CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205625Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	August 20, 2014
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	20-5625
Applicant Name:	GlaxoSmithKline
Date of Submission:	October 22, 2013
PDUFA Goal Date:	August 22, 2014
Proprietary Name:	Arnuity Ellipta
Established Name:	Fluticasone furoate
Dosage form:	Inhalation Powder (inhaler contains foil blister strip with 30 blisters containing powder for oral inhalation)
Strength:	Fluticasone furoate 100 mcg or 200 mcg per blister
Proposed Indications:	Asthma
Action:	Approval

1. Introduction

GlaxoSmithKline (GSK) submitted this 505(b)(1) new drug application for use of Arnuity Ellipta (fluticasone furoate 100 mcg or 200 mcg inhalation powder) for maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. The proposed dose is one inhalation (fluticasone furoate 100 mcg or 200 mcg) once daily, with the starting dose based on prior asthma therapy and disease severity. Fluticasone furoate, a corticosteroid, in the same Ellipta device is marketed as Breo Ellipta (NDA 20-4275, approved in May 2013) for use in patients with COPD. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes available for use in patients with persistent asthma. These include inhaled corticosteroids (ICSs), inhaled long-acting beta-adrenergic agents (LABAs), leukotriene modifying drugs, methylxanthines, and omalizumab. ICSs are considered to be the most effective long-term therapy for persistent asthma, and are commonly used as the first drug when a maintenance therapy is necessary. There are several ICS containing products in the market in the United States, such as Asmanex (mometasone furoate), Alvesco (ciclesonide), Flovent (fluticasone propionate), Pulmicort (budesonide), and Qvar (beclomethasone dipropionae). When an adequate dose of ICS has not provided asthma control, a second drug, such as a LABA is often added, preferably for a limited time period with the intent of discontinuing the LABA once asthma control is achieved and maintained. Since some patients with persistent asthma

use both an ICS and a LABA, these two drugs have been put together in the same formulation and in the same device and marketed as inhaled combination products. There are four such combination products in the market in the United States. These are Advair Diskus and Advair HFA Inhalation Aerosol (both are a combination of fluticasone propionate and salmeterol xinafoate), Symbicort (a combination of budesonide and formoterol fumarate), and Dulera (a combination of mometasone furoate and formoterol fumarate). Arnuity Ellipta will provide another choice of single entity ICS for use in patients with asthma.

Fluticasone furoate is not a new molecular entity as fluticasone furoate is marketed as one of the active components in Breo Ellipta, and as a nasal formulation for the treatment of allergic rhinitis. Fluticasone propionate, another ester of fluticasone and propionic acid, is marketed for a variety of indications, including allergic rhinitis and asthma as a single ingredient product, and as a combination product (Advair) with salmeterol, a LABA, for asthma and COPD. Corticosteroids have a variety of serious adverse effects that are well known. Although ICSs do not usually have the typical serious systemic effects associated with corticosteroids because systemic absorption from the inhaled route is limited, ICSs can have serious local adverse reactions in the lung in COPD patients. For example, Advair (fluticasone propionate plus salmeterol) is known to increase the risk of pneumonia in patients with COPD, particularly at high doses. Such a risk of pneumonia has not been seen in patients with asthma. Also, ICS at high doses have systemic effects, such as changes in bone mineralization in COPD patients, and an effect on linear growth in young growing patients with asthma. Identifying the appropriate dosing frequency of ICSs is also important because the same nominal dose given once daily can have substantially less efficacy compared to twice daily dosing, as was seen with fluticasone propionate and ciclesonide in patients with asthma. [1, 2] Therefore, it is important to select an appropriate dose and dosing frequency for any ICS.

Regulatory interaction between the Agency and GSK:

The Division and GSK had typical milestone meetings for Arnuity Ellipta for asthma, as well as meetings for the development of combination products where fluticasone furoate was one of the components of the combination product, such as Breo Ellipta for COPD. The following timeline highlights some major discussion points that occurred during clinical development of these products that are relevant for Arnuity Ellipta for asthma.

- End-of-Phase-2 meeting for Breo Ellipta asthma program, March 31, 2009: The Division stated the need for confirmation of the dosing interval prior to initiating confirmatory studies.
- Second End-of-Phase 2 meeting for Breo Ellipta asthma program, June 30, 2010: The Division requested that relevant information from the asthma program, such as

[1] Purucker ME, Rosebraugh CJ, Zhou F, Meyer RJ. Inhaled fluticasone propionate by diskus in the treatment of asthma: A comparison of the efficacy of the same nominal dose given either once twice a day. Chest 2003; 124:1584-93.

