CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205625
Priority or Standard	Standard
Submit Date(s)	October 22, 2013
Received Date(s)	October 22, 2013
PDUFA Goal Date	August 22, 2014
Division / Office	ODEII/DPARP
Reviewer Name(s)	Tracy Kruzick, MD, MPH
Review Completion Date	July 18, 2014
Established Name	Fluticasone furoate
(Proposed) Trade Name	Arnuity Ellipta
Therapeutic Class	Inhaled Corticosteroid
Applicant	GlaxoSmithKline
Formulation(s)	Orally inhaled
Dosing Regimen	Once daily
Indication(s)	Maintenance treatment of asthma
Intended Population(s)	Asthma 12 years of age and older

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

At the time of this review, the preliminary recommended regulatory action from a clinical perspective for fluticasone furoate (FF) 100 and 200 mcg inhalation powder is Approval. Per my review of the risk benefit assessment, the submitted data support approval of FF at both dose strengths for the maintenance treatment of asthma in patients 12 years of age and older.

1.2 Risk Benefit Assessment

The proposed indication for fluticasone furoate (FF) is the long-term, once-daily maintenance treatment of asthma. To support the proposed indication, the Applicant conducted a large clinical development program, which included three dose-ranging studies (FFA109687, FFA109685, FFA109684) and three confirmatory clinical studies (FFA112059, HZA106827, FFA114496). The 8-week dose ranging studies evaluated eight doses of FF ranging from 25 to 800 mcg once daily. Based on the dose ranging studies, FF 100 mcg and 200 mcg were chosen for evaluation in the confirmatory studies. The confirmatory studies ranged in duration from 12 to 24 weeks, with mean change from baseline in trough FEV1 as the primary efficacy endpoint. Additionally, study HZA106827 had a co-primary endpoint of mean change from baseline in the weighted mean serial FEV1 over the 24 hours post-dose at Week 12.

The benefit FF 100 mcg provides 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.

The benefit FF 200 mcg provides 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, FFA109865 and 109867.

As a class, the risks of inhaled corticosteroids are well-established. The adverse event profile of FF 100 mcg and 200 mcg appears to be similar to that of other approved ICS

products. In summary, the risk benefit assessment of FF 100 and 200 mcg is favorable, and supports approval of these two dose levels for the treatment of asthma.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended at the time of this review.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements or commitments are recommended at the time of this review.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed drug product is a fixed-dose, inhaled corticosteroid (ICS) inhalation dry-powder, administered by a dry-powder inhaler. A single (b) (4) foil blister strip is contained within the inhaler which provides 30 doses. Two doses are being proposed for approval: 100 mcg and 200 mcg, each administered as 1 inhalation daily. The proposed trade name is Arnuity Ellipta®. The Ellipta device has been reviewed in detail as part of NDA 204275 for Breo Ellipta (FF/Vilanterol) for COPD.

The proposed indication is a standard indication for long-term asthma treatment: maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Currently Available Therapies for the Maintenance Treatment of Asthma

Class	Generic Name	Brand Name
Inhaled corticosteroids	Beclomethasone dipropionate HFA	QVAR
	Budesonide DPI/respules	Pulmicort
	Fluticasone propionate HFA, Diskus	Flovent
	Mometasone DPI/HFA	Asmanex
	Ciclesonide HFA	Alvesco
Combination inhaled corticosteroids/long-acting bronchodilator (ICS/LABA)	Budesonide/Formoterol HFA	Symbicort
	Fluticasone/Salmeterol HFA, Diskus	Advair
	Mometasone/Formoterol HFA	Dulera

Table 1. Currently Available Therapies for the Maintenance Treatment of Asthma		
Class	**Generic Name**	**Brand Name**
Immunomodulators	Omalizumab	Xolair (anti-IgE)
Leukotriene modifiers	Montelukast	Singulair
	Zafirlukast	Accolate
	Zileuton	Zyflo
Xanthines	Theophylline	Multiple

2.3 Availability of Proposed Active Ingredient in the United States

Fluticasone furoate was approved on April 27, 2007 as an intranasal formulation for once-daily treatment for topical use in relieving symptoms of seasonal and perennial allergic rhinitis is adults and children (Veramyst®). The approved dose is 110 mcg once daily for patients > 12 years of age and 55 mcg once daily for children 2-11 years of age.

Fluticasone furoate has also been approved as part of a combination product with Vilanterol (LABA) for the once-daily treatment of COPD (Breo Ellipta®), including both maintenance treatment of airflow obstruction and for reducing exacerbations. The dose is 100 mcg daily for adults 18 years of age and older.

2.4 Important Safety Issues with Consideration to Related Drugs

The safety issues related to the use of inhaled corticosteroids are well-characterized in both the clinical literature, and in the prescribing information of FDA-approved products.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Division and GSK have had multiple prior interactions to discuss the proposed FF development program. Table 2 below provides a timeline of regulatory interactions with major discussion points. It also details the pertinent regulatory interactions from the Breo Ellipta® chronic obstructive pulmonary disease (COPD) development program.

Table 2. Regulatory Activity Related to Submission		
Date	**Interaction**	**Highlights**
July 27, 2005	Clinical Hold	• Full clinical hold due to findings of macrophage accumulation
October 26, 2006	Clinical Hold Release	• Safe-to-proceed
March 31, 2009	EOP2 (COPD)	• Division noted the need to directly compare daily to twice daily

Table 2. Regulatory Activity Related to Submission		
Date	**Interaction**	**Highlights**
		regimens to establish the appropriate dosing frequency
June 17, 2009	EOP2: (COPD)	• Division agreed that QD and BID FF dosing regimens produced similar efficacy results and that FF 50, 100, and 200 mcg were reasonable doses to pursue in the phase 3 COPD program
March 16, 2011	EOP2	• Division noted that use of the double-strip data to support the single-strip device would be a review issue • Division noted that the 200 mcg dose would need a numerical dose response in the primary endpoint as well as support from other efficacy measures
May 11, 2012	Type C	• Division recommended use of FEV1 as the primary endpoint in children as well as adults
October 11, 2012	Type C	• Division noted that study FFA115440 that demonstrated that the single-strip device delivered 20% more drug to the lung than the double-strip device would be a review issue • Division recommend against pooling the single-strip and double-strip data for the safety database
February 11, 2013	Pre-NDA	• Division agreed with carrying forward the 100 and 200 mcg doses for approval as the 50 mcg studies did not replicate • Division noted that the HPA axis data from the FF/VI program is likely acceptable for this application, although this would be a review issue
EOP2 = end of phase 2, IND = investigational new drug, NDA = new drug application		

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission is appropriately indexed and complete to permit review. No sites for an Office of Scientific Investigations (OSI) were chosen for an investigation.

3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in each complete study report.

3.3 Financial Disclosures

GSK provided financial disclosure information for trials covered by the Final Rule on Financial Disclosure by Clinical Investigators which included the following studies:

- HZA106851
- FFA115283
- FFA112202
- FFA106783
- FFA20001
- FFA114496
- FFA115285
- HZA106839
- FFA109684
- FFA109687
- FFA112059
- HZA106827
- HZA106829
- HZA106837

None of the investigators reported any proprietary interest. Four Investigators, (b) (6) reported significant payments of other sort. Two of these investigators, (b) (6), participated in multiple covered studies, and both reported significant payments over the threshold for honoraria. Given the low percentage of overall recruitment for each of these investigators, any potential conflict of interest would not be likely to impact the study results.

GSK failed to obtain follow-up financial disclosure information from one principal investigator, (b) (6), at study site 063804 who refused to provide the financial disclosure form after the site had been closed by GSK.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The drug product is a plastic inhaler with a light grey body, an orange mouthpiece cover and a dose counter, packed in a foil tray which contains a desiccant packet. The tray is sealed with a peelable lid. The inhaler contains one strip of either 30 (commercial product) or 14 (sample product) regularly distributed blisters containing a white powder. The strip contains either 100 or 200 mcg active drug with (b) (4) mg lactose monohydrate.

An approval is recommended from the CMC team. From a CMC perspective, there are no outstanding issues.

4.2 Clinical Microbiology

The drug product is a dry powder for inhalation, and the Sponsor proposed a two-tiered microbial limits testing regimen. An approval of this application is recommended from the product quality microbiology team. Additional details can be found in Dr. Stephen Langille's microbiology review dated June 18, 2014.

4.3 Preclinical Pharmacology/Toxicology

The recommendation from the preclinical review is Approval. Details can be found in the nonclinical review. All FF non clinical data were previously submitted to and reviewed in NDA 22-051 (Veramyst nasal spray; approved April 27, 2007). Per the nonclinical review, FF possesses a toxicity profile typical of inhaled corticosteroids and the drug is non-genotoxic, non-carcinogenic and non-teratogenic.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Fluticasone furoate is an inhaled corticosteroid that acts as an anti-inflammatory. 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. The use of ICS in asthma is considered the most effective treatment for maintenance control.

4.4.2 Pharmacodynamics

Three dose selection trials, FFA 109687, 109685, and 109684, are depicted in Table 5 with the results in Figure 1. From these trials, the doses of 50, 100, and 200 mcg were carried into Phase 3 development. Once versus twice daily dosing was studied in trial FFA11202. These trials were previously reviewed in detail by Dr. Sofia Chaudhry in the review of the Breo Ellipta (NDA 204275) application for COPD, and are therefore briefly summarized here.

Trial FFA109687
Trial FFA109687 was a randomized, double-blind, double-dummy, placebo-controlled, parallel-group, dose-ranging trial evaluating four doses of FF (25, 50, 100, and 200 mcg) once daily, FP (fluticasone propionate) 100 mcg twice-daily, and placebo. A total of 601 adult and adolescent patients with persistent asthma, uncontrolled on non-ICS

maintenance therapy, received treatment for eight weeks. The primary endpoint was a change from baseline in trough FEV1 at Week 8. All doses except the 25 mcg dose demonstrated a statistically significant benefit over placebo.

Trial FFA109685

Trial FFA109685 was similarly designed to FFA109687; however 109685 evaluated higher doses of FF (100, 200, 300, and 400 mcg). Subsequently, the FP comparator arm was 250 mcg BID, and the patient population was controlled on low-dose ICS. A total of 615 patients uncontrolled on low-dose ICS were randomized, and the primary endpoint was change in baseline FEV1 at week 8. All doses showed a statistically significant benefit over placebo, however there was little dose response for doses above FF 200 mcg (see Figure 1).

Trial FFA109684

Trial FFA109684 was similarly designed and evaluated even higher dosage strengths of FF (200, 400, 600 and 800 mcg). Subsequently, the FP comparator was 500 mcg BID. A total of 622 subjects with asthma uncontrolled on medium-dose ICS were randomized; the patient population was more severe, being uncontrolled on medium-dose ICS. A total of 622 subjects were randomized, and the primary endpoint was change in baseline FEV1 at week 8. All doses showed a statistically significant benefit over placebo as shown in Table 3 below.

Table 3. Results of Dose-Ranging Trials

		FF once daily								FP twice daily		
	PBO	25	50	100	200	300	400	600	800	100	250	500
Week 8 Change from Baseline Trough FEV1												
Trial 109687												
N	93	94	97	109	94					101		
LS[1]		0.101	0.129	0.204	0.23					0.106		
P value		0.095	0.033	<0.001	<0.001					0.074		
Trial 109685												
N	106			102	101	102			97		99	
LS[1]				0.207	0.238	0.293			0.279		0.225	
P value				< 0.001	< 0.001	< 0.001			< 0.001		< 0.001	
Trial 109684												

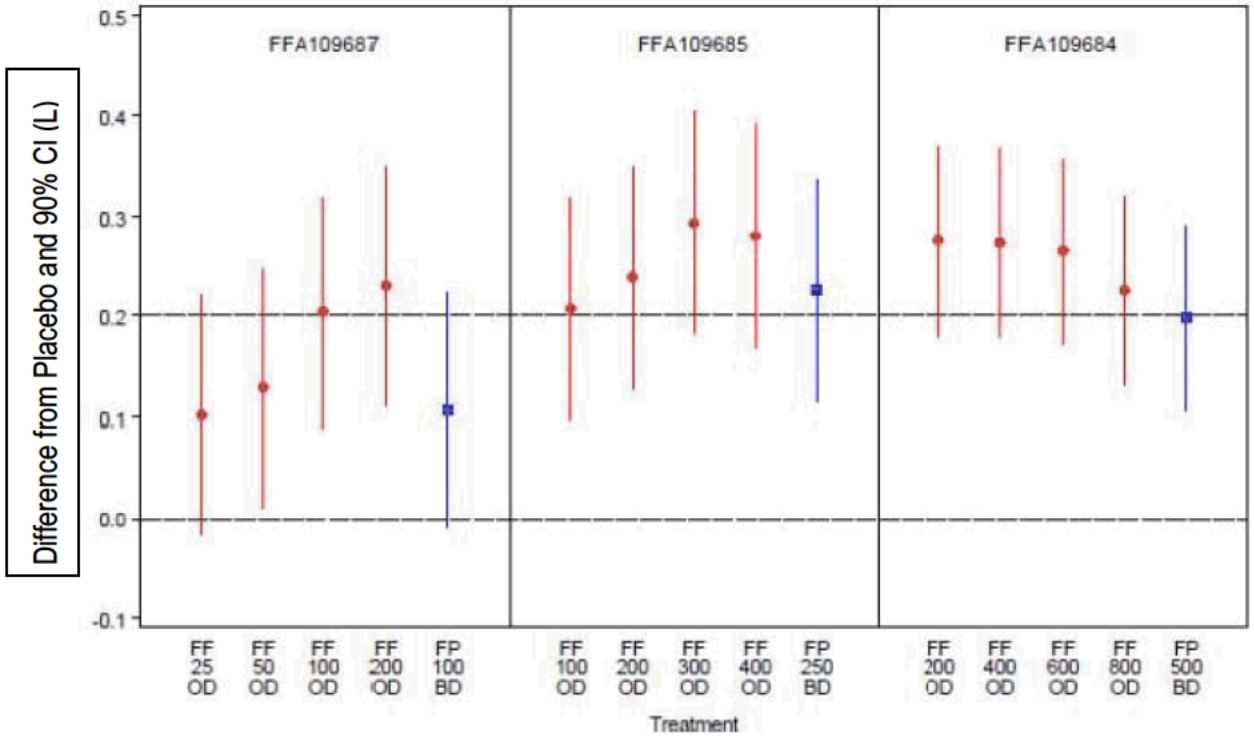
Table 3. Results of Dose-Ranging Trials

		FF once daily								FP twice daily		
	PBO	25	50	100	200	300	400	600	800	100	250	500
Week 8 Change from Baseline Trough FEV1												
N	103				98		101	107	102			107
LS†					0.275		0.272	0.264	0.225			0.198
P value					<0.001		<0.001	<0.001	<0.001			<0.001

† LS Mean Change from placebo (L)
Source: CSR 109687 Table 11,109685 Table 11, 109684 Table11
FP = fluticasone propionate, PBO = placebo,

A dose effect was seen; however, benefit did not increase with doses over 200 mcg as shown in Figure 1.

Figure 1. Fluticasone Furoate Dose Ranging Trials in Asthma



Source: Clinical Overview, Figure 1

Trial FFA11202

Trial FFA11202 was a multicenter, randomized, double-blind, cross-over trial evaluating the non-inferiority of once daily versus twice daily dosing of FF 100 mcg in 190 adult and adolescent patients 12 years of age and older. Additional treatment arms included FP 200 mcg in the evening, FP 100 mcg twice daily, and placebo. Subjects entered a 2 week run-in period followed by randomization to 1 of 12 sequences: 6 cross-over sequences including FF 200 daily, FF 100 twice daily, and placebo OR FP 200 once daily, FP 100 twice daily, and placebo. Each treatment period was separated by a 14-day washout period. The primary efficacy endpoint was trough FEV1 at the end of each 28-day treatment period. A similar treatment effect was noted for the once daily dosing and the twice daily dosing (p=0.641); these results are shown in Table 4. Thus, the doses of 50, 100, and 200 mcg once daily were carried forward into phase 3 development. The Sponsor failed to establish replicate efficacy of FF 50 mcg in the confirmatory trials, and thus is not pursuing registration of this dose.

Table 4. FFA112202 Dose Regimen Trial Results

	FF 200 QD N=140	FF 100 BID N = 142	FP 200 QD N = 42	FP 100 BID N = 43
Trough FEV1: LS mean change from baseline at Day 28				
LS mean change from placebo (L)	0.108	0.098	0.087	0.132
P value	<0.001	<0.001	<0.001	<0.001
LS mean change from FF 100 BID (L)	0.011			
P value	0.641			

Source: CSR FFA112202 Table 12
BID = twice a day, FP = fluticasone propionate, QD = once a day

4.4.3 Pharmacokinetics

The recommendation from the clinical pharmacology team is Approval. Details can be found in the clinical pharmacology review. Systemic exposure for FF increased in proportion to the dose in the dose range of 200-800 mcg for FF ($AUC_{0-\infty}$, C_{max}). Tmax was reached by 0.5-1 hours, and steady state was reached by the 6^{th} day. FF has high in-vitro plasma protein binding, which is independent of concentration with average values of >99.6%. FF is a substrate of CYP3A4 and P-glycoprotein (P-gp), and based on in vitro studies, the potential for FF to inhibit and induce metabolic enzymes is negligible at low inhalation doses. In humans, FF is eliminated primarily in feces, and the apparent terminal phase elimination half-life of FF following oral inhalation administration was on average 23.7 hours.

There is no effect of age, weight, BMI, or gender on the exposure of systemic FF in subjects with asthma. Systemic exposure of FF for East Asian, Japanese and South Asian subjects were on average 23% to 49% higher compared with white Caucasian subjects.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The studies relevant to clinical decision-making for this application are listed in Table 5 and Table 6 below. Table 5 provides an overview of the dose-ranging trials, which had been reviewed in detail as part of the Breo Ellipta application (NDA 204275). The results of these trials are therefore briefly summarized in Section 4.4.2. Table 6 lists the confirmatory trials.

