CLINICAL PHARMACOLOGY REVIEW

NDA	204275
Submission Date	6/30/2014
Proposed Brand Name	BREO ELLIPTA
Generic Name	Fluticasone Furoate/Vilanterol Inhalation Powder
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Sponsor/Authorized Applicant	GSK
Submission Type; Code	Efficacy supplement; standard review
Formulation; Strength(s)	Micronized FF and lactose monohydrate; micronized VI, magnesium stearate and lactose monohydrate. 100/25 mcg administered via NDPI
Indication	Asthma in patients aged 12 years and older
Dosage Regimen	100/25 mcg, 200/25 mcg

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1. Executive Summary

GSK submitted this efficacy supplement to NDA 204275 seeking an indication expansion for BREO ELLIPTA (fluticasone furoate/vilanterol, FF/VI) of "treatment of asthma in patients aged 12 years and older". The proposed doses for asthma are 100/25 and 200/25 mcg.

The Sponsor supports this NDA submission with 56 clinical pharmacology studies in which 52 of these studies were submitted to support the initial approval of NDA 204275 (FF/VI, BREO ELLIPTA). Majority of the clinical pharmacology studies, including the dose-ranging studies in asthma, have been previously reviewed in NDA 204275 (Dr. Jianmeng Chen, review dated 03/18/2013). The two new clinical pharmacology studies (b) (4); HZA115199, Healthy Chinese subjects) and an updated population PK report (2011N130480_00) in asthmatic patients were submitted in this supplement.

The following are the major findings of the current review:

1) The dosing regimen of FF and VI has been adequately explored. FF 100 and 200 mcg QD was approved for treatment of asthma in patients 12 years and older (ARNUITY ELLIPTA, NDA205625). The dose and dosing frequency of VI in asthma were assessed and established in two phase II studies, with asthma patients 12 years and older. The data were in support of VI 25 mcg QD in this population.

2) 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/VI 100/25 and FF/VI 200/25 mcg be made available for patients with moderate and severe hepatic impairment with cautionary labeling language.

3) There was no difference in systemic exposure to either FF or VI in adolescent (12-17 years) subjects with asthma compared with adult (≥18 years) subjects with asthma.

4) The exposure of FF is 34% higher in asthma patients, while the exposure of VI is 37% lower in asthma patients when compared to that in COPD patients

1.1 Recommendations

Office of Clinical Pharmacology finds the application NDA 204275-S(01) acceptable.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

This is an efficacy supplement to the NDA 204275 to support an indication expansion for BREO ELLIPTA (fluticasone furoate/vilanterol, FF/VI) for "treatment of asthma in patients aged 12 years and older". The proposed doses for asthma are 100/25 and 200/25 mcg.

FF/VI is an inhaled corticosteroid (ICS)/long-acting beta2 agonist (LABA) combination for oral inhalation to be administered from a Novel Dry Powder Inhaler (NDPI), and was approved at a dose of 100/25 mcg for the treatment of chronic obstructive pulmonary disease (COPD) in the United States on 10 May 2013. FF was also approved in the US as monotherapy for the treatment of asthma (ARNUITY ELLIPTA, 100 and 200 mcg, NDA205625) on Aug 20, 2014.

The sponsor supports this efficacy supplement with 2 new clinical pharmacology studies (b) (4) HZA115199), along with the 52 clinical pharmacology studies that supported the initial approval of BREO, and 2 studies (FFA115440 and FFA115441) that supported the approval of ANUITY ELLIPTA (NDA205625). Majority of the clinical pharmacology studies have been previously reviewed in NDA 204275 (Dr. Jianmeng Chen, review dated 03/18/2013).

PHARMACOKINETICS

The general ADME of FF and VI have been reviewed under the original BREO submission. PK of FF and VI in asthma patients is reviewed in this supplement.

Asthma vs. COPD

Because of the differences in lung physiology in asthma and COPD patients related to absorption of drugs in the lungs, the systemic exposure is usually different in COPD patients compare to asthma patients. For Breo, the exposure of FF is 34% higher in asthma patients, while the exposure of VI is 37% lower in asthma patients when compared to that in COPD patients (Table 1).

- The order of relative systemic exposure of FF in Asthma and COPD patients and healthy subjects is, COPD< Asthma≈healthy subjects. FF Cmax and AUC(0-24) following FF/VI 100/25 was 34% and 33% higher respectively, in subjects with asthma compared with subjects with COPD.

- For VI, the order of relative systemic exposure in COPD and Asthma patients and in healthy subjects is, Asthma<healthy subjects≠COPD. VI Cmax and AUC(0-24) was 62% and 21% lower in subjects with asthma compared with healthy subjects. VI Cmax was 15% higher and AUC(0-24) was 37% lower following 25 mcg VI in subjects with asthma compared with subjects with COPD.

Table 1. Systemic exposure of FF and VI in asthma and COPD patients.

Drug		PK parameter	Asthma	COPD	Asthma vs COPD
BREO	FF (100mcg)	AUC(pg.hr/mL)	244.3	182.2	1.34
		Cmax (pg/mL)	16.0	12.0	1.33
	VI (25 mcg)	AUC(pg.hr/mL)	168.7	265.7	0.63
		Cmax (pg/mL)	49.5	43.2	1.15

(source: Table 49, summary of clinical pharmacology-asthma)

Age, Weight, and Gender

There was no evidence for age, weight or gender to affect the PK of FF or VI in subjects with asthma. There was no difference in systemic exposure to either FF or VI in adolescent (12-17 years) subjects with asthma compared with adult (≥18 years) subjects with asthma.

Race

Systemic exposure of FF and VI are higher in Asian asthma patients compared to other racial groups. For FF systemic exposure($AUC_{(0-24)}$), East Asian, Japanese and South Asian asthma patients were on average 33% to 53% higher compared with other racial groups. This finding is consistent with results seen previously in healthy subjects of East Asian origin. VI C_{max} is predicted to be 220 to 287% higher and $AUC_{(0-24)}$ comparable for those subjects from an Asian heritage compared with subjects with asthma from a non-Asian heritage.

Rationale for Dosing Regimen of FF/VI

Dosing regimen for FF (100 and 200 mcg QD) was reviewed and approved under NDA205625. In order to support the dose selection for VI, two Phase 2 trials were conducted in asthma.

The 25 mcg dose of VI was selected on the basis of results from a Phase 2 dose-ranging study in subjects with asthma (Study B2C109575, including 27 patients 12-17yrs old [4%]), which tested a range of VI doses (3, 6.25, 12.5, 25 and 50 mcg once daily). Based upon the primary endpoint trough FEV1 (Figure 1) and secondary endpoints (weighted mean FEV1 and others) as well as the safety profile, 25 mcg was the appropriate dose.

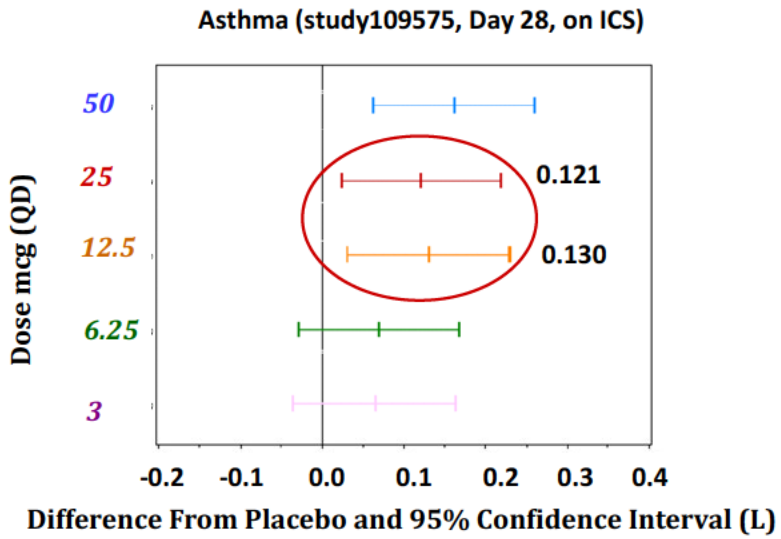


Figure 1. Effect of VI on lung function (trough FEV1) across doses ranging from 3 mcg to 50 mcg QD
(Source –Figure 3, Study HZA109575 report)

A study conducted in subjects with persistent asthma supported the comparability of once and twice daily dosing for VI, where the improvement of mean FEV1 (0-24h) was similar with VI 6.25 mcg twice daily and VI 12.5 mcg once daily dosing. Overall, data for the nominal dose and dosing frequency in asthma appeared reasonable in support of VI 25 mcg QD.

All phase II dose ranging studies for VI included patients 12 years and older. Also, dosing regimen in adolescent asthma patients is the same as adult patients for all approved ICS/LABA products in asthma, as listed below. Therefore, the same dosing regimens for FF/VI were assessed in pediatric patients 12-17yrs of age in phase III studies.

- fluticasone propionate+ salmeterol (Advair)
- budesonide+ formoterol (Symbicort)
- mometasone+formoterol (Dulera)

Rationale for Dosing Recommendations in Patients with Hepatic Impairment

The Clinical Pharmacology reviewer recommends both FF/VI 100/25 and 200/25 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. Based on these data, the

Sponsor recommended no dose adjustments for mild hepatic impairment, (b) (4)

FF was approved for 100 and 200 mcg QD for hepatic impairment patients (NDA205625, clinical pharmacology review dated 7/18/2014). Therefore, this reviewer recommends making both FF/VI 100/25 and FF/VI 200/25 mcg available for patients with moderate and severe hepatic impairment. Cautionary labeling language will be supplied stipulating the potential for deleterious HPA axis effects.

