-related intubation, and asthma related hospitalization. If a subject has multiple events in the composite, only the first event will be used for analysis. Each subject may contribute at most one event for analyses of the composite endpoint.

Secondary endpoints include the individual components of the primary composite, as well as the secondary composite endpoint of asthma-related death and asthma-related intubation.

3.3 Analysis Populations

3.3.1 Primary Analysis Population

The primary analysis population consisted of all subjects randomized in the three adult/adolescent trials who received at least one dose of study treatment. Analyses were based on randomized treatment, regardless of the actual treatment received. Subjects randomized to combination products containing LABAs plus ICS were compared to subjects randomized to treatment with ICS alone. Subjects were analyzed based on their 'on study follow-up' defined as the time until the end of study (approximately 26 weeks of follow-up period) after the first use of study drug or 7 days after the last date of study drug treatment, whichever date was greater.

3.3.2 Sensitivity Analysis Population

The sensitivity analysis population consisted of all subjects randomized in the three trials who received at least one dose of study treatment. Analyses were based on randomized treatment, regardless of the actual treatment received. Subjects were analyzed based on their 'on-treatment' follow-up defined as the time from randomization to the earliest of study completion, loss to follow-up, death, or last dose of randomized treatment + 7 days.

3.3.3 Analysis Population for Subgroup Analyses in Pediatric and Adolescent Subjects

A subgroup analysis in pediatric and adolescent subjects was conducted in the subset of the primary analysis population who were younger than 18 years of age at the time of randomization,

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plus all subjects in the VESTRI pediatric trial who received at least one dose of study treatment. Analyses were based on randomized treatment, regardless of the actual treatment received.

3.4 Analysis Methods

3.4.1 Descriptive Summary

Trial level summaries are provided for all endpoints in each of the four trials. Summaries include the number of subjects by treatment group, subject-years of exposure by treatment group, and number of events by treatment group and subgroup when available.

Kaplan-Meier survival curves are used to summarize the time-pattern (hazard function) of the composite endpoint of asthma-related death, asthma-related intubation, and asthma related hospitalizations, by each trial and pooled across the three adult trials.

3.4.2 Primary Meta-Analysis Method

The primary analysis method estimates the hazard ratio of the time until the first primary composite event associated with LABAs plus ICS vs ICS alone through a Cox proportional hazards model. The model is stratified by trial and includes a single covariate for treatment (LABAs plus ICS vs ICS alone). The primary analysis is conducted in the primary analysis population.

A sensitivity analysis of the primary composite endpoint is conducted using a similar Cox proportional hazards model stratified by trial based on the 'on-treatment' population.

Note that the statistical analysis plans for the individual trials pre-specified trial-specific Cox proportional models that included additional covariates or stratification factors, such as incoming asthma treatment and treatment dose. However, because these factors were not uniformly defined across trials/sponsors, the statistical models in this meta-analysis are stratified by trial and include a single covariate of randomized treatment.

3.4.3 Secondary Meta-Analysis Methods of the Primary Endpoint

The secondary analysis method estimates the Mantel-Haenszel risk difference and associated confidence interval[2] in the primary analysis population. This method incorporates information from trials with no events. The unit of analysis is the subject and the stratification factor is the trial. This analysis method is used to estimate the risk difference of the primary composite endpoint, as well as the risk difference of the secondary outcomes listed in Section 3.2.

3.4.4 Exploratory Analyses

An exploratory Cox proportional hazards model was fit stratified by trial and with covariates for treatment (LABAs plus ICS vs ICS alone), age and age × treatment interaction. All subjects from the three adult/adolescent trials and the pediatric trial are included in this analysis. Parameter estimates and nominal 95% confidence intervals are reported for all parameters in the model.

The goal of this analysis is to explore the association between age and treatment on the risk of serious asthma related adverse events. This analysis is limited by the fact that children aged 4 to 11 were only studied in the VESTRI trial for Advair and that none of these trials were designed or powered to evaluate the interaction of age and treatment.

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3.4.5 Subgroup Analyses

Subgroup analyses of the primary composite endpoint estimate the hazard ratio of the time until the first event associated with LABAs plus ICS vs ICS alone through a Cox proportional hazards model stratified by trial with a single covariate for treatment within subgroups defined by gender, age, race, region, ICS dose level, baseline ACQ score, and asthma hospitalization history within the 12 months prior to randomization. Subgroup analyses were conducted in the primary analysis population only. The subgroup analysis of pediatric and adolescent subjects (age <18) was conducted with data from the VESTRI trial and the corresponding subset from the three adult/adolescent trials.

3.4.6 Analysis of Selection Bias

The trials listed in Section 3.2 were designed and conducted to address the 2011 PMR. They shared a similar trial design which was to actively assess the safety outcomes as well as a Joint Oversight Steering Committee, Joint Adjudication Committee, and a Joint Data Monitoring Committee. This meta-analysis was designed to analyze the combined results of these trials. Therefore, this meta-analysis is not subject to trial selection bias and therefore no plots or trial inclusion diagnostics were computed.

3.4.7 Multiplicity and Statistical Significance

All analyses in this document were conducted and reported using a nominal two-sided Type-I error of 0.05. No multiplicity corrections were made to account for analyses of multiple endpoints or for subgroups analyses.

4. Results

4.1 Summary of Trial Characteristics

The four trials evaluated in this meta-analysis are summarized in Table 2. They were similarly designed with duration of approximately 26 weeks and 1:1 randomization ratio to ICS/LABA combination products or to ICS products alone. The three adult/adolescent trials were each designed to individually rule out a risk margin of 2.0 for the hazard ratio of serious asthma-related adverse events associated with the combination of ICS and LABA. Each of the three adult/adolescent trials randomized approximately 11,700 subjects. The pediatric trial VESTRI was designed to rule out a risk margin of 2.7 and randomized a correspondingly smaller sample size of 6208 subjects. For more details of the results of each trial, refer to the individual NDA reviews.

The dosing schemes were different among these trials; the goal was to mimic real-world use of ICS/LABA combination product[3]. The primary meta-analysis model combined the treatment arms into 2 levels: LABA+ICS or ICS only; the primary analysis was stratified by trial to account for heterogeneity between trials.

Table 2. Summary of Trials in the Meta-Analysis

Brand Name	Trial Name	N (randomized and treated)	ICS/LABA Doses in Combination Products	ICS Doses (matching)

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Advair (Age≥12)	AUSTRI	11679	Fluticasone (FSC) /Salmeterol (FP) 100/50, 250/50, 500/50 mcg	Fluticasone 100, 250, 500 mcg
Symbicort	D5896C00027	11681	Budesonide/Formoterol 160/4.5, 80/4.5 mcg	Budesonide 160, 80 mcg
Dulera	SPIRO	11729	Mometasone/Formoterol 200/10, 400/10 mcg	Mometasone 200, 400 mcg
Advair (Age<12)	VESTRI	6208	FSC/FP 100/50, 250/50 mcg	Fluticasone 100, 250 mcg

Demographic and baseline characteristics, as well as subject disposition summaries of the individual trials are shown in Table 3. Most of the subjects completed the trials. These four trials shared similar design and had similar exposure and follow-up times. The Advair adult/adolescent trial (AUSTRI) had slightly more subjects with premature withdrawal (17%) and shorter average exposure time to treatment (164 days) than the other trials. No obvious imbalance in demographic or baseline characteristics was observed between the ICS and LABA+ICS arms in each of the trials evaluated. Therefore, baseline and demographic characteristics are not shown separately by treatment groups for simplicity. For more details of each trial, refer to the individual NDA reviews.

Table 3. Baseline Characteristics, Demographics and Disposition

	AUSTRI	D5896C00027	SPIRO	VESTRI
# of subjects randomized and treated	11679	11681	11729	6208
# of subjects who completed study	11654	11551	11717	6204
Mean exposure (days)	164	173	170	171
Premature treatment withdrawal (%)	2013 (17)	1139 (10)	1463 (12)	733 (12)
Female (%)	7749 (66)	7660 (66)	7716 (66)	2414 (39)
Age < 18 (%)	1230 (11)	1267 (11)	1037 (9)	6208 (100)
Age 18-64 (%)	9181 (79)	9135 (78)	9094 (78)	0
Age > 64 (%)	1268 (11)	1279 (11)	1598 (14)	0
Race: White (%)	8783 (75)	8044 (69)	9056 (78)	4030 (65)
Race: Black (%)	1726 (15)	797 (7)	705 (6)	1050 (17)

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4.2 Summary of Serious Asthma-Related Adverse Events

A summary of the composite endpoint and its individual components is shown in Table 4. The majority of events in the composite endpoint were asthma-related hospitalizations. No asthma-related intubations or deaths were observed in the Dulera trial or the Advair pediatric trial. The 2 asthma-related deaths were observed in the Symbicort trial, both in the Symbicort arm.

Table 4 Summary of the Composite Endpoint and Individual Components

Trial	Treatment Arms	N	Composite	Hospitalization	Intubation	Death
AUSTRI (Age≥ 12)	Advair	5834	34	34	-	-
	ICS	5845	33	33	2	-
D5896C00027	Symbicort	5838	43	42	1	2
	ICS	5843	40	40	-	-
SPIRO	Dulera	5865	39	39	-	-
	ICS	5864	32	32	-	-
VESTRI (Age<12)	Advair	3107	27	27	-	-
	ICS	3101	21	21	-	-

Figure 1 shows the Kaplan-Meier cumulative incidence curves for the asthma composite endpoint using the ITT (on-study) analysis set pooled across the three adult and adolescent trials. The two curves are close to each other throughout the duration of the trials with no clear separation (see Appendix for confidence bars at 30-day intervals). Note that the Kaplan-Meier plot shown here is intended to illustrate how events accumulated over time in the two treatment arms (ICS plus LABA vs. ICS). While crossing Kaplan-Meier curves could suggest a violation of the proportionality assumption in a Cox model, this Kaplan-Meier plot does not account for stratification by trial and is not intended to test for proportional hazards. The stratified Cox model used for the primary analysis in this meta-analysis only assumes proportionality within each of the trials; this assumption has been checked and verified in trial-specific NDA reviews. Figure 2 shows the Kaplan-Meier cumulative incidence curves using the mITT (on-treatment) analysis set. The two curves are close to each other in the beginning of the trials. However, they start to separate more towards the end of the study, favoring ICS over LABA+ICS.

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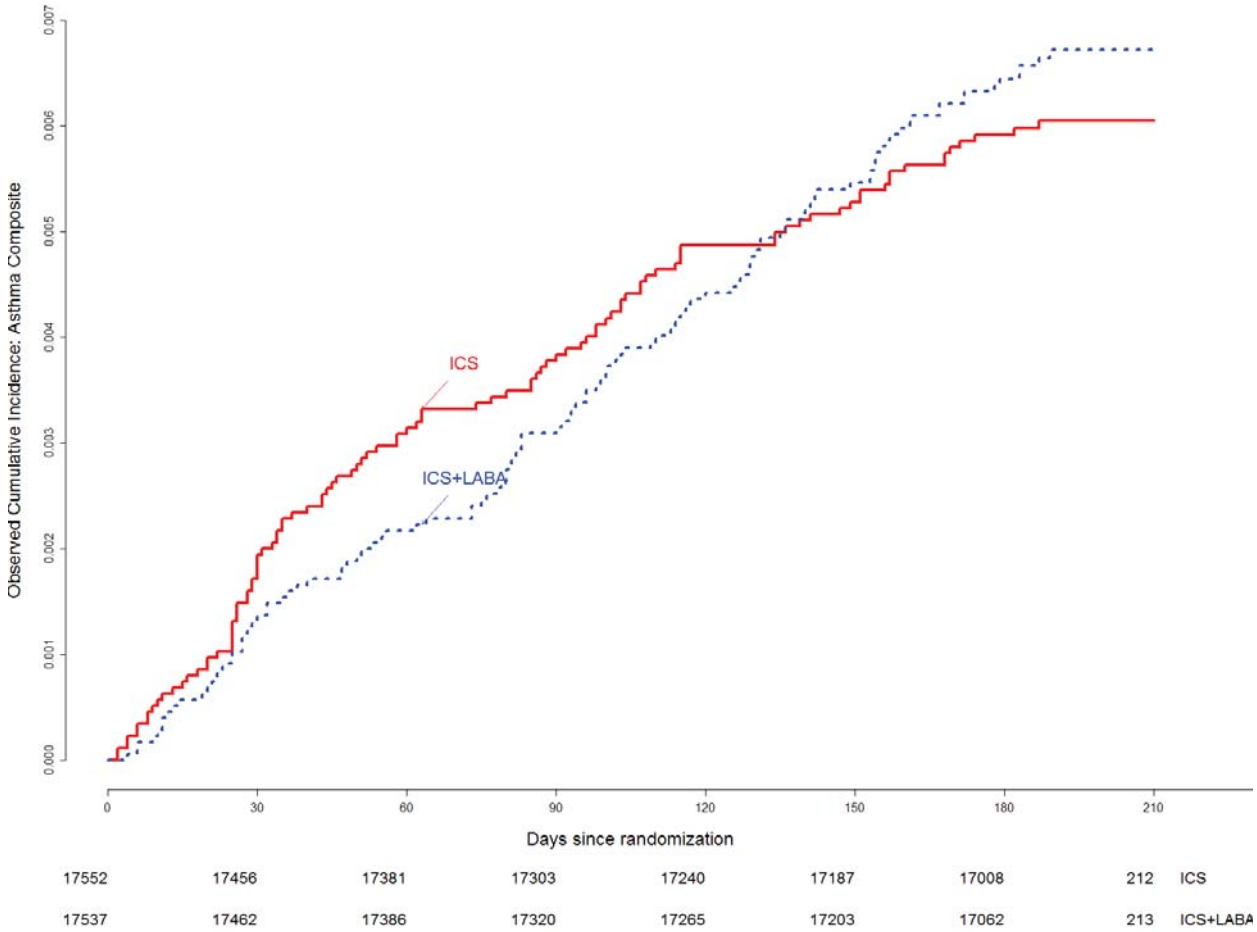
Figure 1. Kaplan-Meier Cumulative Incidence Curves: Asthma Composite (3 Trials, ITT)



Note: The numbers marked below the x-axis represent number of subjects at risk at annotated time points. The "at-risk" set includes the day noted on the x-axis. The corresponding survival probability plot with confidence bars is available in the Appendix.

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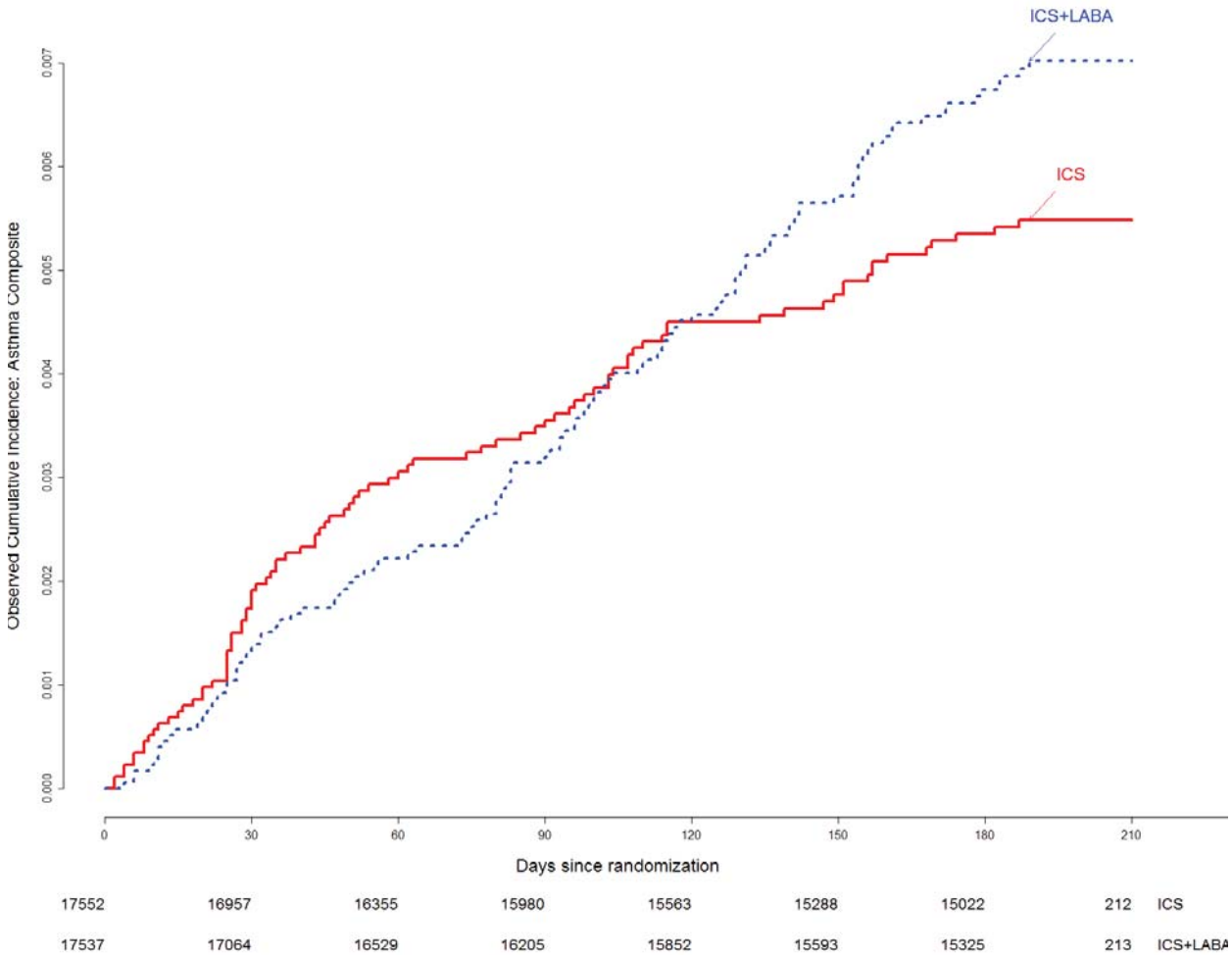
Figure 2. Kaplan-Meier Cumulative Incidence Curves: Asthma Composite (3 Trials, mITT)



Note: The numbers marked below the x-axis represent number of subjects at risk at annotated time points. The "at-risk" set includes the day noted on the x-axis. The corresponding survival probability plot with confidence bars is available in the Appendix.

4.3 Primary and Secondary Analysis Results

4.3.1 Primary Analysis (ITT)

The primary analysis was based on the primary composite endpoint of serious asthma events in the primary analysis population including all subjects who were randomized and treated in the three adult/adolescent trials. The statistical model was a Cox proportional hazards model with baseline hazards stratified by trial, with a single covariate for randomized treatment. Because the proportionality assumption has been checked and verified for each trial in individual NDA reviews and the stratified meta-analysis model only assumes proportionality within each trial, this assumption is not further checked in this meta-analysis. The HR estimate for the meta-analysis was 1.10 with a 95% CI of [0.85, 1.44]. The meta-analysis results were consistent with the results

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from individual trials, but had a narrower CI due to the larger sample size: the HR point estimates in the meta-analysis and in each of the individual trials were all larger than 1.0, numerically favoring ICS over LABA plus ICS, although none were statistically significant. All the upper bounds of the 95% CIs were lower than 2.0, showing no excessive risk of LABA plus ICS compared to ICS in serious asthma events based on the risk margin pre-specified for each individual trial. All lower bounds of the 95% CIs included 1.0, which does not suggest a difference of serious asthma risk between LABA plus ICS and ICS alone.

Table 5. Primary Meta-Analysis in Adult/Adolescent Population (3 Trials, ITT)

	Events/N*	Events/N LABA+ICS**	Events/N ICS**	HR*** [95% CI]
AUSTRI	67/11679	34/5834	33/5845	1.030 [0.638, 1.663]
D5896C00027	83/11681	43/5838	40/5843	1.073 [0.698, 1.650]
SPIRO	71/11729	39/5865	32/5864	1.218 [0.763, 1.944]
Meta-analysis	221/35089	116/17537	105/17552	**1.104 [0.848, 1.437]**

* Randomized subjects who have taken at least one dose of study medication

** Planned treatment

*** Hazard ratio of LABA+ICS to ICS: the HRs for individual trials shown on this table were estimated through a non-stratified Cox proportional hazards model with a single covariate of planned treatment. The models used in the reviews of individual trials incorporated additional covariates and therefore hazard ratio estimates on this table and in the reviews of individual trials might differ. For the meta-analysis, a Cox model stratified by trial was used, with a single covariate of planned treatment.

4.3.2 Sensitivity Analysis for the Primary Endpoint

An on-treatment sensitivity analysis was performed on the primary endpoint, as shown in Table 6. The analysis model, endpoint and the subjects were the same as the primary analysis. The only difference was that the data were truncated 7 days after last treatment date, so if an event happened more than 7 days after last treatment, it would not be counted in this analysis. The mITT meta-analysis showed a larger point estimate (1.25 vs. 1.10) of the HR and a higher upper 95% confidence limit (1.65 vs. 1.44) than the primary ITT (on-study) meta-analysis.

Table 6 Sensitivity Analysis in Adult/Adolescent Population (3 Trials, mITT)

	Events/N*	Events/N LABA+ICS**	Events/N ICS**	HR*** [95% CI]
AUSTRI	63/11679	33/5834	30/5845	1.088 [0.664, 1.794]
D5896C00027	78/11681	43/5838	35/5843	1.216 [0.778, 1.900]
SPIRO	63/11729	38/5865	25/5864	1.500 [0.906, 2.485]
Meta-analysis	204/35089	114/17537	90/17552	**1.253 [0.950, 1.651]**

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* Randomized subjects who have taken at least one dose of study medication
** Planned treatment
*** Hazard ratio of LABA+ICS to ICS: the HRs for individual trials shown on this table were estimated through a non-stratified Cox proportional hazards model with a single covariate of planned treatment. The models used in the reviews of individual trials incorporated additional covariates and therefore hazard ratio estimates on this table and in the reviews of individual trials might differ. For the meta-analysis, a Cox model stratified by trial was used, with a single covariate of planned treatment.

4.3.3 Secondary Analysis of the Primary Endpoint

The Mantel-Haenszel (MH) risk difference (RD) for the primary endpoint was estimated for the primary composite endpoint as summarized in Table 8. The estimated MH RD (LABA plus ICS minus ICS) was 6.32 events per 10,000 subjects, with a wide 95% CI of [-10.23, 22.88] containing 0, indicating no statistically significant difference in risk between the two types of treatment during the 26-week follow up of the completed trials in the adult/adolescent population.

4.3.4 Exploratory Analyses

An additional Cox proportional hazards model was fit to evaluate the primary composite endpoint. The statistical model was stratified by trial and included covariates for treatment (LABA plus ICS vs. ICS alone), age and age × treatment interaction. All subjects from the three adult/adolescent trials and the pediatric trial were included in this analysis. Parameter estimates and nominal 95% confidence intervals are reported for all parameters in the model.

This analysis did not find a statistically significant interaction between age and treatment, as shown in Table 7, where the 95% CI for the interaction term included 1. The age variable was statistically significant with an HR estimate of 1.02 and 95% CI of [1.01, 1.03] and suggests that older subjects were at increased risk of asthma-related serious adverse events than younger subjects regardless of randomized treatment.

Table 7. Modeling Age as a Covariate with Interaction (4 Trials Combined, ITT)

	HR [95% CI]
Treatment (LABA+ICS vs. ICS)	1.155 [0.691, 1.932]
Age	1.017 [1.007, 1.027]
Treatment * Age (interaction term)	1.000 [0.989, 1.011]

4.3.5 Secondary Outcomes

Table 8 shows the meta-analysis results for the secondary outcomes of the individual endpoints in the composite, as described in the Analysis Methods section. The Mantel-Haenszel method stratified by trial was used to calculate the risk difference and the corresponding CIs.

The majority of events in the composite endpoint were asthma-related hospitalizations. There were 2 asthma-related deaths, both of which occurred in the Symbicort arm. No statistically significant

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difference was observed between any of the individual components, including asthma-related hospitalization, asthma-related intubation, asthma-related death, or the composite of asthma-related death and asthma-related intubation. Asthma-related deaths or intubations were rare in these three trials.

Table 8. Meta-Analysis of Secondary Outcomes (3 Trials, ITT)

Trial	Treatment Arms	N	Hospitalization	Intubation	Death	Intubation and Death
AUSTRI	Advair ICS	5834 5845	34 33	- 2	- -	- 2
D5896C00027	Symbicort ICS	5838 5843	42 40	1 -	2 -	2 -
SPIRO	Dulera ICS	5865 5864	39 32	- -	- -	- -
Meta-analysis (3 Trials)	LABA+ICS ICS	17537 17552	115 105	1 2	2 0	2 2
MH RD* (per 10,000 subjects) [95% CI]	-	-	5.75 [-10.77, 22.27]	-0.57 [-2.50, 1.37]	1.14 [-0.44, 2.72]	0 [-2.23, 2.24]

* LABA+ICS minus ICS. A positive number indicates higher risk of LABA+ICS compared to ICS alone, and 0 indicates no difference.

4.4 Subgroup Analyses

4.4.1 Meta-Analysis in Pediatric and Adolescent Subjects (Age<18)

In the analysis of pediatric/adolescent population (age < 18), the Advair pediatric trial (VESTRI) was combined with the 3 adult/adolescent trials. The majority of pediatric and adolescent subjects in the combined dataset came from the Advair pediatric trial. Like the primary meta-analysis, an ITT analysis was conducted and an on-treatment mITT analysis was conducted to check the robustness of the ITT results.

The combined pediatric/adolescent analysis set (age < 18) contained 9,742 subjects, with 4,844 and 4,898 randomized to LABA plus ICS arm and ICS-only arm respectively. A total of 65 events in the composite endpoint were observed, with 35 in LABA plus ICS and 30 in ICS. The estimated HR associated with LABA plus ICS was 1.18 with a 95% confidence interval of [0.73, 1.93]. Both the meta-analysis point estimate (1.18 vs. 1.29) and the upper bound of the 95% CI (1.93 vs. 2.28) were smaller than their counterparts in the analysis of the single Advair pediatric trial. The confidence interval of the meta-analysis was also narrower than that of the single Advair pediatric trial with the larger combined sample size. The on-treatment (mITT) meta-analysis truncating data 7 days after last treatment showed a similar trend as the primary analysis population, with larger point estimate (1.22 vs. 1.18) and upper 95% CI (2.00 vs 1.93) than the ITT analysis. Both upper 95% CIs for the meta-analysis were lower than the pre-specified NI margin of 2.7 for the pediatric trial and 2.0 for individual adult/adolescent trials. Note that the combined sample size of 9,742 was still smaller than the design sample size of 11,700 for each of the adult/adolescent trial, which was one of the factors in determining the 2.0 NI margin.

Reference ID: 4301706

Table 9. Adolescent/Pediatric Population (4 Trials, ITT)

Trial	Events/N*	Events/N LABA+ICS**	Events/N ICS**	HR*** [95% CI]
VESTRI	48/6208	27/3107	21/3101	1.291 [0.730, 2.283]
Meta-analysis (4 Trials)	65/9742	35/4844	30/4898	**1.182 [0.726, 1.926]**

* Randomized subjects who have taken at least one dose of study medication
** Planned treatment
*** Hazard ratio of LABA+ICS to ICS. The single trial analysis used a non-stratified Cox proportional hazards model using a single covariate of planned treatment. The combined analysis used a Cox model stratified by trial.

Table 10. Adolescent/Pediatric Population (4 Trials, mITT)

Trial	Events/N*	Events/N LABA+ICS**	Events/N ICS**	HR*** [95% CI]
VESTRI	47/6208	27/3107	20/3101	1.359 [0.762, 2.423]
Meta-analysis (4 Trials)	63/9742	34/4844	29/4898	**1.221 [0.746, 1.997]**

* Randomized subjects who have taken at least one dose of study medication
** Planned treatment
*** Hazard ratio of LABA+ICS to ICS. The single trial analysis used a non-stratified Cox proportional hazards model using a single covariate of planned treatment. The combined analysis used a Cox model stratified by trial.

4.4.2 Findings in Additional Subgroups

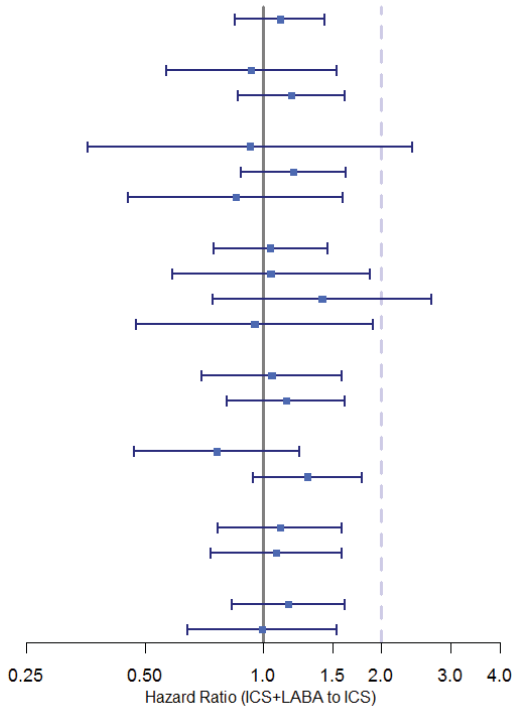
The subgroup analysis in Figure 3 examines the risk of the primary composite safety event associated with the use of LABA + ICS within the following subgroups: gender, age, race, region, ICS dose level, baseline ACQ score, and asthma hospitalization history of last 12 months prior to randomization. All subgroup analyses in this subsection were conducted in the primary analysis population only (3 adult/adolescent trials). The analysis model was the same as the primary analysis model. Confidence intervals are nominal; they are not corrected for multiple comparisons and are considered exploratory.

The largest point estimate was observed in the subgroup of races other than White or Black, with an HR estimate of 1.41 and 95% CI of [0.74, 2.69]. Subjects randomized to medium/high doses of ICS had a higher HR estimate of 1.30 [0.94, 1.64] than those randomized to low doses (HR estimate: 0.76 and 95% CI: [0.47, 1.24]). No obvious imbalances were observed in other subgroups examined, including gender, age, region, baseline ACQ or hospitalization history.

Reference ID: 4301706

Figure 3. Subgroup Analysis (ITT) Combining 3 Adult/Adolescent Trials

Meta-Analysis	LABA+ICS	ICS	HR [95% CI]
All ITT	116/17537	105/17552	1.104 [0.848,1.437]
Gender			
Male	30/5974	32/5960	0.933 [0.567,1.535]
Female	86/11533	73/11592	1.180 [0.864,1.612]
Age			
<18	8/1737	9/1797	0.926 [0.357,2.401]
18-64	90/13630	75/13690	1.195 [0.880,1.624]
>64	18/2080	21/2065	0.852 [0.454,1.599]
Race			
White	70/12935	67/12948	1.044 [0.747,1.460]
Black	24/1653	22/1575	1.046 [0.586,1.866]
Others	22/2949	16/3029	1.413 [0.742,2.690]
(Black&USA)	16/1026	16/980	0.951 [0.475,1.903]
Region			
USA	47/5462	45/5522	1.052 [0.699,1.584]
Others	69/12075	60/12030	1.144 [0.809,1.617]
ICS Dose			
Low	29/7127	38/7138	0.762 [0.470,1.235]
Med/High	87/10410	67/10414	1.298 [0.944,1.685]
ACQ (baseline)			
< 1.5	61/10277	56/10419	1.104 [0.768,1.587]
>=1.5	54/7246	49/7126	1.080 [0.734,1.590]
Past Hosp.(12m)			
0	75/15169	65/15251	1.158 [0.831,1.615]
>0	41/2367	43/2300	0.994 [0.643,1.537]



Note: Planned arm as single covariate for subgroups.

5. Summary and Conclusions

The primary objective of this meta-analysis is to compare the combination products of LABA plus ICS with ICS alone for the composite endpoint of asthma-related hospitalization, asthma-related intubation and asthma-related death during the 26-weeks study period in adolescent/adult population of age 12 or older. As shown in Table 11, the estimated hazard ratio of LABA plus ICS to ICS alone was 1.10, with a 95% CI of [0.85, 1.44]. The upper bound of the 95% CI is lower than the NI margin of 2.0 pre-specified for each adult/adolescent trial, indicating no excessive risk associated with LABA plus ICS compared to ICS alone. The meta-analysis findings for the asthma composite endpoint were consistent with results from individual trials and were supported by an on-treatment (mITT) sensitivity analysis, as well as a secondary analysis calculating MH RD instead of HR. All the estimated parameters (HR and RD) favored ICS over LABA plus ICS, but none of them showed statistical significance to demonstrate a difference between the two types of treatment. Therefore, neither an increase nor a decrease of risk of serious asthma events could be concluded from this meta-analysis. The majority of events in the composite endpoint were driven by asthma-related hospitalizations. Asthma-related intubation and death were rare: there were 2 asthma-related deaths across all 4 trials, both in Symbicort; there were 2 asthma-related intubations in the Advair adult/adolescent trial, both in ICS; there was 1 asthma-related intubation in the Symbicort arm.

Reference ID: 4301706

Table 11. Primary Meta-Analysis Results in Adult/Adolescent Population (3 Trials)

	LABA+ICS	ICS	Total
N	17537	17552	35089
Composite Event (%)	116 (0.66%)	105 (0.59%)	221 (0.63%)
HR [95% CI] (LABA+ICS to ICS)	**1.104 [0.848, 1.437]**		

There was a general trend of numerically higher HR (1.30 with 95% CI [0.94, 1.69]) for those randomized to medium or high ICS doses, as compared to those on low doses (HR: 0.76 [0.47, 1.24]), and this was consistently observed across all 4 trials, although none of the HR estimates were statistically significant. The dose assignment for the corticosteroid was based on the subject's previous asthma-medication regimen and asthma control. Races other than White or Black had a higher HR estimate of 1.41 and 95% CI of [0.74, 2.69]. There were no clear patterns among the other subgroups considered, which included subgroups based on region, baseline ACQ, sex, history of hospitalization, and age.

An examination of the Kaplan-Meier cumulative incidence curves for the asthma composite endpoint showed no clear separation of the two types of treatment over the duration of the trial (26 weeks). The events were driven by asthma hospitalizations as expected prior to the initiation of the trials.

The population of age younger than 18 was a subgroup of special interest in this meta-analysis. An Advair pediatric-only trial was combined with the other 3 adult/adolescent trials for this analysis. As shown in Table 12, the estimated HR for the risk of the asthma composite endpoint associated with LABA + ICS in this subgroup was 1.22 with a 95% CI of [0.75, 2.00]. The upper 95% CI was lower than the pre-specified NI margins of 2.0 (for individual adult/adolescent trials) and 2.7 (for the pediatric trial), showing no excessive risk associated with LABA plus ICS compared to ICS alone during the 26 weeks of study period for subjects younger than 18 years of age. An additional analysis including age as a continuous variable and an interaction between age and treatment was also conducted. The interaction between age and treatment was not shown to be statistically significant, suggesting no modification of treatment effect for subjects of different age.

