CLINICAL PHARMACOLOGY REVIEW

NDA	205625
Submission Date	10/22/2013
Proposed Brand Name	ARNUITY ELLIPTA
Generic Name	Fluticasone furoate (FF) Inhalation Powder
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Sponsor/Authorized Applicant	GSK
Submission Type; Code	505(b)(1); standard review
Formulation; Strength(s)	Micronized FF and lactose monohydrate; administered via DPI
Indication	Asthma
Dosage Regimen	100, 200 mcg

1. Executive Summary

GSK has submitted NDA 205625 seeking the marketing approval for Fluticasone Furoate (FF) Inhalation Powder (ARNUITY ELLIPTA), for the indication of "maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older."

The Sponsor supports this NDA submission with 31 clinical pharmacology studies in which 29 of these studies have been submitted to support another approved NDA 204275 (FF/VI, BREO ELLIPTA). Majority of the clinical pharmacology studies, including the dose-ranging studies, have been previously reviewed in NDA 204275 (Dr. Jianmeng Chen, DARRTS date 03/18/2013).

The following are the major findings of the current review:

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

2) The dosing regimen of FF has been adequately explored. Prior to the confirmatory trials, 3 dose ranging trials were conducted in patients with asthma exploring daily doses from 25 mcg to 800 mcg. A dose response was observed for FF doses ranging from FF 25 mcg to 200 mcg, with no significant additional benefit for FF doses above 200 mcg. The results of these three trials in asthma were the basis for the selection of FF 50, 100, and 200 mcg for further evaluation in the confirmatory trials.

3) The dosing frequency with FF was explored in patients with asthma. Trough FEV1 response for FF 200 mcg QD versus FF 100 mcg BID was similar, whereas FP (fluticasone propionate) 100 mcg BID dosing resulted in a numerically higher trough FEV1 compared to FP 200 mcg QD. These results supported the selection of the QD regimen for FF component for further evaluation.

4) No dosing adjustment is recommended for any intrinsic or extrinsic factors. Although the systemic exposure of FF was higher in patients with all severities of hepatic impairment, the Clinical Pharmacology reviewer recommends both FF 100 and FF 200 mcg be made available for patients with moderate and severe hepatic impairment with cautionary labeling language.

5) Bioequivalence was not demonstrated for the to be marketed product FF(single strip) compared with either FF (two-strip, used in some Phase 3 studies) or FF/VI. The systemic exposure after administration of FF in the single strip (1S) configuration was 29% higher compared to the systemic exposure after administration of FF in the double strip (2S) configuration, and 60% higher compared to FF in FF/VI combination. This observation was consistent with in vitro data in which the 1S

configuration will deliver 20% more fine particle mass compared to 2S configuration. This exposure difference has been communicated to the clinical team (see Dr. Tracy Kruzick's review for safety evaluation of FF(1S)). For FF PK in special populations and drug-drug interactions, we consider that all data with FF (2S) and FF/VI are directly applicable to the FF 1S product.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 205625 and finds the application acceptable.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

FF is an inhaled corticosteroid (ICS) for oral inhalation to be administered from a Novel Dry Powder Inhaler (DPI). The recommended dosing regimen is FF (100 mcg or 200 mcg) once daily for the treatment of asthma. FF is currently available in the US as a nasal spray (VERAMYST™, AVAMYS™, NDA 022051) as 110 mcg once daily for the indication of allergic rhinitis, and as a component of fluticasone furoate/vilanterol (FF/VI) 100/25 mcg once daily oral inhalation (BREO ELLIPTA, NDA 204275) for the maintenance treatment of COPD.

The sponsor supports this NDA submission with 31 clinical pharmacology studies in which 29 of these studies have been submitted to support another approved NDA 204275 (FF/VI, BREO ELLIPTA). Majority of the clinical pharmacology studies have been previously reviewed in NDA 204275 (Dr. Jianmeng Chen, DARRTS date 03/18/2013).

Rationale for Dose and Dosing Frequency Selection

The Clinical Pharmacology reviewer concurs with the selection of both FF 100 and FF 200 mcg, given once daily, for the treatment of asthma. The dose ranging performed in the FF program was adequate for the Phase 3 dose selection.

The proposed doses of FF are 100 and 200 mcg once daily (QD). Three dosing regimens, FF 50, 100 and 200 mcg QD, were tested in the Phase 3 studies in an asthmatic population. The dosing regimens chosen for Phase 3 exploration, including selection of dose, dosing frequency and timing of the dose, was established in dose ranging studies with asthmatic patients.

Traditionally, ICS is approved of several doses for the management of asthma. Usually, higher doses are considered beneficial for patients who have more severe asthma. For the

individual patient, the lowest dose of ICS that maintains asthma control is generally used to reduce corticosteroid related side effects.

Nominal Dose for FF

The results for the effect of different FF doses on trough FEV_1 from the three Phase 2 dose ranging studies are summarized in Figure 1. A dose response relationship is apparent with increasing effect on FEV1 observed with increasing dose from FF 25 to FF 200. A consistent additional benefit is not observed at doses above FF 200. In studies FFA109685 and FFA109684, the pharmacokinetics of FF showed a linear increase in exposure from FF 200 mcg to 800 mcg. However, the FEV1 response does not increase consistently. This suggests that 1) the increase in systemic exposure may not be associated with increase in FEV1 response and/or 2) doses >200 mcg yields exposures that are on the Emax of the concentration-effect relationship (i.e., saturation of effect). Based on the dose ranging data, the Sponsor selected three doses of FF (50, 100 and 200 mcg) for further evaluation in the Phase 3 program.

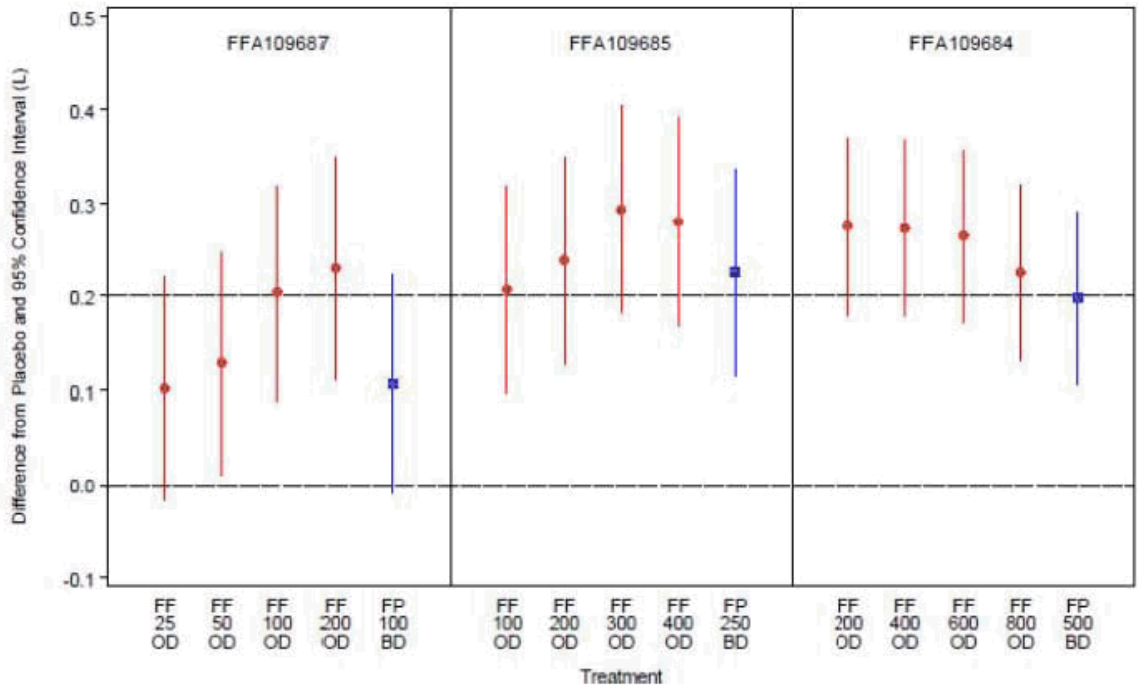


Figure 1. Placebo Adjusted Treatment Differences in Trough FEV1 (L) (Week 8, LOCF) for FF doses ranging from 25-800 mcg QD.
(Source – Figure 19, 2.7.3, Clinical Summary of Efficacy)

Dosing Frequency (QD vs twice daily (BID))

Study FF112202 compared FEV1 response after giving FF once and twice daily (Table 1) in patients with asthma. Unlike fluticasone propionate (FP), dividing the QD dose into BID doses did not result in an improved FEV1 response for FF.

Table 1. Effect of FF dosing in Asthma; Trough FEV1 (L) on Day 28; Trial FFA-112202. Also shown is the Effect of FP dosing in Asthma.

	FF 100 BID	FF 200 QD	FP 100 BID	FP 200 QD
LS Mean difference (L)	0.098	0.108	0.132	0.087
95% CI	(0.054, 0.142)	(0.064, 0.153)	(0.059, 0.205)	(0.014, 0.161)

(Source – Table 12, Study HZA112202 report)

Morning vs. Evening Dosing

Study FFA20001 (100mcg, DISKHALER) and FFA106783 (200mcg, 400mcg, DISKUS) demonstrated that FF, whether dosed in the morning or evening in subjects with asthma, resulted in a similar efficacy compared with placebo.

Following the selection of doses and dosing interval for FF, the sponsor compared the efficacy of FF 50, 100 and 200 mcg in 8 Phase 3 studies in asthmatic patients. All doses of FF evaluated in the primary efficacy studies were administered via a DPI in the evening. The Sponsor reported that FF 50 mcg yielded no significant benefit compared to placebo in terms of lung function. Therefore, the sponsor seeks approval for both FF 100 and 200 mcg strengths for the treatment of asthma.

Rationale for Dosing Recommendations in Patients with Hepatic Impairment

The Clinical Pharmacology reviewer recommends both FF 100 and FF 200 mcg be made available for patients with moderate and severe hepatic impairment with cautionary labeling language.

The systemic exposure of FF is higher in patients with all severities of hepatic impairment. The mean percentage change in FF AUC (90% CI) for subjects with mild, moderate and severe hepatic impairment vs. normal hepatic function were 34% (-18%, 120%), 83% (11%, 199%) and 75% (5%, 191%), respectively. (b) (4)

The magnitude of increased FF exposure observed in the hepatic impairment population is consistent with what observed in other ICS with similar elimination pathways. The largest observed pharmacodynamic change observed was a 34% decrease in serum cortisol with a 200 mcg dose in patients with moderate hepatic impairment. This change in serum cortisol is of a similar magnitude when 200 mcg FF is co-administered with ketoconazole (27% decrease in serum cortisol). As there is no dose limitation in the label for co-administration of FF with ketoconazole, and there is no dose limit for other ICS products that are CYP3A4 substrates in moderate and severe hepatic impairment patients, this reviewer recommends making both FF 100 and FF 200 mcg available for patients

with moderate and severe hepatic impairment. Cautionary labeling language will be supplied stipulating the potential for deleterious HPA axis effects.

Bioequivalence Assessment Between the 1 Strip (to be marketed) and 2 Strip Products

In study FFA115440 bioequivalence was not demonstrated for the to be marketed product (single strip, FF 400 mcg) compared with either FF 400 mcg (two-strip, used in some Phase 3 studies) or FF/VI 400/50 mcg (Table 2).

The systemic exposure (AUCinf) after administration of FF in the single strip (1S) configuration is 29% higher compared to the systemic exposure after administration of FF in the double strip (2S) configuration, and 60% higher compared to FF in FF/VI combination. This observation is consistent with in vitro data in which the 1S configuration will deliver 20% more fine particle mass compared to 2S configuration. This exposure difference may have safety implications, and has been communicated to the clinical team. (See Dr. Tracy Kruzick's review for safety evaluation of FF(1S)) For FF PK in special populations and drug-drug interactions, we consider that all data with FF (2S) and FF/VI are directly applicable to the FF 1S product.

Table 2. Relative FF exposure for 1 strip versus 2 strip products

Parameter	Treatment Comparison	Adjusted Geometric Means	Ratio of Adjusted Geometric Means	90% CI of the Ratio
AUC(0-∞)	FF 400 1 strip / FF 400 2 strip	1144.7 / 889.5	1.29	(1.14, 1.46)
	FF 400 1 strip / FF/VI 400/50	1144.7 / 714.8	1.60	(1.37, 1.87)
AUC(0-t')	FF 400 1 strip / FF 400 2 strip	560.2 / 458.0	1.22	(1.16, 1.29)
	FF 400 1 strip / FF/VI 400/50	560.2 / 401.1	1.40	(1.31, 1.49)
AUC(0-t)	FF 400 1 strip / FF 400 2 strip	723.0 / 531.6	1.36	(1.23, 1.50)
	FF 400 1 strip / FF/VI 400/50	723.0 / 441.2	1.64	(1.44, 1.87)
Cmax	FF 400 1 strip / FF 400 2 strip	67.84 / 60.08	1.13	(1.07, 1.20)
	FF 400 1 strip / FF/VI 400/50	67.84 / 47.75	1.42	(1.33, 1.52)

(Source – Table 12, Study FFA115440 report)

The Sponsor evaluated the PK exposure difference between the FF configurations (1S, 2S or FF/VI) in asthmatic patients by population PK (popPK) analysis including data from study FFA114496 (1S FF). Contrary to the finding that systemic exposure (AUCinf) for FF in single strip configuration is higher than in double strip configuration based on the dedicated BE study FFA115440, the popPK analysis results suggested that there was no notable difference between the configurations. It is in the reviewer's position that results from the dedicated BE study should be considered, since pop PK analysis results in this case were subject to potential noise introduced by variations in design and operations,

difference in sampling schedules and sampling densities, and unbalanced distribution of proportions of BLQ data points across studies.

Pharmacokinetics

Absorption

- The absolute systemic bioavailability for FF was 13.9%. However, the systemic bioavailability of FF was low after oral administration (on average 1.26%). Therefore, the systemic exposure for inhaled FF was primarily due to absorption of the inhaled portion of the dose delivered to the lung. For these reasons, food effect for FF would be negligible.
- The systemic exposure for FF increased was in proportion to the dose within the dose range of 200 to 800 mcg for FF (for both $AUC_{(0-\infty)}$ and C_{max}).
- T_{max} was reached by approximately 0.5-1 hours for FF following oral inhalation administration.
- Upon once-daily dosing, steady-state was reached by the 6th day. Based on $AUC_{(0-t)}$, the systemic accumulation ranged from 74% to 158% for FF.

Distribution

- FF had high *in-vitro* plasma protein binding, which was independent of concentration with average values of ≥99.6%. FF was predominantly bound to albumin (96%) and α1-acid glycoprotein (90%).
- Steady-state volume of distribution (Vd_{ss}) for FF following oral inhalation was 661 L.

Metabolism and Transporters

- FF was a substrate of CYP3A4 and P-glycoprotein (P-gp).
- Based on in vitro studies, the potential for FF to inhibit and induce metabolic enzymes was negligible at low inhalation doses.

Elimination

- In humans, FF was eliminated primarily by metabolism with metabolites excreting predominantly in feces.
- The apparent terminal phase elimination half-life of FF following oral inhalation administration was, on average, 23.7 h.

Asthma vs. Healthy

- For FF systemic exposure, COPD< Asthma<healthy subjects. In subjects with asthma, FF AUC was 25% lower compared to healthy subjects.

Population Pharmacokinetic Analysis

Population PK models were developed to describe the FF systemic exposure in asthmatic subjects and to determine if any intrinsic factors influence the systemic exposure.

Age, Weight and Gender

- There was no effect of age, body weight, body mass index and gender on the systemic exposure of FF in subjects with asthma.

Race

- Systemic exposure of FF for East Asian, Japanese and South Asian subjects were on average 23% to 49% higher compared with white Caucasian subjects. This finding was consistent with results seen in asthmatic subjects of East Asian origin.

Special Populations

Renal Impairment

- The systemic exposure of FF was found to be lower in severe renal impairment patients. At day 7, FF median $AUC_{(0-24)}$ and C_{max} are 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.

Hepatic Impairment

- The systemic exposure of FF was higher in patients with all severities of hepatic impairment. The mean percentage change in FF AUC (90%CI) for subjects with mild, moderate and severe hepatic impairment vs. normal hepatic function were 34% (-18%, 120%), 83% (11%, 199%) and 75% (5%, 191%), respectively. The mean percentage change in FF C_{max} (90% CI) for these cases were18% (-17%, 69%), 43% (0%, 104%) and 37% (-5%, 98%), respectively. There was no evidence for reduced plasma protein binding of FF in plasma from subjects with varying degrees of hepatic impairment.
- The weighted mean (0-24h) serum cortisol was, on average, 34% lower with moderate hepatic impairment subjects compared to the healthy subjects.
- Use with caution in patients with hepatic impairment.

Drug-Drug Interactions (DDI)

Effect of co-administered drugs on FF exposure

- Co-administration of FF with ketoconazole (a strong CYP3A4 and potent P-gp inhibitor) resulted in a modest increase 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) with co-administration of ketoconazole. No dose adjustment is recommended when FF is co-administered with ketoconazole.

Effect of FF on exposure of co-administered drugs

- With low systemic exposures for FF after oral inhalation, the potential for inhibition and induction of metabolic enzymes is negligible.

Pharmacokinetic/Pharmacodynamic Relationships for Safety

FF is administered by oral inhalation and efficacy is presumed to be driven by local effects in the lung. Therefore, the systemic exposure of FF is considered more relevant for safety.

Effect of FF on Serum Cortisol

Although HPA suppression was observed with FF, serum cortisol reduction was not apparent at the proposed dosing. The sponsor conducted a 6-week, double blind, placebo- and active-controlled dedicated study in asthma patients to evaluate the effect of FF on the HPA axis at therapeutic doses (Study HZA106851). Following multiple QD oral inhalations of FF/VI 200/25 mcg (n=56) and 100/25 mcg (n=56), weighted mean cortisol (0-24 hr) values were similar to the placebo (<3% change from baseline). In addition, a pharmacokinetic/pharmacodynamic 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 (181 pg•hr/mL) and 200 mcg (395 pg•hr/mL)in subjects with asthma (Figure 2).

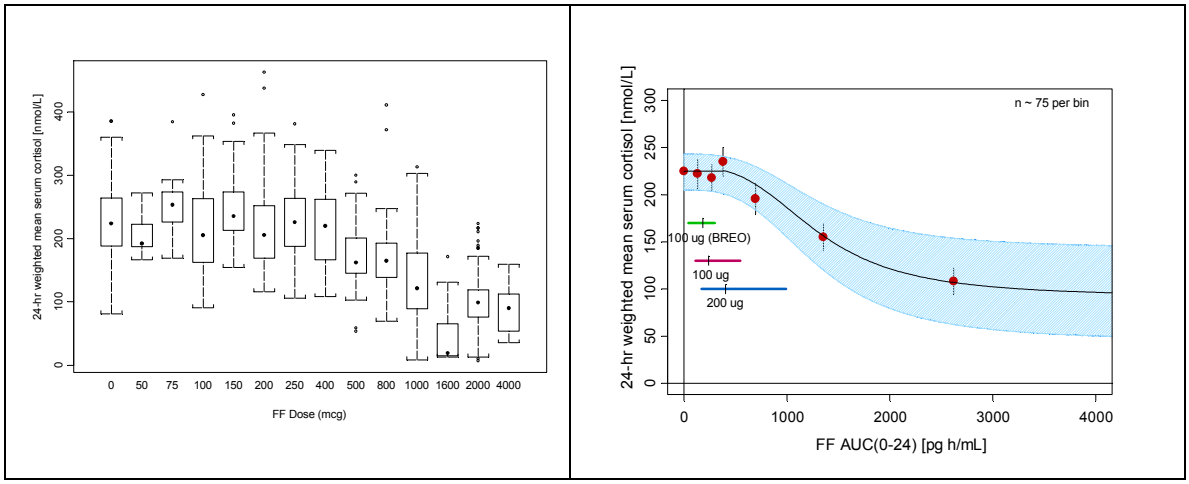


Figure 2. Effect of FF on serum cortisol (nmol/L) across doses ranging from placebo to 4000 mcg QD. Left plot is dose-response while right plot is concentration-response relationship.

2. Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

In vitro studies using human biomaterials were conducted and are listed Table 3.

Table 3. In Vitro Studies for FF Using Human Biomaterials

Drug	ADME	Objective	Study/Report name
FF	Absorption	FF as P-gp substrate	WD2006/00293/00
	Distribution	Blood cell association	WD2001/00979/00
		Human plasma protein binding	WD2001/00979/00 WD2003/01268/00 WD2005/01123/00

		Human albumin, α1-acid glycoprotein binding	WD2005/01123/00
	Metabolism	Metabolism of FF in human liver microsomes and recombinant CYPs	WD2002/00297/00
		Identify CYP450 isoforms responsible for FF oxidation	WD2005/01308/00
		Potential of FF to inhibit CYPs	WD2001/00374/00
		IC 50 of FF to inhibit CYPs	FD2003/00126/00
		Potential for FF's metabolite GW694301 to inhibit CYPs	WD2005/00543/00
FF/VI	Distribution	Healthy, hepatic impairment and renal impairment human plasma, protein binding for FF and VI	2011N118910_00

Thirty one clinical pharmacology studies are summarized in Table 4. Except for the highlighted two studies (FFA 115440 and FFA 115441), the other 29 studies were submitted and reviewed to support NDA 204275 (FF/VI, BREO ELLIPTA).

Table 4. Summary of Clinical Pharmacology studies

Drug		CP Study	Object ve	Population	Device
FF/VI	1	HZA102934	Absolute bioavailability	16 Healthy subjects	NDPI
	2	HZA102936	Thorough QTc	85 Healthy subjects	NDPI
	3	HZA105871	PK-interaction of FF&VI	16 Healthy subjects	NDPI
	4	HZA102940	PK-interaction of FF&VI	16 Healthy Japanese subjects	NDPI
	5	HZA105548	Ketoconazole DDI	18 Healthy subjects	NDPI
	6	HZA111789	Hepatic impairment	9 Healthy, 9 mild, 9 moderate, 8 severe	NDPI
	7	HZA113970	Renal impairment	9 Healthy, 9 severe	NDPI
	8	HZA113090	Bronchoprotective PD effect	52 mild asthma patients	NDPI
	9	HZA113126	Bronchoprotective PD effect	27 mild asthma patients	NDPI
FF	10	FFA115440	BE between 1 and 2 strips	30 Healthy subjects	NDPI
	11	FFA115441	Dose proportionality and absolute bioavailability	30 Healthy subjects	NDPI (1S)
	12	FFA10008	PK Contr bution of the swallowed fraction of inhaled dose to systemic absorption of FF	15 Healthy subjects	Diskhaler
	13	FFR10008	Human radiolabelled ADME/mass balance	5 Healthy subjects	IV, oral
	14	HZA113477	Race PK	Healthy 20 Caucasian, 20 Chinese, 20 Japanese, 20 Korean	NDPI
	15	FFA10001	FTIH	20 Healthy subjects	Diskhaler
	16	FFA10002	FF multiple dose PK	36 Healthy subjects	Diskhaler
	17	FFA10003	Absolute bioavailability of FF with Diskhaler	24 Healthy subjects	Diskhaler
	18	FFA10007	Bronchoprotective PD effect of FF	6 mild asthma patients	Diskhaler
	19	FFA10009	Repeat FF dose safety -cortisol	24 Healthy subjects	Diskus
	20	FFA10013	FF-Hepatic impairment	10 Healthy, 10 Hepatic impairment	Diskus
	21	FFA10022	FF formulation finding based on Bronchoprotective PD effect	40 mild asthma patients	Diskhaler
	22	FFA10026	AMP Challenge	24 mild asthma patients	Diskhaler
	23	FFA10027	AMP Challenge	24 mild asthma patients	Diskhaler
	24	FFA10028	Effect of repeat dosing on exhaled nitric oxide (exNO)	28 mild/moderate asthma patients	Diskhaler
	25	FFA103096	Effect of repeat dosing on serum cortisol	44 Healthy subjects	Diskus
	26	FFR10010	Bioavailability of FF administered intranasally	16 Healthy subjects	Intranasal
	27	FFR101888	Thorough QT	40 Healthy subjects	Diskus
	28	HZA102928	FF effect on serum cortisol	36 Healthy subjects	Diskus
	29	HZA102942	Pediatric	27 children 5-11yr	NDPI
	30	HZA108799	FF effect on serum cortisol	20 mild/moderate asthma patients	Diskus
	31	HZA112018	FF PK in Japanese	48 Healthy Japanese subjects	NDPI

Clinical studies are summarized in Table 5.