Table 5. Dose Ranging Trials in Asthma

Trial (Dates)	Design	Population (number randomized)	Treatment arms	Duration (Weeks)	Primary Endpoint	Sites (Countries)
FFA 109687 *(9/12/11-10/3/12)*	R, PC, DB, PG	Asthma (601) Uncontrolled without ICS	FF 25 QD FF 50 QD FF 100 QD FF 200 QD FP 100 BID Placebo BID	8	Trough FEV1	*107 (US, Canada, Mexico, Korea, Europe, Peru, Philippines)*
FFA 109685 *(12/20/2007-11/24/2008)*	R, PC, DB, PG	Asthma (615) Uncontrolled on low dose ICS	FF 100 QD FF 200 QD FF 300 QD FF 400 QD FP 250 BID Placebo BID	8	Trough FEV1	*98 (US, Canada, Mexico, Europe Korea, Philippines)*
FFA 109684 *(12/20/2007-9/20/2008)*	R, PC, DB, PG	Asthma (622) Uncontrolled on med dose ICS	FF 200 QD FF 400 QD FF 600 QD FF 800 QD FP 500 BID Placebo	8	Trough FEV1	*94 (US, Canada, Mexico, Europe, Australia, S. Africa, Thailand)*
FFA 112202 *(10/9/2008-3/17/2009)*	R, DB, PC, XO	Asthma (190) Uncontrolled without ICS	1st group: FF 200 QD FF 100 BID Placebo BID 2nd group: FP 100 BID FP 200 QD Placebo BID	4	Trough FEV1	*16 (US)*

Source: Module 5.2, Tabular listing of all studies and individual CSR
R = randomized, DB = double-blind, PC = placebo controlled, PG=parallel group, XO=cross-over; S=South, US=United States

Table 6. Confirmatory Trials in Asthma

Trial *(dates)*	Design	Population	Weeks	Treatment Arms	N	Primary Endpoint	Sites *Countries (n)*
FFA 112059 *(6/30/10-1/16/12)*	R, DB, DD, PC, PG	Asthma Low-mid ICS	24	FF 100 QD FP 250 BID Placebo Single-strip	114 114 115	Trough FEV1	*US (197), Poland (61), Romania (41), Germany (24), Belgium (20)*
HZA 106827 *(8/20/2010-10/19/2011)*	R, DB, PG, PC	Asthma Low-mid ICS	12	FF/VI 100/25 QD FF 100 QD Placebo Double-strip	201 205 203	Trough FEV1 0-24 hour weighted mean FEV1	*US (196), Poland (124), Romania (89), Ukraine (83), Germany (67), Japan (50)*
HZA 106837 *(2/22/10-9/15/11)*	R, DB, PG	Asthma Low-high ICS	Up to 76	FF/VI 100/25 QD FF 100 QD Double-strip	1009 1010	Time to first severe exacerbation	*US (373), Russia (300), Mexico (233), Ukraine (231), German (179), Argentina (159), Poland (156), Philippines (154), Romania (153), Japan (62), Australia (19)*
FFA 114496 *(9/12/11-10/3/12)*	R, DB, PG	Asthma Mid-high ICS	24	FF 100 QD FF 200 QD Single-strip	119 119	Trough FEV1	*US (55), Argentina (83), Russia (38), Mexico (23), France (1), Chile (38)*
HZA 106829 *(6/10/10-10/18/11)*	R, DB, DD, PG, AC	Asthma Mid-high ICS	24	FF/VI 200/25 QD FF 200 QD FP 500 BID Double-strip	197 194 195	Trough FEV1 0-24 hour weighted mean FEV1	*Russia (163), US (143), Romania (117), Germany (66), Poland (61), Japan (36)*

Source: Module 5.2, Tabular listing of all studies and individual CSR
R = randomized, DB = double-blind, DD=double dummy, PC = placebo controlled, AC = active control, PG=parallel group; US=United States

The pooled safety database includes data from ten phase 2 and 3 parallel group studies; trial HZA106839 is not part of the pooled safety database, but is included in this review as it supports the long-term safety of FF. The safety review strategy and results are provided in Section 7. Table 7 summarizes the trials comprising the safety database.

Table 7. Safety Database

Trial (Device Type)	Design	Weeks	Population	Treatment Arms	N
8-week trials					
FFA109687 (DS)	R, DB, DD, PC, PG	8	Asthma FEV1 am: 40-85% or pm: 40-90% Uncontrolled without ICS	FF 25 QD FF 50 QD FF 100 QD FF 200 QD FP 100 BID Placebo	97 100 110 95 102 94
FFA109685 (DS)	R, DB, DD, PC, PG	8	Asthma FEV1 am: 40-85% or pm: 40-90% Uncontrolled on low dose ICS	FF 100 QD FF 200 QD FF 300 QD FF 400 QD FP 250 BID Placebo BID	105 101 103 99 100 107
FFA109684 (DS)	R, PC, DB, PG	8	Asthma FEV1 am: 40-85% or pm: 40-90% Uncontrolled on med dose ICS	FF 200 QD FF 400 QD FF 600 QD FF 800 QD FP 500 BID Placebo	99 101 107 102 110 103
12-week Trials					
FFA115283 (SS)	R, DB, PC, PG	12	Asthma FEV1 $\geq$ 60% No ICS	FF 50 QD Placebo	121 121
HZA106827 (DS)	R, DB, PG, PC	12	Asthma	FF/VI 100/25 QD FF 100 QD	201 205

Table 7. Safety Database

Trial (Device Type)	Design	Weeks	Population	Treatment Arms	N
			FEV1 40-90% Low-mid ICS	Placebo	203
24-week trials					
FFA115285 (SS)	R, DB, DD, PC, AC, PG	24	Asthma FEV1 ≥ 60% Not on ICS	FF 50 QD FP 100 BID Placebo	117 115 115
FFA114496 (SS)	R, DB, PG	24	Asthma FEV1 40-90% Mid-high ICS	FF 100 QD FF 200 QD	119 119
FFA112059 (SS)	R, DB, DD, PC, PG	24	Asthma FEV1 40-90% Low-mid ICS	FF 100 QD FP 250 BID Placebo	114 114 115
HZA106829 (DS)	R, DB, DD, PG, AC	24	Asthma FEV1 40-90% Mid-high ICS	FF/VI 200/25 QD FF 200 QD FP 500 BID	197 194 195
52-week trials					
HZA106839 (DS)*	R, DB, DD, AC, PG	52	Asthma FEV1≥50% Mid-high ICS	FF/VI 100/25 QD FF/VI 200/25 QD FP 500 BID	201 202 100
Up to 76-week trials					
HZA106837 (DS)	R, DB, PG	76	Asthma FEV1 50-90% Low-high ICS	FF/VI 100/25 QD FF 100 QD	1009 1010

Source: Module 5.2, Tabular listing of all clinical studies and individual CSR
R = randomized, DB = double-blind, DD=double dummy, PC = placebo controlled; AC = active control, PG=parallel group; SS=single-strip, DS=double-strip
Study HZA106839 was not pooled into the database by the Sponsor.

5.2 Review Strategy

This clinical review will focus on those studies which are clinically relevant to demonstration of the efficacy and safety of FF 100 mcg and 200 mcg. The dose-ranging studies have been previously reviewed in detail as part of the Breo Ellipta application for COPD (NDA 204275), and are summarized in Section 4.4.2.

The protocols of the confirmatory trials are described in Section 5.3. The efficacy and safety results of the confirmatory trials are reviewed in Section 6 and Section 7, respectively. Any supportive efficacy and safety data generated from other trials are reviewed in the applicable efficacy or safety section.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Clinical Studies in Support of FF 100 mcg

5.3.1.1 Study FFA112059

Administrative Information:

- Study Title: A randomized, double-blind, double-dummy, placebo controlled (with rescue medication), multicenter study to evaluate the efficacy and safety of fluticasone furoate inhalation powder in the treatment of persistent asthma in adults and adolescents
- Study Dates: 6/30/10-1/16/12
- Study Sites: US (197), Poland (61), Romania (41), Germany (24), Belgium (20)
- Study Report Date: April 2012

Objectives/Rationale

Primary:

- Efficacy and safety of FF 100 mcg administered once daily in the evening in adolescent and adult subjects 12 years of age and older with persistent bronchial asthma

Study Design and Conduct

Overview:
FFA112059 was a 24-week multicenter, randomized, placebo controlled (with rescue medication), double-blind, double-dummy, parallel group study. Subjects who met eligibility criteria entered in a 4-week run-in period while remaining on their ICS medication and receiving albuterol/salmeterol for rescue. During the study, subjects maintained an electronic diary for twice daily PEF, asthma symptom score, and rescue medicine use. Subjects received a telephone call after visit 1 to ensure compliance, and subjects who were found to be compliant entered into visit 2. At visit 2, subjects were

randomly assigned to receive one of three double-blind treatments in a 1:1:1 ratio: FF100 mcg once daily in the evening/placebo diskus twice daily, FP 250 mcg twice daily/placebo NDPI once daily in the evening, placebo diskus twice daily/placebo NDPI once daily in the evening. Subjects then attended 7 on-treatment visits at Visits 3, 4, 5, 6, 7, 8, and 9 (weeks 2,4, 8, 12, 16, 20, and 24, respectively) conducted in the evening. Visit 10 was conducted one week after completing study medication. Table 8 depicts the schedule of assessments for trial FFA 112059.

Table 8. Study Assessments: Study FFA112059

Visit	**1**	**Phone contact**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Early WD**	**10 (f/u)**
Week	**-4**	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**		**25**
Day	**-28**	**-14**	**0**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		**+7**
Written Informed Consent	X											
Pharmacogenetics Consent	X											
Subject Demography	X											
Medical History	X											
Asthma History	X											
Physical Exam	X									X	X	
Inclusion/Exclusion Criteria	X		X									
Efficacy Assessments												
Spirometry Pulmonary Function	X		X	X	X	X	X	X	X	X	X	
FEV_1 Reversibility	X											
Issue Subject Diary	X											
Asthma Control Test			X	X			X			X	X	
Asthma Quality of Life Questionnaire			X				X			X	X	
Global Asthma Control					X		X			X	X	
Unscheduled healthcare contacts				X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	
Subject Diary Review & Upload			X	X	X	X	X	X	X	X	X	
Safety Assessments												
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X[1]
Oropharyngeal Examination	X		X	X	X	X	X	X	X	X	X	

Table 8. Study Assessments: Study FFA112059

Visit	1	Phone contact	2	3	4	5	6	7	8	9	Early WD	10 (f/u)
Week	**-4**	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**		**25**
Day	**-28**	**-14**	**0**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		**+7**
Vital Signs	X		X	X	X	X	X	X	X	X	X	
Adverse Events			X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X[2]	X[2]	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments												
Hematology	X											
Chemistry	X											
Liver Safety Assessment	X						X			X	X	
HBsAg and Hepatitis C Antibody Screening	X											
Pharmacogenetics Sampling (1 visit only)			X[3]									
24-hour Urine Cortisol Supplies Dispensed	X								X			
24-hour Urinary Cortisol Collection			X							X		
Serum Pregnancy Test	X									X	X	
Urine Pregnancy Test			X				X					X[4]
Dispense Home Urine Pregnancy Testing Kit										X	X[5]	

Source CSR 112059 Table 38
1.Concomitant medication details collected for adverse events only between end of treatment and follow up contact
2.SAEs related to study participation that occurred during run-in were to be recorded in the eCRF
3.The pharmacogenetics (PGx) sample could be collected at any one visit after the PGx consent had been signed and the subject had been randomized
4.Subjects were instructed to use the Urine Pregnancy Test 5 days after the last dose of IP. Subjects were asked to provide the results at the Follow-up contact (Visit 10)
5.Subjects were instructed to use the Urine Pregnancy Test 5 days after the last dose of IP. Subjects were contacted to provide the test results
6.If not performed at End of Treatment Visit (Visit 9)
7.To be completed associated with a severe exacerbation and other asthma related healthcare

Study Population

Inclusion Criteria

- Male or female subjects ≥ 12 years of age at visit 1
- Asthma diagnosis per NIH definition for at least 12 weeks with
    - FEV1 40-90% at visit 1 based on NHANES III
    - Post SABA ≥12% and ≥200 mL reversibility of FEV1
    - On a stable dose of ICS for at least 4 weeks prior to visit 1

Exclusion Criteria

- History of life-threatening asthma in the past 10 years
- Unresolved respiratory infection in the past 4 weeks prior to visit 1 that led to a change in asthma medication or status
- Asthma exacerbation requiring oral corticosteroids or overnight hospitalization within 6 months prior to visit 1
- Concurrent respiratory disease or any clinically significant uncontrolled condition
- No visual evidence of candidiasis at visit 1
- Could not have used any investigational drug within 30 days prior to visit 1, or within five half-lives of the prior investigational drug
- Could not have used inhaled tobacco products in the 3 months prior to screening or have historical use of ≥10-pack years
- Severe milk protein allergy or specific drug allergies, or used prohibited medications as listed below within the specified time periods
    - Within 12 weeks of visit 1 and during the study:
        - Systemic steroids
        - Xolair
    - Within 4 weeks of visit 1 and during the study:
        - Inhaled, oral, or transdermal long-acting beta 2-agonists
        - Combination therapy containing long-acting beta 2-agonists and ICS for asthma
    - Following the morning of visit 1 and during the study:
        - Theophyllines
        - Anti-leukotrienes including suppression of leukotriene production and antagonists
        - Anticholinergics
        - Ketotifen
        - Nedocromil sodium
        - Sodium cromoglycate
    - Up to and including the morning of randomization (visit 2):

        - Inhaled corticosteroids: Subjects must have been maintained on a stable dose for 4 weeks prior to visit 1 and throughout the run-in period
    - Subjects could not concurrently use any other prescription or over-the-counter medication which may affect the course of asthma, or affect ICS metabolism (visit 1 to visit 9 inclusive), such as cytochrome P450 3A4 inhibitors or β-adrenergic blocking agents
- Not have been previously treated with FF or FF/Vilanterol
- No subject was permitted to perform night shift work for 1 week prior to visit 1 until completion of the study treatment period

Randomization Criteria

At the end of the run-in period (visit 2), a subject was eligible to enter the treatment period of the study if they met the following criteria:

- Evening pre-dose FEV1 between 40%-90% of their predicted normal
- Symptoms of asthma (a score of ≥1 on the daytime or nighttime asthma symptom scores) and/or daily albuterol/salbutamol on at least 4 of the last 7 consecutive days of the run-in period
- Compliance with baseline medication on at least 4 of the last 7 consecutive days of run-in
- Compliance with completion of the daily diary

Subjects were not eligible for randomization to double-blind treatment if they met any of the following criteria:

- Evidence of clinically significant abnormal laboratory tests during visit 1 which were still abnormal upon repeat testing
- Changes in asthma medication (excluding albuterol/salbutamol inhalation aerosol provided at visit 1)
- Upper or lower respiratory tract infection that led to a change in asthma management or, in the opinion of the investigator, was expected to affect the subject's asthma status
- Evidence of a severe exacerbation, defined as 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
- Clinical visual evidence of oropharyngeal candidiasis

Withdrawal Criteria

Reasons for withdrawal included:

- Subject experienced an adverse event
- Subject was lost to follow-up
- Subject experienced a protocol violation
- Subject experienced lack of efficacy
- The Sponsor terminated the study

- Non-compliance
- Pregnancy
- Abnormal liver function test
- Abnormal laboratory results

A subject who met any of the following criteria was also to be withdrawn from the study:

- FEV1 below the FEV1 stability limit value (calculated as best pre-salbutamol/albuterol FEV1 at visit 2 x 80%)
- During the 7 days immediately preceding any visit, the subject experienced either at least 4 days in which the PEF fell below the PEF stability limit (calculated as the mean morning PEF from the available 7 days preceding Visit 2 x 80%) or at least 3 days in which ≥12 inhalations/day of albuterol/salbutamol were used
- Subjects who experienced a protocol-defined severe exacerbation
- Clinical asthma worsening, which in the opinion of the investigator required additional asthma treatment other than study medication or study supplied albuterol/salbutamol
- When liver chemistry threshold criteria were met
    - ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
    - ALT ≥8xULN
    - ALT ≥5xULN, but <8xULN that persists for ≥2 weeks
    - ALT ≥3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia
    - ALT ≥5xULN, but <8xULN and cannot be monitored weekly for >2 weeks

Permitted medications

- SABA
- Stable dose, for at least 4 weeks prior to visit 1, of an ICS
- Decongestants
- Intranasal corticosteroids
- Immunotherapy was permitted provided it was initiated 4 weeks prior to visit 1 and the subject remained in the maintenance phase for the duration of the study
- Topical corticosteroids (≤1% hydrocortisone cream)
- Non-corticosteroid containing creams
- Short-acting and long-acting antihistamines
- Antihistamine eye drops

Study Treatments

Treatment groups were as follows:

- FF 100 mcg NDPI once daily in the evening/placebo diskus twice daily
- FP 250 mcg twice daily/placebo NDPI once daily in the evening

- Placebo diskus twice daily/placebo NDPI once daily in the evening

All treatments were double-blinded. The FF 100 mcg NDPI single-strip formulation used was the to-be-marketed product. For the placebo, the NDPI and diskus contained the same foil packs with the active drug moieties removed and all other excipients remaining the same.

Compliance

Compliance was assessed by reviewing the dose counter on the NDPI and the diskus, and subjects who were not compliant were counselled on appropriate dosing of study drug.

Efficacy Endpoints

Primary Endpoint

- Mean change from baseline in clinic visit trough evening (between 5 pm and 1 pm, pre-bronchodilator and pre-dose) FEV1 at the end of the 24-week treatment period

Nominated Powered Secondary Endpoint

- Mean change from baseline in the percentage of rescue-free 24-hour periods during the 24-week treatment period

Secondary Endpoints

- Mean change from baseline in daily trough (pre-dose and pre-rescue bronchodilator)
- PM PEF averaged over the 24-week treatment period
- Mean change from baseline in daily AM PEF averaged over the 24-week treatment period
- Mean change from baseline in the percentage of symptom-free 24-hour periods during the 24-week treatment period
- Change from baseline in total AQLQ (+12) score at the end of week 12 and to the end of the 24-week treatment period

Other Endpoints

- Change in Asthma Control Test (ACT) score from baseline (visit 2), at the end of week 12 (visit 6) and at the end of the 24-week treatment period (visit 9)
- The number of withdrawals due to lack of efficacy during the 24-week treatment period
- Global assessment of change at the end of week 4 (visit 4), week 12 (visit 6), and 24 weeks' of treatment (visit 9)

- Unscheduled healthcare contacts/resource utilization (for severe asthma exacerbations and other asthma-related health care)

Safety Endpoints

- Incidence of AEs
- Incidence of severe exacerbations
- Incidence of oral and oropharyngeal candidiasis
- Liver function safety assessments at screening (visit 1), week 12 (visit 6), and at week 24 (visit 9) or early withdrawal
- 24-hour urine cortisol excretion collected for assessment at visit 2 and at the end of week 24 (visit 9)

Statistical Plan

The Sponsor planned to randomize a total of 330 subjects into this study in a ratio of 1:1:1 giving 110 randomized subjects per arm. It was assumed that 5% of subjects would withdraw within the first 2 weeks and not contribute to the analysis which would yield 104 evaluable subjects per arm.

The overall power of the study to detect treatment differences across the specified treatment comparison of FF versus placebo for the primary endpoint and the nominated powered secondary endpoint was 90%.

The primary population for all analyses of efficacy measures, excluding urinary cortisol analyses, was the intent-to-treat (ITT) population. This population comprised all subjects randomized to treatment who received at least one dose of study medication.

For the analysis of the primary treatment comparison of change from baseline in clinic visit trough FEV1 at the end of the 24-week treatment period between FF 100 once daily versus placebo was derived using last observation carried forward (LOCF). Statistical analysis was performed using Analysis of Covariance (ANCOVA) with effects due to baseline FEV1, region, sex, age, and treatment group. The primary treatment comparison was also analyzed using a mixed model repeated measures model (MMRM).

Protocol Amendment

A single protocol amendment was made effective date January 28, 2011 and applied to all sites except those in Belgium. The amendment broadened the entry criteria and allowed for re-screening of individuals who previously did not qualify:

- FEV1 entry criteria changed from 60% to 90% of their predicted normal to 40% to 90% of their predicted normal

- Changing the requirement for subjects to be on ICS medication for 12 weeks prior to visit 1 and on a stable dose for 4 weeks prior to visit 1 to subjects needing to have been on a stable dose for at least 4 weeks prior to visit 1
- Allowing inclusion of subjects who were currently symptomatic on mid-dose ICS

5.3.1.2 Study HZA106827

Administrative Information:

- Study Title: A randomized, double-blind, placebo-controlled (with rescue medication), parallel group multi-center study of fluticasone furoate/GW642444 inhalation powder and fluticasone furoate Inhalation powder alone in the treatment of persistent asthma in adults and adolescents
- Study Dates: 8/20/2010-10/19/2011
- Study Sites: US (196), Poland (124), Romania (89), Ukraine (83), Germany (67), Japan (50)
- Study Report Date: April 2012

Objectives/Rationale

Primary:

- To compare the efficacy and safety of FF/VI inhalation powder 100/25 mcg and FF 100 mcg both administered once-daily in the evening in adolescent and adult subjects, 12 years of age and older, with persistent bronchial asthma over a 12-week treatment period

Reviewer's comment: This study was part of the FF/VI development program, but because it also contains a placebo treatment group, was used by the sponsor to support the efficacy/safety of FF 100 mcg vs. placebo.