[2] Chowdhury BA. Ciclesonide inhalation aerosol for persistent asthma. J Allergy Clin Immunol 2006; 117:1194-6. And, Alvesco (ciclesonide) Inhalation Aerosol, Package Insert, Product Label, Section 14.

dose selection data for the fluticasone furoate and vilanterol monocomponents be included in the COPD NDA.

- Pre-NDA meeting for Breo Ellipta for asthma, October 12, 2011: The Division requested that an application for asthma be submitted concurrently with the COPD application, given the novelty of both the fluticasone furoate and vilanterol components. GSK stated that the recommendation would be taken under advisement. GSK noted that the strength of the bronchodilator efficacy data in asthma for Breo Ellipta over vilanterol has provided mixed results. [3]
- Pre-NDA meeting for Arnuity Ellipta for asthma, February 11, 2013: The Division agreed with submission of the 100 mcg and 200 mcg doses for registration, and noted that evidence to support the 50 mcg dose was weak.

3. Chemistry, Manufacturing, and Controls

The product Arnuity Ellipta (fluticasone furoate 100 mcg and 200 mcg inhalation powder) includes a novel dry powder inhaler device, the Ellipta inhaler, which contains a foil blister strip with 30 blisters. Each blister contains micronized fluticasone furoate (100 mcg or 200 mcg) and lactose monohydrate. The lactose monohydrate may contain trace amounts of milk proteins. The proposed commercial presentation of Arnuity Ellipta has 30 blisters each of fluticasone furoate, which will be a one-month supply with a once daily dosing regimen. The device has a dose counter. The steps needed to use the product are simple and similar to some other dry powder inhaler devices. To deliver a dose, the patient will open the cover of the device. This action makes the powder from one blister containing fluticasone furoate ready for inhalation at the airflow path inside the device. The patient will then inhale through the mouthpiece of the device. If a patient opens and closes the cover of the device without inhaling, the formulation powder will be held inside the device and will no longer be available to be inhaled. The Arnuity Ellipta device has been tested for usability, reliability, and ruggedness through in vitro testing, human factor studies, and testing of devices used in the clinical program.

Arnuity Ellipta is packaged within a moisture-protecting foil tray with a desiccant packet. GSK submitted adequate stability data to support an expiry of 30 months for the product stored at room temperature inside the protective foil tray. Arnuity Ellipta should be discarded after all doses are used or 6 weeks after removal from the protective package, whichever comes first.

The drug substances are manufactured at a GSK facility in (b) (4), and drug product, including the Arnuity Ellipta device is assembled at a GSK facility in (b) (4) The device components are fabricated by (b) (4) in (b) (4) All manufacturing and testing facilities associated with this drug product have acceptable establishment evaluation status. All DMFs associated with this application were also found to be acceptable.

[3] GSK, January 9, 2012 [press release]. Retrieved from http://us.gsk.com/html/media-news/pressreleases/2012/2012-pressrelease-840722.htm on February 7, 2013.

4. Nonclinical Pharmacology and Toxicology

GSK submitted results from a full preclinical program to the Agency. The program included studies in which animals were dosed with fluticasone furoate. The toxicity profile of fluticasone furoate has been characterized previously for the nasal spray NDA (Veramyst Nasal Spray NDA 22-051, approved on April 27, 2007). Briefly, fluticasone furoate was non-genotoxic, non-carcinogenic, non-teratogenic, and had no effect on fertility in animals. The fluticasone furoate label carries a Pregnancy Category C designation because of the known effects of corticosteroids on embryofetal development.

5. Clinical Pharmacology and Biopharmaceutics

GSK submitted results from a comprehensive clinical pharmacology program that included studies to assess protein binding and metabolism and the pharmacokinetics after single and multiple inhaled doses of fluticasone furoate. The majority of studies were conducted in healthy volunteers, but several studies were done specifically to assess pharmacokinetics in patients and the effect of renal and hepatic impairment. Fluticasone furoate has a low oral bioavailability and systemic exposure primarily due to absorption of the inhaled portion. The estimated half-life for fluticasone furoate is 24 hours. Fluticasone furoate is a substrate of CYP3A4 and P-gp. The inhibition potential is low when administered by the inhaled route and no specific dose adjustments are recommended when the product is administered with other drugs. No significant effects due to age, or renal impairment on pharmacokinetic parameters were observed, so no dose adjustment for age or renal function is recommended. Systemic exposure of fluticasone furoate is higher in hepatic impairment patients. In addition, a decrease in serum cortisol was noted in patients with moderate hepatic impairment. Therefore caution should be used in patients with moderate or severe hepatic impairment. A study to assess QTc effects did not indicate any clinically relevant prolongation of the QTc interval at the therapeutic dose.