Table 5. Overview of Clinical Development Program

FF	Dose ranging	109687 (8w, double strip) 109685 (8w, double strip) 109684 (8w, double strip)
	Dose frequency	112202 (double strip)
	AM vs PM dosing	20001 (Diskhaler) 106783 (DISKUS)
Pivotal Efficacy and Safety lung function trials	100 mcg	112059 (24w, single strip) 106827 (12w, double strip)
	200 mcg	106829 (12w, double strip) 114496 (24w, single strip)
Other studies	Exacerbation	106837
	50 mcg	115283 115285
	Japan	113989

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Fluticasone furoate (FF) is a small molecule drug. Their structures are shown in Figure 3. FF is a white powder with a molecular weight of 538.6, and the empirical formula is $C_{27}H_{29}F_3O_6S$. FF is practically insoluble in water.

Fluticasone furoate

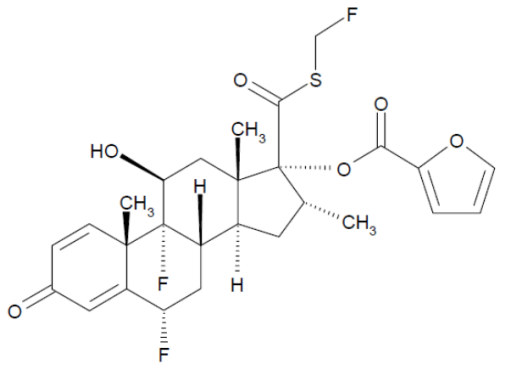


Figure 3: Molecular structure of fluticasone furoate

Drug Product

The Fluticasone Furoate Inhalation Powder 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 or 14 regularly distributed blisters, each containing a white powder,

which is a blend of micronized FF and lactose monohydrate (Table 6). Upon actuation, the inhaler delivers the contents of one blister containing FF.

Table 6. Composition of Fluticasone Furoate Inhalation Powder

Inhalation Powder Strength	100 mcg	200 mcg	Function	Reference to Standard
Component	**Quantity (Per 12.5 mg Blister[1])**			
Fluticasone furoate micronised[2]	100 mcg	200 mcg	Active	GlaxoSmithKline[3]
Lactose monohydrate	(b) (4)			JP, Ph. Eur and USP/NF[4]

Notes: mcg = microgram.
1. A manufacturing overage (b) (4) may be included in the final product.
2. The quantity of drug may be adjusted (b) (4)
3. Details of the specification of the active ingredient are provided in m3.2.S.4.1. Specification.
4. Excipient complies with JP, Ph. Eur. and USP/NF and additional tests to ensure the quality for inhaled use. Details of the specification are provided in m3.2.P.4.1. Specification.

(Source – Table 1, 3.2.P.1. Description and Composition of the Drug Product)

2.2.2 What are the proposed mechanism of action and therapeutic indications?

FF is an inhaled corticosteroid (ICS) for oral inhalation.

The proposed indication is "*maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older.*" FF is not indicated for relief of acute bronchospasm.

2.2.3 What are the proposed dosages and routes of administration?

FF is an inhaled corticosteroid (ICS) for oral inhalation to be administered from a Novel Dry Powder Inhaler (DPI). Recommended dose is 100 or 200 mcg once daily for the treatment of asthma.

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

The drugs which are approved for long term treatment of asthma in the US can be classified into the following classes:

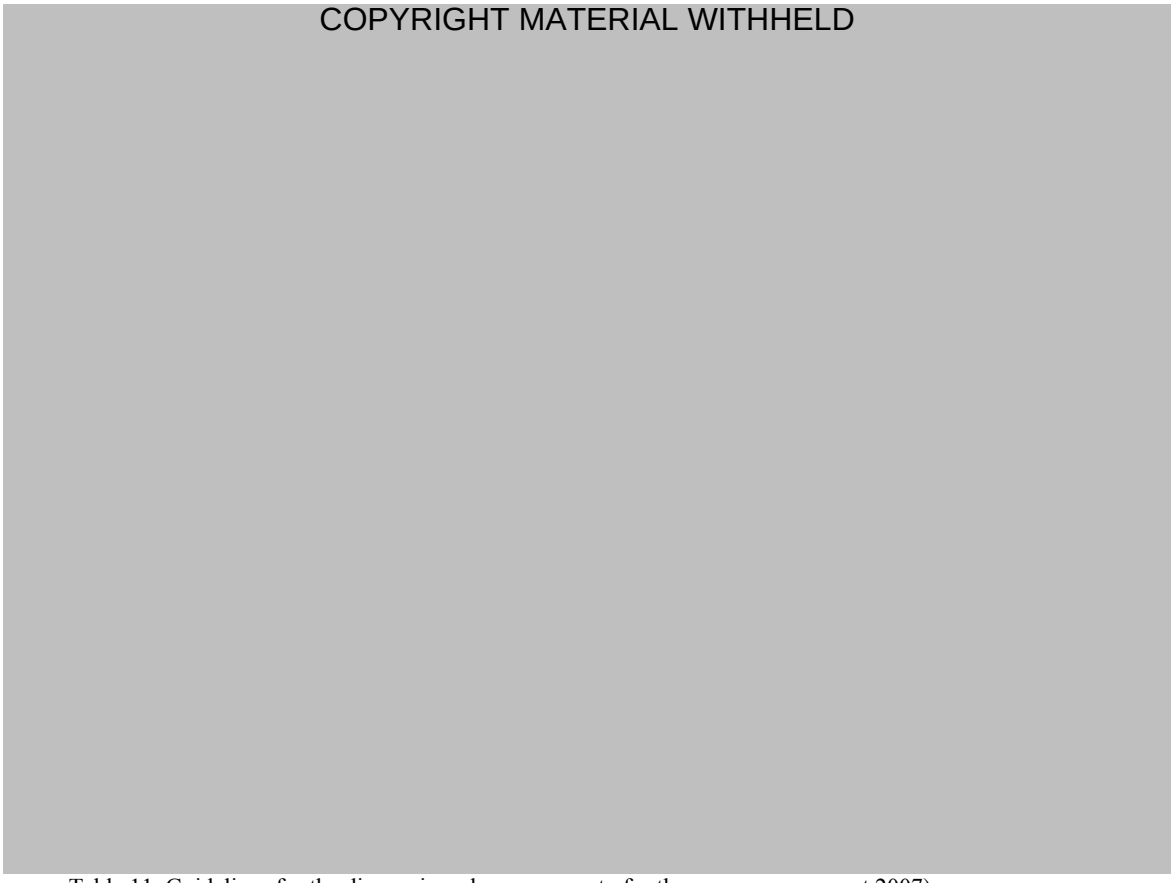
*(a) ICS:*budesonide(Pulmicort), fluticasone propionate (Flovent), mometasone (Asmanex), Beclomethasone (Qvar), Ciclesonide(Alvesco)

(b) LABA: salmeterol (Serevent), formoterol (Foradil, Perforomist)

(c) ICS/LABA Combinations:
- fluticasone propionate+ salmeterol (Advair)
- budesonide+ formoterol (Symbicort)
- mometasone+formoterol (Dulera)

(d) Other medications

- Leukotriene modifiers
    - LTRA: montelukast (Singulair), zafirlukast (Accolate)
    - 5-lipoxygenase inhibitor: zileuton (Zyflo)
- Immunomodulators: omalizumab (Xolair)
- Mast cell stabilizers: Cromolyn sodium and nedocromil
- Systemic corticosteroid
- Methylxanthines: theophylline



(Source – Table 11, Guidelines for the diagnosis and management of asthma, summary report 2007)

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

This development program includes full dose-ranging of FF to establish the appropriate dose regimen before proceeding to studies with the combination product in the Phase 3 studies. Three FF doses (50, 100, and 200 mcg) were assessed in Phase 3 program.

Three dose ranging studies evaluated several dose levels of FF in asthma patients.

- Study FFA109687 was a 8-week, randomized, double-blind, placebo- and active-controlled, parallel group study
- Study FFA109685 was a 8-week, randomized, double-blind, placebo- and active-controlled, parallel group study

- Study FFA109684 was a 8-week, randomized, double-blind, placebo- and active-controlled, parallel group study

The clinical pharmacology and biopharmaceutics studies supporting this NDA and their design features are listed under section 2.1.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

The Sponsor used trough FEV1 as the primary endpoint in all Phase II dose ranging/regimen selection studies. Weighted mean FEV1 (0-24h) and trough FEV1 are the primary endpoints for the Phase 3 studies, claiming lung function improvement. These endpoints have also been used in the development programs of other ICS for asthma.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

In all relevant studies, only FF concentrations were measured. No metabolites were quantified because the metabolites of FF are not active and are not associated with efficacy or safety.

2.4 Exposure-Response

2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

For FF, the systemic exposure is not directly related to clinical response (FEV1). There is evidence of a dose-response relationship with regard to the pertinent pulmonary endpoints. The doses explored in asthma patients included 25 mcg to 800 mcg for FF. A clear dose-response relationship is observed, with an increasing effect with increasing dose, for all endpoints evaluated (see question below). Please refer to pharmacometrics review (Appendix 2.11) for additional details.

2.4.2 Has the dosing of FF been adequately explored?

The dosing regimen of FF has been adequately explored in Phase 2 trials.

For the FF component, 3 dose ranging trials were conducted in asthma patients exploring daily doses from 25 mcg to 800 mcg (Figure 4). A dose response was observed for FF doses ranging from FF 25 mcg to 200 mcg, with no significant additional benefit for FF doses above 200 mcg. The results of these three trials in asthma were the basis for the selection of FF 50, 100, and 200 mcg for further evaluation in confirmatory trials.

Dosing frequency with FF was explored in patients with asthma. A randomized, double-blind, placebo-controlled, cross-over trial in 190 adults and adolescents with asthma compared FF 200 mcg QD, FF 100 mcg BID, FP (fluticasone propionate) 200 mcg QD, and FP 100 mcg BID. Trough FEV1 response for FF 200 mcg QD versus FF 100 mcg BID was similar, whereas FP 100 mcg BID dosing resulted in a numerically higher

trough FEV1 compared to FP 200 mcg QD (Table 7). These results supported the selection of the QD regimen for FF component for further evaluation.

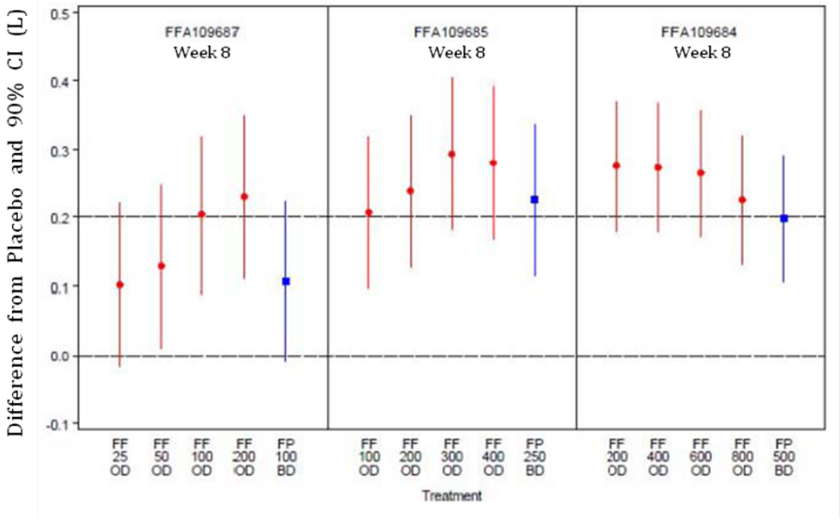


Figure 4 Adjusted Treatment Differences From Placebo of Change from Baseline in Trough FEV1 (L) (LOCF) at Week 8 in Asthma for FF doses ranging from 25-800 mcg QD

Table 7 Mean change from baseline in trough FEV1 for FF (QD vs. BID)

Treatment	N	LS mean (L)	LS mean change from period baseline	Difference from placebo (95% CI)	P
FF 200 QPM	140	2.714	0.221	0.108 (0.064, 0.153)	<0.001
FF 100 BID	142	2.703	0.210	0.098 (0.054, 0.142)	<0.001
FP 200 QD	42	2.693	0.199	0.087 (0.014, 0.161)	0.020
FP 100 BID	43	2.737	0.244	0.132 (0.059, 0.205)	<0.001
Placebo	187	2.605	0.112	-	-

Overall, dose-ranging data for the FF component in asthma supported efficacy for the range of doses (50, 100, and 200 mcg) carried forward for confirmation in the Phase 3 asthma program.

2.4.3 What are the characteristics of the exposure-response relationships for safety?

Effects on hypothalamic pituitary-adrenal (HPA)-axis function are known to occur with systemic administration of corticosteroids and this systemic side effect has also been reported with inhaled and intranasal corticosteroid use. Cortisol suppression data following chronic once daily administration of FF was obtained from two separate sources: 1) Dedicated HPA-axis study (study HZA106851) and 2) meta-analysis (2011N130478_00).

1) Study 106851 was a multi-center, randomized, double-blind, parallel-group, placebo- (double dummy) and active- (prednisolone 10 mg) controlled study. Therapeutic doses of FF/VI (200/25 mcg and 100/25 mcg) were administered by once daily oral inhalation for 6 weeks to evaluate the effect of corticosteroids on the HPA axis. Reduction in weighted mean serum cortisol (0-24 hr) values was similar between treatment and to the placebo groups (<3% change from baseline, Table 8). FF/VI does not have significant HPA axis suppression at 100/25 or 200/25 mcg doses.

Table 8. Analysis of Serum Cortisol Weighted Mean (0-24 h) – Ratio from baseline

	LS Geometric Means		Treatment	
Treatment Comparison	Active	Placebo	Ratio	95% CI
FF/VI 100/25 vs. Placebo	0.98	0.99	0.99	(0.87, 1.12)
FF/VI 200/25 vs. Placebo	0.96	0.99	0.97	(0.86, 1.10)
Prednisolone vs. Placebo	0.33	0.99	0.34	(0.28, 0.41)

(Source – Table 11, Study HZA106851 report)

2) A total of nine studies were included in the meta-analysis; five conducted in healthy subjects with the remaining four studies conducted in subjects with asthma. These studies utilized a range of formulations and inhalers investigated during the clinical development of FF, with FF administered as single and once daily inhalations as the individual component (FF) or as fluticasone furoate/vilanterol (FF/VI).

Although HPA suppression was observed with FF, serum cortisol reduction was not apparent at the proposed dosing. A pharmacokinetic/pharmacodynamic meta-analyses 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% (AUC50) was 1,345 pg•hr/mL, which is several fold higher than average FF AUC(0-24) values observed at the therapeutic dose of FF 100 mcg (181 pg•hr/mL) and 200 mcg (395 pg•hr/mL)in subjects with asthma (see Figure 5 below).

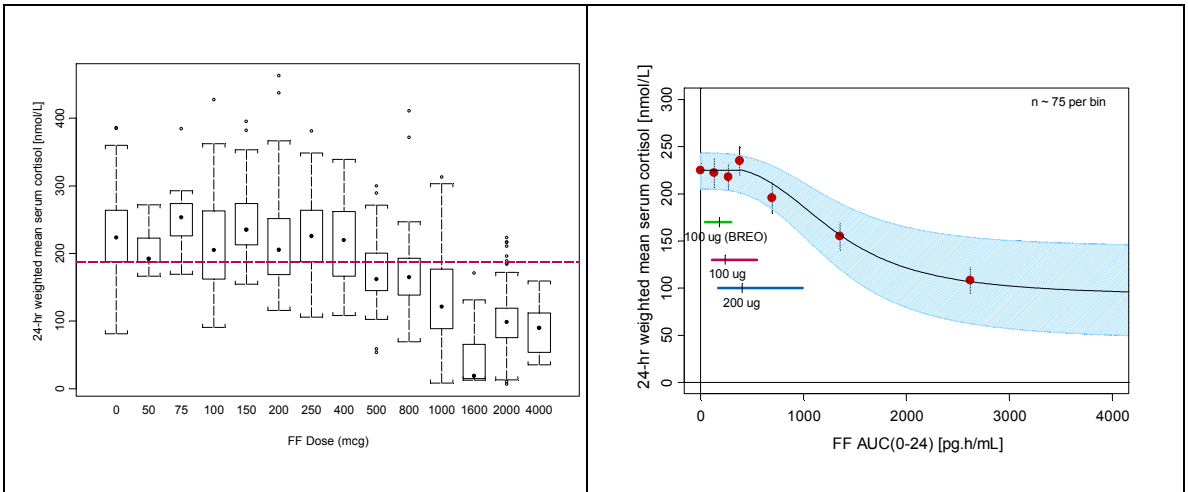


Figure 5 Effect of FF on serum cortisol (nmol/L) across doses ranging from placebo to 4000 mcg QD. Left plot: Boxplot of dose-response where the dashed line represents the lower 25% of the placebo response. Right plot: Concentration-response relationship. Red circles represent the median exposure and corresponding mean response for a bin of ~ 75 subjects (+/- 95% CI). A threshold

Emax model is depicted along with the 95% Prediction Interval. The range of serum FF exposures for the 100mcg (BREO, FF/VI), and the proposed 100 mcg and 200 mcg FF dose is demarcated with a solid line.

2.4.4 Does this drug prolong QT/QTc Interval?

QT effect was evaluated in a randomized, blinded, crossover, single-dose study (FFR101888), in which 40 healthy subjects received single supra-therapeutic oral inhaled dose of 4000 mcg, placebo, and a single dose of moxifloxacin 400 mg. The washout duration between treatment periods was 7 days. No significant QT prolongation effect was detected. The largest upper bound of the 2-sided 90% CI for the mean difference QTcF between FF 4000mcg and placebo less than 5 ms, and was within the threshold for regulatory concern as described in ICH E14 guideline. For further details refer to QT/IRT review for NDA022051.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Single dose PK

FF

In a single dose study in healthy adults, FF PK in DPI (single strip) was characterized for doses ranging from 300 mcg to 1200 mcg. The mean plasma concentration-time profile is shown in Figure 6. Following oral inhalation, maximum plasma concentration (T_{max}) of FF was reached by 0.25 to 1 hour. The terminal half-life after single dose ranged from 16.9 to 27.7 hrs. FF appears to follow poly-exponential disposition kinetics. PK parameters for different dose levels are summarized in Table 9.

It should be noted that the observed terminal half life is 16.9 hrs for FF 300mcg, 24.8 hrs for FF 600 mcg, and 27.7 hrs for FF 1200 mcg. Due to assay sensitivity, the later phase of elimination cannot be captured at the lower dose.

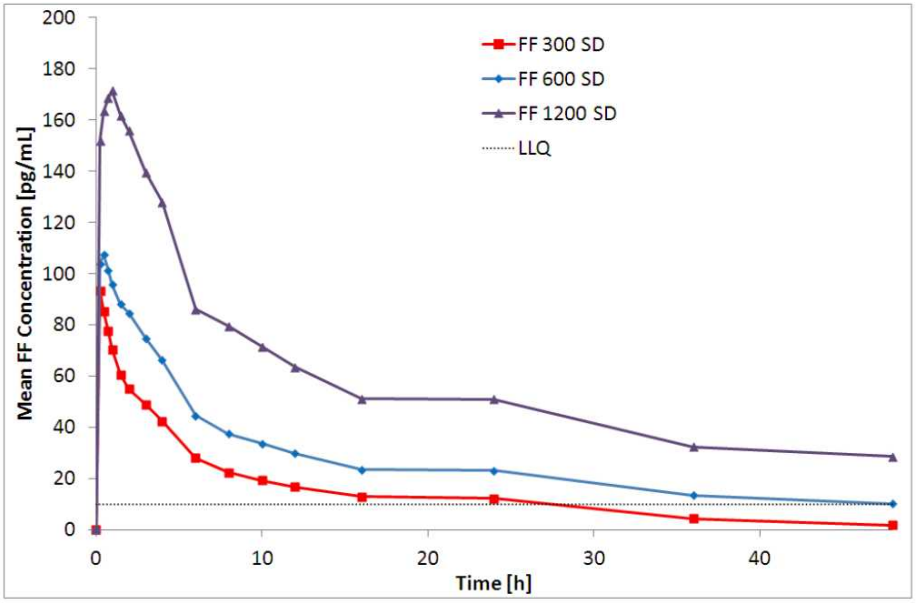


Figure 6: Mean Plasma FF Concentrations vs Times Following Administration of a Single Dose of FF Administered via DPI in Healthy Subjects
(Source – Figure 1, Study FFA115441 report)

Table 9: Pharmacokinetic Parameters of FF Following Administration of a Single Dose of FF by NDPI in Healthy Subjects

Parameter	Treatment	N	n	Geometric Mean (CV%)	95% Confidence Interval
AUC(0-inf) (pg.h/mL)	FF 300	35	27	895.25 (60.2)	(718.44,1115.58)
	FF 600	35	31	1731.86 (43.5)	(1486.56,2017.65)
	FF 1200	35	33	3614.02 (36.9)	(3183.86,4102.29)
AUC(0-12) (pg.h/mL)	FF 300	35	35	414.11 (27.0)	(378.01,453.67)
	FF 600	35	35	626.99 (30.3)	(566.27,694.22)
	FF 1200	35	35	1203.30 (28.0)	(1095.10,1322.20)
Cmax (pg/mL)	FF 300	35	35	93.02 (34.7)	(82.83,104.46)
	FF 600	35	35	109.36 (32.9)	(97.95,122.09)
	FF 1200	35	35	178.59 (32.0)	(160.43,198.82)
t1/2 (h)	FF 300	35	27	16.93 (81.4)	(12.77,22.45)
	FF 600	35	31	24.82 (30.2)	(22.27,27.66)
	FF 1200	35	33	27.69 (19.3)	(25.87,29.63)
tmax (h)[1]	FF 300	35	35	0.25 (0.25-0.75)	NA
	FF 600	35	35	0.50 (0.25-2.00)	NA
	FF 1200	35	35	1.00 (0.25-2.00)	NA
MAT (h)	FF 300	35	34	2.87 (122.1)	(1.95,4.22)
	FF 600	35	34	6.15 (101.9)	(4.58,8.26)
	FF 1200	35	34	9.50 (58.8)	(7.85,11.49)

Source Data: Table 10.2
NA = Not Applicable
n* = number of subjects with parameter not estimated due to non-quantifiable data
[1] Median (range)
(Source – Table 5, Study FFA115441 report)

Multiple dose PK

Multiple dose PK of FF in DPI (single strip) was characterized in healthy volunteers. The mean plasma PK profiles are shown in Figure 7 and summary PK parameters are listed in Table 10. C_{max} was reached by 1 hour for FF, which similar to single dose. From other studies, accumulation after multiple doses was 1.74 to 2.58 fold for FF. Measurement of trough concentrations indicated that steady-state for FF was achieved by the 6th dose.

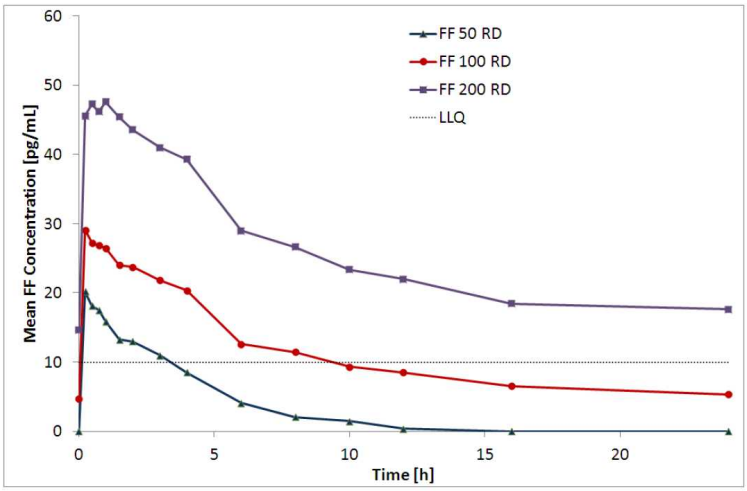


Figure 7. Mean Plasma Concentrations Versus Time on Day 7 Following Multiple Dosing with FF
(Source – Figure 2, Study FFA115441 report)

Table 10: FF Pharmacokinetic Parameters on Days 7 Following Repeated Inhaled Administration of FF in Healthy Volunteers

Parameter	Treatment	N	n	n*	Geometric Mean (CV%)	95% Confidence Interval
AUC(0-t) (pg.h/mL)	FF 50	35	35	2	48.73 (118.9)	(35.30,67.27)
	FF 100	35	35	1	181.65 (131.8)	(128.68,256.41)
	FF 200	35	35	0	538.35 (62.9)	(441.52,656.43)
AUC(0-4) (pg.h/mL)	FF 50	35	23	2	57.52 (52.2)	(46.52,71.13)
	FF 100	35	35	1	85.77 (47.3)	(73.50,100.08)
	FF 200	35	35	0	160.80 (37.6)	(141.90,182.22)
AUC(0-24) (pg.h/mL)	FF 50	35	2	2	126.23 (ND)	ND
	FF 100	35	15	1	372.98 (39.4)	(302.23,460.28)
	FF 200	35	30	0	642.95 (30.4)	(575.38,718.46)
Cmax (pg/mL)	FF 50	35	35	2	20.10 (48.7)	(17.15,23.55)
	FF 100	35	35	0	28.81 (42.3)	(25.06,33.12)
	FF 200	35	35	0	49.01 (37.6)	(43.26,55.52)
tmax (h)[1]	FF 50	35	33	0	0.25 (0.25-1.50)	NA
	FF 100	35	35	0	0.50 (0.25-3.00)	NA
	FF 200	35	35	0	0.75 (0.25-3.00)	N/A
MRT (h)	FF 100	35	35	0	5.293 (71.9)	(4.241,6.607)

Source Data: Table 10.2
NA = Not Applicable
ND = Not determined, only 2 subjects had $AUC_{(0-24)}$ values
n* = number of subjects with parameter not estimated due to non-quantifiable data
[1] Median (range)

(Source – Table 6, Study FFA115441 report)

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

The systemic exposure of FF in asthma patients is lower than in healthy subjects (Table 11). In pop PK analysis, FF AUC was 25% lower in subjects with asthma compared to healthy subjects.