Table 12 Meta-Analysis Results in Pediatric/Adolescent Population (4 Trials)

	LABA+ICS	ICS	Total
N	4844	4898	9742
Composite Event (%)	34 (0.70%)	29 (0.59%)	63 (0.65%)
HR [95% CI] (LABA+ICS to ICS)	**1.221 [0.746, 1.997]**		

Reference ID: 4301706

6. References

1. Levenson, Mark 2008. Long-Acting Beta-Agonists and Adverse Asthma Events Meta-Analysis. Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee. Link: https://wayback.archive-it.org/7993/20170405035612/https://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-01-FDA.pdf

2. Greenland S, Robins JM 1985. Estimation of a common effect parameter from sparse follow-up data. Biometrics 41:55-68.

3. Chowdhury, Badrul A., Sally M. Seymour, and Mark S. Levenson. "Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma." The New England journal of medicine 364.26 (2011): 2473-2475.

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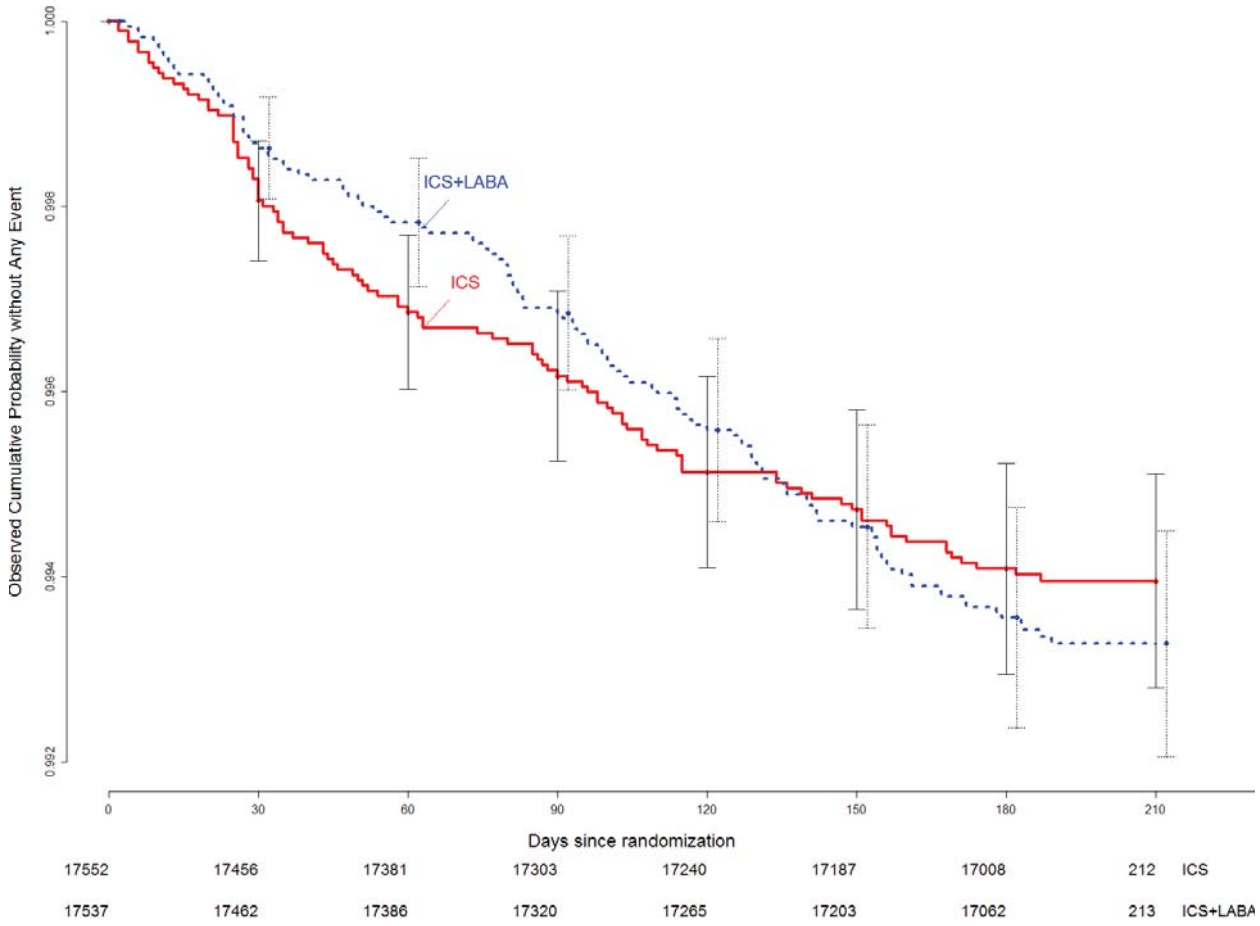
7. Appendix

7.1 Kaplan-Meier Survival Plots with 95% CIs at 30-Day Time Points

Figure 4 Survival Curves for Composite Endpoint with 95% CI (ITT)



Note: The numbers marked below the x-axis represent number of subjects at risk at annotated time points. The "at-risk" set includes the day noted on the x-axis. The 95% confidence bars on the K-M curves were calculated using the log-survival method (Therneau, 2000).

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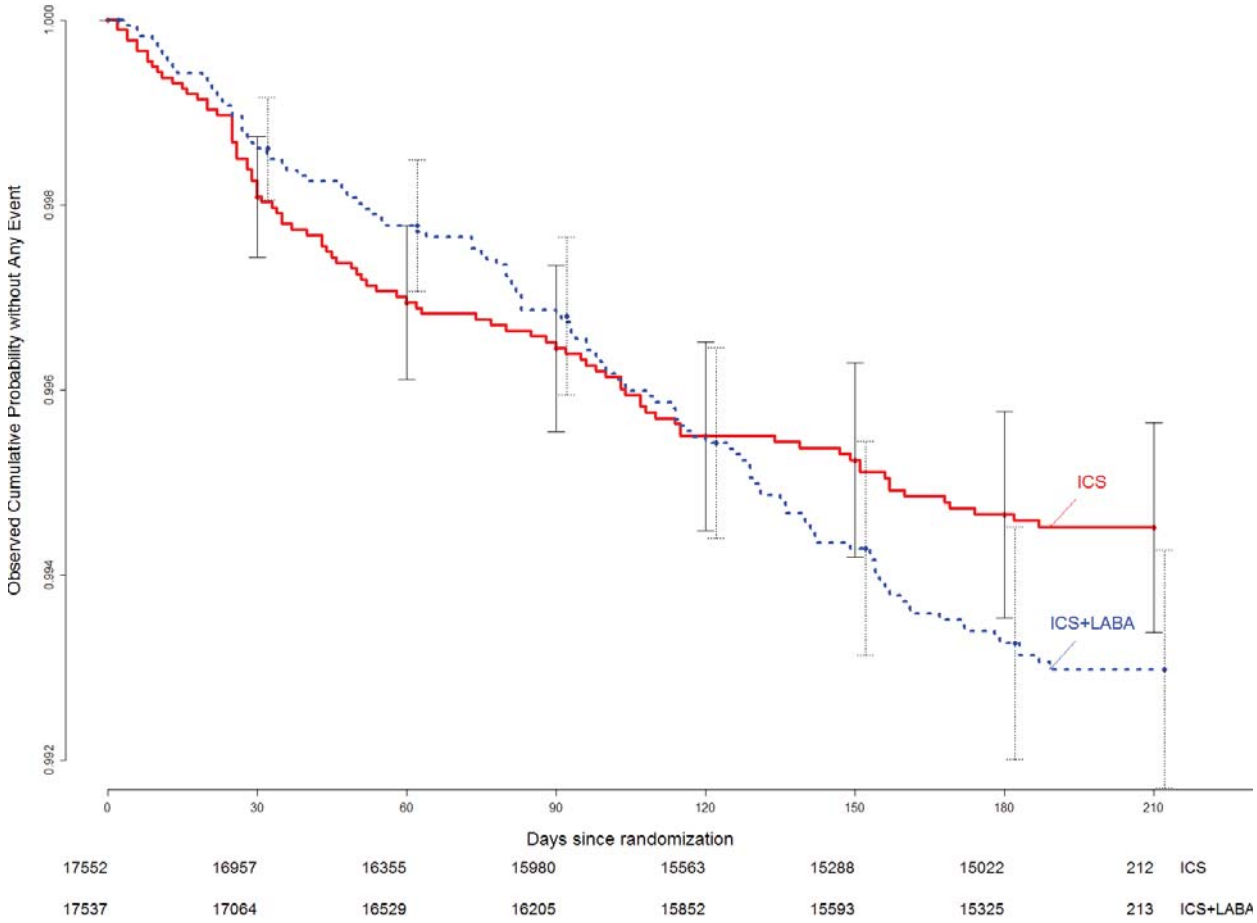
Figure 5 Survival Curves for Composite Endpoint with 95% CI (mITT)



Note: The numbers marked below the x-axis represent number of subjects at risk at annotated time points. The "at-risk" set includes the day noted on the x-axis. The 95% confidence bars on the K-M curves were calculated using the log-survival method (Therneau, 2000).

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	21077
Supplement #:	56/57 (eCTD Sequence Number: 0155/0159)
Drug Name:	Fixed combination of Fluticasone propionate and Salmeterol xinafoate
Indication(s):	Maintenance treatment of asthma
Applicant:	GlaxoSmithKline
Date(s):	Date received by reviewer: 12/9/2016 Stamp Date: 10/3/2016 PDUFA Date: 8/3/2017
Review Priority:	Standard
Biometrics Division:	OB/DB7 (on detail to OB/DB2 from 1/8 to 6/10/2017)
Statistical Reviewer:	Shanti Gomatam, Ph.D., Mathematical Statistician
Concurring Reviewer:	Gregory Levin, Ph.D., Associate Director, OB/DB2
Medical Division:	Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Clinical Team:	Medical Officer: Robert Lim, M.D. Medical Team Leader: Sally Seymour, M. D. (Deputy Division Director)
Project Manager:	Carol Hill
Keywords:	Asthma; efficacy assessment; long acting beta$_2$-agonist (LABA), inhaled corticosteroid (ICS), time to first exacerbations; rescue medication use; percent rescue-free days; percent asthma control days; Survival analysis; Cox proportional hazards model; exacerbations; ANCOVA; adults; adolescents; pediatric

DRAFT

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1 EXECUTIVE SUMMARY

Three doses of the fixed combination of fluticasone propionate (FP), an inhaled corticosteroid (ICS), and salmeterol, a long acting beta2-agonist (LABA), together abbreviated as FSC with tradename ADVAIR DISKUS, were first approved by the United States (US) Food and Drug Administration (FDA) on 8/24/2000 as maintenance treatment of asthma in patients 12 years of age and older. Approval for pediatric patients (4-11 years of age) was obtained on 4/21/2004.

A meta-analysis (Levenson 2008), that suggested a higher risk of serious asthma outcomes (death, intubation, hospitalizations) related to use of LABAs compared to placebo or other asthma drugs, was presented to a Joint meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee in December 2008. For trials that compared LABA/ICS to ICS alone, the effect was less clear. Recommendations for post-marketing safety clinical trials to further examine this possible relationship were presented by the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) to a joint meeting of the Pulmonary-Allergy Drugs Advisory and Drug Safety and Risk Management Advisory Committees in March 2010. Subsequent to this, a post-marketing requirement was issued to all manufacturers of LABA products for asthma to conduct controlled trials to assess the safety of LABA plus ICS versus ICS. Each applicant was to carry out an individual non-inferiority trial of LABA+ICS against an ICS-alone control arm for adults and adolescents 12 years of age and older for the composite of asthma-related deaths, asthma-related hospitalizations and asthma-related endotracheal intubations. The results of the individual applicant-specific studies would be pooled to test a class-wide effect of LABA+ICS versus ICS on the endpoint of asthma-related death. In addition, the FDA required GlaxoSmithKline (GSK), the manufacturer of ADVAIR DISKUS – the only ICS/LABA product approved in the US for use in patients under the age of 12 – to conduct a separate controlled study of pediatric patients.

This review focuses on the post-approval safety studies -- SAS115358 (VESTRI), designed by GSK to assess 2 doses of FSC versus equipotent doses of FP in pediatric patients (4-11 years old) with persistent asthma, and SAS115359 (AUSTRI), designed to assess 3 doses of FSC versus equipotent doses of FP in adolescent and adult subjects (≥ 12 years old) with persistent asthma. This statistical review evaluates the efficacy aspects of FSC relative to FP. A statistical review of the safety aspects of these trials is being conducted by Dr. Changming (Sherman) Xia.

1.1 Conclusions and Recommendations

The primary objective of the large, 26-week trials VESTRI and AUSTRI was to assess whether the addition of the LABA to ICS was non-inferior to ICS therapy alone in terms of the risk of serious asthma-related events (asthma-related hospitalization, endotracheal intubation and death). Dr. Xia's statistical assessment of the safety aspects indicates that the PMR can be considered successfully fulfilled from the safety perspective.

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A secondary objective of these trials was to assess whether the addition of LABA to ICS therapy was superior to ICS therapy alone in terms of measures of efficacy. The primary efficacy measure for both trials was time to first asthma exacerbation.

The assessment of efficacy in the adult and adolescent population (≥ 12 year olds) in the AUSTRI trial was based on the primary efficacy endpoint of asthma exacerbation and secondary efficacy endpoint of rescue medication use. Of the 11679 subjects who were randomized and took at least one dose of study drug in the AUSTRI trial, a total of 1077 subjects had at least one exacerbation. The pre-specified Cox-proportional hazards model-based analysis estimated a hazard ratio of **0.79** with an associated 95% confidence interval (CI) whose upper bound of **0.89** was less than 1.0 indicating a protective effect of FSC over FP for time to first exacerbation. The secondary endpoint of rescue medication use in AUSTRI estimated a mean difference of −0.19, for the mean number of rescue puffs/24 hours on the FSC arm minus that on the FP arm, with an associated 95% confidence interval of (−0.24, −0.14) for the overall Month 1-6 data. Overall the results for the secondary endpoint in AUSTRI generally support the primary efficacy conclusion of superiority of FSC over FP for the adult and adolescent population.

The assessment of efficacy in the pediatric population (4-11 year olds) in the VESTRI trial was based on the primary efficacy endpoint of asthma exacerbations and secondary efficacy endpoints of rescue-free days and asthma control days. Of the 6208 subjects who were randomized and took at least one dose of study drug in this trial, a total of 574 subjects had at least one exacerbation. A hazard ratio of **0.86** with an associated 95% confidence interval of (**0.73, 1.01**) was estimated for the primary efficacy endpoint. Since the upper bound of the confidence interval exceeded 1, superiority of FSC over FP has not been established in terms of time to first exacerbation for this pediatric population. However, it should be kept in mind that the trial was not powered for the efficacy endpoints.

A difference of **0.7**, with an associated 95% CI of **(-0.9, 2.3)**, was estimated for the secondary endpoint of mean percent of rescue-free days on the FSC arm minus that on the FP arm in the overall population; a difference of **0.7** with an associated 95% CI of **(-0.7, 2.1)** was estimated for the mean secondary endpoint of asthma control days. So, although the mean percent of rescue-free days and asthma control days both tended to be higher on average in the FSC arm for the overall Month 1-6 period, they were not significantly higher at the nominal 5% level.

Although statistical superiority was not established for primary and secondary efficacy endpoints in the VESTRI trial the results for these endpoints trended in the right direction. It should be kept in mind that the VESTRI trial was not powered for the efficacy endpoints. The determination of superiority for efficacy endpoints in the adult and adolescent population, along with the results observed for the pediatric population, lend credibility to potential superiority for efficacy in the pediatric population if there is clinical evidence of the similarity of disease processes in the two populations.

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1.2 Statistical Issues and Findings

VESTRI and AUSTRI were large post-approval safety studies designed by GSK – VESTRI to assess 2 doses of FSC versus equipotent doses of FP in pediatric patients (4-11 years old) with persistent asthma, and AUSTRI to assess 3 doses of FSC versus equipotent doses of FP in adolescent and adult subjects (>= 12 years old) with persistent asthma.

The following statistical issue is noted:

> For both trials the primary efficacy endpoint analysis was time to first exacerbation which was analyzed using survival analysis methods which rely on the assumption of non-informative censoring. For the primary efficacy analyses the applicant censored subjects without exacerbation events at the date of last treatment – this follows neither the intention-to-treat (ITT) (up to 6 months of follow-up) nor the modified intention-to-treat (mITT) (follow-up up to 7 days post-treatment-discontinuation) analysis approaches that were pre-specified. No missing data sensitivity analyses were proposed or conducted by the applicant for the efficacy endpoints. A discussion of the potential impact of missing data on the primary efficacy endpoint is included in the body of the review and indicates that result of superiority for the primary efficacy endpoint in AUSTRI is likely robust to the missing data.

The assessment of efficacy in the adult and adolescent population (≥ 12 year olds) in the AUSTRI trial was based on the primary efficacy endpoint of asthma exacerbations and secondary efficacy endpoints of rescue medication use. Of the 11679 subjects who were randomized and took at least one dose of study drug in this trial, approximately 83% completed the study treatment in both treatment arms. A total of 1077 subjects had at least one exacerbation. Table 1 contains details of the primary efficacy endpoint estimate for the ITT population.

Table 1: Pre-specified Primary Analysis of Primary Efficacy Endpoint (ITT; AUSTRI)

	FSC	**FP**	**Hazard Ratio**[1] (95% CI)
All Ages (≥ 12 years) (n=11679)	**5834**	**5845**	
First exacerbation events (1077)	480	597	0.79 (0.70, 0.89)
[1]: Cox proportional model with fixed treatment effect and randomization strata as covariates used for these analyses as pre-specified in RAP.			

Source: Created by reviewer using adtte xpt

The secondary endpoint of rescue medication use in AUSTRI estimated a mean difference of **−0.19**, for the mean number of rescue puffs/24 hours on the FSC arm minus that on the FP arm, for the ITT analysis, with an associated 95% confidence interval of **(−0.24, −0.14)** for the overall

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Month 1-6 data. t population. Overall the results for AUSTRI generally support the primary efficacy conclusion of superiority of FSC over FP for the adult and adolescent population.

The assessment of efficacy in the pediatric population (4-11 year olds) in the VESTRI trial was based on the primary efficacy endpoint of asthma exacerbations and secondary efficacy endpoints of rescue-free days and asthma control days. Of the 6208 subjects who were randomized and took at least one dose of study drug in this trial, approximately 88% completed the study treatment in both treatment arms. A total of 574 subjects had at least one exacerbation. Table 2 contains details of the primary efficacy endpoint estimate for the ITT analysis.

Table 2: Pre-specified Primary Analysis of Primary Efficacy Endpoint (ITT; VESTRI)

	FSC	**FP**	**Hazard Ratio**[1] (95% CI)
All Ages (4-11 years)[2] **(n=6208)**	**3107**	**3101**	
First exacerbation events(574)	265 (8.53%)	309 (9.96%)	0.86 (0.73, 1.01)

[1]: Cox proportional model with fixed treatment effect and randomization strata as covariates used for these analyses as pre-specified in the RAP/SAP.
2: One subject on the FSC arm was listed as being 12 years old, this subject was included in the analyses in the 4-11 age group.

Source: Created by reviewer using adtte xpt

A difference of **0.7**, with an associated 95% CI of **(-0.9, 2.3)**, was estimated for the mean percent of rescue-free days on the FSC arm minus that on the FP arm in the overall population; a difference of **0.7** with an associated 95% CI of **(-0.7, 2.1)** was estimated for the mean percent of asthma control days. So, although the mean percent of rescue-free days and asthma control days both tended to be higher on average in the FSC arm for the overall Month 1-6 period, they were not significantly higher.
Statistical superiority of FSC over FP was not established for either primary or secondary endpoints in the VESTRI trial although results trended favorably.

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2 INTRODUCTION

2.1 Overview

Asthma is a chronic disease of the airways characterized by inflammation, bronchoconstriction, and airway hyper-responsiveness.

Fluticasone propionate (FP), an inhaled corticosteroid (ICS), has been shown to be effective in the treatment of the inflammatory component of asthma, and salmeterol, a long acting beta$_2$-agonist (LABA), has been shown to be effective in alleviating smooth muscle contraction. Studies in adults and adolescents have demonstrated that the addition of a LABA to an ICS improves several aspects of asthma control, such as improving lung function and current control of asthma symptoms as well as reducing the risk of asthma deterioration requiring treatment with systemic corticosteroids.

The fixed combination of fluticasone propionate with salmeterol (FSC) was first approved by the FDA on 8/24/2000 for patients 12 and older. It was first approved in the 4-11 year old pediatric population on 04/21/2004. FSC is marketed in the US as ADVAIR (and outside the US as SERETIDE, VIANI, ADOAIR and other trade names).

Subsequent to this approval a clinical study, (Salmeterol Multicenter Asthma Research Trial [SMART]), initiated shortly after the approval of salmeterol (Nelson, 2006) and comparing the safety of salmeterol to placebo added to usual therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol. A meta-analysis (Levenson 2008), that suggested a higher risk of serious asthma outcomes (death, intubation, hospitalizations) related to use of LABAs compared to placebo or other asthma drugs, was presented to a Joint meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee in December 2008. For trials that compared LABA with ICS to ICS alone, the effect was less clear. Recommendations for post-marketing safety clinical trials to further examine this possible relationship were presented by the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) to a joint meeting of the Pulmonary-Allergy Drugs Advisory and Drug Safety and Risk Management Advisory Committees in March 2010. FDA developed the structure of the trials and approximate sample size based on the March 2010 advisory committee meeting, meetings with LABA manufacturers, and in consultation with academic experts.

As a result of these discussions, a post-marketing requirement was issued to all manufacturers of LABA-containing products for asthma to conduct controlled trials to assess the safety of LABA plus ICS versus ICS alone. Each applicant was to carry out an individual non-inferiority trial of LABA+ICS against an ICS-alone control arm for adults and adolescents 12 years of age and older. The results of the individual applicant-specific studies would be pooled to test a class-wide effect of LABA+ICS versus ICS on the endpoint of asthma-related death. In addition, the FDA

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required GlaxoSmithKline (GSK), the manufacturer of Advair Diskus the only ICS/LABA product approved in the US for use in patients under the age of 12, to conduct a separate controlled study of pediatric patients. Specifically, on April 14, 2011, FDA issued two post-marketing requirements to GlaxoSmithKline:

- 1750-1 for a study in adults and adolescents (12 years and older) and
- 1750-2 for pediatric patients (4-11 years of age).

Prior to submission of this NDA design aspects of these studies submitted in the associated INDs (IND044090 and IND050703) were reviewed by the FDA primarily from the safety perspective (OB/DB7 reviewer, Dr. S. Gomatam). A pre-NDA review of a submission dated 5/3/2016 was conducted by Dr. Lan Zeng of OB/DB2. Dr. Zeng's review indicated the lack of information on multiplicity adjustments across primary safety and secondary efficacy endpoints in study synopses provided. In addition, her review mentioned that there was no information on pre-specification of pooling of FSC and FP dose groups in the efficacy analyses, and on whether such pooling was deemed acceptable by the FDA.

This review focuses on the post-approval safety studies SAS115359 (AUSTRI) and SAS115358 (VESTRI) designed by GSK in response to PMR 1750-1 and PMR 1750-2 respectively. SAS115359 assesses 3 doses of FSC versus equipotent doses of inhaled FP over 26 weeks in adolescent and adult subjects (≥ 12 year olds) with persistent asthma. SAS115358 assesses two doses of FSC versus equipotent doses of FP over 26 weeks in pediatric (7-11 year olds).
This statistical review evaluates the efficacy aspects of FSC relative to FP in terms of asthma exacerbations and albuterol/salbutamol use (AUSTRI), and asthma exacerbations, rescue-free days and asthma control days (VESTRI). The filing review for efficacy aspects of this supplement was conducted by Dr. Lan Zheng of OB/DB2. The statistical review of the safety aspects of this trial was conducted by OB/DB7 -- Dr. Shanti Gomatam conducted the filing review and Dr. Changming (Sherman) Xia carried out all other aspects of the safety statistical review.

2.2 Data Sources

The applicant submitted study summaries, clinical study reports and analysis datasets for this supplement on October 3, 2016. The study reports are available at the following EDR link:
\\cdsesub1\evsprod\NDA021077\0147\
\\cdsesub1\evsprod\NDA021077\0153\

3 STATISTICAL EVALUATION

This statistical review is focused on two Phase IV safety trials – AUSTRI in the adult and adolescent population, and VESTRI in the pediatric population. For a statistical evaluation of safety aspects of this supplement refer to the review by Dr. Changming (Sherman) Xia.

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3.1 Data and Analysis Quality

Data and reports for this submission were submitted electronically. The reviewer was able to perform all analyses in the review below using the submitted electronic data.

3.2 Evaluation of Efficacy

3.2.1 Efficacy Evaluation for Adult and Adolescent Population based on SAS115359 (AUSTRI)

3.2.1.1 Study Design and Endpoints for AUSTRI

This study was a GSK-specific protocol that was designed to evaluate the composite endpoint of serious asthma-related outcomes. The results from this study were to be combined with those from other product-specific studies in a meta-analysis to specifically assess the composite endpoint of asthma-related endotracheal intubation and death, and to assess separately the endpoint of asthma-related death.

A Phase IV, global, multicenter, randomized, stratified, double-blind, parallel group, active comparator, 26-week trial was to be conducted in 11,664 adolescent (12-17 years of age) and adult (≥ 18 years of age) subjects whose asthma warranted treatment with controller asthma therapy. The study was to be conducted in 1100 centers in approximately 50 countries, with each site to recruit approximately 10-12 subjects.
The **primary objective** of the trial was to evaluate whether the addition of LABA to ICS therapy (FSC) is non-inferior to ICS alone (FP) in terms of the risk of serious asthma related events (asthma-related hospitalization, endotracheal intubation, and death). To declare non-inferiority the upper bound of the 95% confidence interval on the estimate of relative risk of serious events associated with LABA plus ICS compared with ICS alone was to be less than 2.0.
A **secondary objective** of the study was to evaluate whether the addition of LABA to ICS therapy (FSC) was superior to ICS therapy alone (FP) in terms of measures of efficacy. The primary measure of efficacy in the trial was the occurrence of severe asthma exacerbation. The upper bound of the 95% confidence interval of the relative risk of an asthma exacerbation associated with LABA plus ICS compared with ICS alone would have to be less than 1.0 to declare superiority. A secondary measure of accuracy was albuterol/salbutamol use.

Subjects who provided informed consent and met all of the inclusion criteria and none of the exclusion criteria were to be randomized based on their ACQ-6 scores and previous asthma medications. Randomization within each stratum was to be 1:1 for FSC vs. FP, stratified by current asthma medication, and ACQ-6 score. ACQ-6 score and current asthma medication were to be assessed at Visit 1 and determined the dose of FSC or FP that was assigned. Subjects were

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to be assigned to one of the following six possible blinded study treatments which were to be administered through one inhalation twice daily (morning and evening approximately 12 hours apart) via dry powder inhaler (DPI):

- FP 100mcg
- FSC 100/50 mcg
- FP 250 mcg
- FSC 250/50 mcg
- FP 500 mcg
- FSC 500/50 mcg

The applicant presented the treatment assignment in Table 1 in its protocol.

Table 3: Treatment assignment (AUSTRI)

Randomization Strata	ACQ-6 Score and Current Asthma Medication	Randomization Assignment
A	**ACQ-6 <1.5*** on low dose ICS or on low dose ICS and one or more adjunctive therapy (LABA, LTRA, theophylline)	FSC 100/50 or FP 100
B	**ACQ-6 <1.5*** on medium dose ICS or on medium dose ICS and one or more adjunctive therapy (LABA, LTRA, theophylline)	FSC 250/50 or FP 250
C	**ACQ-6 <1.5*** on high dose ICS or high dose ICS and one or more adjunctive therapy (LABA, LTRA, theophylline)	FSC 500/50 or FP 500
D	**ACQ-6 ≥1.5*** on daily rescue medication or LTRA monotherapy or daily theophylline**	FSC 100/50 or FP 100
E	**ACQ-6 ≥1.5*** on low dose ICS or on low dose ICS and one or more adjunctive therapy (LABA, LTRA, theophylline)	FSC 250/50 or FP 250
F	**ACQ-6 ≥1.5*** on medium dose ICS or medium dose ICS and one or more adjunctive therapy (LABA, LTRA, theophylline)	FSC 500/50 or FP 500

*For the purpose of this protocol ACQ-6<1.5 = controlled status; ACQ-6≥1.5 = not well controlled asthma
**For subjects entering on daily rescue medication or LTRA monotherapy or theophylline, must be using daily rescue medication or LTRA monotherapy or daily theophylline for at least 4-weeks prior to randomization with no other controller.

Source: Applicant protocol for SAS115359, Amendment 4

Subjects were to participate in the trial for a maximum of 29 weeks comprised of a randomized visit (Visit 2) followed by a treatment period of 26 weeks and a follow-up phone call to assess for serious adverse events that occur within the 7 days after cessation of double-blind study treatment. The study design schematic in Figure 1 is presented by the applicant.

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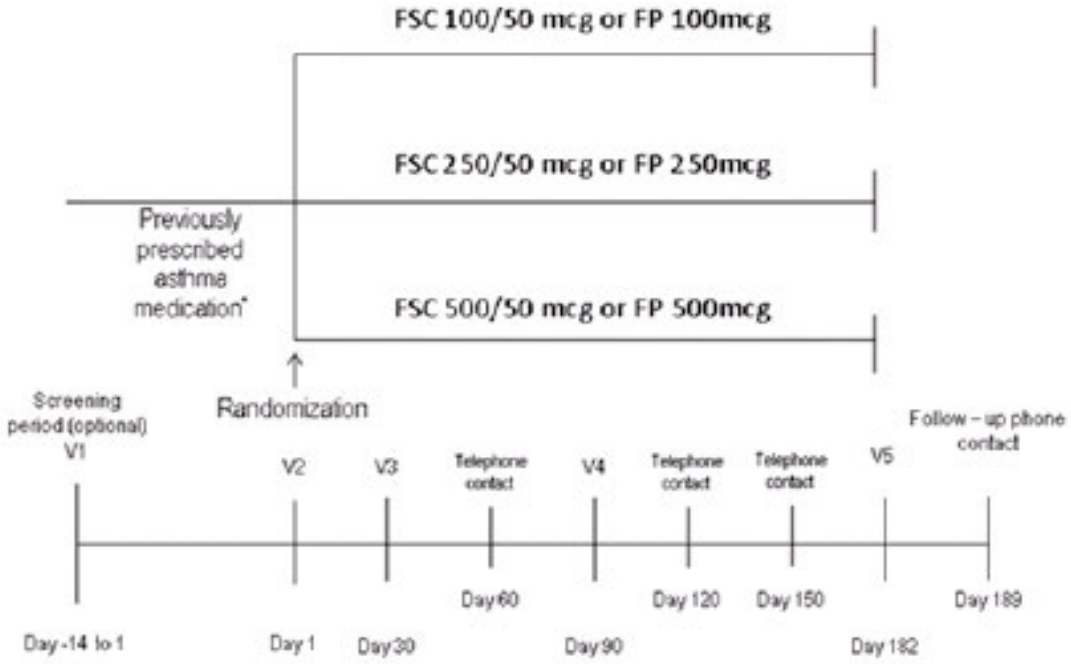
Figure 1: AUSTRI Study Design Schematic



Source: CSR for SAS115359

Primary Safety Endpoint: The primary safety endpoint was the number of subjects experiencing an event in the composite endpoint of serious asthma outcomes (asthma-related hospitalizations, asthma-related endotracheal intubation, or asthma-related death) over the 26-week study period.

Secondary Safety Endpoints: The following secondary safety endpoints were pre-specified:

- Asthma-related deaths;
- Asthma-related endotracheal intubations;
- Asthma-related hospitalizations;
- Withdrawals due to asthma exacerbation.

Analyses aspects of the above safety endpoints are discussed in the safety statistical review by Dr. Changming (Sherman) Xia and will not be addressed here. This review focuses on the efficacy aspects of the trial.

The following efficacy endpoints were pre-specified:

- **Primary Efficacy Endpoint**: The primary efficacy endpoint was asthma exacerbation, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. For the purpose of this protocol a single depo-injectable dose of corticosteroid was to be considered

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equivalent to a 3-day course. Asthma exacerbations were to be obtained from the electronic case report forms (eCRF) exacerbation logs. Distinct exacerbations were to be separated by one week. If resolution date of first exacerbation to onset date of the second was ≤ 7 days then this event would be considered as a single exacerbation, rather than as two separate exacerbations.

- **The secondary efficacy endpoint** was albuterol/salbutamol use.

3.2.1.2 Statistical Methodologies for AUSTRI

Statistical methodologies used by the applicant for the primary and secondary efficacy endpoints are discussed below.

3.2.1.2.1 Analysis Methods for Primary and Secondary Efficacy Endpoints

Analysis Populations

The following analysis populations were defined in the Protocol (Amendment 4, dated May 4, 2014) and the Reporting and Analysis Plan (dated 6/10/2015):

Intention-to-treat (ITT): The Intention-to-treat (ITT) population was defined as all subjects randomized to study drug who took study drug. For this population subjects were to be analyzed according to the study drug they were assigned at randomization. ITT analyses were to include all data recorded within six months after first use of study treatment or within seven days after the last date of study treatment, whichever date falls later.

Modified Intention-to-treat (mITT)[1]: The modified intention-to-treat (mITT) population was the same as the ITT population. However, mITT analyses were to include data recorded during the period spanning a subject's first dose of study treatment to seven days after the last dose of study treatment.

Reviewer Comment: *The protocol states that the primary analysis population is the ITT population and the secondary analysis population is the mITT population, whereas the RAP states that the mITT population "will form the basis of all summaries of efficacy data."*

Primary Efficacy Endpoint Analyses:

Time to first asthma exacerbation was to be compared between treatment groups using a Cox proportional hazards regression model with terms for treatment group and asthma medication/asthma control randomization stratum. The estimated hazard ratio was to be

[1] The ITT and mITT populations include the same subjects – any differences in the ITT and mITT analyses would be due to differences in how events are censored for the two populations, i.e., whereas ITT analyses include events that occur in the period from 7 days after last dose to 6 months after the first dose if the 7-day window ends before the six-month window, the mITT analyses would exclude these events.

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presented with two-sided 95% confidence interval and p-value. For the time to first exacerbation analysis, subjects who withdrew early from the study treatment without experiencing an exacerbation were to be censored at the last date at which they are known not to have the event (i.e., treatment stop date). A Kaplan-Meier plot, showing the time-to-event curves of the two treatment groups was also to be presented.

As a supportive analysis the numbers of asthma exacerbations were to be compared between treatment groups using a negative binomial regression model with terms for treatment group and randomization stratum with log(time on treatment) as an offset variable. Treatment group adjusted mean exacerbation rates, the rate ratio, a 95% CI and corresponding p-value from the regression analysis were to be presented.