Study Design and Conduct

Overview:
This was a 12-week, multi-center, randomized, double-blind, placebo-controlled (with rescue medication), parallel group study. Subjects meeting all the eligibility criteria during visit 1 entered a four-week run-in period. At visit 3 (end of run-in), subjects were stratified according to their concurrent asthma medication (ICS or ICS/LABA). Once stratified, subjects were randomized to one of the following treatments via the NDPI for 12 weeks:

- FF/VI (100 mcg/25 mcg) once daily in the evening
- FF (100 mcg) once daily in the evening
- Placebo once daily in the evening

Randomized subjects attended four on-treatment visits at visits 4, 5, 6 and 7 (weeks 2, 4, 8 and 12, respectively). A follow-up clinic visit (visit 8) was performed 2 weeks after completing study medication. Subjects participated in the study for up to a maximum of 18 weeks from screening to follow-up. The schedule of assessments is shown in Table 9 below.

Table 9. Study Assessments: Study HZA106827

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**EW**	**8**
Week	**-4**	**-2**	**0**	**2**	**4**	**8**	**12**		
Day	**-28**	**-14**	**0**	**14**	**28**	**56**	**84**		**14 post V7 or EW**
Written Informed Consent	X								
Subject Demography	X								
Medical History	X								
Asthma History	X								
Therapy History	X								
Physical Exam	X						X	X	
Inclusion/ Exclusion Criteria	X		X						
Efficacy Assessments									
Spirometry Pulmonary Function	X		X	X	X	X	X	X	
Reversibility	X								
Serial FEV_1 (0-24h) in subset of subjects			X[1]				X[1]		
Issue Subject Diaries	X								
Subject Diary Review & Upload		X	X	X	X	X	X	X	
Safety Assessments									
Concomitant Medication	X	X	X	X	X	X	X	X	X[2]
OP Examination	X		X	X	X	X	X	X	
12-lead ECG		X	X[3]				X[3]	X	
Vital Signs	X		X	X	X	X	X	X	

Table 9. Study Assessments: Study HZA106827									
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**EW**	**8**
Week	**-4**	**-2**	**0**	**2**	**4**	**8**	**12**		
Day	**-28**	**-14**	**0**	**14**	**28**	**56**	**84**		**14 post V7 or EW**
Adverse Events			X	X	X	X	X	X	X
Serious Adverse Events	X[5]	X[5]	X[5]	X	X	X	X	X	X
Laboratory Assessments									
Hematology	X								
Chemistry (includes liver safety testing)	X						X	X	
Glucose and Potassium in subset of subjects			X[4]				X[4]		
PGx Sampling (one visit only)				X[7]					
Serum pregnancy test	X						X	X	
Urine Pregnancy test			X						X
24-hr Urine Collection Supplies dispensed		X				X			
24-hr Urine collection			X				X		
HBsAg and hepatitis C antibody screening	X								
PK sampling						X[8]	X[8]		
Questionnaires									
ACT	X		X				X	X	
AQLQ (+12)			X				X	X	
Global Change					X	X	X	X	
Inhaler use assessment			X	X	X				
Ease of use questions for					X				

Table 9. Study Assessments: Study HZA106827

Visit	1	2	3	4	5	6	7	EW	8
Week	-4	-2	0	2	4	8	12		
Day	-28	-14	0	14	28	56	84		14 post V7 or EW
inhaler									
Unscheduled Healthcare Contact			X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	

Source CSR 106827 Table 3
1.In addition to pre-dose assessment (within 30 minutes prior to dosing at Visit 3 and within 5 minutes prior to dosing at Visit 7), serial FEV_1 measurements were taken at 5, 15,30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23 and 24 hours post-dose.
2.Concomitant medication details collected for adverse events only between end of treatment and Follow-up Visit.
3.ECGs: Pre-dose ECGs at Visit 2, Visit 3, Visit 7 and Early Withdrawal in all subjects. In addition post-dose (5-20minutes for VI) assessments at Visit 3 (Day 0) and Visit 7 (end of 12 weeks of treatment) in subset of subjects NOT performing Serial Lung Function measurements.
4.Potassium and Glucose: Pre-dose in all subjects at Visit 3 and Visit 7. In addition post dose (5-20 minutes) at Visit 3 (Day 0) and Visit 7 (end of 12 weeks of treatment) in subset of subjects performing Serial Lung Function measurements. Subjects were not to be fasted for ≥4hours prior to blood draw.
5.SAEs related to study participation that occurred during Run-in were recorded in the eCRF.
6.If not performed at End of Treatment (Visit 7 or Early Withdrawal visit)
7.The PGx sample could be collected at any one visit after the PGx consent had been signed and the subject had been randomized.
8.Upon arrival at the clinic, a 4 mL blood sample was collected and the subjects administered their evening dose of study medication after all pre-dose assessments were completed. Prior to leaving the clinic, two more 4mL blood samples were collected from the subject between 5-15 minutes post-dose and between 1 – 1.5 hours post dose.
9.To be completed if associated with a severe asthma exacerbation and for any other asthma-related health care utilization.

Study Population

Inclusion Criteria
Inclusion criteria were similar to Study FFA112059 with the exception that subjects could also be on a low dose ICS/LABA combination product for at least 4 weeks prior to visit 1.

Exclusion Criteria
Exclusion criteria were similar to Study FFA112059 with the exception that an asthma exacerbation could not have occurred within 3, not 6, months prior to visit 1.

Prohibited Medications
Prohibited medications were similar to those in Study FFA122059.

Randomization Criteria
Randomization criteria were similar to Study FFA112059 with the exception that subjects were not eligible if they demonstrated evidence of significant abnormality on a 12-lead EKG.

Withdrawal Criteria
Withdrawal criteria were the same as for Study FFA112059.

Permitted Medications
Permitted medications were similar to Study FFA112059 with the exception of no allowance of antihistamine eye drops.

Study Treatments

Treatment groups were as follows:

- FF 100 mcg one inhalation once daily in the evening via NDPI
- FF/VI 100/25 mcg one inhalation once daily in the evening via NDPI
- Placebo one inhalation once daily in the evening via NDPI

All treatments were double-blinded. The FF 100 mcg NDPI double-strip formulation that was used is not the to-be-marketed drug product. For the placebo, the NDPI contained the same foil packs with the active drug moieties removed with all other excipients remaining the same.

Compliance

Compliance was assessed by reviewing the dose counter on the NDPI at visits 4-7, and subjects who were not compliant were counselled on appropriate dosing of study drug.

Efficacy Endpoints

Co-primary Endpoints

- Mean change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at the end of the 84-week treatment period
- Weighted mean serial FEV1 over 0-24 hours post-dose calculated in a subset of subjects at the end of the 84-day double-blind treatment period. 24-hour serial FEV1 included post-dose assessments after 5, 15, 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23 and 24 hours

Powered Secondary Endpoint

- Mean change from baseline in the percentage of rescue-free 24-hour periods during the 12-week treatment period

Secondary Endpoints

- Change from baseline in the percentage of symptom-free 24-hour periods during the 12-week treatment period

- Change from baseline in total AQLQ (+12) score at the end of 12-week treatment period
- The number of withdrawals due to lack of efficacy during the 12-week treatment period

Other Endpoints

- Clinic visit 12-hour FEV1 at the end of the 84-day treatment period and was assessed in the subset of subjects that were performing serial FEV1 assessments
- Weighted mean serial FEV1 over 0-24 hours post-dose calculated in a subset of subjects on day 0
- Weighted mean serial FEV1 over 0-4 hours post-dose calculated in the subset of subjects that were performing serial FEV1 assessments, on day 0 and day 84
- Time to onset of bronchodilator effect taken from serial measurements at visit 3
- Mean change from baseline in daily AM PEF averaged over the 12-week treatment period
- Mean change from baseline in daily PM PEF averaged over the 12-week treatment period
- Change from baseline in Asthma Control Test (ACT) at the end of the 12-week treatment period
- Global Assessment of Change at the end of 4, 8, and 12 weeks of treatment
- Unscheduled healthcare contacts/resource utilization (for severe asthma exacerbations and other asthma-related health care)
- Inhaler-use assessment at randomization, at the end of 2 weeks and 4 weeks of treatment
- Ease of use questions on inhaler at end of 4 weeks of treatment

Safety Endpoints

- Incidence of adverse events throughout the 12-week treatment period
- Incidence of severe asthma exacerbations throughout the 12-week treatment period
- Incidence of oropharyngeal candidiasis assessed by examination of the oropharynx at all clinic visits, including early withdrawal
- Clinical chemistry before and after the 12-week treatment period
- Serum potassium and glucose pre-dose on day 0 and 5-20 minutes post dose (Tmax for VI) on the first and last day of dosing in subset of subjects performing serial FEV1 assessments. Subjects were fasted for ≥ 4 hours prior to blood draw. The following endpoints were derived:
    - change from baseline in potassium at day 0 and day 84
    - change from baseline in glucose at day 0 and day 84
- Liver function safety assessments at screening (visit 1) and week 12 (visit 7) or early withdrawal visit

- 24-hr urine cortisol excretion assessment before and at the end of the 12-week treatment period
- Vital signs (including pulse and blood pressure) were assessed at all clinic visits prior to dosing in all subjects. The following endpoints were derived:
    - change from baseline in systolic blood pressure (BP) at day 84
    - change from baseline in diastolic BP at day 84
    - change from baseline in pulse rate at day 84
- 12-lead ECG before dosing on day 0 and day 84 in all subjects
- In addition, for subjects NOT performing serial FEV1 measurements (~40%) 12-lead ECG was also performed post-dose at Tmax (5-20 minutes for VI) on the first and last day of dosing (day 0 and day 84) to derive the mean QTc and change from baseline in mean QTc

Statistical Plan
Approximately 570 subjects were randomized in a ratio of 1:1:1 to give 190 randomized subjects per arm. The sample size calculation assumed a 5% withdrawal rate in the first 2 weeks of the study and a 15% withdrawal rate over the whole treatment period of the study. This ensured 180 subjects per arm who contributed to the analysis of trough FEV1 and the analysis of % rescue-free 24-hour periods. 60% of all randomized subjects had serial FEV1 measurements at week 12 if they completed the treatment period. A 15% withdrawal rate ensured 96 subjects per arm who contributed to the analysis of weighted mean serial FEV1 over 0-24 hours at week 12.

The overall power of the study to detect treatment differences across the specified treatment comparisons for the co-primary endpoints and the nominated secondary endpoint was 83%.

The primary population for all analyses of efficacy and safety measures (excluding urinary cortisol analyses) was the ITT population which was comprised of all subjects who were randomized to treatment and who received at least one dose of study medication.

The primary analysis for both co-primary endpoints was performed using an Analysis of Covariance (ANCOVA) model allowing for the effects due to baseline (pre-dose measurement on day 0) FEV1, region, sex, age and treatment group. Estimated treatment differences for treatment comparisons were presented together with 95% Confidence Intervals (CIs) for the mean differences and p-values for comparisons, as appropriate.

For the analysis of trough FEV1, Last Observation Carried Forward (LOCF) was used to impute missing data. A supporting analysis was also performed using a Repeated Measures Mixed Model. Missing data were not implicitly imputed in this analysis; however, all non-missing data for a subject were used within the analysis to estimate the day 84 treatment effects.

Protocol Amendment

The original protocol was amended twice:

- August 31, 2010
  - Applied to all sites
  - Added a new European Union and International Medical Monitor
  - Extended the pre-dose FEV1 and dosing timeline from 5 to 30 minutes
- April 6, 2011
  - Only applied to sites in Poland
  - Allowed adolescent subjects to be considered for study participation in order to meet the elements of the PIP agreed with by the EMA to randomize at least 68 adolescent subjects

5.3.2 Clinical Studies in Support of FF 200 mcg

5.3.2.1 Study FFA114496

Administrative Information:

- Study Title: A randomized, double-blind, multicenter study to evaluate the efficacy and safety of inhaled fluticasone furoate in the treatment of persistent asthma in adults and adolescents currently receiving mid to high strength inhaled corticosteroids
- Study Dates: 9/12/11-10/3/12
- Study Sites: US (55), Argentina (83), Russia (38), Mexico (23), France (1), Chile (38)
- Study Report Date: May 28, 2013

Objectives/Rationale

Primary:

- To evaluate the efficacy and safety of inhaled FF (100 mcg and 200 mcg) administered OD in the evening in adolescent and adult subjects 12 years of age and older with persistent asthma over a 24-week treatment period

Secondary:

- To characterize the population pharmacokinetics of FF in subjects with persistent asthma

Study Design and Conduct

Overview:
This was a multicenter, randomized, double-blind, parallel-group study. Subjects entered a 4-week run-in period after screening, and during the run-in period, subjects remained on their baseline ICS medication, but stopped taking any non-corticosteroid controllers and/or short-acting beta 2-agonists (SABA). All subjects were provided with albuterol/salbutamol to be used as needed for symptomatic relief of asthma symptoms during both the run-in and the treatment periods.

Subjects who meet the eligibility criteria at the end of the run-in period were stratified in an approximately 1:1 ratio according to their baseline forced expiratory volume in 1 second (FEV1) as a percentage of predicted normal with one stratum for each of the following:

- FEV1 percent predicted ≥40% to ≤65%
- FEV1 percent predicted ≥65% to ≤90%.

Once stratified, subjects were randomized to receive either FF 100 or 200 mcg once daily in the evening.

Subjects attended 6 on-treatment visits (visits 3, 4, 5, 6, 7 and 8). All visits were conducted in the evening between 5 PM and 11 PM. At visits 2, 3, 4 and 5 subjects were supplied with a single DPI for 4 weeks treatment. At Visits 6 and 7 subjects were supplied with two DPIs sufficient for 4 weeks treatment each, one of which remained unopened. During telephone contacts 6b and 7b subjects were instructed when to open the second DPI. A follow-up contact was performed 1 week after completing study medication. Total duration of study participation was up to a maximum of 29 weeks (including screening, treatment and follow-up).

The study was designed appropriately to assess the effects of FF placebo for airflow obstruction. Similar trial designs have been used by previous ICS asthma programs to support a maintenance treatment of airflow obstruction indication. Table 10 depicts the schedule of assessments.

Table 10. Study Assessments: Study FFA114496

Visit	1	1b	2	3	4	5	6	6b	7	7b	8	EW	9
Week	-4	-2	0	2	4	8	12	16	18	22	24		25
Day	-28	-14	0	14	28	56	84	112	126	154	168		+7
Written Informed Consent	X												
Pharmacogenetics Consent	X												
Subject Demography	X												

Table 10. Study Assessments: Study FFA114496													
Visit	**1**	**1b**	**2**	**3**	**4**	**5**	**6**	**6b**	**7**	**7b**	**8**	**EW**	**9**
Week	**-4**	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**18**	**22**	**24**		**25**
Day	**-28**	**-14**	**0**	**14**	**28**	**56**	**84**	**112**	**126**	**154**	**168**		**+7**
Medical History	X												
Asthma History	X												
Therapy History	X												
Physical Exam	X										X	X	
Inclusion/Exclusion Criteria	X		X										
Efficacy Assessments													
Spirometry Pulmonary Function	X			X	X	X	X		X		X	X	
FEV_1 Reversibility	X												
Issue Subject eDiary	X												
Asthma Control Test							X				X	X	
Issue/Review Unscheduled Healthcare Contacts	X	X[1]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	
Inhaler Use Assessment				X	X								
Ease Of Use Questions					X								
Subject Training With eDiary	X												
Subject eDiary Review & Upload		X[2]		X	X	X	X		X		X	X	
Safety Assessments													
Concomitant Medication	X	X		X	X	X	X		X		X	X	
Oropharyngeal Examination	X			X	X	X	X		X		X	X	
Vital Signs	X			X	X	X	X		X		X	X	
Adverse Events				X	X	X	X		X		X	X	
Serious Adverse Events	X[4]	X[4]		X	X	X	X		X		X	X	
Issue Medical Problems/Med Diary	X	X		X	X	X	X		X				
Collect/Review Medical Problems/ Med Diary		X		X	X	X	X		X				
Laboratory Assessments													
Hematology	X										X	X	
Chemistry	X										X	X	

Table 10. Study Assessments: Study FFA114496

Visit	1	1b	2	3	4	5	6	6b	7	7b	8	EW	9
Week	-4	-2	0	2	4	8	12	16	18	22	24		25
Day	-28	-14	0	14	28	56	84	112	126	154	168		+7
Liver Safety Assessment	X								X		X	X	
HBsAg and Hepatitis C Antibody Screening[6]	X[6]												
Pharmacogenetics Sampling													
Serum IgE (total and specific)													
Pharmacokinetic Sampling					X[7]				X[7]				
24 hr Urine Cortisol Supplies Dispensed	X								X				
24 hr Urinary Cortisol Collection											X		
Serum Pregnancy Test	X										X	X	
Urine Pregnancy Test							X						
Dispense Urine Pregnancy Test											X[8]	X[8]	

Source CSR114496 Table 38
1. Health care contacts issued from Visit 1 through 7. Completed associated with a severe exacerbation and other asthma related healthcare.
2. The purpose of the phone contact was to ensure subjects were compliant with completing the diary and understood how to complete each question appropriately.
3. Concomitant medication details collected for adverse events only between end of treatment and follow-up contact.
4. SAEs related to study participation or GSK concomitant medication that occurred during run-in were recorded in the eCRF.
5. The pharmacogenetics (PGx) sample was collected after the PGx consent was signed and the subject had been randomized.
6. Hepatitis B surface antigen and hepatitis C antibody (if hepatitis C antibody positive, a hepatitis C RIBA was reflexively performed on the same sample to confirm the result).
7. A sample was taken pre-dose and between 45 and 75 minutes post-dose. Note: PK samples were not collected for subjects recruited in France
8. Subjects were instructed to use the urine pregnancy test 5 days after the last dose of Investigational Product (IP). Subjects were asked to provide the results by telephone contact or at the follow-up contact (Visit 7).
9. An 8-week supply of study medication was dispensed.
10. Only applicable to sites selected to return partially used DPIs.
11. Review of albuterol/salbutamol use and a new inhaler was dispensed if needed. If a new inhaler was dispensed, the used inhaler was collected.
12. If not performed at End of Treatment Visit (Visit 8)

Reviewer's Comment: This study was designed appropriately to demonstrate the benefit of the FF 200 mcg over 100 mcg dose.

Study Population

The inclusion criteria were similar to Study FFA112059 with the exception that subjects were to be on a stable mid-to-high strength dose and regimen of ICS for at least four weeks prior. Exclusion criteria, randomization criteria, withdrawal criteria, permitted and prohibited medications were the same as Study FFA112059.

Study Treatments

Treatment groups were as follows:

- FF 100 mcg one inhalation once daily in the evening via NDPI
- FF 200 mcg one inhalation daily in the evening via NDPI

All treatments were double-blinded. Both doses of FF were the single-strip, to-be-marketed drug product.

Compliance

Compliance was assessed by reviewing the dose counter on the NDPI at visits 3-8, and subjects who were not compliant were counselled on appropriate dosing of study drug.

