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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 23, 2014
From	Banu A. Karimi-Shah, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 205-625
Supplement#	
Applicant	GlaxoSmithKline (GSK)
Date of Submission	October 22, 2013
PDUFA Goal Date	August 22, 2014
Proprietary Name / Established (USAN) names	Arnuity Ellipta®/fluticasone furoate inhalation powder
Dosage forms / Strength	Fluticasone furoate 100 and 200 mcg inhalation powder
Proposed Indication(s)	Maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older
Recommended:	<i>Approval</i>

1. Introduction

GlaxoSmithKline (GSK) submitted a 505(b)(1) New Drug Application (NDA) 205-625 on October 22, 2013, for fluticasone furoate (FF) inhalation powder (Arnuity Ellipta®) indicated for the maintenance treatment of asthma as prophylactic therapy in adults and children 12 years of age and older. The dry powder inhaler (DPI) will be available in two dosage strengths, 100 and 200 mcg per actuation. FF is an inhaled corticosteroid (ICS), which is already approved in combination with vilanterol (VI: a long-acting beta-agonist, or LABA), for the long-term maintenance treatment and reduction of exacerbations in COPD patients (FF/VI, Breo Ellipta, NDA 204-275). FF is also available as an intranasal formulation for the treatment of allergic rhinitis (Veramyst Nasal Spray). FF is supplied as a dry powder inhalation formulation administered by the Ellipta inhaler device.

To support the FF 100 mcg and 200 mcg once daily (QD) doses for the asthma indication, GSK conducted a clinical program that included 4 dose-ranging trials, 3 confirmatory phase 3 clinical trials, and 3 supportive trials (including 2 long-term safety trials).

This memo provides an overview of the application, reviewing the data which demonstrate the efficacy and safety of FF 100 mcg and 200 mcg in patients with asthma. Focus is placed on the trough FEV1, the pulmonary function endpoint generally utilized to determine the efficacy of inhaled corticosteroid products for asthma, such as FF. The memo also addresses the recommendations from each of the individual review disciplines.

2. Background

Asthma is a chronic inflammatory respiratory disease characterized by periods of acute symptoms of wheezing and shortness of breath. Inhaled corticosteroids play a principal therapeutic role in the management of patients with persistent asthma. Patients with persistent asthma whose disease remains uncontrolled in spite of treatment with controller therapy such as inhaled corticosteroids are candidates for treatment with LABA/ICS fixed-dose combination products.

According to NHLBI and GINA guidelines, ICS products like FF are first-line anti-inflammatory therapies for persistent asthma. There are several ICS-containing products currently approved for treatment of patients with asthma including Asmanex (mometasone), Alvesco (ciclesonide), Flovent (fluticasone), Pulmicort (budesonide), and QVAR (beclomethasone dipropionate). Combination ICS plus LABA products to treat patients with more severe asthma include Advair MDI and DPI (fluticasone/salmeterol), Dulera MDI (mometasone furoate/ formoterol fumarate), and Symbicort MDI (budesonide/ formoterol fumarate). Other non-steroid classes of drug used in the treatment of asthma include beta-2 agonists, leukotriene inhibitors, nonspecific phosphodiesterase inhibitors such as theophylline, and anti-IgE therapy (omalizumab).

Relevant Regulatory History for FF

GSK conducted the program for FF in asthma concurrently with the development of FF/VI for both COPD and asthma, so many of the regulatory interactions included discussion of both the mono-components and combination products for both indications. The following timeline highlights the major discussions with respect to the clinical development of FF:

- **March 31, 2009, End-of-Phase 2 Meeting (for FF/VI):** The Division noted that the Applicant should directly compare the proposed daily dosing of their drug to the twice daily regimens for approved ICS products to establish the appropriate dosing frequency.
- **March 16, 2011, End-of-Phase 2 Meeting (for FF):** The Division informed the Applicant that the applicability of the double-strip data to the single-strip device would be a review issue. In addition, the Division noted that approval of the 200 mcg dose would require that it be at least numerically better than the 100 mcg dose in trough FEV₁, and that secondary endpoints should also support the added benefit of the higher dose.
- **February 11, 2013, Pre-NDA Meeting (for FF):** The Division agreed with submission of the 100 mcg and 200 mcg doses for registration, as the replicate efficacy for the 50 mcg dose had not been demonstrated.

3. CMC/Device

The recommended action from a CMC/Quality perspective is Approval.