Reviewer Comment*: The exacerbation count is a different endpoint from the "time to first exacerbation." Thus what applicant lists as a "supportive analysis" for the primary endpoint is actually an analysis on a different, but potentially correlated, endpoint.*

Secondary Efficacy Endpoint Analysis:

The secondary endpoint for each subgroup was albuterol/salbutamol use. Mean values for albuterol/salbutamol use (puffs/24 hours) were to be compared between treatment groups using an analysis of covariance (ANCOVA) model, including terms for treatment group and randomization stratum. Differences in treatment group means for the overall six-month treatment period and for each one-month period were to be tested for statistical differences. Least square means and standard errors from the ANCOVA model were to be presented with the corresponding p-values and 95% CIs.

3.2.1.2.2 Brand-specific Interim Analysis and Multiple testing plan

No interim analyses were planned for the efficacy endpoints although a single interim analysis on the primary safety endpoint was planned when approximately half of the expected total number of subjects experiencing the composite primary safety endpoint had been observed. This brand-specific interim analysis was conducted by a third party not associated with the conduct of the study, reviewed by a Data Monitoring Committee (DMC) and governed by a DMC Charter.

A Joint DMC (JDMC) was to monitor accumulating asthma-related deaths and endotracheal intubations across applicant studies (four applicants were to conduct studies for the adult and adolescent indication; however, one applicant discontinued its study). A separate JDMC Charter included procedures of these statistical interim analyses to monitor asthma-related deaths and endotracheal intubations.
These interim analyses are being reviewed by the safety statistical team. Refer to the review(s) by Dr. Changming Xia for further details.

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No coherent multiple testing plan that covered all study endpoints was proposed in either the protocol or the RAP/SAP.
Reviewer Comments: *The applicant proposed to address only efficacy measures in its multiple testing plan. To control study-wise type I error all hypotheses in the trial should be considered collectively. In addition to the efficacy endpoints, the study also includes primary and secondary safety endpoints that are not addressed in the proposed multiple testing approach above.*

3.2.1.2.3 Missing Data Handling

Survival analysis methods (Cox proportional hazards models) that accounted for loss-to-follow-up via censoring were used for the primary efficacy analyses of time to first asthma-related exacerbation. The Cox proportional hazards model assumes non-informative censoring.

No missing data methods were specified in the protocol for efficacy endpoints.

3.2.2 Results and Conclusions (AUSTRI)

3.2.2.1 Patient Disposition, Baseline Demographic and Clinical Characteristics

The AUSTRI study was initiated on November 18, 2011 and completed on June 23, 2015. This study was conducted in 710 study centers worldwide in 33 countries in 5 regions – North America, Latin America, Europe, Africa and Asia Pacific regions. There were 12857 subjects screened/enrolled in the study. Of these subjects 1298 subjects failed screening, including 192 subjects who were re-screened and randomized. Of the 11751 subjects (12857-1298+192) who were randomized 40 subjects on the FSC arm and 32 subjects on the FP arm did not take a single dose of the study drug. These subjects are not included in the ITT/mITT population, which thus consisted of 11679 subjects.

Figure 2 and Table 4 present the disposition of study subjects. Approximately 99% of the ITT subjects completed the study and about 83% completed the treatment – 16% on the FSC arm and 18% on the FP arm discontinued study treatment.

Figure 2: Disposition of study subjects in AUSTRI

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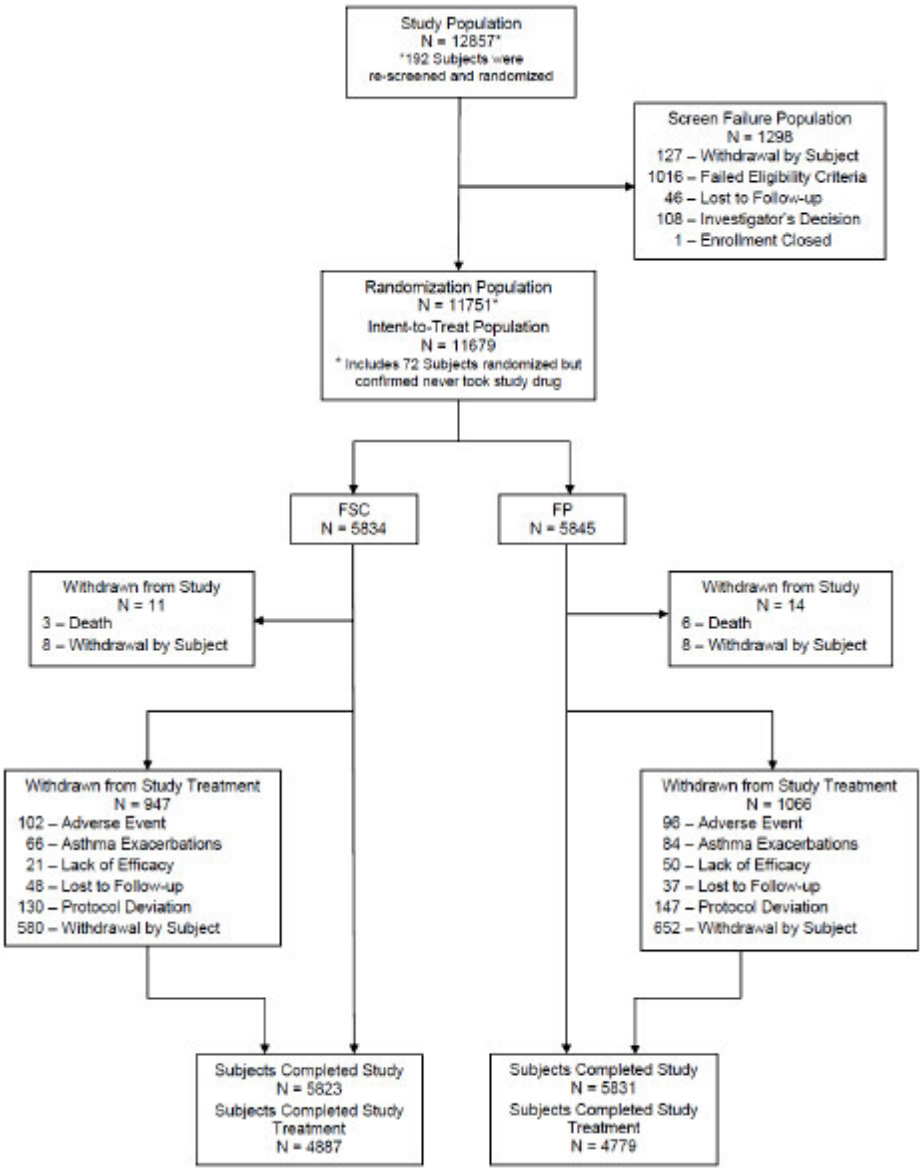

Source: CSR for SAS115359

Table 4: Disposition (All Randomized; AUSTRI)

N(% of ITT)	FSC	FP	Total
Randomized	5874	5877	11751
Randomized +Treated (ITT)	**5834 (100)**	**5845 (100)**	**11679 (100)**
Completed study	**5823 (99.1)**	**5831 (99.2)**	**11645 (99.2)**
Completed treatment	4887 (84)	4778 (82)	9665 (83)

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Withdrawn from treatment	936 (16)	1053 (18)	1989 (17)
Withdrawn from study; completed treatment	0	1	1
Withdrawn from study; withdrew from treatment	11	13	24
All patients not completing treatment	**947 (16.1)**	**1066 (18.1)**	**2013 (17.1)**
Adverse Event	102	96	198
Asthma exacerbation	66	84	150
Lack of efficacy	21	50	71
Lost to follow-up	48	37	85
Protocol deviation	130	147	277
Study closed/terminated	0	0	0
Withdrawal by subject	580	652	1232
Other			
Withdrew from study	**11 (0.2)**	**14 (0.2)**	**25 (0.2)**
Death	3	6	9
Lost to follow-up	0	0	0
Study closed/terminated	0	0	0
Withdrawal by subject	8	8	16
Other			

Source: CSR for SAS115359.

Baseline demographic characteristics for ITT (and also mITT) subjects are presented in Table 5 and baseline clinical characteristics are presented in Table 6. These tables indicate that the treatment arms are well-balanced in terms of demographics and key clinical covariates.

Table 5: Baseline Demographic Characteristics (ITT; AUSTRI)

	FSC (N=5834)	**FP (N=5845)**
Age (in years)		
Mean ± std dev	43.42±17.5	43.37±17.3
Median	45	45
12-17	615 (10.54 %)	615(10.5 %)
18-64	4576 (78.4 %)	4605 (78.8 %)
>64	643 (11.0 %)	625 (10.7 %)
Sex		
Female	3851 (66.01%)	3898 (66.69%)

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Male	1983 (33.99%)	3930 (33.65%)
Race		
White	4374 (74.97%)	4409 (75.20%)
Black or African American	870 (14.91%)	856 (14.64%)
Asian	368 (6.31%)	360 (6.16%)
Native Hawaiin or other Pacific Islander	8 (0.14%)	10 (0.17%)
Americian Indian or Alaskan Native	109 (1.87%)	116 (1.98%)
Multiracial	102 (1.75%)	91 (1.56%)
Other	0 (0 %)	0 (0%)
Ethnic Group (Hisp/Latino**)**	1013 (17.36%)	989 (16.92%)
U.S.A.	2637 (45.20%)	2587 (44.26%)
Region		
North America	2623 (44.96%)	2680 (45.85%)
Latin America	339 (5.81%)	338 (5.78%)
Europe	2110 (36.17%)	2091 (35.77%)
Asia/Pacific	285 (4.89%)	262 (4.48%)
Africa	477 (4.18%)	474 (8.11%)

Source: Created by reviewer using adsl xpt.

Table 6: Baseline Clinical Characteristics (ITT; AUSTRI)

	FSC (N=5834)	**FP (N=5845)**
Number of exacerbations requiring systemic corticosteroids in past 12 months		
0	50 (0.9)	46 (0.8)
1	4778 (81.9)	4795 (82.0)
2	775 (13.3)	740 (12.7)
3	186 (3.19)	202 (3.5)
4	45 (0.8)	62 (1.1)
Number of asthma-related hospitalizations in past 12 months		
0	4944 (84.7%)	4976 (85.1%)

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1	837 (14.3%)	800 (13.7%)
2	53 (0.9%)	69 (1.2%)
Asthma Duration[a] (in years)		
Mean ± std dev	16.9 ± 14.5	16.7 ± 14.3
Median	13	12
Smoking Status[b]		
Current Smoker	291 (5.0)	288 (4.9)
Former Smoker	876 (15.0)	896 (15.3)
Non-smoker	4667 (80.0)	4660 (79.7)
Pack Years[c]	4.13±3.8	4.02 ± 3.3
Mean ± std dev	4.13±3.8	4.02 ± 3.3
Median	3.5	3.5

a: There were no missing values for asthma duration.
b: Smoking history was missing for one subject on the FP arm.
c: Pack years were available for only 1166 subjects on the FSC arm and 1181 subjects on the FP arm.

Source: Created by the reviewer using adsl xpt and adexaca xpt

3.2.2.1.1 Primary Efficacy endpoint analyses

The pre-specified primary analysis for the efficacy endpoint, time to first asthma exacerbation, was a Cox proportional hazards model analysis that included terms for treatment group and randomization stratum.

The protocol and RAP were inconsistent on the approach for handling data collected after treatment discontinuation to be used for the primary efficacy analysis. In the analysis of the primary efficacy endpoint the applicant has not included information on exacerbations after treatment discontinuation – this is hence an "on-treatment" analysis that is neither the ITT nor mITT analyses discussed in the protocol and RAP.

Reviewer Comments:
Per the applicant's RAP (dated 6/10/2015) treatment group and randomization stratum were to be used as terms in the Cox proportional hazards model for the primary efficacy analysis. Table 7 below presents these analyses for the overall population. The applicant's analyses, as reported in the Clinical Study Report, used a Cox proportional hazards model stratified by randomization strata and including a fixed treatment effect. No differences were noted between results of the pre-specified model and that of the stratified model.
Neither were there differences between results of the ITT and mITT analyses for the primary efficacy endpoint – as expected, given that the applicant's analyses censored primary efficacy events post-treatment-discontinuation.

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For simplicity we present results on the RAP pre-specified Cox proportional hazards model labeled for the "ITT population" for the primary efficacy endpoint throughout this review unless otherwise noted.

Table 7: Pre-specified Primary Analysis of Primary Efficacy Endpoint (ITT; AUSTRI)

	FSC N= 5834	**FP** N= 5845	**Hazard Ratio**[1] (95% CI)
All Ages (≥ 12 years) (n=11679)	**5834**	**5845**	
First exacerbation events (1077)	480	597	0.79 (0.70, 0.89)
[1]: Cox proportional model with fixed treatment effect and randomization strata as covariates used for these analyses as pre-specified in RAP.			

Source: Created by reviewer using adtte xpt

Figure 3: Kaplan-Meier plots for time to first asthma exacerbation by treatment arm (ITT; AUSTRI)

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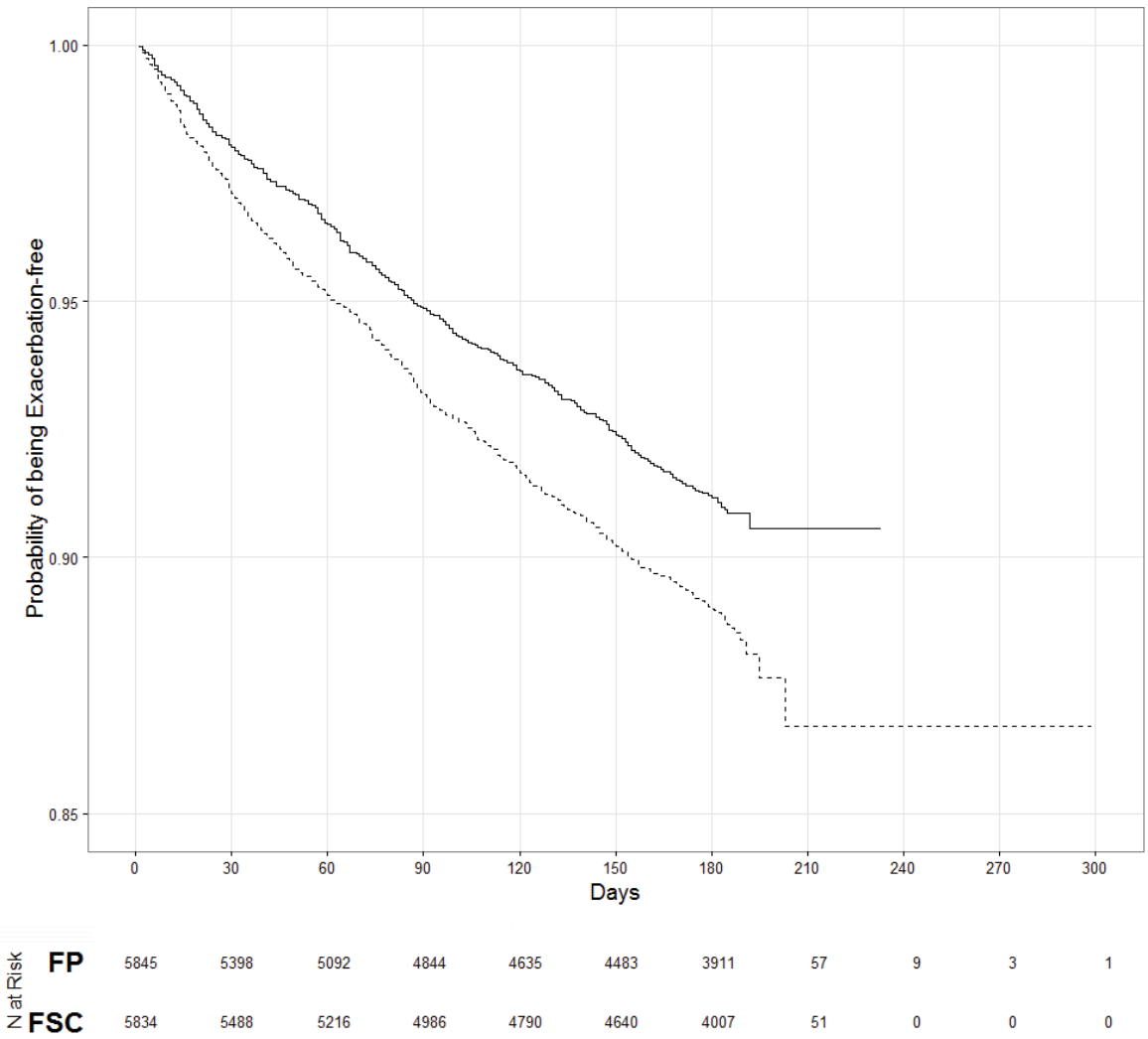

Source: Created by reviewer using adtte xpt.

Analysis of Primary Efficacy Endpoint by FSC/FP Dose Pairs

The study included 3 doses of FSC (FSC 100/50, FSC 250/50 and FSC 500/50) and 3 corresponding doses of FP (FP 100, FP 250, and FP 500). Table 8 below compares each FSC dose with the corresponding FP dose using a Cox proportional hazards model that includes treatment as fixed effect, and Figure 4 presents the corresponding Kaplan-Meier plots. We see from the table and figure that for every dose pair the probability of being exacerbation-free is higher for the FSC arm than the corresponding FP arm. For all except the highest dose pair (FSC 500/50 versus FP 500) the hazard ratio is significantly less than 1 at the nominal significance level. These results are generally supportive of the superiority of FSC over FP for time to first asthma exacerbation. The lack of statistical significance at the highest dose should be considered

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in conjunction with the fact that there is a smaller separation at the highest dose and that the study was not powered by dose.

Table 8: Cox PH model results for Primary Efficacy Endpoint by FSC/FP dose pairs (ITT; AUSTRI)

# events/# subjects (%)	FSC N= 5834	FP N=5845	Hazard Ratio[1] (95% CI)
FSC versus FP (all doses) 1077/11679 (9.22)	480/5834 (8.23)	597/5845 (10.21)	0.79 (0.70,0.89)
FSC 100/50 versus FP 100 248/3774 (6.57)	106/1882 (5.63)	142/1892 (7.51)	0.72 (0.56,0.93)
FSC 250/50 and FP 250 429/4420 (9.71)	186/2209 (8.42)	243/2211 (11.0)	0.75 (0.62, 0.91)
FSC 500/50 and FP 500 400/3485 (11.48)	188/1743 (10.79)	212/1742 (12.17)	0.87 (0.72, 1.06)

[1]: The Cox PH model with fixed treatment effect is used for all analyses in this table (randomization strata are confounded with dosing).

Source: Created by reviewer using adtte xpt and adsl xpt

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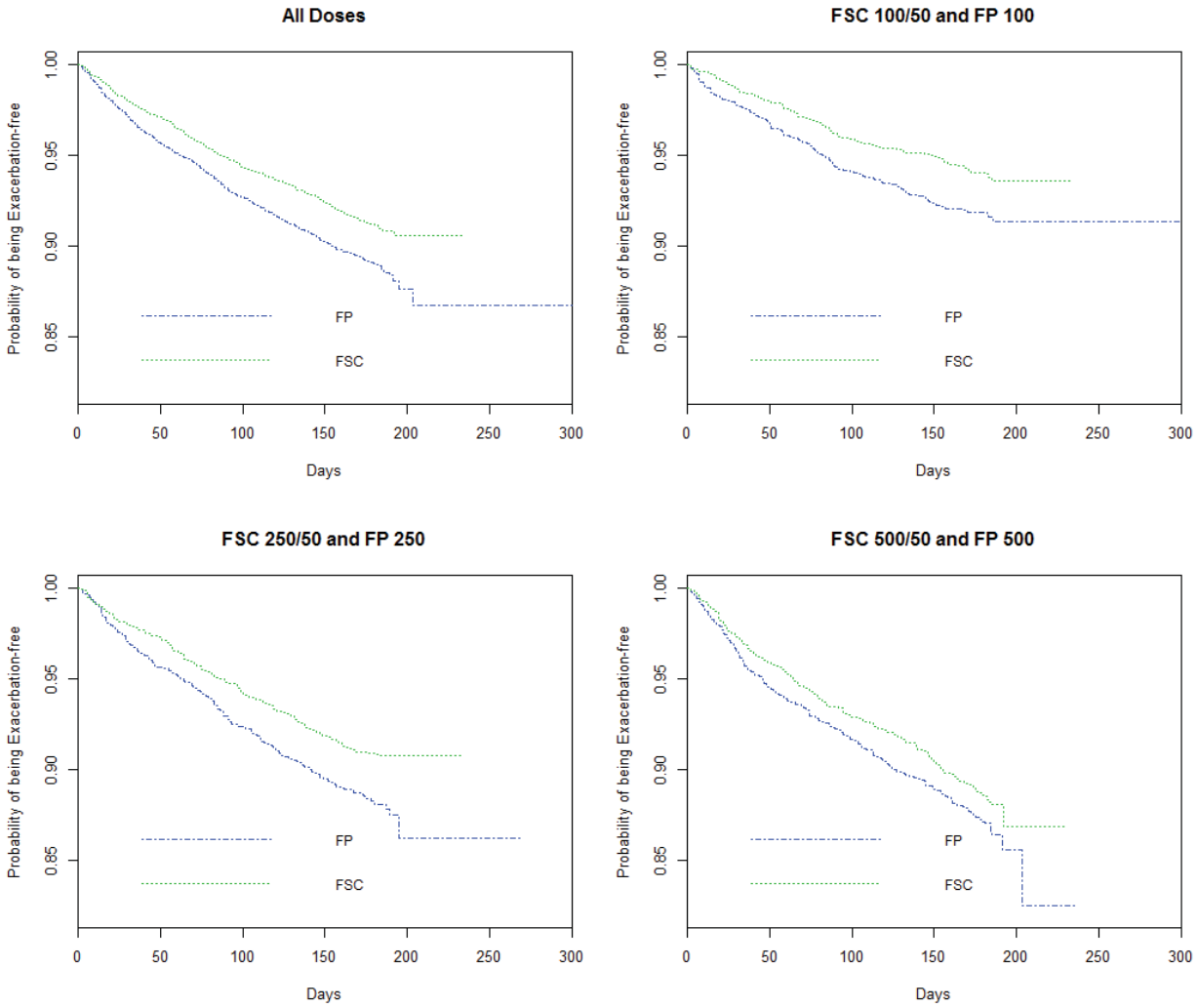
Figure 4: Figure Kaplan-Meier plots for Primary Efficacy Endpoint by FSC/FP dose pairs (ITT; AUSTRI)



Source: Created by reviewer using adtte xpt and adsl xpt

Potential Impact of Missing Data on the Primary Efficacy Endpoint

Although the applicant defines ITT (including events from up to 6 months of follow-up) and mITT (including events that happened up to 7 days after last treatment dose) analyses in its protocol and RAP, for the primary efficacy endpoint subjects without events until last treatment dose were censored at the last treatment dose date, i.e., any exacerbation events that may have occurred after day of last treatment dose were not included in the primary efficacy analyses which was carried out using a Cox proportional hazards model – his approach relies on the

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assumption of non-informative censoring. Had such events been included, would the estimated hazard ratio have been different enough to change the conclusion? Ideally a tipping point analysis that assessed how a change in hazards (varied by treatment arm) in the post-treatment discontinuation data could affect the estimated hazard ratio would have been carried out. However, neither the applicant nor this reviewer carried out such an analysis. As the violin[2] plot in Figure 5 and the statistics on exposure distribution by arm in Table 9 show, treatment exposure was similar across both treatment arms. Table 10 and Table 11 indicate that the distribution of key baseline demographic and clinical characteristics was similar across treatment groups for the subjects who had no event and were censored at last treatment date. Since a hazard ratio of 0.79 with an associated 95% confidence interval of (0.70, 0.89) was estimated for the primary efficacy endpoint in AUSTRI it is unlikely that the conclusion of superiority would be over-turned unless hazards in the post-treatment discontinuation period were much worse in the FSC arm than in the FP arm, which is unlikely given the above. Thus it seems reasonable to infer that the conclusion of superiority for FSC over FP in the AUSTRI trial is robust to the missing information.

[2] Violin plots are combinations of box plots and density plots. The central line shows the information in a traditional box plot while the outlines provide information on distribution of values through a density plot. Reflection of the density plot on either side of the central line is purely for visual effect.

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Figure 5: Distribution of Days of treatment exposure by Treatment Arm (ITT, AUSTRI)

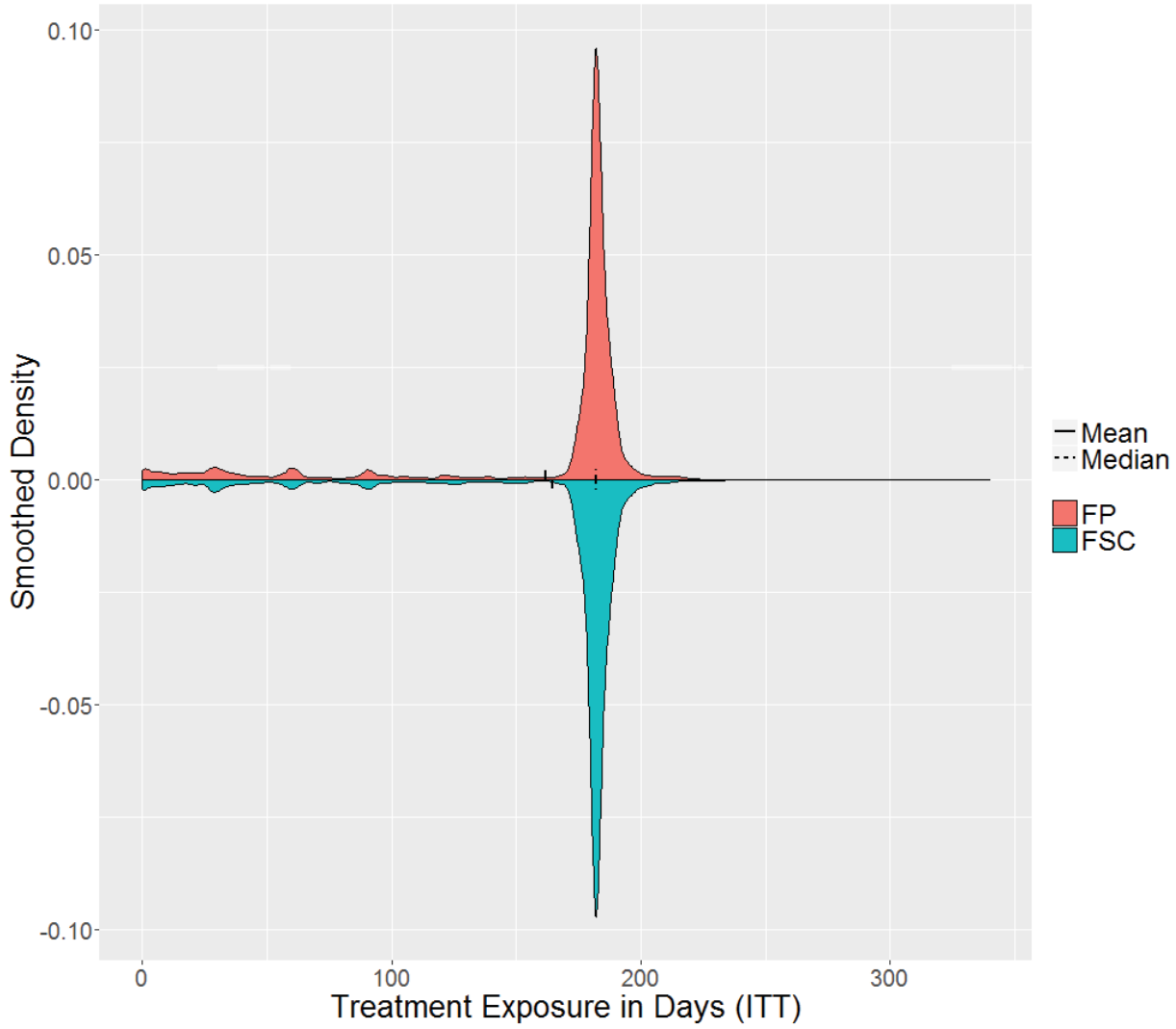

Table 9: Statistics on Days of Exposure (ITT, AUSTRI)

	ITT subjects	
	FSC	**FP**
Mean (std.dev.)	164.52 (47.37)	161.85 (50.85)
Median	182	182

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Table 10: Baseline Demographic Characteristics for subjects who were censored at treatment discontinuation date with no event (AUSTRI)

	FSC (N=83)	FP (N=131)
12-17	4 (4.8)	11 (8.4)
18-64	67 (80.7)	104 (79.4)
>64	12 (14.5)	16 (12.2)
Sex		
Female	66 (79.5)	101 (77.1)
Male	17 (20.5)	30 (22.9)
Race		
White	66 (79.5)	105 (80.2)
Black or African American	11 (13.3)	17 (13.0)
Asian	4 (4.8)	6 (4.6)
U.S.A.	54 (65.1)	87 (66.4)

Source: Created by reviewer using adsl xpt.

Table 11: Baseline Clinical Characteristics for subjects who were censored at treatment discontinuation date with no event (AUSTRI)

	FSC (N=83)	FP (N=131)
Number of exacerbations requiring systemic corticosteroids in past 12 months		
0	0	0
1	59 (71.1%)	88 (67.2%)
2	19 (22.9%)	32 (24.4%)
3	3 (3.6%)	11 (8.4%)
4	2 (2.4%)	0 (0%)
Number of asthma-related hospitalizations in past 12 months		

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0	77 (92.8%)	121 (92.4%)
1	5 (6.0%)	9 (3.8%)
2	1 (1.2%)	1 (10.8%)
Asthma Duration (in years)		
Mean ± std dev	21.2 ± 16.47	20.1 ± 15.58
Median	14	14
Smoking Status		
Current Smoker	6 (7.2%)	10 (7.6%)
Former Smoker	15 (18.1%)	29 (22.1%)
Non-smoker	62 (74.7%)	92 (70.2%)
Pack Years[a]		
Mean ± std dev	4.22±3.20	4.10 ± 3.10
Median	4.5	3
a: 62 subjects on the FSC arm and 92 subjects on the FP arm were missing values for pack years.		

Source: Created by reviewer using adsl.xpt and adexaca.xpt.

3.2.2.1.2 Secondary Efficacy Endpoint Analyses – Rescue Medication Use

The pre-specified analysis on the secondary efficacy endpoint of rescue medication use compares mean values for albuterol/salbutamol use in puffs/24 hours between treatment groups using an ANCOVA model, including terms for treatment group and randomization stratum. Least square means and standard errors from the ANCOVA model are presented with the corresponding estimated differences and 95% CIs in Table 11 for the overall six-month treatment period and for each one-month period. The upper bounds of the nominal 95% CIs for the estimated mean differences are <0 for all comparisons, thus indicating reduced rescue medication use on the FSC arm over the treatment period.

Table 12: Results of pre-specified ANCOVA model analysis for rescue medication use (AUSTRI)

Mean ± SE (95% CI)	FSC N= 5834	FP N=5845	Estimated Difference[1] (95% CI)
Month 1	1.05 ±0.02 (1.01, 1.10)	1.23± 0.02 (1.20, 1.28)	-0.18 (-0.24, -0.13)
Month 2	0.89± 0.02 (0.85, 0.93)	1.09± 0.02 (0.05, 1.13)	-0.20 (-0.25, -0.14)

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Month 3	0.87± 0.02 (0.83, 0.91)	1.04± 0.02 (1.00, 1.08)	-0.17 (-0.23, -0.11)
Month 4	0.86± 0.02 (0.82, 0.90)	1.01± 0.02 (0.96, 1.05)	-0.15 (-0.21, -0.09)
Month 5	0.86 0.02 (0.82, 0.90)	0.99 0.02 (0.95, 1.03)	-0.12 (-0.19, -0.07)
Month 6	0.82± 0.02 (0.78, 0.86	0.99± 0.02 (0.95, 1.03	-0.17 (-0.23, -0.11)
Month 1-6	0.95± 0.02 (0.91, 0.99)	1.14±0.02 (1.10, 1.17)	-0.19 (-0.24, -0.14)

[1]: The ANCOVA model used for analysis is the pre-specified model for month 1-6 rescue use, with terms for treatment and randomization stratum. Difference estimated is of mean rescue medication use for the FSC arm minus that for the FP arm.

Source: Created by reviewer using adexaca xpt

3.2.3 Efficacy Evaluation for Pediatric Population based on SAS115358 (VESTRI)

3.2.3.1 Study Design and Endpoints for VESTRI

SAS115358 is a GSK-specific protocol to assess the effect of the inhaled fluticasone propionate (FP)/salmeterol combination (FSC) versus inhaled fluticasone propionate (FP) with respect to the composite endpoint of serious asthma-related outcomes.

A Phase IV, multi-center, randomized, stratified, double-blind, parallel group, 6-month study was to be conducted in pediatric subjects 4-11 years of age with persistent asthma. Approximately 6200 pediatric subjects were to be randomized 1:1:1:1 to 2 doses of FSC and 2 doses of FP.

The **primary objective** of the study was to evaluate whether the addition of a LABA to an ICS (FSC) therapy was non-inferior in terms of risk of serious asthma-related events (asthma-related hospitalization, endotracheal intubations, and deaths) compared with ICS alone in pediatric subjects (ages 4-11 years) with persistent asthma. To declare non-inferiority, the relative risk of serious asthma-related events associated with LABA plus ICS compared with ICS alone was to be less than 2.7 (a 2.7-fold increase), based on the upper bound of the 95% confidence interval (CI) on the estimate of relative risk.

A **secondary objective** of the study was to evaluate whether the addition of LABA to ICS therapy (FSC) was superior to ICS therapy alone in terms of measures of efficacy in pediatric subjects (4-11 years) with persistent asthma. The primary measure of efficacy was the occurrence of a severe asthma exacerbation. To declare superiority, the relative risk of an asthma exacerbation associated with LABA plus ICS compared with ICS alone was to be less than 1.0, based on the upper bound of the 95% CI on the estimate of relative risk.

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Potential subjects were to be screened at Visit 1 to assess eligibility which was based on pre-study asthma medications, assessment of asthma control based on Childhood Asthma Control Test, and a history of an asthma exacerbation requiring systemic corticosteroids in the previous year. At Visit 2, subjects were to be randomized to either inhaled FP 100mcg or FSC 100/50mcg, or FP 250mcg or FSC 250/50mcg based on the Childhood Asthma Control Test, number of exacerbations in the prior year and their prior asthma medication (parental/guardian observation was to be encouraged) as one inhalation from their inhaler each morning and evening at approximately 12 hours apart and approximately at the same time each day.

The applicant summarizes eligibility criteria in Table 13.