Efficacy Endpoints

Primary Efficacy Endpoint

- Change from baseline in evening clinic visit pre-bronchodilator, pre-dose (trough) FEV1 at the end of the 24-week treatment period
    - FEV1 was measured electronically by spirometer in the evening at all clinic visits (visits 1 to 8) between 5 PM and 11 PM
    - The highest of three technically acceptable measurements were recorded

Secondary Efficacy Endpoints

- Change from baseline in the percentage of rescue-free 24-hour periods during the 24-week treatment period
- Change from baseline in daily PM PEF, averaged over the 24-week treatment period
- Change from baseline in daily AM PEF, averaged over the 24-week treatment period
- Change from baseline in the percentage of symptom-free 24-hour periods during the 24-week treatment period

Other Efficacy Endpoints

- Change from baseline in ACT score at the end of the 24-week treatment period
- Percentage of subjects controlled, defined as an ACT score ≥20, at the end of the 24-week treatment period or EW
- Incidence of protocol defined severe exacerbations throughout the 24-week treatment period
- Unscheduled healthcare contacts/resource utilization for severe asthma exacerbations and other asthma-related healthcare
- Inhaler use assessment at the end of 2 and 4 weeks of treatment
- Ease of use questions on the DPI at the end of 4 weeks of treatment

Safety Endpoints

- Incidence of adverse events throughout the 24-week treatment period
- Clinical laboratory tests at screening and Week 24 or EW
- Liver function safety assessments at screening and Week 24 or EW
- 24-hour urine cortisol excretion collected for assessment at end of run-in (Visit 2) and at the end of Week 24

Statistical Plan

A total of 220 randomized subjects (110 subjects per arm) were expected to give 104 evaluable subjects per arm. This sample size would ensure the half-width of the 95% confidence interval (CI) was no larger than 110.1 mL providing an estimated mean treatment difference between treatment groups in change from baseline in PM FEV1 at the end of the 24-week treatment period.

The overall power of the study to detect treatment differences across the specified treatment comparisons for the co-primary endpoints and the nominated secondary endpoint was 83%.

The safety population comprised all subjects randomized to treatment who received at least one dose of study medication. This population was used for all safety measures (with the exception of 24-hour urinary cortisol excretion).The Intent-to-Treat (ITT) population comprised all subjects in the Safety Population except for the subjects of Investigator 040688, due to GCP compliance issues at this site identified during a site audit for previous studies. This population constituted the primary population for all efficacy measures.

The analysis of the primary efficacy endpoint of change from baseline in evening (trough) FEV1 at the end of the 24-week treatment period was performed using an ANCOVA model allowing for the effects due to baseline FEV1, region, sex, age, and

treatment group. Last Observation Carried Forward (LOCF) was used to impute missing data. The adjusted means for each treatment and the estimated treatment differences for the treatment comparison were presented with 95% CI for the differences. Adjusted means for each treatment were plotted along with the corresponding 95% CIs.

Protocol Amendment

The original protocol was amended twice:

- November 2011
  - Clarification in the Time and Events table and in the body of the protocol that chemistry and hematology samples were collected at the early withdraw visit, plus administrative edits
  - Added clarification in Section 5.6.1.2 Non-Asthma Medications, Intranasal Corticosteroids indicating that the use of fluticasone furoate 4 weeks prior to visit 1 was not allowed
  - In Section 6.3.3. Adverse Events, clarification was added to explain that the medical conditions diary was dispensed and reviewed at each visit and that the site staff needed to review and record as necessary
  - Appendix 4 was added to detail the laboratory analyses collected during the study
- January 2012
  - At the request of the French EC
  - Specified French sites would not participate in the PK portion of the protocol

5.3.3.2 Study HZA106829

Reviewer's Comment: The study was designed as a non-inferiority trial for FF 200 versus FP 500. It provides important information for providers who want to switch their patients from FP to FF, as the doses are 5-fold different. The results of this study will be included in the product label as they are clinically relevant to providers.

Administrative Information:

- Study Title: A Randomized, Double-Blind, Parallel Group, Multicenter Study of fluticasone furoate/GW642444 inhalation powder, fluticasone furoate inhalation powder alone, and fluticasone propionate alone in the treatment of persistent asthma in adults and adolescents
- Study Dates: 6/10/10-10/18/11
- Study Sites: Russia (163), US (143), Romania (117), Germany (66), Poland (61), Japan (36)
- Study Report Date: April 30, 2012

Objectives/Rationale

Primary:

- To compare the efficacy and safety of FF/VI inhalation powder 200 mcg/25 mcg administered once daily each evening to FF inhalation powder 200 mcg administered alone once daily each evening in adolescent and adult subjects 12 years of age and older with persistent bronchial asthma over a 24-week treatment period

Secondary:

- To compare the efficacy of FF 200 mcg administered once daily each evening with FP 500 mcg administered twice daily

Additional objectives

- To assess the safety of FF 200 mcg and FP 500 mcg over the 24-week treatment period

Study Design and Conduct

Overview:
This was a multicenter, stratified, randomized, double-blind, double-dummy, active control, parallel group study. After screening, subjects entered a 4-week run-in period. During this time, subjects remained on their baseline ICS medication. At visit 3, the end of the run-in period, subjects were stratified according to their medication (ICS or ICS/LABA) at screening. Once stratified, subjects were randomized in a 1:1:1 ratio to the treatment phase of the study where they received one of the following treatments:

• FF/VI 200/25 mcg inhalation powder via NDPI once daily in the evening plus placebo diskus twice daily
• FF 200 mcg via NDPI once daily in the evening plus placebo diskus twice daily
• FP 500 mcg via diskus twice daily plus placebo NDPI once daily in the evening

Randomized subjects attended seven on-treatment clinic visits (visits 4, 5, 6, 7, 8, 9 and 10). Spirometry, dosing of study medication, PK and download of the electronic diary were to be conducted between 5:00 PM and 11:00 PM at all appropriate clinic visits except visit 2. A follow-up clinic contact was performed 1 week after completing study medication. The overall study duration for each subject was a maximum of 29 weeks.

Table 11 depicts the schedule of assessments.

Table 11. Study Assessments: Study HZA106829

Visit	1	2	3	4	5	6	7	8	9	10	EW	11
Week	-4	-2	0	2	4	8	12	16	20	24		25

Day	-28	-14	0	14	28	56	84	112	140	268		+7
Written Informed Consent	X											
Subject Demography	X											
Medical History	X											
Asthma History	X											
Therapy History	X											
Physical Exam	X									X		
Inclusion/Exclusion Criteria	X											
Efficacy Assessments												
Spirometry Pulmonary Function	X			X	X	X	X	X	X	X		
Reversibility	X											
Serial FEV1 (subset of subjects)										X[a]		
PK Sampling							X[h]			X[h]		
Issue Subject Diaries	X											
Subject Diary Review & Upload		X		X	X	X	X	X	X	X		
Safety Assessments												
Oropharyngeal Examination	X			X	X	X	X	X	X	X		
Concomitant Medication	X	X		X	X	X	X	X	X	X		X[b]
Vital Signs (pre-dose)	X			X	X	X	X	X	X	X		
Adverse Events				X	X	X	X	X	X	X		X
Serious Adverse Events (SAEs)	X[d]	X[d]		X	X	X	X	X	X	X		X
Laboratory Assessments												
Hematology	X											
Chemistry (includes liver safety testing)	X						X[e]			X		
PGx Sampling (one visit only)[g]					X							
Serum pregnancy test	X									X		
Urine Pregnancy test												X

Table 11. Study Assessments: Study HZA106829

Visit	1	2	3	4	5	6	7	8	9	10	EW	11
Week	-4	-2	0	2	4	8	12	16	20	24		25
Day	-28	-14	0	14	28	56	84	112	140	268		+7
24-h Urine supplies dispensed		X							X			
24-h Urine collection										X		
PK Sampling							X[h]			X[h]		
HBsAg and hepatitis C antibody screening	X											
Questionnaires												
ACT	X						X			X		
AQLQ 12+							X			X		
Unscheduled Healthcare contact/Resource Utilization9				X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]		
Global Assessment of Change					X		X			X		

Source CSR Table 56
a.In addition to pre-dose assessment (within 5 minutes prior to dosing), serial FEV1 measurements were taken at 5, 15, 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23 and 24 hours post-dose.
b. Concomitant medication details collected for adverse events only between end of treatment and follow-up contact.
c.ECG pre-dose and Tmax (5 to 20 minutes post-dose for VI) at Visit 3 (Day 0) for all subjects; ECG pre-dose and Tmax (5 to 20 minutes post-dose for VI) at Visit 10 (end of 24 weeks of treatment) in subjects not performing serial FEV1; ECGs at Visit 2 and Early Withdrawal were pre-dose only.
d. SAEs related to study participation that occurred during run-in were to be recorded in the eCRF.
e. For liver safety testing only.
f. If not performed at End of treatment.
g. The PGx sample could be collected at any one visit after the PGx consent had been signed and the subject had been randomized
h. Upon arrival at the clinic a 4 mL blood sample was collected and the subjects administered their evening dose of study medication after all pre-dose assessments were completed.
Prior to leaving the clinic, two more 4 mL blood samples were collected from the subject between 5 to 15 minutes post-dose and between 1 to 1.5 hours post-dose.
i. Completed when associated with a severe exacerbation and other asthma-related healthcare.

Study Population

Inclusion Criteria were similar to FFA112059 except that subjects were to be on an ICS or ICS/LABA combination product for at least 12 weeks prior to visit 1 as well as on a

stable ICS dose equivalent to FP 500 mcg twice daily or a mid-dose combination product equivalent to Advair 250/50 twice daily for at least four weeks prior to visit 1. Exclusion criteria, randomization criteria, withdrawal criteria, permitted and prohibited medications were similar to Study FFA112059.

Study Treatments

Treatment groups were as follows:

- FF/VI 200/25 mcg inhalation powder via NDPI once daily in the evening plus placebo diskus twice daily
- FF 200 mcg via NDPI once daily in the evening plus placebo diskus twice daily
- FP 500 mcg via diskus twice daily plus placebo NDPI once daily in the evening

All treatments were double-blinded. The FF 200 mcg NDPI double-strip formulation that was used is not the to-be-marketed drug product. For the placebo, the NDPI contained the same foil packs with the active drug moieties removed and all other excipients remaining the same. For the diskus placebo, only lactose was used.

Compliance

Compliance was assessed by reviewing the dose counter on the NDPI and diskus at visits 4-10, and subjects who were not compliant were counselled on appropriate dosing of study drug.

Efficacy Endpoints

Co-primary Endpoints

- Mean change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at the end of the 168-day (24 week) treatment period
- Weighted mean serial FEV1 over 0 to 24 hours post-dose, calculated in a subset of subjects performing serial FEV1 at the end of the double-blind treatment period

FEV1 was measured in the evening at clinic visit 1, and visits 3 to 10 between 5:00 PM and 11:00 PM electronically by spirometry. The highest of three technically acceptable measurements was recorded.

Nominated Powered Secondary Endpoint

- Mean change from baseline in the percentage of rescue-free 24-hour periods during the 24-week treatment period

Secondary Endpoints

- Change from baseline in the percentage of symptom-free 24-hour periods during the 24-week treatment period
- Change from baseline in total AQLQ (+12) score during 12 and 24 weeks of treatment

Other Endpoints

- Clinic visit 12 hour FEV1 at the end of the 168-day treatment period and was assessed in the subset of subjects that were performing serial FEV1 assessments
- Weighted mean serial FEV1 over 0 to 4 hours post-dose calculated in the subset of subjects performing serial FEV1 on Day 168
- Mean change from baseline in daily AM PEF averaged over the first 12 weeks and over the 24-week treatment period
- Mean change from baseline in daily PM PEF averaged over the first 12 weeks and over the 24-week treatment period
- The number of withdrawals due to lack of efficacy during the 24-week treatment period
- Change from baseline in the Asthma Control Test (ACT) at the end of 12 and 24 weeks of treatment
- Global assessment of change at the end of 4, 12, and 24 weeks of treatment
- Unscheduled healthcare contacts/resource utilization for severe asthma exacerbations and other asthma-related health care

Safety Endpoints

- Incidence of adverse events throughout the 24-week treatment period
- Incidence of severe asthma exacerbations throughout the 24-week treatment period
- Incidence of oropharyngeal candidiasis assessed by examination of the oropharynx at all clinic visits, including early withdrawal
- Clinical chemistry before and after the 24-week treatment period
- Liver function safety assessments at screening (visit 1), week 12 (visit 7), and week 24 (visit 10) or early withdrawal visit
- 24-hr urine cortisol excretion assessment before and at the end of the 24-week treatment period
- Vital signs were assessed at all clinic visits prior to dosing in all subjects. The following endpoints were derived:
    - change from baseline in systolic blood pressure (BP) at Day 168
    - change from baseline in diastolic BP at Day 168
    - change from baseline in pulse rate at Day 168

- 12-lead EKG before dosing on Day 0 and Day 168 in all subjects before dosing and at the time of maximum plasma concentration following drug administration to derive the QTc

Statistical Plan
It was planned to randomize a total of 588 subjects into this study in a ratio of 1:1:1 (196 subjects per arm). It was anticipated that there would be a 4% withdrawal rate for the first 2 weeks, which would still ensure 188 subjects per arm who contribute to the analysis of trough FEV1 and the analysis of % rescue-free 24-hour periods. Sixty percent of all randomized subjects would have had serial FEV1 measurements at week 24 if they completed the treatment period. It was anticipated that 15% of subjects would withdraw over the entire treatment period of the study, which would still ensure that 99 subjects per arm contributed to the analysis of weighted mean serial FEV1 over 0 to 24 hours at week 24.

The overall power of the study to detect treatment differences for both primary endpoints was 92%.

The primary population for all analyses of efficacy measures and safety measures was the ITT population which was comprised of all subjects randomized to treatment who received at least one dose of study medication.

The co-primary endpoints were derived by imputing any missing data with the last observation carried forward (LOCF). Statistical analysis was performed using an ANCOVA model.

Protocol Amendment

There were no protocol amendments to this study.

6 Review of Efficacy

Efficacy Summary

The Applicant conducted a large clinical development program to support the efficacy of FF 100 mcg and FF 200 mcg for the maintenance treatment of asthma. The development program included three 8-week dose ranging studies (discussed in Section 4.4.2), three confirmatory studies (FFA112059, HZA106827, FFA114496), and an additional study (HZA106829) which compared FF 200 mcg to fluticasone propionate (FP) 500 mcg BID. The confirmatory studies ranged in duration from 12 to 24 weeks, with mean change from baseline in trough FEV1 as the primary efficacy endpoint. Additionally, studies HZA106827 and HZA106829 had co-primary endpoints of mean change from baseline in weighted mean serial FEV1 over 24-hours post-dose.

Clinical Studies in Support of FF 100 mcg

Study FFA112059 was a 24-week trial that randomized 343 subjects. 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 therapy (i.e., fluticasone propionate 100 to 500 mcg daily or equivalent). 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]).

Study HZA106827 was a 12-week trial that evaluated the efficacy of FF 100 mcg on lung function in subjects with asthma compared with placebo. The combination of FF 100 mcg and Vilanterol 25 mcg was also included as a treatment arm. Of the 609 randomized subjects, 58% were female and 84% were Caucasian. The mean age was 40 years. 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). Mean baseline percent predicted FEV_1 was approximately 70% in both 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 and 95% CI: 51, 222). Lung function improvements were sustained over 24 hours. Compared with placebo at Week 12, the change from baseline in weighted mean FEV_1 was significantly greater for FF 100 mcg (mean difference of 186 mL; 95% CI: 62, 310;).

In general, secondary endpoints, such rescue medication use, also supported the primary endpoint.

Clinical Studies in Support of FF 200 mcg

Trial FFA114496 was a 24-week trial that evaluated the relative efficacy of FF 100 mcg and FF 200 mcg on lung function in subjects with asthma. Of the 219 randomized subjects, 68% were female and 87% were Caucasian. The mean age was 46 years. 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 therapy (i.e., fluticasone propionate >250 to 1,000 mcg/day or equivalent). Mean baseline percent predicted FEV_1 was approximately 68% overall and similar in the two treatment groups. Sixteen 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 FEV_1 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 (see Figure 3). At Week 24 or the last available on-treatment visit prior to Week 24, the mean change from baseline in trough FEV_1 was 208 mL for FF 100 mcg, as compared to 284 mL for FF 200 mcg (difference of 77 mL, 95% CI: -39, 192).

Trial HZA106829 was a 24-week trial that evaluated the efficacy of FF 200 mcg once daily and fluticasone propionate 500 mcg twice daily on lung function in subjects with asthma. The combination of fluticasone furoate 200 mcg and Vilanterol 25 mcg was also included as a treatment arm. Of the 586 randomized subjects, 59% were female and 84% were Caucasian. The mean age was 46 years. 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. Mean baseline percent predicted FEV_1 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 FEV_1 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 FEV_1 was 328 mL for FF 200 once daily and 258 mL for fluticasone propionate 500 twice daily.

Overall, the clinical development program establishes the efficacy of both FF 100 mcg and FF 200 mcg in the maintenance treatment of asthma.

6.1 Indication

The proposed indication for FF 100 mcg and 200 mcg is the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older.

6.1.1 Methods

To support the proposed indication, the Applicant conducted a large clinical development program, which included both dose ranging and confirmatory trials. The focus of this section will be to describe the two confirmatory studies which support the efficacy of FF 100 mcg (FFA112059 and HZA106827) and the one confirmatory study

(FFA114496) which provides information regarding the added benefit of the higher dose of FF 200 mcg. Study HZA106829 included a comparison of FF 200 mcg QD to FP 500 mcg BID. This active comparator data will be summarized in Section 6.1.10.

6.1.2 Demographics

Overall, the age, gender, race, and asthma severity were the same across treatment groups within in each confirmatory study. Subjects were more commonly female, white, had asthma for over 10 years, and were on other asthma medications.

Table 12, Table 13, Table 14, and Table 15 detail the demographic and baseline characteristics of subjects in the submitted pivotal phase 3 studies.