6. Clinical Microbiology

GSK proposed acceptable testing regimen involving the bulk drug product and the product packaged in the blister packs.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision-making for this application are shown in Table 1 and Table 2. Table 1 summarizes the main studies conducted to support dose selection and dosing frequency for fluticasone furoate. Table 2 summarizes the main studies conducted in patients with asthma. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in Section 8. For brevity, the studies are referenced later in this review by the last four digits of the study number.

Table 1. Relevant dose selection studies for fluticasone furoate in patients with asthma

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variables ¶**	**Regions and Countries**
Fluticasone furoate -- Dose-ranging studies					
109684 [2007-2008]	- 12 to 78 yr - Asthma, medium dose ICS - Parallel arm, DB - 8 weeks	FF 200 mg QD PM FF 400 mcg QD PM FF 600 QD PM FF 800 mcg QD PM FP 500 mcg BID Placebo	99 101 107 102 110 103	FEV_1 trough at week 8	US, Canada, Mexico, W Eur, E Eur, S Africa, Australia, Thailand (18% US)
109685 [2007-2008]	- 12 to 80 yr - Asthma, low dose ICS - Parallel arm, DB - 8 weeks	FF 100 mcg QD PM FF 200 mg QD PM FF 300 mcg QD PM FF 400 mcg QD PM FP 250 mcg BID Placebo	105 101 103 99 100 107	FEV_1 trough at week 8	US, Canada, Mexico, W Eur, E Eur, S Korea, Philippines (32% US)
109687 [2007-2008]	- 12 to 78 yr - Asthma, no ICS - Parallel arm, DB - 8 weeks	FF 25 mcg QD PM FF 50 mcg QD PM FF 100 mcg QD PM FF 200 mcg QD PM FP 100 mcg BID Placebo	97 100 110 95 110 94	FEV_1 trough at week 8	US, Canada, S Africa, Other (36% US)
Fluticasone furoate -- Dose-regimen study					
112202 [2007-2008]	- 12 to 76 yr - Asthma - Cross over, DB - 28 days	FF 200 mcg QD PM FF 100 mcg BID FP 200 mcg QD PM FP 100 mcg BID Placebo	140 142 42 43 187	FEV_1 trough at the end of 28-day treatment period	US

* Study ID shown (top to bottom) as GSK's study number, and [year study started-completed]
† DB=double blind, DD=double dummy
‡ FF=fluticasone furoate in Arnuity device; FP=fluticasone propionate
§ Intent to treat
¶ Primary efficacy variables are shown.

Table 2. Relevant clinical studies with Arnuity Ellipta (fluticasone furoate) in patients with asthma

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variable ¶**	**Regions and Countries**
Pivotal efficacy and safety studies supporting Arnuity Ellipta 100 mcg					
112059 Trial 1 [2010-2012]	- ≥ 12 yr, mean 41 yrs - On ICS, ± LABA - Parallel arm, DB - 24 weeks	FF 100 mcg QD FP 250 mcg BID Placebo	114 114 115	1^o: ΔFEV_1 trough baseline to week 24	US, Poland, Romania, Germany, Belgium (57% US)
106827 Trial 2 [2010-2011]	- ≥ 12 yr, mean 40 yrs - On ICS, ± LABA - Parallel arm, DB - 12 weeks	FF 100 mcg QD FF/VI 100/25 mcg QD Placebo	205 201 203	1^o: ΔFEV_1 trough baseline to week 12 1^o: ΔFEV_1 0-24 hr baseline to week 12	US, Poland, Romania, Ukraine, Germany, Japan (32% US)