2. Question Based Review

BREO ELLIPTA (FF/VI 100/25 mcg) has been reviewed previously under NDA 204275 (Submission Date: 07/12/ 2012). For brevity purposes, only QBR questions relevant to this current supplement NDA submission will be addressed. For additional information, please see the clinical pharmacology review for the original NDA 204275 by Dr. Jianmeng Chen (review dated 03/18/2013).

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

Fifty six clinical pharmacology studies are summarized in Table 2. Study (b) (4) 13 (b) (4) HZA115199, Healthy Chinese subjects) were new clinical pharmacology studies submitted in this supplement. Study 14 and 15 were submitted and reviewed in NDA205625. The rest of studies were submitted and reviewed under the original submission of NDA204275. An updated population PK report (2011N130480_00) in asthmatic patients was also submitted in this supplement.

Table 2. Summary of Clinical Pharmacology studies

Drug		CP Study	Objective	Population	Device
FF/VI	1	HZA102932	Dose proportionality	24 Healthy subjects	NDPI
	2	HZA102934	Absolute bioavailability	16 Healthy subjects	NDPI
	3	HZA102936	Thorough QTc	85 Healthy subjects	NDPI
	4	HZA105871	PK-interaction of FF&VI	16 Healthy subjects	NDPI
	5	HZA102940	PK-interaction of FF&VI	16 Healthy Japanese subjects	NDPI
	6	HZA105548	Ketoconazole DDI	18 Healthy subjects	NDPI
	7	HZA111789	Hepatic impairment	9 Healthy, 9 mild, 9 moderate, 8 severe	NDPI
	8	HZA113970	Renal impairment	9 Healthy, 9 severe	NDPI
	9	HZA114624	AM vs PM	26 persistent asthma	NDPI
	10	HZA113090	Bronchoprotective PD effect	52 mild asthma patients	NDPI
	11	HZA113126	Bronchoprotective PD effect	27 mild asthma patients	NDPI
					(b) (4)
FF	13	HZA115199	PK and safety (HPA axis, QT)	16 Healthy Chinese subjects	NDPI
	14	FFA115440	BE between 1 and 2 strips	30 Healthy subjects	NDPI
	15	FFA115441	Dose proportionality and absolute bioavailability	30 Healthy subjects	NDPI (1S)
	16	FFA10008	PK Contribution of the swallowed fraction of inhaled dose to systemic absorption of FF	15 Healthy subjects	Diskhaler
	17	FFR10008	Human radiolabelled ADME/mass balance	5 Healthy subjects	
	18	HZA113477	Race PK	Healthy 20 Caucasian, 20 Chinese, 20 Japanese, 20 Korean	NDPI
	19	FFA10001	FTIH	20 Healthy subjects	Diskhaler
	20	FFA10002	FF multiple dose PK	36 Healthy subjects	Diskhaler
	21	FFA10003	Absolute bioavailability of FF with Diskhaler	24 Healthy subjects	Diskhaler
	22	FFA10007	Bronchoprotective PD effect of FF	6 mild asthma patients	Diskhaler
	23	FFA10009	Repeat FF dose safety -cortisol	24 Healthy subjects	Diskus
	24	FFA10013	FF-Hepatic impairment	10 Healthy, 10 Hepatic impairment	Diskus
	25	FFA10022	FF formulation finding based on Bronchoprotective PD effect	40 mild asthma patients	Diskhaler
	26	FFA10026	AMP Challenge	24 mild asthma patients	Diskhaler
	27	FFA10027	AMP Challenge	24 mild asthma patients	Diskhaler
	28	FFA10028	Effect of repeat dosing on exhaled nitric oxide (exNO)	28 mild/moderate asthma patients	Diskhaler
	29	FFA103096	Effect of repeat dosing on serum cortisol	44 Healthy subjects	Diskus
	30	FFR10010	Bioavailability of FF administered intranasally	16 Healthy subjects	Intranasal
	31	FFR101888	Thorough QT	40 Healthy subjects	Diskus
	32	HZA102928	FF effect on serum cortisol	36 Healthy subjects	Diskus
	33	HZA102942	Pediatric	27 children 5-11yr	NDPI
	34	HZA108799	FF effect on serum cortisol	20 mild/moderate asthma patients	Diskus
	35	HZA112018	FF PK in Japanese	48 Healthy Japanese subjects	NDPI
VI	36	B2C106181	Human radiolabelled ADME/mass balance	6 Healthy subjects	
	37	DB2113950	DDI verapamil-coadministration of VI/GSK573719	32 Healthy subjects	NDPI
	38	B2C111401	PK/PD for VI systemic effect Bronchodilation in asthma	24 persistent asthma patients	NDPI
	39	B2C10001	VI earlier formulation PD-FEV1	20 Healthy subjects	Diskus
	40	B2C101762	VI earlier formulation PK	28 mild/moderate asthma patients	Diskus
	41	B2C106093	VI earlier formulation PK	55 persistent asthma patients	Diskus
	42	B2C104604	VI formulation finding	14 persistent asthma patients	Diskus
	43	B2C106996	VI formulation finding	15 persistent asthma patients	Diskus
	44	B2C110165	VI formulation finding	20 COPD patients	Diskus
	45	B2C106180	Oral/iv systemic PK for VI, safety margin	9 Healthy subjects	
	46	B2C108784	PK/PD for VI systemic effect	36 Healthy subjects	Diskus
	47	B2C112205	DDI VI vs ketoconazole	20 Healthy subjects	NDPI
	48	HZA112776	Pediatric	28 children 5-11yr	NDPI
	49	DB1111509	Combined to another product GSK233705	16 Healthy subjects	NDPI
	50	DB1112146	Combined to another product GSK233705	16 Healthy Japanese subjects	NDPI
	51	DB1112017	Multiple dose PK in Japanese	32 Healthy Japanese subjects	NDPI
	52	DB2113208	Combined to another product GSK573719	16 Healthy Japanese subjects	NDPI
	53	FFA10004	Dosedependent skin blanching study	24 Healthy subjects	
	54	SIG102337	Dosedependent skin blanching study; Combined to another product GW870086X	24 Healthy subjects	
	55	ODS10004	Skin blanching study	24 Healthy subjects	
	56	BGS104270	Skin blanching study	30 Healthy subjects	

Clinical studies are summarized in Table 3.

Table 3. Overview of Clinical Development Program

VI	Dose ranging	9575 (Asthma)
	Dose frequency	3310 (Asthma)
FF	Dose ranging	9687 (Asthma) 9685 (Asthma) 9684 (Asthma)
	Dose frequency	2202 (Asthma)
Pivotal Efficacy and Safety	24 week lung function trials	HZA 106829
	12 week lung function trials	HZA106827 HZA116863
	52 week exacerbation trials	HZA106837
Active Comparator	Advair comparator trials	HZA113091

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?

Drug Product

Fluticasone Furoate/Vilanterol Inhalation Powder is a pre-dispensed multi dose dry powder for oral inhalation. The novel dry powder inhaler (NDPI) incorporates two blister strips, one containing (b) (4) micronised fluticasone furoate (FF) and lactose monohydrate and the other containing (b) (4) micronised vilanterol trifenatate (VI), lactose monohydrate and magnesium stearate (Table 4). Upon actuation, the inhaler delivers the contents of one blister containing FF (b) (4) and one blister containing VI (b) (4)

Table 4. Composition of Fluticasone Furoate/Vilanterol Inhalation Powder 100/25 and 200/25 microgram

Inhalation Powder Strength	100/25 mcg	200/25 mcg	Function	Reference to Standard
Component	Quantity (per 12.5 mg blister[1])			
Fluticasone Furoate Blister Strip				
Fluticasone furoate micronised[2]	100 mcg	200 mcg	Active	GlaxoSmithKline[3]
Lactose monohydrate	To 12 (b) (4) mg	To 12 (b) (4) mg	(b) (4)	JP, Ph. Eur and USP/NF[5]
Vilanterol Blister Strip				
Vilanterol trifenatate micronised[2]	40 mcg[4]	40 mcg[4]	Active	GlaxoSmithKline[3]
Magnesium stearate	125 mcg	125 mcg	(b) (4)	JP, Ph. Eur and USP/NF[5]
Lactose monohydrate	To 12 (b) (4) mg	To 12 (b) (4) mg		JP, Ph. Eur and USP/NF[5]

Note: mcg= microgram

1. A manufacturing overage of (b) (4) may be included in the final product.
2. The quantity of each drug may be adjusted to reflect the assigned purity of the input drug substances.
3. Details of the specification(s) of the active ingredient(s) are provided in S.4.1. Specifications.
4. 40 microgram of vilanterol trifenatate is equivalent to 25 microgram of vilanterol.
5. Excipients comply with JP, Ph. Eur and USP/NF and additional tests to ensure the quality for inhaled use. Details of the specification are provided in 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?

Fluticasone Furoate/Vilanterol Inhalation Powder is an inhaled corticosteroid (ICS)/long-acting beta2 agonist (LABA) combination for oral inhalation.

The proposed indication is "*Once-daily treatment of asthma in patients aged 12 years and older"* FF/VI is not indicated for relief of acute bronchospasm.