Table 12. Demographic and Baseline Characteristics: FFA112059

	Placebo N=115	FF 100 N=114	FP 250 BD N=114	Total N = 343
Age				
Mean	40.3	40.1	41.4	40.6
Min	12	12	12	12
Max	84	76	172	84
Sex, n (%)				
Female	68 (59)	63 (55)	72 (63)	203 (59)
Male	47 (41)	51 (45)	42 (37)	40 (41)
Race, n (%)				
African Heritage	23 (20)	22 (19)	19 (17)	64 (19)
Amer. Indian or Alaska Native	1 (<1)	0	0	1 (<1)
Asian	2 (2)	1 (<1)	2 (2)	5 (1)
White	88 (77)	90 (80)	92 (81)	370 (79)
Duration of Asthma, n (%)				
<6 mo	1 (<1)	0	0	1 (<1)
≥6 mo to <1 year	0	1 (<1)	0	1 (<1)
≥1 to < 5 years	16 (14)	11 (10)	19 (17)	46 (13)
≥5 to <10 years	21 (18)	24 (31)	20 (18)	65 (19)
≥10 years	77 (67)	78 (68)	75 (66)	230 (67)
Baseline Lung Function				
Mean pre-bronchodilator FEV1 (L)	2.221	2.274	2.271	2.256
Percent predicted	69.39	69.16	70.09	69.55
Reversibility				
Absolute FEV1 reversibility (mL)	564.9	593.7	549.9	569.5
Percent reversibility FEV1 (%)	25.43	27.32	25.07	25.94
Concomitant Medications				
On other asthma medications	114 (>99)	112 (98)	114 (100)	340 (>99)

Source: CSR FFA112059 Tables 4, 5, 6

Table 13. Demographic and Baseline Characteristics: HZA 106827				
	Placebo N=203	FF 100 N=205	FF/VI 100/25 N=201	Total N=609
Age				
Mean	38.1	40.4	40.7	39.7
Min	12	12	12	12
Max	72	84	82	84
Sex, n (%)				
Female	111 (55)	126(61)	116 (58)	353 (58)
Male	92 (45)	79 (39)	85 (42)	256 (42)
Race, n (%)				
African Heritage	14 (7)	16 (8)	13(6)	43 (7)
Amer. Indian or Alaska Native	0	1 (<1)	0	1 (<1)
Asian	9 (9)	16 (8)	16 (8)	51 (8)
White	169 (83)	171 (83)	172 (86)	512 (84)
Duration of Asthma, n (%)				
<6 mo	5 (2)	1 (<1)	5 (2)	11 (2)
≥6 mo to <1 year	11 (5)	9 (4)	12 (6)	32 (5)
≥1 to < 5 years	52 (26)	44 (21)	54 (27)	150 (25)
≥5 to <10 years	36 (18)	44 (21)	7 (23)	127 (21)
≥10 years	99 (49)	107 (52)	83 (41)	289 (47)
Baseline Lung Function				
Mean pre-bronchodilator FEV1 (L)	2.277	2.174	2.227	2.226
Percent predicted	68.47	67.04	67.25	67.59
Reversibility				
Absolute FEV1 reversibility (mL)	597.6	641.9	603.1.	614.2
Percent reversibility FEV1 (%)	27.47	30.66	27.98	28.71
Concomitant Medications				
ICS alone	119 (59)	122 (60)	120 (60)	361 (59)
ICS/LABA	84 (42)	83 (41)	81 (40)	248 (41)
Source: CSR HZA 106827 Tables 5.15, 11, 12, 14				

Table 14. Demographics and Baseline Characteristics: FFA 114496			
	FF 100 N=119	FF 200 N=119	Total N=238
Age			
Mean	46.6	45.1	45.9
Min	12	12	12
Max	76	70	76
Sex, n (%)			
Female	81 (68)	79 (66)	160 (67)
Male	3 (32)	40 (34)	78 (33)
Race, n (%)			
African Heritage	5 (4)	4 (3)	9 (4)
Amer. Indian or Alaska Native	11 (9)	12 (10)	23 (10)

Table 14. Demographics and Baseline Characteristics: FFA 114496			
	FF 100 N=119	FF 200 N=119	Total N=238
Asian	1 (<1)	3 (3)	4 (2)
White	101 (85)	0	20 (84)
Duration of Asthma, n (%)			
<6 mo	1 (<1)	0	1 (<1)
≥6 mo to <1 year	0	3 (3)	3 (1)
≥1 to < 5 years	17 (14)	12 (10)	29 (12)
≥5 to <10 years	20 (17)	12 (10)	32 (14)
≥10 years	80 (68)	92 (77)	172 (73)
Number of Exacerbations in the Last 12 Months			
0	46 (39)	52 (44)	98 (41)
1	63 (53)	53 (45)	116 (49)
2	9 (8)	13 (11)	22 (9)
3	1 (<1)	0	1 (<1)
4	0	1 (<1)	1 (<1)
>4	0	0	0
Baseline Lung Function			
Mean pre-bronchodilator FEV1 (L)	1.926	2.010	1.968
Percent predicted	65.15	65.48	65.32
Reversibility			
Absolute FEV1 reversibility (mL)	594.1	647.1	621.0
Percent reversibility FEV1 (%)	30.64	33.85	32.27
Concomitant Medications			
Mid-dose ICS	88 (74)	93 (78)	181 (76)
High-dose ICS	31 (26)	25 (21)	56 (24)
Source: CSR FFA114496 Tables 6, 7, 9, 11			

Table 15. Demographics and Baseline Characteristics: HZA 106829				
	FF 200 N=194	FF 200/25 N=197	FP 500 BID N=195	Total N=586
Age				
Mean	44.6	46.6	47.3	46.2
Min	12	14	12	12
Max	74	74	76	76
Sex, n (%)				
Female	113 (58)	116 (59)	116 (59)	345 (59)
Male	1 (42)	81 (41)	79 (41)	241 (41)
Race, n (%)				
African Heritage	16 (8)	16 (8)	19 (10)	51 (9)
Amer. Indian or Alaska Native	0	0	1 (<1)	1 (<1)
Asian	12 (6)	15 (8)	13 (7)	40 (7)
White	165 (85)	165 (84)	162 (83)	492 (84)
Duration of Asthma, n (%)				
<6 mo	2 (1)	1 (<1)	1 (<1)	4 (<1)

Table 15. Demographics and Baseline Characteristics: HZA 106829				
	FF 200 N=194	FF 200/25 N=197	FP 500 BID N=195	Total N=586
≥6 mo to <1 year ≥1 to < 5 years ≥5 to <10 years ≥10 years	4 (2) 27 (14) 49 (250 112 (58)	1 (<1) 31 (16) 35 (18) 129 (65)	2 (1) 35 (18) 45 (23) 112 (57)	7 (1) 93 (16) 129 (22) 353 (60)
Baseline Lung Function				
Mean pre-bronchodilator FEV1 (L) Percent predicted	2.072 63.27	2.017 62.99	2.017 63.59	2.035 63.28
Reversibility				
Absolute FEV1 reversibility (mL) Percent reversibility FEV1 (%)	583.3 29.17	561.7 29.58	568.0 29.56	570.9 29.44
Concomitant Medications				
On ICS On ICS+LABA	44 (23) 150 (78)	47 (24) 150 (76)	49 (25) 146 (75)	140 (24) 446 (76)
Source: CSR HZA 106829 Table 5, 6, 7				

6.1.3 Subject Disposition

A total of 1,190 patients were randomized in studies FFA112059, HZA106827, and FFA114496. The majority of patients completed the studies (74% to 86%). Overall, the most common reason for patient withdrawal was due to lack of efficacy, followed by adverse events. In general, patients on active treatment withdrew less frequently for lack of efficacy than those in the placebo groups. Table 16, Table 17, and Table 18 depict patient disposition for studies FFA112059, HZA106827, and FFA114496 respectively.

Table 16. Patient Disposition: FFA112059				
	Placebo N=115	FF 100 N=114	FP 250 BD N=114	Total N=343
Completed	75 (65)	92 (81)	88 (77)	255 (74)
Withdrawn	40 (35)	22 (19)	26 (23)	88 (26)
Primary reason for withdrawal				
Adverse event	2 (2)[1]	2 (2)	3 (3)	7 (2)
Lack of Efficacy	23 (20)	15 (13)	14 (12)	52 (15)
Exacerbation	6 (5)	2 (2)	2 (2)	10 (3)
Protocol Deviation	1 (<1)	2 (2)	0	3 (<1)
Lost to Follow-up	4 (3)	0	0	4 (<1)
Source: CSR FFA112059 Table 2 1. Subject 20027 in the FF 100 OD group had an adverse event leading to withdrawal, but this withdrawal was recorded as "Lack of efficacy" with the sub-reason of "Exacerbation"				

Table 17. Patient Disposition: HZA106827				
	Placebo N=203	**FF 100 N=205**	**FF/VI 100/25 N=201**	**Total N=609**
Completed	151 (74)	185 (90)	179 (89)	515 (85)
Withdrawn	52 (26)	20 (10)	22 (11)	94 (15)
Primary reason for withdrawal				
Adverse event	1 (<1)	0	2 (<1)	3 (<1)
Lack of Efficacy	32 (16)	6 (3)	7 (3)	45 (7)
Exacerbation	9 (4)	2 (<1)	1 (<1)	12 (2)
Protocol Deviation	7 (3)	0	2 (<1)	9 (1)
Lost to Follow-up	0	1 (<1)	2 (<1)	3 (<1)

Source: CSR HZA106827 Table 7

Table 18. Patient Disposition: FFA114496			
	FF 100 N=119	**FF 200 N=119**	**Total N=238**
Completed	100 (84)	104 (87)	204 (86)
Withdrawn	19 (16)	15 (13)	34 (14)
Primary reason for withdrawal			
Adverse event[1]	2 (2)	2 (2)	4 (2)
Lack of Efficacy	2 (2)	1 (<1)	3 (1)
Exacerbation	1 (<1)	0	1 (<1)
Protocol Deviation	2 (2)	3 (3)	5 (2)
Lost to Follow-up	0	1 (<1)	1 (<1)

Source: CSR FFA114496 Table 3, Table 5.4
1. Five subjects (3 in the FF 100 group and 2 in the FF/VI 100/25 group) were withdrawn due to asthma exacerbations which were SAEs

Protocol Deviations

Protocol deviations were infrequent (<1-3%); the most frequent reasons for protocol deviations were no reason provided, pregnancy, lack of adherence, and prohibited medication use.

Compliance

Compliance was assessed through a review of device dose counters. Overall, rates were high across all treatment groups in all studies (FFA112059 >92.1%, HZA106827 >97.5%, FFA114496 >97.8%, HZA106829 >95.2%).

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 Clinical Studies in Support of FF 100 mcg

Studies FFA112059 and HZA106827 evaluated the change from baseline in trough FEV1. HZA106827 also had the co-primary endpoint of 24-hour weighted mean FEV1. Both trials demonstrated a statistically significant difference in FF 100 versus placebo in regards to change from baseline trough FEV1 (112059: 0.146, p=0.009, 106827: 0.121, p=0.010) as is shown in Table 19,

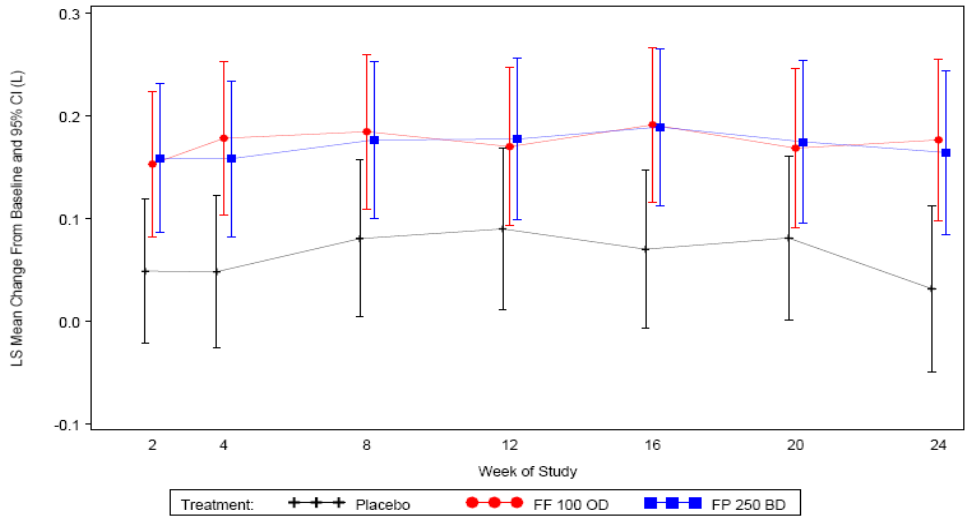
Figure 2, and Figure 3.

Table 19. Mean Change from Baseline in Trough FEV1: Studies FFA112059 and HZA106827

	Placebo	FF 100 QD	FP 250 BID	FF/VI 100/25
FFA112059				
Week 24 Change in Baseline Trough FEV1				
N	113	111	107	
LS Mean (L)	2.372	2.519	2.517	
LS Mean Change (L)	0.015	0.161	0.159	
Difference from placebo (L)		0.146	0.145	
95% CI		(0.036, 0.257)	(0.033, 0.257)	
p-value		0.009	0.011	
HZA106827				
Week 12 Change in Baseline Trough FEV1				
N	193	203		200
LS Mean (L)	2.525	2.661		2.697
LS Mean Change (L)	0.196	0.332		0.268
Difference from placebo (L)		0.136		0.172
95% CI		(0.051, 0.222)		(0.087, 0.258)
p-value		0.002		<0.001

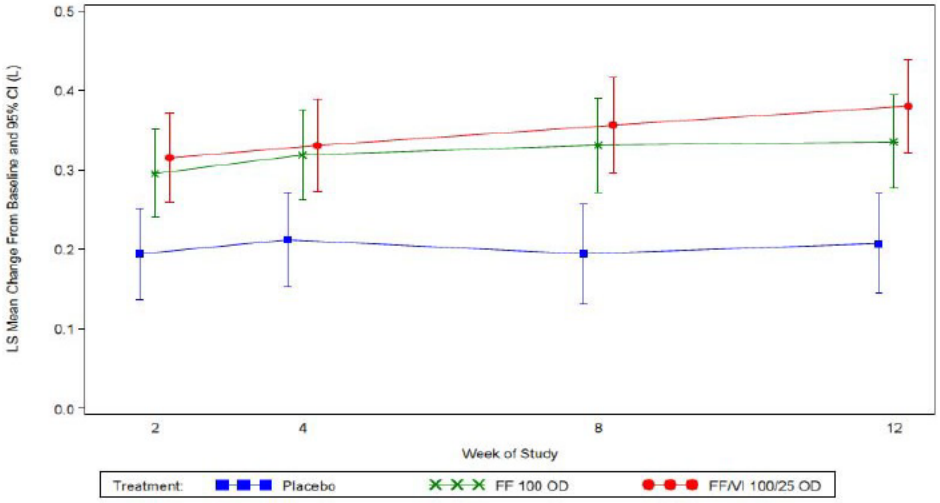
Source: CSR FFA112059 Table 6.2, CSR HZA106827 Table 6.2

Figure 2. Repeated Measures Analysis of Change from Baseline in Trough FEV1 (L) (ITT population): Study FFA112059



Source Data: Figure 6.3
Note: Repeated Measures analysis adjusted for baseline, region, sex, age, treatment visit, visit by baseline interaction and visit by treatment interaction.

Figure 3. Change from Baseline in Trough FEV1 (L) Using Repeated Measures Analysis (ITT population): Study HZA106827



Source: Figure 6.3
Note: Repeated Measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit by baseline interaction and visit by treatment interaction

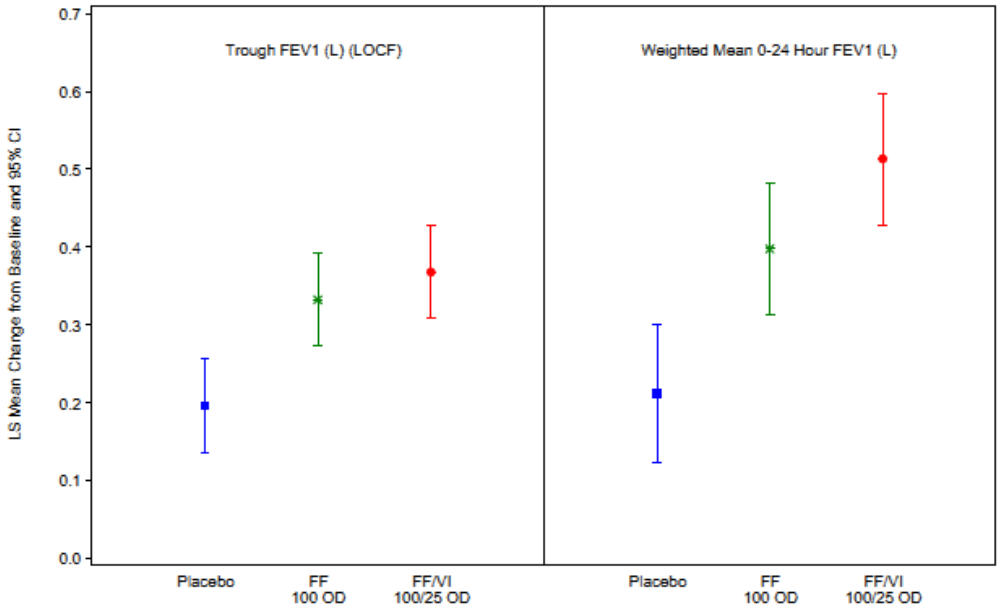
HZA 106827 also demonstrated a statistically significant difference in 0-24 hour weighted mean FEV1 (0.136, p=0.222) as is shown in Table 20 and Figure 4 (provided by the Sponsor).

Table 20. Week 12 Weighted Mean 24 Hour FEV1: Study HZA106827

	Placebo N=203	FF 100 N =205	FF/VI N = 201
Week 12 Weighted Mean 24 hour FEV1			
N	95	106	108
LS Mean	2.542	2.728	2.843
LS Mean Change	0.212	0.396	0.513
Difference from placebo		0.186	0.302
95% CI		(0.062,0.310)	(0.178, 0.426)
p-value		0.003	<0.001

Source: CSR HZA106827 Table 6.9

Figure 4. Adjusted Means for Co-Primary Endpoints at Week 12 (ITT population): Study HZA106827



Source: Figure 6.1
Note: Analysis performed using ANCOVA with covariates of baseline, region, sex, age and treatment

6.1.4.2 Clinical Study in Support of FF 200 mcg

FFA114496

FFA114496 examined the benefit of the 200 mcg dose over the 100 mcg dose over a 24-week period in subjects who were uncontrolled on mid-low dose ICS. The primary endpoint was mean change from baseline evening trough FEV1. A 77 mL greater treatment difference was observed for the 200 group compared with the FF 100 group as depicted in Table 21.

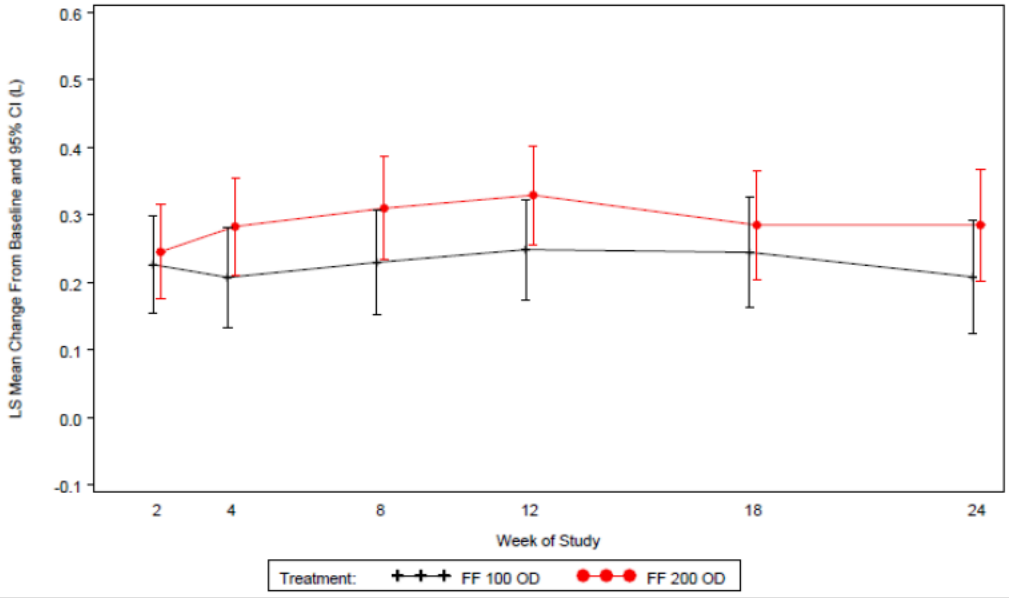
Table 21. Mean Change from Baseline in Trough FEV1: Trial FFA114496

	FF 100 QD	FF 200 QD
FFA114496		
N	106	109
LS Mean	2.271	2.347
LS Mean Change	0.208	0.284
Difference		0.077
95% CI		(-0.039, 0.192)

Source: CSR FFA114496 Table 6.2

When repeated measures analysis without imputation was conducted, FF 200 showed greater LS mean changes from baseline for weeks 2-24 than the FF 100 group as shown in Figure 5.

Figure 5. Repeated Measures Analysis of Change from Baseline in Trough FEV1 (L)



Source: CSR FFA 114496, Figure 6.5

6.1.5 Analysis of Secondary Endpoints

6.1.5.1 Clinical Studies in Support of FF 100 mcg

In trial FFA112059, there was a statistically significant difference compared with placebo for percentage of rescue-free days (p <0.001), percentage of symptom-free 24-hour periods (p=0.025), and AQLQ scores (p=0.007) which was similar to FP 250 BID, although FP 250 BID did not show a statistically significant difference in AQLQ scores. There was no statistically significant difference in PM or AM PEF. Table 22 depicts these results.