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variable ¶**	**Regions and Countries**
Pivotal efficacy and safety studies supporting Arnuity Ellipta 200 mcg					
114496 Trial 3 [2011-2012]	- ≥ 12 yr mean 46 yrs - On ICS, no LABA - Parallel arm, DB - 24 weeks	FF 100 mcg QD FF 200 mcg QD	119 119	1^{o}: ΔFEV_1 trough baseline to week 24	US, Argentina, Russia, Mexico, France, Chile (23% US)
106829 Trial 4 [2010-2011]	- ≥ 12 yr, mean 46 yrs - On ICS, no LABA - Parallel arm, DB - 24 weeks	FF 200 mcg QD FF/VI 200/25 mcg QD FP 500 mcg BID	194 197 195	1^{o}: ΔFEV_1 trough baseline to week 24 1^{o}: ΔFEV_1 0-24 hr baseline to week 24	US, E and W Europe, Japan (24% US)
Supporting long-term safety studies					
106837 [2010-2011]	- ≥ 12 yr, mean 42 yrs - Asthma - Parallel arm, DB - 76 weeks	FF 100 mcg QD FF/VI 100/25 mcg QD	1010 1009		US, E and W Europe, Japan, Philippines, Mexico, S Amer (18% US)
106839 [2009-2011]	- ≥ 12 yr, mean 39 yrs - Asthma - Parallel arm, DB - 52 weeks	FF/VI 100/25 mcg QD FF/VI 200/25 mcg QD FP 500 BID	201 202 100		US, Germany, Ukraine, Thailand (38% US)

* Study ID shown (top to bottom) as GSK's study number, as referenced in the proposed Breo Ellipta product label, and [year study started-completed]
† DB=double blind, DD=double dummy
‡ FF=fluticasone furoate in Arnuity Ellipta; FP=fluticasone propionate; FF/VI = Breo Ellipta (fluticasone furoate and vilanterol inhalation powder);
§ Intent to treat (ITT)
¶ Analyzed based on linear regression models (ANCOVA) adjusting for baseline FEV_1, region, sex, and age. In the analysis of trough FEV_1, last observation carried forward was used to missing measurement in patients who withdrew from the study. Analysis of post-dose 0-24 hr serial FEV_1 was on weighted mean and restricted to patient who completed the study with no imputation for missing data.

b. Design and conduct of the studies

Fluticasone furoate dose ranging (9684, 9685, 9787) and dose regimen (2202) studies:

These studies were conducted in patients with persistent asthma with varying severity commensurate to the doses of fluticasone that were used in these studies: study 9684 enrolled patients who were symptomatic on moderate-dose ICS, study 9685 enrolled patients who were symptomatic on low-dose ICS, study 9687 enrolled patients who were symptomatic on SABA, and study 2202 enrolled patients with persistent asthma. Study treatment arms and primary efficacy variable are shown in Table 1. The primary analysis for studies 9684, 9685, and 9687 was linear trend in dose response in trough FEV_1 at week 8. The primary analysis of study 2202 was non-inferiority of fluticasone furoate 200 mg QD to fluticasone furoate 100 mg BID trough FEV_1 at week 8. Safety assessments included adverse event recording, vital signs, physical examination including oropharyngeal examination, clinical laboratory and hematology measures, and 24-hour urinary cortisol excretion.

Pivotal efficacy and safety studies (2059, 6827, 4496, 6829):

These studies were similar in design conducted in patients with persistent asthma with varying severity commensurate to the dose of study drug, and for duration of study and treatment arms (Table 2). Patients eligible for the studies were required to have a diagnosis of asthma for at least 12 weeks, had been using an ICS at a stable dose for at least 4 weeks, with or without a concomitant LABA treatment. Eligible patients entered a 4-week run-in period to establish eligibility, assess compliance, and measure baseline characteristics, followed by double-blind treatment period (Table 2). Concomitant LABA was prohibited during run-in and double-blind periods. Patients withdrawing from taking the study treatment were not followed up for efficacy or safety assessment. Primary efficacy variables are shown in Table 2. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs.

Supportive long-term safety studies (6837, 6839):

These studies were conducted in patients with persistent asthma. Study treatment arms are shown in Table 1. Safety assessments included adverse event recording, vital signs, physical examination, and clinical laboratory and hematology measures.

c. Efficacy findings and conclusions

The clinical program is adequate to support efficacy of Arnuity Ellipta 100 mcg and 200 mcg (fluticasone furoate 100 mcg and 200 mcg) in patients with asthma.

Fluticasone furoate dose ranging and dose regimen:

As discussed in section 2 above, selection of an appropriate dose and dosing regimen is an important consideration for the development of ICSs. GSK conducted adequate exploration of dose ranges in 3 studies and dose regimen in 1 study (Table 1).