Table 11. Comparison of FF Systemic Exposure in Healthy Subjects vs. Subjects with Asthma following Repeat Dosing with FF

Population FF dose (mcg)	N	$AUC_{(0-24)}$ (pg.h/mL)
Asthma 100	116	180.7 [117.4, 292.0]
Healthy Subjects 200/25	116	534.4 [501.7, 567.1]
Asthma 200	115	394.5 [194.4, 917.8]

(source: Table 71, summary of clinical pharmacology)

2.5.3 What are the characteristics of drug absorption?

The estimate of absolute bioavailability for inhaled FF (single strip configuration) was ~13.9%. The oral bioavailability of FF was low, on average 1.26%, because of the extensive first pass metabolism. The systemic exposure of FF is primarily due to absorption of the drugs in lung. In vitro studies show that FF is not metabolized by human lung.

Absorption is rate limiting for FF. Mean absorption time for FF following inhaled administration of FF via DPI was 10.53 h (Table 12). In single- and multiple-dose studies, maximum plasma concentrations were reached within 0.1-2 hr for FF after oral inhalation administration. In-vitro studies using transfected MDCK cells, demonstrated that FF is a substrate of P-gp. However, because of low oral bioavailability, inhibition of P-gp is unlikely to have an impact on the overall bioavailability of FF.

Table 12. Summary of FF/VI absorption pharmacokinetic parameters following inhaled administration via NDPI in healthy subjects

Parameter (units)	FF (N = 16) n	FF (N = 16) Geometric mean (95% CI)	VI (N = 16) n	VI (N = 16) Geometric mean (95% CI)
MAT (h)	16	10.53 (8.52, 13.01)	16	0.659 (0.286, 1.517)
T90 (h)	16	35.2 (32.0, 38.7)	16	3.83 (2.64, 5.57)
t½, absorp (h)	16	8.76 (7.82, 9.81)	16	1.074 (0.775, 1.489)

Source Data: Table 10.2 and Table 10.4
FF = fluticasone furoate; VI = vilanterol; CI - confidence interval

(source, Table 9, study 102934 report)

2.5.4 What are the characteristics of drug distribution?

Following intravenous dosing, the average steady-state volume of distribution (V_{ss}) of FF was estimated to be 661 L, suggesting distribution into tissues. In vitro studies determined low blood cell association for FF with an in vitro blood-to-plasma ratio of 0.6. Plasma protein binding was very high (> 99%) regardless of concentration and

FF was predominantly bound to albumin (96%) and α1-acid glycoprotein (90%).

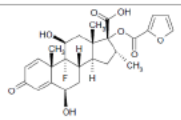
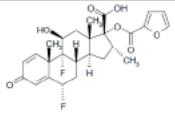
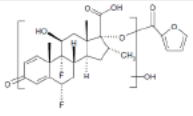
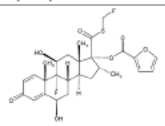
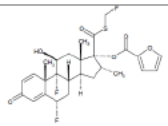
2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Hepatic elimination is the major route of elimination for FF. Mass balance study show that most (oral 101%, iv 90%) of the orally and intravenously administered FF was recovered in feces; Excretion of total radioactivity *via* urine accounted for less than 2% of total administered FF.

2.5.6 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Following a single intravenous administration of [14C]-GW685698, the principle radio-labeled component in plasma was parent compound. Following oral administration of [14C]-GW685698, a small percentage of the total circulating radioactivity was accounted for by unchanged FF (P in the table), with the rest circulating in form of metabolites (Table 13).

Table 13: Percentage of Circulating Metabolites of FF in Male Subjects Following Oral Administration of [14C]GW685698

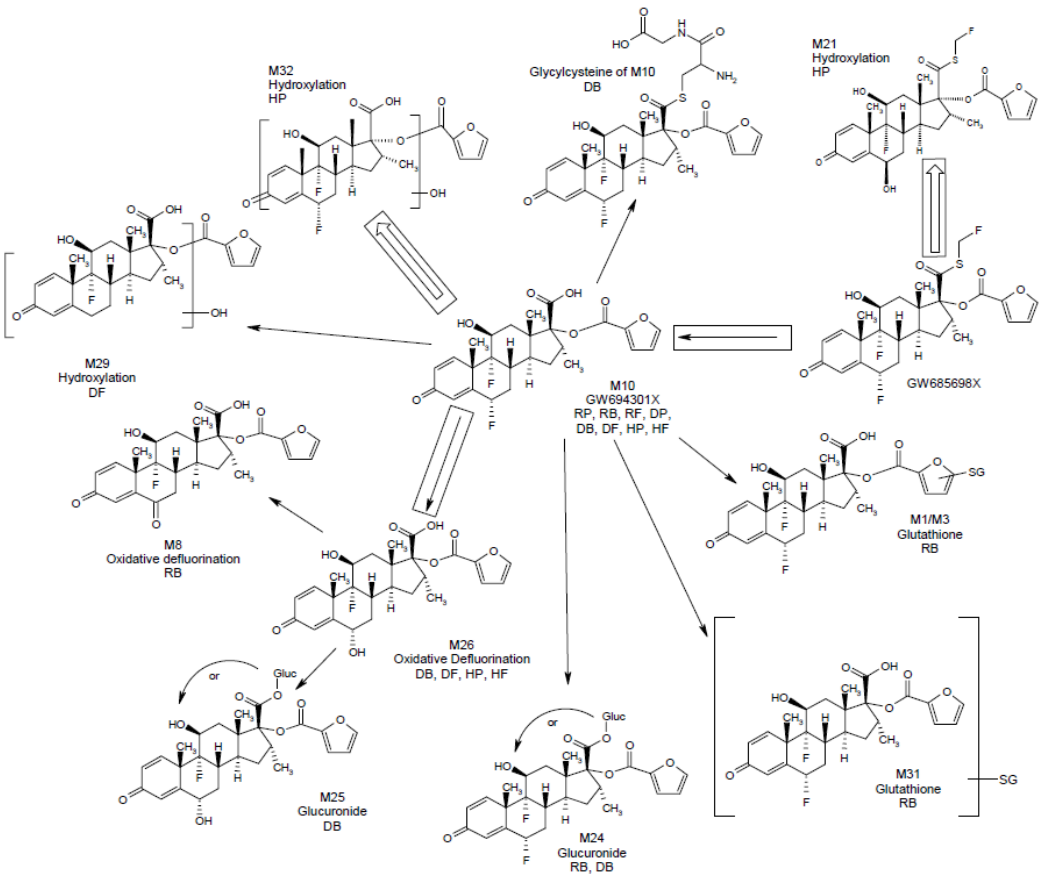
Peak ID	Metabolite Structure (assigned by retention time only)	Oral Administration		Intravenous Administration	
		Plasma (0.5 h)	Plasma (2 h)	Plasma (0.75 h)	Plasma (1.5 h)
		% sample radioactivity (pg equivalents [14C]-GW685698/mL)			
M26	 GSK728920A	2.0 (12.2)	< 1 (< 6.5)	ND	< 1 (< 4)
M10	 GW694301X	28.0 (175)	5.9 (52.1)	3.6 (44.9)	4.7 (33.2)
M32	 Hydroxylated GW694301X	4.0 (24.9)	2.9 (25.1)	< 1 (9.4)	< 1 (5.9)
M21	 GSK728921A	0.9 (5.9)	1.6 (14.0)	2.1 (26.3)	< 1 (< 4)
P	 GW685698X	17.1 (107)	6.7 (59.4)	64.3 (793)	51.8 (366)
Total radioactive material assigned		51.9 (324)	17.8 (157)	70.8 (874)	58.3 (412)
Non-extracted radioactive material		26.1 (163)	55.9 (493)	18.4 (227)	28.2 (199)
Total in sample (pg equivalents [14C]-GW685698)		624	882	1234	706

ND: Not detected, M8 was also run and not detected in any of the samples
% sample radioactivity values have been corrected for the extraction efficiency

(Source – Table 2, Report WD2005/01496/00)

2.5.7 What are the characteristics of drug metabolism?

The proposed metabolic pathway for FF is shown in Figure 8. Both in vitro and in vivo studies indicate that FF is extensively metabolized. The principal route of metabolism was via hydrolysis of the S-fluoromethyl carbothioate group to form GW694301X (M10). Two other minor drug-related components were identified in the human fecal extracts which were formed as a result of either defluorination and hydroxylation (M26) or by hydroxylation of GW694301X (M32). There was no *in vivo* evidence for cleavage of the furoate moiety resulting in the formation of fluticasone.



HP: Human Plasma; HF: Human Faeces
DP: Dog Plasma; DB: Dog Bile ; DF: Dog Faeces
RP: Rat Plasma; RB: Rat Bile; RF: Rat Faeces
Hollow arrow represents a component observed in plasma assigned by retention time alone, which represents less than 5% of sample radioactivity.
Boxed arrows represent metabolic route identified in humans

Figure 8. Putative Metabolic scheme for FF in Animals and Human
(Source – adapted from Figure 2, Section 2.7.2, Summary of Clinical Pharmacology)

2.5.8 Is there evidence for excretion of parent drug and/or metabolites into bile?

Following intravenous administration of [^{14}C]FF to healthy male subjects (study FFR10008), 90% of the total radioactivity was excreted in feces, indicating biliary excretion.

2.5.9 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

The available plasma concentration-time profile information does not suggest enterohepatic recirculation for FF.

2.5.10 What are the characteristics of drug excretion in urine?

Mass balance study suggested that renal clearance constitutes only 1-2% of FF elimination.

2.5.11 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

FF AUC increased in a dose proportional manner and FF Cmax increased in a less than proportional manner with increase in dose from 300 to 1200 mcg based on data from single dose PK study (
Table 14). After multiple-dose, FF AUC and FF Cmax increased in a less than proportional manner in dose from 50 to 200 mcg QD. The lack of dose proportionality for FF Cmax might reflect rate-limited absorption from the lung, as the Tmax also increased from 15 min (300 mcg) to 1 hour (1200 mcg).

Table 14. FF Dose Proportionality Following Single Dose and Repeat Dose of FF Administered via DPI in Healthy Subjects (Power Model)

	Parameter	Effect	Point Estimate	90% CI
Single Dose	AUC(0-∞)	Log (dose)	1.040	(0.956, 1.123)
	AUC(0-12)	Log (dose)	0.775	(0.722, 0.829)
	Cmax	Log (dose)	0.477	(0.416, 0.539)
Repeat Dose	AUC(0-4)	Log (dose)	0.758	(0.690, 0.827)
	Cmax	Log (dose)	0.606	(0.538, 0.674)

(Source, Table 7, Study FFA115441)

2.5.12 How do the PK parameters change with time following chronic dosing?

AUC_{inf} for FF after single dose inhalation via DPI is compared with $AUC_{tau\ (0\text{-}24h)}$ at steady state. Normalized AUC_{inf} for FF after a single dose is similar to $AUC_{(0\text{-}24h)}$ at steady state (602 vs 643 pg.h/mL/200 mcg, Table 15), supporting a time-independent PK following once-daily inhaled administration.

Table 15. FF Pharmacokinetic Parameters after single dose vs steady state in Healthy Volunteers

Study	Parameters (Units)	Treatment (via DPI)	N (n)	Geometric mean (CV%)	95% CI
115441	AUCinf (pg.h/mL)	FF 1200 mcg SD	35(33)	3614 (36.9)	3184,4102
	$AUC_{(0\text{-}24h)}$ (pg.h/mL)	FF 200 mcg day 9	35(30)	643 (30.4)	575, 718

N: Total subjects; n: subjects with no missing data for the parameter.
(Source, Table 5 and 6, Study FFA115441)

PK information was collected in Phase 2 and Phase 3 studies in asthmatic patients. While limited by assay sensitivity, the available time-concentration profiles of FF are similar between week 4 and week 18; and week 2, week 12 and week 52, indicating no time dependency in PK of FF after the concentration reached steady state.

2.5.13 Is there evidence for a circadian rhythm of the PK?

The circadian rhythm of FF PK and PD (HPA axis suppression) was assessed in study FFA106783 (FF, Diskus). The exposure of FF was comparable when it was administered morning or evening. The population clearance (CL/F) for once-daily in the morning was 782 L/h, for once daily in the evening was 842 L/h.
The 24-hour urinary cortisol excretion ratios (Week 8/Baseline) were comparable with placebo (0.87) for all groups (range 0.78 to 1.03) and between morning and evening dosing and once-daily and twice-daily dosing (Table 16).

Table 16. Summary of Statistical Analysis of 24-Hour Urinary Cortisol Excretion (nmol/24hr) – Urinary Cortisol Population

24-Hour Urinary Cortisol (nmol/24 Hr)	Placebo N=45	GW685698X Dose				
		200mcg AM N=75	200mcg PM N=66	400mcg AM N=73	400mcg PM N=74	200mcg BID N=74
n	45	75	66	73	74	74
LS Geometric Mean	48.24	55.99	57.23	48.21	48.39	43.41
LS Ratio to Baseline	0.87	1.01	1.03	0.87	0.87	0.78
Ratio of Column to Placebo		1.16	1.19	1.00	1.00	0.90
95% CL		(0.87,1.55)	(0.88,1.60)	(0.75,1.34)	(0.75,1.34)	(0.67,1.20)
p-value		0.312	0.260	0.997	0.983	0.478

Source: (Table 21, study report FFA106783)

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

Population PK models were developed to describe the FF systemic exposure in patients with asthma. Please see Pharmacometrics review in Appendix 2.11 for additional details.

There is no effect of age, weight or gender on the exposure of systemic FF in subjects with asthma.
The systemic exposure of FF for East Asian, Japanese and South Asian subjects were on average 23% to 49% higher compared with white Caucasian subjects. This finding is consistent with results seen in asthmatic subjects of East Asian origin.

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

No dose adjustments are needed for any of the aforementioned covariates.

2.6.2.1 Severity of Disease State

Not assessed.

2.6.2.2 Body Weight

As stated in section 2.6.1.

2.6.2.3 Elderly

As stated in section 2.6.1.

2.6.2.4 Pediatric Patients

The sponsor is requesting a waiver for children under 5 years old, and a deferral for children 5-11 years old. The current submission includes children above 12 years old.

The proposed FF development program in children aged 5 – 11 years consists of:

- Two completed clinical pharmacology studies (HZA102942 (n=27), HZA112777 (n=26)) to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics in children with asthma (completed) followed by:

- An ongoing combined Phase 2b dose ranging/ single Phase 3 study (HZA106855) to determine efficacy and safety in the target population (575 children uncontrolled on non-ICS asthma medication and/or low dose ICS)

- Three planned studies to evaluate the safety of fluticasone furoate (hypothalamo-pituitary-adrenal axis (HZA107118), knemometry (HZA107112) and growth studies (HZA114971))

The timeline of proposed FF pediatric plan submitted to EMA is demonstrated in Figure 9**.**

Reviewer's comment: The HPA axis study (HZA107118) in children 5-11 years was mentioned in the PIP to EMA, but not in the clinical studies section in the pediatric study plan submitted to FDA. In an earlier communication for BREO ELLIPTA (IND77855) on Nov 15, 2013, the division stated that "Based on the available information regarding relative exposure in patients 5 to 11 years of age, your pediatric development program

should include an assessment of the effect on the HPA axis."

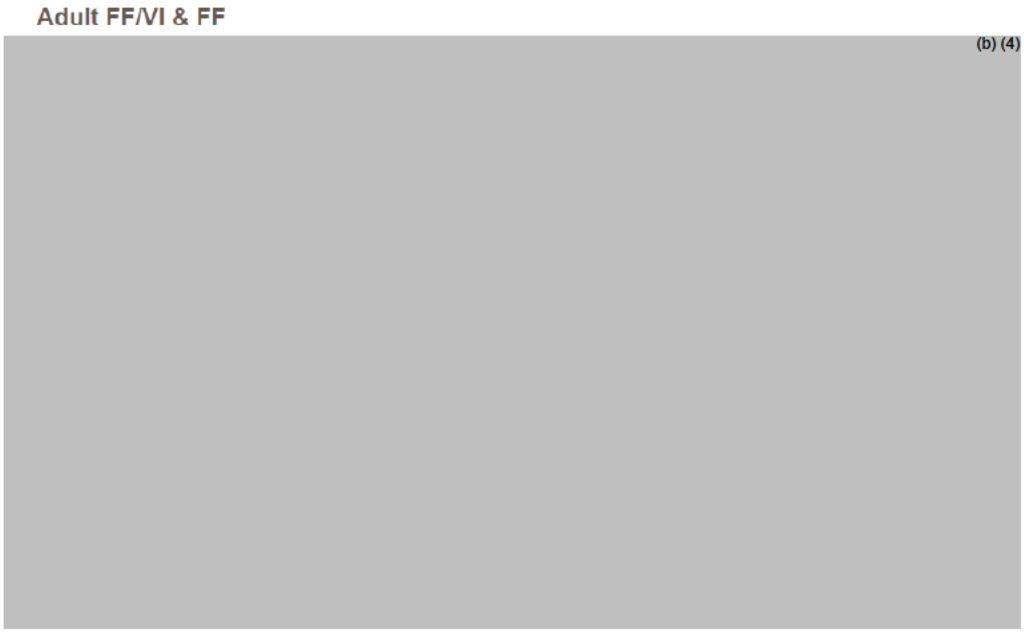


Figure 9. Timeline of Pediatric development plan submitted to EMA

2.6.2.5 Race/Ethnicity

As stated in section 2.6.1.

In addition, FF PK between Western and Asian subjects was compared in a dedicated study HZA113477. The exposure of FF as measured by AUC(0-24) and Cmax is higher in east Asian population (Table 17 and Figure 10) with inhaled doses, but is similar with iv administration (Figure 10).

After a single IV dose of 250 mcg, CL is similar among ethnic groups after adjusting for weight. After 7 inhaled doses, FF AUC(0-24) in east Asian is 27% to 49% higher and FF Cmax in east Asian is 37% to 78% higher compared to Caucasian. The higher bioavailability in Asian is possibly due to increased absorption at lung, since the activity of the major elimination pathway (CYP3A4) is similar among ethnic groups. The increased FF exposure is not related to HPA axis suppression in the Asian population, and the PK difference is not clinically significant.

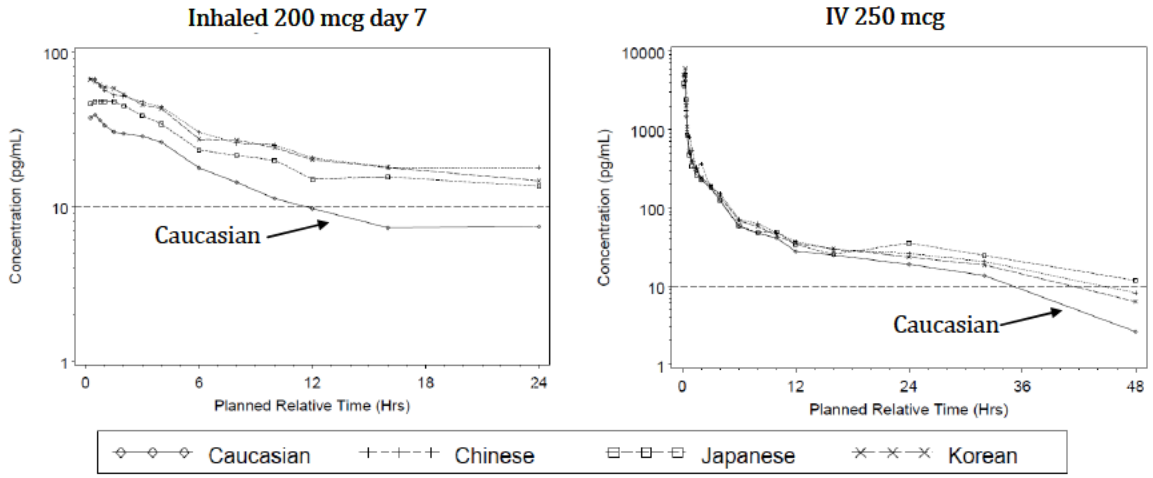


Figure 10. Mean plasma concentration of FF following inhaled or iv dose administration in healthy Asian and Caucasian subjects
(Source – Figure 10.4 and Figure 10.6, Study HZA113477 report)

Table 17 Mean PK parameters of inhaled FF 200 mcg (7 days) in healthy Asian and Caucasian subjects

Parameter (units)	Ethnic group comparison	Ratio of adjusted geometric mean	90% CI of ratio
Cmax (pg/mL)	Chinese:Caucasian	1.637	(1.361, 1.969)
	Japanese:Caucasian	1.373	(1.141, 1.653)
	Korean:Caucasian	1.776	(1.477, 2.137)
AUC(0-24) (pg.h/mL)	Chinese:Caucasian	1.487	(1.190, 1.858)
	Japanese:Caucasian	1.274	(1.015, 1.598)
	Korean:Caucasian	1.439	(1.153, 1.797)

(Source – Table 7, HZA113477 report)

2.6.2.6 Renal Impairment

Renal function affected FF/VI exposure based on a 7 day PK study, such that exposure decreased for FF in severe renal impairment patients as shown in Figure 11. There was no evidence for reduced plasma protein binding of FF in plasma from subjects with severe renal impairment, compared with plasma from healthy subjects (>99.8% vs. >99.7%).

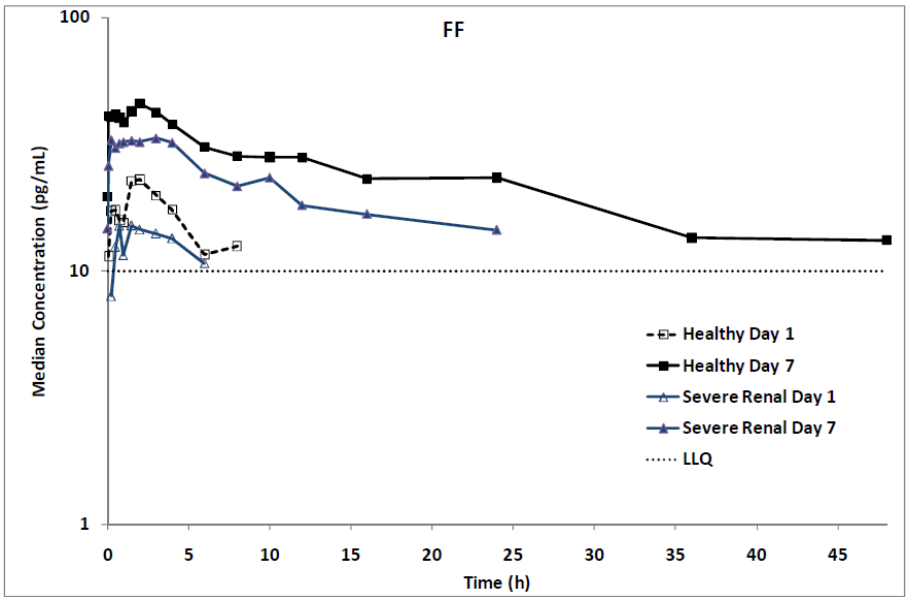


Figure 11. Median FF Plasma Concentration-Time Profiles in Subjects with Severe Renal Impairment and Healthy Subjects After Single and Repeat Dose (7 Days) FF/VI (200/25 mcg)
(Source – Figure 1, Study HZA113970 report)

The median $AUC_{(0-24)}$ and Cmax for FF was lower in severe renal impairment subjects. Median $AUC_{(0-24)}$ is 21% lower (546 vs 694 pg.h/mL) and median C_{max} is 27% lower (33.3 vs 45.7 pg/mL) compared to healthy subjects. Because of low assay sensitivity for FF, PK parameters (AUC), concentrations and Cmax were imputed as a fixed value of ½ LLQ for several subjects. Therefore, the geometric mean ratio was close to 1 (Table 18), despite the lower median concentrations(Figure 11) for FF in severe renal impairment patients. As Figure 11 was the observed data without imputation, the time concentration plot better described the PK profiles in severe renal impairment subjects and healthy subjects.