2.2.3 What are the proposed dosages and routes of administration?

Recommended dose is FF/VI (100/25 mcg and 200/25 mcg) 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: **fluticasone furoate (Arnuity),** budesonide(Pulmicort), fluticasone propionate (Flovent), mometasone (Asmanex), Beclomethasone (Qvar), Ciclesonide(Alvesco)

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

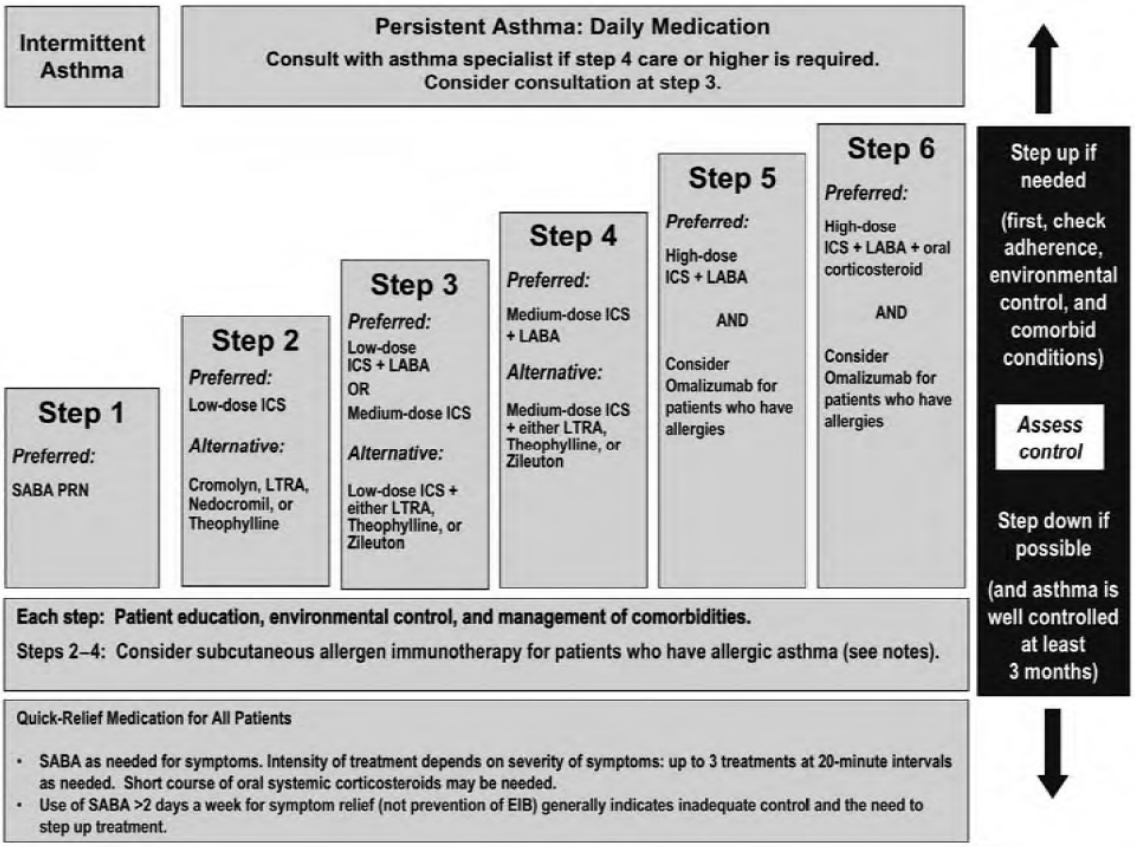
(c) ICS/LABA Combinations:

- 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

Guidelines for the diagnosis and management of asthma were summarized in the diagram below:



(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 characterization (dose-ranging) of the individual components (FF and VI) to establish the appropriate dose for each component, before proceeding to studies with the combination product in the Phase 3 studies (Table 3). Three FF/VI doses (50/25, 100/25, and 200/25 mcg) were assessed in phase III program. 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 were 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/LABA 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/VI concentrations were measured. No metabolites were quantified because the metabolites of FF and VI 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 and VI, 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 and 3, 6.25, 12.5, 25 and 50 mcg for VI. A clear dose-response relationship is observed, with an increasing effect with increasing dose, for all endpoints evaluated (see section 2.4.2 below).

2.4.2 Has the dosing of FF/VI been adequately explored?

The dosing regimen of FF/VI has been thoroughly explored in Phase 2 trials. The dosing regimen for FF (100 and 200 mcg QD) was reviewed and approved under NDA205625. In order to support the dose selection for VI, two Phase 2 trials were conducted in asthma.

The 25 mcg dose of VI was selected on the basis of results from a Phase 2 dose-ranging study in subjects with asthma (Study B2C109575), which tested a range of VI doses (3, 6.25, 12.5, 25 and 50 mcg once daily). 27 subjects [4%] were 12 - 17 years of age: 7 in the placebo group, 2 in the 3 μg group, 2 in the 6.25 μg group, 7 in the 12.5 μg group, 5 in the 25 μg group, 4 in the 50 μg group. Based upon the primary endpoint trough FEV1 (Figure 2) and secondary endpoints (weighted mean FEV1 and others, Figure 3) as well as the safety profile, 25 mcg was the appropriate dose. Due to limited number of patients 12-17 years old, it is not clear whether the dose response is the same in adolescent subjects as in adult subjects in asthma.

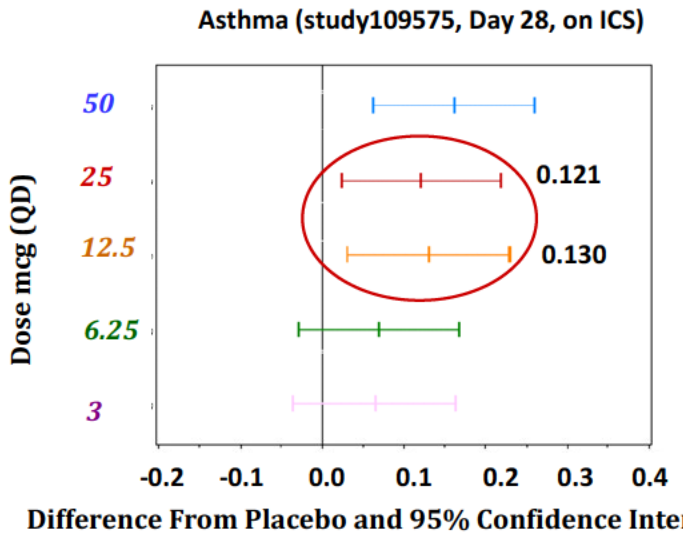


Figure 2. Effect of VI on lung function (trough FEV1) across doses ranging from 3 mcg to 50 mcg QD

(Source –Figure 3, Study HZA109575 report)

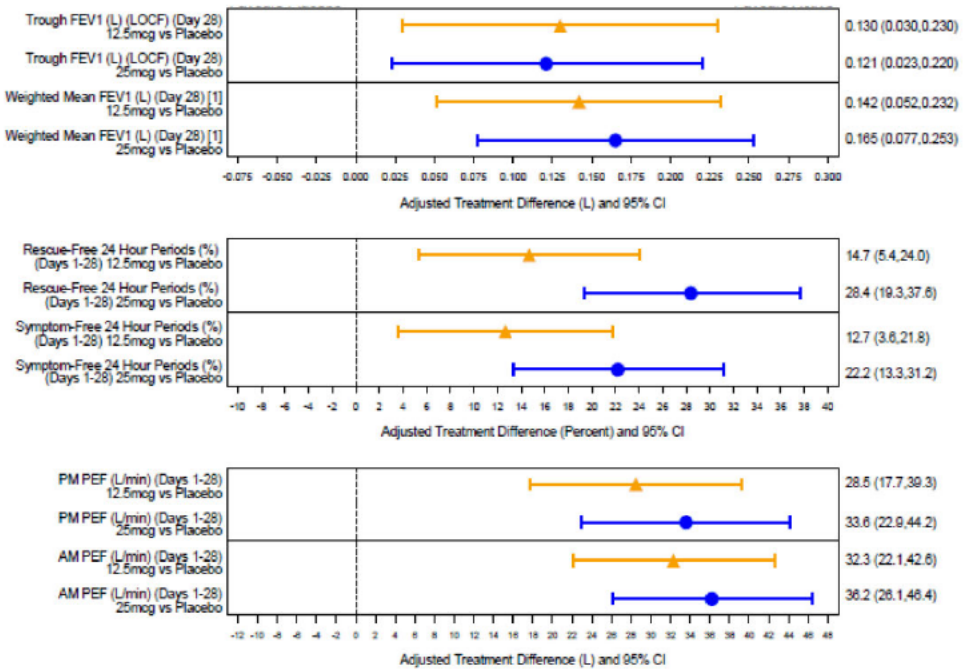


Figure 3. Primary and Secondary Endpoints – Comparison of VI 25 (ICS) and VI 12.5 (ICS) with Placebo in Subjects with Asthma (Study B2C109575, ITT Population)

(Source –Figure 3, Asthma clinical overview)

A study conducted in subjects with persistent asthma supported the comparability of once and twice daily dosing for VI, where the improvement of mean FEV1 (0-24h) was similar with VI 6.25 mcg twice daily and VI 12.5 mcg once daily dosing.

In conclusion, data for the nominal dose and dosing frequency in asthma appeared reasonable in support of VI 25 mcg QD.

All phase II dose ranging studies for VI included patients 12 years and older. Also, dosing in adolescent asthma patients is the same as adult patients for all approved ICS/LABA products in asthma, as listed below. Therefore, the same dosing regimens for FF/VI were assessed in pediatric patients 12-17yrs of age as in adult patients in phase III studies.

- fluticasone propionate+ salmeterol (Advair)
- budesonide+ formoterol (Symbicort)
- mometasone+formoterol (Dulera)

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

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. Cortisol suppression data following chronic once daily administration of FF has been reviewed under original NDA 204275 and NDA205625. Based on the metaanalysis of nine studies including healthy subjects and asthmatic patients, the average estimate of FF $AUC_{(0-24)}$ required to reduce cortisol by 50% (AUC_{50}) was 1,345 pg.hr/mL, which is 2.7-fold higher than average FF $AUC_{(0-24)}$ values observed at the therapeutic dose of FF 200 mcg (495 pg.hr/mL) in subjects with asthma.