The drug substance is fluticasone furoate, a well described glucocorticoid used in many pharmaceutical products, including the Applicant's recently approved drug product, Breo Ellipta (NDA 204-275). Information for FF has been provided by the Applicant via cross-reference to the approved NDA 204-275. The dry powder inhaler, the Ellipta, (b) (4) was approved under NDA 204-275 (b) (4) only a single blister strip (b) (4) is enclosed within the device during manufacturing.

The FF drug product is formulated in two strengths, 100 and 200 mcg/actuation (ex-actuator). The drug product consists of a plastic inhaler with a light grey body, an orange mouthpiece cover, and a dose counter packed in a foil tray with a desiccant packet. The tray is sealed with a peelable lid. The inhaler contains a single strip of (b) (4) blister (b) (4) containing either 30 blisters (trade) or 14 blisters (institution and sample of FF/lactose inhalation powder). At the time of drug administration, one actuation (the opening/turning of the inhalation mouthpiece to make the dose ready) and inhalation by the patient deliver one dose of dry powder formulation from one blister.

All registration batches of the drug product met the proposed specifications, and are consistent with the clinical batches in terms of quality and performance. Twenty-four months of long-term stability data, and 3 months of in-use stability data are provided and were satisfactory. The proposed shelf life of 30 months with 6 weeks of in-use period is appropriate. For further CMC information, see the primary CMC review of Dr. Edwin Jao.

The drug substance and product are manufactured by Glaxo (b) (4) (b) (4) with alternative stability testing conducted at GlaxoSmithKline LLC (b) (4). The facilities inspections were deemed "Acceptable" from the Office of Compliance.

4. Nonclinical Pharmacology/Toxicology

The recommended regulatory action from a Nonclinical Pharmacology/Toxicology perspective is Approval. There are no outstanding nonclinical issues at this time.

No new nonclinical pharmacology or toxicology data were required or submitted with this NDA, as the necessary pharmacology/toxicology data were submitted under NDA 20-551 (Veramyst Nasal Spray) and NDA 204-275 (Breo Ellipta).

The preclinical program included studies in which animals were dosed with FF via inhalation to assess general toxicity, genetic toxicity, carcinogenicity, and reproductive toxicity of FF. FF possesses a toxicity profile typical of inhaled corticosteroids. FF was non-genotoxic, non-carcinogenic, non-teratogenic, and had no effect on fertility in humans. FF carries a

Pregnancy Category C designation because of known effects of corticosteroids on embryofetal development.

5. Clinical Pharmacology/Biopharmaceutics

The recommended regulatory action from a Clinical Pharmacology/Biopharmaceutics perspective is Approval. There are no outstanding clinical pharmacology issues at this time.

To support this NDA submission, the Applicant provided information from 31 clinical pharmacology studies, 29 of which originated in NDA 204-275 (FF/VI, Breo Ellipta). The majority of the clinical pharmacology studies, including the dose ranging studies, were previously reviewed in NDA 204-275. Highlights of the clinical pharmacology review are summarized here. For further details, refer to the review of Dr. Jianmeng Chen.

The absolute systemic bioavailability of FF is 13.9%. T_{max} is reached by 0.5-1 hours for FF following oral inhalation. FF is eliminated primarily by metabolism with the metabolites predominately excreted in feces. The apparent elimination half-life of FF following oral inhalation administration is ~23.7 h. FF is a substrate of CYP3A4 and P-glycoprotein (P-gp). Based on *in vitro* studies, the potential for FF to inhibit and induce metabolic enzymes is negligible.

The dose and dosing frequency have been adequately explored in patients with asthma, and the chosen doses are acceptable. No dosing adjustment is recommended for any intrinsic or extrinsic factors. Although the systemic exposure of FF is higher in patients with all severities of hepatic impairment, the clinical pharmacology review recommends that both FF 100 mcg and 200 mcg be made available for patients with moderate to severe hepatic impairment with cautionary labeling language.

The clinical development program for FF monotherapy was conducted concurrently with the development program for FF combination therapy with vilanterol (VI). As a result, many of the initial FF studies were conducted with a double-strip configuration, in which one strip contained FF, and the other strip contained either VI or excipient. The systemic exposure after administration of FF in the single strip configuration (to-be-marketed) was found to be 29% higher compared to the systemic exposure after administration of FF in the double-strip configuration (FF/excipient), and 60% higher compared to FF in FF/VI combination. This observation is consistent with *in vitro* data which demonstrates that the single-strip configuration delivers 20% more fine particle mass compared to the double-strip configurations. As a result, bioequivalence was not demonstrated between the to-be-marketed FF single-strip configurations when compared with either of the double-strip configurations.