Table 13: Summary of eligibility criteria for VESTRI

Prior Asthma Therapy	Childhood Asthma Control Test score at Visit 1	One exacerbation in previous year	Two or more exacerbations in previous year
SABA, LTRA, theophylline or cromolyn	≥20	Not eligible	Not eligible
	≤19	Not eligible	Eligible
Low-dose ICS monotherapy	≥20	Not eligible	Eligible
	≤19	Eligible	Eligible
Low-dose ICS and one or more adjunctive therapy	≥20	Eligible	Eligible
	≤19	Eligible	Eligible
Medium-dose ICS monotherapy	≥20	Eligible	Eligible
	≤19	Eligible	Eligible
Medium-dose ICS and one or more adjunctive therapy	≥20	Eligible	Not eligible
	≤19	Not eligible	Not eligible

Source: Protocol for SAS 115358 (page 22/61)

The four possible blinded study treatments were:

- FP 100 mcg inhalation powder, 1 inhalation twice daily (morning and evening) via dry powder inhaler (FP DISKUS 100 mcg)
- FP 100 mcg and salmeterol 50 mcg inhalation powder, 1 inhalation twice daily (morning and evening) via dry powder inhaler (FSC DISKUS 100/50 mcg)
- FP 250 mcg inhalation powder, 1 inhalation twice daily (morning and evening) via dry powder inhaler (FP DISKUS 250 mcg)
- FP 250 mcg and salmeterol 50 mcg inhalation powder, 1 inhalation twice daily (morning and evening) via dry powder inhaler (FSC DISKUS 250/50 mcg).

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Subjects were to be categorized into one of 7 randomization groups based on their pre-study asthma medication, Childhood Asthma Control Test score, and number of asthma exacerbations in the prior year. The applicant's randomization groups are presented in Table 14.

Table 14: Randomization groups and treatment assignment (VESTRI)

Prior Asthma Therapy	Childhood Asthma Control Test score at Visit 1*	One exacerbation in previous year	Two or more exacerbations in previous year†	Randomization Group
SABA, LTRA, theophylline or cromolyn	≥20	Not eligible	Not eligible	Not eligible
	≤19	Not eligible	FSC 100/50 or FP 100	A
Low-dose ICS monotherapy	≥20	Not eligible	FSC 100/50 or FP 100	C
	≤19	FSC 250/50 or FP 250	FSC 250/50 or FP 250	B
Low-dose ICS and one or more adjunctive therapy	≥20	FSC 100/50 or FP 100	FSC 250/50 or FP 250	D f
	≤19	FSC 250/50 or FP 250	FSC 250/50 or FP 250	D
Medium-dose ICS monotherapy	≥20	FSC 100/50 or FP 100	FSC 250/50 or FP 250	E f
	≤19	FSC 250/50 or FP 250	FSC 250/50 or FP 250	E
Medium-dose ICS and one or more adjunctive therapy	≥20	FSC 250/50 or FP 250	Not eligible	G
	≤19	Not eligible	Not eligible	Not eligible

FP = fluticasone propionate FSC = FP/salmeterol combination; ICS = Inhaled corticosteroid; LABA =long acting beta$_2$- agonist; LTRA = leukotriene receptor antagonist

*Control defined by Childhood Asthma Control Test - **Controlled** defined as Childhood Asthma Control Test score≥20;

†Subjects with more than 4 separate exacerbations in the last 12 months from Visit 1 are not eligible for randomization.

Source: Protocol for SAS115358

Randomization within each stratum would be 1:1 for FSC vs. FP. Study treatments were double-blinded with respect to FSC vs. FP (but not in terms of ICS dose). Unblinding was only permitted in case of an emergency that required knowledge of study treatment for appropriate clinical management or welfare of the subject.

Subjects were to return to the clinic in 2 weeks (Visit 3), 2 months (Visit 4), 4 months (Visit 5) and 6 months (Visit 6). The Childhood Asthma Control Test was to be administered at Visits 1, 4, 5, 6 and at early withdrawal. Subjects were to be contacted via telephone at 1, 3, and 5 months post-randomization to monitor asthma status and study outcomes of interest. The study design schematic is presented in Figure 6.

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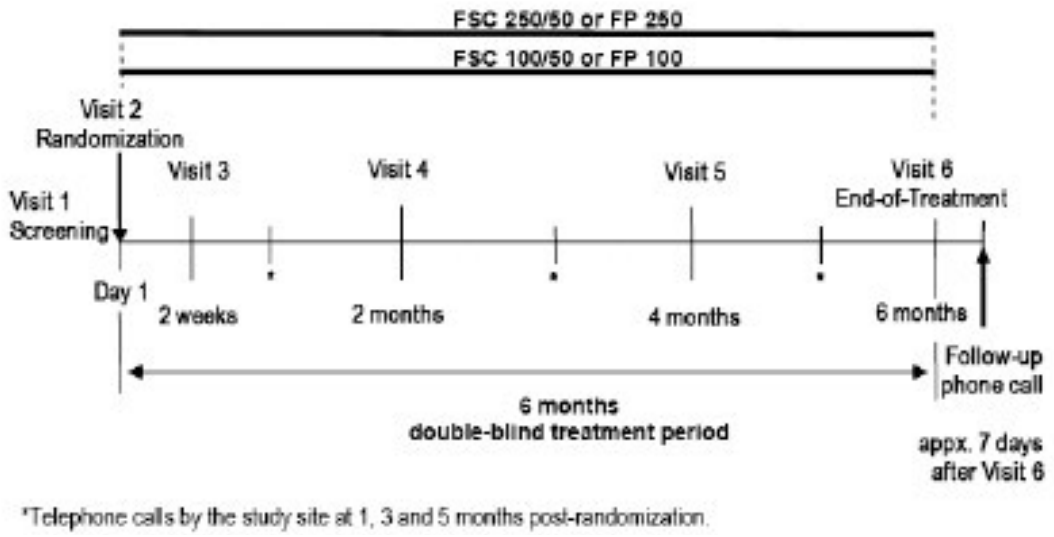
Figure 6: Study design schematic for VESTRI



Source: CSR for SAS 115358

Study Endpoints

Primary Safety Endpoint: The primary safety endpoint was the number of subjects experiencing the composite endpoint of serious asthma-related outcomes (asthma-related hospitalizations, endotracheal intubations, or deaths) over the 6-month study treatment period.

Hospitalization was defined as an inpatient stay or ≥ 24 hour stay in an observation area in an ED or other equivalent facility.

Secondary Safety Endpoints:

- Asthma-related deaths
- Asthma-related endotracheal intubations
- Asthma-related hospitalizations
- Withdrawals from study treatment due to asthma exacerbation

Analysis aspects of the above safety endpoints are discussed in the safety statistical review by Dr. Changming (Sherman) Xia and will not be addressed here. This review focuses on the efficacy aspects of this trial.

The following efficacy endpoints were pre-specified:

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Primary Efficacy Endpoint: The primary efficacy endpoint was time to first asthma exacerbation, where exacerbation was defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days (up to 10 days) or a single depot corticosteroid injection. Each exacerbation must have been separated by > 7 days from the discontinuation of oral corticosteroid (OCS) to be considered an individual event.

Secondary Efficacy Endpoints:

- Rescue-free days:
- Asthma control days: defined as days without
    - Rescue albuterol/salbutamol use (other than pre-exercise treatment)
    - Nighttime awakenings due to asthma
    - Asthma exacerbation
    - Missed work (caregiver) or school/daycare (subject) due to asthma and
    - When coughing from asthma score ≤ 1 and wheezing score =0.

3.2.3.2 Statistical Methologies for VESTRI

Statistical methodologies used by the applicant for the primary and secondary efficacy endpoints and additional analyses performed by the statistical reviewer are discussed below.

3.2.3.2.1 Analysis Methods for Primary and Secondary Efficacy Endpoints

The following analysis populations were defined in the Protocol (dated July 1, 2011) and the Reporting and Analysis Plan (dated December 9, 2015):

Intention-to-treat (ITT): The ITT population was to include all subjects randomized to study drug who took study treatment. Subjects were to be analyzed according to the study drug they were assigned at randomization. The ITT analysis was to include events that occur within six months after the first use of the study drug or seven days after the last use of study drug treatment, whichever date is greater. The ITT population was to be used for the primary analysis of the primary safety endpoint and its components, and for all summaries of background/demography data.

Modified Intention-to-treat (mITT): The mITT population included the same subjects included in the ITT population; however, the events included in the mITT analysis were to be those that occurred during the subject's period of exposure to study drug plus seven days after the last date of study drug treatment.

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Efficacy Analyses

The applicant's RAP stated that all of the efficacy analyses were to be based on the mITT population or the efficacy subgroups selected from the mITT population, and would test the hypothesis of superiority.

Primary Efficacy Endpoint Analyses:
The primary analysis of the asthma exacerbations compared the time to first asthma exacerbation between treatment groups using a Cox proportional hazards regression model with terms for treatment group and randomization stratum. The hazard ratio and corresponding 95% CI and p-value were to be presented. Time to first exacerbation was also to be summarized by treatment group using Kaplan-Meier estimates and Kaplan-Meier curves.

Subjects who withdrew early from study treatment without experiencing an exacerbation were to be censored at the last date at which they were known not to have the event (i.e., treatment stop date).

Secondary Efficacy Endpoint Analyses:

The mean percentages of rescue-free and asthma control days over the six-month study period were each to be summarized for the mITT population and each efficacy subgroup, and would be compared in each efficacy subgroup between treatment groups using an analysis of covariance (ANCOVA) model that includes terms for treatment group and randomization stratum. Each measure would be summarized for the overall six-month treatment period and each one-month period.

The applicant planned to provide "summaries of efficacy measures for the mITT population."

3.2.3.2.2 Missing Data Handling

Per the RAP, subjects who withdrew early from study treatment were to remain in the study through the six-month study period and be followed via telephone contact approximately every four weeks for events of interest (asthma-related deaths, intubation, or hospitalization). The RAP did not indicate that subjects were to be followed for efficacy endpoints.

Survival analysis methods (Cox proportional hazards models) that accounted for loss-to-follow-up via censoring were used for the primary efficacy analyses of time to first asthma-related exacerbation. The Cox proportional hazards model assumes non-informative censoring.

No missing data methods were specified in the protocol for the efficacy endpoints.

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3.2.3.2.3 Interim Analyses and Multiple Testing Plan

Two types of interim analyses were planned for the trial based on the primary composite safety endpoint – analyses to assess subject enrolment rates that would be governed by a Pediatric Steering Committee (PSC) and a formal statistical interim analysis for the primary safety composite event endpoint when approximately half of the expected total number of subjects experiencing an event in the composite endpoint had been observed. The interim analysis was to be unblinded to study treatment and conducted by a third party not associated with the conduct of the trial. Unblinded interim results were to be provided to the DMC; a DMC charter contains the formal statistical interim analyses procedures.

No interim analyses were planned on the efficacy endpoints.

No coherent multiple testing plan that covered all endpoints in the study was presented in either the RAP or the protocol.

3.2.3.3 Results and Conclusions (VESTRI)

3.2.3.4 Patient Disposition, Baseline Demographic and Clinical Characteristics

This study screened and enrolled 6759 subjects in 5 regions of the world including North America, Latin America, Europe, Africa and Asia/Pacific. 635 subjects failed screening, including 126 subjects who were subsequently re-screened and then randomized. Of these 6250 (6759-635+126) subjects, 42 did not take study medication – 19 in the FSC arm and 23 in the FP arm. Thus the ITT population consisted of 6208 subjects: 3107 receiving FSC and 3101 receiving FP.

Figure 7 and Table 15 show disposition of subjects in the trial. Approximately 88% of the subjects completed the treatment– with similar percentages completing in each of the two treatment arms. Approximately 12% of subjects overall did not complete the treatment – 12% in the FSC arm and 11% in the FP arm.

As Table 15 and Table 17 show, baseline demographic and key clinical characteristics were well-balanced across treatment arms.

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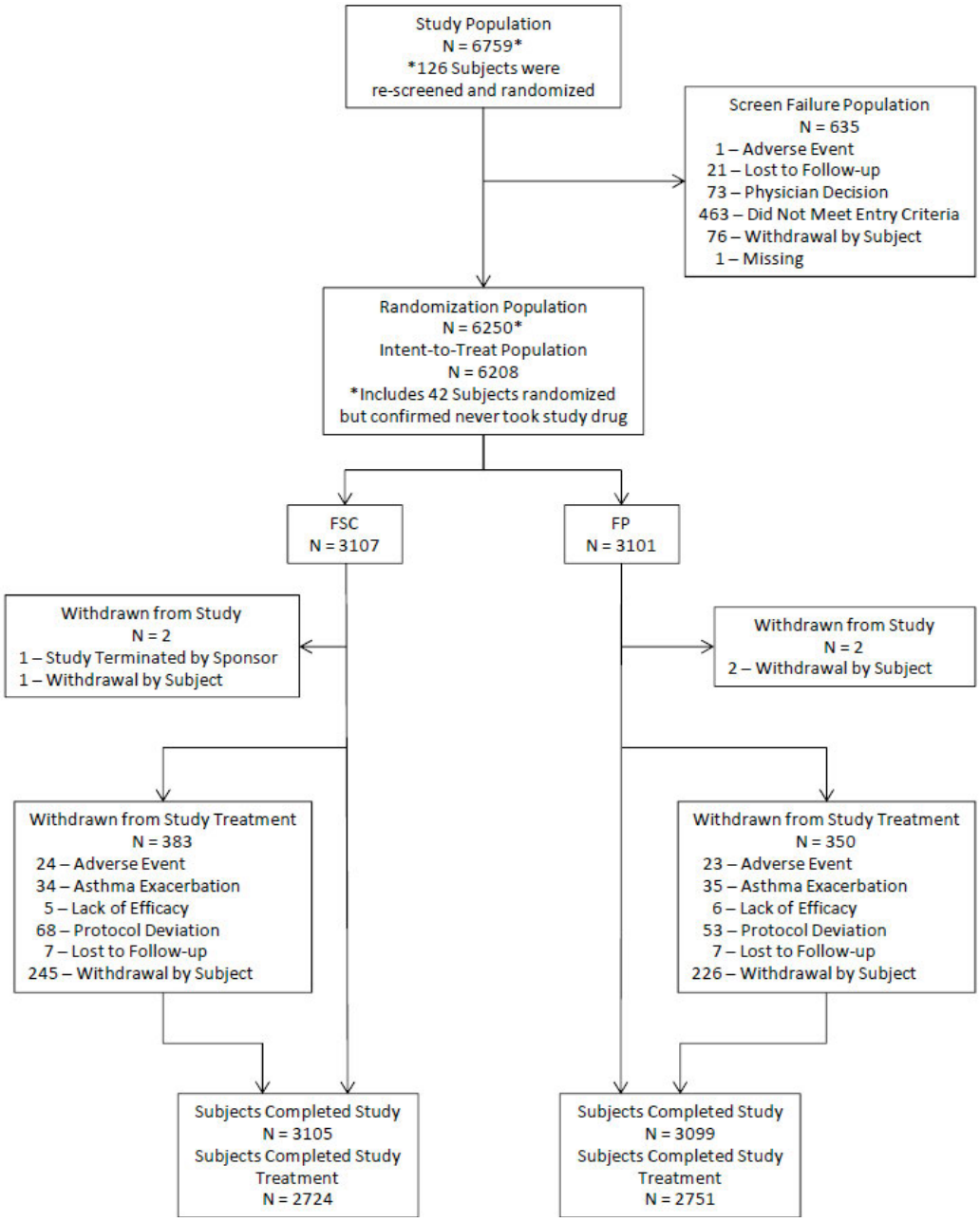
Figure 7: Subject disposition (VESTRI)



Source: CSR for SAS115358

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Table 15: Disposition (All Randomized; VESTRI)

N(% of ITT)	FSC	FP	Total
Randomized	3126	3124	6250
Randomized +Treated (ITT)	**3107 (100)**	**3101 (100)**	**6208 (100)**
Completed study	**3105 (99.9)**	**3099 (99.9)**	**6204 (99.9)**
Completed treatment	2724 (87.7)	2751 (88.7)	5475 (88.2)
Withdrawn from treatment	381	348	729
Withdrawn from study; completed treatment	0	0	0
Withdrawn from study; withdrew from treatment	2	2	4
All withdrawals not completing treatment	**383 (12.3)**	**350 (11.3)**	**733 (11.8)**
Adverse Event	24	23	47
Asthma exacerbation	34	35	69
Lack of efficacy	5	6	11
Lost to follow-up	7	7	14
Protocol deviation	68	53	121
Study closed/terminated	1	0	1
Withdrawal by subject	245	226	471
Other			
Withdrew from study	**2**	**2**	**4**
Study closed/terminated	1	0	1
Withdrawal by subject	1	2	3
Other			

Source: CSR Table 5.3

Table 16: Baseline Demographic Characteristics (ITT; VESTRI)

	FSC (N=3107)	FP (N=3101)
Age (in years)		
Mean ± std dev	7.69±2.2	7.56±2.2
Median	8	8
4--6	1096(35.3%)	1114 (35.9%)
≥ 7	2011 (64.7%)	1987 (64.08%)
Sex		
Female	1187 (38.20%)	1227 (39.6%)

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Male	1920 (61.8%)	1874 (60.4%)
Race		
White	1998 (64.3%)	2032 (65.5%)
Black or African American	539 (17.4%)	511 (16.5%)
Asian	249 (8.0%)	257 (8.2%)
Native Hawaiin or other Pacific Islander	5 (0.1%)	1 (0.0%)
American Indian or Alaskan Native	144 (4.6%)	118 (3.8%)
Multiracial	167 (5.4%)	180 (5.8%)
Other	0 (0)	0 (0)
Missing	5 (0.2%)	2 (0.1%)
Ethnic Group (Hisp/Latino)	910 (29.3%)	868 (28.0%)
	2197 (70.7%)	2233 (72.0%)
U.S.A.	2637 (84.9%)	2587 (83.4%)
Region		
North America	1439 46.3%)	1433 (46.2%)
Latin America	335 (10.8%)	322 (10.4%)
Europe	774 (24.9%)	789 (25.4%)
Asia/Pacific	209 (6.7%)	208 (6.7%)
Africa	350 (11.3%)	349 (11.3%)

Source: Created by reviewer using adsl.xpt

Table 17: Baseline Clinical Characteristics (ITT; VESTRI)

	FSC (N=3107)	**FP (N=3101)**
Number of Exacerbations requiring systemic corticosteroids in past 12m		
0	138 (4.4)	132 (4.3)
1	1935 (62.3)	1956 (63.1)
2	834 (26.8)	818 (26.4)
3	161 (5.2%)	173 (5.6)
≥ 4	39 (1.2%)	22 (0.7)
Number of asthma-related hospitalizations in past 12m		
0	2663 (85.7)	2679 (86.4)

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1	394 (12.7)	370 (11.9)
2	50 (1.6)	52 (1.7)
Asthma Duration[a] (in years)		
Mean ± std dev	4.1 ± 2.8	4.0 ± 2.7
Median	4	4

Source: Created by reviewer using adsl.xpt and adexaca.xpt

3.2.3.4.1 Analyses of the Primary Efficacy Endpoint for VESTRI

The pre-specified primary analysis for the efficacy endpoint, time to first asthma exacerbation, was a Cox proportional hazards model analysis that included terms for treatment group and randomization stratum. Results in Table 18 and a Kaplan-Meier plot in Figure 8 show that the probability of being exacerbation-free tends to be slightly better on the FSC arm but the difference was not statistically significant.

Table 18: Pre-specified Primary Analysis of Primary Efficacy Endpoint (ITT; VESTRI)

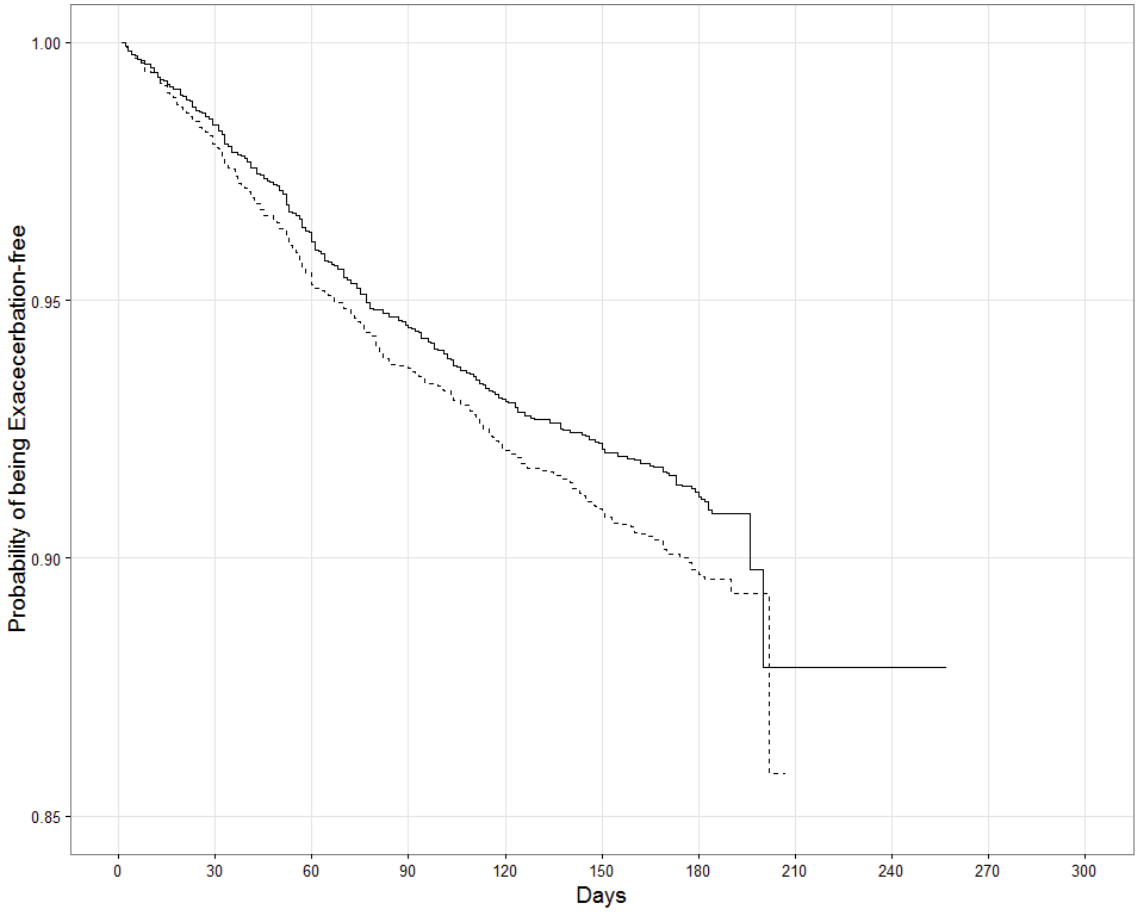
	FSC	**FP**	**Hazard Ratio[1]** (95% CI)
All Ages (4-11 years)[2] (n=6208)	**3107**	**3101**	
First exacerbation events(574)	265 (8.53%)	309 (9.96%)	0.86 (0.73, 1.01)

[1]: Cox proportional model with fixed treatment effect and randomization strata as covariates used for these analyses as pre-specified in the RAP/SAP.
2: One subject on the FSC arm was listed as being 12 years old, this subject was included in the analyses in the 4-11 age group.

Source: Created by reviewer using adtte xpt

Reference ID: 4136139

Figure 8: Kaplan-Meier plot for time to first asthma exacerbation by treatment arm (ITT; VESTRI)



Source: Created by reviewer using adtte xpt

Reference ID: 4136139

Analysis of Primary Efficacy Endpoint by FSC/FP Dose Pairs (ITT)

The study included 2 doses of FSC (FSC 100/50 and FSC 250/50) and 2 corresponding doses of FP (FP 100 and FP 250). The results in Table 19 and Figure 9 show that the hazard ratios are not significantly less than 1 at the nominal 5% level of significance; however, the probability of being exacerbation-free for the FSC arm is consistently higher than that on the FP arm for all doses. The separation of the event-free probability curves[3] is less than that observed for the adult and adolescent population in the AUSTRI trial.

Table 19: Cox PH model results for Time to First Asthma Exacerbation by FSC/FP dose pairs (ITT; VESTRI)

# events/# subjects (%)	FSC N= 3107	FP N=3101	Hazard Ratio[1] (95% CI)
FSC versus FP (all doses) 574/6208 (9.24)	265/3107 (8.6)	309/3101 (10.0)	0.86(0.73,1.01)
FSC 100/50 versus FP 100 174/2536 (6.9)	81/1269 (6.4)	93/1267 (7.3)	0.88 (0.65, 1.18)
FSC 250/50 and FP 250 400/3672 (10.9)	184/1838 (10.0)	216/1834 (11.8)	0.85 (0.7, 1.03)

[1]: The Cox PH model with fixed treatment effect is used for all analyses in this table (randomization strata are confounded with dosing).

Source: Created by reviewer using adtte.xpt

[3] The apparent crossing over of the curves at around Day 200 is probably an artifact – estimates at this time point are based on very few observations.

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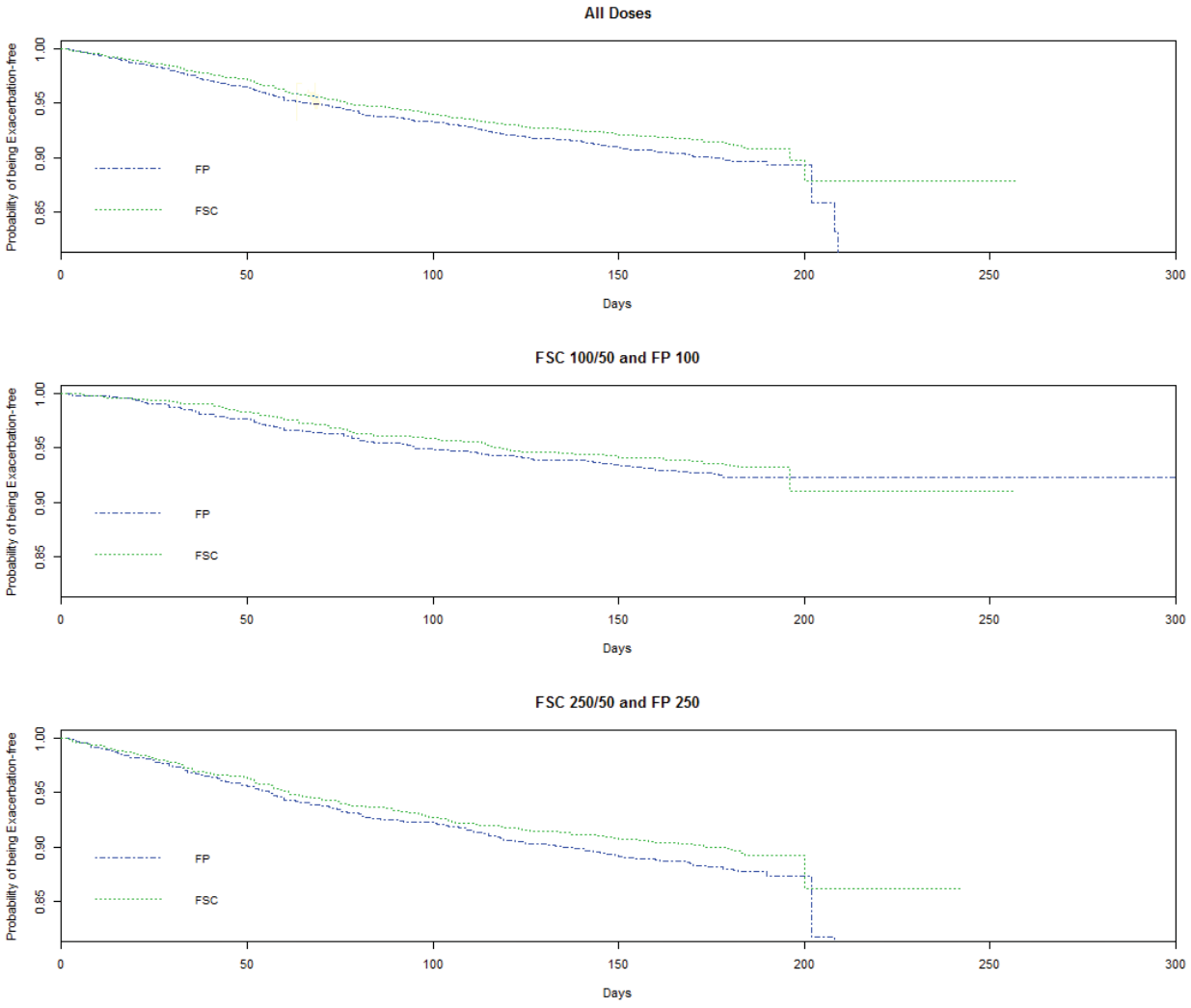
Figure 9: Kaplan-Meier plots for Time to First Asthma Exacerbation by FSC/FP dose pairs (ITT; VESTRI)



Reference ID: 4136139

Assessing the Potential Impact of Missing Data on the Primary Efficacy Endpoint

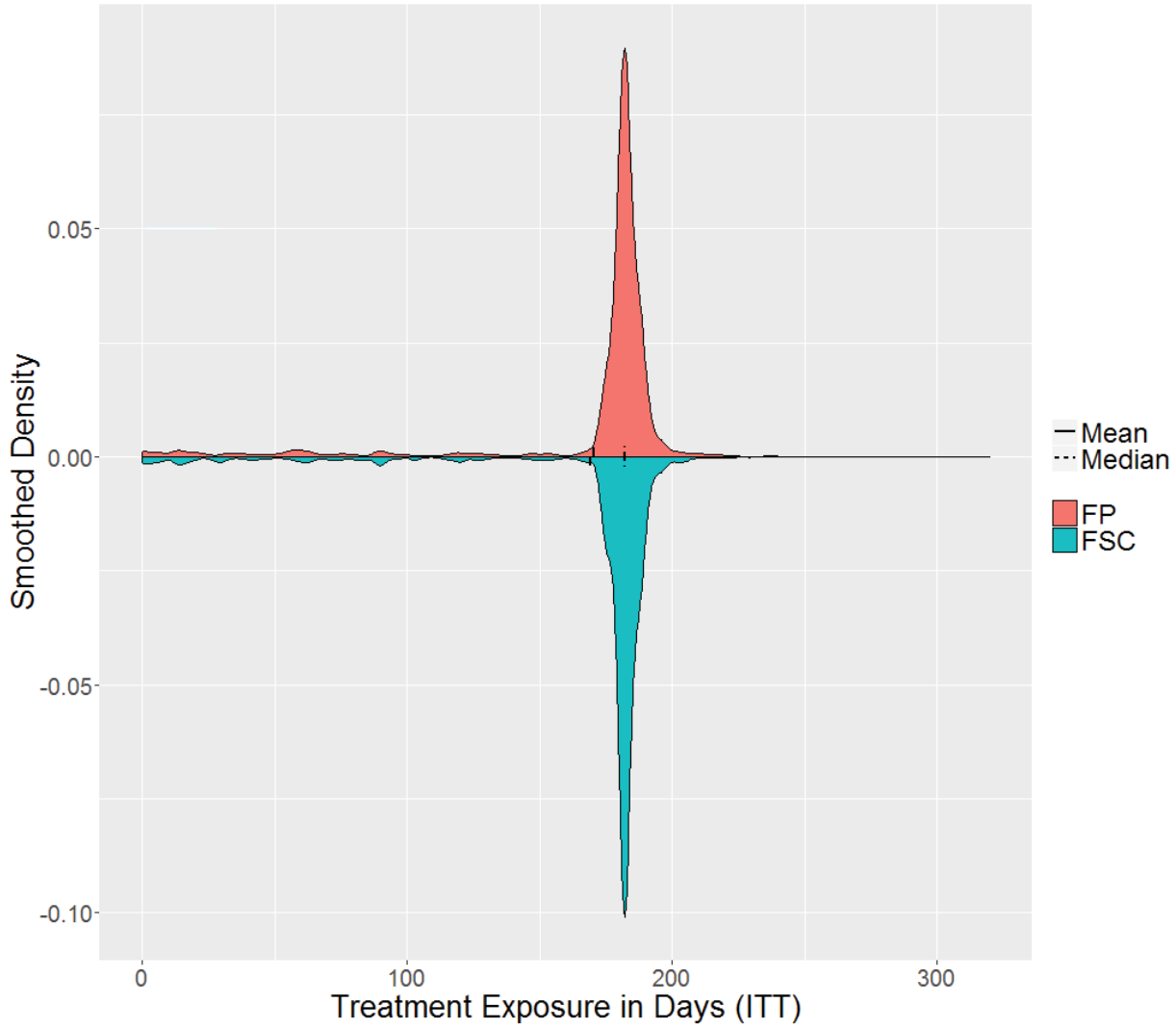
Although the applicant defined ITT (including events from up to 6 months of follow-up) and mITT (including events that happened up to 7 days after last treatment dose) analyses in its design, for the primary efficacy endpoint subjects without events until last treatment dose were censored at the last treatment dose date, i.e., exacerbation events that occurred after day of last treatment dose were not included in the primary efficacy analyses. Since the results for the primary endpoint in the VESTRI trial do not indicate statistical superiority, a tipping point analysis that assess what values of hazard rates (varied by treatment arm) in the post-treatment discontinuation data could "tip" the results over to where the FSC arm is no longer superior to the FP arm in terms of primary efficacy is not relevant.

An exploration of the treatment exposure distribution is provided in the violin[4] plot in Figure 10 and the statistics on exposure distribution by arm are provided in Table 20. Treatment exposure was fairly similar across the treatment arms.

[4] Violin plots are combinations of box plots and density plots. The central line shows the information in a traditional box plot while the outlines provide information on distribution of values through a density plot. Reflection of the density plot on either side of the central line is purely for visual effect.

Reference ID: 4136139

Figure 10: Distribution of Days of treatment exposure by Treatment Arm (VESTRI)



Source: Created by reviewer using adsl xpt.

Table 20: Statistics on Days of Exposure (ITT, VESTRI)

	ITT subjects	
	FSC	**FP**
Mean (std.dev.)	170.7 (39.6)	169.3 (40.9)
Median	182	182

Reference ID: 4136139

3.2.3.4.2 Secondary Efficacy Endpoint Analyses – Percent Rescue-free days

The pre-specified analysis of the two secondary efficacy endpoints – percentage of rescue-free days and percentage of asthma control days over the six-month period was an ANCOVA modeling analysis that included terms for treatment group and randomization stratum. Each endpoint was to be summarized for the overall six-month treatment period and each one-month period. The mean percentages of rescue-free and asthma control days over the six-month study period were each to be summarized for the mITT population, and to be compared in each efficacy subgroup between treatment groups using an ANCOVA model that included terms for treatment group and randomization stratum.

Results for the percent rescue-free days for the mITT analysis are presented in Table 21. If percent of rescue-free days were significantly higher for the FSC arm at the nominal 5% level then the estimated difference in the table ($Mean_{FSC}$ - $Mean_{FP}$) would have a lower bound greater than 0. This is not true for any of the Month 1 to Month 6 periods, nor is it true for the overall Month 1-6 period. Thus there is insufficient evidence to conclude that there is a statistically significant increase in the percent of recue-free days on the FSC arm. However, the estimated difference is positive for all except the first month.