2.5 What are the PK characteristics of the drug?

2.5.2 How does the PK of the drug in patients with asthma compare to that in patients with asthma, and that in healthy subjects?

- The order of relative systemic exposure of FF in Asthma and COPD patients and healthy subjects is, COPD< Asthma≈healthy subjects (Table 5). FF Cmax and AUC(0-24) following FF/VI 200/25 was 35% and 42% lower respectively, in subjects with COPD compared with subjects with asthma.

- For VI, the order of relative systemic exposure in COPD and Asthma patients and in healthy subjects is, Asthma<healthy subjects≠COPD. Compared with healthy subjects VI Cmax and AUC(0-24) was 62% and 21% lower in subjects with asthma. VI Cmax was 13% lower and AUC(0-24) was 57% higher following 25 mcg VI (as FF/VI or VI) in subjects with COPD compared with subjects with asthma (Table 6).

Table 5. Comparison of FF Systemic Exposure in Healthy Subjects vs. Subjects with COPD and Asthma following Repeat Dosing with FF

Population FF dose (mcg)	N	C_{max} (pg/mL)	$AUC_{(0-24)}$ (pg.h/mL)
COPD 100/25	391	11.96 [10.94, 12.99]	182.15 [169.61, 194.69]
Asthma 100/25	434	16.01 [15.55, 16.48]	244.25 [235.98, 252.51]
Asthma 100	186	15.50 [14.81, 16.19]	238.24 [228.01, 248.47]
Healthy Subjects 200/25	116	38.1 [36.5, 39.8]	534.4 [501.7, 567.1]
COPD 200/25	234	20.3 [18.41, 22.18]	288.02 [260.78, 315.27]
Asthma 200/25	432	31.35 [30.33, 32.37]	495.33 [480.06, 510.60]
Asthma 200	161	30.63 [29.20, 32.06]	477.77 [455.93, 499.61]

(source: Table 49, summary of clinical pharmacology)

Table 6. Comparison of VI Systemic Exposure in Healthy Subjects vs. Subjects with COPD and Asthma following Repeat Dosing with VI

Treatment	N	C_{max} (pg/mL)	$AUC_{(0-24)}$ (pg.h/mL)
Healthy Subjects	110	130.5 [118.6, 143.5]	213.9 [197.0, 232.2]
COPD	1091	43.2 [41.8, 44.6]	265.7[259.5, 271.9]
Asthma	856	49.5 [46.6, 52.5]	168.7 [163.9, 173.5]

(source: Table 50, summary of clinical pharmacology)

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 and VI systemic exposure in patients with asthma. Please see Pharmacometrics review in Appendix 4.2 for additional details.

Age

There was no difference in systemic exposure to either FF or VI in adolescent (12-17 years) subjects with asthma compared with adult (≥18 years) subjects with asthma. (b) (4)

[redacted]

Weight

There is no influence of weight or body mass index on the pharmacokinetics of either FF or VI in subjects with asthma.

Gender

There is no influence of gender on the pharmacokinetics of either FF or VI in subjects with asthma.

Race

Systemic exposure of FF and VI are higher in Asian asthma patients compared to other racial groups. For FF systemic exposure($AUC_{(0-24)}$), East Asian, Japanese and South Asian asthma patients were on average 33% to 53% higher compared with other racial groups. This finding is consistent with results seen in healthy subjects of East Asian origin (Study HZA113477 and study HZA115199). VI Cmax is predicted to be 220 to 287% higher and AUC(0-24) comparable for those subjects from an Asian heritage compared with subjects with asthma from a non-Asian heritage.

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.

Hepatic Impairment

The impact of hepatic impairment was assessed in a dedicated study with multiple doses of FF/VI via NDPI 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, upper 90% CI limits of $AUC_{(0–24)}$ ratio (hepatic/healthy) for each hepatic impairment group were all greater than 2 (Table 7). 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.

No change of VI exposure in hepatic impairment patients: Subjects with various degrees of hepatic impairment had no significant change in AUC and C_{max} of VI compared to normal hepatic function (Table 8). There is no VI related PD changes observed in hepatic impairment patients.

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

No dose adjustments are recommended for mild hepatic impairment.

Table 7: 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)

Table 8: VI 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	81.76 / 204.61	0.40	(0.26, 0.62)
		Hepatic Moderate /Healthy	189.74 / 204.61	0.93	(0.58, 1.48)
		Hepatic Severe /Healthy	118.17 / 204.61	0.58	(0.37, 0.91)
AUC(0–24)	7	Hepatic Mild /Healthy	335.74 / 511.10	0.66	(0.40, 1.08)
		Hepatic Moderate /Healthy	678.27 / 511.10	1.33	(0.78, 2.26)
		Hepatic Severe /Healthy	367.69 / 511.10	0.72	(0.43, 1.20)
Cmax	1	Hepatic Mild /Healthy	107.08 / 225.69	0.47	(0.33, 0.69)
		Hepatic Moderate /Healthy	167.93/ 225.69	0.74	(0.50, 1.11)
		Hepatic Severe /Healthy	167.02 / 225.69	0.74	(0.50, 1.09)
	7	Hepatic Mild /Healthy	154.51 / 246.82	0.63	(0.43, 0.91)
		Hepatic Moderate /Healthy	193.31/ 246.82	0.78	(0.52, 1.17)
		Hepatic Severe /Healthy	206.04 / 246.82	0.83	(0.57, 1.23)

(Source – Table 8, Study HZA111789 report)

Reviewer's comment:
The Clinical Pharmacology reviewer recommends both FF/VI 100/25 and 200/25 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. Based on these data, the Sponsor recommended no dose adjustments for mild hepatic impairment, (b) (4)

FF was approved for 100 and 200 mcg QD for hepatic impairment patients (NDA205625, clinical pharmacology review dated 7/18/2014). Therefore, this reviewer recommends making both FF/VI 100/25 and FF/VI 200/25 mcg available for patients with moderate and severe hepatic impairment. Cautionary labeling language will be supplied stipulating the potential for deleterious HPA axis effects.

3. Detailed Labeling Recommendations

The revised labeling language based on the preliminary review is as below. Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

(b) (4)

1 Page of Draft Labeling has been Wtihheld in Full as b4 (CCI/TS) immediately following this page

4. Appendix

4.1 Appendix –PM Review

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

NDA Number	204275-S(01)
Brand Name	BREO ELLIPTA
Drug Components	Fluticasone furoate (FF) and vilanterol (VI)
Proposed dosing	FF / VI (100/25 mcg and 200/25 mcg) once daily
Pharmacometrics Reviewer	Jianmeng Chen, M.D., Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Sponsor	GlaxoSmithKline

The pop PK study report 2011n130480 on population PK analysis for FF and VI in asthmatic patients with FF/VI combination product was submitted to the original NDA204275, but has not been reviewed. This PM review will focus on report 2011n130480.

The same dose ranging studies had been submitted to support the dose selection of FF and VI for the original 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 is applicable to this efficacy supplement, and the pertinent information regarding dose selection from previous review was therefore adopted with minor changes.

SUMMARY OF FINDINGS

Key Review Questions

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

Has the dosing of FF/VI been adequately explored?

The dosing regimen of FF/VI has been thoroughly explored in Phase 2 trials. The dosing regimen for FF (100 and 200 mcg QD) was reviewed and approved under NDA205625. In order to support the dose selection for VI, two Phase 2 trials were conducted in asthma.

The 25 mcg dose of VI was selected on the basis of results from a Phase 2 dose-ranging study in subjects with asthma (Study B2C109575), which tested a range of VI doses (3, 6.25, 12.5, 25 and 50 mcg once daily). Based upon the primary endpoint trough FEV1 (Figure 4) and secondary endpoints (weighted mean FEV1 and others, Figure 6) as well as the safety profile, 25 mcg was the appropriate dose.

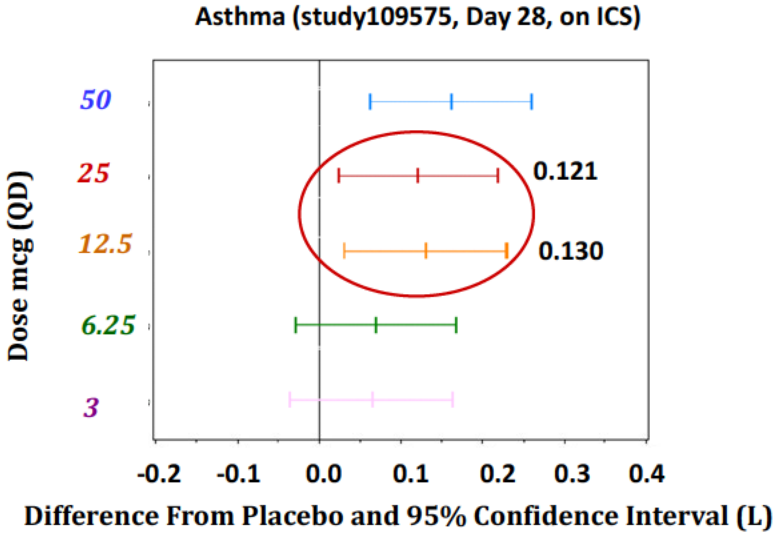


Figure 4. Effect of VI on lung function (trough FEV1) across doses ranging from 3 mcg to 50 mcg QD
(Source –Figure 3, Study HZA109575 report)

A study conducted in subjects with persistent asthma supported the comparability of once and twice daily dosing for VI, where the improvement of mean FEV1 (0-24h) was similar with VI 6.25 mcg twice daily and VI 12.5 mcg once daily dosing.