FF is an oral inhalation drug intended for local action, and the systemic exposure is more related to safety rather than efficacy. Therefore, a lower systemic exposure of FF in the renal impairment population is not of concern.

Table 18: Summary of FF Pharmacokinetic Parameters in Subjects with Severe Renal Impairment and Healthy Subjects After Single and Repeat Dose (7 Days) FF/VI (200/25 mcg)

Parameter	Day	Group comparison	Adjusted geometric means	Ratio of adjusted geometric means	90% CI of the ratio
$AUC_{(0–8)}$ [pg.h/mL]	1	Severe renal impairment / healthy	126.11 / 131.82	0.96	(0.54, 1.70)
$AUC_{(0–24)}$ [pg.h/mL]	7	Severe renal impairment / healthy	554.12 / 609.06	0.91	(0.60, 1.38)
C_{max} [pg/mL]	1	Severe renal impairment / healthy	17.99 / 19.54	0.92	(0.55, 1.54)
	7	Severe renal impairment / healthy	36.91 / 38.44	0.96	(0.57, 1.61)
t½ [h]	7	Severe renal impairment / healthy	34.55 / 35.07	0.98	(0.79, 1.23)

CI = confidence interval
C_{max} was analysed using a mixed effects model with fixed effects for group (healthy or renal impairment), day and group-by-day interaction, and subject fitted as a random effect.
$AUC_{(0-8)}$, $AUC_{(0-24)}$ and t½ were analysed using a fixed effects model adjusting for group
(Source – Table 6, Study HZA113970 report)

2.6.2.7 Hepatic Impairment

The impact of hepatic impairment was assessed in a dedicated study with multiple doses of FF/VI via DPI in mild, moderate and severe hepatic impairment patients.

Higher systemic FF exposure in all hepatic impairment patients: Mean plasma FF concentrations tended to be higher in subjects with all severities of hepatic impairment compared with healthy subjects after repeat dose FF/VI. On Day 7,the upper 90% CI limits of $AUC_{(0–24)}$ ratio (hepatic/healthy) for each hepatic impairment group were all greater than 2 (Table 19). On day 7, the weighted mean (0-24h) serum cortisol, was on average 34% lower with moderate hepatic impairment subjects compare to the healthy subjects.

There was no evidence for reduced plasma protein binding of FF in plasma from subjects with varying degrees of hepatic impairment, compared with plasma from healthy subjects.

An earlier hepatic impairment study, FFA10013, was submitted to support VERAMYST approval in NDA 022051. Following a single inhaled dose of 400 mcg of FF administered via DISKUS, there was a 3 fold increase in FF exposure and 20% reduction in serum cortisol level in patients with moderate hepatic impairment patients compared with healthy subjects

Based on these studies, the sponsor recommended no dose adjustments for mild hepatic impairment, and capping the maximum dose as 100mcg for moderate or severe hepatic impairment patients.

For ARNUITY ELLIPTA, the magnitude of increased exposure for FF in hepatic impairment population is consistent with the earlier observations and other ICS. The biggest observed PD change is 34% decrease in serum cortisol with 200mcg dose in moderate hepatic impairment patients. This change in serum cortisol is of similar

amplitude as when 200 mcg FF is co-administered with ketoconazole (27%). As there is no dose limiting in label for co-administration of FF and ketoconazole, and there is no dose capping for other ICS with similar elimination pathways in moderate and severe hepatic impairment patients, **this reviewer recommends making both FF 100 and FF 200 mcg available for patients with moderate and severe hepatic impairment** with a cautionary labeling language.

Table 19: FF PK Parameters (day 7): Hepatic impairment groups vs. normal hepatic function group

Parameter	Day	Group Comparison	Adjusted Geometric Means	Ratio of Adjusted Geometric Means	90% CI of the Ratio
AUC(0–8)	1	Hepatic Mild /Healthy	99.71 / 148.73	0.67	(0.33, 1.35)
		Hepatic Moderate /Healthy	146.44 / 148.73	0.98	(0.49, 1.98)
		Hepatic Severe /Healthy	27.38 / 148.73	0.18	(0.09, 0.38)
AUC(0–24)	7	Hepatic Mild /Healthy	634.50 / 472.74	1.34	(0.82, 2.20)
		Hepatic Moderate /Healthy	863.50 / 472.74	1.83	(1.11, 2.99)
		Hepatic Severe /Healthy	825.75 / 472.74	1.75	(1.05, 2.91)
Cmax	1	Hepatic Mild /Healthy	29.10 / 36.05	0.81	(0.57, 1.15)
		Hepatic Moderate /Healthy	29.36 / 36.05	0.81	(0.57, 1.16)
		Hepatic Severe /Healthy	21.61 / 36.05	0.60	(0.42, 0.86)
	7	Hepatic Mild /Healthy	51.36 / 43.48	1.18	(0.83, 1.69)
		Hepatic Moderate /Healthy	62.33 / 43.48	1.43	(1.00, 2.04)
		Hepatic Severe /Healthy	59.58 / 43.48	1.37	(0.95, 1.98)

(Source – Table 5, Study HZA111789 report)

2.6.3 Does genetic variation impact exposure and/or response?

The in-vitro assay suggested that FF is metabolized by CYP3A4. The DNA samples were collected in some studies; however, the pharmacogenetic impact was not assessed.

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

The potential for drug-drug interaction because of induction or inhibition of CYP enzymes by FF is less likely at the low concentrations with clinical doses. Please see sections 2.7.2 and 2.7.4 for further details.

2.7.2 Is the drug a substrate of CYP enzymes?

FF is a substrate of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp). In vitro studies and in vivo study with ketoconazole indicated that FF was CYP3A4 substrate. In vitro studies also suggest that FF is not metabolized in the human lung, indicating that inhibition of lung metabolism is unlikely to influence the pharmacokinetics of FF.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes/transporters?

In vitro studies demonstrated that FF is an inhibitor of the cytochrome P450 enzymes CYP2C8 and CYP3A4 (IC50 values between 0.5 and 1.5 microM). FF and its major metabolite GW694301X were in vitro inhibitors of the human transporter protein OATP1B1 (IC50 values of 0.2 and 2.6 microM, respectively). At clinical doses, FF concentration is at least 1000-fold lower than the lowest IC50 values. FF is not inducer of CYP enzymes.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

In vitro permeability assessments indicated that FF is a substrate for P-gp. FF and its major metabolite GW694301X were found to inhibit the human transporter protein OATP1B1 (IC50 values of 0.2 and 2.6 microM, respectively). The inhibition potential of FF at low inhaled clinical doses is considered to be negligible.

2.7.5 Are there other metabolic/transporter pathways that may be important?

No other metabolic enzyme or transporters are known to be important for disposition of FF in addition to those already discussed in sections 2.7.2 and 2.7.4

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

With regard to extrinsic factors, only the effect of co-administration with other drugs on FF exposure has been evaluated, which is discussed under section 2.7.7. The differences in measured systemic exposures are not relevant for efficacy; however, it may have implications with respect to safety. Increased FF exposure may lead to increased glucocorticoid side effect such as HPA axis suppression.

2.7.7 What are the drug-drug interactions?

Effects of co-administered drugs on FF PK are summarized in Table 20.

Table 20: Effect of co-administered drugs on FF

Co-administered drug	Co-administered drug	GMR* (90% CI)	
		AUC	C_{max}
Ketoconazole (potent P-gp and CYP3A4 inhibitor) 400 mg QD (monotherapy: days 1 -4, with FF/VI on days 5-11)	FF/VI (200/25 mcg) inhaled once daily on days 5-11.	1.36 (1.16-1.59)	1.33 (1.12-1.58)

*GMR: Ratio of Geometric Means

Effect of co-administered drugs on FF/VI PD is also assessed. There was an average 27% reduction in weighted mean serum cortisol (0–24 h) following repeat dosing of FF/VI with ketoconazole compared with FF/VI with placebo, with the 90% confidence intervals between 14% and 38% (Table 21).

Table 21. Summary of statistical analysis of serum cortisol weighted mean (0–24 h) (mmol/L) on Day 11

Treatment comparison	Adjusted geometric means test/reference	Ratio of adjusted geometric means	90% CI of the ratio
Ketoconazole + FF/VI 200/25 mcg : placebo + FF/VI 200/25 mcg	104.62 / 142.49	0.73	(0.62, 0.86)

(Source – Table 7, Study HZA105548 report)

FF is an oral inhalation drug intended for local action, and the systemic exposure is related to safety rather than efficacy. The serum cortisol change with ketoconazole co-administration is similar to the serum cortisol reduction observed in hepatic impairment patients. Therefore, this reviewer recommends no dose adjustment, and monitoring for corticosteroid related side effects.

The PK information from this study can be extrapolated to the to-be-marketed product (FF 100 and 200 mcg), because the FF component is used in the same dose, the plasma FF exposure in this study is comparable to the FF exposure in asthmatic patients in Phase 3 studies, and that VI was unlikely to interact with FF.

2.7.8 Does the label specify co-administration of another drug?

The FF label does not mention specific co-administration with other drugs.

2.7.9 What other co-medications are likely to be administered to the target population?

All asthmatic patients are likely to take other medications for treatment of asthma as listed under 2.2.4.

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

No.

2.8 General Biopharmaceutics

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

This is an inhalation drug and the sponsor did not provide BCS classification information in this submission.

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

FF is delivered via the DPI as a single strip inhaler in the to-be-marketed product. In some previous FF monotherapy studies, including the Phase 2b program, conducted using the DPI, the inhaler contained FF formulated with lactose in the first strip and a second

strip containing [redacted] (b) (4). Both of these excipients comprise placebo to match the vilanterol (VI) strip in the FF/VI combination product. This two strip configuration was used for the majority of FF monotherapy treatment arms in the FF /VI combination Phase 3 clinical studies and the Phase 2b dose ranging studies. Bioequivalence was not demonstrated in the relative BA or BE study 115440.

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

The effect of food on the PK of FF is not assessed. Since the oral bioavailability of FF is minimal, it is not likely that inhaled FF PK is changed by food.

2.8.4 Was the bioequivalence of the different strengths of the to-be-marketed formulation tested? If so were they bioequivalent or not?

In study FFA115440, bioequivalence was not demonstrated for the to be marketed product (single strip, FF 400 mcg) compared with either FF 400 mcg (two-strip, used in some Phase 3 studies) or compared with FF/VI 400/50 mcg (Table 22). In general, systemic exposure (AUCinf) for FF in single strip configuration is 29% higher compared to FF in double strip configuration, and 60% higher compared to FF in FF/VI combination. This observation is consistent with the in vitro data that single strip configuration will deliver 20% more fine particle mass compared to two strip configuration. This exposure difference may have implication for safety analysis, and has been communicated to the clinical team.

Table 22. Relative FF exposure for 1 strip vs 2 strip products

Parameter	Treatment Comparison	Adjusted Geometric Means	Ratio of Adjusted Geometric Means	90% CI of the Ratio
AUC(0-∞)	FF 400 1 strip / FF 400 2 strip	1144.7 / 889.5	1.29	(1.14, 1.46)
	FF 400 1 strip / FF/VI 400/50	1144.7 / 714.8	1.60	(1.37, 1.87)
AUC(0-t')	FF 400 1 strip / FF 400 2 strip	560.2 / 458.0	1.22	(1.16, 1.29)
	FF 400 1 strip / FF/VI 400/50	560.2 / 401.1	1.40	(1.31, 1.49)
AUC(0-t)	FF 400 1 strip / FF 400 2 strip	723.0 / 531.6	1.36	(1.23, 1.50)
	FF 400 1 strip / FF/VI 400/50	723.0 / 441.2	1.64	(1.44, 1.87)
Cmax	FF 400 1 strip / FF 400 2 strip	67.84 / 60.08	1.13	(1.07, 1.20)
	FF 400 1 strip / FF/VI 400/50	67.84 / 47.75	1.42	(1.33, 1.52)

(Source – Table 12, Study FFA115440 report)

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

The methods for analysis of FF in plasma samples involved solid phase extraction and high pressure liquid chromatography with tandem mass spectrometric detection (SPE-HPLC-MS/MS).

Different analytical methods were developed and validated throughout the development, and there are 6 analytical reports submitted in this NDA. Analytical methods used in different studies are listed in Table 23. Of all the analytical methodologies, the best lower limit of quantification (LLOQ) for FF is 10 pg/mL. At a single clinical dose of FF (≤200 mcg), plasma concentrations of FF are at or below the LLOQ for most of the time points. Due to the analytical sensitivity limitation, some clinical pharmacology studies were conducted with supra-therapeutic doses of FF, such as the single dose proportional study in healthy volunteers (FFA115441).

FF was analyzed in three sites: (b) (4), Glaxo SmithKline (GSK), Hertfordshire, UK; (b) (4) and (b) (4). There was no cross validation between the sites. In this review, we summarized the most common method for FF, which were used to analyze samples in most of the pop-PK studies and DDI studies.

Analytical method for FF: report # WD2008/01148/00 and WD2010/00145/00

The bioanalytical methods to measure FF in human plasma PK samples were developed and validated at (b) (4) GSK (Hertfordshire, UK). FF is extracted from 150 µL human plasma by solid phase extraction using [$^{13}C_2H_3$]- GW685698 as an internal standard. Extracts are analyzed by HPLC-MS/MS using a ACE 50 *2.1mm, C18 3µm column with a mobile phase of 5 mM ammonium formate (native pH) and methanol, with a Turbo IonSpray interface and multiple reaction monitoring. The lower limit of quantitation (LLOQ) for FF in human plasma was 10 pg/mL, with linearity demonstrable to 1000 pg/mL.

Table 23: Summary of analytical methods for analysis of FF in clinical trials

Validation Report	Clinical Studies Supported	Method Description and Performance	
Fluticasone Furoate (GW685698X)			
WD2002/00273/00	FFA10001 FFA10002 FFA10008 FFR10008	GW685698X, GW694301X and GR51608X are extracted from 500 µL human plasma by solid phase extraction using [(b) (4)] as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	10.0 pg/mL for GW685698X and GR51608X 20.0 pg/mL for GW694301X
		Validated Range	10.0 to 2000 pg/mL for GW685698X 10.0 to 2000 pg/mL for GR51608X 20.0 to 2000 pg/mL for GW694301X
		Within-run Precision (%CV)	≤8.5% GW685698X ≤ 7.9% GW694301X ≤ 9.0% GR51608X
		Between-run Precision (%CV)	≤ 3.5% GW685698X ≤9.1% GR51608X ≤ 8.0% GW694301X
		Accuracy (%Bias)	<± 7.1 GW685698X <± 4.5 GR51608X <± 4.0 GW694301X
		Stability in Human Plasma	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature
		Processed Extract Stability	at least 24 hours at ambient temperature
WD2002/01057/00	FFA10003 FFA10009 FFA10013 FFA10022 FFA10026 FFA10027 FFA10028 FFA20001 FFA103096	GW685698X is extracted from 500 µL human plasma by solid phase extraction using [(b) (4)] as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	10.0 pg/mL
		Validated Range	10.0 to 1000 pg/mL
		Within-run Precision (%CV)	≤13.7%
		Between-run Precision (%CV)	≤7.9%
		Accuracy (%Bias)	-9.3%
		Stability in Human Plasma	3 freeze-thaw cycles at -20°C at least 24 hours at ambient temperature
		Processed Extract Stability	Not determined
FD2005/00013/00	FFA106783 FFA109684 FFA109685 FFA109687 FFR101688 HZA102940 HZA105871 HZA108799 HZA102928	GW685698X is extracted from 150 µL human plasma by solid phase extraction using [$^{13}C^{2}H_{3}$]- GW685698 as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	10.0 pg/mL
		Validated Range	10.0 to 1000pg/mL
		Within-run Precision (%CV)	≤14.3%
		Between-run Precision (%CV)	≤8.2%
		Accuracy (%Bias)	-12.5% ≤ bias ≤11.6%
		Stability in Human Plasma	3 freeze-thaw cycles at -20°C at least 24 hours at ambient temperature
		Processed Extract Stability	at least 24 hours at ambient temperature
FD2008/00136/00	FFA10003	GW685698X is extracted from 150 µL human plasma by solid phase extraction using [$^{13}C^{2}H_{3}$]- GW685698 as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	10.0 pg/mL
		Validated Range	10.0 to 1000pg/mL
		Within-run Precision (%CV)	≤14.3%
		Between-run Precision (%CV)	≤8.2%
		Accuracy (%Bias)	-12.5% ≤ bias ≤11.6%
		Stability in Human Plasma	3 freeze-thaw cycles at -20°C at least 24 hours at ambient temperature
		Processed Extract Stability	at least 24 hours at ambient temperature

Validation Report	Clinical Studies Supported	Method Description and Performance	
WD2008/01148/00	HZA106851 HZA113477 HZA106839	GW685698X is extracted from 150 µL human plasma by solid phase extraction using [$^{13}C^{2}H_{3}$]- GW685698 as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	10.0 pg/mL
		Validated Range	10.0 to 1000pg/mL
		Within-run Precision (%CV)	≤12.6%
		Between-run Precision (%CV)	≤5.1%
		Accuracy (%Bias)	-2.6% ≤ bias ≤14.3%
		Stability in Human Plasma	See WD2010/00145/00
		Processed Extract Stability	See WD2010/00145/00
WD2010/00145/00	HZA102942 HZA105548 HZA106827 HZA106829 HZA106839	GW685698X is extracted from 150 µL human plasma by solid phase extraction using [$^{13}C^{2}H_{3}$]- GW685698 as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	10.0 pg/mL
		Validated Range	10.0 to 1000pg/mL
		Within-run Precision (%CV)	≤13.1%
		Between-run Precision (%CV)	≤7.5%
		Accuracy (%Bias)	-11.0% ≤ bias ≤3.5%
		Stability in Human Plasma	5 freeze-thaw cycles at -20°C or - 80°C at least 24 hours at ambient temperature at least 290 days at -20°C
		Processed Extract Stability	at least 72 hours at ambient temperature
2011N118918_00	HZA111789 HZA113970	GW685698X is extracted from 150 µL human plasma by solid phase extraction using [$^{13}C^{2}H_{3}$]- GW685698 as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	10.0 pg/mL
		Validated Range	10.0 to 1000pg/mL
		Within-run Precision (%CV)	≤11.6%
		Between-run Precision (%CV)	≤11%
		Accuracy (%Bias)	- ≤11.7%
		Stability in Human Plasma	3 freeze-thaw cycles at -20°C at least 24 hours at ambient temperature 412 days at nominally -20°C
		Processed Extract Stability	at least 4 days at ambient temperature
2012N136667_00	FFA114496 FFA115440	GW685698X is extracted from 500 µL human plasma by solid phase extraction using (b) (4) as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	10.0 pg/mL
		Validated Range	10.0 to 1000pg/mL
		Within-run Precision (%CV)	≤16.0%
		Between-run Precision (%CV) Accuracy (%Bias)	≤7.9% ≤9.3%
		Stability in Human Plasma	3 freeze-thaw cycles at -20°C at least 24 hours at ambient temperature 412 days at nominally -20°C
		Processed Extract Stability	at least 24 hours at ambient temperature
2012N153939_00	FFA115441	GW685698X is extracted from 150 µL human plasma by solid phase extraction using [$^{13}C^{2}H_{3}$]- GW685698 as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	10.0 pg/mL
		Validated Range	10.0 to 1000pg/mL
		Within-run Precision (%CV)	≤10.2%
		Between-run Precision (%CV)	≤9.8%
		Accuracy (%Bias)	≤8.0%
		Stability in Human Plasma	3 freeze-thaw cycles at -20°C at least 24 hours at ambient temperature 412 days at nominally -20°C
		Processed Extract Stability	At least 68 hours ar 4°C at least 4 days at ambient temperature

Source – Appendix Table 3, Section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods)

2.9.2 Which metabolites have been selected for analysis and why?

No metabolites were measured in the PK samples. As stated in section 2.5.7, the metabolites are not active metabolites.

2.9.3 For all moieties measured, is free, bound, or total measured?

Total (bound + unbound) concentrations were measured in plasma PK samples.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Table 23 presents a summary of analytical methods used for quantification of FF and lists out the respective validation report numbers. Details of the main bioanalytical methods are discussed in section 2.9.1.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

The standard curve for FF's analysis in plasma ranged from 10 to 1000 pg/mL. A linear regression model, with weighting factor of $1/concentration^2$ was used for the curve fitting for FF.

2.9.5.1 What are the lower and upper limits of quantitation?

LLOQ and ULOQ for FF were 10 pg/mL and 1000 pg/mL, respectively. A 10-fold dilution factor was also validated for 2000 pg/mL concentration.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

The accuracy and precision of analytical methods for FF is listed in Table 23. The bias and imprecision for 10-fold dilution factor was less than 8%.

The selectivity of both the methods was evaluated by extracting and analyzing blank human plasma from six individual sources both with and without addition of internal standard. All lots were free from significant interfering peaks in the drug and internal standard regions.

2.9.5.3 What is the sample stability under conditions used in the study?

For the bioanalytical methods, stability was demonstrated under different conditions as discussed below:

FF

Stability of FF was established under various conditions: stability of FF in human whole blood at 37°C for at least 4 hours. stability of FF in human plasma for at least 24 hours at room temperature and for at least 412 days at -20°C; stability for five freeze thaw cycles at -20°C; stability of processed samples (auto sampler reinjection and reproducibility) under ambient conditions (bench-top) for 72 hours. For each of the stability assessments %CV was less than 15%. Stock solution stability was also assessed for 44 days at 4°C.

3. Detailed Labeling Recommendations

The revised labeling language based on the preliminary review is as below:

5.6 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of TRADENAME ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin,troleandomycin, voriconazole) because increased systemic corticosteroid adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone furoate is a substrate of CYP3A4. Concomitant administration of the (b) (4) CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate. Caution should be exercised when considering the coadministration of ARNUITY ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.6), Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and efficacy in pediatric patients under 12 years of age have not been established.

Effects on Growth: Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. A reduction of growth velocity in children (b) (4) may occur as a result of poorly controlled asthma or from use of corticosteroids, including inhaled corticosteroids. The effects of long-term treatment of children and adolescents with inhaled corticosteroids, including fluticasone furoate, on final adult height are not known.

Controlled clinical trials have shown that inhaled corticosteroids may cause a reduction in growth in (b) (4). In these trials, the mean reduction in growth velocity was approximately 1 cm/year (range: 0.3 to 1.8 cm/year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in (b) (4) than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The growth of children and adolescents receiving orally inhaled corticosteroids, including TRADENAME ELLIPTA, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed

against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including TRADENAME ELLIPTA, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

A randomized, double-blind, parallel-group, multicenter, 1-year, placebo-controlled trial evaluated the effect of once-daily treatment with 110 mcg of fluticasone furoate in the nasal spray formulation on growth velocity assessed by stadiometry. The systemic exposure of fluticasone furoate in this study is lower than that of TRADENAME ELLIPTA. The subjects were 474 prepubescent children (girls aged 5 to 7.5 years and boys aged 5 to 8.5 years). Mean growth velocity over the 52-week treatment period was lower in the (b) (4) receiving fluticasone furoate nasal spray (5.19 cm/year) compared with placebo (5.46 cm/year). The mean reduction in growth velocity was 0.27 cm/year (95% CI: 0.06 to 0.48) *[see Warnings and Precautions (5.10)]*.

8.6 Hepatic Impairment

Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Use TRADENAME ELLIPTA with caution in patients with moderate or severe hepatic (b) (4) Monitor patients for corticosteroid-related side effects *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

There were no significant increases in fluticasone furoate exposure in subjects with severe renal impairment (CrCl<30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

The pharmacodynamics of fluticasone furoate were characterized in (b) (4) of fluticasone furoate given as a single component and also in (b) (4) of fluticasone furoate given in combination with vilanterol.