Table 21: Results of pre-specified ANCOVA model analysis for percent rescue-free days (mITT; VESTRI)

Mean ± SE (95% CI)	FSC N= 3107	FP N=3101	Estimated Difference[1] (95% CI)
dMonth 1 N_{FSC}=2732; N_{FP}=2724	79.4 ± 0.6 (78.2,80.6)	79.6 ± 0.6 (78.4, 80.8)	-0.2 (-1.8, 1.4)
Month 2 N_{FSC}=25566; N_{FP}=2557	83.3 ± 0.6 82.2, 84.5	82.7 ± 0.6 81.6, 83.9	0.6 (-1.0, 2.1)
Month 3 N_{FSC}=2467; N_{FP}=2454	84.9 ± 0.6 (83.7, 86.0)	83.6 ± 0.6 (82.4, 84.8	1.2 (-0.3, 2.8)
Month 4 N_{FSC}=2362; N_{FP}=2361	85.6 ± 0.6 84.4, 86.8	84.9 ± 0.6 83.7, 86.1	0.7 (-0.8, 2.3)
Month 5 N_{FSC}=2286; N_{FP}=2306	85.4 ± 0.6 84.2, 86.6	84.8 ± 0.6 83.6, 86.0	0.6 (-0.9, 2.2)
Month 6 N_{FSC}=2215; N_{FP}= 2224	85.9 ± 0.6 84.7, 87.1)	85.2 ± 0.6 84.0, 86.4	0.7 (-0.9,2.3)
Month 1-6 N_{FSC}=2757; N_{FP}=2748	82.51 ±0.55 (81.4,83.6)	81.8 ± 0.55 (80.7,82.9)	0.7 (-0.7, 2.1)

[1]: The ANCOVA model used for estimating differences between mean of FSC minus mean of FP is the pre-specified model with terms for treatment and randomization stratum.

Source: Created by reviewer using adexaca.xpt

Reference ID: 4136139

3.2.3.4.3 Secondary Endpoint Analysis – Percent Asthma Control Days (VESTRI)

The pre-specified analysis on the secondary efficacy endpoint percent of Asthma Control days was the same as that specified for the percentage of rescue-free days, i.e., an ANCOVA model analysis that included terms for treatment group and randomization stratum. Results for the percent of asthma control days are presented in Table 22. If percent of asthma control days were significantly higher for the FSC arm at the nominal 5% level, then the estimated difference in the table ($Mean_{FSC}$ - $Mean_{FP}$) would have a lower bound greater than 0. This is not true for any of the Month 1 to Month 6 periods, nor is it true for the overall Month 1-6 period. Thus there is insufficient evidence to conclude that there is a statistically significant increase in the percent of asthma control days on the FSC arm. However, as for rescue-free days, the estimated difference is positive for all except the first month.

Table 22: Results of pre-specified ANCOVA model analysis for Percent Asthma Control Days (mITT; VESTRI)

Mean ± SE (95% CI)	FSC N= 3107	FP N=3101	Estimated Difference[1] (95% CI)
Month 1 N_{FSC}=2739; N_{FP}=2726	69.7 ± 0.7 (68.3, 71.1)	69.8 ± 0.7 (68.4, 71.2)	-0.1 (-1.9, 1.7)
Month 2 N_{FSC}=2557; N_{FP}=2558	75.6 ± 0.7 74.2, 77.0	75.2 ± 0.7 73.8, 76.7	0.4 (-1.6, 2.3)
Month 3 N_{FSC}=2467; N_{FP}=2454	77.8 ± 0.7 76.4, 79.3	77.0 ± 0.7 75.5, 78.4	0.9 (-1.1, 2.8)
Month 4 N_{FSC}=2363; N_{FP}=2362	79.3 ± 0.7 77.9, 80.8	78.7 ± 0.7 77.2, 80.1	0.7 (-1.3, 2.6)
Month 5 N_{FSC}=2287; N_{FP}=2307	79.8 ± 0.7 17.7, 80.6	79.2 ± 0.7 77.7, 80.6	0.6 (-1.4, 2.5)
Month 6 N_{FSC}=2217; N_{FP}= 2224	80.5 ± 0.8 79.0,82.0	79.8 ± 0.8 78.3, 81.2	0.7 (-1.2, 2.7)
Month 1-6 N_{FSC}=2759; N_{FP}=2749	74.3 ± 0.6 (73.0, 75.5	73.1 ± 0.6 (71.9, 74.3	1.2 (-0.4, 2.8)

[1]: The ANCOVA model used for estimating differences between mean of FSC minus mean of FP is the pre-specified model with terms for treatment group and randomization stratum.

Source: Created by reviewer using adexaca.xpt

Reference ID: 4136139

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section presents subgroup analyses for the primary efficacy endpoint of time to first exacerbation for both AUSTRI (Adult and Adolescent population) and VESTRI (Pediatric population). Subgroups presented here are defined by baseline demographic factors. Note that these subgroup analyses are for exploratory purposes only; the study was not powered for these subgroup analyses and statistical findings are based on the two-sided nominal alpha level of 0.05. Analyses of subgroups are based on a Cox proportional hazards model with term for treatment effect and randomization stratum; this model was used to estimate the hazard ratio and corresponding nominal 95% confidence interval. All analyses are based on the ITT analysis population.

4.1 Adult and Adolescent Population (AUSTRI)

4.1.1 Subgroup Analyses for Primary Efficacy Endpoint

4.1.1.1 Sex

Among the ITT subjects the majority (~66%) were female. As indicated in Table 23 the hazard ratio estimate was the same for both sexes, and FSC was superior to FP at the nominal 5% level for both male and female subgroups.

Table 23: Analyses of Primary Efficacy Endpoint by Sex (ITT; AUSTRI)

	FSC N= 5834	**FP** N=5845	**Hazard Ratio** (95% CI)
Female (N=7749; 66.35%)	343/3851 (8.91%)	431/3898 (11.06%)	0.79 (0.68, 0.92)
Males (N=5930; 33.65%)	137/1983 (6.91%)	166/1947 (8.53%)	0.79 (0.63, 0.99)

Source: Created by reviewer using adtte xpt and adsl xpt

4.1.1.2 Age

Among the randomized subjects, the vast majority (79%) were in the 18-64 age group with approximately 11% in the 12-17 and >64 age groups. Table 24 shows that all except the >64 group indicated superiority of FSC over FP at the nominal 5% level, with favorable estimates in all subgroups.

Table 24: Analyses of Primary Efficacy by Age at Baseline (ITT; AUSTRI)

	FSC N= 5834	**FP** N=5845	**Hazard Ratio** (95% CI)
12-17 years (N=1230; 10.53%)	42/615 (6.83%)	64/615 (10.41%)	0.64 (0.43,0.94)

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18-64 Years (N=9181; 10.78.61%)	386/4576 (8.44%)	469/4605 (10.18%)	0.81 (0.71, 0.92)
> 64 years (N=1268; 10.86%)	52/643 (3.09%)	64/625 (10.24%)	0.78 (0.54, 1.12)

Source: Created by reviewer using adtte.xpt and adsl.xpt

4.1.1.3 Race

Subjects of seven different racial categories were included in the ITT population as indicated in Table 25. Approximately 75% were of White race and approximately 15% were Black or African American. For all race groups except "Black or African American", "American Indian or Alaskan Native "and the multi-racial group, FSC was superior to FP at the nominal 5% level of significance.

Table 25: Analyses of Primary Efficacy Endpoint by Race (ITT; AUSTRI)

	FSC N= 5834	**FP** N=5845	**Hazard Ratio** (95% CI)
White (N= 8783; 75.20%)	348/4374 (7.96%)	467/4409 (10.59%)	0.73 (0.64, 0.84)
Black or African American (N=1726; 14.78%)	79/870 (9.08%)	79/856 (9.23%)	0.94 (0.69, 1.29)
Asian (N=728; 6.23%)	31/368 (8.42)	32/360 (8.89%)	0.81 (0.71,0.92)
Native Hawaiin or other Pacific Islander (N=18; 0.15%)	0/8 (0%)	0/10 (0%)	NA
American Indian or Alaska Native (N=225; 1.93%)	9/109 (8.26%)	8/116 (6.90%)	0.96 (0.36,2.51)
Multi-racial (N=193; 1.65%)	13/102 (12.75%)	11/91 (12.09%)	1 (0.44, 2.24)
Other (N=0; 0%)	0/0 (NA)	0/0 (NA)	NA
Missing (N=6; 0.05%)	0/3 (0%)	0/3 (0%)	NA

Source: Created by reviewer using adtte xpt and adsl xpt

4.1.1.4 US versus Outside US

Table 26 gives the breakup of study subjects within and outside the US. Although a majority of the subjects were outside the US (OUS), about 47% were US subjects. Hazard ratios for both US and OUS subjects were around 0.8 and both subgroups indicated superiority of FSC over FP at the nominal 5% level.

Table 26: Analyses of Primary Efficacy by US/OUS categories (ITT; AUSTRI)

	FSC N= 5834	**FP** N=5845	**Hazard Ratio** (95% CI)
USA (N=5524; 47.30%)	277/2587 (10.71%)	344/2637 (13.04%)	0.80 (0.68,0.93)
OUS (N=6455; 55.27%)	203/3247 (25.19%)	253/3208 (7.89%)	0.78 (0.65, 0.94)

Source: Created by reviewer using adtte xpt and adsl.xpt

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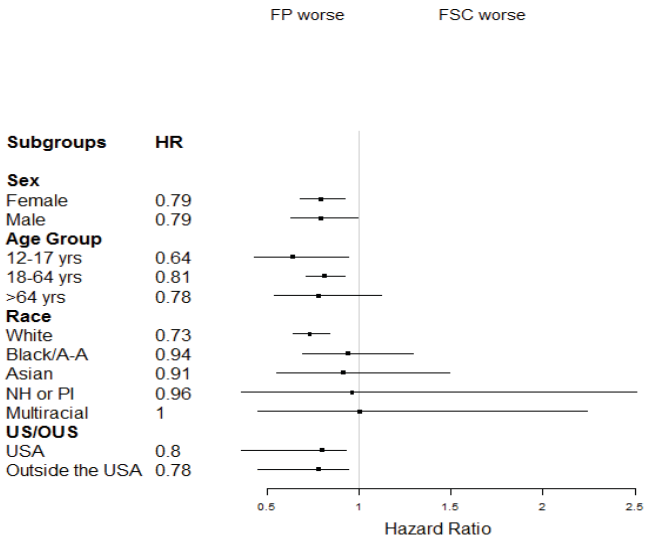
Figure 11: Forest plot for subgroup analyses of Primary Efficacy endpoint (ITT; AUSTRI)



4.2 Subgroup Analyses for Pediatric Population (VESTRI)

4.2.1 Subgroup Analyses for Primary Efficacy Endpoint

For all subgroup ITT analyses below the Cox proportional hazards model that included terms for the treatment effect and randomization stratum was used. The trial was not powered for subgroup analyses and nominal 95% confidence intervals are provided.

4.2.1.1 Sex

Among the ITT subjects for VESTRI the majority were males. As Table 27 shows, although point estimates of hazard ratios for both males and females were less than 1, upper bounds of 95% confidence intervals for both hazard ratios were above 1.

Table 27: Analyses of Primary Efficacy Endpoint by Sex (ITT; VESTRI)

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	FSC N= 3107	FP N=3101	Hazard Ratio (95% CI)
Female (N=2204; 35.50%)	98/1089 (9.0%)	112/1115 (10.0%)	0.92 (0.7, 1.2)
Males (N=3627; 58.42%)	167/1753 (9.5%)	197/1874 (10.5%)	0.82 (0.67, 1.01)

Source: Created by reviewer using adtte xpt and adsl.xpt

4.2.1.2 Age

A little over a third of the VESTRI trial population was between 4-6 years old as seen in Table 28. Although hazard ratios for both age subgroups trended toward favoring FSC over FP, neither hazard ratio was significantly below 1.

Table 28: Analyses of Primary Efficacy by Age at Baseline (ITT; VESTRI)

	FSC N= 3107	FP N=3101	Hazard Ratio (95% CI)
4--6 years (N=2210; 35.60%)	100/1096 (9.1%)	118/1114 (10.6%)	0.84 (0.65,1.1)
7--11Years (N=3997; 64.38%)	165/2010 (8.2%)	191/1987 (9.6%)	0.87 (0.7,1.07)

Source: Created by reviewer using adtte.xpt and adsl.xpt

4.2.1.3 Race

Table 29 shows that six different racial categories were present in the ITT population for VESTRI. Hazard ratios and 95% CIs were estimable for five of these 6 races. Although the hazard ratio trended towards favoring FSC over FP for all except the "American Indian or Alaskan Native" category, in no case was the upper bound of the nominal 95% confidence interval below 1.

Table 29: Analyses of Primary Efficacy Endpoint by Race (ITT; VESTRI)

	FSC N= 3107	FP N=3101	Hazard Ratio (95% CI)
White (N= 4030; 64.9%)	172/1998 (8.6%)	200/2032 (9.8)	0.88 (0.71, 1.07)
Black or African American (N=1050; 16.9%)	36/539 6.7	43/511 (8.4)	0.81 (0.52, 1.26)
Asian (N=506; 8.2%)	16/249 14.5	28/257 (6.4)	0.58 (0.31, 1.08)
Native Hawaiin or other Pacific Islander (N=6; 0.1%)	5/5 100	1/1 (100)	-
American Indian or Alaska Native (N=262; 4.2%)	17/144 11.8	11/118 (9.3)	1.23

Reference ID: 4136139

			(0.57, 2.64)
Multi-racial (N=347; 5.6%)	23/167 13.8	27/180 (15)	0.93 (0.53, 1.63)
There were 7 missing Race values -- 5 in the FSC group and 2 in the FP group; Estimates for "Native Hawaiin or other Pacific Islander", and "Other" races were not possible either due to lack of convergence or lack of non-missing observations.			

Source: Created by reviewer using adtte xpt and adsl xpt

4.2.1.4 US versus Outside US

We see from Table 30 that although a majority of subjects in VESTRI were from outside the US (OUS), ~45%, i.e., over 2700 subjects – were from the US. Neither for the US nor for the OUS population was the upper bound of the confidence interval for the hazard ratio for FSC versus FP less than 1.

Table 30: Analyses of Primary Efficacy by US/OUS categories (ITT; VESTRI)

	FSC N= 3107	**FP** N=3101	**Hazard Ratio** (95% CI)
USA (N=2777; 44.7 %)	168/2390 (7.0 %)	186/1387 (13.4%)	0.91 (0.74, 1.13)
OUS (N=3431; 55.3%)	97/1717 (5.6 %)	123/1714 (7.2%)	0.78 (0.6, 1.01)

Source: Created by reviewer using adtte xpt and adsl.xpt

A Forest plot that displays the hazard ratios and subgroups for the above factors is presented in Figure 12.

Figure 12 Forest plot for subgroup analyses of Primary Efficacy endpoint (ITT; VESTRI)

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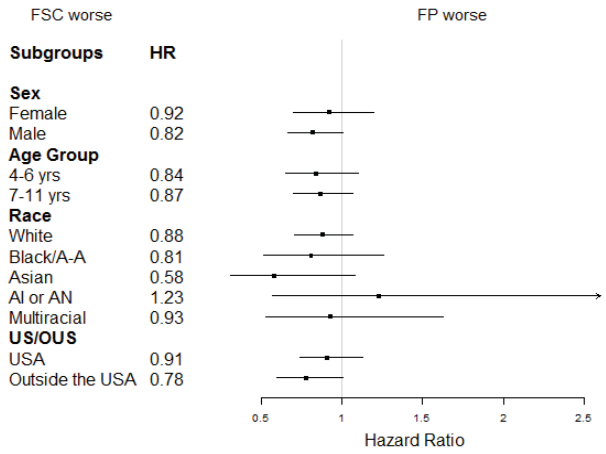

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Trials SAS115358 and SAS115359 were post-approval safety studies designed by GSK – SAS115358 (VESTRI) to assess 2 doses of FSC versus equipotent doses of FP in pediatric patients (4-11 years old) with persistent asthma, and SAS115359 (AUSTRI) to assess 3 doses of FSC versus equipotent doses of FP in adolescent and adult subjects (>= 12 years old) with persistent asthma.

The following statistical issue is noted:

1. For the primary efficacy analysis the applicant censored subjects without exacerbation events at the date of last treatment – this follows neither the ITT (up to 6 months of follow-up) nor the mITT (follow-up up to 7 days post-treatment-discontinuation) analysis approaches that were planned. No missing data sensitivity analyses were proposed or conducted by the applicant for the efficacy endpoints. For both trials the primary efficacy endpoint analysis was time to first exacerbation which was analyzed using survival analysis methods which rely on an assumption of non-informative censoring. A discussion of the potential impact of missing data on the primary efficacy endpoint for

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AUSTRI is included in the body of the review and indicates that results for the primary efficacy endpoint are likely robust to the missing data.

5.2 Collective Evidence

Trials SAS115358 (VESTRI) and SAS115359 (AUSTRI) were randomized, double-blind, parallel group, active-controlled trials designed primarily to assess safety via time to first composite safety event (asthma-related death, asthma-related intubation, asthma-related hospitalization). Dr. Changming (Sherman) Xia's review, that covered the safety aspects of this trial, indicates that from the statistical safety perspective the PMRs can be considered to have been met.

For the AUSTRI trial the analysis of the primary efficacy endpoint (time to first exacerbation) indicates that the probability of being exacerbation-free is lower on the FP arm compared to the FSC arm, i.e., the FSC arm has a protective effect for time to first exacerbation when all doses were combined. The results of the secondary endpoint in this study – rescue medication use – generally support the conclusion of superiority of FSC over FP.

For the VESTRI trial superiority of FSC to FP was not established statistically in terms of time to first exacerbation, although there was a trend toward benefit. Furthermore, although secondary endpoints of rescue-free days and asthma control days trended in the right direction, superiority on these endpoints was not established at the nominal 5% level. However, it should be kept in mind that the trial was not powered for efficacy endpoints. The determination of superiority in the adult and adolescent population, combined with the trends toward benefit in pediatric patients, lends credibility to potential superiority in the pediatric population, especially if disease processes in the two populations are similar.

5.3 Conclusions and Recommendations

The primary objective of the large, 26-week trials VESTRI and AUSTRI was to assess whether the addition of the long acting beta$_2$-agonist to inhaled corticosteroid was non-inferior to ICS therapy alone in terms of the risk of serious asthma-related events (asthma-related hospitalization, endotracheal intubation and death). Dr. Xia's statistical assessment of the safety aspects indicates that the PMR can be considered successfully fulfilled from the safety perspective.

A secondary objective of these trials was to assess whether the addition of LABA to ICS therapy was superior to ICS therapy alone in terms of measures of efficacy. The primary efficacy measure for both trials was time to first asthma exacerbation. The assessment of efficacy in the adult and adolescent population (≥ 12 year olds) in the AUSTRI trial was based on the primary efficacy endpoint of asthma exacerbation and secondary efficacy endpoint of rescue medication use. Of the 11679 subjects who were randomized and took at least one dose of study drug in the AUSTRI trial, a total of 1077 subjects had at least one exacerbation. The pre-specified Cox-

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proportional hazards model-based analysis estimated a hazard ratio of **0.79** with an associated 95% confidence interval whose upper bound of **0.89** was less than 1.0 indicating a protective effect of FSC over FP for time to first exacerbation.

The secondary endpoint of rescue medication use in AUSTRI estimated a mean difference of −0.19, for the mean number of rescue puffs/24 hours on the FSC arm minus that on the FP arm, for the ITT analysis, with an associated 95% confidence interval of (−0.24, −0.14) for the overall Month 1-6 data. Overall the results for the secondary endpoint in AUSTRI generally support the primary efficacy conclusion of superiority of FSC over FP for the adult and adolescent population.

The assessment of efficacy in the pediatric population (4-11 year olds) in the VESTRI trial was based on the primary efficacy endpoint of asthma exacerbations and secondary efficacy endpoints of rescue-free days and asthma control days. Of the 6208 subjects who were randomized and took at least one dose of study drug in this trial, a total of 574 subjects had at least one exacerbation. A hazard ratio of **0.86** with an associated 95% confidence interval of (**0.73, 1.01**) was estimated for the primary efficacy endpoint. Since the upper bound of the confidence interval exceeded 1, a conclusion of statistical superiority of FSC to FP cannot be drawn for this endpoint.

A difference of **0.7**, with an associated 95% CI of **(-0.9, 2.3)**, was estimated for the mean percent of rescue-free days on the FSC arm minus that on the FP arm in the overall population; a difference of **0.7** with an associated 95% CI of **(-0.7, 2.1)** was estimated for the mean percent of asthma control days. So, although the mean percent of rescue-free days and asthma control days both tended to be higher on average in the FSC arm for the overall Month 1-6 period, they were not significantly higher at the nominal 5% level. Thus statistical superiority has not been established for these secondary endpoints either.

Although statistical superiority was not established for primary and secondary efficacy endpoints in the VESTRI trial the results for these endpoints trended in the right direction. It should be kept in mind that the VESTRI trial was not powered for the efficacy endpoints. The determination of superiority for efficacy endpoints in the adult and adolescent population, along with the results observed for the pediatric population, lend credibility to potential superiority for efficacy in the pediatric population if there is clinical evidence of the similarity of disease processes in the two populations.

6 REFERENCES

Nelson, H.S., Weiss S.T., Bleecker E.R., Yancey, S.W., and Dorinsky, P.M. (2006), "The Salmeterol Multicenter Asthma Research Trial: A Comparison of Usual Pharmacotherapy for Asthma or Usual Pharmacotherapy plus Salmeterol," Chest, 129(1): 15-26

Reference ID: 4136139

Levenson, M. (2008), "Long-Acting Beta-Agonists and Adverse Asthma Events Meta-Analysis," Statistical Briefing Package for Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee on December 10-11, 2008

7 APPENDIX

7.1 Evaluation of Proportional Hazards Assumption for Primary Efficacy Endpoint Analysis (AUSTRI)

The primary analysis used a Cox proportional hazards model with terms for treatment effect and randomization stratum to estimate hazard ratios and associated confidence intervals. The scaled Schoenfeld residual plot in Figure 13 evaluates the proportional hazards assumption for this model. The plot includes a fitted line; deviation of this line from the horizontal would indicate potential violation of the proportional hazards assumption. This plot does not indicate violation of the proportional hazards assumption for the pre-specified primary efficacy analysis.

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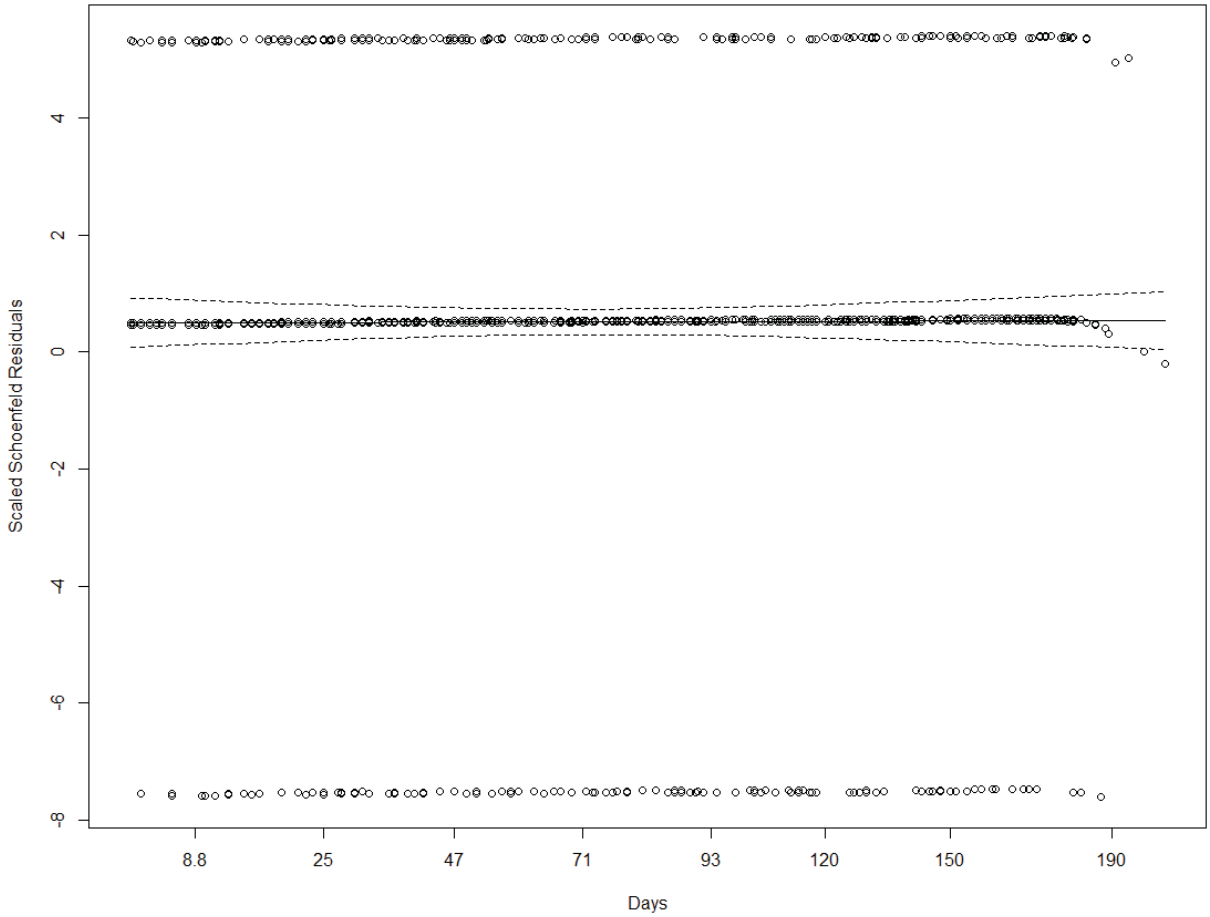
Figure 13: Plot of Scaled Schoenfeld Residual versus Time for Primary Endpoint (ITT; AUSTRI)



7.2 Analysis of Primary Efficacy Endpoint for Stratified Cox Proportional Hazards Model (AUSTRI)

The primary analysis used a Cox proportional hazards model with fixed terms for treatment effect and randomization stratum. However, the applicant's CSR reports analyses for the Cox proportional hazards model stratified by randomization strata with fixed treatment effect. Table 30 presents these analyses for the overall population and for the different age groups.

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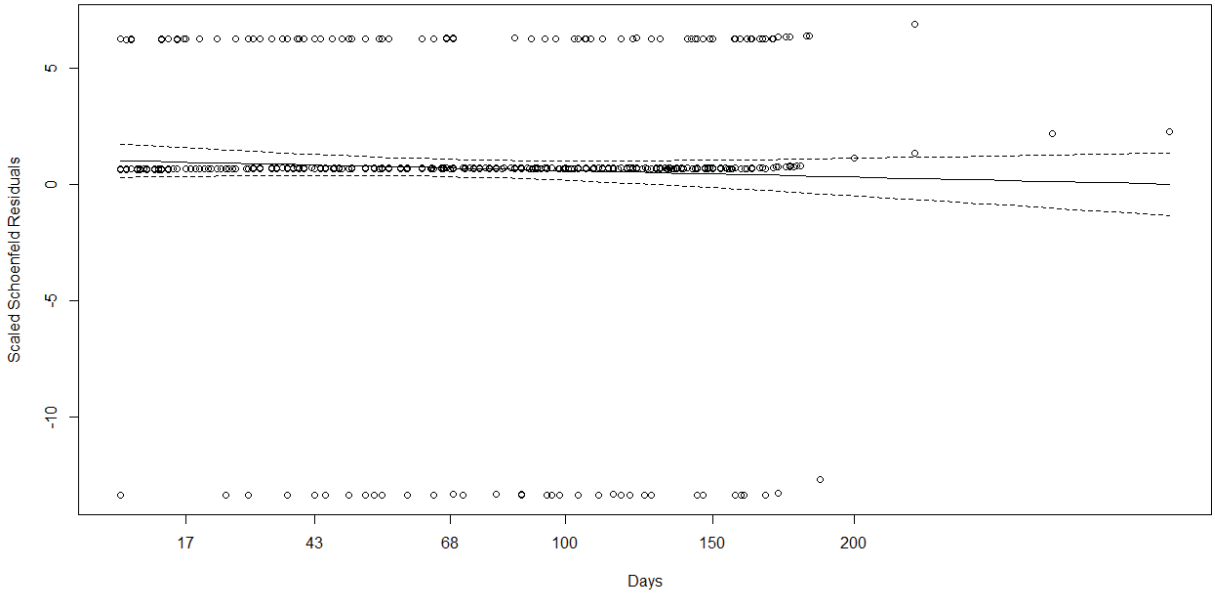
7.3 Evaluation of Proportional Hazards Assumption for Primary Efficacy Endpoint Analysis (VESTRI)

The primary analysis used a Cox proportional hazards model with terms for treatment effect and randomization stratum to estimate hazard ratios and associated confidence intervals. The scaled Schoenfeld residual plot in Figure 14 evaluates the proportional hazards assumption for this model. The plot includes a fitted line; deviation of this line from the horizontal would indicate potential violation of the proportional hazards assumption. This plot does not indicate violation of the proportional hazards assumption for the pre-specified primary efficacy analysis.

Reference ID: 4136139

Figure 14: Plot of Scaled Schoenfeld Residual versus Time for Primary Endpoint (ITT; VESTRI)



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/s/

SHANTI V GOMATAM
08/07/2017

GREGORY P LEVIN
08/14/2017

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	21077
Supplement #:	S-056/057 (eCTD Sequence Number: 0155/0159)
Drug Name:	Fluticasone/Salmeterol
Indication(s):	Asthma and COPD
Applicant:	GlaxoSmithKline
Date(s):	Date received by reviewer: 10/3/2016 Stamp Date: 10/3/2016 PDUFA Date: 8/3/2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Changming (Sherman) Xia, Ph.D., Mathematical Statistician
Concurring Reviewers:	Eugenio, Andraca-Carrera, Ph.D., Team Leader Mat Soukup, Ph.D., Deputy Division Director
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Medical Officer: Robert Lim Medical Team Leader: Sally Seymour
Project Manager:	Carol Hill
Keywords:	Asthma; Safety assessment; Survival analysis; long acting beta$_2$-agonist (LABA), inhaled corticosteroid (ICS); serious asthma adverse events; non-inferiority trial

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

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Reference ID: 4116469

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1 EXECUTIVE SUMMARY

1.1 Background

This is a statistical review of two post-marketing safety trials, AUSTRI SAS115359 and VESTRI SAS115358, to compare the risk of serious asthma-related adverse events of the fluticasone propionate/salmeterol combination (FSC) to fluticasone propionate (FP) alone. The fixed combination of fluticasone propionate (FP) (an inhaled corticosteroid [ICS]), and salmeterol (a long acting beta$_2$-agonist [LABA]), together abbreviated as FSC with trade name ADVAIR DISKUS in the United States (US), was first approved by the US Food and Drug Administration (FDA) on 8/24/2000 as maintenance treatment of asthma in patients 12 years of age and older, and later approved for the indication of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis on 11/17/2003 and the indication of treatment of asthma for children 4-11 years of age on 4/21/2004.

A meta-analysis conducted by the FDA (Levenson 2008) showed that LABAs were associated with an increased risk of asthma-related events relative to non-LABA treatments as measured by the asthma composite endpoint consisting of asthma-related death, asthma-related intubation, and asthma-related hospitalization, with an estimated risk difference (RD) of 2.80 (95% CI: [1.11, 4.49]) per 1000 subjects. The meta-analysis found no difference in risk between LABA with ICS relative to ICS alone (RD: 0.25; 95% CI: [-1.69, 2.18] per 1000 subjects). A limitation of this meta-analysis was that the trials included were generally not designed to collect the endpoints considered.

On April 14, 2011, FDA issued a post-marketing requirement (PMR) to all manufacturers of LABA products indicated for treatment of asthma to conduct controlled trials to assess the safety of LABAs plus ICS. Each sponsor was to carry out an individual non-inferiority trial of LABA+ICS against an ICS-alone control arm in a population of adults and adolescents 12 years of age and older. In addition, FDA required GlaxoSmithKline (GSK), the only manufacturer of a LABA-containing respiratory inhaled medicine approved in the US for the treatment of asthma in 4- to-11-year-old patients, to conduct a separate controlled trial of pediatric patients.

1.2 Findings and Recommendations

This review focuses on two post-marketing safety trials: AUSTRI SAS115359 designed by GSK to assess 3 doses of FSC versus equipotent doses of inhaled FP administered twice daily over 26 weeks in adolescent and adult subjects with persistent asthma, and VESTRI SAS11538 to assess 2 doses of FSC versus equipotent doses of inhaled FP administered twice daily over 26 weeks in the pediatric population. The purpose of this statistical review is to evaluate the safety of FSC relative to FP in terms of serious asthma-related events based on the results of these two trials.

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The primary safety endpoint in both trials consisted of a composite of at least one of the following endpoints:

- asthma-related death
- asthma-related intubation
- asthma-related hospitalization.

Table 1 shows a summary of composite safety events observed in both trials. A total of 67 events were observed in trial SAS115359 and 48 events in trial SAS115358. The majority of these events were adjudicated as asthma-related hospitalizations. Two events were adjudicated as asthma-related intubation in the FP arm of trial SAS115359, and no asthma-related deaths were observed in either trial.

Table 1 Analysis of the Composite Safety Endpoint in Trials SAS115358 and SAS115359

Trial		FSC (Advair)	FP
SAS115359 N=11679	Events/N (%) *IR per 100 PY*	34/5834 (0.58%) *1.16*	33/5845 (0.56%) *1.12*
	HR (95% CI)	**1.029 (0.638, 1.662)**	
SAS115358 N=6208	Events/N (%) *IR per 100 PY*	27/3107 (0.87%) *1.74*	21/3101 (0.68%) *1.36*
	HR (95% CI)	**1.285 (0.726, 2.272)**	

Source: Created by the statistical reviewer using datasets adtte.xpt.

The two trials were designed to rule out pre-specified hazard ratio margins of the primary safety endpoint associated with FSC. In accordance with the PMR, Trial SAS115359 was designed to rule out a hazard ratio margin of **2.0** and Trial SAS115358 was designed to rule out a margin of **2.675**. The 95% confidence intervals (CIs) of the estimated hazard ratios (HRs) for the composite endpoint were (0.638, **1.662**) for SAS115359 and (0.726, **2.272**) for SAS115358. Both upper bounds of the CIs were below the pre-specified risk margins of **2.0** and **2.675**, respectively. Therefore the trials successfully ruled out an excessive risk of serious asthma-related events associated with FSC relative to FP. Based on the results of trials SAS115359 and SAS115358, we recommend that the PMR be considered successfully fulfilled from a statistical perspective.