In conclusion, data for the nominal dose and dosing frequency in asthma appeared reasonable in support of VI 25 mcg QD.

Dosing in adolescent asthma patients is the same as adult patients for all approved ICS/LABA products in asthma, as listed below. Therefore, the same dosing regimens for FF/VI were assessed in pediatric patients 12-17yrs of age in phase III studies.

- fluticasone propionate+ salmeterol (Advair)
- budesonide+ formoterol (Symbicort)
- mometasone+formoterol (Dulera)

Are there any covariates that influence the systemic exposure of FF and VI?

With regard to FF, the only covariate found to be significant was race (East Asian, Japanese and South Asian) on inhaled clearance (CL/F). Based on the final model, the population mean estimate for CL/F was 185 L/h for a subject with asthma. Estimates of FF AUC(0-24) for East Asian, Japanese and South Asian subjects were on average 33% to 53% higher compared with subjects in other racial groups. 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.**

For VI, the population estimate for VI V1/F is predicted to be lower (81%) for those subjects with an Asian heritage (East Asian, Japanese, South East Asian) compared with subjects with asthma from a non-Asian heritage. As a result, VI Cmax is predicted to be 220 to 287% higher and AUC(0-24) comparable for those subjects from an Asian heritage compared with subjects with asthma from a non-Asian heritage. However, there was no evidence that the higher VI Cmax resulted in a greater effect on observed heart rate (change from baseline 5-20 minutes post-dose) compared with subjects with asthma from a non-Asian heritage. **For these exposure differences, no dosing adjustments are recommended.**

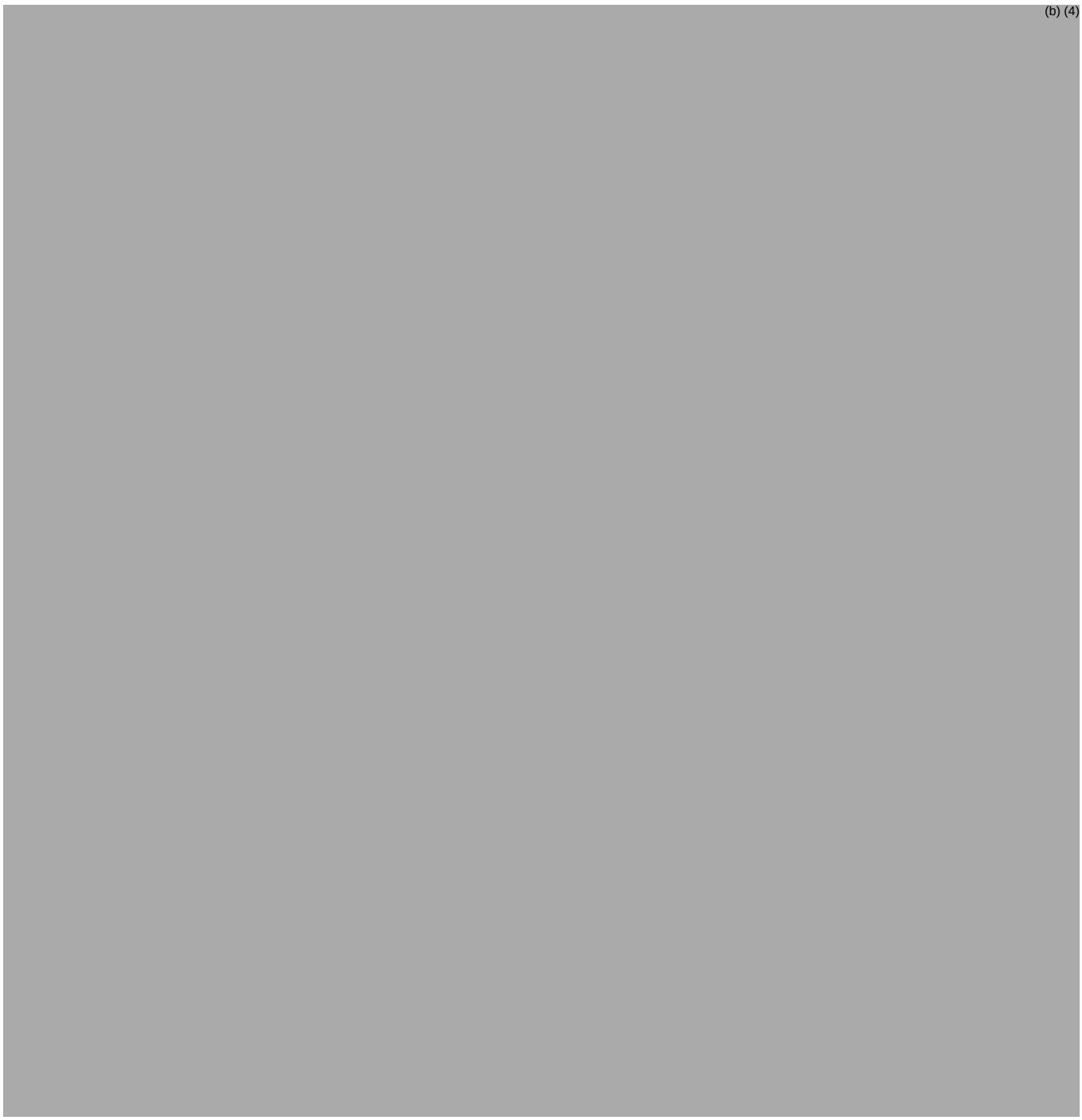
Recommendations

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.

(b) (4)



PERTINENT REGULATORY BACKGROUND

GlaxoSmithKline (GSK) submitted an efficacy supplement for use of BREO ELLIPTA (FF/VI 100/25 mcg and 200/25 mcg inhalation powder) for the maintenance treatment of asthma in patients aged 12 years and older. BREO ELLIPTA (FF/VI 100/25 mcg) has been approved for the maintenance treatment of COPD. FF was also approved in the US

as monotherapy for the treatment of asthma (ARNUITY ELLIPTA, 100 and 200 mcg, NDA205625). The proposed dose is one inhalation (FF/VI 100/25 mcg and 200/25 mcg) once daily.

GSK studied several different doses for FF as single entity and in combination with VI 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 was submitted to the US FDA for FF/VI on January 31, 2007. 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/VI.

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.

Table 9. Phase II Studies to Support Doses and Dose Regimen for FF/VI

Study Duration (Total N[1])	Baseline Lung Function Baseline Treatment (asthma studies only)	FF or VI Dose(s) (mcg)	Other Treatments and Doses (mcg)
FF efficacy and safety; FF dose ranging (asthmatic population)			
FFA109687 8 weeks (N=598)	FEV_1 % predicted 40-85% (AM) or 40-90% (PM) Non-corticosteroid controller or SABA with no ICS in 6 weeks prior to screening	FF 25 QD PM FF 50 QD PM FF 100 QD PM FF 200 QD PM	Placebo FP 100 BID
FFA109685 8 weeks (N=615)	FEV_1 % predicted 40-85% (AM) or 40-90% (PM) FP ≤125 mcg BID or equivalent ICS	FF 100 QD PM FF 200 QD PM FF 300 QD PM FF 400 QD PM	Placebo FP 250 BID
FFA109684 8 weeks (N=622)	FEV_1 40-85% (AM) or 40-90% (PM) predicted FP >100 to 250 mcg BID or equivalent ICS	FF 200 QD PM FF 400 QD PM FF 600 QD PM FF 800 QDPM	Placebo FP 500 BID
VI efficacy and safety; VI dose ranging (asthmatic population)			
B2C109575 28 days (N=607)	FEV_1 40-90% predicted FP ≤500 mcg BID or equivalent ICS	VI 3 QD PM[2] VI 6.25 QD PM[2] VI 12.5 QD PM[2] VI 25 QD PM[2] VI 50 QD PM[2]	Placebo[2]
VI efficacy and safety; VI dose ranging (COPD population)			
B2C111045[3] 28 days (N=602)	Post-bronchodilator FEV_1 ≥35-70% predicted Post-bronchodilator FEV_1/FVC ratio ≤0.70	VI 3 QD AM VI 6.25 QD AM VI 12.5 QD AM VI 25 QD AM VI 50 QD AM	Placebo
Once versus twice-daily dosing with FF (asthmatic population)			
FFA112202 28 days (N=190)	FEV_1 40-85% predicted Non-corticosteroid controller or SABA with no ICS in 8 weeks prior to screening	FF 200 QD PM FF 100 BID	Placebo FP 200 QD PM FP 100 BID
Once versus twice-daily dosing with VI (asthmatic population)			
HZA113310 7 days (N=75)	FEV_1 40-85% predicted FP ≤500 mcg BID or equivalent ICS	VI 6.25 QD PM[2] VI 6.25 BID[2] VI 12.5 QD PM[2] VI 25 QD PM[2]	Placebo[2]
Morning versus evening dosing with FF/VI (asthmatic population)			
HZA114624 14 days (N=26)	FEV_1 ≥60% predicted FP 100 to 250 mcg BID or equivalent ICS	FF/VI 100/25 QD AM FF/VI 100/25 QD PM	Placebo

Source: Clinical Overview for COPD, Table 4, page 26

RESULTS OF SPONSOR'S ANALYSIS

Dose selection

The dosing regimen for FF (100 and 200 mcg QD) was reviewed and approved under NDA205625. In order to support the dose selection for VI, two Phase 2 trials were conducted in asthma. The rationale for dosing regimen, including selection of dose and dosing frequency for VI is summarized below.