In dose ranging studies, trough FEV_1 responses showed efficacy of fluticasone furoate 100 mcg once daily near the maximal efficacy with fluticasone furoate 200 mcg once daily (Figure 1). Efficacy was also demonstrated with fluticasone furoate 50 mcg once daily, but the difference compared to placebo and compared to other doses was less. With increasing doses of fluticasone furoate, the trough FEV_1 response reached a plateau, but also seemed to numerically decrease at the very high end of doses (Figure 1). Based on these data, GSK selected the nominal dose of fluticasone furoate 100 and 200 mcg for confirmatory studies. This was reasonable and acceptable to the Agency.

Results of the dose regimen study showed numerically similar changes in trough FEV_1 from baseline compared to placebo for fluticasone furoate 200 mcg once daily and fluticasone furoate 100 mcg twice daily, which supports a once-daily dosing regimen for fluticasone furoate. The study had sensitivity to detect a difference between once- and twice-daily ICS dosing, since a numerically superior improvement in FEV_1 compared to placebo was seen for the true twice-daily comparator, fluticasone propionate (Figure 2).

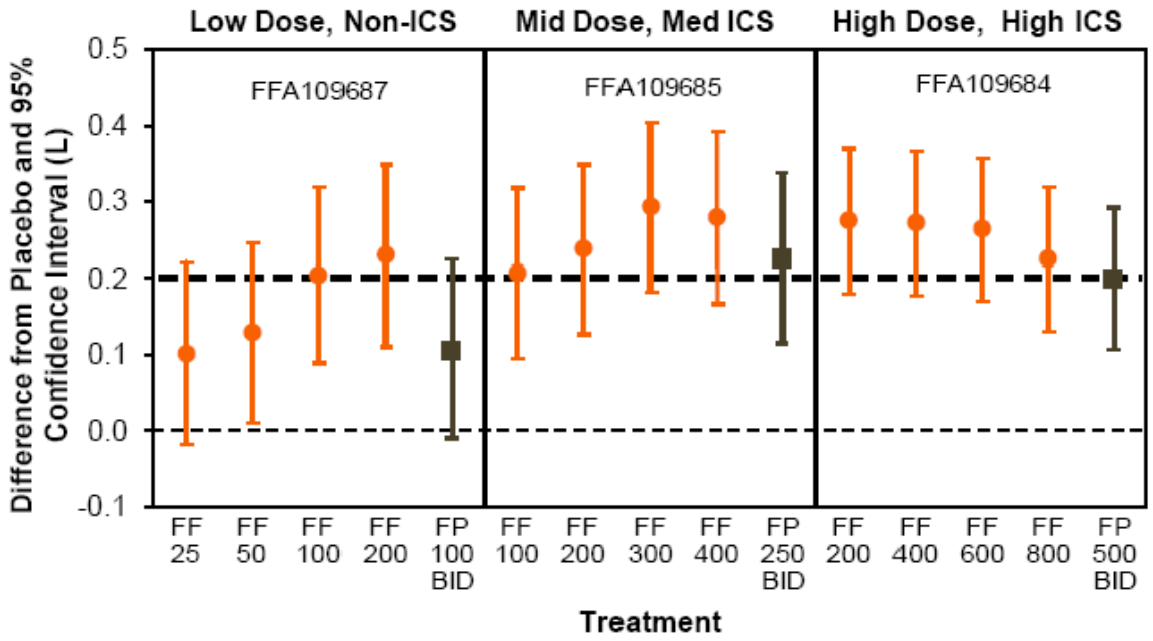

Figure 1. Adjusted treatment difference from placebo for change from baseline in trough FEV1 in liters at week 8 from three dose ranging studies in asthma (FF=fluticasone furoate, FP=fluticasone propionate).