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2 INTRODUCTION

2.1 Overview and Regulatory Background

Fluticasone propionate (FP), an inhaled corticosteroid (ICS), has been shown to be effective in the treatment of the inflammatory component of asthma, and salmeterol, a long acting beta$_2$-agonist (LABA), has been shown to be effective in alleviating smooth muscle contraction. Studies (Condemi, 1999; Bateman, 2008) in adults and adolescents have demonstrated that the addition of a LABA to an ICS improves several aspects of asthma control, such as improving lung function and current control of asthma symptoms as well as reducing the risk of asthma deterioration requiring treatment with systemic corticosteroids.

The fixed combination of fluticasone propionate with salmeterol (FSC) was approved by the FDA on 8/24/2000 for the treatment of asthma and on 11/17/2003 for chronic obstructive pulmonary disease associated with chronic bronchitis. This review discusses the safety of FSC for the treatment of asthma only. FSC is marketed in the US as ADVAIR DISKUS.

A clinical trial (Salmeterol Multicenter Asthma Research Trial [SMART]), initiated shortly after the approval of salmeterol (Nelson, 2006) comparing the safety of salmeterol to placebo added to usual therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. A meta-analysis (Levenson 2008), which suggested a higher risk of serious asthma outcomes (death, intubation, hospitalization) related to use of LABAs relative to placebo or other non-LABA asthma drugs, was presented to a joint meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee in December 2008. The meta-analysis had limited data to compare LABAs with ICS to ICS alone. Recommendations for post-marketing safety clinical trials to further examine this possible relationship were presented by the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) at a joint meeting of the Pulmonary-Allergy Drugs Advisory and Drug Safety and Risk Management Advisory Committees in March 2010. In April 2011 a post-marketing requirement (PMR) was issued to all manufacturers of LABA products to conduct controlled trials to assess the safety of LABA plus ICS versus ICS alone. The language in the PMR is quoted below:

> *To further evaluate the safety of Long-Acting Beta-Agonists (LABAs) when used in combination with inhaled corticosteroids for the treatment of asthma, the U.S. Food and Drug Administration (FDA) is requiring the manufacturers of LABAs to conduct five randomized, double-blind, controlled clinical trials comparing the addition of LABAs to inhaled corticosteroids versus inhaled corticosteroids alone.*
>
> *Four clinical trials will be conducted in adult and adolescent patients 12 years of age and older. The adult and adolescent trials will include 11,700 patients in each trial for a total of 46,800 patients. Each trial will evaluate one of the*

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following LABA-containing drugs: 1) Symbicort (budesonide and formoterol); 2) Advair Diskus (fluticasone and salmeterol); 3) Dulera (mometasone and formoterol); and 4) Foradil (formoterol). The Foradil trial will also include treatment with fluticasone, which will be provided in a separate inhaler.

One clinical trial will be conducted in pediatric patients aged 4 to 11 years with Advair Diskus. The pediatric trial will include 6,200 patients. Patients in all trials will be treated for six months, and the primary endpoint will be a composite of serious asthma outcomes: asthma-related death, intubation, or hospitalization. The pediatric trial will also assess other relevant quality of life endpoints such as days of school missed and emergency room visits because of asthma related illness.

The clinical trials will begin in 2011 and FDA expects to receive results in 2017.

The sponsors of Symbicort (AstraZeneca), Advair Diskus (GSK), and Dulera (Merck) have completed the clinical trials requested in this PMR. Novartis withdrew Foradil from the USA market and no additional clinical trials were conducted for this product. The trials conducted by each sponsor were independently powered to evaluate the primary safety endpoint of the composite of asthma-related death, asthma-related intubation and asthma-related hospitalization. This review focuses on the results of the post-marketing safety trials SAS115359 and SAS115358 designed by GSK to address this PMR.

The approved doses of ADVAIR DISKUS for the treatment of asthma are one inhalation of ADVAIR DISKUS 100/50 (fluticasone propionate 100 mcg and salmeterol xinafoate 50 mcg inhalation powder), ADVAIR DISKUS 250/50 (fluticasone propionate 250 mcg and salmeterol xinafoate 50 mcg inhalation powder) and ADVAIR DISKUS 500/50 (fluticasone propionate 500 mcg and salmeterol xinafoate 50 mcg inhalation powder) twice daily in patients aged 12 years and older. The only dose approved dose for patients aged 4 to 11 years is one inhalation of ADVAIR DISKUS 100/50 twice daily.

Trial SAS115359 compared 3 doses (100/50, 250/50, 500/50) of FSC versus equipotent doses of inhaled FP administered twice daily over 26 weeks in adolescent and adult subjects with persistent asthma. SAS115358 compared 2 doses (100/50, 250/50) of FSC versus equipotent doses of inhaled FP administered twice daily over 26 weeks in pediatric subjects with persistent asthma.

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2.2 Data Sources

The sponsor submitted study summaries, clinical study reports and analysis datasets for these two supplements on January 15, 2016 for the adult and adolescent trial (SAS115359) and on May 19, 2016 for the pediatric trial (SAS115358). The format, content and documentation of the datasets were adequate to conduct a statistical review of the pre-specified composite safety endpoint in both clinical trials. The EDR links are listed below.

\\cdsesub1\evsprod\NDA021077\0147\ (SAS115359, AUSTRI)
\\cdsesub1\evsprod\NDA021077\0153\ (SAS115358, VESTRI)

The following datasets were used to conduct the analyses of safety endpoints, including serious asthma-related adverse events:

(Time-to-event)
\\cdsesub1\evsprod\NDA021077\0147\m5\datasets\sas115359\analysis\adam\datasets\adtte.xpt
\\cdsesub1\evsprod\NDA021077\0153\m5\datasets\sas115358\analysis\adam\datasets\adtte.xpt

(Subject level)
\\cdsesub1\evsprod\NDA021077\0147\m5\datasets\sas115359\analysis\adam\datasets\adsl.xpt
\\cdsesub1\evsprod\NDA021077\0153\m5\datasets\sas115358\analysis\adam\datasets\adsl.xpt

(Exposure/Compliance)
\\cdsesub1\evsprod\NDA021077\0147\m5\datasets\sas115359\analysis\adam\datasets\adex.xpt
\\cdsesub1\evsprod\NDA021077\0153\m5\datasets\sas115358\analysis\adam\datasets\adex.xpt

(Disposition)
\\cdsesub1\evsprod\NDA021077\0147\m5\datasets\sas115359\analysis\adam\datasets\addisp.xpt
\\cdsesub1\evsprod\NDA021077\0153\m5\datasets\sas115358\analysis\adam\datasets\addisp.xpt

(Define files)
\\cdsesub1\evsprod\NDA021077\0147\m5\datasets\sas115359\analysis\adam\datasets\define.pdf
\\cdsesub1\evsprod\NDA021077\0153\m5\datasets\sas115358\analysis\adam\datasets\define.pdf

3 STATISTICAL EVALUATION

This statistical review is focused on the safety aspect of two post-marketing safety trials (AUSTRI SAS115359 and VESTRI SAS115358) described in two supplements submitted by GSK, S-056 and S-057. The primary outcome in both trials is a safety composite endpoint of serious asthma-related adverse events. For a statistical evaluation of efficacy of trials SAS115359 and SAS115358, the reader is referred to the review authored by Dr. Shanti

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Gomatam. For a statistical evaluation of the original NDA submission, the reader is referred to the review authored by Ms. Barbara Elashoff on 9/29/1999. Note that Supplement S-057 was submitted for administrative purposes only and does not include new contents beyond S-056.

3.1 Data and Analysis Quality

Data and reports for these trials were submitted electronically. The reviewer was able to perform all analyses in the review below and reproduce major findings included in the study report using the submitted electronic data files. No major data quality issues were identified.

3.2 Evaluation of Safety

Two Phase IV trials – SAS115359 (AUSTRI) in the adult and adolescent population, and SAS115358 (VESTRI) in the pediatric population are reviewed in separate sections of this document.

3.2.1 Safety Evaluation for Adult and Adolescent Population Based on Trial SAS115359

3.2.1.1 Study Design and Endpoints

3.2.1.1.1 Study Design

Trial SAS115359 (AUSTRI) was a global, multicenter, randomized, stratified, double-blind, parallel-group, active-comparator, 26-week trial in adolescent (12-17 years of age) and adult subjects (18 years of age and older) whose asthma warranted treatment with controller asthma therapy.

Subjects participated in the trial for a maximum of 29 weeks, including a screening visit (Visit 1), a randomization visit (Visit 2) followed by a treatment period of 26 weeks and a 1-week follow-up phone call to assess serious adverse events. At Visit 1 (screening visit), subjects were assessed for eligibility and categorized into one of six randomization strata (Table 2) by ACQ-6 score and current asthma medication. At Visit 2 (randomization visit), subjects were randomized to either FSC or FP in a 1:1 ratio within each stratum. See Figure 1.

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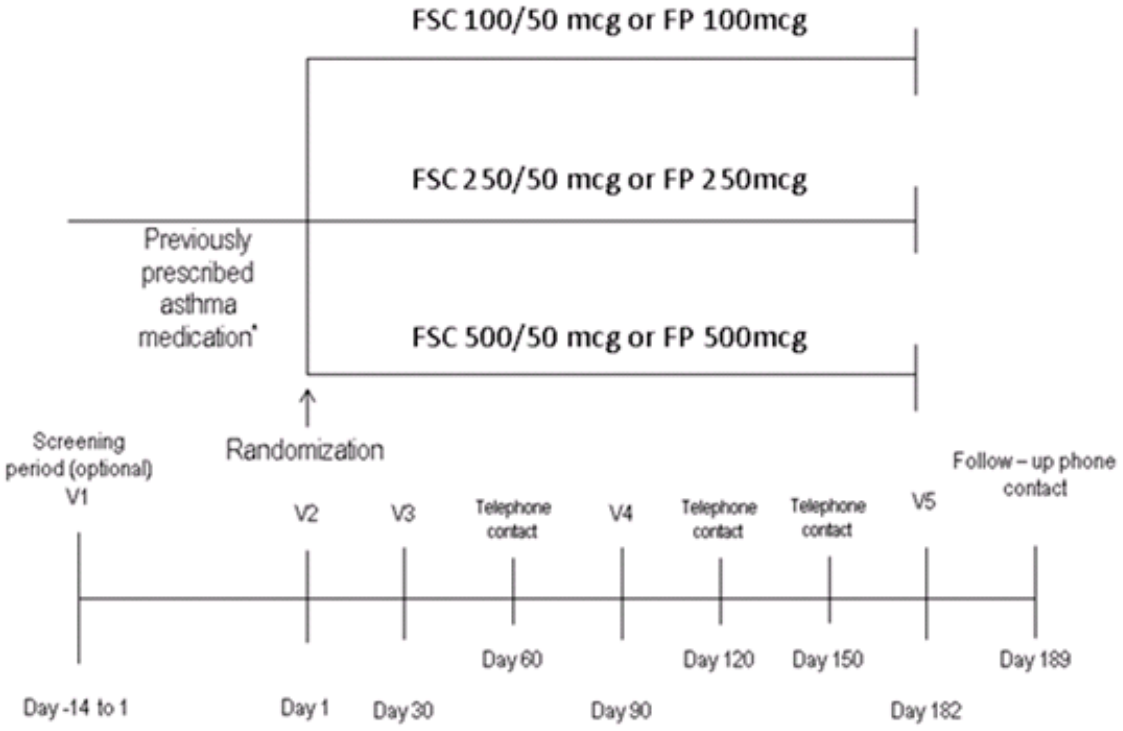
Figure 1 Trial Schematic, SAS115359



Source: Clinical study report by the sponsor

The statistical design was based on demonstrating non-excessive risk (i.e. non-inferiority) of serious asthma events in FSC compared to FP (active comparator). It was estimated that approximately 87 events, or 11,664 subjects, would be needed to rule out a hazard ratio larger than 2.0 associated with FSC with a one-sided alpha of 0.025 and 90% power, under the assumptions of a true hazard ratio of 1.0 and an event rate of 0.75% for a 6-month period, according to a statistical memorandum regarding the PMR authored by Dr. Benjamin Neustifter in 2011.

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Table 2 Randomization Strata (Treatment Assignment) for SAS115359

Randomization Strata	ACQ-6 Score and Current Asthma Medication	Randomization Assignment
A	**ACQ-6 <1.5*** on low dose ICS or on low dose ICS and one or more adjunctive therapy (LABA, leukotriene receptor antagonist (LTRA), theophylline)	FSC 100/50 or FP 100
B	**ACQ-6 <1.5*** on medium dose ICS or on medium dose ICS and one or more adjunctive therapy (LABA, LTRA, theophylline)	FSC 250/50 or FP 250
C	**ACQ-6 <1.5*** on high dose ICS or high dose ICS and one or more adjunctive therapy (LABA, LTRA, theophylline)	FSC 500/50 or FP 500
D	**ACQ-6 ≥1.5*** on daily rescue medication or LTRA monotherapy or daily theophylline**	FSC 100/50 or FP 100
E	**ACQ-6 ≥1.5*** on low dose ICS or on low dose ICS and one or more adjunctive therapy (LABA, LTRA, theophylline)	FSC 250/50 or FP 250
F	**ACQ-6 ≥1.5*** on medium dose ICS or medium dose ICS and one or more adjunctive therapy (LABA, LTRA, theophylline)	FSC 500/50 or FP 500

LTRA = Leukotriene receptor antagonist
*ACQ-6<1.5 = controlled status; ACQ-6≥1.5 = not well controlled asthma
**For subjects entering on daily rescue medication or LTRA monotherapy or theophylline, must be using daily rescue medication or LTRA monotherapy or daily theophylline for at least 4 weeks prior to randomization with no other controller.

Source: Reporting and Analysis Plan by the sponsor

3.2.1.1.2 Study Endpoints

According to the Reporting and Analysis Plan (RAP), the pre-specified primary safety endpoint is a composite of serious asthma outcomes (asthma-related hospitalization, asthma-related endotracheal intubation, or asthma-related death) observed over the 26-week study period.

Secondary safety endpoints include the individual components of the composite endpoint, and withdrawals from study treatment due to asthma exacerbation.

Other safety assessments are adverse events (AEs) leading to withdrawal from study treatment and serious adverse events (SAEs).

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3.2.1.1.3 Adjudication Methods

An independent Joint Adjudication Committee (JAC) was set up to adjudicate events in the trials designed to address the PMR for Symbicort, Advair Diskus, and Dulera. The JAC consisted of 3 independent, external physicians and was designed to follow the same adjudication process for all trials. A Joint Oversight Steering Committee (JOSC) and a Joint Data Monitoring Committee (JDMC) were also formed to harmonize study conduct and facilitate combined analysis. The charters for these committees were included in the present NDA submission.

Study sites submitted adjudication packages blinded to treatment assignment for all possible events of death, endotracheal intubation, and/or hospitalization based on pre-specified criteria. The JAC reviewed and categorized the cause of death, endotracheal intubation, and/or hospitalization for asthma relatedness for each subject where one of these outcomes was recorded.

All reported intubations and deaths automatically qualified for full JAC adjudication for asthma causality. Reported hospitalizations (as defined in the sponsor protocols) first underwent pre-adjudication screening (PAS) by a single rotating member of the JAC. Hospitalizations which, according to the information presented to the rotating JAC member, could not have an asthma relationship clearly ruled out were referred for full adjudication by the JAC.

3.2.1.2 Statistical Methodologies

The AUSTRI trial compared FSC versus FP on the composite endpoint of asthma-related hospitalization, endotracheal intubation, and death. The primary hypothesis for this trial was that the addition of LABA to ICS therapy (FSC) did not increase the risk of serious asthma-related outcomes beyond a pre-specified safety margin of 2.0 when compared to ICS therapy alone (FP). This hypothesis was assessed through a Cox proportional hazards model for the time to first serious asthma-related outcome with terms for randomized treatment and stratified by incoming asthma treatment/asthma control. If the resulting upper bound of the 95% confidence interval (CI) for the hazard ratio (HR) of the time to first serious asthma-related outcome for subjects in the FSC group relative to subjects in the FP group is <2.0, then non-inferiority is concluded.

Reviewer's comment: *Relative risk (RR) was used interchangeably with hazard ratio (HR) by the sponsor. RR is generally defined as the ratio of probabilities or proportions (e.g. ratio of incidence rates), while HR is defined as the ratio of hazard functions in the context of time-to-event survival analysis. It should be clarified that HR, instead of RR, was used to quantify risk and establish the pre-specified non-inferiority risk margin of 2.0. The pre-study sample size calculation was also based on HR instead of RR using a log-rank test.*

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3.2.1.2.1 Statistical Hypothesis

The primary safety evaluation estimated the hazard radio (HR) of the time-to-composite-event in the FSC arm compared to the FP arm. This non-inferiority analysis compared the HR to the pre-specified non-inferiority (NI) margin of 2.0:

$$H_0: HR \geqslant 2.0 \text{ vs. } H_1: HR < 2.0$$

3.2.1.2.2 Interim Analyses

A formal interim analysis was planned when approximately half (44) of the expected events (87) had been observed using the Haybittle-Peto method of alpha-spending. A one-sided alpha level of 0.0001 was used for the interim analysis (with an inferiority margin of 1.0).

This interim analysis was performed unblinded to study treatment by an independent statistical team within (b) (4) not associated with conduct of the study, and reviewed by the trial-specific Data Monitoring Committee (DMC). The intention of this interim analysis was to assess safety in the comparison of FSC versus FP treatment at an interim time point during the conduct of the study. After a review of the interim analysis results, the DMC recommended to continue the trial without any modifications. The charter and meeting minutes for the DMC were included with this submission.

A one-sided alpha level of 0.024988 was used in the final analysis in order to maintain the overall significance level of 0.025. If the upper bound of the 95.0024% confidence interval of the hazard ratio estimate in the final analysis is less than 2.0, non-inferiority is concluded, with an overall one-sided Type-I error α of 2.5%.

3.2.1.2.3 Analysis Populations

The following four analysis populations were defined in the RAP:

Intention-to-treat (ITT): The ITT population included all randomized subjects who took at least one dose of study drug. Subjects were analyzed according to the study drug assigned at randomization. Unless otherwise specified, this is the primary analysis population for safety data. This population includes outcomes that occurred within six months after the first use of study drug or seven days after the last date of study drug treatment, whichever date is greater. This population also forms the basis of all summaries of background/demographics data.

Modified intention-to-treat (mITT): This population consists of the same ITT subjects with a different data cut-off for supportive (on-treatment) analyses of the primary composite safety endpoint. The data was truncated seven days after the end of study drug exposure for mITT analysis.

The screen failure population: It includes all subjects screened for inclusion in the study and not randomized to blinded study drug.

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The randomization population: It consists of all subjects randomized to study treatment, regardless of whether those subjects used study treatment. This population consists of all subjects in the ITT population, as well as any subjects for whom documentation exists that they were randomized but never used study treatment.

This multicenter study was conducted in 710 centers in 33 countries in 5 regions: North America, Latin America, Europe, Africa, and Asia/Pacific. Of the 710 centers that enrolled subjects, 693 centers contributed subjects to the intent-to-treat population (i.e., randomized and took study drug).

Table 3 Analysis Populations, SAS115359

Population	FSC	FP	Total
Number of Subjects Screened	--	--	12857
Screen Failure Population*	--	--	1298
Randomization Population	5874	5877	11751
Intent-to-Treat Population**	5834	5845	11679
Modified Intent-to-Treat Population	5834	5845	11679

* 192 subjects were re-screened and randomized
** Randomized subjects who took at least one dose of study drug
Source: Created by the statistical reviewer using dataset adsl.xpt

3.2.1.2.4 Primary Analysis

The primary analysis of time to the composite endpoint was evaluated through a Cox proportional hazards regression model with treatment group (a 2-level categorical variable) as the only covariate, and baseline hazards stratified by incoming asthma medication/asthma control randomization stratum (a 6-level categorical variable as shown in Table 2) determined at Visit 1 (Screening Visit). The primary analysis was conducted on the ITT population. If the upper bound of the 95% confidence interval (CI) for the estimated hazard ratio (HR) of time to first asthma-related outcome for subjects in the FSC group relative to subjects in the FP group is <2.0, then non-inferiority was concluded.

Reviewer's comment: *Sponsor's RAP, as well as CSR, has conflicting accounts on whether the incoming asthma medication/asthma control randomization stratum is used as a covariate in the Cox model, or as a stratification factor for the baseline hazards. It was confirmed through examining the sponsor's submitted SAS programs that the randomization stratum was used as a stratification factor for the baseline hazards to derive the results in the CSR. While it is acceptable from a statistical perspective to use it as a stratification factor, the reviewer has also*

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performed a sensitivity analysis using the randomization stratum as a covariate instead of a stratification factor for the baseline hazards. Also, the RAP did not specify how ties are handled in the Cox model; Efron's method has been used to handle ties in this review.

3.2.1.2.5 Sensitivity Analyses of the Primary Endpoint

An on-treatment analysis was planned by the sponsor for the primary endpoint using the mITT population.

Because the model stratification/covariate specification is unclear in RAP/CSR, sensitivity analyses using randomization stratum as a covariate in the Cox model with no baseline stratification are performed for both the mITT and ITT populations for the primary endpoint.

3.2.1.2.6 Analysis of Secondary Endpoints

As pre-specified in the RAP, a similar time-to-event analysis as the primary endpoint was planned for the following secondary endpoint:

- Withdrawals from study treatment due to asthma exacerbation.

The following individual components of the primary composite endpoint were considered secondary endpoints and are summarized by treatment group:

- Asthma-related hospitalization
- Asthma-related endotracheal intubation
- Asthma-related death.

3.2.1.3 Demographic, Baseline Characteristics and Patient Disposition

Table 4 shows the demographic characteristics of subjects in the ITT population by treatment. All the characteristics summarized in this table appear balanced between the two arms. Approximately 66% of the subjects in the trial were female. The mean age at baseline was 43.4 years, and approximately 75% of the subjects were classified as White.

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Table 4 Demographics, SAS115359 (ITT)

Treatment	FSC n=5834	FP n=5845
Female (%)	3851 (66)	3898 (67)
Age (years): Mean ± SD	43.4 ± 17	43.4 ± 17
12-17 (%)	615 (11)	615 (11)
18-64 (%)	4576 (78)	4605 (79)
>64 (%)	643 (11)	625 (11)
Race		
White (%)	4374 (75)	4409 (75)
Black (%)	870 (15)	856 (15)
Other (%)	587 (10)	577 (10)
Missing (%)	3 (0)	3 (0)

Source: Created by the statistical reviewer using dataset adtte.xpt.

Table 5 shows the disposition and exposure of subjects in the ITT population by treatment arm. The majority of the patients in the ITT population (>99%) completed the study in both arms. The mean length of treatment exposure (on-treatment time) was 164 days (23.5 weeks). Approximately 17% of the subjects discontinued treatment before completion of the trial. Subjects in the FP arm were more than twice as likely to have premature treatment withdrawal due to lack of efficacy (53 vs 25) and were more likely to voluntarily withdraw from randomized treatment (655 vs 583).

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Table 5 Disposition and Exposure, SAS115359 (ITT)

Treatment	FSC n=5834	FP n=5845
Exposure (Days): Mean ± SD	166 ± 47	163 ± 51
Study Completion		
Completed	5823	5831
Death	3	6
Withdrawal by Subject	8	8
Premature Treatment Withdrawal (%)	947 (16)	1066 (18)
Adverse Event*	160	174
Lack Of Efficacy	25	53
Lost To Follow-Up	48	37
Protocol Deviation	131	147
Withdrawal By Subject	583	655

* "Adverse Event" category included "Asthma Exacerbation" in the adsl.xpt dataset.
Source: Created by the statistical reviewer using dataset adsl.xpt.

3.2.1.4 Results and Conclusions

3.2.1.4.1 Summary of Primary Composite Events

Table 6 shows that 34 subjects in the FSC treatment arm and 33 subjects in FP experienced at least one event in the primary composite. The majority of these events were adjudicated as asthma-related hospitalizations. Only 2 subjects in the FP arm experienced an endotracheal intubation. No asthma-related deaths were observed in this trial.

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Table 6 Individual Adverse Events in the Composite Endpoint SAS115359 (ITT)

Number of Subjects Experiencing:	**FSC (n=5834)**	**FP (n=5845)**	**Total (n=11679)**
Any Event in the Composite Safety Endpoint (%)	34 (<1)	33 (<1)	77 (<1)
Asthma-related Hospitalization (%)	34 (<1)	33 (<1)	77 (<1)
Asthma-related Endotracheal Intubation (%)	0	2 (<1)	2 (<1)
Asthma-related Death (%)	0	0	0

Source: Created by the statistical reviewer using datasets adtte.xpt and adae.xpt

3.2.1.4.2 Primary Analysis Results

Table 7 shows results of the pre-specified primary analysis of the composite endpoint of serious asthma events. The percentage of subjects who experienced an event during the study period was 0.58% in the FSC treatment arm and 0.56% in the FP arm. The estimated hazard ratio associated with FSC was 1.029. The upper bound of the 95% CI of the HR was 1.662 (<2.0) and therefore successfully ruled out a risk associated with FSC in the composite endpoint being larger than 2.0 relative to FP.

Table 7 Primary Analysis of Serious Asthma Events, SAS115359 (ITT Population)

	FSC (Advair)	FP
Events/N (%) *IR per 100 PY*	34/5834 (0.58%) *1.16*	33/5845 (0.56%) *1.12*
HR (95% CI)*	**1.029 (0.638, 1.662)**	

* Adjusting for the planned interim analysis using the Haybittle-Peto method, the CI displayed is actually 95.0024% CI, which is identical to third decimal place as the 95% CI here.

Source: Created by the statistical reviewer using dataset adtte.xpt.

Kaplan-Meier curves for the time to event are shown in Figure 2 with estimated 95% confidence intervals for the survival function at 28-day intervals. The confidence intervals all overlapped and no statistically significant difference between the two arms was observed.

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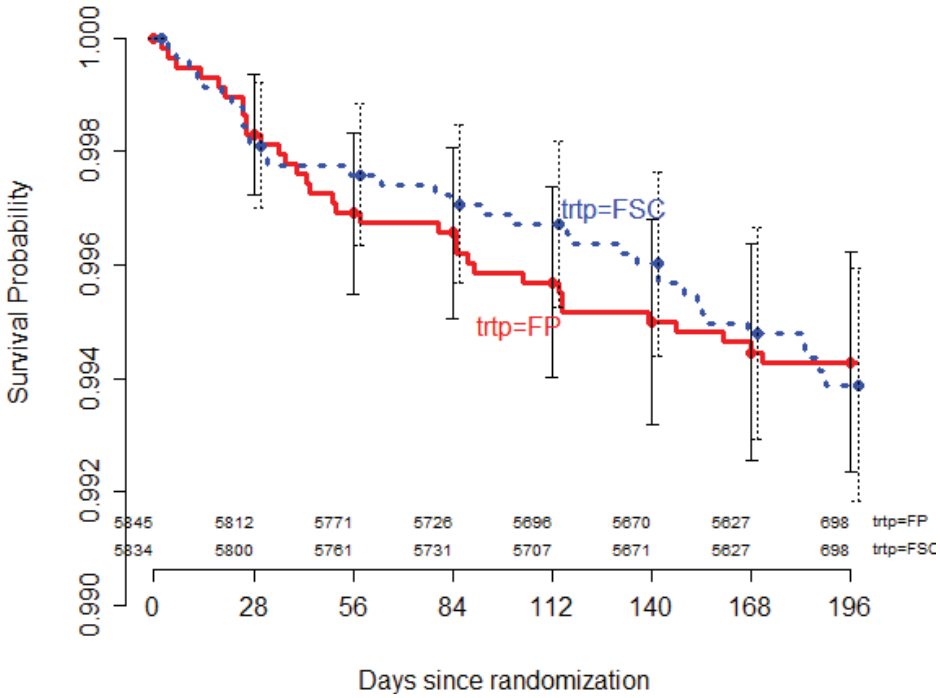
Figure 2 Kaplan-Meier Curves for Primary Endpoint, SAS115359 (ITT)



Note: The numbers marked above the x-axis represent number of subjects at risk at annotated time points. The "at-risk" set includes the day noted on the x-axis. The 95% confidence bars on the K-M curves were calculated using the log-survival method.

Source: Created by the statistical reviewer using dataset adtte.xpt

3.2.1.4.3 Sensitivity Analyses of the Primary Endpoint

Table 8 shows the sensitivity analysis results for the primary endpoint using the mITT (on-treatment) population while keeping everything else the same as the primary analysis model. Table 9 and Table 10 show results from non-stratified Cox proportional hazards models. These models were evaluated because it was unclear in the sponsor's RAP and CSR whether the incoming asthma status/medication variable was to be used as a stratification factor or a covariate. The sensitivity analyses in Table 8, Table 9, Table 10 are consistent with the primary analysis for Trial SAS115359 and show no evidence of increased risk of asthma-related adverse serious events associated with FSC when compared to FP.

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Table 8. Primary Endpoint Sensitivity Analysis, SAS115359 (mITT)

	FSC (Advair)	FP
Events/N (%) *IR per 100 PY*	33/5834 (0.57%) *1.14*	30/5845 (0.51%) *1.02*
HR (95% CI)	**1.087 (0.663, 1.782)**	

Source: Created by the statistical reviewer using dataset adtte.xpt

Table 9 Primary Endpoint Sensitivity Analysis: Stratum as Covariate, SAS115359 (ITT)

	FSC (Advair)	FP
Events/N (%) *IR per 100 PY*	34/5834 (0.58%) *1.16*	33/5845 (0.56%) *1.12*
HR (95% CI)	**1.030 (0.638, 1.663)**	

Source: Created by the statistical reviewer using dataset adtte.xpt

Table 10 Primary Endpoint Sensitivity Analysis: Stratum as Covariate, SAS115359 (mITT)

	FSC (Advair)	FP
Events/N (%) *IR per 100 PY*	33/5834 (0.57%) *1.14*	30/5845 (0.51%) *1.02*
HR (95% CI)	**1.089 (0.664, 1.785)**	

Source: Created by the statistical reviewer using dataset adtte.xpt

3.2.1.4.4 Analyses of Secondary Endpoints

There were 66 subjects on FSC and 84 on FP who withdrew from the study due to asthma exacerbations. Table 11 shows the time-to-event analysis results of this endpoint: the estimated

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hazard ratio and corresponding 95% confidence interval associated with FSC were 0.776 (0.562, 1.071) and showed no statistically significant difference between the two treatment arms on the risk of asthma exacerbations.

A total of 9 deaths were observed in Trial SAS 115359 (3 on FSC and 6 on FP, see Table 12). All deaths were adjudicated by the JAC as non-asthma related.

Table 11 Time-to-Event Analysis for Withdrawals from Study Treatment Due to Asthma Exacerbation, SAS115359 (ITT)

	FSC (Advair)	FP
Events/N (%) *IR per 100 PY*	66/5834 (1.13%) *2.26*	84/5845 (1.44%) *2.88*
HR (95% CI)	**0.776 (0.562, 1.071)**	

Source: Created by the statistical reviewer using dataset adtte.xpt

Table 12 All-Cause Deaths, SAS115359 (ITT)

Number of Subjects Experiencing:	**FSC (n=5834)**	**FP (n=5845)**	**Total (n=11679)**
All-cause Death (%)	3 (<1)	6 (<1)	9 (<1)

Source: Created by the statistical reviewer using datasets adae.xpt

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3.2.2 Safety Evaluation for Pediatric Population Based on Trial SAS115358

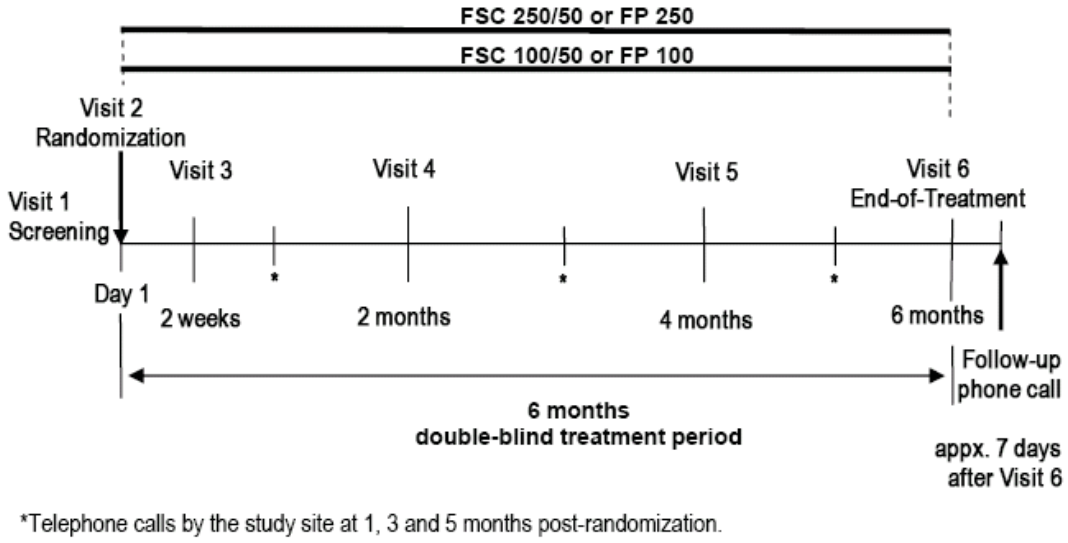
3.2.2.1 Study Design and Endpoints for Trial SAS115358

3.2.2.1.1 Study Design

This study was a global, multi-center, randomized, stratified, double-blind, parallel group, 6-month study in pediatric subjects with persistent asthma (Figure 1). The study randomized 6250 subjects with representation throughout the ages of 4 to 11 years.

Subjects participated in the study for a maximum of 29 weeks, including a screening visit (Visit 1), a randomization visit (Visit 2) followed by a treatment period of 26 weeks and a 1-week follow-up phone call to assess serious adverse events. At Visit 1 (screening visit), subjects were assessed for eligibility and stratified into one of 7 strata (Table 13) based on the C-ACT, number of exacerbations in the prior year and their prior asthma medication use. Prior to randomization, subjects remained on their current asthma medication. At Visit 2 (randomization visit), subjects were randomized to either FSC or FP in a 1:1 ratio within their stratum. See Figure 3.

Figure 3 Trial Schematic, SAS115358



Source: Clinical study report by the sponsor

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Table 13 Randomization Strata (Treatment Assignment) for SAS115358

Prior Asthma Therapy	Childhood Asthma Control Test score at Visit 1*	One exacerbation in previous year	Two to four exacerbations in previous year†	Randomization Stratum
SABA, LTRA, theophylline or cromolyn	≥20	Not eligible	Not eligible	Not eligible
	≤19	Not eligible	FSC 100/50 or FP 100	a
Low Dose ICS monotherapy	≥20	Not eligible	FSC 100/50 or FP 100‡	c
	≤19	FSC 250/50 or FP 250	FSC 250/50 or FP 250	b
Low Dose ICS and one or more adjunctive therapy	≥20	FSC 100/50 or FP 100	FSC 250/50 or FP 250	d f
	≤19	FSC 250/50 or FP 250	FSC 250/50 or FP 250	d
Medium-dose ICS monotherapy	≥20	FSC 100/50 or FP 100	FSC 250/50 or FP 250	e f
	≤19	FSC 250/50 or FP 250	FSC 250/50 or FP 250	e
Medium-dose ICS and one or more adjunctive therapy	≥20	FSC 250/50 or FP 250	Not eligible	g
	≤19	Not eligible	Not eligible	Not eligible

FP = fluticasone propionate FSC = FP/salmeterol combination; ICS = Inhaled corticosteroid; LABA =long-acting beta$_2$-agonist; LTRA = leukotriene receptor antagonist, SABA = short-acting beta$_2$-agonist

*Control defined by Childhood Asthma Control Test - Controlled defined as Childhood Asthma Control Test score ≥20;

†Subjects with more than 4 separate exacerbations in the last 12 months from Visit 1 are not eligible for randomization.