Table 22. Secondary Endpoints in Trial FFA112059

	Placebo	FF 100	FP 250 BID
Rescue-Free 24-hr Periods %[1]			
N	114	112	113
LS Mean Change	6.5	21.3	24.3
Difference v Placebo		14.8	17.9
95% CI		(6.9,22.7)	(10,25.7)
p-value		<0.001	<0.001
PM, PEF L/min			
N	114	112	112
LS Mean Change	-1.3	1.5	4.3
Difference v Placebo		2.8	5.5
95% CI		(-6.6,12.2)	(-3.9,15)
p-value		0.564	0.248
AM, PEF L/min			
N	114	112	113
LS Mean Change	5.0	13.9	9.9
Difference v Placebo		8.9	4.9
95% CI		(-0.7,18.5)	(-4.7,14.5)
p-value		0.071	0.319
Symptom-free 24-hr periods %			
N	114	112	113
LS Mean Change	10.4	19.3	19.2
Difference v Placebo		8.9	8.8
95% CI		(1.1,16.7)	(1.1,16.6)
p-value		0.025	0.025
AQLQ, units			
N[1]	87	102	99
LS Mean Change	0.51	0.84	0.67
Difference v Placebo		0.33	0.16
95% CI		(0.09,0.57)	(-0.08,0.4)

Table 22. Secondary Endpoints in Trial FFA112059			
	Placebo	**FF 100**	**FP 250 BID**
p-value		0.007	0.185
Source: ISE Table 11, CSR FFA112059 Table 6.10, 6.15, 6.17, 6.19, 6.21 1. Nominated Powered Secondary Endpoint			

In trial HZA106827, there was a statistically significant difference between FF 100 and placebo for percentage of rescue-free days (p=0.007) and PM and AM PEF (<0.001 for both) as depicted in Table 23.

Table 23. Secondary Endpoints in HZA106827			
	Placebo	**FF 100**	**FF /VI 100/25**
Rescue-Free 24-hr Periods %[1] N LS Mean Change Difference v Placebo 95% CI p-value	 202 17.8	 204 26.5 8.7 (2.4,15.0) 0.007	 201 27.1 19.2 (13, 25.6) <0.001
Symptom-free 24-hr periods % N LS Mean Difference v Placebo 95% CI p-value	 202	 204 5.8 (-0.1,11.8) 0.055	 201 18.0 (12, 23.9) <0.001
AQLQ, units N[2] LS Mean Change Difference v Placebo 95% CI p-value	 149 0.61	 184 0.76 0.15 (-0.01,0.3) 0.073	 180 0.91 0.30 (0.13,0.46) <0.001
Number of withdrawals due to lack of efficacy N (%) p-value	 32 (16)	 6 (3) <0.001	 7 (3) <0.001
Source: ISE Table 12, CSR HZA106827 Table 6.13, 6.21, 6.23 1. Nominated Powered Secondary Endpoint			

Reviewer's Comment: Thus, overall, as can be seen in the summary Table 24 below, secondary endpoints trended towards supporting the efficacy of FF 100.

Table 24. Summary of Secondary Endpoints Supporting the 100 mcg Dose				
Secondary Endpoints	**FF112059**		**HZA106827**	
	FF 100	**FP 250 BID**	**FF 100**	**FF 100/25**
Rescue-Free 24 hour periods Difference v Pbo P value	14.8 <0.001	17.9 <0.001	8.7 0.007	19.2 <0.001
Symptom Free 24 Hour Periods Difference v Pbo P value	8.9 0.025	8.8 0.025	5.8 0.055	18.0 <0.001
PM, PEF Difference v Pbo P value	2.8 0.564	5.5 0.248		
AM, PEF Difference v Pbo P value	8.9 0.071	4.9 0.319		
AQLQ Difference v Pbo P value	0.33 0.007	0.16 0.185	0.15 0.073	0.30 <0.001
Number of withdrawals N (%) P value			6 (3) <0.001	7 (3) <0.001
Source: ISE Table 11, CSR FFA112059 Table 6.10, 6.15, 6.17, 6.19, 6.21, ISE Table 12, CSR HZA106827 Table 6.13, 6.21, 6.23				

6.1.5.2 Clinical Study in Support of FF 200 mcg

FFA114496

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 period as shown in Table 25. There was a slight numerical benefit for the FF 200 dose over the FF 100 dose for all secondary endpoints with the exception of AM PEF; however, no secondary endpoints were statistically better for the 200 mcg group.

Table 25. Secondary Endpoints for Trial FFA114496		
	FF 100	**FF 200**
Rescue-Free 24-hr Periods % N LS Mean Change Difference 95% CI	 108 21.3	 109 23.1 1.8 (-6.7, 10.3)
PM, PEF L/min N LS Mean Change Difference 95% CI	 108 5.9	 109 7.2 1.3 (-7.8, 10.4)
AM, PEF L/min N Change LS Mean Difference 95% CI	 108 13.4	 109 13.2 -0.2 (-9.2,8.8)
Symptom-free 24-hr periods % N LS Mean Change Difference 95% CI	 108 17.5	 109 19.6 2.1 (-5.7,9.9)
Source: CSR FFA112059 Table 6.14, 6.19, 6.23, 6.25		

Reviewer's Comment: Thus, in overall examination of both primary and secondary endpoints in this trial, there is numerical support for the benefit of the 200 mcg dose over the 100 mcg dose.

6.1.6 Other Endpoints

6.1.6.1 Clinical Studies in Support of FF 100 mcg

Other endpoints for study FFA112059 are depicted in Table 26 below, focusing on week 24 results for the ACT and Global Assessment of Change scores. FF 100 showed a statistically significant improvement versus placebo for ACT score and Global Assessment of Change, with no difference in withdrawals due to lack of efficacy or unscheduled healthcare visits for asthma. These results were similar for FP 250 BID.

Table 26. Supportive Efficacy Endpoints for Study FFA112059			
	Placebo	**FF 100**	**FP 250 BID**
ACT at 24 weeks, units N[2] LS Mean Change Difference v Placebo 95% CI p-value	 89 2.5	 102 3.9 1.4 (0.4,2.5) 0.006	 99 3.6 1.1 (0.1,2.1) 0.038
Global Assessment of Change at week 24 N Difference v Placebo OR 95% CI P value	 74	 92 2.08 (0.95, 4.53) 0.066	 89 1.43 (0.67,3.03) 0.353
Number of withdrawals due to lack of efficacy Versus placebo (p value)	 23	 15 0.214	 14 0.150
Unscheduled asthma healthcare contacts	115 110 (96%)	114 110 (96%)	114 11 (97%)
Source CSR FFA112059 6.25, 6.26, 6.28, 6.30			

Supportive efficacy endpoints for study HZA106827 are depicted in Table 27 below. There was a statistically significant difference for FF 100 versus placebo with regards to PM PEF, AM PEF, ACT, and Global Assessment scores, with no difference from placebo regarding healthcare visits.

Table 27. Supportive Efficacy Endpoints for Study HZA106827			
	Placebo	**FF 100**	**FF 100/VI 100/25**
PM, PEF L/min N LS Mean Difference v Placebo 95% CI p-value	 202	 204 15.9 (9.4,22.5) <0.001	 201 28.2 (21.7,34.8) <0.001
AM, PEF L/min N LS Mean Difference v Placebo 95% CI p-value	 203	 204 18.7 (12,25.4) <0.001	 201 33.3 (26.5,40) <0.001

Table 27. Supportive Efficacy Endpoints for Study HZA106827			
	Placebo	**FF 100**	**FF 100/VI 100/25**
ACT, units N[1] LS Mean Change Difference v Placebo 95% CI p-value	 154 2.5	 189 2.8 1.3 (0.6, 2) <0.001	 185 4.4 1.9 (1.2, 2.6) <0.001
Global Assessment of Change at week 12 N Difference v Placebo OR 95% CI P value	 152	 187 2.13 (1.26, 3.58) 0.005	 182 2.57 (1.50, 4.40) <0.001
Unscheduled asthma healthcare contacts N Unscheduled contacts	 203 197 (97%)	 205 201 (98%)	 201 199 (>99%)
Source: CSR HZA106827 Tables 6.38, 6.40, 6.42 1.Number of subjects with analyzable data from 1 or more visits			

Reviewer's Comment: Overall, the other endpoints examined in the above trials support the efficacy of the FF 100 mcg dose.

6.1.6.2 Clinical Study in Support of FF 200 mcg

FFA114496

Other endpoints in study FFA114496 included change from baseline in the ACT score, the incidence of severe asthma exacerbations, unscheduled healthcare contacts, subjects' competence with inhaler use, and ease of use questions.

The majority of subjects (>86% in each FF group) had poorly controlled asthma (ACT score less than 20) at baseline. At 24 weeks, ACT score changes were similar between FF 100 and FF 200 (difference of 0.2 (CI -0.7, 1.2)). When the Sponsor examined the data as percent of subjects controlled (ACT greater than or equal to 20), then the odds ratio was 1.42 (0.76, 2.68) indicating that the odds of a patient being well controlled on FF 200 versus FF 100 is 42% greater. There was no difference between severe asthma exacerbations or unscheduled healthcare contacts for asthma between the two doses. Both the FF 100 group and the FF 200 group used the inhaler correctly at week 4 (>98% and >99%, respectively), and both groups felt similarly that the inhaler was very easy to use (71% versus 66%, respectively).

Table 28. Supportive Efficacy Endpoints for Trial FFA114496		
	FF 100	**FF 200**
ACT, units N[1] LS Mean Change Difference v FF 100 95% CI	 104 4.6	 103 4.8 0.2 (-0.7, 1.2)
Incidence of severe exacerbations N Any on-treatment asthma exacerbation	 108 14	 111 13
Unscheduled healthcare contacts N All asthma-related unscheduled healthcare resource utilization	 108 107 (>99%)	 111 110 (>99%)
Source: CSR FFA112059 Table 6.29, 6.32, 6.34 1.Number of subjects with analyzable data from 1 or more visits		

6.1.7 Subpopulations

The statistical review team conducted subgroup analyses by sex, race (White, Black, Asian), age (≤ 18, 18-65, ≥ 65), and geographic region (non-U.S. versus U.S.) in studies HZA106827 and FFA XXXX29. Per the statistical review of Dr. Greg Levinson, estimated differences in mean trough FEV_1 comparing FF with placebo were largely consistent across the subgroups. There was a trend toward a smaller observed treatment effect in older patients in both studies, although tests for interaction between treatment and age (as a continuous variable) suggested that these observed differences may have been due to random chance (p-values of 0.63 and 0.25 in Studies 27 and 59, respectively). The limited numbers of Black and Asian patients led to large variability in the estimated treatment effects in these subgroups, and the number of Asians in Study 59 was too small to get a sufficiently reliable estimated treatment effect to report.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See information regarding dose-ranging studies in Section 4.4.2.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Efficacy persisted over the treatment period based on the data provided.

6.1.10 Additional Efficacy Issues/Analyses

HZA106829

HZA106829 was designed to assess for non-inferiority of FF 200 QD vs. FP 500 BID for the primary endpoint of mean change from baseline in trough FEV1 at week 24 with a pre-defined non-inferiority margin of -125 mL. The study had a co-primary endpoint of 0-24 hour weighted mean FEV1. Table 29 depicts the patient disposition for this study, and Table 30 depicts the primary efficacy analyses.

Table 29. Patient Disposition: HZA106829

	FF 200 N=194	FF/VI 200/25 N=197	FP 500 BID N=195	Total N=586
Completed	146 (75)	169 (86)	161 (83)	476 (81)
Withdrawn	48 (25)	28 (14)	34 (17)	110 (19)
Primary reason for withdrawal				
Adverse event	3 (2)	7 (4)	2 (1)	12 (2)
Lack of Efficacy	21 (11)	6 (3)	18 (9)	45 (8)
Exacerbation	5 (3)	0	1 (<1)	6 (1)
Protocol Deviation	5 (3)	3 (2)	5 (3)	13 (2)
Lost to Follow-up	2 (1)	0	1 (<1)	3 (<1)

Source: CSR HZA106829 Table 3

Table 30. Co-primary Endpoints for Study HZA106829

	FF 200	FP 500 BID
Week 24 Change in Baseline Trough FEV1		
N	186	190
LS Mean	2.358	2.341
LS Mean Change	0.201	0.183
Difference from FP 500 BID	0.018	
95% CI	(-0.066, 0.102)	
Week 24 Weighted Mean FEV1 (0-24 hr)		
N	83	86
LS Mean	2.532	2.463
LS Mean Change	0.328	0.258

Source: CSR HZA106829 Table 6.2, 6.9

Reviewer's Comment: [redacted] (b) (4) *this study provides guidance to providers who wish to switch their*

patients from FP to FF. Information regarding this study will be inserted into the product label, (b) (4) . It is of note, that both the trough and serial FEV1 measurements for FF 200 were numerically greater than those for FP 500 BID.

The secondary and other endpoints for trial HZA106829 were change in baseline AQLQ and percentage of symptom-free 24-hour periods as shown in Table 31 and Table 32. There was a slight numerical benefit of FP 500 BID over FF 200 for these endpoints.

Table 31. Secondary Endpoints for Trial HZA106829

	FF 200	FP 500 BID
AQLQ, units		
N[1]	157	195
LS Mean Change	0.88	0.90
Equivalent number of symptom free days per week, LS Mean Change from Baseline	1.5	1.7
Symptom-free 24-hr periods %		
N	193	194
LS Mean Change	21.0	24.5

Source: CSR HZA106829 Table 6.20, 6.22
1.Number of subjects with analyzable data from 1 or more visits

Table 32. Other Endpoints for Trial HZA106829

	FF 200	FP 500 BID
PM, PEF L/min		
N	192	194
LS Mean Change	9.1	13.6
AM, PEF L/min		
N	193	195
LS Mean Change	15.1	17.1
ACT, units		
N[1]	164	169
LS Mean Change	5.2	4.7
Number of withdrawals due to lack of efficacy, N, %	21/194 (11)	18/195 (9)

Source: CSR HZA106829 Table 6.27, 6.30, 6.31, 6.35

7 Review of Safety

Summary of Safety

To evaluate the safety of FF 100 mcg and 200 mcg, the Applicant has submitted a large safety database. The pooled safety database 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 and 608 subjects received FF 200. 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, which are described below. Serious adverse events were infrequent in the clinical development program. The most common SAE was asthma exacerbation, and most cases were from the FF 100 group from trial HZA106837 which allowed for a more severe asthma history and was of the longest duration (up to 76 weeks).

Drug discontinuation or withdrawal secondary to adverse events was also low in this clinical development program. In general, those adverse events that led to withdrawal are known to occur in asthma clinical development programs for ICS products. The most common adverse events 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.

Long-term safety of FF 100 mcg and FF 200 mcg was evaluated in trials HZA106837 and HZA106839. respectively. Overall, the long-term safety data was consistent with the safety see in the clinical development program.

Overall, the safety database is adequate, and no new safety signals were found for either the 100 mcg or 200 mcg dose of this ICS.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

For the assessment of FF safety, the Applicant utilized their pooled safety database which consists of the ten phase 2 and 3 studies listed in Table 34. A total of 6,219 subjects were exposed to at least one dose of study medication, including active comparators. Of note, these are not unique subjects, as subjects who participated in more than one study are counted more than once.

This review includes an evaluation of safety per the pooled safety database, focusing on the FF 100 mcg and FF 200 mcg, as these are the doses for which the Applicant seeks registration.

While HZA106839 is not part of the pooled safety database, it provides important safety information regarding FF 200 mcg, and is therefore also included in the long-term safety evaluation.

Table 33 summarizes the trials comprising the pooled safety database.

Table 33. Pooled Safety Database

Trial (device type)	Design	Weeks	Population	Treatment Arms	N
8-week trials					
FFA109687 (DS)	R, DB, DD, PC, PG	8	Asthma FEV1 am: 40-85% or pm: 40-90% Uncontrolled without ICS	FF 25 QD FF 50 QD FF 100 QD FF 200 QD FP 100 BID Placebo	97 100 110 95 102 94
FFA109685 (DS)	R, DB, DD, PC, PG	8	Asthma FEV1 am: 40-85% or pm: 40-90% Uncontrolled on low dose ICS	FF 100 QD FF 200 QD FF 300 QD FF 400 QD FP 250 BID Placebo BID	105 101 103 99 100 107
FFA109684 (DS)	R, PC, DB, PG	8	Asthma FEV1 am: 40-	FF 200 QD FF 400 QD FF 600 QD	99 101 107

Table 33. Pooled Safety Database					
Trial (device type)	**Design**	**Weeks**	**Population**	**Treatment Arms**	**N**
			85% or pm: 40-90% Uncontrolled on med dose ICS	FF 800 QD FP 500 BID Placebo	102 110 103
12-week Trials					
FFA115283 (SS)	R, DB, PC, PG	12	Asthma FEV1 ≥ 60% No ICS	FF 50 QD Placebo	121 121
HZA106827 (DS)	R, DB, PG, PC	12	Asthma FEV1 40-90% Low-mid ICS	FF/VI 100/25 QD FF 100 QD Placebo	201 205 203
24-week trials					
FFA115285 (SS)	R, DB, DD, PC, AC, PG	24	Asthma FEV1 ≥ 60% Not on ICS	FF 50 QD FP 100 BID Placebo	117 115 115
FFA1114496 (SS)	R, DB, PG	24	Asthma FEV1 40-90% Mid-high ICS	FF 100 QD FF 200 QD	119 119
FFA112059 (SS)	R, DB, DD, PC, PG	24	Asthma FEV1 40-90% Low-mid ICS	FF 100 QD FP 250 BID Placebo	114 114 115
HZA106829 (DS)	R, DB, DD, PG, AC	24	Asthma FEV1 40-90% Mid-high ICS	FF/VI 200/25 QD FF 200 QD FP 500 BID	197 194 195
Up to 76-week trials					

Table 33. Pooled Safety Database					
Trial (device type)	**Design**	**Weeks**	**Population**	**Treatment Arms**	**N**
HZA106837 (DS)	R, DB, PG	76	Asthma FEV1 50-90% Low-high ICS	FF/VI 100/25 QD FF 100 QD	1009 1010
Source: Module 5.2, Tabular listing of all clinical studies and individual CSR R = randomized, DB = double-blind, DD=double dummy, PC = placebo controlled; AC = active control, PG=parallel group; SS=single-strip, DS=double-strip					

In addition, study HZA106839 was 52-week, randomized, double-blind, active comparator, parallel-group study examining FF/VI 100/25 QD, FF/VI 200/25 mcg QD, and FP 500 mcg BID that provides support for the long-term safety of FF 200.

7.1.2 Categorization of Adverse Events

In the Applicant's Integrated Summary of Safety (ISS), Adverse Events (AEs) are defined as any untoward medical occurrence in a patient or clinical investigational subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A Serious Adverse Event (SAE) is defined according to the regulatory definition[1].

All adverse events in the ISS were coded or re-coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1. For specific safety concerns associated with use of ICSs, GSK identified a list of specific Adverse Events of Special Interest and defined these using a comprehensive list of MedDRA Preferred Terms. The events, categorized into Groups and Subgroups, are as follows:

- Bone Disorders
- Effects on Glucose
- Hypersensitivity
- Local Steroid Effects
- Ocular Effects
- Pneumonia and Lower Respiratory Tract Infection
    - Pneumonia

[1] 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.