From a clinical pharmacology perspective, regarding PK in special populations and drug-drug interactions, data with the double-strip configuration were considered to be directly applicable to the single-strip product. From a clinical standpoint, a safety comparison of the single-strip and double-strip configurations did not demonstrate any consistent differences between configurations with respect to common AEs, SAEs, or AEs leading to withdrawal. While some AEs of

special interest occurred more frequently in the single-strip versus double strip configuration, these were not consistent across dose-strengths, types of AEs, or AE severity. Additionally, the long-term safety data provided by the Applicant relies on the double-strip (lower exposure) configuration. While we acknowledge that the exposure to FF in the double-strip configuration is less than the to-be-marketed single strip FF configuration, requesting additional long-term safety data for the single-strip formulation for a class of drugs (ICS) whose safety profile is well-characterized, is of limited value and highly unlikely to change the safety profile of FF in asthma. Therefore, from a clinical standpoint, we consider the long-term safety data to be acceptable for this application.

6. Clinical Microbiology

The recommended regulatory action from a Clinical Microbiology perspective is Approval. There are no outstanding clinical microbiology issues at this time.

The Applicant proposes a two-tiered microbial limits testing regimen involving the bulk drug product and product packaged in the blister packs. The proposed approach to microbiological testing was deemed acceptable based upon the process control and validation data provided. For further details, refer to the review of Dr. Stephen Langille.

7. Clinical/Statistical-Efficacy

Overview of the clinical program

The studies relevant to regulatory decision-making for this application are listed in Table 1.

Table 1: Fluticasone Furoate Clinical Studies in Asthma					
Trial <i>Trial period</i>	Design	Treatment (mcg)	N	Endpoint	Sites <i>% US sites</i>
<i>Dose Selection Trials</i>					
FFA109684 <i>Dec 2007 – Sep 2008</i>	8-wk, R, DB, DD, PC, PG	FF 200 QD FF 400 QD FF 600 QD FF 800 QD FP 500 BID Placebo	99 101 107 102 110 103	Trough FEV1	94 sites (US, Canada, Mexico, E. and W. Europe, Australia, S. Africa, Thailand <i>18%</i>
FFA109685 <i>Dec 2007- Nov 2008</i>	8-wk, R, DB, DD, PC, PG	FF 100 QD FF 200 QD FF 300 QD FF 400 QD FP 250 BID Placebo	105 101 103 99 100 107	Trough FEV1	98 sites (US, Canada, Mexico, E. and W. Europe, Korea, Philippines) <i>32%</i>
FFA109687 <i>Dec 2007 – Oct 2008</i>	8-wk, R, DB, DD, PC, PG	FF 25 QD FF 50 QD FF 100 QD FF 200 QD FP 100 BID Placebo	97 100 110 95 110 94	Trough FEV1	107 sites (US, Canada, Mexico, Korea, E. and W. Europe, Peru, Philippines) <i>36%</i>

Table 1: Fluticasone Furoate Clinical Studies in Asthma					
Trial <i>Trial period</i>	Design	Treatment (mcg)	N	Endpoint	Sites <i>% US sites</i>
FFA112202 <i>Oct 2008 – Mar 2009</i>	28-day, R, DB, XO, PC to assess dosing frequency	FF 200 QPM FF 100 BID FP 200 QPM FP 100 BID	190	Trough FEV1	16 sites (US) 100%
Confirmatory Trials					
FFA112059 <i>Jun 2010 – Jan 2012</i>	24-wk, R, DB, DD, PC, PG	FP 100 QD FP 250 BID Placebo	114 114 115	Trough FEV1	343 sites (US, Poland, Romania, Germany, Belgium) 57%
HZA 106827 <i>Aug 2010 – Oct 2011</i>	12-wk, R, DB, PC, PG	FF 100 QD FF/VI 100 QD Placebo	205 201 203	Trough FEV1 Serial FEV1	609 sites (US, Poland, Romania, Ukraine, Germany, Japan) 32%
FFA 114496 <i>Sep 2011 – Oct 2012</i>	24-wk, R, DB, PC, PG	FF 100 QD FF 200 QD	119 119	Trough FEV1	238 sites (US, Argentina, Russia, Mexico, France, Chile) 23%
Supportive Trials					
HZA106829 <i>Jun 2010 – Oct 2011</i>	24-wk, R, DB, DD, AC, PG	FF 200 QD FP 500 BID FF/VI 200/25 QD	194 195 197	Trough FEV1 Serial FEV1	586 sites (US, E. and W. Europe, Japan) 24%
HZA106837 <i>Feb 2010 – Sep 2011</i>	76-wk, R, DB, PG	FF 100 QD FF/VI 100/25 QD	1010 1009	Long-Term Safety	2,019 sites (US, Mexico, E. and W. Europe, S. America, Australia, Philippines, Japan) 18%
HZA106839 <i>Oct 2009 – May 2011</i>	52-wk, R, DB, DD, AC, PG	FF/VI 100/25 QD FF/VI 200/25 QD FP 500 BID	201 202 100	Long-Term Safety	45 sites (US, Germany, Ukraine, Thailand) 38%
R=randomized, DB=double-blind, DD=double dummy, PG=parallel group, PC=placebo controlled, AC=active controlled, XO=crossover, FP: fluticasone propionate, VI=vilanterol					