‡The most recent exacerbation must have occurred while prescribed an ICS-containing controller medication by parent/guardian report [subjects are eligible if use of an ICS during the most recent exacerbation is not known]).

Source: Reporting and Analysis Plan by the sponsor

3.2.2.1.2 Study Endpoints

The primary safety endpoint was the composite of serious asthma-related outcomes (asthma-related hospitalization, endotracheal intubation, or death) over the 6-month study treatment period. Hospitalization was defined as an inpatient stay or a ≥24-hour stay in an observation area in an ED or other equivalent facility.

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The secondary safety endpoints include the individual components of the primary endpoint and withdrawals from study treatment due to asthma exacerbation.

3.2.2.1.3 Adjudication Methods

A trial-specific Pediatric Adjudication Committee (PAC) periodically reviewed the subject data and adjudicated whether each event was asthma-related or not. All hospitalizations, endotracheal intubations, and deaths were subject to adjudication procedures to determine asthma causality as defined in the PAC charter. The PAC consisted of three independent, external physicians. One of the three PAC members served as the chair.

All reported intubations and deaths automatically qualified for the full PAC adjudication for asthma causality. Reported hospitalizations (as defined in the study protocol) first underwent pre-adjudication screening (PAS) by a single rotating member of the PAC. All hospitalizations considered to be possibly asthma-related by the rotating PAC member based upon the SAE summary information were referred for full adjudication by the PAC. Hospitalizations that have been deemed not asthma-related after PAS did not require full PAC adjudication.

3.2.2.2 Statistical Methologies for Trial SAS115358

This trial compared FSC versus FP on the composite endpoint of asthma-related hospitalization, endotracheal intubation, and death. The primary hypothesis was that the addition of LABA to ICS therapy (FSC) did not increase the risk of serious asthma-related outcomes beyond a pre-specified safety margin of 2.675 when compared to ICS therapy alone (FP). This hypothesis was assessed by a Cox proportional hazards model of the time to first serious asthma-related outcome with randomized treatment as the only covariate and baseline hazards stratified by the randomization stratum as defined in Table 13. If the resulting upper bound of the 95% confidence interval (CI) for the hazard ratio (HR) of the time to first serious asthma-related outcome for subjects in the FSC group relative to subjects in the FP group is < 2.675, then non-inferiority is concluded. This non-inferiority margin is larger than that in the adult/adolescent trial because of the smaller sample size in the pediatric trial.

Reviewer's comment: *Relative risk (RR) was used interchangeably with hazard ratio (HR) by the sponsor. RR is generally defined as the ratio of probabilities or proportions (e.g. ratio of incidence rates), while HR is defined as the ratio of hazard functions in the context of time-to-event survival analysis. It should be clarified that HR, instead of RR, was used to establish the pre-specified non-inferiority risk margin of 2.675 and to conduct the pre-study sample size calculation.*

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3.2.2.2.1 Statistical Hypothesis

The primary safety evaluation will analyze the hazard radio (HR) of the time-to-composite-event in the FSC arm compared to the FP arm. This non-inferiority analysis will compare the HR to the pre-specified non-inferiority (NI) margin of 2.675:

H_0: $HR \geqslant 2.675$; v.s. H_1: $HR < 2.675$.

3.2.2.2.2 Interim Analysis

A formal interim analysis was planned when approximately half of the total expected events are observed using the Haybittle-Peto method of alpha-spending. The interim analysis was conducted with an alpha level 0.0001 and was performed unblinded to study treatment (FP and FSC) by a third party not associated with the conduct of the study, and reviewed by the DMC. The intention of this interim analysis was to assess safety in the comparison of FSC vs. FP treatment at an interim time point after approximately 50% of the predetermined number of events occurred during the conduct of the study. After a review of the interim analysis results, the DMC recommended to continue the trial without any modifications.

If the upper bound of the 95.0024% confidence interval of the hazard ratio estimate in the final analysis is less than 2.675, non-inferiority is concluded, with an overall Type-I error α of 2.5%.

3.2.2.2.3 Analysis Populations

The following four analysis populations were defined in the RAP:

Intention-to-treat (ITT): The ITT population included all subjects randomized to study drug (and who took a dose of study drug). Subjects were analyzed according to the study drug they were assigned at randomization. Unless otherwise specified, this was the primary analysis population for summary and analysis of safety data. This population included outcomes that occurred within six months after the first use of study drug or seven days after the last date of study drug treatment, whichever date was greater. This population also formed the basis of all summaries of background/demographics data.

Modified intention-to-treat (mITT): This population consists of the same ITT subjects with a different data cut-off for supportive (on-treatment) analyses of the primary composite safety endpoint. The analysis data is truncated 7 days after the end of study drug exposure.

The screen failure population: It includes all subjects screened for inclusion in the study and not randomized to blinded study drug.

The randomization population: It consists of all subjects randomized to study treatment, regardless of whether those subjects used study treatment. This population consists of all subjects in the ITT population, as well as any subjects for whom documentation exists that they were randomized but never used study treatment.

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Table 14 Analysis Populations, SAS115358

Population	FSC	FP	Total
Number of Subjects Screened	--	--	6759
Screen Failure Population*	--	--	635
Randomization Population	3107	3101	6250
Intent-to-Treat Population**	3107	3101	6208
Modified Intent-to-Treat Population	3107	3101	6208

* 126 subjects were re-screened and randomized
** Randomized subjects who took at least one dose of study drug
Source: Created by the statistical reviewer using dataset adsl.xpt

3.2.2.2.4 Primary Analysis

The primary analysis of time to the composite endpoint is evaluated through a Cox proportional hazards model with treatment group (a 2-level categorical variable) as the only covariate, and baseline hazards stratified randomization stratum (a 7-level categorical variable) determined at Visit 1 (Screening Visit).The primary analysis was conducted based on the ITT population. If the resulting upper 95% confidence interval (CI) estimate for the hazard ratio (HR) of time to first asthma-related outcome for subjects in the FSC group relative to subjects in the FP group is < 2.675, then non-inferiority is concluded.

Reviewer's comment: *Sponsor's RAP, as well as CSR, has conflicting accounts on whether the randomization stratum is used as a covariate in the Cox model, or as a stratification factor for the baseline hazards. It was confirmed through examining the sponsor's submitted SAS programs that the randomization stratum was used as a stratification factor for the baseline hazards to derive the results in the CSR. While it is acceptable from a statistical perspective to use it as a stratification factor, the reviewer has performed a sensitivity analysis using the randomization stratum as a covariate instead of a stratification factor. Also, it was not specified in the RAP how ties are handled; Efron's method has been used to handle ties for survival times in this review.*

3.2.2.2.5 Sensitivity Analyses of the Primary Endpoint

An on-treatment analysis was planned for the primary endpoint using the mITT population. A sensitivity analysis using randomization stratum as a covariate in the Cox model with no baseline hazard stratification was performed using both the mITT and ITT populations for the primary endpoint.

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3.2.2.2.6 Analyses of Secondary Endpoints

As pre-specified in the RAP, similar time-to-event analyses are planned for the following secondary endpoint:

- Withdrawals from study treatment due to asthma exacerbation.

The number and percentage of individual endpoints in the primary composite endpoint will be summarized by treatment group for the other three secondary endpoints:

- Asthma-related hospitalization
- Asthma-related endotracheal intubation
- Asthma-related death.
-

3.2.2.3 Patient Demographics, Baseline Characteristics and Disposition

This trial was conducted in 566 centers in 31 countries in 5 regions, including 2 countries in North America, 4 countries in Latin America, 18 countries in Europe, 1 country in Africa and 6 countries in the Asia/Pacific region. Of the 566 centers that were initiated, 429 centers contributed subjects to the Intent-to-Treat Population (i.e., randomized and took study drug).

Table 15 shows that demographics characteristics were generally balanced between the two arms. Approximately 39% of the subjects were female. The mean age at baseline was 7.6 years, and about 65% of the subjects were classified as white.

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Table 15 Demographics, SAS115358 (ITT)

Study	**SAS115358** (ITT, N=6208)	
Treatment	**FSC (Advair)** n=3107	**FP** n=3101
Female (%)	1187 (38)	1227 (40)
Age ± SD (years)	7.6 ± 2	7.6 ± 2
4-6 (%)	1096 (35)	1114 (36)
7-11 (%)	2010 (65)	1987 (64)
12-17 (%)	1 (0) *	N/A
Race		
White	1998 (64)	2032 (66)
Black	539 (17)	511 (16)
Other	565 (18)	556 (18)
Missing	5 (0)	2 (0)

* One subject censored at Day 190 from (b) (6) had an age of 12. The corresponding age group was set to missing in the dataset.

Source: Created by the statistical reviewer using dataset adtte.xpt

Table 16 shows generally balanced exposure and disposition results between the two treatment arms. The majority (>99%) of ITT subjects in both arms completed the trial. The mean length of treatment exposure (on-treatment time) was 171 days (24.5 weeks). 12% of the ITT subjects discontinued treatment prematurely.

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Table 16 Disposition and Exposure, SAS115358 (ITT)

Study	**SAS115358** (N=6208)	
Treatment	**FSC** n=3107	**FP** n=3101
Total Exposure (Days) ± SD	170 ± 41	172 ± 40
Study Completion		
Completed	3105	3099
Death	1	0
Withdrawal by Subject	1	2
Premature Treatment Withdrawal (%)	383 (12)	350 (11)
Adverse Event*	58	58
Lack Of Efficacy	5	6
Lost To Follow-Up	7	7
Protocol Deviation	68	53
Withdrawal By Subject	245	226

* The "Adverse Event" category includes "Asthma Exacerbation" in adsl.xpt.

Source: Created by the statistical reviewer using dataset adsl.xpt.

Reference ID: 4116469

3.2.2.4 Results and Conclusions

3.2.2.4.1 Summary of Primary Composite Events

Table 17 shows that 27 subjects in the FSC treatment arm and 21 subjects in FP experienced at least one event in the primary composite. All of these events were adjudicated as asthma-related hospitalizations. No asthma-related deaths or intubations were observed in this trial.

Table 17 Individual Adverse Events in the Composite Endpoint and Deaths, SAS115358 (ITT)

Number of Subjects Experiencing …	**FSC (n=3107)**	**FP (n=3101)**	**Total (N=6208)**
Any Event in the Composite Safety Endpoint (%)	27 (<1)	21 (<1)	48 (<1)
Asthma-related Hospitalization (%)	27 (<1)	21 (<1)	48 (<1)
Asthma-related Endotracheal Intubation (%)	0	0	0
Asthma-related Death (%)	0	0	0
All-cause Death (%)	0	0	0

Source: Created by the statistical reviewer using datasets adtte.xpt and adae.xpt

3.2.2.4.2 Primary Analysis Results

Table 18 shows results of the pre-specified primary analysis of the composite endpoint of serious asthma events. The percentage of subjects who experienced an event during the study period was 0.87% in the FSC treatment arm and 0.68% in the FP arm. The estimated hazard ratio associated with FSC was 1.285 when compared to FP. The upper bound of the 95% CI of the HR was 2.272 (<2.675) and therefore successfully ruled out a risk associated with FSC in the composite endpoint being larger than 2.675 relative to FP.

Reference ID: 4116469

Table 18 Primary Analysis of Serious Asthma Events, SAS115358 (ITT Population)

	FSC (Advair)	FP
Events/N (%) *IR per 100 PY*	27/3107 (0.87%) *1.74*	21/3101 (0.68%) *1.36*
HR (95% CI)*	**1.285 (0.726, 2.272)**	

* Adjusting for the planned interim analysis using the Haybittle-Peto method, the CI displayed is actually 95.0024% CI, which is identical to third decimal place as the 95% CI here.

Source: Created by the statistical reviewer using dataset adtte.xpt.

Kaplan-Meier curves for the primary composite endpoint are shown in Figure 4 with 95% confidence intervals at 28-day intervals. The survival curve for the FP treatment arm was consistently higher than the curve for FSC throughout the duration of the trial. However, the confidence intervals at various time points all overlapped and the overall difference between the two curves was not statistically significant.

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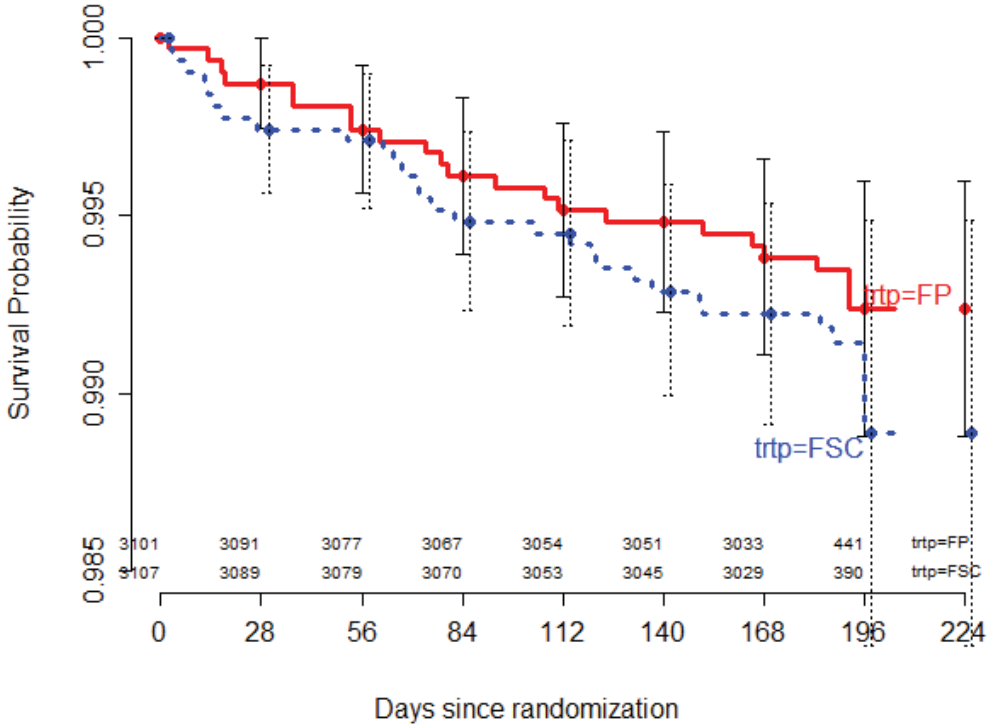
Figure 4 Kaplan-Meier Curves for the Primary Endpoint, SAS115358 (ITT)



Note: The numbers above the x-axis represent number of subjects at risk at annotated time points. The "at-risk" set includes the day noted on the x-axis. The 95% confidence bars on the K-M curves were calculated using the log-survival method.

Source: Created by the statistical reviewer using dataset adtte.xpt

3.2.2.4.3 Sensitivity Analyses of the Primary Endpoint

Table 19 shows the sensitivity analysis results for the primary endpoint using the mITT (on-treatment) population while keeping everything else the same as the primary analysis model. Table 20 and Table 21 show results from non-stratified models using the stratum as a covariate instead. These models were evaluated because it was unclear in the sponsor's RAP and CSR whether incoming asthma status/medication was to be used as a stratification factor or a covariate. The sensitivity analyses in Table 19, Table 20 and Table 21 are consistent with the primary analysis for Trial SAS115358, showing no evidence of increased risk of asthma-related adverse serious events associated with FSC relative to FP.

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Table 19 Primary Endpoint Sensitivity Analysis, SAS115358 (mITT)

	FSC (Advair)	FP
Events/N (%) *IR per 100 PY*	27/3107 (0.87%) *1.74*	20/3101 (0.64%) *1.28*
HR (95% CI)	**1.350 (0.757, 2.407)**	

Source: Created by the statistical reviewer using dataset adtte.xpt

Table 20 Primary Endpoint Sensitivity Analysis: Stratum as a Covariate, SAS115358 (ITT)

	FSC (Advair)	FP
Events/N (%) *IR per 100 PY*	27/3107 (0.87%) *1.74*	21/3101 (0.68%) *1.36*
HR (95% CI)	**1.291 (0.730, 2.284)**	

Source: Created by the statistical reviewer using dataset adtte.xpt

Table 21 Primary Endpoint Sensitivity Analysis: Stratum as a Covariate, SAS115358 (mITT)

	FSC (Advair)	FP
Events/N (%) *IR per 100 PY*	27/3107 (0.87%) *1.74*	20/3101 (0.64%) *1.28*
HR (95% CI)	**1.358 (0.762, 2.421)**	

Source: Created by the statistical reviewer using dataset adtte.xpt

3.2.2.4.4 Analysis of Secondary Endpoints

33 subjects on FSC and 35 on FP withdrew from the study due to asthma exacerbations. Table 22 shows the time-to-event analysis results corresponding to this endpoint: the estimated hazard

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ratio and corresponding 95% confidence interval associated with FSC were 0.944 (0.587, 1.519) and showed no statistically significant difference between the two treatment arms on the risk of asthma exacerbations.

The individual components of the composite endpoint were not analyzed separately because all serious asthma events in the composite endpoint were asthma-related hospitalizations. No deaths from any cause were observed in this trial.

Table 22 Time-to-Event Analysis for Withdrawals from Study Treatment Due to Asthma Exacerbation, SAS115358 (ITT)

	FSC (Advair)	FP
Events/N (%) *IR per 100 PY*	33/3107 (1.06%) *2.12*	35/3101 (1.13%) *2.26*
HR (95% CI)	**0.944 (0.587, 1.519)**	

Source: Created by the statistical reviewer using datasets adtte.xpt

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section discusses subgroup analyses based on the ITT population for the primary composite endpoint for both Trial SAS115359 (adult and adolescent population) and Trial SAS115358 (pediatric population). The subgroups presented here are defined by baseline demographic factors and dose levels determined before randomization according to pre-study asthma medication, asthma control status (ACQ-6 score for SAS115359 and CAT score for SAS115358) and previous exacerbation history (used for SAS115358 only), as shown in Table 2 and Table 13. Note that these subgroup analyses are for exploratory purposes only; these analyses were not powered for formal hypothesis testing, and were not adjusted for multiple comparisons. As such, estimated hazard ratios are presented with corresponding nominal 95% CIs. Analyses of subgroups are based upon the same model as that for primary analysis: a Cox proportional hazards model with randomized treatment as the only covariate, stratified by randomization stratum.

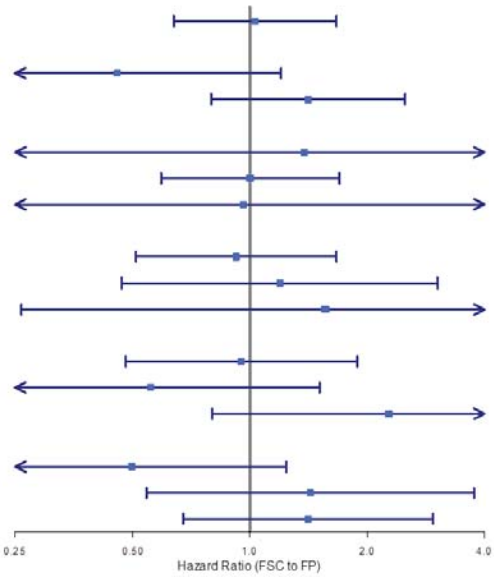
Reference ID: 4116469

4.1 Adult and Adolescent Population (SAS115359)

Figure 5 shows subgroup analyses with HR estimates and corresponding 95% CIs for the primary composite endpoint by gender, age, race, geographic region, and dose in SAS115359. The largest difference among subgroups was observed by gender: females had an estimated HR and 95% CI of 1.411 (0.795, 2.505) associated with FSC whereas the estimate for males was 0.457 (0.174, 1.202). No clear difference in risk was observed in subgroups defined by age or race. Small numerical imbalances were observed by region (a higher risk with FSC was observed in regions other than North America or Europe) and by dose (higher doses of FSC had higher estimated hazard ratios).

Figure 5 Subgroup Analysis Forest Plot for SAS115359 (ITT)

SAS115359	FSC	FP	HR [95% CI]
All ITT	34/5834	33/5845	1.029 [0.638,1.662]
Gender			
Male	6/1983	13/1947	0.457 [0.174,1.202]
Female	28/3851	20/3898	1.411 [0.795,2.505]
Age			
12-17	3/615	2/615	1.377 [0.229,8.266]
18-64	28/4576	28/4605	1.002 [0.593,1.692]
>64	3/643	3/625	0.965 [0.195,4.781]
Race			
White	21/4374	23/4409	0.923 [0.511,1.667]
Black	10/870	8/856	1.193 [0.470,3.027]
Others	3/590	2/580	1.560 [0.260,9.359]
Region			
North America	16/2623	17/2680	0.952 [0.481,1.885]
Europe	6/2110	11/2091	0.557 [0.206,1.506]
Others	12/1101	5/1074	2.274 [0.801,6.457]
Dose (mcg)			
100	7/1882	14/1892	0.499 [0.202,1.237]
250	10/2209	7/2211	1.430 [0.543,3.757]
500	17/1743	12/1742	1.413 [0.675,2.958]



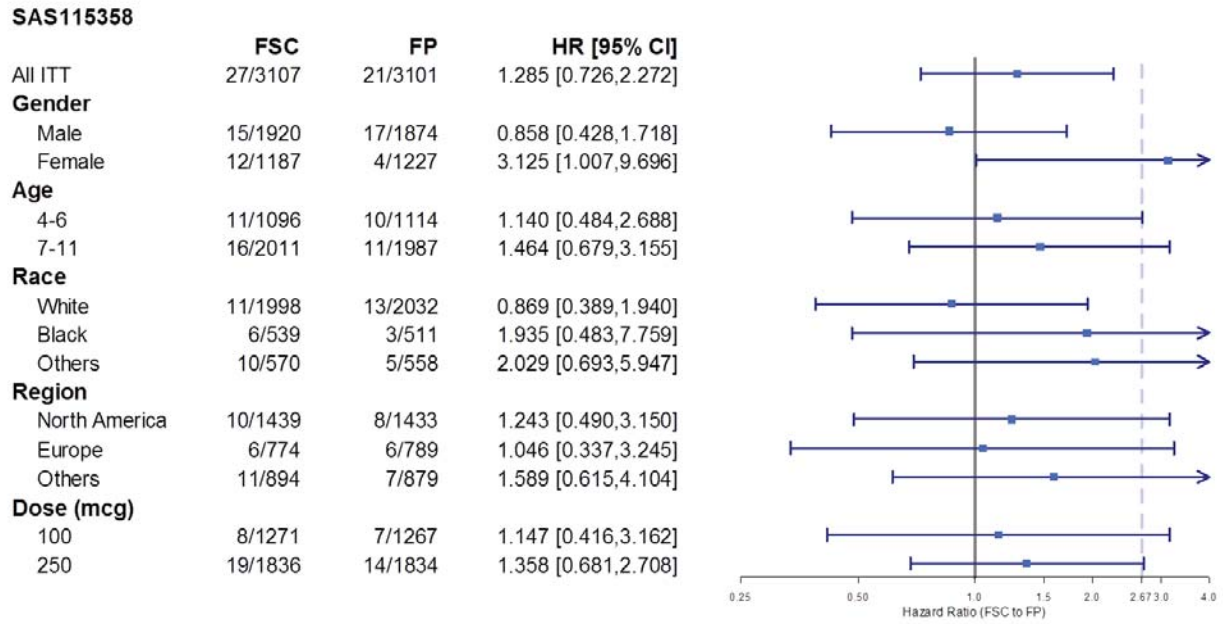
Source: Created by statistical reviewer using datasets adtte.xpt and adsl.xpt.

Reference ID: 4116469

4.2 Pediatric Population (SAS115358)

Figure 6 shows subgroup analyses with HR estimates and corresponding 95% CIs for the primary composite endpoint by gender, age, race, geographic region, and dose in SAS115358. The largest difference among subgroups was observed by gender: females had an estimated HR and 95% CI of 3.125 (1.007, 9.696) associated with FSC whereas the estimate for males was 0.858 (0.428, 1.718). No clear difference in risk was observed in subgroups defined by age, race, region, or dose.

Figure 6 Subgroup Analysis Forest Plot for SAS115358 (ITT)



SAS115358	FSC	FP	HR [95% CI]
All ITT	27/3107	21/3101	1.285 [0.726,2.272]
Gender			
Male	15/1920	17/1874	0.858 [0.428,1.718]
Female	12/1187	4/1227	3.125 [1.007,9.696]
Age			
4-6	11/1096	10/1114	1.140 [0.484,2.688]
7-11	16/2011	11/1987	1.464 [0.679,3.155]
Race			
White	11/1998	13/2032	0.869 [0.389,1.940]
Black	6/539	3/511	1.935 [0.483,7.759]
Others	10/570	5/558	2.029 [0.693,5.947]
Region			
North America	10/1439	8/1433	1.243 [0.490,3.150]
Europe	6/774	6/789	1.046 [0.337,3.245]
Others	11/894	7/879	1.589 [0.615,4.104]
Dose (mcg)			
100	8/1271	7/1267	1.147 [0.416,3.162]
250	19/1836	14/1834	1.358 [0.681,2.708]

Source: Created by statistical reviewer using datasets adtte.xpt and adsl.xpt.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

SAS115359 and SAS115358 were large-scale trials designed and powered to rule out a relative excessive risk of serious asthma-related events (asthma-related death, intubation and hospitalization) associated with FSC (ICS+LABA) compared to FP (ICS alone), with 11679 adult/adolescent and 6208 pediatric subjects followed up for 26 weeks, respectively. These trials were designed to have 90% power to rule out a pre-specified risk margins of 2.0 (SAS115359) and 2.675 (SAS115358) with a one-sided 2.5% significance level.

Reference ID: 4116469

The endpoint of asthma-related death was expected to be rare and difficult to analyze in a single trial. No asthma-related deaths were observed in trials SAS115359 or SAS115358. An analysis of this endpoint will be conducted with combined data from the PMR trials for Symbicort (AstraZeneca), Advair Diskus (GSK), and Dulera (Merck) in the adult/adolescent population after all trials have completed (Neustifter, 2012).

5.2 Collective Evidence

As summarized in Table 23, both SAS115359 and SAS115358 demonstrated non-inferiority of asthma-related serious events with upper bounds of 95% CIs lower than the pre-specified risk margins. Sensitivity and supportive analysis results were consistent with this conclusion. The trials found no evidence of excessive risk of FSC compared to FP based on the pre-specified risk margins. It should be noted that the number of events in the composite endpoint and asthma-related deaths were lower than expected in SAS115359. The trial was designed and powered based on assumed event rates of 0.75% for the composite endpoint and 0.06% for asthma-related deaths for a 6-month period (Neustifter, 2012). The observed event rates for the composite endpoint were 0.57% in trial SAS115359 and 0.77% in SAS115358. The expected counts of asthma-related deaths at the planning stage were 8 for SAS115359 and 4 for SAS115358; however, no adjudicated asthma-related deaths were observed in either trial.

Table 23 Primary Results for SAS115359 and SAS115358

Study		FSC (Advair)	FP
SAS115359 N=11679 (ITT)	Events/N (%) *IR per 100 PY*	34/5834 (0.58%) *1.16*	33/5845 (0.56%) *1.12*
	HR (95% CI)	**1.029 (0.638, 1.662)**	
SAS115358 N=6208 (ITT)	Events/N (%) *IR per 100 PY*	27/3107 (0.87%) *1.74*	21/3101 (0.68%) *1.36*
	HR (95% CI)	**1.285 (0.726, 2.272)**	

Source: Statistical reviewer

Subgroup analyses showed a higher hazard ratio for the primary composite endpoint in females (FSC relative to FP) than males in both trials as discussed in Section 4. Note that this subgroup imbalance was also suggested in the FDA meta-analysis comparing LABA to non-LABAs

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(Levenson, 2008). No clear differences in risk were observed in subgroups defined by age or race.

5.3 Conclusions and Recommendations

This is a statistical safety review of two post-marketing safety trials, SAS115359 and SAS115358, submitted by GSK, the applicant of this NDA, to satisfy PMR 1750-1 and 1750-2 to assess the safety in serious asthma outcomes of Advair (FSC) compared to Fluticasone Propionate (FP). The estimated HRs for the pre-specified endpoint of asthma-related serious events associated with FSC are 1.029 with 95% CI (0.638, 1.662) for SAS115359, and 1.285 with 95% CI (0.726, 2.272) for SAS115358. Both of the upper bounds of the 95% CIs are below the pre-specified risk margins of 2.0 and 2.675, respectively, demonstrating FSC's non-inferiority in risk of serious asthma-related outcomes to FP in both the adult/adolescent and pediatric populations.

Based on our review of trials SAS115359 and SAS115358, it is our opinion that PMR 1750-1 and 1750-2 have been successfully fulfilled from a statistical point of view.

6 REFERENCES

Nelson, Harold S., et al. "The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol." *CHEST Journal* 129.1 (2006): 15-26.

Levenson, Mark, "Long-Acting Beta-Agonists and Adverse Asthma Events Meta-Analysis", Statistical Briefing Package for Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee on December 10-11, 2008

Condemi, John J., et al. "The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma." *Annals of Allergy, Asthma & Immunology* 82.4 (1999): 383-389.

Bateman, Eric, et al. "Meta-analysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events." *Annals of internal medicine* 149.1 (2008): 33-42.

Neustifter, Benjamin. Statistical Memorandum for tracked safety issue #: 000351. Signed into DARRTS on 12/13/2012.

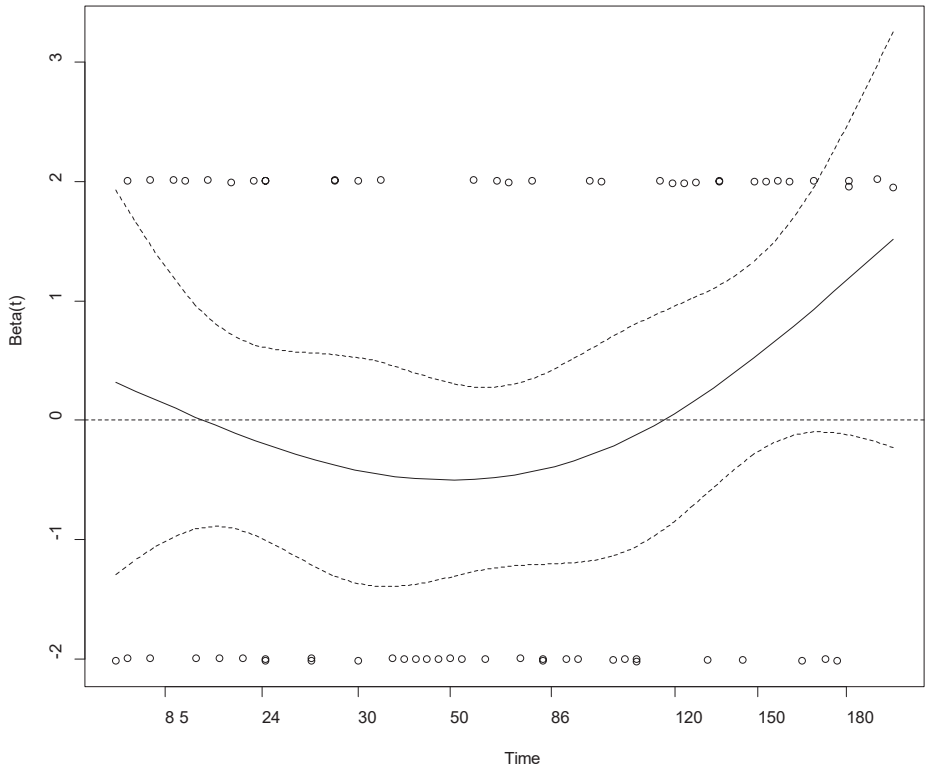
Reference ID: 4116469

APPENDIX

6.1 Assessment of Proportional Hazards Assumption in the Primary Analysis Model

The primary analysis used a Cox proportional hazards model to estimate hazard ratio and associated confidence intervals, with stratification of the baseline hazards by the incoming asthma status/medications. The proportionality assumption is examined for both studies.

Figure 7: Scaled Schoenfeld Residual Plot for the Primary Analysis, SAS115359 (ITT)



Source: Created by statistical reviewer from adtte.xpt

From the above scaled Schoefeld residual plot, there is no violation of the proportional hazard assumption for the variable of planned treatment, since the 95% confidence band contains the zero line. The p-value is 0.227 against the null hypothesis of proportional hazards in the variable *trtp* (planned treatment), and does not reject the proportionality assumption in the primary analysis model.

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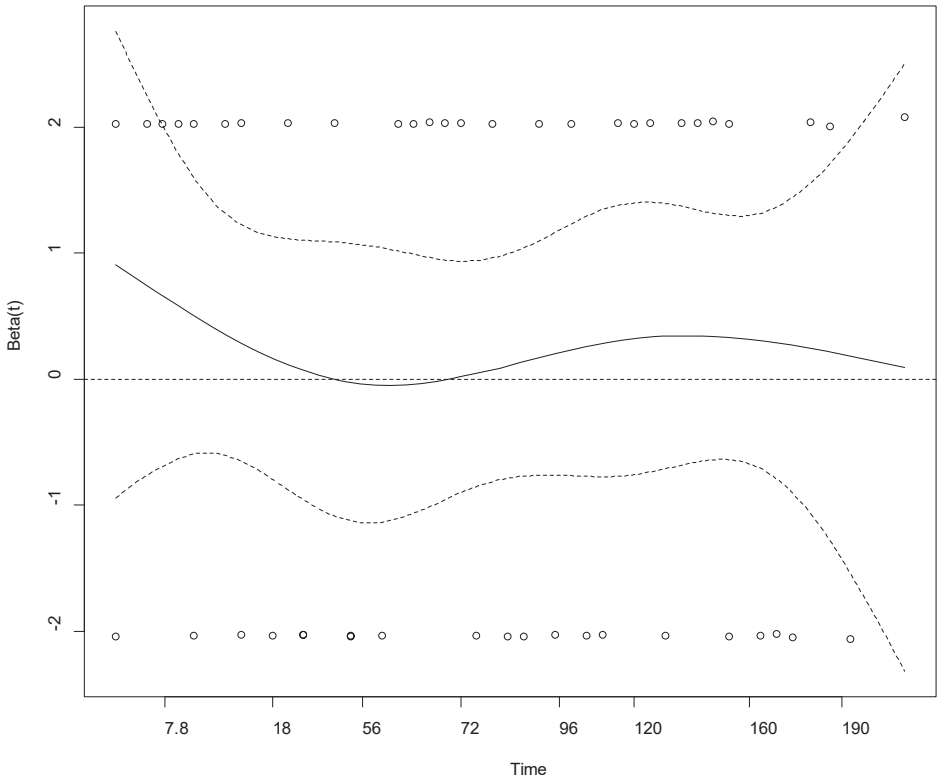
Figure 8: Scaled Schoenfeld Residual Plot for the Primary Analysis, SAS115358 (ITT)



Source: Created by statistical reviewer from adtte.xpt

The proportional hazards assumption also holds for the pediatric trial, SAS115358.