Dose for VI

The 25 mcg dose of VI was selected on the basis of results from a Phase 2 dose-ranging study in subjects with asthma (Study B2C109575), which tested a range of VI doses (3, 6.25, 12.5, 25 and 50 mcg once daily). Based upon the primary endpoint trough FEV1 (Figure 5) and secondary endpoints (weighted mean FEV1 and others, Figure 6) as well as the safety profile, 25 mcg was the appropriate dose.

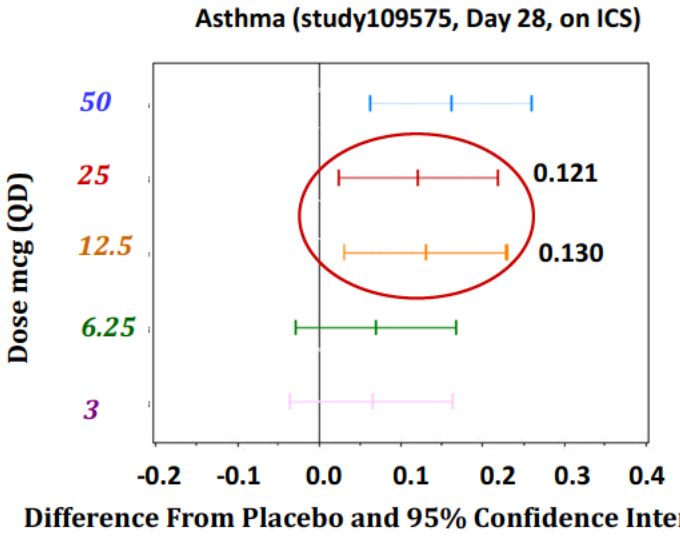


Figure 5. Effect of VI on lung function (trough FEV1) across doses ranging from 3 mcg to 50 mcg QD

(Source –Figure 3, Study HZA109575 report)

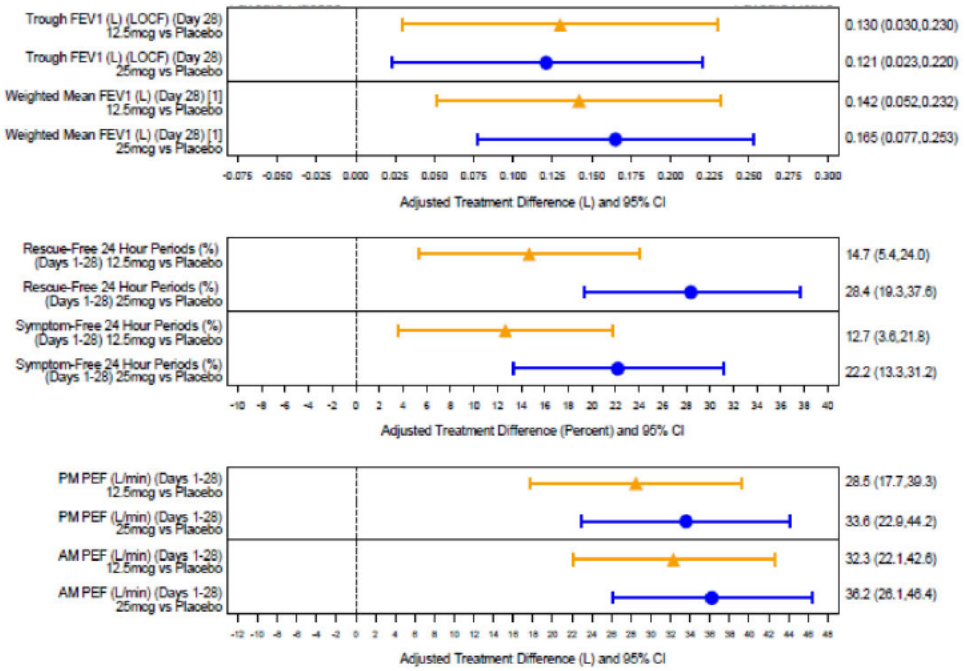


Figure 6. Primary and Secondary Endpoints – Comparison of VI 25 (ICS) and VI 12.5 (ICS) with Placebo in Subjects with Asthma (Study B2C109575, ITT Population)

(Source –Figure 3, Asthma clinical overview)

Dose frequency for VI

HZA113310 in subjects with persistent asthma compared once and twice daily dosing for VI. Figure 7 demonstrates that the improvement of weighted mean FEV1 (0-24h) was similar with VI 6.25 mcg twice daily and VI 12.5 mcg once daily dosing.

Change from Baseline FEV1 (L) Over Time on Day 7

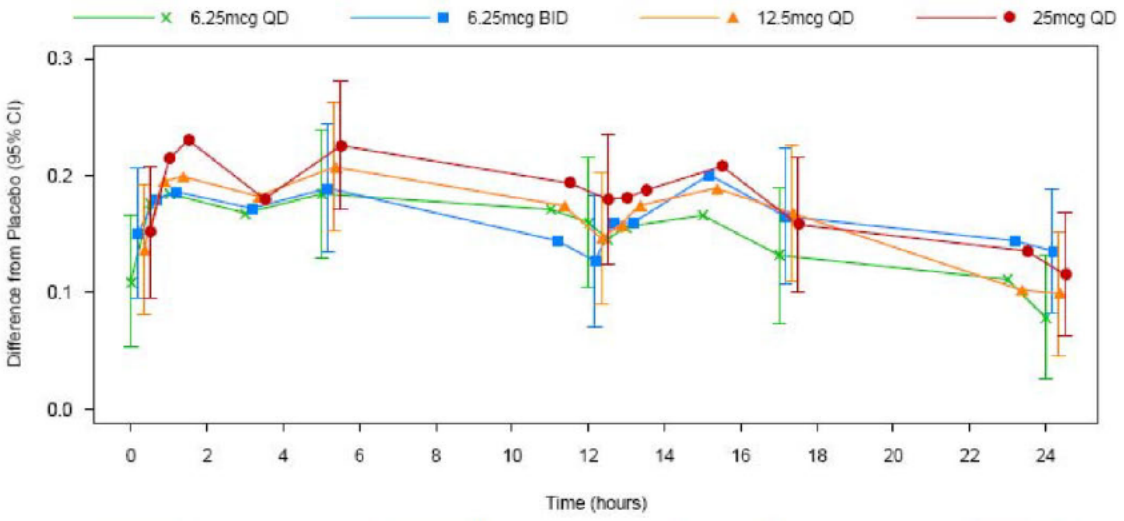


Figure 7. Effect of VI dosing on FEV1 in subjects with persistent asthma
(Source – Figure 6.13, Study HZA113310 report)

Dose for VI in patients 12-17 yrs of age

In study B2C109575 which tested a range of VI doses (3, 6.25, 12.5, 25 and 50 mcg once daily), 27 subjects [4%] were 12 - 17 years of age: 7 in the placebo group, 2 in the 3 µg group, 2 in the 6.25 µg group, 7 in the 12.5 µg group, 5 in the 25 µg group, 4 in the 50 µg group. Due to limited number of patients 12-17 years old, it is not clear whether the dose response is the same in adolescent subjects as in adult subjects in asthma.

All phase II dose ranging studies for VI included patients 12 years and older. Also, dosing in adolescent asthma patients is the same as adult patients for all approved ICS/LABA products in asthma, as listed below. Therefore, the same dosing regimens for FF/VI were assessed in pediatric patients 12-17yrs of age as in adult patients in phase III studies.

- fluticasone propionate+ salmeterol (Advair)
- budesonide+ formoterol (Symbicort)
- mometasone+formoterol (Dulera)

Summary

In conclusion, data for the nominal dose and dosing frequency in asthma appeared reasonable in support of VI 25 mcg QD in patients 12 years and older. While assessment of VI's effect on trough FEV1 in asthma suggested that a lower dose of VI 12.5 mcg QD or 6.25 mcg BID might also be efficacious, a comparison of the serial FEV1 time curves showed a numerically greater effect for the 25 mcg QD dose. Therefore, the selection of VI 25 mcg QD for further study in the confirmatory trials in asthma appeared reasonable.

Reviewer's comments: The Pharmacometrics Reviewer concurs with the dosing regimens selected for the Phase 3 trials.

Population PK Meta-Analysis for FF/VI in Subjects with Asthma

Methods

Four Phase II and III (HZA106827, HZA106829, HZA106839 and HZA106851) multicentre, randomized, double-blind, placebo or active comparator-controlled studies in subjects with asthma were included in the FF and VI meta-analyses (Table 10). A further Phase I randomized, repeat-dose, placebo-controlled investigation (HZA102936), with intense PK sampling, was included to support population PK modeling. Population PK models were developed to describe the FF and VI systemic exposure in subjects with asthma. Data from five studies conducted in subjects with asthma and healthy subjects contributed to the meta-analysis for FF (n=1295; 9283 observations) and VI (n=932; 6934 observations). Four of the five studies included in the meta-analysis were Phase II and IIIa studies conducted in subjects with asthma and provided the vast majority of the observations (94% for FF and 92% for VI).The attributes of each trial are described in Table 10 below.

Table 10. Study Designs used for the Population PK of FF and VI in asthma

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
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

The Sponsor reported high proportion of records reporting both FF and VI concentrations below the lower limit of quantification (LLQ; 10 or 20 pg/mL) particularly at the lower doses of FF in the Phase III studies and beyond 4 hours post-dose following VI, modeling the concentration-time data from the Phase II/III data alone to appropriately characterize the PK profile of each molecule 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) and also the highest Phase III dose (200/25) was required to achieve an appropriate structural model to describe the data. 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. Supporting application interfaces for data handling, exploratory diagnostics and simulation included Xpose V4 [Jonsson, 1999], R (The R Foundation for Statistical Computing Version 2.10.1 or above) and WinNonLin 5.2 (Pharsight Corporation).