The clinical development program consisted of 4 dose selection trials (FFA109684, FFA109685, FFA109687, and FFA112202), 3 confirmatory phase 3 clinical trials (FFA112059, HZA106827, FFA114496) and 3 supportive trials (HZA106829, HZA106837, HZA106839). With respect to efficacy, this summary review focuses on studies FFA112059, HZA106827, and FFA114496. In these studies, the efficacy of FF was evaluated in three randomized, double-blind, placebo- or active-controlled multicenter clinical trials of 12 or 24 weeks duration, in patients 12 years of age and older with persistent asthma. The dose selection trials and supportive trial HZA106289 will also be summarized here. The long-term safety trials (HZA106837 and HZA106839) are summarized briefly in the safety discussion.

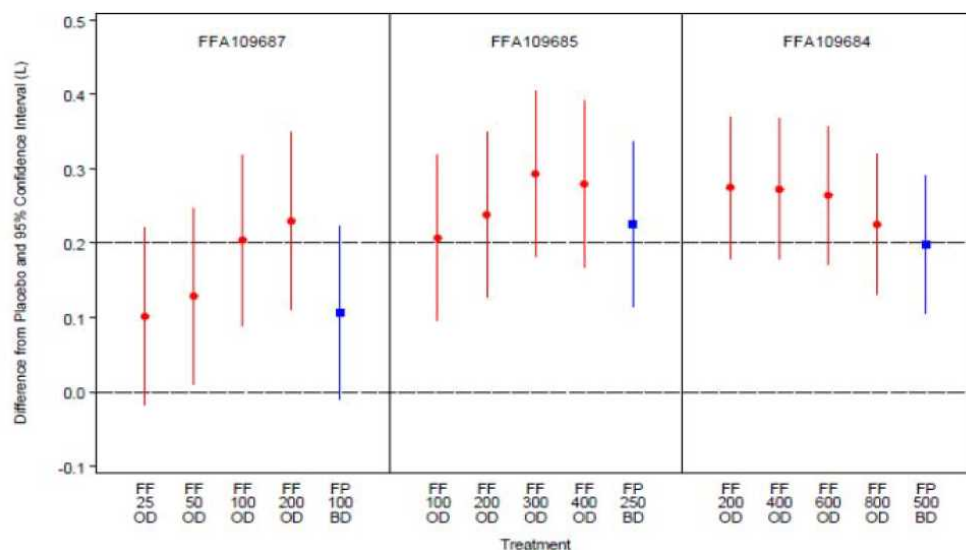
Dose selection

The dose selection trials evaluated eight doses of FF ranging from 25 to 800 mcg once daily, as well as a trial to evaluate dosing frequency (QD vs. BID). The dose selection trials were reviewed in detail as part of NDA 204-275 and are therefore briefly summarized here.

- **Nominal dose selection**

The results of three dose-ranging trials in asthma are summarized in Figure 1. The trials were similarly designed and were randomized, double-blind, placebo-controlled, 8-week trials that included an approved dose for fluticasone propionate as a benchmark. A relative dose response was observed for FF doses ranging from FF 25 mcg to 200 mcg. There did not appear to be a consistent additive benefit for FF doses above 200 mcg. The results of these three trials in asthma were the basis for the selection of FF 50, 100, and 200 mcg for further evaluation in confirmatory trials. The Applicant was not able to demonstrate replicate efficacy for FF 50 mcg in the confirmatory trials, and therefore, does not seek approval for the 50 mcg dose.