Reference ID: 4116469

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/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021077Orig1s056

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration Center for Drug
Evaluation and Research Office of Surveillance and
Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Boxed Warning Regarding Asthma-Related Deaths and Long-Acting β2-Agonist (LABA) Products

Date:	November 28, 2017
Reviewer(s):	Veronica Sansing-Foster, Ph.D., M.S. Division of Epidemiology II
Team Leader:	Margie Goulding, PhD Division of Epidemiology II
Deputy Director:	Lockwood Taylor, PhD, MPH, DEPI-II Division of Epidemiology II
Subject:	LABA Postmarketing Requirement Trials Review
Drug Name(s):	Advair (fluticasone propionate/salmeterol) Symbicort (budesonide/formoterol) Dulera (mometasone furoate and formoterol fumarate dehydrate) Breo Ellipta (fluticasone furoate and vilanterol) AirDuo RespiClick (fluticasone propionate and salmeterol)
Application Type/Number:	NDAs 021077/S056, 021929/S042, 022518/S022, 021254/S027, 0204275/S015, 208799
Applicants/sponsors:	Glaxo Smith Klein, AstraZeneca, Merck
OSE RCM #:	RCM 2016-1378

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EXECUTIVE SUMMARY

As part of a postmarketing requirement (PMR), FDA's Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) worked with the Glaxo Smith Kline (GSK), Novartis, Merck, and AstraZeneca (AZ) to design randomized clinical trials examining the safety and efficacy of a combination of inhaled corticosteroid (ICS) and a Long-Acting β2-Agonist (LABA) (ICS/LABA) as compared to treatment with ICS only, in adult, adolescent, and pediatric subjects with persistent asthma. Concerns were raised that the addition of LABA to ICS would result in an increase of serious asthma-related adverse events, including asthma–related deaths (TSI #351). Upon the completion and analyses of the five trials, FDA was to consider making class-wide changes to the Boxed Warnings regarding asthma-related deaths on these combination products. Novartis terminated their PMR upon withdrawal of Foradil from the US. On August 30, 2017 DPARP consulted the Division of Epidemiology II (DEPI-II) to review the PMRs examining ICS/LABA and asthma-related events within the Advair (NDA 021077), Symbicort (NDA 021929) and Dulera (NDA 22518) trials.

Based on DEPI-II's review of the data, all trials met demonstrated non-inferiority of ICS/LABA versus the ICS-only comparator drug. The quantities of asthma-related deaths (n=2), asthma–related intubations (n=3), and asthma-related hospitalizations (<1%) in the four PMR trials were low. The individual PMR trials were not powered to formally examine any differences seen by race and gender subgroups.

The preliminary meta-analysis conducted by the FDA indicates no increased risk of asthma-related outcomes for ICS/LABA as compared to ICS only in adult/adolescents (HR=1.10; 95% CI 0.85 - 1.44) and pediatrics (HR=1.29; 95 % CI 0.73 - 2.27). Although the preliminary meta-analysis does not yet contain the hazard ratios for the individual outcomes, the anticipated hazard ratios in the final meta-analysis will not show an increased risk of the individual events in ICS/LABA groups compared to ICS only.

In conclusion, data from the four individual PMR trials and preliminary meta-analysis provide no evidence to support maintaining the Boxed Warning on ICS/LABA combination medicines regarding increased risk of asthma-related events, notably asthma-related death and asthma-related hospitalizations. DEPI recommends removal of the Boxed Warning regarding asthma-related deaths, hospitalization and intubations on ICS/LABA combination medicines. DEPI plans to provide labeling recommendations for the subgroups of race and gender after our review of the final meta-analysis results.

Reference ID: 4187361

1 INTRODUCTION

This review is to determine if the results of four postmarketing requirement (PMR) trials support the Boxed Warning of asthma-related deaths on inhaled corticosteroid (ICS) and Long-Acting β2-Agonist (LABA) combination medicines. The ICS are fluticasone propionate, fluticasone furoate, mometasone, and budesonide, and the LABAs are salmeterol, formoteral and vilanterol. FDA's Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) worked with four drug companies – Glaxo Smith Kline (GSK), Novartis, Merck, and AstraZeneca (AZ) – to design randomized clinical trials. These trials examined the safety and efficacy of treatment with a combination of ICS/LABA as compared to treatment with ICS only in adult, adolescent, and pediatric subjects with persistent asthma. Concerns were raised that the addition of LABA to ICS would result in an increase of serious asthma-related events, notably asthma-related death (TSI #351). Upon the completion and analyses of the trials, FDA was to consider making class-wide changes to the Boxed Warnings regarding asthma-related deaths on the following ICS/LABA combination medicines: Symbicort (NDA 21929), Dulera (NDA 22518), Advair (NDA 21077), Advair HFA (NDA 21254), Breo Ellipta (NDA 204275), and AirDuo RespiClick (NDA 208799).

On August 30, 2017, DPARP consulted the Division of Epidemiology II (DEPI-II) to review the PMR trial results by GSK, AZ, and Merck to assess if the results support the current Boxed Warning on all ICS/LABA combination medicines. Novartis terminated their PMR upon withdrawal of Foradil from the US market. On September 6, 2017, Advair HFA (NDA 204275) and Breo Ellipta (NDA 204275/S-015) were included in the ICS/LABA class labeling updates.

As of November 15, 2017, the final results of the meta-analysis conducted by FDA have not yet been released to DEPI-II. However, the draft language regarding the meta-analysis has been included in the draft label for AirDuo RespiClick ICS/LABA combination medicine. Please see DEPI-II's review of the ICS/LABA labeling language for more details, dated November 8, 2017.

2 REVIEW METHODS AND MATERIALS

DEPI-II reviewed the final reports, synopses, and sponsor-proposed labels of the following trials, focusing primarily on the safety results:

- GSK Study SAS115258 (Advair): A 6-month Safety and Benefit Study of Inhaled Fluticasone Propionate/Salmeterol Combination vs. Inhaled Fluticasone Propionate in the Treatment of 6,200 Pediatric Subjects 4-11 Years Old with Persistent Asthma
- GSK Study SAS115359 (Advair): A Safety and Efficacy Study of Inhaled Fluticasone Propionate/Salmeterol Combination vs. Inhaled Fluticasone Propionate in the Treatment of Adolescent and Adult Subjects with Asthma
- AZ Study D5896C00027 (Symbicort): Multicenter, Multinational Safety Study Evaluating the Risk of Serious Asthma-Related Events During Treatment with Symbicort, a Fixed Combination of Inhaled Corticosteroid (ICS) (Budesonide) and a

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Long-Acting β2-Agonist (LABA) (Formoterol) as Compared to Treatment with ICS (Budesonide) Alone in Adult and Adolescent (≥12 Years of Age) Subjects with Asthma

- Preliminary data from the Meta-analysis of the Primary Endpoints as presented in the draft labeling for AirDuo (as of November 15, 2017)

3 CURRENT BOXED WARNING

In 2010, FDA issued a class-wide labeling change, the addition of the Boxed Warning, based on analyses from the randomized controlled trial Salmeterol Multi-center Asthma Research Trial (SMART), the Salmeterol Nationwide Surveillance study (SNS), and a meta-analysis conducted by FDA in 2008.[4] According to all three sources, there was an increased risk of asthma-related deaths in subjects treated with LABA as compared to subjects treated with ICS only. Although the safety data came from a single ingredient LABA (salmeterol), ICS/LABA combination medicines were labeled with the same safety information as the LABA-only products. Also, a Boxed Warning was placed in the label of the products containing other LABAs, formoterol and vilanterol.

To date, each of the LABA-containing products carries a boxed warning regarding asthma-related deaths. This is the Boxed Warning for Advair:

> *WARNING: RISK OF ASTHMA-RELATED DEATH See full prescribing information for complete boxed warning.*
>
> *• Long-acting beta2-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. A US study showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 out of 13,179 subjects on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent subjects. (5.1)*
>
> *• When treating subjects with asthma, only prescribe ADVAIR DISKUS for subjects not adequately controlled on other asthma controller medications or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. (1.1, 5.1)*

4 PMR TRIAL METHODS

The four ICS/LABA PMR trials shared similar methods to allow for the rare events (asthma-related intubations, asthma-related deaths) and patient subgroups (age, race, gender) to be analyzed in a pooled analysis.

Objectives - The primary safety objective was to examine if the addition of LABA to ICS therapy (ICS/LABA) was non-inferior to ICS therapy alone in terms of the risk of serious asthma-related events in pediatric (Advair), adult and adolescent subjects (Advair, Dulera and

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Symbicort). The secondary objective was to examine if ICS/LABA was superior to LABA in terms of asthma-free days (efficacy).

Design & Follow-up - These were global, multi-center, randomized, stratified, double-blind, parallel group designed trials conducted in the US and internationally. Subjects were followed monthly for 6-months post-treatment through alternating clinical visits (2 weeks, months 2, 4, 6) and phone calls (months 1, 3, 5).

Population –The trials enrolled pediatric subjects age 4-11 years with persistent asthma for at least 6 months (Advair only) and adolescent/adult subjects age 12 years and above with a diagnosis of persistent asthma for at least 1 year who were using corticosteroids, LABA, leukotriene receptor antagonists (LTRA), or theophylline 4 weeks prior to randomization. Subjects with unstable asthma, intensively treated or a history of life-threatening asthma were excluded.

Exposure - Subjects were randomized to either ICS or ICS/LABA exposure within a stratum based on incoming asthma medication use and incoming asthma control within the past year.

Safety Outcome - The primary safety endpoint was the number of subjects experiencing the composite endpoint of serious asthma-related outcomes (asthma-related hospitalizations, endotracheal intubations, or deaths) over the trial period. Secondary safety endpoints included asthma-related deaths, asthma-related endotracheal intubations, asthma-related hospitalizations, and withdrawals from trial treatment due to asthma exacerbation. Each endpoint was examined in a pooled-analysis of all LABA PMR trial results. Serious adverse events (SAEs) and AE leading to discontinuation were also captured.

Covariates– The trial covariates were age, sex, race, randomization stratum and efficacy stratum.

Sample Size and Statistical Analyses - A sample size of 6202 pediatrics and 11,700 adolescent/adult subjects provided power=90% for each individual study to rule out a 1-sided non-inferiority margin of 2.75 for pediatrics and 2 for adolescent/adults. The primary safety hypothesis was assessed by Cox proportional hazards regression of the time to first serious asthma-related event by randomized treatment and randomization stratum.

5 RESULTS

5.1 SUMMARY OF INDIVIDUAL STUDIES

Based on the results, there was not a significantly increased risk in the primary composite safety outcome (asthma-related deaths, intubations or hospitalizations) in the ICS/LABA groups compared to the ICS-only groups within each trial (Table 1). For the secondary individual endpoints intended for the pooled analysis, there are only 2 asthma-related deaths within the ICS/LABA group, 3 asthma-related intubations, and all asthma-related hospitalizations occurred in <1% of the group. There were no significant differences between ICS/LABA and ICS for rescue free days, asthma-free days, symptom-free days, and rescue medication use between the efficacy subgroups. The individual trial results are detailed in the sub-sections below.

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Table 1. Summary of primary safety results across all four trials

	Advair (Adolescent/Adult)		Advair (Pediatrics)		Symbicort** (Adolescent/Adult)		Dulera** (Adolescent/Adult)	
Outcomes	Advair N=5834	FP N=5845	Advair N=3107	FP N=3101	Symbicort N=5846[ǂ]	BUD N=5847	Dulera N=5868	MF N=5861
Asthma-related SAEs, n (%)	34 (0.6)	33 (0.6)	27 (0.9)	21 (0.7)	43 (0.7)	40 (0.4)	39 (0.7)	32 (0.5)
Hazard Ratio (95% CI)	1.03 (0.6,1.7)		1.29 (0.7,2.3)		1.07 (0.7, 1.7)		1.22 (0.8, 1.9) p=0.41	
Asthma-related deaths, n (%)	0	0	0	0	2 (0.0)	0	0	0
Asthma-related intubations, n (%)	0	2 (<1)	0	0	1 (0.0)	0	0	0
Asthma-related hospitalizations, n (%)	34 (<1)	33 (<1)	27 (<1)	21 (<1)	42 (0.7)	40 (0.7)	39 (0.7)	32 (0.5)

KEY: BUD – budesonide, CI – confidence interval, FP- fluticasone propionate, MF - mometasone, SAE – serious adverse events

* Pre-specified non-inferiority for adolescent/adult trials 2.0, pre-specific non-inferiority for pediatric trial 2.675

** Per sponsor analyses

[ǂ] The Center Director's Briefing packet contains an error in which "5846" is written as "5486."

Reference: Modified from the Center Director Briefing Packet 17_04_17

5.1.1 GSK ADVAIR TRIALS: SAS115258 PEDIATRICS & SAS115359 ADOLESCENTS AND ADULTS

Pediatrics

Of the 6759 pediatric (ages 4-11) subjects screened, 3107 were randomized to Advair and 3101 to fluticasone propionate. Advair demonstrated non-inferiority compared with fluticasone propionate for the risk of serious asthma-related events (composite), with an HR of 1.285 (95% CI=0.726 - 2.272). All events were asthma-related hospitalizations, occurring in <1% of both the Advair (n=27) and fluticasone propionate (n=21) groups. There were no asthma-related deaths and no asthma-related intubations. The incidence of any post-randomization serious adverse events (1% in both the Advair and fluticasone propionate arms) and any post-randomization serious adverse event leading to withdrawal (1%) was very low. The most frequent SAEs were asthma, pneumonia and bronchitis. There were no statistically significant differences by age, gender or race.

Overall, Advair did not demonstrate superiority over fluticasone propionate for the efficacy endpoint despite a 14% decrease in the time to first asthma exacerbation (HR= 0.859; 95% CI=0.729, 1.012).

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Adolescents and Adults
Of the 11,679 subjects enrolled, 5834 were randomized to receive Advair and 5845 to fluticasone propionate. Advair demonstrated non-inferiority compared with fluticasone propionate for risk of serious asthma-related events, with a HR of 1.029 (95% CI=0.638-1.662), even after adjusting for age. There were no differences between the proportion of asthma-related hospitalizations between the treatment groups (<1% in both). There were no asthma-related deaths in the trial, and two asthma-related intubations in the fluticasone propionate arm. Nine subjects (Advair=3 and fluticasone propionate=6) died during the trial, but none were adjudicated as asthma-related or treatment related. Overall, the incidence of any post-randomization SAEs (2% in both the Advair and fluticasone propionate arms) and any post-randomization SAE leading to withdrawal was very low (1%). The most frequent SAEs were asthma exacerbation and pneumonia.

There were no clinically relevant differences with gender subgroups, age subgroups, or randomization strata. The incidence of a hospitalization was higher in Black subjects compared to Whites. Black subjects comprised 14.8% of subjects randomized but accounted for 27% of the subjects experiencing an asthma-related hospitalization.

When examining efficacy, there was a 12% decrease in the time to first asthma exacerbation for Advair relative to fluticasone propionate (HR= 0.787, 95% CI=0.698- 0.888), demonstrating superiority.

5.1.2 AZ SYMBICORT STUDY D5896C00027: ADOLESCENTS AND ADULTS

Of the 12,460 subjects enrolled in the trial, 5846 were randomly assigned to Symbicort and 5847 to budesonide. Symbicort was non-inferior to budesonide for the composite safety endpoint (HR=1.073, 95% CI 0.698 -1.650). Less than 1% of subjects in both treatment arms experienced an asthma-related SAE, many of whom experienced an asthma-related hospitalization. There were two asthma-related deaths (both in the Symbicort arm) and one asthma-related intubation (in 1 of the subjects who died). The incidence of any post-randomization SAEs (2.1% in both the Symbicort and Budesonide arms) and any post-randomization SAE leading to withdrawal was very low (~1%). The most frequent SAEs were asthma exacerbation and pneumonia.

The adverse event rate was lower in younger subjects (aged 12 to 17 years) as compared to older subjects. In Black subjects, the event rate was higher than in the whole trial population (2.01% and 3.02% per 6 months in the Symbicort and budesonide arms, respectively, as compared with 0.72% and 0.67%). Despite these differences, there was no evidence of an increased risk of adverse events in the Symbicort arm compared with the budesonide arm in regards to age, race or even gender.

When examining efficacy, Symbicort use demonstrated superiority in time to first asthma exacerbation compared to budesonide (HR=0.84, 95% CI=0.7-0.94).

5.1.3 MERCK DULERA STUDY: ADOLESCENTS AND ADULTS

Of the 11,729 subjects enrolled, 5868 were randomized to receive Dulera and 5861 to mometasone furoate. Dulera was non-inferior to mometasone alone for the first asthma-related SAE (HR=1.22, 95% CI: 0.76 to 1.94, p=0.411). Less than 1% of subjects in both treatment arms

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experienced an asthma-related SAE, many of whom experienced an asthma-related hospitalization. No asthma-related intubations (endotracheal) or asthma-related deaths were observed. The incidence of any post-randomization SAEs was 2.3% and any post-randomization SAEs leading to withdrawal was very low (1.3%). The most frequent SAEs were asthma exacerbation, pneumonia, and appendicitis.

When examining efficacy, Dulera use demonstrated superiority in time to first asthma exacerbation compared to mometasone furoate (HR=0.89; 95% CI 0.80 to 0.98, p=0.021).

5.2 PRELIMINARY DATA FROM THE META-ANALYSIS

A meta-analysis of the four completed ICS/LABA trials is being done by the Office of Biostatistics. The preliminary results of this meta-analysis are summarized here.

In patients age 12 years and older, the use of ICS/LABA in fixed-dose combination did not result in a significantly increased risk of a serious asthma-related event compared to ICS only (HR=1.10; 95% CI 0.85 - 1.44). In patients ages 4-11 years, the use of ICS/LABA in fixed-dose combination did not result in a significant increase compared to ICS only (HR=1.29; 95 % CI 0.73 - 2.27).

Table 2. Meta-Analysis of Serious Asthma-Related Events in Patients with Asthma*

	ICS/LABA [a]	ICS [a]	ICS/LABA vs. ICS Hazard ratio (95% CI)[b]
Adolescents/Adults (12 years and over)	*(N =17,537)*	*(N =17,552)*	
Serious asthma-related event[c]	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related endotracheal intubation	1	2	
Asthma-related hospitalization	115	105	
Pediatrics (4 – 11 years)	*(N=3107)*	*(N=3103)*	1.29 (0.73, 2.27)
Serious asthma-related event[c]	27	21	
Asthma-related death	0	0	
Asthma-related endotracheal intubation	0	0	
Asthma-related hospitalization	27	21	

ICS = Inhaled Corticosteroid, LABA = Long-acting $Beta_2$-adrenergic Agonist.

[a] Randomized patients who had taken at least one dose of study drug. Planned treatment used for analysis.

[b] Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials.

[c] Events that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug treatment, whichever date was later. A single, blinded, independent adjudication committee determined whether events were asthma-related

Reference: Modified from the draft of "Efficacy (1) and prior approval labeling (3) supplements for AirDuo RespiClick (NDA 21254), October 25, 2017"

6 CRITIQUE

All four of the ICS-LABA safety trials met their recruitment goal and with most subjects completing the trial. Randomization to study treatment was successful as all baseline attributes were evenly distributed between the two treatment groups, reducing potential confounding.

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Double-blinding from the time of medication administration to the reporting of the results eliminated reporting bias by the subjects and ascertainment/detection bias by the assessors. However, the reports do not specify the cross-over rate for usage, if any.

There are two concerns that limit the interpretability of the data:

There are too few asthma-related deaths, hospitalizations, and intubations to formally examine the PMR safety outcomes in the individual trials and pooled analyses. Two asthma-related deaths (Symbicort treated subjects,only) in the PMR trials are not enough evidence to support keeping the Boxed Warning regarding asthma-related deaths. The proportion of asthma-related hospitalizations (<1%) across all age groups in the PMR trials is too low to support keeping the Boxed Warning regarding asthma-related hospitalizations in pediatric and adolescent subjects. Although the preliminary meta-analysis does not yet contain the hazard ratios for the individual outcomes, the hazard ratios in the final meta-analysis are not expected to show a significantly increased risk of the individual events in ICS/LABA groups compared to ICS only.

The individual PMR trials were not powered to formally examine any differences seen by race and gender subgroups. The concern regarding elevated risks in subgroups stems from the SMART trial in which Blacks comprised only 18% of the trial subjects, yet accounted for 59% of the serious asthma-related adverse events and 50% of the asthma- related deaths. DEPI-II will forego drawing conclusions regarding the subgroups until we review the final results of the meta-analysis that is anticipated to have more power for race and gender subgroup analyses.

7 CONCLUSIONS

Data from the four individual PMR trials and preliminary meta-analysis provide no evidence to support maintaining the Boxed Warning on ICS/LABA combination medicines regarding increased risk of serious asthma-related events, notably asthma-related death and asthma-related hospitalizations. The quantities of asthma-related deaths (n=2), asthma–related intubations (n=3), and asthma-related hospitalizations (<1%) in the four PMR trials are low. DEPI plans to provide conclusions and labeling recommendations regarding the subgroups of race and gender after our review of the final meta-analysis results.

8 RECOMMENDATIONS

Based on the individual PMR trial results, DEPI recommends removal of the Boxed Warning regarding asthma-related death, hospitalizations and intubations on ICS/LABA combination medicines. DEPI plans to provide labeling recommendations for the subgroups of race and gender after our review of the final meta-analysis results.

Reference ID: 4187361

9 REFERENCES

1. Spruance SL, Reid JE, Grace M, Samore M. Hazard ratio in clinical trials. *Antimicrob Agents Chemother*. 2004;48(8):2787-2792.
2. Bartlett J. Adjusting for baseline covariates in randomized controlled trials. 2014; http://thestatsgeek.com/2014/02/01/adjusting-for-baseline-covariates-in-randomized-controlled-trials/.
3. Walters SJ. What is a Cox model? http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/cox_model.pdf.
4. FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs) https://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforsubjectsandproviders/ucm200776.htm (accessed: April 19, 2017)

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/s/

VERONICA V SANSING FOSTER
11/28/2017

MARGIE R GOULDING
11/29/2017

LOCKWOOD G TAYLOR
11/29/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: A Review of the Revised Labeing for the Long-Acting β2-Agonist (LABA) Postmarketing Requirements (PMR)

Date:	November 7, 2017
Reviewer:	Veronica Sansing-Foster, Ph.D., M.S. Division of Epidemiology II
Team Leader:	Margie Goulding, PhD Division of Epidemiology II
Deputy Director:	Lockwood Taylor, PhD, MPH Division of Epidemiology II
Subject:	LABA Postmarketing Requirement Studies Review
Application Type/Number:	NDAs 021077/S056, 021929/S042, 022518/S022, 021254/S027, 0204275/S015, 208799/S001, TSI #351
Applicants/Sponsors:	Glaxo Smith Klein, Merck, Teva
OSE RCM #:	2017-1830

Reference ID: 4178382

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EXECUTIVE SUMMARY

This review assesses the draft of the sponsor-proposed (Teva Pharmaceuticals) labeling changes to the inhaled corticosteroid (ICS) fluticasone propionate and Long-Acting β2-Agonist (LABA) salmeterol combination medicine, AirDuo RespiClick based on 4 postmarketing requirement (PMR) trials. After the SMART trial, concerns were raised that the addition of LABA to ICS would result in an increase of adverse events, specifically asthma–related deaths (TSI #351). Upon the completion and analyses of the ICS/LABA trials, FDA was to consider making class-wide changes to the Boxed Warnings regarding asthma-related deaths on the following combination products: Symbicort (NDA 021929), Dulera (NDA 22518), Advair (NDA 21077), Advair HFA (NDA 21254), Breo Ellipta (NDA 204275), and AirDuo RespiClick (NDA 208799).

DEPI-II and DPARP both concluded **data from the four PMR trials provide no evidence to support maintaining the Boxed Warning on ICS/LABA combination medicines regarding increased risk of asthma-related events, notably asthma-related death.** FDA recommended the removal of the Boxed Warning on ICS/LABA combination medicines. FDA requested Teva to provide a supplement to NDA 208799/AirDuo RespiClick with labeling revisions regarding this recommendation.

The AirDuo revised label does not fully comply with FDA's recommendation to remove asthma-related adverse event language in the boxed warning and throughout the label of this ICS/LABA combination medicine. Based on DEPI-II's review of the revised AirDuo label, there are three recommendations for FDA to address, listed in order of importance:

1. Remove the language that associates combination therapy LABA containing medicines with adverse asthma-related events.
2. Address three issues regarding the results of the meta-analysis in Table 1 on page (b) (4)
3. Replace the word (b) (4) with "to" for clarity in Section 5.1 of the Warnings and Precautions on page (b) (4)

In conclusion, DEPI-II recommends additional edits to AirDuo's label to comply with FDA's recommendation regarding the removal of the Boxed Warning for asthma-related death on all ICS/LABA combination medicines.

Reference ID: 4178382

1 INTRODUCTION

This review assesses the draft of the sponsor-proposed (Teva Pharmaceuticals) labeling changes to the inhaled corticosteroid (ICS) and Long-Acting β2-Agonist (LABA) combination medicine, AirDuo RespiClick for serious asthma-related events, especially asthma–related deaths (TSI #351). As part of a postmarketing requirement (PMR), FDA's Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) worked with three other drug companies – Glaxo Smith Kline (GSK), Merck, and AstraZeneca (AZ) – to design randomized clinical trials. These trials examined the safety and efficacy of treatment with a combination of ICS/LABA as compared to treatment with ICS alone in adult, adolescent, and pediatric subjects with persistent asthma. Concerns were raised that the addition of LABA to ICS would result in an increase of serious asthma-related events, notably asthma-related death. Upon the completion and analyses of the trials, FDA considered class-wide changes to the Boxed Warnings regarding asthma-related deaths on the following ICS/LABA combination medicines: Symbicort (NDA 021929), Dulera (NDA 22518), Advair (NDA 21077), Advair HFA (NDA 21254), Breo Ellipta (NDA 204275), and AirDuo RespiClick (NDA 208799).

The 3 adult and adolescent trials were designed to rule out a relative risk of 2.0, and the pediatric trial was designed to rule out a relative risk of 2.7. All studies demonstrated non-inferiority of ICS/LABA versus the comparator ICS drug. ICS/LABA did not show an elevated risk of serious asthma-related events compared with ICS alone in adults and adolescents (HR=1.10, 95% CI 0.85, 1.44) and pediatrics (hazard ration [HR]=1.29; 95% CI 0.73, 2.27). There were too few asthma-related deaths (n=2), hospitalizations (<1%), and intubations (n=1) to formally examine these separate safety outcomes within both the individual and pooled analyses.

The Division of Epidemiology II (DEPI-II) and DPARP both concluded that data from the four PMR trials do not support maintaining the Boxed Warning on ICS/LABA combination medicines regarding increased risk of asthma-related events, notably asthma-related death. FDA recommended the removal of the Boxed Warning on ICS/LABA combination medicines.

FDA requested that Teva provide a supplement to AirDuo RespiClick (NDA 208799) with labeling revisions regarding the removal of the Boxed Warning from ICS/LABA combination medicines. FDA received a redline copy of the labeling changes on October 25, 2017 (Appendix). Each of the ICS/LABA combination medicine labels will contain the final approved revisions. On October 26, 2017, DPARP consulted DEPI to review the draft of AirDuo RespiClick's labeling revisions.

2 REVIEW MATERIALS

- Efficacy (1) and Prior Approval Labeling (3) Supplements for AirDup RespiClick (NDA 21254), October 25, 2017

3 REVIEW

The sponsor's revised label does not fully comply with DPARP's recommendation. DPARP recommended the sponsor remove asthma-related adverse event language in the boxed warning and throughout the label of this ICS/LABA combination medicine. Based on DEPI-II's review of

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the revised AirDuo label, there are three recommendations for DPARP to address, listed in order of importance (see proposed edits in red).

First, please remove the language that associates both monotherapy and combination therapy LABA containing medicines with asthma-related events from the following sections:

1. the Prescribing Information on page 1:
   *FULL PRESCRIBING INFORMATION: CONTENTS**
   ~~*WARNING: ASTHMA-RELATED DEATH.*~~
2. the Medication Guide on page 48:
   ~~*AIRDUO RESPICLICK can cause serious side effects, including:*~~
   ~~*People with asthma who take long-acting beta2-adrenergic agonist (LABA) medicines such as salmeterol (one of the medicines in AIRDUO RESPICLICK), have an increased risk of death from asthma problems.*~~
   ~~*Adolescents who take LABA medicines may have an increased risk of being hospitalized for asthma problems.*~~

Second, please address three issues regarding the results of the meta-analysis in Table 1 on page (b) (4)

1. The number of patients in the ICS/LABA and ICS groups, n=17,537 and 17,552. respectively, are different from the number of patients in the Center Director's briefing (n= (b) (4) and (b) (4) respectively) and in the four PMR reports (n= (b) (4) and (b) (4) respectively).
2. We recommend placing CI=Confidence Interval in the table key.
3. The table key states, (b) (4) (b) (4) The word "stratified" contradicts the word "combined." We recommend the Division of Biostatics clarify this sentence.

Third, please replace the word (b) (4) with "to" for clarity in Section 5.1 of the Warnings and Precautions on page 8.

> *Three (3) trials included adult and adolescent subjects aged 12 years and older: 1 trial compared budesonide/formoterol to budesonide, 1 trial compared fluticasone propionate/salmeterol dry powder inhaler to fluticasone propionate dry powder inhaler, and 1 trial compared mometasone furoate/formoterol to mometasone furoate. The fourth trial included pediatric subjects aged 4 to 11 years and compared fluticasone propionate/salmeterol dry powder inhaler to fluticasone propionate dry powder inhaler.*

4 CONCLUSION

DEPI-II recommends additional edits to AirDuo's label to comply with DPARP's recommendation regarding the removal of the Boxed Warning for asthma-related death on all ICS/LABA combination medicines.

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LOCKWOOD G TAYLOR
11/08/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 3, 2017
To:	Badrul Chowdhury, MD, PhD Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Taylor Burnett, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Long Acting Beta Agonist (LABA) Class Labeling for the Patient Package Insert (PPIs) and Instructions for Use (IFUs)
Drug Name (established name), Dosage Form and Route, Application Type/Number, and Applicant:	ADVAIR DISKUS (fluticasone propionate and salmeterol inhalation powder) for oral inhalation use, NDA 21077, S-056/S-057, GlaxoSmithKline

1 INTRODUCTION

In accordance with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, sponsors GlaxoSmithKline, Merck, and AstraZeneca have submitted joint sponsor inhaled corticosteroid and long acting beta agonist (ICS/LABA) class labeling in response to required post-marketing safety studies.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on November 21, 2016 and November 21, 2016 respectively for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPIs) and Instructions for Use (IFUs) for the LABAs.

2 MATERIAL REVIEWED

- Draft ADVAIR DISKUS (fluticasone propionate and salmeterol inhalation powder) PPI and IFU received on October 3, 2016, and received by DMPP on October 20, 2017 and OPDP on October 20, 2017 respectively.
- Draft ADVAIR DISKUS (fluticasone propionate and salmeterol inhalation powder) Prescribing Information (PI) received on October 3, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and on October 20, 2017 and OPDP on October 20, 2017 respectively.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU, we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
11/03/2017

TAYLOR B BURNETT
11/03/2017

MARCIA B WILLIAMS
11/03/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 3, 2017

To: Carol Hill
Safety Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Taylor Burnett
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm
Team Leader
OPDP

Subject: OPDP Labeling Comments

ADVAIR DISKUS (fluticasone propionate and salmeterol inhalation powder), for oral inhalation (Advair Diskus)

NDA: 21077/S-056, S-057

In response to DPARP's consult request dated November 21, 2016, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and Instructions for Use (IFU) for Advair Diskus. These supplements (S-056 and S-057) provide for the removal of the Boxed Warning from ICS/LABA products.

OPDP has reviewed the proposed draft PI received by electronic mail from DPARP on October 19, 2017, and we do not have any comments.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFU were sent under separate cover on November 3, 2017.

Thank you for your consult. If you have any questions, please contact Taylor Burnett at (240) 402-1349 or Taylor.Burnett@fda.hhs.gov.

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TAYLOR B BURNETT
11/03/2017

Division of Pulmonary, Allergy, and Rheumatology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 21077/Prior Approval Efficacy Supplement/S-056 & S-057

Name of Drug: ADVAIR DISKUS 100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder), for oral inhalation
ADVAIR DISKUS 250/50 (fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder), for oral inhalation
ADVAIR DISKUS 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder), for oral inhalation

Applicant: GlaxoSmithKline

Labeling Reviewed

Submission Date: October 3, 2016, and March 13, July 13, August 4, and 31, 2017

Receipt Date: October 3, 2016, and March 13, July 13, August 4, and 31, 2017

Background and Summary Description:

On October 3, 2016, GSK submitted prior approval efficacy supplements proposing to update the labeling to include the safety and efficacy LABA data and to comply with the Pregnancy and Lactation Labeling Final Rule. Additionally, minor editorial changes were proposed for the package insert and patient labeling (Patient Information Leaflet and Medication Guide) to conform to FDA formatting standards and to align with other GSK inhalation product labeling. Subsequent to the October 3, 2016, prior approval efficacy supplements, GSK submitted a prior approval labeling supplement dated February1, 2017 in response to the December 21, 2016, Prior Approval Supplement Request Letter. The supplement was approved on February 28, 2017. The labeling submitted on October 3, 2017 was amended on March 13, July 13, August 4, and 17, 2017, to incorporate the labeling revisions approved on February 28, 2017, and the recommendations made by the team.

Review

A side-by-side comparison of the October 3, 2016, supplements and the last approved labeling at the time of submission dated April 29, 2016, was conducted. There were no changes to the labeling other than those proposed in the October 3, 2016, submissions. The March 13, 2017 labeling was compared to the labeling approved on February 28, 2017. Note, the March 13, 2017 incorporated the February 28, 2017, labeling changes along with those proposed in the October 3,

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2016. GAK also submitted amendments noted above to incorporate changes requested by the team. There were no additional changes other than those listed here.

Recommendation

I recommend approval of these supplements pending completion of discipline and consult reviews.

Carol F. Hill	September 21, 2017
Regulatory Project Manager	Date
Ladan Jafari	September 21, 2017
Chief, Project Management Staff	Date

Reference ID: 4156081

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/s/

CAROL F HILL
09/21/2017

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