HPA Axis Effects: *Healthy Subjects:* Inhaled fluticasone furoate at repeat doses up to 400 mcg was not associated with statistically significant decreases in serum or urinary cortisol in healthy subjects. Decreases in serum and urine cortisol levels were observed at fluticasone furoate exposures several-fold higher than exposures observed at the therapeutic dose.

Subjects with Asthma: A randomized, double-blind, parallel-group trial in 185 subjects with asthma showed no difference between once-daily treatment with fluticasone furoate/vilanterol 100 mcg/25 mcg or fluticasone furoate/vilanterol 200 mcg/25 mcg compared with placebo on serum cortisol weighted mean (0 to 24 hours), serum cortisol $AUC_{(0-24)}$, and 24-hour urinary cortisol after 6 weeks of treatment, whereas prednisolone 10 mg given once daily for 7 days resulted in significant cortisol suppression.

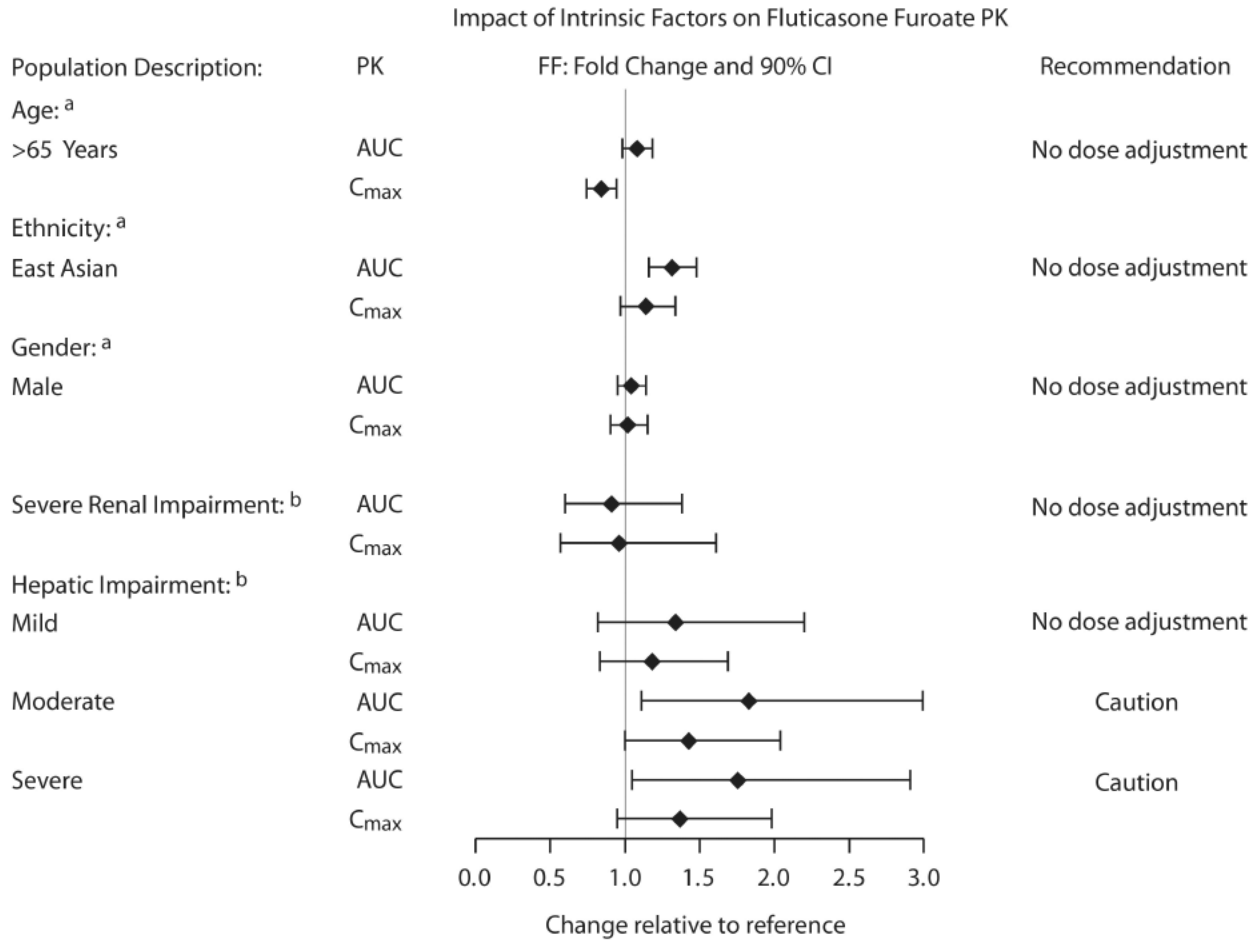
Cardiac Effects: A QT/QTc study did not demonstrate an effect of fluticasone furoate administration on the QTc interval. The effect of a single dose of 4,000 mcg of orally inhaled fluticasone furoate on the QTc interval was evaluated over 24 hours in 40 healthy male and female subjects in a placebo and positive (a single dose of 400 mg oral moxifloxacin) controlled cross-over study. The QTcF maximal mean change from baseline following fluticasone furoate was similar to that observed with placebo with a treatment difference of 0.788 msec (90% CI: -1.802, 3.378). In contrast, moxifloxacin given as a 400-mg tablet resulted in prolongation of the QTcF maximal mean change from baseline compared with placebo with a treatment difference of 9.929 msec (90% CI: 7.339, 12.520).

12.3 Pharmacokinetics

The pharmacokinetics of fluticasone furoate were characterized in (b) (4) of fluticasone furoate given as a single component and also in (b) (4) of fluticasone furoate given in combination with vilanterol. Linear pharmacokinetics were observed for fluticasone furoate (200 to 800 mcg). On repeated once-daily inhalation administration, steady state of fluticasone furoate plasma concentration was achieved after 6 days, and the accumulation was up to 2.6-fold as compared with single dose.

Absorption: Fluticasone furoate plasma levels may not predict therapeutic effect. Peak plasma concentrations are reached within 0.5 to 1 hour. Absolute bioavailability of fluticasone furoate when administrated by inhalation was 13.9%, primarily due to absorption of the inhaled portion of the dose delivered to the lung. Oral bioavailability from the swallowed portion of the dose is low (approximately 1.3%) due to extensive first-pass metabolism. Systemic exposure (AUC) in subjects with asthma was 26% lower than observed in healthy subjects.
Distribution: Following intravenous administration to healthy subjects, the mean volume of distribution at steady state was 661 L. Binding of fluticasone furoate to human plasma proteins was high (99.6%).
Metabolism: Fluticasone furoate is cleared from systemic circulation principally by hepatic metabolism via CYP3A4 to metabolites with significantly reduced corticosteroid activity. There was no in vivo evidence for cleavage of the furoate moiety resulting in the formation of fluticasone.
Elimination: Fluticasone furoate and its metabolites are eliminated primarily in the feces, accounting for approximately 101% and 90% of the orally and intravenously administered dose, respectively. Urinary excretion accounted for approximately 1% and 2% of the orally and intravenously administered doses, respectively. Following repeat-dose inhaled administration, the plasma elimination phase half-life averaged 24 hours.
Special Populations: The effect of renal and hepatic impairment and other intrinsic factors on the pharmacokinetics of fluticasone furoate is shown in Figure 1.

Figure 1. Impact of Intrinsic Factors on the Pharmacokinetics (PK) of Fluticasone Furoate (FF)



[a] Age, gender, and ethnicity comparison for TRADENAME ELLIPTA in subjects with asthma.

[b] Renal groups (fluticasone furoate/vilanterol 200 mcg/25 mcg) and hepatic groups (fluticasone furoate/vilanterol 200 mcg/25 mcg or fluticasone furoate/vilanterol 100 mcg/12.5 mcg) compared with healthy control group.

Race: Systemic exposure (AUC(0-24)) to inhaled fluticasone furoate 200 mcg was 27% to 49% higher in healthy subjects of Japanese, Korean, and Chinese heritage compared with Caucasian subjects. Similar differences were observed for subjects with asthma (b) (4) Figure 1). (b) (4) there is no evidence that this higher exposure to fluticasone furoate results in clinically relevant effects on urinary cortisol excretion or on efficacy in these racial groups.

Hepatic Impairment: Following repeat dosing of fluticasone furoate/vilanterol 200 mcg/25 mcg (100 mcg/12.5 mcg in the severe impairment group) for 7 days, fluticasone furoate systemic exposure (AUC) increased 34%, 83%, and 75% in subjects with mild, moderate, and severe hepatic impairment, respectively, compared with healthy

subjects (see Figure 1).

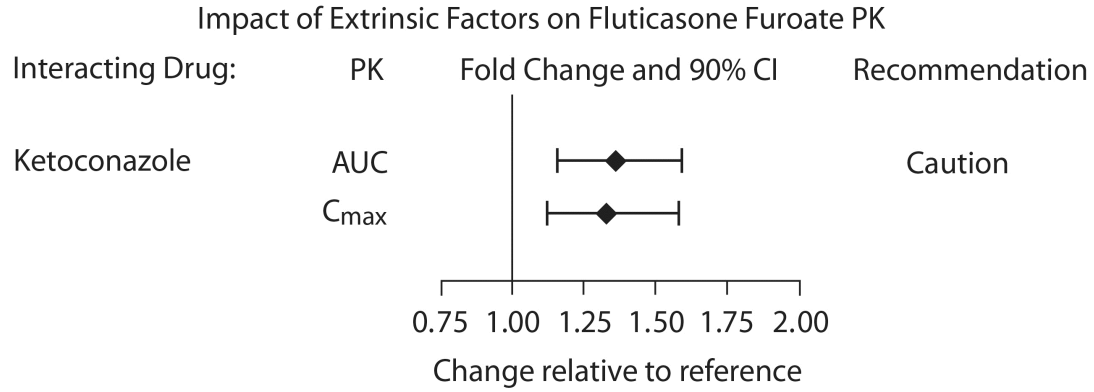
In subjects with moderate hepatic impairment receiving fluticasone furoate/vilanterol 200 mcg/25 mcg, mean serum cortisol (0 to 24 hours) was reduced by 34% ([(b)(4)]% CI: 11%, 51%) compared with healthy subjects. In subjects with severe hepatic impairment receiving fluticasone furoate/vilanterol 100 mcg/12.5 mcg, mean serum cortisol (0 to 24 hours) was increased by 14% ([(b)(4)]% CI: -16%, 55%) compared with healthy subjects. Patients with moderate to severe hepatic disease should be closely monitored.

Renal Impairment: Fluticasone furoate systemic exposure was not increased in subjects with severe renal impairment compared with healthy subjects (see Figure 1). There was no evidence of greater corticosteroid class-related systemic effects (assessed by serum cortisol) in subjects with severe renal impairment compared with healthy subjects.

Drug Interactions: The potential for fluticasone furoate to inhibit or induce metabolic enzymes and transporter systems is negligible at low inhalation doses.

Inhibitors of Cytochrome P450 3A4: The exposure (AUC) of fluticasone furoate was 36% higher after single and repeated doses when coadministered with ketoconazole 400 mg compared with placebo (see Figure 2). The increase in fluticasone furoate exposure was associated with a 27% reduction in weighted mean serum cortisol (0 to 24 hours).

Figure 2. Impact of Coadministered Ketoconazole[a] on the Pharmacokinetics (PK) of Fluticasone Furoate



[a] Compared with placebo group.

4. Appendix

4.1 Appendix –PM Review

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

NDA Number	205625
Brand Name	ARNUITY ELLIPTA
Drug Components	Fluticasone furoate (FF)
Proposed dosing	FF (100 mcg, 200 mcg) once daily
Pharmacometrics Reviewer	Jianmeng Chen, M.D., Ph.D.
Pharmacometrics Team Leader	Liang Zhao, Ph.D.
Sponsor	GlaxoSmithKline

The sponsor submitted four pop PK study reports in this NDA. Three of the reports (2011n130480 and 2011n130718 on population PK analysis for FF in FF/VI combination product; 2011n130478 on PK/PD analysis of the relationship between FF systemic exposure and HPA axis suppression) have been submitted to support NDA204275. The same dose ranging studies 109687, 109685, and 109684 had been submitted to support the dose selection of FF for NDA 204275. These studies and reports were reviewed under NDA 204275 (FF/VI) by Dr. Satjit Brar (DARRTS date 03/18/2013). The previous review and conclusion regarding dose selection and HPA axis PK/PD analysis is applicable to the current submission NDA205625 (FF), and the pertinent information regarding dose selection and HPA axis suppression from previous review were therefore adopted with minor changes. A new popPK report 2013n162904 was submitted for the current NDA for asthmatic patients. Upon request of FDA, the fifth report 2014N199523 was submitted for an updated analysis of FF pop PK by including data from study FFA115440. This reviewer will focus on the review of report 2013n162904 and 2014N99523.

SUMMARY OF FINDINGS

Key Review Questions

The purpose of this review is to address the following key questions.

Has the dosing of FF been adequately explored?

ICS is a center piece of asthma medications. Traditionally, ICS is approved of several doses for the management of asthma. Based on results of Phase 2 studies, three doses (50, 100, and 200 mcg) were carried forward for confirmation in the Phase 3 program.

Three dose ranging studies were conducted in asthma patients exploring daily doses of FF from 25 mcg to 800 mcg (Figure 12). A dose response was observed for FF doses ranging from FF 25 mcg to 200 mcg, with no significant additional benefit for FF doses above 200 mcg. The results of these three studies in asthma formed the basis for the selection of FF 50, 100, and 200 mcg in confirmatory trials.

Dosing frequency with FF was explored in patients with asthma. A randomized, double-blind, placebo-controlled, cross-over trial in 190 adults and adolescents with asthma to compare FF 200 mcg QD, FF 100 mcg BID, FP (fluticasone propionate) 200 mcg QD, and FP 100 mcg BID. Trough FEV1 responses of FF 200 mcg QD and FF 100 mcg BID appeared comparable. In contrast, FP 100 mcg BID dosing resulted in a numerically higher trough FEV1 than FP 200 mcg QD (Table 24). These results supported the selection of the QD regimen for further evaluation.

Figure 12. Adjusted Treatment Differences From Placebo in Trough FEV1 (L) (LOCF) at Week 8 in Asthma for FF doses ranging from 25-800 mcg QD and comparison to fluticasone propionate (FP) given BID.

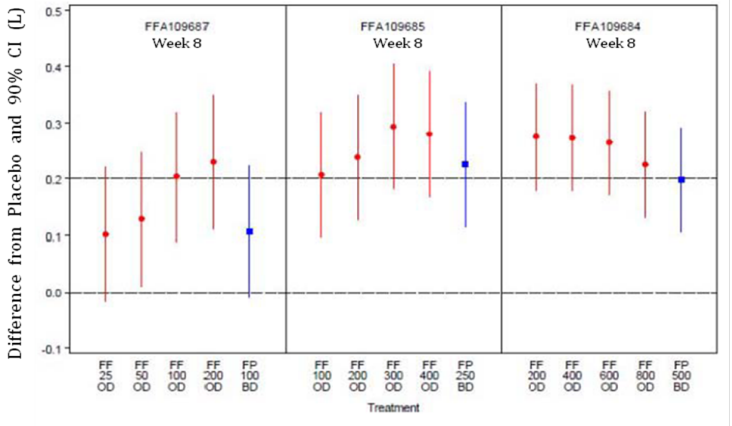


Table 24. Mean change from baseline in trough FEV1 for FF (QD vs. BID)

Treatment	N	LS mean (L)	LS mean change from period baseline	Difference from placebo (95% CI)	P
FF 200 QPM	140	2.714	0.221	0.108 (0.064, 0.153)	<0.001
FF 100 BID	142	2.703	0.210	0.098 (0.054, 0.142)	<0.001
FP 200 QD	42	2.693	0.199	0.087 (0.014, 0.161)	0.020
FP 100 BID	43	2.737	0.244	0.132 (0.059, 0.205)	<0.001
Placebo	187	2.605	0.112	-	-

In conclusion, dose-ranging data for the FF component in asthma supported efficacy for the range of doses (50, 100, and 200 mcg) carried forward for confirmation in the Phase 3 program.

Are there any covariates, such as configuration of 1s vs 2s, that influence the systemic exposure of FF?

With regard to FF, race and disease (asthma vs healthy) were found to be significant on clearance (CL/F). Based on the final model, the population mean estimate for CL/F was 523 L/h for a white Caucasian subject with asthma. Estimates of FF AUC(0-24) for healthy subjects were on average 33% higher than for astmatic subjects. Estimates of FF AUC(0-24) for East Asian, Japanese and South Asian subjects were on average 41% to 43% higher than for white Caucasian subjects. Although there is evidence for higher systemic exposure in these ethnic groups, the magnitude of increase in exposure is not considered to lead to clinically significant effects on the HPA-axis (cortisol suppression). **Therefore, no dosing adjustments are recommended for racial factors.**

Configuration (1s vs 2s vs FF/VI) is not a significant covariate in the FF popPK model. The popPK analysis suggested that there was no evidence for a difference in FF systemic exposure following the single-strip configuration compared to following the two-strip configuration as FF or FF/VI.

However, the popPK analysis cannot reconcile the PK difference observed in different configurations in the bridging study (FFA115440), which showed higher exposure for FF administered with the single-strip DPI than FF or FF/VI administered with the two-strip DPI. The different results of pop PK and dedicated PK study can be attributable to the following reasons:

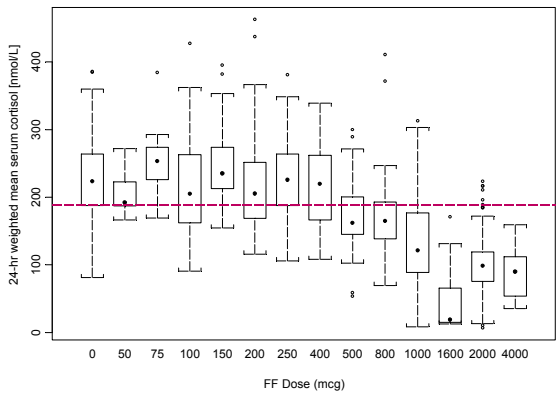
1. Different doses. The dedicated bridging study FFA115440 used a higher dose of FF(400 mcg) to accommodate the analytical sensitivity. In pop PK analysis, study FFA114496 and other studies used FF 100-200 mcg, and had a large portion of BLQ data, which may limit the capability for popPK model to detect the difference in terminal elimination phase between two configurations.
2. Cross study variation. Except for the dedicated BE study FFA115440, other studies included for popPK analysis did not contain PK information for both single strip and double strip FF configurations. The comparison of different configurations can be complicated by imbalance in factors that can impact PK exposure across studies.
3. Difference in sampling schedule and imbalanced distribution of BLQ values across studies. Study 114496 is the only study using single strip FF in asthmatic patients in the pop PK analysis. The sparse sampling timepoints of study 114496 mainly consists of predose concentration, which is largely BLQ, and one time point around Tmax. This sampling schedule is practical in the conduction of clinical studies, but may not be able to detect potential difference in elimination phase after Tmax.

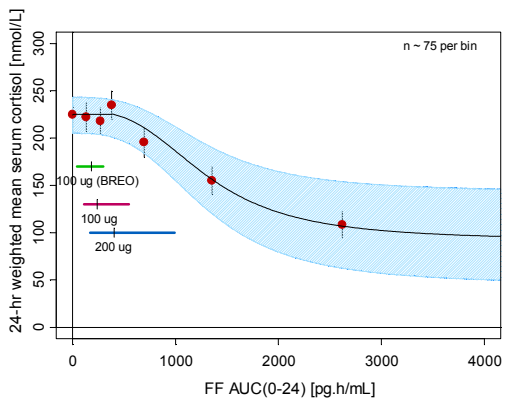
Given the above reasons, only results from the dedicated BE study FFA115440 is considered to compare PK exposures between the two configurations for bridging of safety data.

Is there an influence of FF systemic exposure on HPA axis (serum cortisol) suppression?

Although HPA suppression was observed with FF treatment, serum cortisol reduction was not apparent at the proposed dosing. A pharmacokinetic/pharmacodynamic meta-analyses of 9 studies was conducted to characterize the relationship between FF AUC(0-24) and 24 hour weighted mean serum cortisol. The 24-hour serum cortisol weighted mean was derived by dividing the area under the curve (calculated AUC) by the sample collection time interval. The average estimate of FF AUC(0-24) required to reduce cortisol by 50% (AUC50) was 1,345 pg•hr/mL, which is several fold higher than average FF AUC(0-24) values observed at the therapeutic dose of FF 100 mcg (181 pg•hr/mL) and 200 mcg (395 pg•hr/mL)in subjects with asthma (see Figure 13 below).

Figure 13. Effect of FF on serum cortisol (nmol/L) across doses ranging from placebo to 4000 mcg QD. Left plot: Boxplot of dose-response where the dashed line represents the lower 25% of the placebo response. Right plot: Concentration-response relationship. Red circles represent the median exposure and corresponding mean response for a bin of ~ 75 subjects (+/- 95% CI). A threshold Emax model is depicted along with the 95% Prediction Interval. The range of serum FF exposures for the 100mcg (BREO, FF/VI), and the proposed 100 mcg and 200 mcg FF dose is demarcated with a solid line.





Recommendations

The Pharmacometrics reviewer finds the application acceptable.

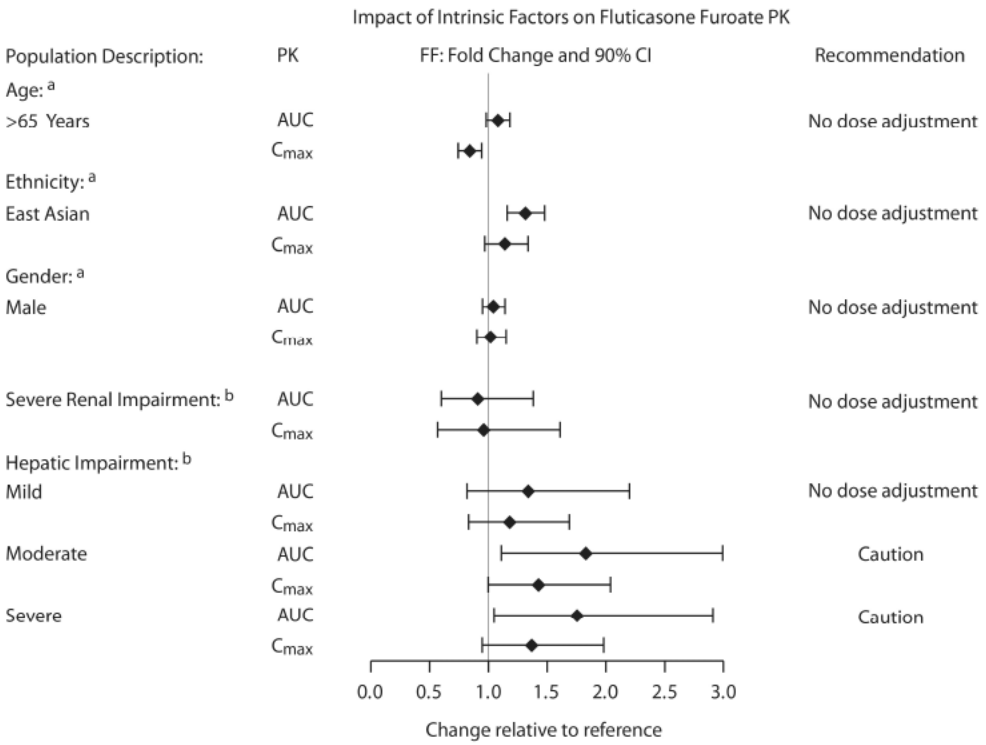
Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

12.3 Pharmacokinetics

Special Populations: The effect of renal and hepatic impairment and other intrinsic factors on the pharmacokinetics of fluticasone furoate is shown in Figure 1.

Figure 1. Impact of Intrinsic Factors on the Pharmacokinetics (PK) of Fluticasone Furoate (FF)



[a] Age, gender, and ethnicity comparison for TRADENAME ELLIPTA in subjects with asthma.
[b] Renal groups (fluticasone furoate/vilanterol 200 mcg/25 mcg) and hepatic groups (fluticasone furoate/vilanterol 200 mcg/25 mcg or fluticasone furoate/vilanterol 100 mcg/12.5 mcg) compared with healthy control group.

Race: (b) (4) there is no evidence that this higher exposure to fluticasone furoate results in clinically relevant effects on urinary cortisol excretion or on efficacy in these racial groups.

Hepatic Impairment: Following repeat dosing of fluticasone furoate/vilanterol 200 mcg/25 mcg (100 mcg/12.5 mcg in the severe impairment group) for 7 days, fluticasone furoate systemic exposure (AUC) increased 34%, 83%, and 75% in subjects with mild, moderate, and severe hepatic impairment, respectively, compared with healthy subjects (see Figure 1).