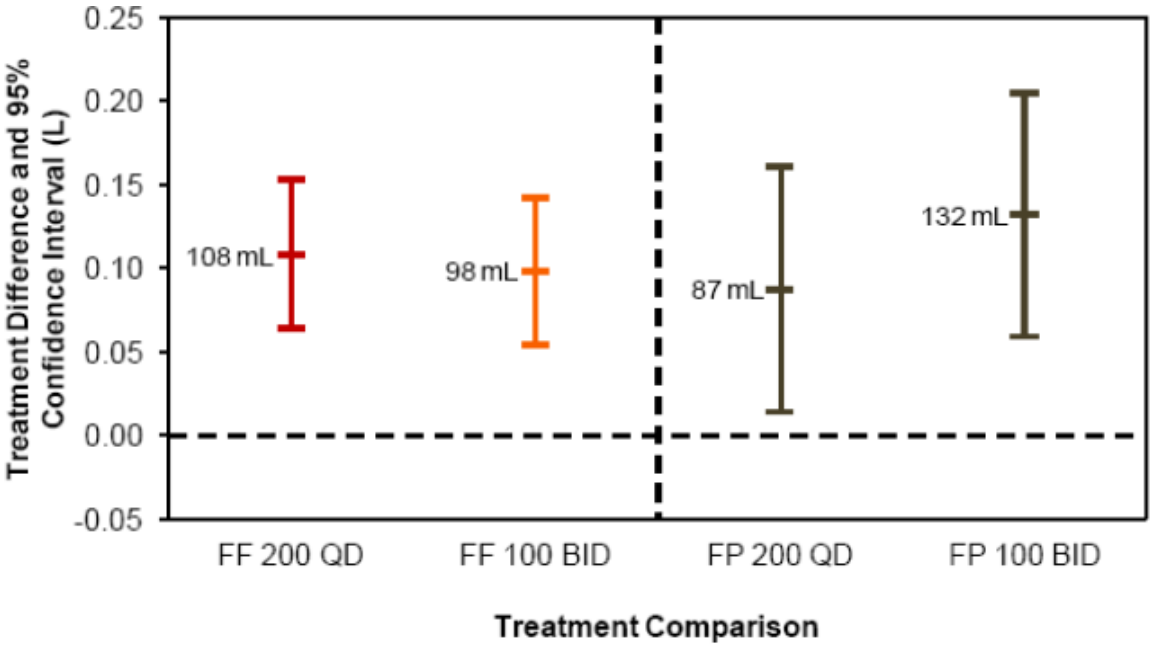

Figure 2. Adjusted treatment difference from placebo for change from baseline in trough FEV1 in liters at day 28 from dose regimen study in asthma (FF=fluticasone furoate, FP=fluticasone propionate).

Fluticasone furoate pivotal efficacy:

The submitted data support efficacy of both Arnuity Ellipta 100 mcg and 200 mcg once daily doses. The 100 mcg dose demonstrated statistically significant difference from placebo in FEV_1 based on primary efficacy measures in two studies (Table 3 and Table 4). Various secondary efficacy measures, such as symptom-free period, rescue medication use, and ACT score, were also supportive. The 200 mcg dose showed numerical trend of higher response compared to the 100 mcg dose for the primary efficacy measure (Table 5), and also for various secondary efficacy measures. The efficacy of fluticasone furoate 100 mcg once-daily and fluticasone propionate 250 mcg twice-daily were numerically comparable (Table 3), and the efficacy of fluticasone furoate 200 mcg once-daily and fluticasone propionate 500 mcg twice-daily were also numerically comparable (Table 6).

Table 3. Primary efficacy variable results from Study 2059

	Placebo N=115	FF 100 mcg QD N=114	FP 250 mcg BID N=114
Change from baseline in trough FEV_1 in L to week 24, All Patients			
Mean change Difference [95% CI], p value	0.02	0.17 0.15 [0.04, 0.26], 0.01	0.15 0.14 [0.03, 0.26], 0.01

Table 4. Primary efficacy variable results from Study 6827

	Placebo N=203	FF 100 mcg QD N=205
Change from baseline in trough FEV_1 in L to week 12, All Patients		
Lease squares mean change Difference [95% CI], p value	0.22	0.32 0.14 [0.05, 0.22], 0.002
Change from baseline in FEV_1 0-24 hr in L to week 12, Completers		
Mean change Difference [95% CI], p value	0.25	0.38 0.19 [0.06, 0.31], 0.003

Table 5. Primary efficacy variable results from Study 4496

	FF 100 mcg QD N=108	FF 200 mcg QD N=111
Change from baseline in trough FEV_1 in L to week 24 All Patients		
Mean change Difference [95% CI]	0.20	0.29 0.08 [-0.04, 0.19]

Table 6. Primary efficacy variable results from Study 6829

	FP 500 mcg BID N=195	FP 200 mcg QD N=195
Change from baseline in trough FEV_1 in L to week 24 All Patients		
Lease squares mean change Difference [95% CI]	0.17	0.22 0.02 [-0.07, 0.10]
Change from baseline in FEV_1 0-24 hr in L to week 24, Completers		
Mean change Difference [95% CI]	0.26	0.33 0.07 [-0.07, 0.21]