- Lower Respiratory Tract Infection (excluding pneumonia)
- Systemic Corticosteroid Effects – Effect on HPA-Axis

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

The pooled safety database includes ten parallel-group Phase 2 and 3 studies conducted with either the single-strip or double-strip DPI. Other studies conducted were not integrated as they had a different design (i.e. crossover) or were ongoing. While the duration of studies varies from 8 weeks to 76 weeks, the pooling strategy was adequate to allow for review.

7.2 Adequacy of Safety Assessments

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

Table 34 illustrates the total number of subjects exposed per dose strength in the pooled safety database.

Table 34. Number Exposed Per Dose in the Pooled Safety Database

		FF (mcg) once a day							
	Placebo	**25**	**50**	**100**	**200**	**300**	**400**	**600**	**800**
All studies	858	97	338	1663	608	103	200	107	102
8 week									
FFA109687 (DS)	94	97	100	110	95				
FFA109685 (DS)	107			105	101	103	99		
FFA109684 (DS)	103				99		101	107	102
12 week									
FFA115283 (SS)	121		121						
HZA106827 (DS)	203			205					
24 week									
FFA115285 (SS)	115		117						
FFA114496 (SS)				119	119				
FFA112059 (SS)	115			114					
HZA106829 (DS)					194				
Up to 76 weeks									
HZA106837 (DS)				1010					

Source: Tabular Listing of all Clinical Studies

Table 35 illustrates the total number exposed per the dose strengths 100 and 200 mcg doses, including study HZA106839 and is divided by single-strip and double-strip device.

Table 35. Total Safety Database

Pooled Safety Database						
	100 mcg			**200 mcg**		
	SS	**DS**	**Both**	**SS**	**DS**	**Both**
Total number exposed	233	1430	1663	119	489	608
At least 6 months	233	1010	1243	119	194	313
At least 1 year	0	1010	1010	0	0	0
Pooled Safety Database plus HZA106839 (52 weeks)						
	100 mcg			**200 mcg**		
	SS	**DS**	**Both**	**SS**	**DS**	**Both**
Total number exposed	233	1631	1864	119	691	810
At least 6 months	233	1211	1444	119	396	515
At least 1 year	0	1211	1211	0	202	202

Source: Tabular Listing of Clinical Studies

This review will focus on the treatment groups of FF 100 mcg and FF 200 mcg, as these are the doses for which the Applicant seeks registration. The extent of exposure to FF 100 mcg and FF 200 mcg in the pooled safety database is summarized below in Table 36.

Table 36. Extent of Exposure in the Pooled Safety Database		
Study drug	**FF 100 N=1663**	**FF 200 N=608**
Exposure (Days)		
Mean	259.3	102.3
Total Subject Years		
	259.3	102.3
Range of Exposure, n (%)		
1 day – 4 weeks	50 (3)	42 (7)
>4 – 8 weeks	107 (6)	120 (20)
>8 – 12 weeks	204 (12)	166 (27)
>12 – 16 weeks	138 (8)	9 (1)
>16 – 20 weeks	20 (1)	6 (<1)
>20 – 24 weeks	113 (7)	132 (22)
>24 – 28 weeks	103 (6)	129 (21)
>28 – 32 weeks	9 (<1)	0
>32 – 36 weeks	11 (<1)	0
>36 – 40 weeks	7 (<1)	0
>40 – 44 weeks	7 (<1)	0
>44 – 48 weeks	48 (3)	0
>48 – 52 weeks	307 (18)	0
>52 weeks	537 (32)	0
Source: ISS Table 11		

The extent of exposure for FF 100 mcg was 1180 subject-years. The extent of exposure for FF 200 mcg was 170 subject years. Exposure was greatest for FF 100

because it was administered in the asthma exacerbation study HZA106837 with a potential duration of up to 76 weeks. The duration of exposure was longest for the FF 100 treatment arm (mean exposure 259.0). The extent of exposure to both FF 100 and 200 mcg was adequate.

Demographics

The demographics of the safety database was similar to that described for the confirmatory trials in Section 6. The safety population was comprised predominantly of female Caucasian subjects, with a mean age of 40-41 years, who had asthma for over 10 years. See Section 6.1.2 for specific demographic data.

7.2.2 Explorations for Dose Response

The inclusion of two doses of FF (100 mcg, 200 mcg) into the phase 3 trials allows for an exploration of dose dependency for ICS safety and is discussed throughout this review.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in-vitro testing was performed nor required for this application.

7.2.4 Routine Clinical Testing

Routine testing in this development program included serum chemistry including liver function tests, hematology, pregnancy testing, hepatitis B testing, and hepatitis C testing. Other testing, depending on the study, included serum IgE, pharmacogenetics, urinary cortisol, and 12-lead ECGs.

Serum chemistry evaluation generally included measurements of albumin, alkaline phosphatase, alanine amino-transferase, aspartate amino-transferase, direct/indirect/total bilirubin, calcium, chloride, bicarbonate, creatinine, creatinine phosphokinase, gamma glutamyl transferase, glucose, phosphorus, potassium, total protein, sodium, urea nitrogen and uric acid. The hematology evaluation included hemoglobin, hematocrit, platelet count, white blood cell count, neutrophil, segmented neutrophils, basophils, eosinophils, lymphocytes and monocytes.

7.2.5 Metabolic, Clearance, and Interaction Workup

Data from three FF/VI clinical pharmacology studies have been used to support this submission. Study HZA111789 examined the effects of hepatic impairment, study HZA113970 examined the effects on renal impairment, and study HZA105548 examined drug-drug interactions. The clinical impact of these studies is summarized in

Section 7.5.4 and 7.5.5, and the results are discussed in further detail in the Clinical Pharmacology Summary Document.

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

The pivotal trials incorporated monitoring for toxicities associated with ICS use by evaluating AEs for episodes of pneumonia, bone disorders, local and systemic corticosteroid effects, and ocular disorders, and these results are provided in Section 7.3.5.1.

7.3 Major Safety Results

7.3.1 Deaths

There were two deaths in the pooled safety database. Both subjects were receiving FF 100 mcg as part of trial HZA106837. The first subject was a 65-year-old Asian male who was diagnosed with stage IV bronchogenic carcinoma 173 days after starting treatment with FF. He expired 91 days later from respiratory failure. The second subject was a 62-year-old White male who developed pneumonia 114 days after starting treatment with FF. He was hospitalized 2 days later and died of sepsis and pneumonia with a secondary cause of death of diabetes mellitus. Overall, these deaths do no raise any new safety signals.

7.3.2 Nonfatal Serious Adverse Events

The serious adverse events in the pooled safety database are presented in Table 37.

Table 37. Serious Adverse Events in the Pooled Safety Database

	Placebo N= 858	**FF100 N=1663**	**FF200 N=608**
Any Event	7 (<1%)	38 (2%)	7 (1%)
Infections and Infestations	3 (<1%)	10 (<1%)	3 (<1%)
Pneumonia	1 (<1%)	4 (<1%)	1 (<1%)
Abscess	0	1 (<1%)	1 (<1%)
Pyelonephritis	1 (<1%)	1 (<1%)	0

Table 37. Serious Adverse Events in the Pooled Safety Database

	Placebo N= 858	FF100 N=1663	FF200 N=608
Respir, thorac & mediast.	1 (<1%)	11 (<1%)	1 (<1%)
Asthma	1 (<1%)	9 (<1%)	1 (<1%)
Muskuloskeletal and connective tissue	0	3 (<1%)	2 (<1%)
Intervertebral disk protrusion	0	1 (<1%)	1 (<1%)
Chondromalacia	0	1 (<1%)	0
Neoplasms	0	4 (<1%)	1 (<1%)
Breast Cancer	0	1 (<1%)	0
Prostate cancer	0	1 (<1%)	0
Skin and subcutaneous tissue disorders	0	2 (<1%)	0
Angioedema	0	1 (<1%)	0
Gastrointestinal disorders	0	2 (<1%)	0
Pancreatitis	0	1 (<1%)	0
Hepatobiliary Disorders	1 (<1%)	1 (<1%)	1 (<1%)
Cholelithiasis	1 (<1%)	1 (<1%)	0
Nervous system disorders	0	3 (<1%)	0
Cerebrovascular accident	0	1 (<1%)	0
Subarachnoid hemorrhage	0	1 (<1%)	0
Psychiatric disorders	0	2 (<1%)	0
Anxiety	0	1 (<1%)	0
Depression	0	1 (<1%)	0

Source: ISS table 2.27 and 2.28

Overall, 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 as 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.

7.3.3 Dropouts and/or Discontinuations

This section discusses rates of adverse events leading to study drug discontinuation or withdrawal; rates of overall study dropout are discussed in Section 6.1.3. The most frequent AEs leading to withdrawal were asthma exacerbations (N=3 (<1%) in the FF 100 group, N=1 (<1%) in the FF 200 group, and N=1 (<1%) in the placebo group), dyspnea (N=1 (<1%) in the FF 100 group and N=1 (<1%) in the placebo group), and pneumonia (N=2 (<1%) in the FF 100 group, N=1 (<1%) in the FF 200 group, and N=1 (<1%) in the placebo group).

Overall, drug discontinuation or withdrawal secondary to adverse events was low in this clinical development program. In general, those adverse events that led to withdrawal are known to occur in asthma clinical development programs for ICS products. Review of the adverse events leading to dropout/discontinuation does not reveal any new safety signals.

7.3.4 Significant Adverse Events

Adverse events of special interest for ICS are discussed in Section 7.3.5.1. Rates of study drug discontinuation and withdrawals due to Adverse Events are discussed in Section 7.3.3.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) related to ICS use were categorized as the following by the Sponsor:

- Bone Disorders
- Effects on Glucose
- Hypersensitivity
- Local Steroid Effects
- Ocular Effects
- Pneumonia and Lower Respiratory Tract Infection
    - Pneumonia
    - Lower Respiratory Tract Infection (excluding pneumonia)
- Systemic Corticosteroid Effects – Effect on HPA-Axis

These AESI are listed in Table 38 below.

Table 38. Adverse Events of Special Interest

AE of Special Interest (Preferred Term), n (%)	Placebo N=858	FF 100 N=1663	FF 200 N=608
Local Steroid Effects	15 (2)	122 (7)	48 (8)
LRTI excluding pna	16 (2)	114 (7)	19 (3)
Hypersensitivity	13 (2)	41 (2)	6 (<1)
Bone disorders	0	21 (1)	2 (<1)
Pneumonia	2 (<1)	10 (<1)	4 (<1)
Effects on Glucose	0	11 (<1)	2 (<1)
Ocular Effects	0	6 (<1)	0

AE of Special Interest (Preferred Term), EA[1]	Placebo (185.6)[2]	FF 100 (1179.4)	FF 200 (169.2)
Local Steroid Effects	80.0	103.4	283.8
LRTI excluding pna	86.2	96.7	112.3
Hypersensitivity	70.0	34.8	35.5
Bone disorders	0	17.8	11.8
Pneumonia	10.8	8.5	23.6
Effects on Glucose	0	9.3	11.8
Ocular Effects	0	5.1	0

Source: ISS Table 40
1.Exposure adjusted representing the number of subjects with an event per 1000 subject-years exposure
2.Subject years

The most frequent adverse events of special interest were local steroid effects and lower respiratory tract infections excluding pneumonia. Hypersensitivity, bone disorders, pneumonia, effects on glucose, and ocular effects occurred in ≤ 1% of subjects.

7.3.5.2 Safety Analysis by Device Configuration

The clinical development program for FF monotherapy was conducted concurrently with the development program for FF combination therapy with Vilanterol. As a result, many of the initial FF studies were conducted with a double-strip device, in which one strip contained FF and the other strip contained placebo. The exposure to FF via the single-strip (to-be-marketed) device was found to be more than the delivered dose of FF as part of the double-strip device (whether the second strip contained placebo or another active drug (VI)), there was concern that the safety data (much of which was generated with the double strip device) submitted may not be representative of the to-be-marketed device. The differences between devices are detailed further in the review of Dr. Jianmeng Chen, the clinical pharmacology reviewer. As a result, the safety data by

device configuration was compared and reviewed, so as to evaluate any potential clinical safety differences between the single-strip and double-strip devices. Safety analysis by device configuration is summarized in Table 39.

Table 39. Safety Analysis by Device Configuration

Dose	Placebo	FF 100		FF 200	
Device Configuration		**Single-strip**	**Double-strip**	**Single-strip**	**Double-strip**
Total Exposed	858	233	1430	119	489
Common AEs[1], n (%)					
Any AE	278 (32)	1130 (56)	782 (55)	75 (63)	181 (37)
Headache	66 (8)	19 (8)	209 (15)	15 (13)	29 (6)
Nasopharyngitis	45 (5)	23 (10)	158 (11)	15 (13)	38 (8)
URTI	16 (2)	9 (4)	102 (7)	7 (6)	8 (2)
Bronchitis	15 (2)	22 (9)	76 (5)	8 (7)	7 (1)
Oropharyngeal pain	11 (1)	6 (3)	65 (5)	5 (4)	14 (3)
SAE, n (%)					
Any SAE	7 (<1)	7 (3)	31 (2)	4 (3)	3 (<1)
Deaths	0	0	2 (<1)	0	0
Asthma	1 (<1)	0	9 (<1)	0	1 (<1)
Pneumonia	1 (<1)	0	4 (<1)	0	1 (<1)
Abscess	0	1 (<1)	0	1 (<1)	0
Pyelonephritis	1 (<1)	1 (<1)	0	0	0
AE Leading to Withdrawal, n (%)					
Any AE	8 (<1)	5 (2)	23 (2)	2 (2)	8 (2)
Asthma	1 (<1)	0	3 (<1)	0	1 (<1)
Pneumonia	1 (<1)	0	2 (<1)	0	1 (<1)
AE of Special Interest, n (%)					
Local Steroid Effect	15 (2)	15 (6)	107 (7)	15 (13)	33 (7)
LRTI (excluding pna)	16 (2)	22 (9)	92 (6)	10 (8)	9 (2)
-Bronchitis	15 (2)	22 (9)	76 (5)	8 (7)	7 (1)
Hypersensitivity	13 (2)	8 (3)	33 (2)	2 (2)	4 (<1)
Bone disorders	0	2 (<1)	19 (1)	1 (<1)	1 (<1)
Effects on Glucose	0	3 (1)	8 (<1)	0	2 (<1)
Pneumonia	2 (<1)	1 (<1)	9 (<1)	1 (<1)	3 (<1)
Ocular Effects	0	1 (<1)	5 (<1)	0	0

Table 39. Safety Analysis by Device Configuration					
Dose	**Placebo**	**FF 100**		**FF 200**	
Device Configuration		**Single-strip**	**Double-strip**	**Single-strip**	**Double-strip**
Total Exposed	858	233	1430	119	489
Total subject years	185.6	98.2	1081.14	51.71	117.44
Common AEs[1,2]					
Headache	355.6	193.4	193.3	290.1	246.9
Nasopharyngitis	242.5	234.2	146.1	290.1	323.6
URTI	86.2	91.6	94.3	135.4	68.1
Bronchitis	80.8	224.0	70.3	154.7	59.6
Oropharyngeal pain	59.3	61.1	60.1	96.7	119.2
SAE[2]					
Asthma	5.4	0	8.3	0	8.5
Pneumonia	5.4	0	3.7	0	8.5
Abscess	0	10.2	0	19.3	0
Pyelonephritis	5.4	10.2	0	0	0
AE Leading to Withdrawal[2]					
Asthma	5.4	0	2.8	0	8.5
Pneumonia	5.4	0	1.8	0	8.5
AE of Special Interest[2]					
Local Steroid Effect	80.8	152.7	99.0	290.1	281.0
LRTI (excluding pna)	86.2	224.0	85.1	193.4	76.6
Bronchitis	80.8	224.0	70.3	154.7	59.6
Hypersensitivity	70.0	81.4	30.5	38.7	34.1
Bone disorders	0	20.4	17.6	19.3	8.5
Effects on Glucose	0	30.5	7.4	0	17.0
Pneumonia	10.8	10.2	8.3	19.3	25.5
Ocular Effects	0	10.2	4.6	0	0

Source: ISS Table 24, 33, 36, 39
1.Five most frequently observed common AEs
2.Number of subjects with an event per 1000 subject years exposure

For common AEs, SAEs, AE leading to withdrawals, and AESI, no clear pattern emerged that illustrated higher risk with the single-strip device. While some AESI occurred more frequently in the single-strip versus double-strip configuration, this was not consistent across dose-strengths, types of AESIs, or AE severity.

While the clinical review acknowledges that the delivery characteristics of FF are different when single- and double-strip devices are compared, the information from the double-strip device is not markedly different, and therefore, can be used to support the safety of the single-strip device.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse events (occurring in > 3% of subjects) are shown in Table 40 below.

Table 40. Most Common Adverse Events (≥3%) in the Pooled Safety Database

	Placebo N=858	FF100 N=1663	FF200 N=608
Preferred Term, n (%)			
Any AE	278 (32)	912 (55)	256 (42)
Headache	66 (8)	228 (14)	44 (7)
Nasopharyngitis	45 (5)	181 (11)	53 (9)
Upper respiratory tract infection	16 (2)	111 (7)	15 (2)
Bronchitis	15 (2)	98 (6)	15 (2)
Oropharyngeal pain	11 (1)	71 (4)	19 (3)
Cough	9 (1)	68 (4)	13 (2)
Pharyngitis	24 (3)	55 (3)	8 (1)
Sinusitis	8 (<1)	53 (3)	15 (2)
Influenza	9 (1)	45 (3)	17 (3)
Back pain	4 (<1)	52 (3)	11 (2)
Dysphonia	4 (<1)	23 (<1)	11 (2)
Rhinitis	7 (<1)	27 (2)	7 (1)
Respiratory Tract infection - viral	0	18 (1)	8 (1)

Source: ISS Table 25

The most common adverse events 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. These adverse events do not raise any new safety signals for an ICS.

7.4.2 Laboratory Findings

There were no clinically meaningful effects on hematologic or chemistry parameters noted from the FF development program.

7.4.3 Vital Signs

A review of the vital sign data from the pooled safety database does not reveal any clinically meaningful differences among treatment groups.

7.4.4 Electrocardiograms (ECGs)

There were no ECG abnormalities observed in the key treatment groups in the pooled safety database.

7.4.5 Special Safety Studies/Clinical Trials

Data from the FF/VI trial HZA106851 is being used to support HPA-axis safety in this application. This was a 6-week, double-blind, placebo-and active-controlled study in asthmatic subjects to evaluate HPA axis suppression at the therapeutic doses. Fifty-six subjects each were given multiple, once daily inhalations of either FF/VI 100/25 or 200/25, 58 subjects received placebo, and 15 subjects received placebo plus prednisolone 10 mg daily on the last 7 days of treatment. 0-24 hour weighted mean serum cortisol was assessed at baseline and at the end of a 6-week treatment period. The derived serum cortisol weighted means (0-24 h) were similar at baseline and 6 weeks for placebo and the FF/VI groups (<3% change from baseline).

Additionally, a PK/PD meta-analysis of 9 studies was conducted to characterize the relationship between FF $AUC_{(0-24)}$ and 24-hour weighted mean serum cortisol. The average estimate of FF $AUC_{(0-24)}$ required to reduce cortisol by 50% (AUC_{50}) was 1,345 pg•hr/mL, which is several-fold higher than average FF $AUC_{(0-24)}$ values observed at the therapeutic dose of fluticasone furoate 100 mcg (184 pg•hr/mL) in subjects with COPD.

7.4.6 Immunogenicity

Immunogenicity is not applicable to this product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

As noted in Section 7.2.2, the dose dependency for adverse events is discussed throughout this review.

7.5.2 Time Dependency for Adverse Events

GSK provided summary tables for adverse events with an onset during the first 6 months of studies and with onset greater than 6 months after randomization for the two

long-term studies, HZA106837 and HZA113989. An analysis of both reveals no difference in the most common adverse events.