In subjects with moderate hepatic impairment receiving fluticasone furoate/vilanterol 200 mcg/25 mcg, mean serum cortisol (0 to 24 hours) was reduced by 34% ((b) (4)% CI: 11%, 51%) compared with healthy subjects. In subjects with severe hepatic impairment receiving fluticasone furoate/vilaterol 100 mcg/12.5 mcg, mean serum cortisol (0 to 24 hours) was increased by 14% ((b) (4)% CI: -16%, 55%) compared with healthy subjects. Patients with moderate to severe hepatic disease should be closely monitored.

Renal Impairment: Fluticasone furoate systemic exposure was not increased in subjects with severe renal impairment compared with healthy subjects (see Figure 1). There was no evidence of greater corticosteroid class-related systemic effects (assessed by serum cortisol) in subjects with severe renal impairment compared with healthy subjects.

PERTINENT REGULATORY BACKGROUND

GlaxoSmithKline (GSK) submitted a new drug application for use of ARNUITY ELLIPTA (fluticasone furoate 100 mcg and 200 mcg inhalation powder) for the maintenance treatment of asthma in patients aged 12 years and older. ARNUITY ELLIPTA is a new inhaled corticosteroid (ICS) for asthma, while FF has been approved as a component of FF/VI (100/25 mcg, BREO ELLIPTA) for the maintenance treatment of COPD. Fluticasone furoate is also marketed as an intranasal formulation for the treatment of allergic rhinitis.

The proposed dose is one inhalation (fluticasone furoate 100 mcg and 200 mcg) once daily.

GSK studied several different doses for FF as single entity and in combination with VI or UMEC in its asthma development program. The program was conducted concurrently with the development of the individual components in both COPD and asthma, so many of the regulatory interactions encompassed one or more components and the combination as well as both disease indications. An IND application(070297) was submitted to the US FDA for FF on June 23, 2005. A number of interactions have occurred between the Division of Pulmonary and Allergy Drug Products and the Sponsor regarding clinical, non-clinical and CMC aspects of the development of FF.

For the asthma indication, the End-of-Phase 2 meeting was held on June 17, 2009 and Mar 16, 2011 to discuss the design of the Phase 3 clinical trials, the adequacy of the proposed clinical pharmacology and non-clinical data packages, as well as the clinical safety exposure planned to be available at time of NDA submission. The FDA agreed with the Sponsor's proposal to evaluate doses of 50, 100, and 200 mcg FF QD.

The clinical program for FF comprised a total of 31 clinical pharmacology studies, 6 Phase 2 studies on dose and dose regimen, and 8 Phase 3 studies, including 2 studies with FF 50mcg that did not replicate efficacy (FFA115283 and FFA115285) and 1 study in Japanese subjects (HZA113989). Table 25 depicts the attributes of the 5 primary studies that support the efficacy and safety of FF 100mcg and 200mcg. The Phase 2 studies that were conducted to support dose selection and dosing frequency for FF are outlined in Table 26.

Table 25. Efficacy and Safety Studies for FF in Asthma

Trial	Design	Population	Weeks	Treatment (mcg)	N	Primary Endpoint
FFA 112059	R, DB, DD, PC, PG	Asthma Low-mid ICS	24	FF 100 QD FP 250 BID Placebo Single-strip	114 114 115	Trough FEV1
HZA 106827	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
FFA 114496	R, DB, PG	Asthma Mid-high ICS	24	FF 100 QD FF 200 QD Single-strip	119 119	Trough FEV1
HZA 106829	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
HZA 106837	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

Table 26. Phase 2 Studies to Support Doses and Dose Regimen for FF

Study	Study Objectives	Treatment Duration	Treatments (mcg) and Regimen[1]	Inhaler
AM vs. PM Dosing				
FFA20001 (Phase IIa)	Evaluate effect of time of dosing; compare efficacy and safety	28 days	FF 100 AM FF 100 FF 250 Placebo	DISKHALER (all treatments)
FFA106783 (Phase IIa)	Evaluate relative efficacy and safety of OD and BD dosing and of AM and PM dosing	8 weeks	FF 200 AM FF 200 FF 400 AM FF 400 FF 200 BD Placebo	DISKUS (all treatments)
OD vs. BD Dosing				
FFA112202 (Phase IIb)	Assess for non-inferiority of once-daily FF compared with twice-daily FF	3 treatment periods of 28 days each	FF 200 FF 100 BD FP 200 FP 100 BD Placebo	Two-strip DPI (FF) DISKUS (FP)
Dose Ranging				
FFA109684 (Phase IIb)	Evaluate dose response, efficacy, and safety	8 weeks	FF 200 FF 400 FF 600 FF 800 FP 500 BD Placebo	Two-strip DPI (FF) DISKUS (FP)
FFA109685 (Phase IIb)	Evaluate dose response, efficacy, and safety	8 weeks	FF 100 FF 200 FF 300 FF 400 FP 250 BD Placebo	Two-strip DPI (FF) DISKUS (FP)
FFA109687 (Phase IIb)	Evaluate dose response, efficacy, and safety	8 weeks	FF 25 FF 50 FF 100 FF 200 FP 100 BD Placebo	Two-strip DPI (FF) DISKUS (FP)

1. OD in the PM unless otherwise stated

AM = morning; PM = evening; BD = twice daily; DPI = dry powder inhaler; OD = once daily; DB = double-blind; PG = parallel group

(Source: Summary clin efficacy asthma, Table 2, page 10)

RESULTS OF SPONSOR'S ANALYSIS

Dose selection

In order to support the dose regimens for Phase 3 investigation, a total of six Phase 2 trials were conducted in asthma patients (Table 26). Three dosing regimens, FF 50, 100 and 200 mcg, were tested in Phase 3 studies in asthmatic patients.

Dose for FF

Results for different FF doses on trough FEV1 from the three Phase 2 dose ranging studies (FFA109687, FFA109685, FFA109684) in subjects with varying severity of asthma are summarized in Figure 4 , which show substantial efficacy with FF 100 and near maximal efficacy with FF 300. In study FFA109685 and FFA109684, linear PK was observed from FF doses 200 mcg to 800 mcg. The systemic exposure is not correlated with clinical response (FEV1). Sponsor selected three doses of FF (50, 100 and 200 mcg) for further evaluation in the asthma Phase 3 program.

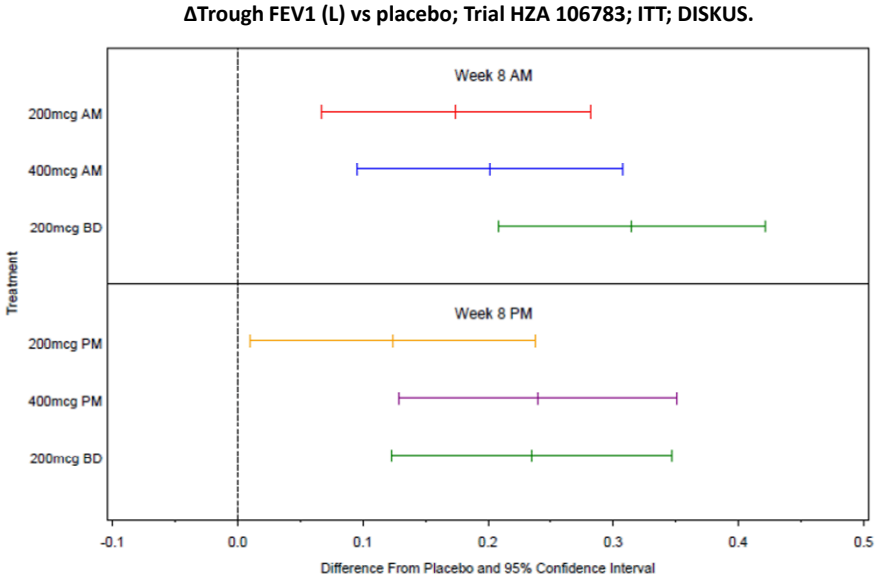
Dosing Frequency (QD vs. BID)

Study FF112202 was conducted in subjects with asthma supported the comparability of once and twice daily dosing for FF (Table 7).

Morning vs. Evening Dosing

Study FFA20001 (100mcg, DISKHALER) and FFA106783 (200mcg, 400mcg, DISKUS) in subjects with asthma demonstrated that FF, whether dosed in the morning or evening, resulted in a similar efficacy compared with placebo (Figure 14).

Figure 14. Change of Trough FEV1 compared to placebo with AM, PM, or BID Dosing (studyHZA106783)



Summary

In conclusion, the dose-ranging data for the FF component in asthma supported efficacy for the range of doses (50, 100, and 200 mcg) carried forward for confirmation in the Phase 3 program.

Reviewer's comments: The Pharmacometrics Reviewer concurs with the dosing regimens selected for the Phase 3 trials. Dose regimen selection was discussed during EOP2 meetings with the sponsor and was agreed upon.

Overall Efficacy Results

-Lung function trials (112059, 106827, 114496, and 106829)

Four trials were conducted in support of lung function claims (**112059, 106827, 114496, and 106829, Table 23**). The primary endpoint is trough FEV1.

The efficacy of FF 100 was replicated in Studies FFA112059 (single-strip DPI) and HZA106827 (two-strip DPI), where the treatment differences between FF 100 and Placebo for change from baseline in trough FEV1 were 146 mL (p=0.009) and 136 mL (p=0.002), respectively (Table 25). Additionally, in Study FFA112059, the magnitude of effect of FP 250 BID compared with Placebo for change from baseline in trough FEV1 (difference 145 mL; p=0.011) was similar to FF 100 compared with Placebo.

The efficacy of FF 200 was assessed in two studies. In Study FFA114496, the LS mean change from baseline in trough FEV1 at Week 24 was greater in the FF 200 group (284 mL) than in the FF 100 group (208 mL); the treatment difference was 77 mL
. In Study HZA106829, FF 200 produced a slightly greater LS mean change from baseline in trough FEV1 (201 mL) compared with FP 500 BID (183 mL); the treatment effect of FF 200 was statistically non-inferior to FP 500 BID using a predefined non-inferiority margin of -125 mL (treatment difference of 18 mL, 95% CI: -66, 102).

-Exacerbation trials (106837)

HZA106837 evaluated whether FF/VI 100/25 significantly decreased the risk of severe asthma exacerbations as measured by time to first severe asthma exacerbation when compared with FF 100. Both treatments were administered for up to 76 weeks. The primary endpoint was time to first severe asthma exacerbation. As there is no placebo arm in this study, no conclusion can be made on the efficacy of FF. The sponsor did not pursue the indication of exacerbation in this submission.

Overall Safety Results

The safety database for FF includes safety information for FF as single component in one strip or two strip configuration, as well as in combination with VI in asthmatic patients. The nature of the adverse events identified for FF appears consistent with the safety profile of similar ICS products, with no outstanding AEs particularly observed for FF.

Reviewer's comments: The Pharmacometrics Reviewer defers efficacy and safety evaluation of FF to the reviews of DPARP Medical Officer (Tracy Kruzick, MD) and Biometrics Reviewer (Gregory Levin, Ph.D.)

Population PK Meta-Analysis for FF in Subjects with Asthma

Report 2013N162904_02 &2014N199523_00

Methods

In report 2013N162904_02, the population PK of FF was assessed via a meta-analysis of five Phase 3 (FFA114496, HZA106827, HZA106829, HZA106839 and HZA106851) multicenter, randomized, double-blind, placebo-controlled studies in subjects with asthma. A further Phase 1 randomized, placebo-controlled investigation in healthy subjects (HZA102936), with intense PK sampling, was included to support population PK modeling. Upon request from FDA, the sponsor included another Phase 1 study with healthy subjects (115440) in the updated report 2014N199523_00.

FF concentration-time data for the following treatments were included: 100 mcg FF, 200 mcg FF, 100/25 mcg FF/VI, 200/25 mcg and 800/100 mcg. Configuration (FF single-strip DPI, FF two-strip DPI or FF/VI) was included as a variable.

Population PK models were developed to describe the FF systemic exposure in subjects with asthma. Healthy subjects and subjects with asthma contributed to the meta-analysis for FF (n=1556; 12554 observations for report 2014N199523_00). Five of the seven studies included in the meta-analysis were conducted in subjects with asthma, and the vast majority of subjects in the dataset were subjects with asthma (93%).The attributes of each trial are described in Table 27 below.

Table 27. Study Designs used for the Population PK of FF

Report 2013n162904 (Run 25)

Protocol No.	Design (Phase)	Disease	No. subjects ITT (M/F)	Formulation(s). Device	Doses (mcg) Frequency	Treatment Duration. PK sampling Occasion	PK sampling post-dose
FFA114496	Multicentre, randomised, double-blind, parallel-group (Phase IIIa)	Asthma	219 (72/147)	FF (single-strip) NDPI	100, 200 mcg QD	24 weeks Week 4 and 18	PK: pre-dose & 45-75 minutes
HZA106827	Multicentre, randomised, double-blind, placebo-controlled, parallel-group (Phase IIIa)	Asthma	406 (164/242)	FF/VI FF Placebo NDPI	100/25 mcg QD 100 mcg QD Placebo QD Once daily (pm)	12 weeks Weeks 8 and 12	PK : pre-dose & post-dose 5-15 minutes, 1-1.5 hours
HZA106829	Multicentre, randomised, double-blind, double-dummy, active-controlled, parallel-group (Phase IIIa)	Asthma	391 (162/229)	FF/VI NDPI FF NDPI FP DISKUS	200/25 mcg QD (pm) 200 mcg QD (pm) 500 mcg BID	24 weeks Weeks 12 and 24	PK : pre-dose & post-dose 5-15 minutes, 1-1.5 hours
HZA106839	Multicentre, randomised, double-blind, double-dummy, active-controlled, parallel-group (Phase IIIa)	Asthma	403 (149/254)	FF/VI NDPI FP DISKUS	100/25, 200/25 mcg OD (pm) 500 mcg BID	52 weeks Weeks 2, 12 and 52	PK : Pre-dose and post-dose 5-30 minutes on Week 2, pre-dose and post-dose 5-30 minutes on Week 12 and post-dose 5-30 minutes and 45 minutes-1.5 hours on Week 52
HZA106851	Multicentre, randomised, placebo-controlled, double-dummy and active-controlled, parallel-group (Phase IIIa)	Asthma	185 (98/87)	FF/VI Placebo NDPI Prednisolone oral	100/25, 200/25 mcg QD Placebo QD Once daily (pm)	6 weeks Day 42	PK[1] : pre-dose & post-dose 5, 10, & 30 minutes, 1, 2, 4, 8 12 & 24 hours
HZA102936	Randomised, placebo-controlled, 4-way cross-over (Phase I)	HVT	85 (49/36)	FF/VI Placebo NDPI Moxifloxacin oral	200/25; 800/100 mcg Placebo Once daily (am)	1 week Day 7	PK[1] : pre-dose & post-dose 5, 15, & 30 minutes, 1, 2, 4, 9 12 16, 20 & 24 hours

Report 2014N199523_00 (Run 24)

Protocol	Design	Disease	N	Formulation Device	Dose	Treatment duration, PK sampling occasion	PK sampling schedule
FFA115440	Randomised 6-way crossover	HVT	30	FF (1S) FF (2S) FF/VI	400 400 400/50	Single dose	pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 and 36 hour

The Sponsor reported high proportion of records reporting FF concentration below the lower limit of quantification (LLQ; 10 pg/mL), modeling the concentration-time data from the Phase 2/3 data alone to appropriately characterize the PK profile of FF proved to be difficult. Addition of more extensively sampled concentration-time data from a FF/VI study in healthy subjects (HZA102936) at a higher dose (800/100) was required to achieve an appropriate structural model to describe the data. Upon request from FDA, the sponsor included another Phase 1 study with healthy subjects (115440) using different configurations of device in the updated report 2014N199523_00. As a consequence of the

large extent of non-quantifiable data in each dataset it was necessary to use methodology that maximized the likelihood for all the data, treating those data below the LLQ as censored (referred to as M3; Ahn, 2008).

Population PK modeling was performed via NONMEM v7.1.2 (ICON Development Solutions) running in a UNIX server based environment for NONMEM analysis. The method selected for minimisation was Stochastic Approximation Expectation Maximization (SAEM) with interaction. Supporting application interfaces for data handling, exploratory diagnostics and simulation included Xpose V4 [Jonsson, 1999] and R (The R Foundation for Statistical Computing Version 2.10.1 or above).

The covariates considered for evaluation of the effect on FF pharmacokinetics included population (healthy subjects or subjects with asthma), age, weight, height, sex, ethnicity, race, BMI, tobacco use (number of pack years), smoking status at screening (former or current), PFEV (FEV1 % predicted) and study. Due to limited numbers of subjects in some of the race categories subjects were categorized as RACE1 as follows: RACE1=1 - White Caucasian; RACE1=2 – East Asian, Japanese and South Asian; RACE1=3 – African American; RACE1=4 – Asian Central, White Arabic, American Indian/Native Alaskan and Other. Concomitant cytochrome P450 3A4 inhibitor medication was to be evaluated but since only 6 subjects were on strong inhibitors this was not assessed as a covariate.

Model evaluation to assess the adequacy of the final models, including the effects of statistically significant covariates was performed using a Visual Predictive Check (VPC) procedure. This procedure was conducted as follows: 1000 replicates of the original dataset were simulated, based on the parameter estimates of the final model, and a 95% prediction interval computed based on the simulated datasets. The observed plasma concentration-time data was plotted on the prediction interval to visually assess the concordance between the simulated and observed data.

Individual AUC(0-24) was derived as the ratio of nominal dose divided by individual post-hoc estimate of CL/F from the final population PK model.

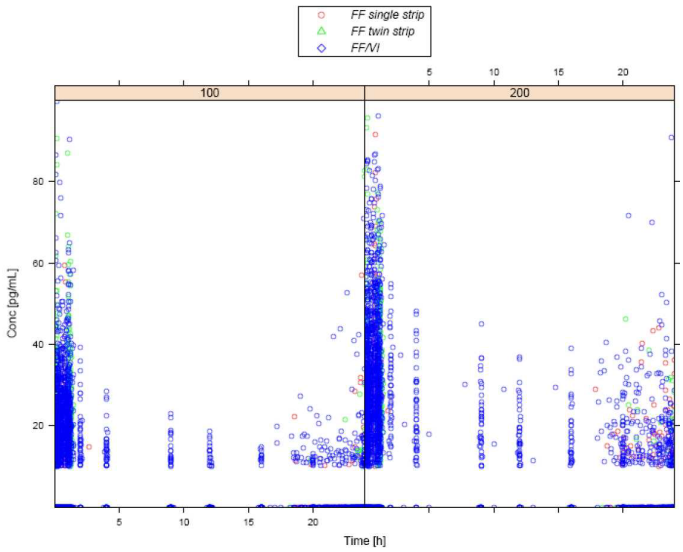
Results

A total of 1526 subjects were included in the FF PK dataset for report 2013N162904_02, and additional 30 subjects (total of 1556 subjects) were included in the dataset for report 2014N199523.

2013N162904_02

The FF population PK analysis dataset comprised of 1526 subjects (healthy subjects or subjects with asthma). The vast majority were subjects with asthma (95%). The 1526 subjects provided a total of 10127 sample records of which 31.2% were reported as NQ (<LLQ 10 pg/mL). Concentration vs. time profiles for FF can be viewed in the Figure 15 below.

Figure 15. FF Concentration vs. Time Profile

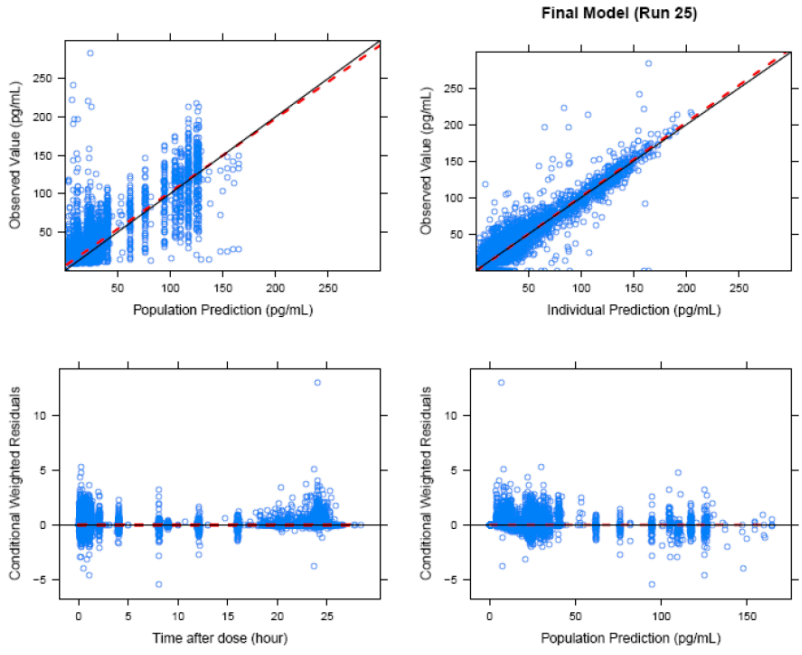


(Source: Figure MA1, page 47, Report 2013n162904)

A two compartment linear model, with first order absorption and first order elimination, was used to describe the FF concentration-time data.

The final population PK model for FF incorporated the effect of race on CL/F. Goodness of fit plot for the final model is presented in Figure 16 and the VPC for PK and BLQ prediction in Figure 18. The population parameters from the final model are shown below in Table 28.

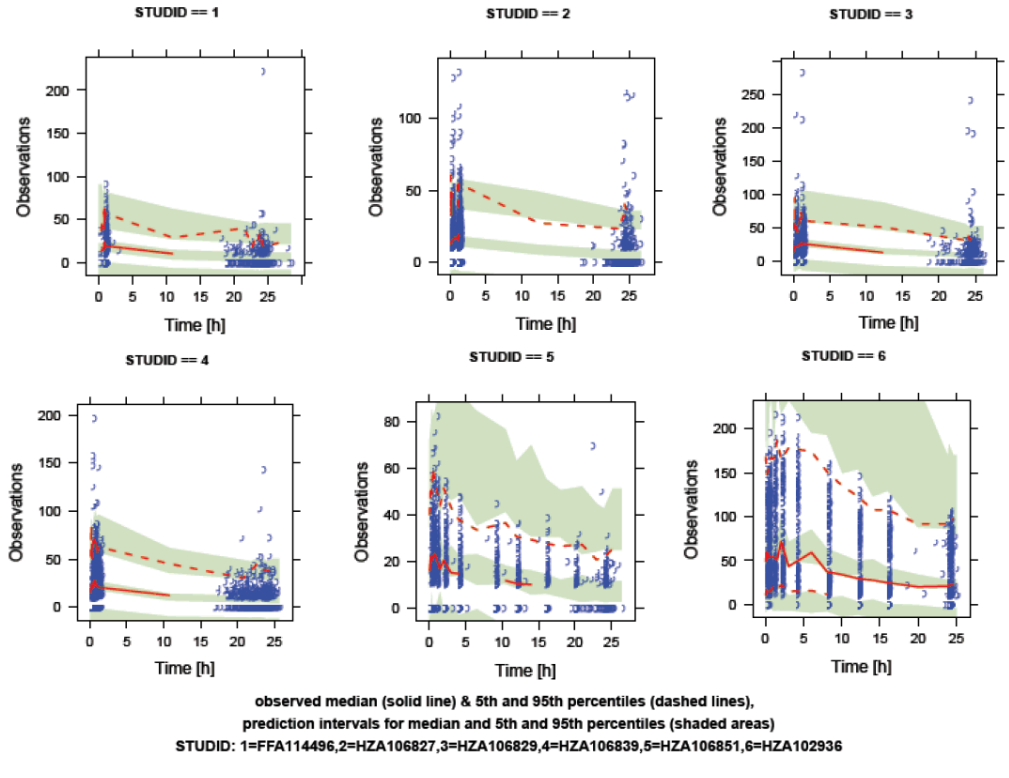
Figure 16. Goodness of Fit plots for the Final FF Population PK Model



(Source: Figure MA2, page 48, Report 2013n162904)

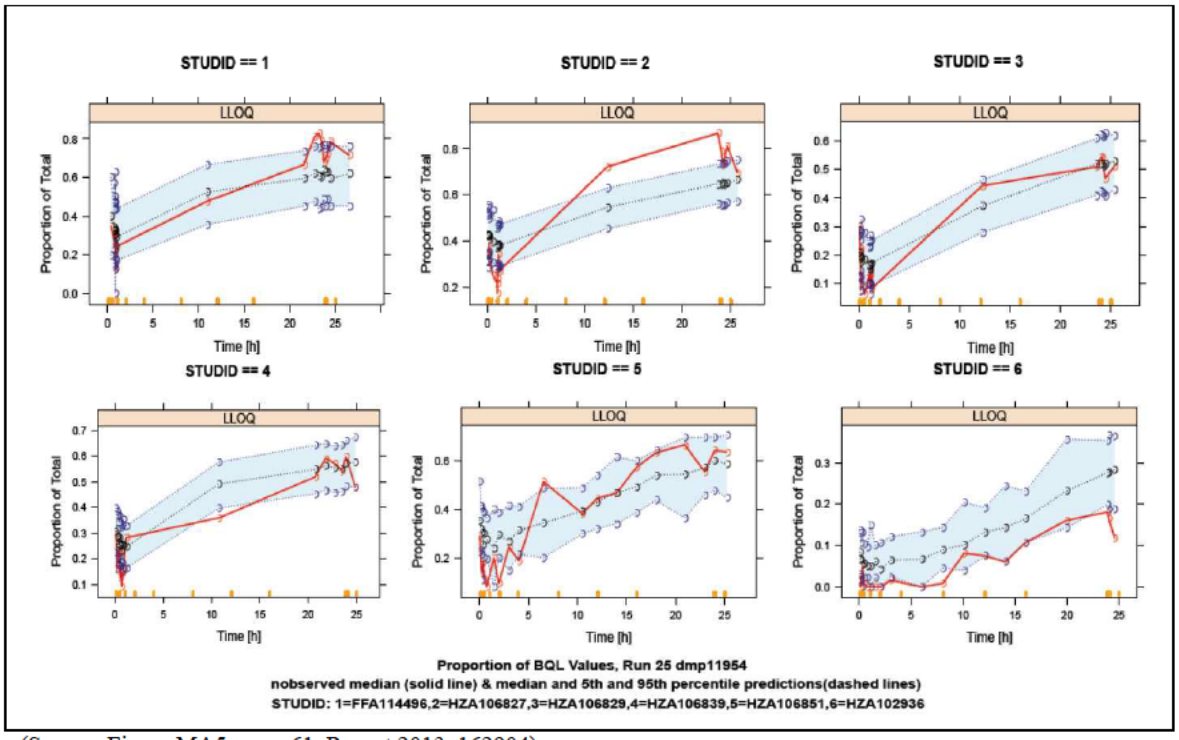
The plot for the VPC (Figure 17) showed that the majority of the data is captured in the prediction interval encompassing 90% of the population as indicated by the 5th and 95th percentile boundary, indicating that the model is reasonable for this asthma dataset. In addition, the observed proportion of the BLQ data was plotted with the model prediction interval to visually assess the concordance between the simulated and observed BLQ data (Figure 18).