Figure 1: Trials FFA109687, FFA109685, and 109687: Adjusted treatment differences from placebo of change from baseline in trough FEV1 (L) at Week 8



- **Dosing frequency**

GSK conducted Trial FFA112202, a randomized, double-blind, placebo-controlled, cross-over trial in 190 adults and adolescents with asthma to compare FF 200 mcg QD (PM), FF 100 mcg BID, FP 200 mcg QD (PM), and FP 100 mcg BID. Based on trough FEV1, FF 200 mcg QD versus FF 100 mcg BID appeared similar, whereas FP 100 mcg BID dosing resulted in a numerically higher trough FEV1 compared to FP 200 mcg QD. These results supported the selection of the QD regimen for further evaluation.

Confirmatory Trials

The confirmatory trials were designed to evaluate the safety and efficacy of FF 100 mcg or 200 mcg given once daily in the evening on lung function in subjects who were not controlled on their current treatments of inhaled corticosteroids or combination therapy consisting of an inhaled corticosteroid plus a long-acting beta2-adrenergic agonist (LABA). Study treatments

were delivered as inhalation powders. The primary endpoint in all trials was change from baseline in evening trough FEV1 measured approximately 24 hours after the final dose of study medication. Trough FEV1 (assessed at approximately 24 hours after the previous dose) was also assessed at clinic visits throughout the trials. Trial HZA106827 also had a co-primary endpoint of change from baseline in weighted mean serial FEV1 measured after the final dose of study medication at 5, 15, and 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23, and 24 hours post-dose.

1) FFA112059 & HZA106827: Clinical Trials to Support the FF 100 mcg Once Daily Dose

- Study FFA112059

FFA112059 was a 24-week, randomized, double-dummy, placebo-controlled, and active-controlled trial which evaluated 343 asthma patients 12 years of age and older. Of these patients, 114 patients received FF 100 mcg QD, 114 patients received FP 250 mcg BID, and 115 patients received placebo. The study included a 4-week run-in period during which the subjects were symptomatic while taking their usual low- to mid-dose inhaled corticosteroid therapy (i.e. FP 100 to 500 mcg daily or equivalent).

Patients ranged from 12 to 84 years old, with a mean age of 40 years, with 41% being male and 79% Caucasian. Mean baseline percent predicted FEV1 was approximately 73% overall and similar across each of the 3 treatment groups. Thirty-five percent (35%) of patients on placebo and 19% of patients on FF 100 mcg failed to complete the 24-week trial. The change in trough FEV1 from baseline to Week 24, or the last available on-treatment visit prior to Week 24, compared to placebo was assessed as the primary endpoint to evaluate the efficacy of FF 100 mcg. The mean change from baseline to week 24 in trough FEV1 was statistically greater among patients receiving FF 100 mcg than among those receiving placebo (treatment difference from placebo 146 mL [95% CI: 36, 257], or when expressed in liters, 0.15 L [95% CI: 0.04, 0.26]).

Table 2. FFA112059 – Change from Baseline in Trough FEV1 at Week 24			
	Treatment Group		
	Placebo n = 115	FF 100 mcg QD n = 114	FP 250 mcg BID n = 114
Trough FEV ₁ (Week 24)			
Least squares mean, L	2.4	2.5	2.5
Least squares mean change, L (SE)	0.02 (0.47)	0.17 (0.45)	0.15 (0.40)
Difference vs. Placebo (L) ¹	---	0.15	0.14
95% CI	---	(0.04, 0.26)	(0.03, 0.26)
p-value	---	0.01	0.01

1. Based on linear regression model of last available observation adjusting for baseline FEV1, region, sex, age.
 Source: Statistical Review, Dr. Greg Levinson

FF also showed benefit, or trends toward benefit, for additional endpoints of interest, including the percent of rescue-free 24-hour periods, percent of symptom-free 24-hour periods, morning peak expiratory flow, evening peak expiratory flow, AQLQ (+12) total score, and ACT score.

- Study HZA106827

HZA106827 was a 12-week, randomized, placebo-controlled trial which evaluated 609 asthma patients 12 years of age and older. Of these patients, 205 patients received FF 100 mcg QD, 201 patients received FF/VI 100/25 mcg QD, and 203 patients received placebo. The trial included a 4-week run-in period during which the subjects were symptomatic while taking their usual low- to mid-dose inhaled corticosteroid (fluticasone propionate 200 to 500 mcg/day or equivalent).