7.5.3 Drug-Demographic Interactions

The application includes an analysis of adverse events by gender, age, and race. Overall, the same adverse events are reported by male and female patients as well as those ≤ 64 and > 65 years of age. A review of the data by race is limited by the low number of patients in non-white race groups; however no consistent pattern is evident in the pooled safety database.

7.5.4 Drug-Disease Interactions

The application includes an analysis of adverse events based on renal and hepatic impairment. The effect of renal impairment was assessed in trial HZA113970, an open-label, non-randomized, PK and safety study. Systemic FF exposure was lower in severe renal impairment patients; at day 7, FF median $AUC_{(0-24)}$ and C_{max} were 21% and 27% lower in subjects with severe renal impairment compared to subjects with normal renal function. No dose adjustments are recommended for subjects with renal impairment

The effect of hepatic impairment was assessed in trial HZA111789, and the results indicate that FF exposure increases in patients with all severities of hepatic impairment. Mean percentage change in FF AUC for subjects with mild, moderate and severe hepatic impairment versus normal hepatic function were 34%, 83%, and 75%, respectively. The biggest observed PD change was a 34% decrease in serum cortisol with the 200 mcg dose in moderate hepatic impairment patients. This change in serum cortisol is similar to the level when 200 mcg FF is co-administered with ketoconazole (27%). As the magnitude of increased exposure for FF in hepatic impairment patients is similar to other inhaled corticosteroids and as there is no dose cap for patients on ketoconazole in combination with FF, at the time of this review, the clinical pharmacology team recommends making both FF 100 and 200 mcg doses available to moderate and severe hepatic impaired patients with cautionary labeling language.

7.5.5 Drug-Drug Interactions

Trial HZA105548 evaluated the effects of co-administration with ketoconazole. Co-administration with ketoconazole resulted in modest increases in mean FF $AUC_{(0-24)}$ and C_{max} (by 36% and 33%, respectively). Steroid-mediated systemic effects were observed with a 27% reduction in weighted mean serum cortisol (0-24 h). The labeling will indicate that caution should be exercised when considering co-administration with ketoconazole and other known strong CYP3A4 inhibitors, and per the clinical pharmacology team at the time of this review, no dose adjustment is recommended for FF when co-administered with ketoconazole.

In regards to other drug-drug interactions, FF oral inhalation produces low systemic exposures, so the potential for inhibition and induction of metabolic enzymes is negligible.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No specific trials were conducted to assess for carcinogenicity in humans. See Division Memorandum for an overview of the toxicology program.

7.6.2 Human Reproduction and Pregnancy Data

To date, 19 pregnancies were reported from the placebo and FF arms of the FF clinical program. Of these, 16 had known outcomes at the time of the report. Of the 16 known outcomes, 7 pregnancies resulted in live births, 7 were spontaneous abortions, 1 was a stillbirth, and 1 was electively terminated. There is no consistent imbalance noted in the reports of spontaneous abortion amongst placebo, FF, and FP (placebo: 1; FF 50: 0; FF 100: 2; FF 200: 1; FF other doses: 3; FP: 0) and stillbirths (placebo: 0; FF 50: 0; FF 100: 1; FF 200: 0; FF other does: 0; FP: 1).

Twelve (12) pregnancies were reported in subjects receiving FF/VI. Of these, 11 had known outcomes. There were 7 live births and 2 spontaneous abortions. There is one report of a congenital abnormality of a patent ductus arteriosus and ventricular septal defect that occurred in the FF/VI 100/25 mcg dose group, and there was one premature delivery in which the neonate died 5 days after delivery from respiratory distress syndrome in the FF/VI 100/25 mcg group.

Three pregnancies were reported in trial HZA116863 in the 120-day safety update. Two of the pregnancies were ongoing at the time of the report, and the third had resulted in miscarriage. This patient was receiving FF 200/25 once daily.

Given the background frequency of events expected in pregnancy, it is not possible to establish a causal relationship between the reported pregnancy outcomes and FF.

7.6.3 Pediatrics and Assessment of Effects on Growth

GSK has requested that a deferral be granted for pediatric patients 5-11 years of age and has also requested a waiver for pediatric patients <5 years of age (b) (4)

Table 41 depicts the pediatric clinical pharmacology studies.

Table 41: Pediatric Clinical Pharmacology Studies

Trial	Design	Population	N	Treatment	Duration (weeks)	Primary endpoint
HZA102942 (Completed)	R, DB, CO, PC	5-11 yo Persistent asthma	27	FF 100 mcg QD Placebo	2, 2 week periods	Safety/tolerability
HZA112777 (Ongoing)	R, DB, CO	5-11 yo Persistent asthma	26	FF/VI 100/25 mcg QD FF 100 mcg QD	2, 2 week periods	PK

Source: PSP, Section 9.1
yo=years old; SABA=short-acting bronchodilator

Table 42 depicts the studies in the proposed pediatric clinical studies.

Table 42. Proposed Pediatric Clinical Studies

Trial	Design	Population	N	Treatment	Duration (weeks)	Primary endpoint
HZA106855 (Ongoing)	R, DB, DD, PG, PC, AC	5-11 yo Asthma on LTM or ICS	575	FF 100 mcg QHS FF 50 mcg QHS FF 25 mcg QHS FP 100 mcg BID Placebo BID	12	PEF
HZA107112 (Planned)	R, DB, PC, CO	5-11 yo Asthma not on ICS/INS	75	FF QHS[1] Placebo QHS	2, 2 week periods	Mean growth rate in lower leg length
HZA114971 (Planned)	R, DB, PG, AC	5-<8 yo females 5-<9 yo males Asthma not on ICS	TBD	FF QHS[1] Montelukast QHS	52	Mean growth velocity
HZA107118 (Planned)	R, DB, PG, PC	5-11 yo No ICS/INS	80	FF QHS[1] Placebo QHS	6	0-24 hour weighted mean serum cortisol; non-inferiority

Source: PSP, Table 2
yo=years old; ICS=Inhaled corticosteroid; LTM=leukotriene modifier; INS=intranasal steroid; PEF=peak end expiratory flow; QHS=every evening. 1.Dose selected from phase 2b studies.

The initial pediatric plan was submitted July 26, 2013 in advance of the NDA submission, and 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, and HPA axis study. GSK agreed and resubmitted the pediatric study plan as part of the NDA on January 22, 2014. The second submission was reviewed by PeRC on February 12, 2014 and found to be acceptable, with the request to change the reason for a waiver from (b) (4)" to "clinical studies in this population are impractical."

As of the 120-day safety update, 495 subjects have been randomized into the pediatric development program.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Given the nature of the drug components, drug abuse, withdrawal, and rebound are not anticipated for this drug product. Additionally, the mode of administration and low systemic bioavailability (14%) make abuse less likely. However, theoretically, abrupt stoppage of excessive dosages of FF may result in an adrenal crisis. The product labels for other ICS-containing products contain warning language regarding this risk.

7.7 Additional Submissions / Safety Issues

7.7.1 120-day safety update

GSK submitted its 120-day safety update on February 20, 2014, which includes all new clinical safety data from the clinical program from February 16, 2013 through January 1, 2014. In general, the data from this safety update are similar to those seen within the initial NDA application. There were no additional deaths in any of the trials. The adverse event profile reported in the safety update was similar to that which has been described in this review. No new safety signals were noted in the 120-day safety update.

7.7.2 Long-term Safety

Two studies provide long-term safety information for FF 100 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.

7.7.2.1 Study HZA106837

Objectives/Rationale

Primary:

- To demonstrate that treatment with FF/VI once-daily administered in the evening significantly decreases the risk of severe asthma exacerbations as measured by time to first severe asthma exacerbation when compared with the same dose of FF alone administered once-daily in the evening in subjects 12 years of age and older with asthma

Study Design and Conduct

Overview:
HZA106837 was a multicenter, randomized, double-blind, parallel group study. Subjects entered a 2-week run-in, and during this time, subjects continued to use their current ICS therapy at a fixed dose. At randomization (visit 2), subjects who met the eligibility criteria were required to stop their ICS therapy for the duration of the treatment period and were randomly assigned to receive one of the following two double-blind treatments in a 1:1 ratio:

• FF/VI 100/25 via NDPI once-daily in the evening
• FF 100 via NDPI once-daily in the evening

The duration of the treatment period was variable and was dependent on the number of events (number of subjects with one or more severe asthma exacerbations) that occurred. The study continued until 330 events occurred. Treatment duration was at least 24 weeks and did not exceed 76 weeks for any completed subject. Subjects attended up to 11 on treatment visits (visits 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13/End of Study). Visits 3-12 were to be as-needed, dependent on the subject's treatment length. Visits 2 through 13 were in the evening between 5 PM and 11 PM. A follow-up contact was performed 1 week after completing study medication. Total duration of study participation was up to a maximum of 79 weeks (including screening, treatment and follow-up). Table 43 summarizes the study assessments.

Table 43. Study Assessments: Study HZA106837

Visit	1	2	3	4	5	6	7	8	9	10	11	12	EOS	EW	+14
Week	-2		2	6	12	20	28	36	44	52	60	68	76		
Day	-14	1	14	42	84	140	196	252	308	364	420	476	532		+7
Written Informed Consent	X														
Subject Demography	X														

Table 43. Study Assessments: Study HZA106837															
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**EOS**	**EW**	**+14**
Week	**-2**		**2**	**6**	**12**	**20**	**28**	**36**	**44**	**52**	**60**	**68**	**76**		
Day	**-14**	**1**	**14**	**42**	**84**	**140**	**196**	**252**	**308**	**364**	**420**	**476**	**532**		**+7**
Medical History	X														
Asthma History	X														
Therapy History	X														
Physical Examination	X							X					X	X	
Inclusion/Exclusion Criteria	X	X													
Dispense Investigational Product		X	X	X	X	X	X	X	X	X	X	X			
Collect Investigational Product			X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Rescue Medication	X	X	X	X	X	X	X	X	X	X	X	X			
Collect Rescue Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy Assessments															
FEV_1[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
FEV_1 Reversibility	X														
ACQ7		X			X			X					X	X	
Subject Diary Review/Collection		X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Subject Diary	X	X	X	X	X	X	X	X	X	X	X	X			
Safety Assessments															
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG Assessment	X														
Vital Sign Assessment[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Assessment		X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Severe Asthma Exacerbation		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments															
Clinical Laboratory Assessment[6]	X														

Table 43. Study Assessments: Study HZA106837

Visit	1	2	3	4	5	6	7	8	9	10	11	12	EOS	EW	+14
Week	-2		2	6	12	20	28	36	44	52	60	68	76		
Day	-14	1	14	42	84	140	196	252	308	364	420	476	532		+7
Liver Safety Assessment					X		X			X			X	X	
Serum Pregnancy Testing[7]	X				X		X			X			X	X	
Urine Pregnancy Testing[7]		X	X	X		X		X	X		X	X			X
PGx Sampling[8]							X[8]								

Source CSR 106837 Table 31
EOS=End of study
EW=Early Withdrawal
1.Visit 1 was performed at any time during the day. Visits 2 through 13 were performed in the evening between 5 PM and 11 PM.
2.Final treatment date was dependent on the number of events (number of subjects with one or more severe asthma exacerbation) that occurred. Final treatment day was to include all assessments as specified for Visit 13.
3.Assessment performed pre-dose.
4.Only SAEs related to study participation were supposed to be recorded in the eCRF.
5.Includes Liver Safety Assessment
6.Women of childbearing potential only
7.The PGx sample was collected at any one visit after the PGx consent was signed and the subject was randomized.

Study Population

Inclusion Criteria
Inclusion criteria were similar to the other integrated studies in Section 5 with the exception of:

- The lower limit of FEV1 was 50%, not 40%
- Subjects were to be on a dose of ICS equivalent to FP 200-1000 mcg/day or combination product equivalent to FP/salmeterol 200/100-500/100 mcg/day for at least 12 weeks prior to visit 1
- Subjects were to have a history of ≥1 asthma exacerbations that required treatment with systemic corticosteroids, emergency department visits, or in-patient hospitalization within 12 months prior

Exclusion Criteria
Exclusion criteria were similar to the other integrated studies in Section 5 with the exception that subjects could not have a history of life-threatening asthma in the past 5, not 10, years.

Study Treatments

Treatment groups were as follows:

- FF/VI 100/25 via NDPI once-daily in the evening

- FF 100 via NDPI once-daily in the evening

All treatments were double-blinded. The FF 100 mcg NDPI was the double-strip device, not the to-be-marketed drug device.

Efficacy Endpoints

Primary Efficacy Endpoint

- Time to first severe asthma exacerbation

Secondary Efficacy Endpoints

- Rate of severe asthma exacerbation per subject per year
- Change from baseline at week 36 in PM pre-dose trough FEV1
    - At visit 1, pre-dose FEV1 was measured at any time of day. For all other visits, pre-dose PM trough FEV1 was measured between 5:00 PM and 11:00 PM.
    - The highest of three technically acceptable measurements was recorded

Other Efficacy Endpoints

- Characterization of severe asthma exacerbations through exploration of use of rescue medication ±14 days around the onset of a severe asthma exacerbation
- Change from baseline in PM pre-dose trough FEV1
- Proportion of subjects with an ACQ7 score of ≤0.75 at week 36
- Proportion of subjects with an ACQ7 score of ≤0.75 at week 12

Safety Endpoints

- Number of hospitalizations due to severe asthma exacerbations
- Number of emergency department/urgent care clinic visits due to severe asthma exacerbations
- Number of unscheduled health care provider visits due to severe asthma exacerbations
- Number of intubations due to severe asthma exacerbations
- Incidence of adverse events throughout the treatment period
- Pre-dose vital sign assessments at all visits
- Liver safety assessments at screening, week 12, week 28, week 52 and last on treatment visit
- Clinical chemistry and hematology laboratory evaluations for Japanese subjects

7.7.2.2 Study HZA106839

Objectives/Rationale

- To assess the safety and tolerability of 12 months treatment with two strengths of inhaled FF/VI once-daily in the evening in subjects 12 years of age and older with asthma

Study Design and Conduct

Overview:
HZA106839 was a multicenter, randomized, double-blind, double-dummy, active control parallel group safety study. After screening, subjects entered a 2-week run-in period followed by visit 2 at which point subjects stopped their usual asthma treatments and were randomized in a 2:2:1 ratio to receive one of the following three treatments: FF 100/25 mcg once daily, FF/VI 200/25 mcg once daily, or FP 500 mcg twice daily. Subjects attended nine on-treatment clinic visits (Visits 3, 4, 5, 6, 7, 8, 9, 10 and 11) occurring at Weeks 2, 4, 8, 12, 20, 28, 36, 44 and 52. A follow-up contact was performed 1 week after completing study medication. Total duration of study participation was planned to be up to a maximum of 55 weeks (including screening, treatment and follow up). Study assessments were similar to trial HZA106837 with the exception that ophthalmic assessments were done at baseline, 28 weeks, and end of study.

Study Population

Inclusion Criteria
Inclusion criteria were similar the integrated studies in Section 5 with the exception of:

- Subjects were to be on a dose of ICS equivalent to FP 200-1000 mcg/day or combination product equivalent for at least 4 weeks prior to visit 1

Exclusion Criteria
Exclusion criteria were similar the integrated studies in Section 5 with the exception that subjects could not have a history of life-threatening asthma

Study Treatments

Treatment groups were as follows:

- FF/VI 100/25 mcg once daily
- FF/VI 200/25 mcg once daily
- FP 500 mcg twice daily

Safety Endpoints

- Incidence of adverse events or of severe asthma exacerbations throughout the 52-week treatment period
- Laboratory assessments
- 24-hour urinary cortisol excretion
- Oropharyngeal examinations
- Vital signs
- ECG assessments
- Ophthalmic assessments

7.7.2.3 Safety results for studies HZA106837 and HZA106839

In trial HZA106837, overall incidence of AEs during treatment was 65% in the FF 100 group and 63% in the FF/VI 100/25 group.. AEs leading to withdrawal occurred in 2% of subjects in each group. Post-treatment AEs occurred in ≤2% of subjects. On-treatment SAEs occurred in 3% of subjects in the FF 100 group and 4% of subjects in the FF/VI 100/25 group.

Two deaths occurred on-treatment (one in each treatment group) and one death occurred in the FF 100 mcg group post-treatment. The first subject that died on-treatment was a 62-year-old male who developed pneumonia 114 days after starting treatment with FF 100 mcg. The subject was then hospitalized 2 days later and died. The second subject that died on-treatment was a 68-year-old female who died as the result of a motor vehicle accident. The subject that died post-treatment was a 65-year-old male that was diagnosed with stage IV lung cancer 173 days after starting treatment with FF 100 mcg. He was withdrawn from the study at the time of diagnosis and died 91 days later.

The most frequently reported AEs during the treatment period in either treatment group were headache (18% in the FF 100 group and 19% in the FF/VI 100/25 group) and nasopharyngitis (13% in the FF 100 group and 15% in the FF/VI 100/25 group).

Of the AEs of special interest, local corticosteroid effects (8% in the FF 100 and FF/VI 100/25 groups) and lower respiratory tract infections excluding pneumonia (9% in the FF 100 group and 7% in the FF/VI 100/25 group) were the most common.

In trial HZA106829, the results were similar for frequency and type of AEs, SAEs, and AEs leading to withdrawal. However, there were no deaths in trial HZA106829.

Overall, the long-term safety data did not raise any new safety signals when compared to those seen in the shorter-term studies.

8 Postmarket Experience

Arnuity Ellipta is not available for marketing in any country.

9 Appendices

9.1 Literature Review/References

The application included a listing of references but no systemic literature review.

A PubMed search performed by this Reviewer [search term: inhaled fluticasone furoate AND asthma; no limits] was conducted on April 9, 2014, and yielded 26 references. A brief review of these reports was performed. No new safety signals were identified from these reports.

9.2 Labeling Recommendations

Trade name

The proposed trade name for fluticasone furoate, Arnuity Ellipta, has been reviewed by the Division of Medication Errors and Technical Support (DMETS) and was determined to be acceptable.

Suggested Revisions to Proposed Labeling

While the label has not been finalized at the time of this review, the following major revisions are proposed:

Table 44. Labeling Recommendations

Label Section	General Recommendations
General	• Addition of language throughout the label to make it more consistent with the labeling for the most recently approved inhaled corticosteroids
	•
5.1 and 5.2	• Section 5.1 "Local Effects" was moved after Section 5.2 "Acute Asthma Episodes" to reorder according to severity.
6	• Inclusion of 24-week safety data for the 100 mcg dose versus placebo with a comparative statement to the 12-week data. Additional inclusion of 24-week data comparing the 100 and 200 mcg doses (no placebo group included). Addition of long-term safety information from trials HZA106837 and HZA106839.
8.5	• Removal of claim that there is (b) (4)

Table 44. Labeling Recommendations	
	[redacted] (b) (4) .
14	• Division into Dose-Ranging and Confirmatory Trials • Dose-ranging trials: Trial HZA109687 was included under the dose-ranging section. In addition, a dose-ranging figure from the three dose-ranging trials was inserted. • Confirmatory trials: Reorganized by dose rather than [redacted] (b) (4) . • Both studies used to support FF 100 mc dose described, with results of 24 week study in tabular format, and result of 12 week study described in text. . • • Maintained description of Study HZA106829, however removed information regarding [redacted] (b) (4) . Reported results only. :

9.3 Advisory Committee Meeting

The risk-benefit of ICS in the treatment of asthma is well-established. No advisory committee was convened, nor required, for this application.

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

/s/

TRACY L KRUZICK
07/18/2014

BANU A KARIMI SHAH
07/18/2014