Figure 17. VPC for the Final FF Population PK Model (by Study).



(Source: Figure MA5, page 60, Report 2013n162904)

Figure 18. VPC for the model prediction of BQL data (by Study). The black dashed lines represent the model predicted median and corresponding 5th and 95th percentiles (blue dashed lines). Observed median is in solid red line. The prediction intervals of the median, 5th and 95 percentiles are depicted in blue shading.



(Source: Figure MA5, page 61, Report 2013n162904)

Reviewer comment: As shown in Figure 18, t*he concordance between the simulated and observed BLQ data was evaluated by the VPC. From the VPC, the overall predictions for the data BLQ were adequately characterized by the model. However, for study HZA106827 (N=406, , with FF(2S) and FF/VI), there is a trend toward under prediction of proportion of BLQ data at later time points. In other words, concentration at later time points was over predicted in study 106827. This finding is consistent with the assessment by goodness of fit plot.*

Based on popPK analysis (report 2013n162904), estimated FF AUC(0-24) values for FFA114496 following FF monotherapy (single-strip DPI) were similar to or lower than those estimated for FF administered as double-strip or FF/VI in other studies (Table 28). This is opposite of the findings in the dedicated BE study FFA115440, where the FF exposure in single strip configuration is 19-60% higher compared to two strip configuration and FF/VI. In an effort to reconcile the difference, FDA sent an IR during review, requesting the PK data in study 115440 be incorporated in the pop PK analysis. The sponsor response to the IR, and submitted an updated pop PK report 2014n199523_00.

2014n199523_00

With the dataset including study FFA115440, the parameter estimates are similar to that of report 2013n162904 (Table 27).

Table 28. Parameter estimates for the Final FF Population PK Model

Report 2013n162904 (Run 25)

Parameter	Ln Estimate [95% CI]	Estimate [95% CI]
CL/F (RACE1=1 and 3)	6.26 [6.20, 6.32]	523 [493, 556]
RACE1=2 on CL/F	-0.355 [-0.479, -0.231]	0.701 [0.619, 0.794]
POP on CL/F (Healthy)	-0.231 [-0.379, -0.083]	0.794 [0.685, 0.920]
TMT2=FF one-strip on CL/F	0.138 [-0.002, 0.278]	1.148 [0.998, 1.320]
TMT2=FF two-strip on CL/F	-0.0218 [-0.127, 0.084]	0.978 [0.881, 1.088]
V2/F [L]	0.225 FIXED	1.25 FIXED
Q/F [L/h]	5.67 FIXED	290 FIXED
V3 /F [L]	6.14 [5.91, 6.37]	464 [369, 584]
TMT2= FF one-strip on V3/F	0.533 [-0.286, 1.35]	1.704 [0.751, 3.857]
TMT2= FF two-strip on V3/F	0.632 [0.066, 1.20]	1.881 [1.068, 3.320]
KA [h^{-1}]	-2.93 [-2.99, -2.87]	0.0534 [0.0503, 0.0567]

Report 2014n199523_00 (Run 24, including study 115440)

Parameter	Ln Estimate [95% CI]	Estimate [95% CI]
CL/F (RACE1=1 and 3 and TMT2=FF/VI)	6.30 [6.24, 6.36]	545 [513, 578]
RACE1=2 on CL/F	-0.338 [-0.461, -0.215]	0.713 [0.631, 0.807]
POP on CL/F (Healthy)	-0.286 [-0.414, -0.158]	0.751 [0.661, 0.854]
TMT2=FF one-strip on CL/F	0.151 [0.027, 0.275]	1.163 [1.027, 1.310]
TMT2=FF two-strip on CL/F	0.0248 [-0.074, 0.123]	1.025 [0.929, 1.131]
V2/F [L]	0.225 FIXED	1.25 FIXED
Q/F [L/h]	5.67 FIXED	290 FIXED
V3 /F [L]	6.20 [5.80, 6.60]	493 [330, 735]
KA [h^{-1}]	-2.78 [-2.84, -2.72]	0.0620 [0.0584, 0.0659]

CL/F=inhaled clearance; V2/F = volume of central compartment; Q/F= intercompartmental clearances; V3/F= volumes of peripheral compartment, KA=absorption rate, CI=Confidence Interval
RACE1=1 - White Caucasian; RACE1=2 – East Asian, Japanese and South East Asian; RACE1=3 – African American, Asian Central, White Arabic, American Indian/Native Alaskan and Other

Reviewer's comments: *This reviewer did sensitivity analysis by including TMT2, the configuration covariate, on V3/F with the dataset of report 2014n199523. Similar analysis was done with the dataset excluding study 102936 (the other healthy subject study with FF/VI). All parameter estimates were similar to the original report 2013n162904 and 2014n199523, and the configuration covariate estimation always suggested that the exposure was lower or similar in FF single strip configuration compared to the other two configurations (two strip, FF/VI).*

Table 29. Model Predicted Systemic Exposure (Geometric Mean [95% CI]) for FF (Cmax and AUC(0-24)) by Dose and Configuration Following Administration of FF (as FF/VI or FF) in Subjects with Asthma

A. Study FFA114496, HZA106827, HZA106829, HZA106839, HZA106851

B. Study 115440 (Model prediction and observed)

A. Report 2013n162904 (Run 25)

Treatment	Dose (mcg)	n	Geometric Mean [pg.h/mL]	95% CI [pg.h/mL]
FF single strip	100	116	180.7	117.4, 292.0
FF two strip	100	186	240.9	112.5, 546.4
FF/VI	100	434	235.0	108.8, 505.4
FF single strip	200	115	394.5	194.4, 917.8
FF two strip	200	161	405.4	169.7, 990.7
FF/VI	200	432	427.5	191.7, 930.3

(Source: Report 2013n162904, Table 9)

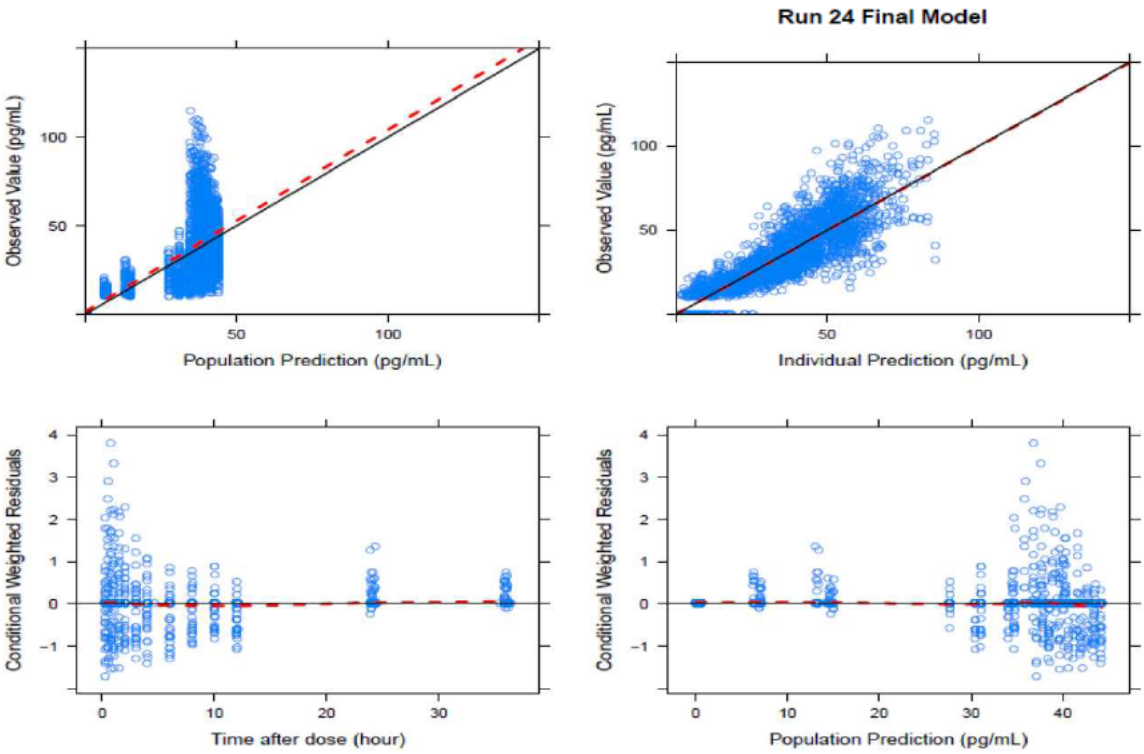
B. Report 2014n199523_00 (Run 24, including study 115440)

Treatment	Dose (mcg)	n	AUCinf (CI) [pg h/ml]		Cmax (CI) [pg/ml]	
			Predicted	Observed	Predicted	Observed
FF single strip	400	30	887.6 (360.0-2255.8)	1144.7 (983.8-1332.0)	45.7 (14.0-117.9)	67.8 (62.1-74.1)
FF double strip	400	30	971.2 (393.9-2468.0)	889.5 (740.3-1068.6)	42.7 (12.9-110.5)	60.1 (54.9-65.8)
FF/VI	400	30	988.5 (400.9-2512.1)	714.8 (568.4-898.9)	42.1 (12.6-109.1)	47.8 (43.2-52.9)

(Source: Report 2014n199523_00, Table S5, CSR 115440, Table 10.3)

Reviewer's comments: *With the updated pop PK report 2014N199523_00, the model did not adequately describe the PK profile in study 115440. The relative FF exposure with FF single strip, FF double strip, and FF/VI based on model prediction does not agree with observation (Table 29B). The goodness of fit plots suggest over prediction of concentrations at later time point (Figure 19, lower left panel), and significant under prediction of higher concentrations based on population prediction (Figure 19, upper left panel).*

Figure 19. Goodness of Fit plots for the Final FF Population PK Model with FFA115440 data



(Source: Report 2014n199523_00, Figure S2)

Sponsor's Conclusions for reports 2013n162904 and 2014n199523_00

Although not significant, configuration (FF single-strip DPI, FF two-strip DPI or FF/VI) was included as a potential covariate on apparent clearance (CL/F) and on peripheral volume of distribution (V3/F) in the population pharmacokinetic model building. There was no evidence for a difference in FF systemic exposure following the single-strip configuration, compared with data following the two-strip configuration as FF or FF/VI with model estimated FF AUC(0-24) values for FFA114496 following FF monotherapy (single-strip DPI) being similar to or lower than those estimated for studies HZA106827, HZA106829, HZA106839 and HZA106851 from the final pharmacokinetic model.

The pharmacokinetics (PK) of FF was well described by a two-compartment model with 1st order absorption and 1st order elimination. The only covariates found to be significant were race (East Asian, Japanese and South East Asian) and population (asthma or healthy subjects) on inhaled clearance (CL/F). Based on the final model, the population mean estimate for CL/F was 523 L/h for a white Caucasian subject with asthma. Estimates of FF AUC(0-24) for East Asian, Japanese and South East Asian subjects were on average 41% to 43% higher compared with White Caucasian subjects. Although there is evidence for higher systemic exposure in these ethnic groups values are still below those associated with unwanted systemic effects on the HPA-axis.

Reviewer's comments: *A rigorous analysis assessing the of the covariate effects on FF exposure was performed in the popPK analysis. Residual diagnostics based on the sponsor's analyses showed that the model fitted the data reasonably well. With regard to the covariates chosen, the reviewer's independent analysis of FF generated comparable results with similar parameter estimates. Therefore, the reviewer concludes the analysis presented by the sponsor is reasonable in describing the PK profile of FF in asthmatic patients.*

This reviewer disagrees with the sponsor's conclusion of PK similarity in FF administered with different configurations. With the updated pop PK report 2014N199523_00, the model did not adequately describe the PK profile in study 115440. The pop PK analysis cannot reconcile the PK difference observed in different configurations in the dedicated bridging study (FFA115440), which showed higher exposure with FF administered with the single-strip DPI compared to FF or FF/VI administered with the two-strip DPI. The different results of pop PK and dedicated PK study can be attributable to the following reasons:

1. Different doses. The dedicated bridging study FFA115440 used a higher dose of FF(400 mcg) to accommodate the analytical sensitivity. In pop PK analysis, study FFA114496 and other studies used FF 100-200 mcg, and had a large portion of BLQ data, which may limit the capability for popPK model to detect the difference in terminal elimination phase between two configurations.

2. Cross study variation. Except for the dedicated BE study FFA115440, other studies included for popPK analysis did not contain PK information for both single strip and double strip FF configurations. The comparison of different configurations can be complicated by imbalance in factors that can impact PK exposure across studies..

3. Difference in sampling schedule and imbalanced distribution of BLQ values across studies. Study 114496 is the only study using single strip FF in asthmatic patients in the pop PK analysis. The sparse sampling timepoints of study 114496 mainly consists of predose concentration, which is largely BLQ, and one time point around Tmax. This sampling schedule is practical in the conduction of clinical studies, but may not be able to detect potential difference in elimination phase after Tmax.

Given the above reasons, ***only results from the dedicated BE study FFA115440 is considered to compare PK exposures between the two configurations for bridging of efficacy and safety data.***

REVIEWER'S ANALYSIS

Objectives

Analysis objectives are:

1. To characterize the relationship between fluticasone furoate (FF) AUC(0-24) and 0-24 hour serum cortisol.
2. To graphically explore the significant exposure-response relationships for major adverse events.

Methods

Effects on HPA-axis function are known to occur with systemic administration of corticosteroids and this systemic side effect has also been reported with inhaled and intranasal corticosteroid use. A total of nine studies were included in the analysis; five conducted in healthy subjects with the remaining four studies conducted in subjects with asthma. These studies utilized the range of formulations and inhalers investigated during the clinical development of FF, with FF administered as single and once daily inhalations as the individual component (FF) or as fluticasone furoate/vilanterol (FF/VI). Data from 372 subjects providing 752 observations were included in the final analysis for serum cortisol meta-analysis. Graphical analysis of FF dose- and concentration-response curves were evaluated using 24-hour weighted mean serum cortisol. FF AUC(0-24) was used as an exposure metric for the concentration-response analysis.

The datasets and final sponsor model used for the FF and VI population analysis were used to graphically explore the exposure-covariate relationships.

Data Sets

Data sets used are summarized in Table 30.

Table 30. Analysis Data Sets

Study Number(s)	Name	Link to EDR
FFA10001 FFA10002 FFA10003 FFA10009 FFA103096 FFA100022 FFA10028 HZA106851	scffpkpd.xpt	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Fluticasone_Vilanterol_NDA204275_SSB\Sponsor Data and Reports\pop-pk-pd\analysis\legacy\datasets

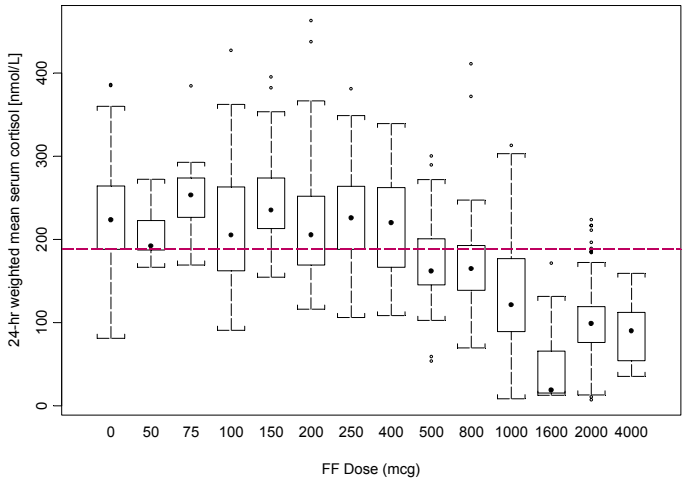
Software

TIBCO Spotfire S-PLUS 8.0 was used for data organization, as well as graphical and statistical analysis.

Results

For the meta-analysis, a range of once-daily doses from 50 to 4000 mcg FF was investigated. Figure 20 depicts the dose response relationship with increasing dose yielding a decrease in serum cortisol. Deviations from normal values are observed at doses ≥ 500 mcg. Of note, the proposed dose for FF is 100 mcg.

Figure 20. Boxplot of FF Dose-Response of 24 hr weighted mean serum cortisol. Dashed line represents the 25th percentile of the placebo response.



An Emax threshold exposure-response relationship was observed between FF AUC(0-24 hours) and the 24-hour weighted mean serum cortisol, where a threshold FF exposure of ~380 pg*h/mL was required to observe a decrease in serum cortisol At concentrations above the threshold, the relationship was best described by an inhibitory E_{max} model:

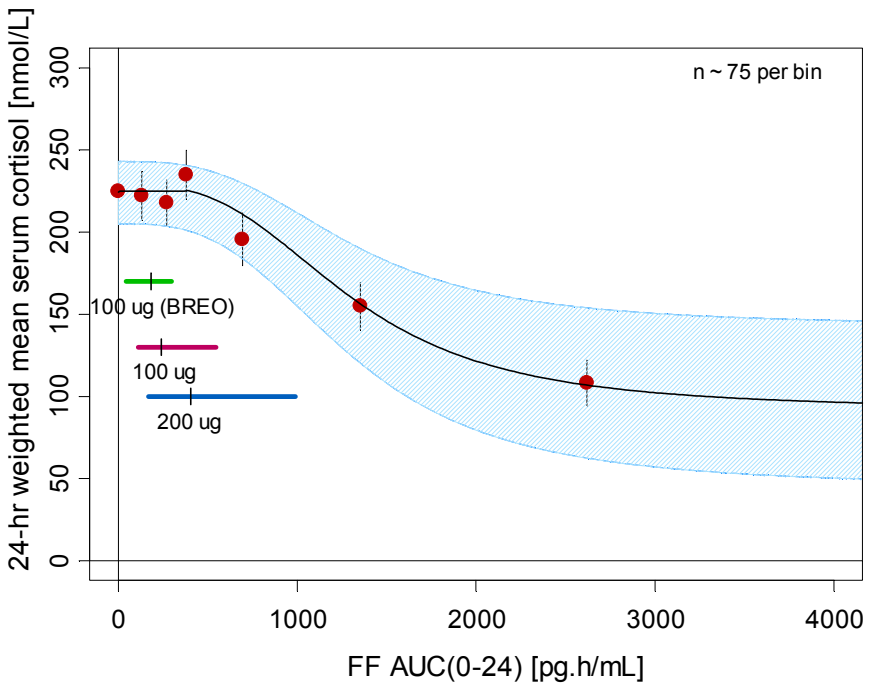
If $AUC_s \leq AUC_{threshold}$, then $E = E_0$, and

$AUC_s > AUC_{threshold}$, $E = E_0 - (E_{max} * AUC_s^n)/(AUC50^n)+(AUC_s^n))$

where:

AUC_s is the serum exposure of FF, $AUC_{threshold}$ is the derived threshold exposure of FF, E is the effect on 24-hr serum cortisol, E is the baseline effect, AUC50 is the exposure in which 50% of maximal inhibition is observed and n is the Hill coefficient.

Figure 21. FF Exposure-Response of 24 hr weighted mean serum cortisol. Red circles represent the median exposure and corresponding mean response for a bin of ~ 75 subjects (+/- 95% CI). A threshold Emax model is depicted along with the 95% Prediction Interval. The range of serum FF exposures for the 100mcg (BREO, FF/VI), and the proposed 100 mcg and 200 mcg FF dose is demarcated with a solid line.



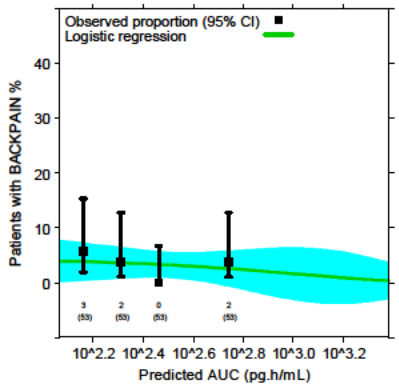
*$AUC_{threshold}$ = 380.1 pg*h/mL; E_0 = 225 nmol/L, AUC50 = 1345 pg*h/mL and n = 3.2*

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 (181 pg•hr/mL) and 200 mcg (395 pg•hr/mL)in subjects with asthma (see Figure 22 below).

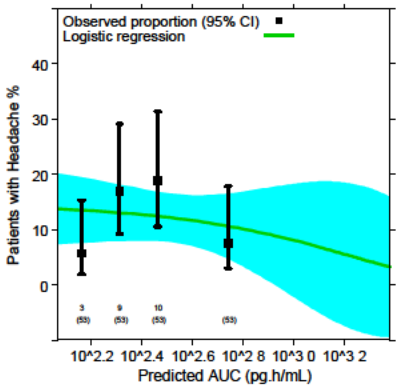
Exposure-response relationships for FF and common AEs were assessed by univariate logistic regression model (Figure 22). There was no clear relationship between FF systemic exposure and any of the AEs reported by 3% or more of subjects.