Patients ranged from 12 to 84 years old, with a mean age of 40 years, 42% were male, and 84% were Caucasian. Mean baseline percent predicted FEV1 was approximately 70% overall and similar across each of the 3 treatment groups. Twenty-six percent (26%) of patients on placebo and 10% of patients on FF 100 mcg failed to complete the 12-week trial. The co-primary efficacy endpoints in this trial were change from baseline in trough FEV1 at Week 12 and weighted mean FEV1 (0-24 hours) at the end of the 12-week treatment period. FF 100 mcg once daily had statistically greater mean changes from baseline in trough FEV1 than placebo throughout the study. At Week 12, or the last available on-treatment visit prior to Week 12, the mean change from baseline in trough FEV1 was significantly greater among patients receiving FF 100 mcg once daily than among those receiving placebo (treatment difference from placebo: 136 mL [95% CI: 51, 222], or when expressed in liters, 0.14 L [95% CI: 0.05, 0.22]).

	Treatment Group	
	Placebo n = 203	FF 100 mcg QD n = 205
Trough FEV ₁ (Week 12)		
Least squares mean, L	2.5	2.7
Least squares mean change, L (SE)	0.22 (0.47)	0.32 (0.45)
Difference vs. Placebo (L) ¹	---	0.14
95% CI	---	(0.05, 0.22)
p-value	---	0.002

1. Based on linear regression model of last available observation adjusting for baseline FEV1, region, sex, age.
 Source: Statistical Review, Dr. Greg Levinson

Lung function improvements were sustained over 24 hours. Compared with placebo at Week 12, the change from baseline in weighted mean FEV1 was significantly greater for FF 100 mcg (treatment difference of 186 mL [95% CI: 62, 310], or when expressed in liters, 0.19L [95% CI: 0.06, 0.31]).

FFA114496 and HZA106829: Clinical Trials to Support the FF 200 mcg Once Daily Dose

- Study FFA114496

FFA114496 was a 24-week, randomized, double-blind, parallel group trial which evaluated 219 asthma patients 12 years of age and older. Of these patients, 108 patients received FF 100 mcg and 111 patients received FF 200 mcg daily. There was no placebo group. The study included a 4-week run-in period during which the subjects were symptomatic while taking their usual mid-

to high-dose inhaled corticosteroid therapy (i.e., fluticasone propionate > 250 to 1,000 mcg/day or equivalent).

Patients ranged from 12 to 76 years old, with a mean age of 46 years, with 32% being male and 84% Caucasian. Mean baseline percent predicted FEV₁ was approximately 68% overall and similar in the two treatment groups. Sixteen (16%) percent of patients on FF 100 mcg and 13% of patients on FF 200 mcg failed to complete the 24-week trial. The primary efficacy endpoint was mean change from baseline in trough FEV₁ at Week 24. There were trends toward greater mean changes from baseline in the group receiving FF 200 mcg than the group receiving FF 100 mcg throughout the study. At Week 24 or the last available on-treatment visit prior to Week 24, the mean change from baseline in trough FEV₁ was 208 mL for FF 100 mcg, as compared to 284 mL for FF 200 mcg (difference of 77 mL [95% CI: -39,192], or when expressed in liters, 0.08L [95% CI: -0.04, 0.19]).

Table 4. FFA114496– Change from Baseline in Trough FEV₁ at Week 24		
	Treatment Group	
	FF 100 mcg QD n = 108	FF 200 mcg QD n = 111
Trough FEV ₁ (Week 12)		
Least squares mean, L	2.04	2.08
Least squares mean change, L (SE)	0.20 (0.41)	0.29 (0.45)
Difference vs. 100 mcg (L) ¹	---	0.08
95% CI	---	(-0.04, 0.19)

1. Based on linear regression models adjusting for baseline FEV₁, region, sex, age.
 Source: Statistical Review, Dr. Greg Levinson

In trial FFA114496, secondary endpoints included change from baseline in the percentage of rescue-free and symptom-free 24-hour periods over the 24-week treatment period and the AM/PM PEF averaged over the 24 week periods. With the exception of AM PEF, secondary endpoints demonstrated a trend towards numerical benefit for the FF 200 mcg dose over the FF 100 mcg dose.