8. Safety

a. Safety database

The safety assessment of Arnuity Ellipta is based on studies shown in Table 1 and Table 2. The safety database for Arnuity Ellipta was large and adequate.

b. Safety findings and conclusion

The submitted data support the safety of Arnuity Ellipta 100 mcg and 200 mcg (fluticasone furoate 100 mcg and 200 mcg) in patients with asthma

GSK conducted a comprehensive safety analysis of the available data. Safety analysis included evaluation of deaths, serious adverse events (SAEs[4]), common adverse events (AEs), and assessment of adverse events of interest related to HPA axis.

There were 2 deaths in the clinical program, both in patients receiving Arnuity Ellipta 100 mcg dose. One death was in a 65 year-old male patient from respiratory failure secondary to lung cancer, and another death was in a 62 year-old patient with concomitant diabetes who developed sepsis. SAEs were reported in 52 subjects across treatment groups. The most frequent SAE was asthma exacerbations. The SAEs were generally balanced across treatment groups and do not raise any specific concerns. Common adverse events included headache, nasopharyngitis, upper respiratory tract infection, bronchitis, oropharyngeal pain, and cough. There were no dose-dependent increases in adverse events. There were no clinically meaningful changes in laboratory parameters, or ECGs.

c. REMS/RiskMAP

GSK submitted a Risk Management Plan for Arnuity Ellipta, which consists of routine pharmacovigilance practices. A REMS is not necessary for Arnuity Ellipta as inhaled corticosteroids have a well-established safety profile and there were no unique safety signals identified for Arnuity Ellipta that would require a REMS.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held to discus this application as the safety and efficacy for an ICS such as fluticasone furoate in asthma is well understood. There were no unique findings in the Arnuity Ellipta program that would warrant a discussion at an Advisory Committee meeting.

[4] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

10. Pediatric

GSK requested a deferral for studies in patients 5 to 11 years of age and a waiver for patients below 5 years of age with the reasoning that effective treatments for asthma for these ages are already available in the market and clinical in these patients are impractical. There are four deferred studies in pediatric patients 5-11 years of age: 1) a 12-week dose ranging, efficacy and safety study; 2) a 2 week knemometry study; 3) a 6 week HPA axis study; and 4) a 52 week growth study. GSKs proposal was discussed at PeRC meeting on September 25, 2013, before the application was submitted, and on February 12, 2014, during review of this application, and PeRC found GSKs request acceptable.

11. Other Relevant Regulatory Issues

a. DSI Audits

A DSI audit was not necessary and not conducted for this application. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. Two investigators had significant financial interest in GSK. The number of subjects enrolled at these investigator sites was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that financial interest could have influenced or biased the results of these studies.

c. Others

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

12. Labeling

a. Proprietary Name

GSK submitted Arnuity Ellipta as the proposed proprietary name, which was accepted by DMEPA.

b. Physician Labeling

GSK submitted a label in the Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, the Division of Medical Policy Programs (DMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were done to reflect the data accurately and to better communicate the findings to healthcare providers. The Division and GSK have agreed on the final label language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

Arnuity Ellipta will have a patient labeling. There will not be a Medication Guide for Arnuity Ellipta.

13. Action and Risk Benefit Assessment

a. Regulatory Action

GSK has submitted adequate data to support approval of Arnuity Ellipta (fluticasone furoate 100 mcg or 200 mcg inhalation powder) for maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. The regulatory action for this application is Approval.

b. Risk-Benefit Assessment

The overall risk-benefit assessment supports approval of Arnuity Ellipta inhalation powder at a dose of one inhalation (fluticasone furoate 100 mcg or 200 mcg) once daily for treatment of asthma. The risks with the use of Arnuity Ellipta are typical of ICSs, such as effects on adrenal axis. The safety findings from the clinical program did not identify adrenal axis suppression and clinically significant findings related to effects on adrenal axis. The safety findings were typical of other ICSs for the treatment of asthma. The efficacy findings of the two doses were robust and consistent with expected efficacy of ICSs in asthma. The benefit of Arnuity Ellipta in asthma outweighs the potential risk.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

None, other than PREA required pediatric studies.

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/s/

BADRUL A CHOWDHURY
08/20/2014