Figure 22. FF AUC (at steady state) vs. major AEs Reported by 3% or more subjects in study FFA114496

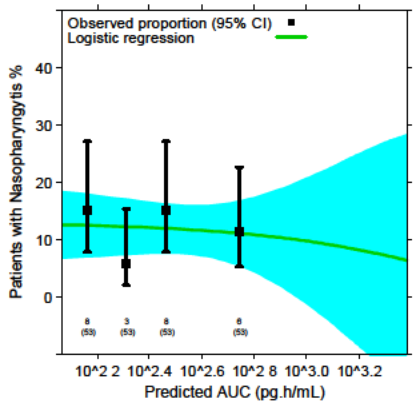
Backpain



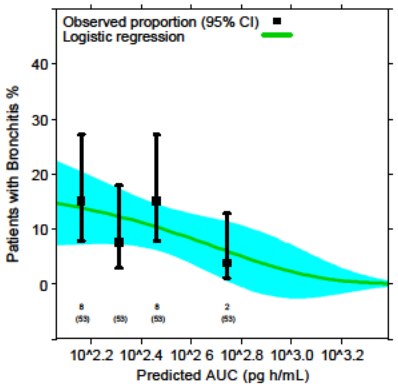
Headache



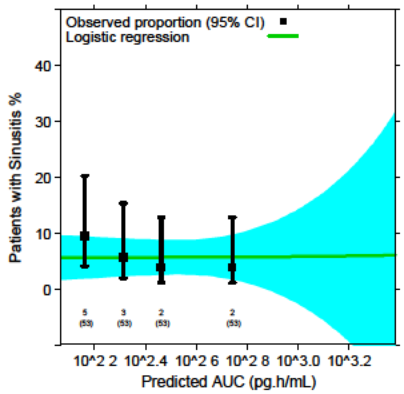
Nasopharyngytis



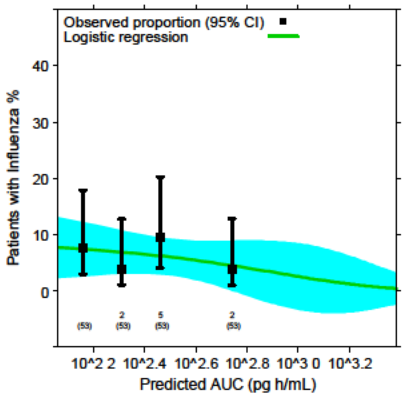
Bronchitis



Sinusitis



Influenza



Conclusion: The average systemic exposure of FF at therapeutic doses did not have a significant impact on HPA axis suppression. No apparent relationship was identified between systemic exposure and major AEs.

4.2. Appendix – Individual Study Review

INDIVIDUAL STUDY REVIEW

Note –

All relevant ADME in vitro studies for FF, and all clinical pharmacology studies with FF(2s) and FF/VI have been reviewed under NDA204275 (FF/VI) by Dr. Jianmeng Chen (DARRTS date 03/18/2013). In this review, this reviewer will focus on the two study reports (study 115440 and 115441) using FF(1s) submitted to this NDA.

Absolute Bioavailability, SAD, MAD for FF(1S)

FF

Trial # FFA115441

Title: An Open label, Part-randomized, Four-way Crossover, Single and Repeat Dose Study to Determine the Dose Proportionality and Absolute Bioavailability of Fluticasone Furoate (FF) when Administered as FF Inhalation Powder from the Novel Dry Powder Inhaler in Healthy Subjects

Objective:

Primary

- To demonstrate dose proportionality of FF following single dose administration (multiple inhalations) of three strengths of FF (50 mcg, 100 mcg and 200 mcg) leading to doses of 300 mcg, 600 mcg, 1200 mcg respectively via the novel dry powder inhaler (DPI) in healthy subjects.
- To demonstrate dose proportionality of FF following repeat dose (7 days) administration (single inhalation) of three strengths of FF (50 mcg, 100 mcg and 200 mcg) via the DPI in healthy subjects.
- To determine the absolute bioavailability of FF following single dose administration (multiple inhalations) of the high strength of FF (200 mcg) leading to a dose of 1200 mcg via the DPI in healthy subjects.

Secondary

- To determine the pharmacokinetics (PK) of FF following single and repeat dose administration of three strengths of FF (50 mcg, 100 mcg and 200 mcg) via the DPI in healthy subjects.
- Safety and tolerability.

Study design and treatment schedule:

Part-randomized, open-label, four-way cross-over single and repeat dose study in healthy male and female subjects. Each subject (n=36) participated in three treatment periods. The four treatment periods were separated by a washout period of at least 7 days.

- Treatment A: A single dose of 300 mcg FF (6 inhalations of 50 mcg FF) on Day 1, followed by 50 mcg FF once daily for 7 days, on Days 3-9 inclusive, administered from the DPI.
- Treatment B: A single dose of 600 mcg FF (6 inhalations of 100 mcg FF) on Day 1, followed by 100 mcg FF once daily for 7 days, on Days 3-9 inclusive, administered from the DPI.
- Treatment C: A single dose of 1200 mcg FF (6 inhalations of 200 mcg FF) on Day 1, followed by 200 mcg FF once daily for 7 days, on Days 3-9 inclusive, administered from the DPI.
- Treatment D: A single dose of 250 mcg FF, administered as an IV infusion over 20 minutes on Day 1.

PK Sampling Schedule
Blood – Inhaled treatment period day 1-3 at pre-dose, 5, 10, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hour after dosing; **Inhaled treatment Period day 9-10 at** pre-dose, 10, 20, 25, 30, 45 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hour after dosing; **Intravenous treatment period at** pre-dose, 30, 45 min, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hour after dosing;

Results
Absolute bioavailability
The absolute bioavailability of FF following oral inhalation administration was **13.9%** for FF (Table 31).

Table 31. Summary of Results from Statistical Analysis of Absolute Bioavailability of FF

Dose-Normalized Parameter	Treatment Comparison	Geometric Means	Ratio of Geometric Means	90% CI of the Ratio
AUC(0-∞)	FF 1200 SD / FF IV 250 SD	3.01 / 21.59	0.139	(0.127, 0.153)

(Source – Table 10, Study HZA115441 report)

Dose proportionality
Dose proportionality was demonstrated for AUC_{inf} but not C_{max} (Table 32). Evaluation of dose proportionality using Cmax and partial AUCs was confounded by rate limited absorption.

Table 32. Statistical Analysis to assess dose proportionality of FF

	Parameter	Effect	Point Estimate	90% CI
Single Dose	AUC(0-∞)	Log (dose)	1.040	(0.956, 1.123)
	AUC(0-12)	Log (dose)	0.775	(0.722, 0.829)
	Cmax	Log (dose)	0.477	(0.416, 0.539)
Repeat Dose	AUC(0-4)	Log (dose)	0.758	(0.690, 0.827)
	Cmax	Log (dose)	0.606	(0.538, 0.674)

(Source – Table 8, Study HZA115441 report)

Single dose escalation

Mean serum FF concentration vs. time profiles are shown in Figure 23. On average, the maximum plasma concentrations of FF were achieved at later times (Tmax) as the FF dose increased: FF 300 at 15 minutes, FF 600 at 30 minutes and FF 1200 mcg at 60 minutes. FF appears to follow poly-exponential disposition kinetics for all tested dose levels. PK parameters for different dose levels are listed in Table 33. Terminal half-life of FF was approximately 16.9 to 27.7 hours.

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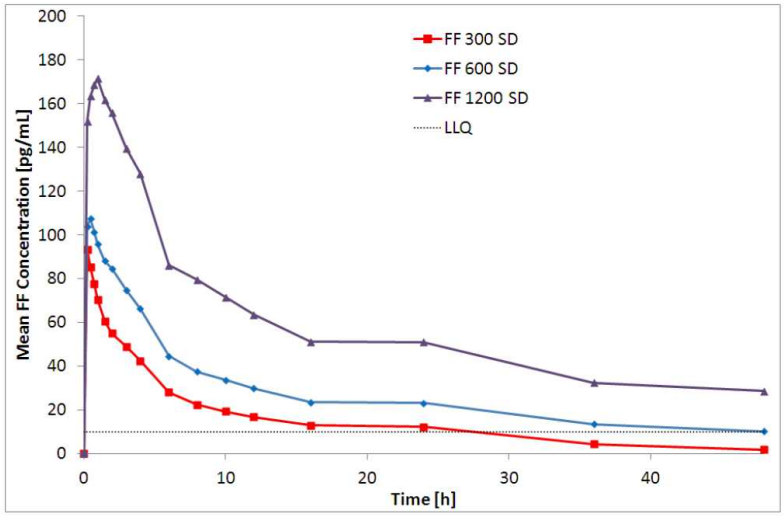

Figure 23. Mean Plasma FF Concentrations vs Times Following Administration of a Single Dose of FF Administered via DPI in Healthy Subjects

(Source – Figure 1, Study FFA115441 report)

Table 33: Pharmacokinetic Parameters of FF Following Administration of a Single Dose of FF by NDPI in Healthy Subjects

Parameter	Treatment	N	n	Geometric Mean (CV%)	95% Confidence Interval
AUC(0-inf) (pg.h/mL)	FF 300	35	27	895.25 (60.2)	(718.44,1115.58)
	FF 600	35	31	1731.86 (43.5)	(1486.56,2017.65)
	FF 1200	35	33	3614.02 (36.9)	(3183.86,4102.29)
AUC(0-12) (pg.h/mL)	FF 300	35	35	414.11 (27.0)	(378.01,453.67)
	FF 600	35	35	626.99 (30.3)	(566.27,694.22)
	FF 1200	35	35	1203.30 (28.0)	(1095.10,1322.20)
Cmax (pg/mL)	FF 300	35	35	93.02 (34.7)	(82.83,104.46)
	FF 600	35	35	109.36 (32.9)	(97.95,122.09)
	FF 1200	35	35	178.59 (32.0)	(160.43,198.82)
t1/2 (h)	FF 300	35	27	16.93 (81.4)	(12.77,22.45)
	FF 600	35	31	24.82 (30.2)	(22.27,27.66)
	FF 1200	35	33	27.69 (19.3)	(25.87,29.63)
tmax (h)[1]	FF 300	35	35	0.25 (0.25-0.75)	NA
	FF 600	35	35	0.50 (0.25-2.00)	NA
	FF 1200	35	35	1.00 (0.25-2.00)	NA
MAT (h)	FF 300	35	34	2.87 (122.1)	(1.95,4.22)
	FF 600	35	34	6.15 (101.9)	(4.58,8.26)
	FF 1200	35	34	9.50 (58.8)	(7.85,11.49)

Source Data: Table 10.2
NA = Not Applicable
n* = number of subjects with parameter not estimated due to non-quantifiable data
[1] Median (range)

(Source – Table 5, Study FFA115441 report)

Multiple dose escalation

Multiple dose PK of FF in DPI (single strip) was characterized in healthy volunteers. Mean plasma PK profiles are shown in Figure 24 and summary PK parameters are listed in Table 34. Cmax was reached by 1 hour for FF, which similar to single dose.

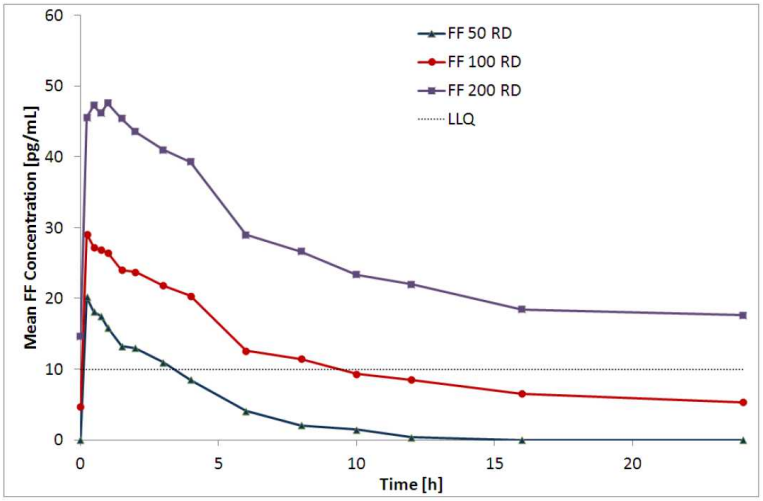

Figure 24. Mean Plasma Concentrations Versus Time on Day 7 Following Multiple Dosing with FF
(Source – Figure 2, Study FFA115441 report)

Table 34: FF Pharmacokinetic Parameters on Days 7 Following Repeated Inhaled Administration of FF in Healthy Volunteers

Parameter	Treatment	N	n	n*	Geometric Mean (CV%)	95% Confidence Interval
AUC(0-t) (pg.h/mL)	FF 50	35	35	2	48.73 (118.9)	(35.30,67.27)
	FF 100	35	35	1	181.65 (131.8)	(128.68,256.41)
	FF 200	35	35	0	538.35 (62.9)	(441.52,656.43)
AUC(0-4) (pg.h/mL)	FF 50	35	23	2	57.52 (52.2)	(46.52,71.13)
	FF 100	35	35	1	85.77 (47.3)	(73.50,100.08)
	FF 200	35	35	0	160.80 (37.6)	(141.90,182.22)
AUC(0-24) (pg.h/mL)	FF 50	35	2	2	126.23 (ND)	ND
	FF 100	35	15	1	372.98 (39.4)	(302.23,460.28)
	FF 200	35	30	0	642.95 (30.4)	(575.38,718.46)
Cmax (pg/mL)	FF 50	35	35	2	20.10 (48.7)	(17.15,23.55)
	FF 100	35	35	0	28.81 (42.3)	(25.06,33.12)
	FF 200	35	35	0	49.01 (37.6)	(43.26,55.52)
tmax (h)[1]	FF 50	35	33	0	0.25 (0.25-1.50)	NA
	FF 100	35	35	0	0.50 (0.25-3.00)	NA
	FF 200	35	35	0	0.75 (0.25-3.00)	N/A
MRT (h)	FF 100	35	35	0	5.293 (71.9)	(4.241,6.607)

Source Data: Table 10.2
NA = Not Applicable
ND = Not determined, only 2 subjects had $AUC_{(0-24)}$ values
n* = number of subjects with parameter not estimated due to non-quantifiable data
[1] Median (range)

(Source – Table 6, Study FFA115441 report)

Conclusion:
The estimate of absolute bioavailability for inhaled FF (single strip configuration) is13.9%. Dose proportionality was demonstrated for AUC_{inf} but not C_{max}.

Relative Bioavailability for FF in different configurations

FF

Trial # FFA115440

Title: An Open-label, Randomized, Replicate, Six-way Crossover, Single Dose Study to Determine the Bioequivalence of Fluticasone Furoate (FF) Inhalation Powder (Single Strip Configuration) Compared with FF Inhalation Powder (Two Strip Configuration) and Compared with FF / Vilanterol (VI) Inhalation Powder Administered via the Dry Powder Inhaler

Objective:
Primary
• To demonstrate bioequivalence of FF monotherapy (single strip configuration) compared with FF monotherapy (two strip configuration) administered via the dry powder inhaler (DPI) in healthy subjects.
• To demonstrate bioequivalence of FF monotherapy (single strip configuration) compared with FF administered as FF/VI via the DPI in healthy subjects.
Secondary
• Safety and tolerability.

Study design and treatment schedule:

This was a randomized, open-label, replicate, six-way crossover, single dose study in healthy male and female subjects. Each subject (n=16) received the following three treatments, on two separate occasions for each. The three treatment periods were separated by a washout period of at least 7 days and no more than 14 days.

• FF monotherapy 400 mcg (2 inhalations of 200 mcg), administered from the DPI with no second strip (single strip configuration).
• FF monotherapy 400 mcg (2 inhalations of 200 mcg) administered from the DPI with a filled ((b) (4)) second strip (two strip configuration).
• FF/VI 400/50 mcg (2 inhalations of 200/25 mcg) administered from the DPI.

PK Sampling Schedule
Blood – Period 1-6 at pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 and 36 hour after dosing

Results
The relative bioavailability of FF(two strip) vs FF (single strip) following oral inhalation administration was **77.5%,** and the relative bioavailability of FF(as FF/VI) vs FF (single strip) following oral inhalation administration was **62.5%** (**Error! Reference source not found.**). This reviewer did independent analysis of relative bioavailability of FF among different configurations, and the result is consistent with sponsor analysis. (Figure 26)

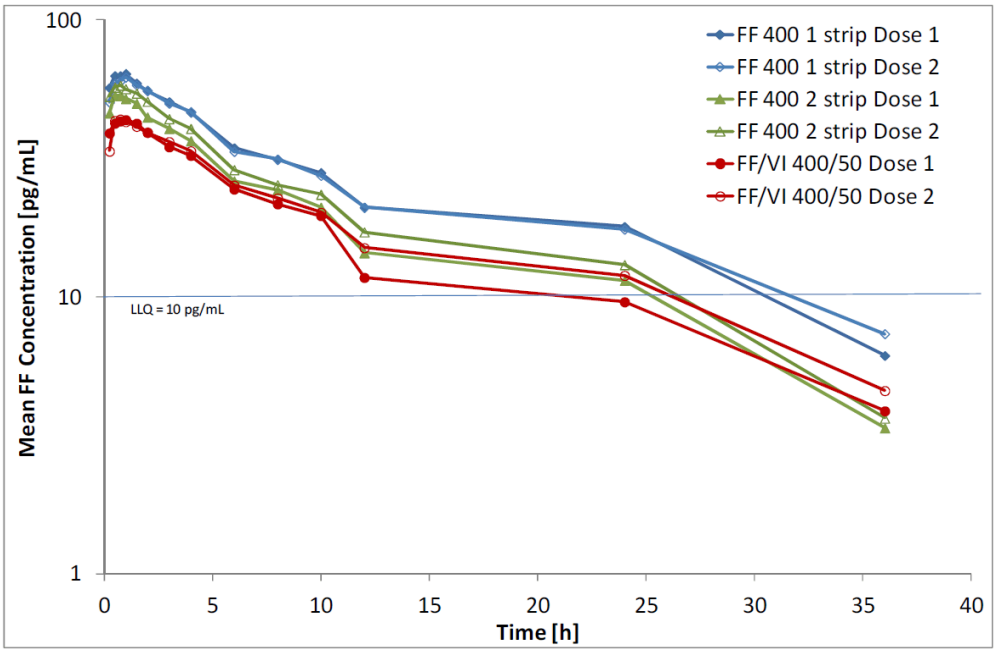

Figure 25. Mean Fluticasone Furoate Concentration-Time Profiles following a Single Inhaled Administration of FF or FF/VI
(Source – Figure 1, Study HZA115440 report)

Table 35. Statistical Analysis to Estimate relative Bioavailability of FF in Healthy Subjects

Parameter	Treatment Comparison	Adjusted Geometric Means	Ratio of Adjusted Geometric Means	90% CI of the Ratio
AUC(0-∞)	FF 400 1 strip / FF 400 2 strip	1144.7 / 889.5	1.29	(1.14, 1.46)
	FF 400 1 strip / FF/VI 400/50	1144.7 / 714.8	1.60	(1.37, 1.87)
AUC(0-t')	FF 400 1 strip / FF 400 2 strip	560.2 / 458.0	1.22	(1.16, 1.29)
	FF 400 1 strip / FF/VI 400/50	560.2 / 401.1	1.40	(1.31, 1.49)
AUC(0-t)	FF 400 1 strip / FF 400 2 strip	723.0 / 531.6	1.36	(1.23, 1.50)
	FF 400 1 strip / FF/VI 400/50	723.0 / 441.2	1.64	(1.44, 1.87)
Cmax	FF 400 1 strip / FF 400 2 strip	67.84 / 60.08	1.13	(1.07, 1.20)
	FF 400 1 strip / FF/VI 400/50	67.84 / 47.75	1.42	(1.33, 1.52)

(Source – Table 8, Study FFA115440 report)

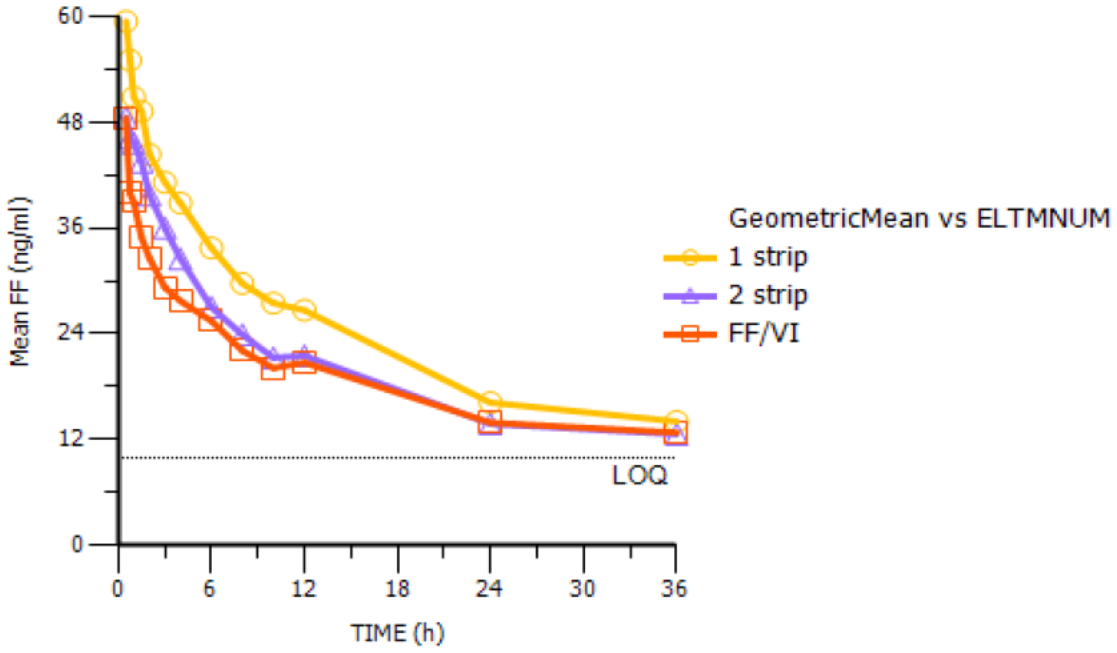

Figure 26. Mean Fluticasone Furoate Concentration-Time Profiles following a Single Inhaled Administration of FF or FF/VI

Conclusions

Bioequivalence was not demonstrated for FF 400 mcg (single strip) compared with FF 400 mcg (two strip) or for FF 400 mcg (single strip) compared with FF/VI 400/50 mcg, administered via the DPI in healthy subjects.

The exposure difference in the three configurations was communicated to the clinical team, as FF is administered by oral inhalation and the systemic exposure is associated with safety rather than efficacy. For FF PK in special population and drug-drug interaction, we consider that all data with FF(2s) and FF/VI are directly applicable to the FF single strip product.

4.3. Appendix – New Drug Application Filing and Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**205625**	**Brand Name**	**ARNUITY ELLIPTA**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Fluticasone Furoate Inhalation Powder**
Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**Inhaled ICS/ LABA**
OCP Reviewer	**Jianmeng Chen MD, Ph.D.**	**Indication(s)**	**Asthma**
OCP Team Leader	**Satjit Brar Pharm.D., Ph.D.**	**Dosage Form**	**Inhalation powder administered from DPI**
Pharmacometrics Reviewer	**Jianmeng Chen MD, Ph. D**	**Dosing Regimen**	**FF (100 mcg qd, 200 mcg qd)**
Pharmacometrics Team Leader	**Liang Zhao, Ph.D.**		
Date of Submission	**10/22/2013**	**Route of Administration**	**Oral Inhalation**
Estimated Due Date of OCP Review		**Sponsor**	**GSK**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**8/22/2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			SPE- HPLC-MS/MS
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		FFR10008 –FF
Isozyme characterization:	**X**	**1**		WD2005/01308/00
Blood/plasma ratio:	**X**	**1**		WD2001/00979/00
Plasma protein binding:	**X**	**4**		WD2001/00979/00 WD2003/01268/00 WD2005/01123/00 2011N118910_00
Transporter specificity:	**X**	**1**		WD2006/00293/00,
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				2011N130718_00
single dose:	**X**	**3**		FFA115440, FFA115441, HZA102934
multiple dose:	**X**	**1**		FFA10002
Patients-				2013N162904
single dose:				
multiple dose:	**X**	**3**		FFA109684, FFA109685 and FFA109687

Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**		FFA115441
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**1**		HZA105548 –Ketoconazole
In-vivo effects of primary drug:	**X**	**2**		HZA105871, HZA102940
In-vitro:	**X**	**3**		WD2001/00374/00, FD2003/00126/00, WD2005/00543/00
Subpopulation studies -				
ethnicity:	**X**	**1**		HZA113477
gender:	**X**			No dedicated study, but gender effect was assessed in several phase II and III studies in pop PK analysis
pediatrics:	**X**	**1**		HZA102942
geriatrics:	**X**			No dedicated study, but age effect was assessed in several phase II and III studies in pop PK analysis
renal impairment:	**X**	**1**		HZA113970
hepatic impairment:	**X**	**1**		HZA111789
PD -				
Phase 2:	**X**	**4**		HZA112202, FFA109687, FFA109685, FFA109684
Phase 3:	**X**			
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**			
Phase 3 clinical trial:	**X**	**5**		HZA106827, HZA106829, HZA106839, HZA106851, FFA114496
Population Analyses -				
Data rich:	**X**			
Data sparse:	**X**			
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**		HZA115441
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies	**X**			
Genotype/phenotype studies				
Chronopharmacokinetics				Chronopharmacodynamics was assessed in FFA20001, FFA106783
Pediatric development plan	**X**			
Literature References	**X**			
Total Number of Studies		**31**		

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

/s/

JIANMENG CHEN
07/18/2014

LIANG ZHAO
07/18/2014

SATJIT S BRAR
07/18/2014