The covariates considered for evaluation of effects on FF and VI pharmacokinetics included population (healthy subjects or subjects with asthma), age, weight, height, sex, ethnicity (hispanic or latino/ non-hispanic or latino), race, BMI, PFEV (FEV1 % predicted) and study. Due to limited numbers of subjects in some of the race categories subjects were grouped and categorized as 'RACE1' as follows: RACE1=1 – White Caucasian; RACE1=2 – East Asian, Japanese and South Asian; RACE1=3 – African American/African, White Arabic, American Indian/Native Alaskan and Mixed. The effects of concomitant cytochrome P450 3A4 inhibitor medication were to be evaluated but since <1% of the population in each dataset received strong 3A4 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 [Post, 2008]. This procedure was conducted as follows: at least 200 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. In addition the observed proportion of the BLQ data was plotted with the model prediction interval for proportion of the BLQ data to visually assess the concordance between the simulated and observed BLQ data.

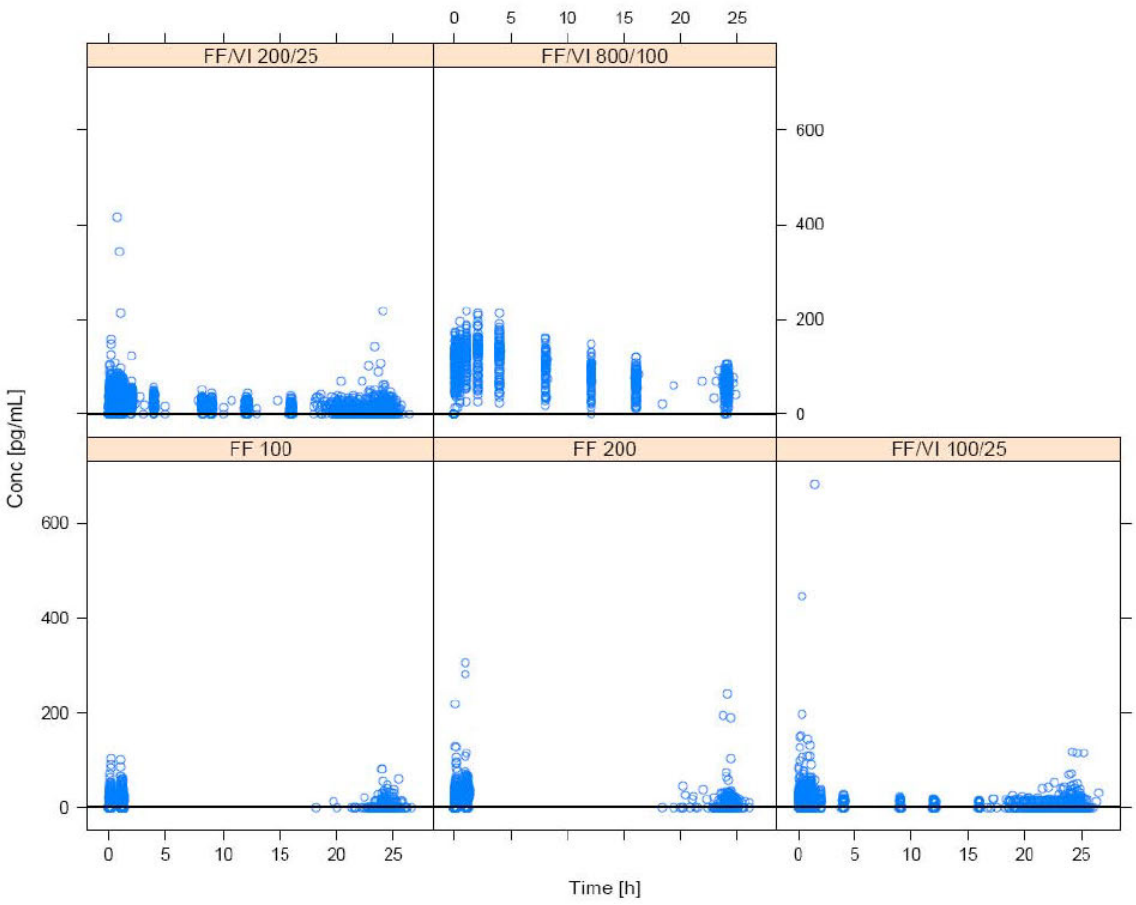
Individual AUC(0-24) was derived as the ratio of nominal dose divided by individual post-hoc estimate of CL/F from the final population PK model. VI Cmax for each subject was derived from the simulated VI concentration-time profile using the parameter estimates from the final model.

Results

FF

The FF population PK analysis dataset comprised of 1295 subjects (healthy subjects or subjects with asthma). The vast majority were subjects with asthma (94%). Healthy subjects represented 6% of the FF population PK population. The 1295 subjects provided a total of 9247 sample records of which 29.5% were reported as NQ (<LLQ 10 pg/mL). Concentration vs. time profiles for FF can be viewed in the figure below.

Figure 8. FF Concentration vs. Time Profile



(source: Figure 1, pop PK report 2011N130480)

A two compartment linear model, with first order absorption and first order elimination was found to describe the FF concentration-time data. The final population PK model for FF incorporated the effect of race on CL/F. The population parameters from the final model are shown below in Table 11. Goodness of fit plot for the final model is presented in Figure 9.

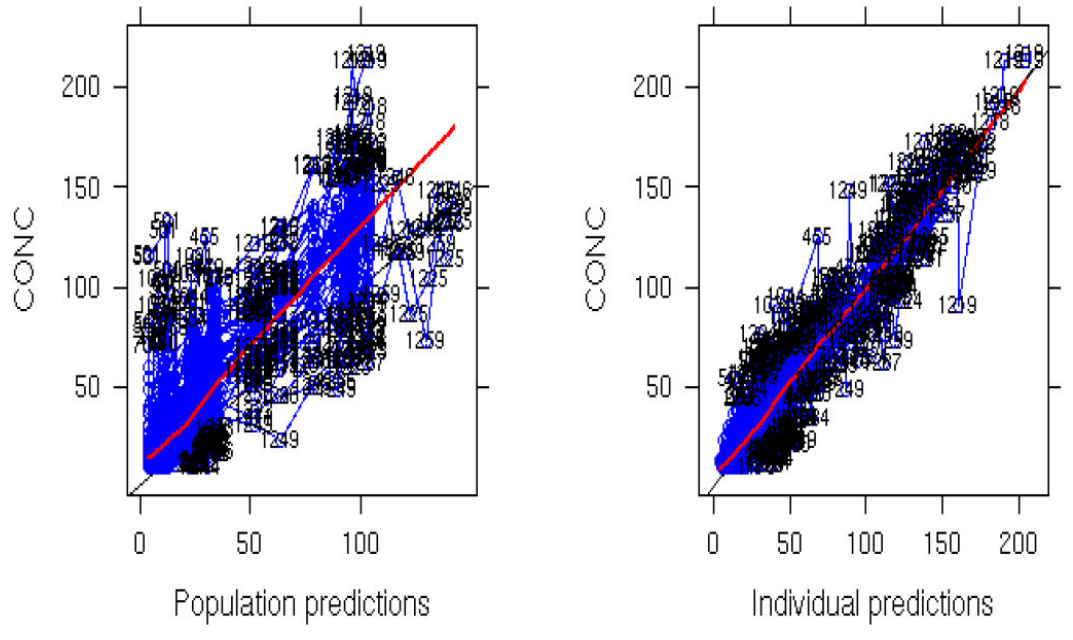
Table 11. Parameter estimates for the Final FF Population PK Model

Parameter	Ln Estimate [95% CI]	Estimate [95% CI]
CL/F (RACE1=1 and 3)	5.21 [5.16, 5.26]	183 [174, 192]
RACE1=2 on CL/F	-0.331 [-0.451, -0.211]	0.718 [0.637, 0.810]
V2/F [L]	0.225 FIXED	1.25 FIXED
Q/F [L/h]	5.67 FIXED	290 FIXED
V3 /F [L]	5.14 [4.91, 5.37]	171 [136, 215]
KA [h^{-1}]	-2.96 [-3;02, -2.90]	0.0518 [0.0488, 0.0550]

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 Asian; RACE1=3 – African American, Asian Central, White Arabic, American Indian/Native Alaskan and Other

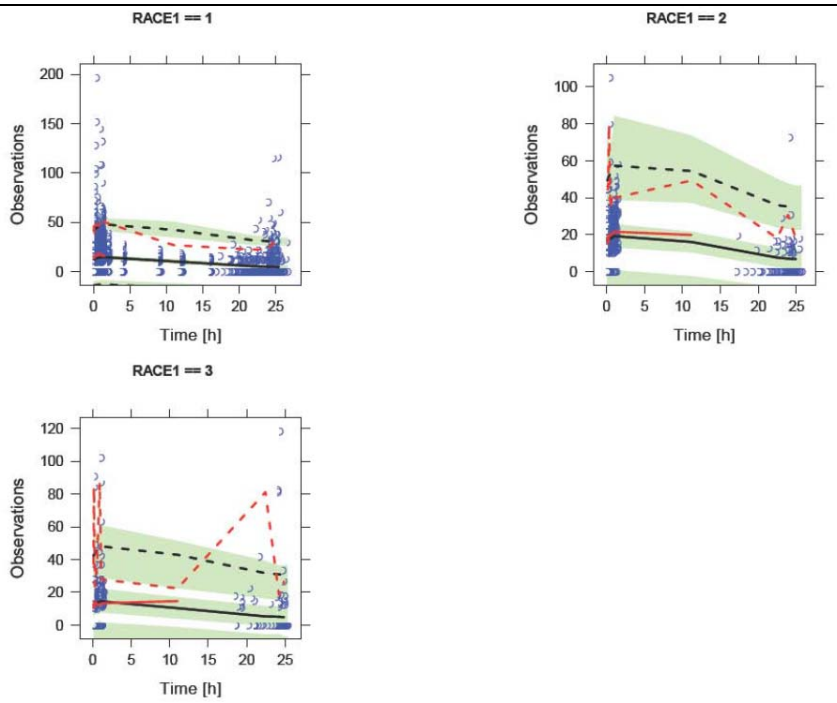
(source: Table 9, pop PK report 2011N130480)