- Study HZA106829

HZA106829 was a 24-week, randomized, double-blind, double-dummy, active-controlled study that evaluated the efficacy of FF 200 mcg once daily and fluticasone propionate 500 mcg twice daily on lung function in 586 subjects with asthma. The combination of fluticasone furoate 200 mcg and vilanterol 25 mcg (FF/VI) was also included as a treatment arm. The trial included a 4-week run-in period during which the subjects were symptomatic while taking their usual mid- to high-dose inhaled corticosteroid (fluticasone propionate 500 to 1,000 mcg/day or equivalent). If LABAs were used prior to screening, their use was discontinued during the run-in.

Of the 586 randomized subjects, 59% were female and 84% were Caucasian. The mean age was 46 years. Mean baseline percent predicted FEV₁ was approximately 67% in both treatment groups. Both FF 200 mcg once daily and fluticasone propionate 500 mcg twice daily produced improvement from baseline in lung function. At Week 24, the mean change from baseline in trough FEV₁ was 201 mL for FF 200 mcg once daily and 183 mL for fluticasone propionate 500

mcg twice daily (treatment difference of 18 mL [95% CI: -66, 102]). Lung function improvements were sustained over the 24-hour period following the final dose of FF 200 mcg. At Week 24, the change from baseline in weighted mean FEV1 was 328 mL for FF 200 mcg once daily and 258 mL for fluticasone propionate 500 twice daily.

The Applicant designed this study with a pre-specified non-inferiority margin of -125 mL, which has not been accepted by the Agency. However, the information comparing FP to FF in this study is considered important to prescribers who may be switching patients from FP to FF, as the dose is ~5-fold different.

Efficacy Conclusions

The Applicant provides support for the efficacy of both the FF 100 mcg and FF 200 mcg once daily doses. Support of the FF 100 mcg dose was demonstrated through comparison to placebo in 2 studies (FFA112059 and HZA106827). In both studies, FF 100 mcg demonstrated a statistically significant improvement compared to placebo. The efficacy of FF 100 mcg compared to placebo was also supported by serial FEV1 measurements over 24 hours in study HZA106827.

Support for the FF 200 mcg QD dose was demonstrated through comparison to FF 100 mcg in study FFA114496. Due to the known poor dose response curve for ICS, a statistically significant difference between dose strengths is not required. In this study, there was a numerical trend towards slightly greater FEV1 improvement with the higher 200 mcg dose. In general, secondary endpoints (e.g. rescue-free 24 hour periods, symptom-free 24 hour periods, PM PEF, and ACT scores) also demonstrated the added benefit of FF 200 mcg over FF 100 mcg. In addition, the added benefit of the 200 mcg dose was also demonstrated in the two 8-week dose ranging studies, FFA109685 and 109687. Study HZA106829 provides important information to prescribers regarding the efficacy of FP 500 BID and FF 200 mcg QD.

The clinical and statistical review teams are in agreement that the data provided are adequate to support the efficacy of both FF 100 mcg and 200 mcg once daily for the maintenance treatment of asthma.

8. Safety

To evaluate the safety of FF 100 mcg and 200 mcg, the Applicant submitted a pooled safety database that includes ten phase 2 and 3 studies, ranging from 8 to 76 weeks in duration, which enrolled a total of 6,219 patients (including all comparator groups). In the safety database, doses of FF studied ranged from 25 to 800 mcg. The focus of this review will be the safety evaluation of FF 100 mcg and FF 200 mcg, as these are the two doses for which the Applicant seeks registration. In the pooled safety database, 1663 subjects received FF 100 mcg and 608 subjects received FF 200 mcg. An adequate number of patients were exposed to both doses for up to 6 months and 1 year.

The majority of the subjects were white and female, with a mean age of 41 years. Twenty-one percent (21%) of subjects were Hispanic. The majority of subjects had asthma for 10 years or more, with a mean disease duration of 16.2 years.

There were two deaths in the clinical development program, both in patients receiving FF 100 mcg, and are not likely to be related to study treatment: a 65-year old male with respiratory failure due to bronchogenic carcinoma and a 62-year old with diabetes who developed sepsis.

Serious adverse events were infrequent in the clinical development program. In the pooled safety database, 52 subjects reported SAEs (1 to 2%) across treatment groups, with the highest incidence occurring in the FF 100 mcg group. The most frequent SAE was asthma exacerbations reported by 9 (<1%) subjects in the FF 100 mcg group and 1 subject each in the placebo and FF 200 mcg groups. All 9 subjects in the FF 100 mcg treatment arm were from the exacerbation study which had a duration of up to 76 weeks. Other SAEs occurred in fewer than 2 subjects. Analysis of SAEs did not raise concern for any new safety signals.

The most common adverse events in the pooled safety database were headache, nasopharyngitis, upper respiratory tract infection, bronchitis, oropharyngeal pain, and cough. There were no dose-dependent increases from FF 100 mcg to FF 200 mcg with respect to these common AEs. There were no clinically meaningful changes in laboratory parameters, vital signs, and or ECGs.

Two studies provide long-term safety information for FF 100 mcg and 200 mcg. The first, HZA106837, is a 76-week study examining FF 100/25 mcg once daily and FF 100 mcg once daily. The second, HZA106839, is a 52-week study examining FF/VI 100/25 mcg once daily, FF/VI 200/25 mcg once daily, and FP 500 mcg BID. Overall, the long-term safety data was consistent with the safety seen in the clinical development program.

Safety Conclusions

In summary, the safety data for the FF development program in asthma do not reveal any new ICS-related safety concerns. Adverse events were few and generally those observed with similar approved ICS products. The safety of both FF 100 mcg and FF 200 mg is supported.

9. Advisory Committee Meeting

A pulmonary allergy drug advisory committee (PADAC) meeting was neither convened nor required for this submission as the safety and efficacy of an ICS such as FF in the maintenance treatment of asthma is well-described and well-understood.

10. Pediatrics

As a new dosage form (new dose), FF triggered PREA and the subsequent need for a development plan in pediatric patients < 12 years of age. The initial pediatric plan was submitted on July 26, 2013, in advance of the NDA submission, in which the Applicant requested that a deferral be granted for pediatric patients 5-11 years of age and a waiver be granted for patients <5 years of age, (b) (4). The pediatric plan was presented to the Pediatric Review Committee (PeRC) on September 25, 2013. It was found to be acceptable, with a request to include study HZA107118, an HPA axis study. The Applicant included a revised pediatric study plan with the NDA submission. The second submission was reviewed by PeRC on February 12, 2014, and found to be acceptable, with the request to change the reason for waiver from “(b) (4)” to “clinical studies in this population are impractical”.

11. Other Relevant Regulatory Issues

- **Financial Disclosure:** Appropriate financial disclosure information was provided by the Applicant. None of the investigators reported any proprietary interests. Two investigators who participated in multiple covered studies reported significant payments over the threshold of honoraria; however, given the low percentage of overall recruitment for each of these investigators, any potential conflict of interest is not likely to impact study results.
- **DSI audits information:** No DSI audits were conducted nor required of this application.
- **Office of Compliance:** The overall EES conclusion is Acceptable

12. Labeling

The Applicant submitted a proposed label and Patient IFU for FF which contained elements from the label of the recently approved FF-containing product for COPD, Breo Ellipta. The proposed label, carton and container labeling, and Patient IFU have been reviewed by the appropriate disciplines within the Division as well as OPDP, DMPP, OSE, and DMEP.

Labeling edits by the review team revolved around amending the submitted FF label to better describe the efficacy of FF (Section 14) and make the description of the safety of FF (Sections 5 and 6) consistent with the safety labeling of recently approved ICS products indicated for the treatment of patients with asthma. Section 14 has been substantially reorganized and divided into two major sections: Dose Ranging Trials and Confirmatory Trials. Within the confirmatory trial section, studies are grouped by FF dose studied (either 100 mcg or 200 mcg), rather than by patient population and prior asthma treatment.

The FDA-edited labeling has not been conveyed to the Applicant at this time. Final labeling language between the Applicant and the Division is still under discussion at the time of this review.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The recommended regulatory action is Approval for both FF 100 mcg and FF 200 mcg QD in patients 12 years of age and older for the maintenance treatment of asthma, with revisions to proposed labeling.

- **Risk Benefit Assessment**

The overall risk benefit assessment supports the approval of FF. The potential benefit of FF as an anti-inflammatory therapy in patients with asthma 12 years of age and older outweighs any unlikely potential risks such as immunosuppression, adrenal suppression, or effects on growth.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

No additional post-marketing risk management activities are recommended beyond standard pharmacovigilance methods.

- **Recommendation for other Postmarketing Requirements and Commitments**

No additional post-marketing commitments or required studies are recommended beyond the PREA requirements which have been addressed by the Applicant in their pediatric study plan.

- **Recommended Comments to Applicant**

No additional comments are necessary at this time.

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/s/

BANU A KARIMI SHAH
07/23/2014