Figure 9. Goodness of Fit plots for the Final FF Population PK Model



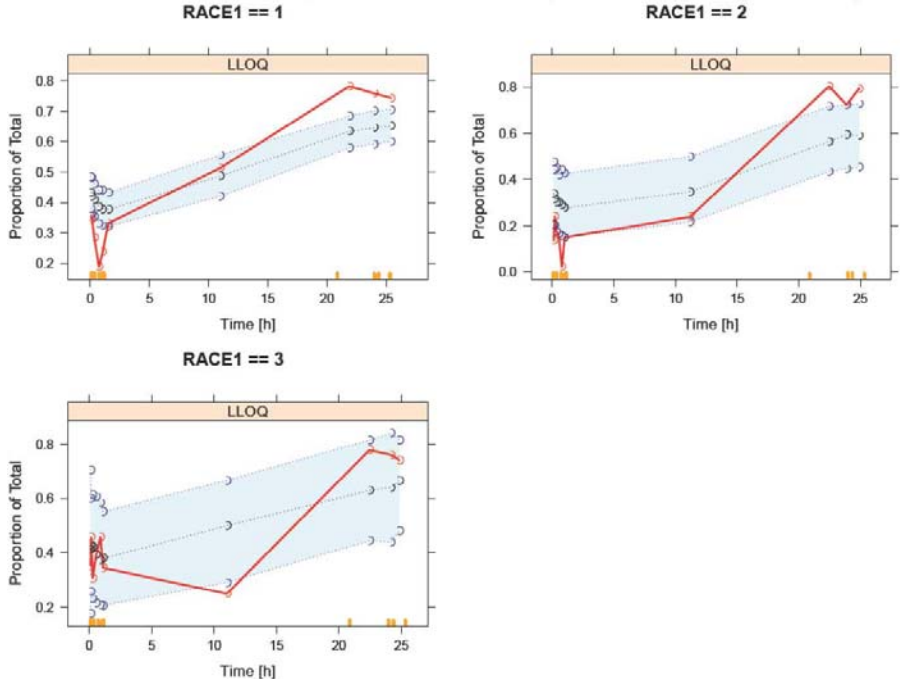
The VPC for PK (**Figure 10**) showed that the majority of the data is captured in the prediction interval encompassing 90% of the population as indicated by the 5th and 95th percentile boundary, indicating that the model was reasonable for this asthma dataset. In addition, the observed proportion of the BLQ data was plotted with the model prediction interval to visually assess the concordance between the simulated and observed BLQ data (Figure 11).

Figure 10. VPC for the Final FF Population PK Model (by Race). Points represent observed values while the black lines represent the model predicted median and corresponding 5th and 95th percentiles (black dashed lines). Observed median (solid red line) and 5th and 95th percentiles are in red dashed lines. The prediction intervals of the median, 5th and 95 percentiles are depicted in green shading.



(source: Figure 1, pop PK report 2011N130480)

Figure 11. VPC for the model prediction of BQL data (by Race) for FF 100 mcg. The dashed lines represent the model predicted median and corresponding 5th and 95th percentiles. Observed median is in solid red line. The prediction intervals of the median, 5th and 95 percentiles are depicted in blue shading.



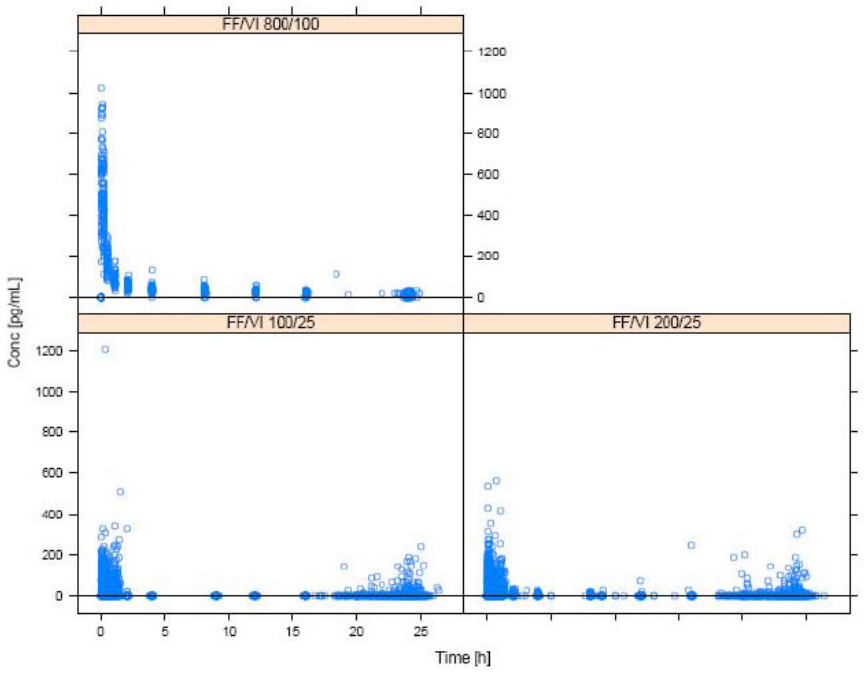
(source: Figure 10.6, pop PK report 2011N130480)

Reviewer comment: As shown in Figure 25, the 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, there is a trend toward under prediction of proportion of BLQ data at later time points for FF100 mcg. In other words, concentration at later time points was over predicted in all races for FF 100 mcg.

VI

The VI population PK analysis dataset comprised of 6934 observations from 932 subjects (healthy subjects or subjects with asthma). The vast majority of the VIPK population came from subjects with asthma (92%). Healthy subjects represented 8% of the VI PK population. The majority of observations (56%) were reported as NQ (<LLQ 10 to 50 pg/mL). Concentration vs. time profiles for VI can be viewed in Figure 12.

Figure 12. VI Concentration vs. Time Profile



(source: Figure 2, pop PK report 2011N130480)

A three-compartment linear model, with zero-order absorption and 1st order elimination was found to adequately describe the VI concentration-time data. The final population PK model incorporated the effect of study (HZA106851) on CL/F and race (RACE1=2) and study (HZA106851) on V1/F for subjects with asthma. The population parameters from the final model are shown in **Table 12**. The VPC for the final model is presented in Figure 13.

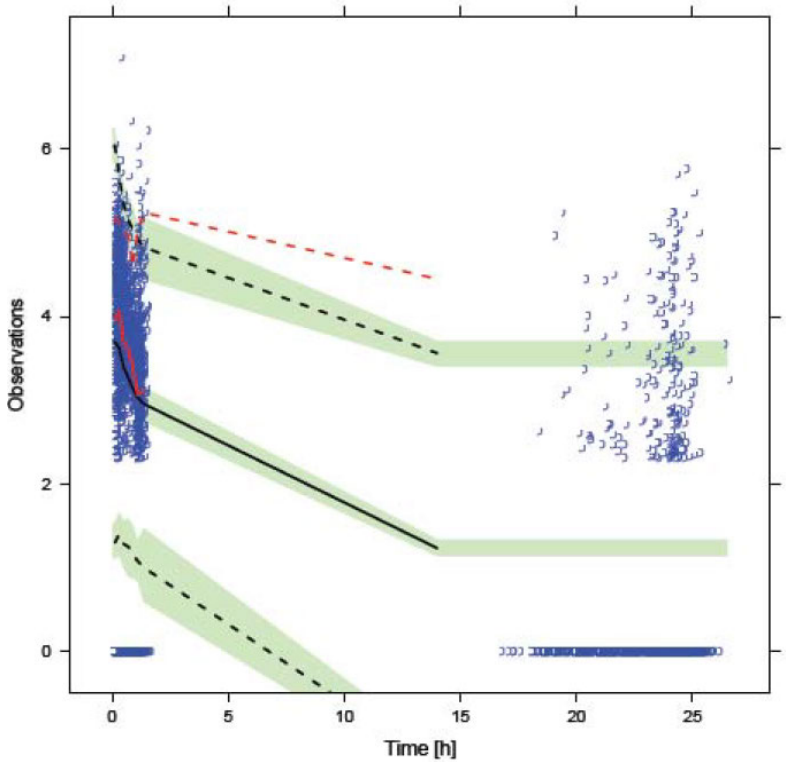
Table 12. Parameter estimates for the Final VI Population PK Model

Parameter	Ln Estimate [95% CI]	Estimate [95% CI]
CL/F (L/h)	4.90 [4.84, 4.96]	134.3 [126.5, 142.6]
Study1 on CL/F	0.659 [0.490, 0.828]	1.93 [1.63, 2.29]
V1/F (HVT) (L)	5.08 FIXED	160.8 FIXED
V1/F (Asthma) (L)	6.59 [6.45, 6.73]	727.8 [632.7, 873.1]
Study1 on V1/F (Asthma)	-0.776 [-1.13, -0.425]	0.460 [0.323,0.654]
Race2 on V1/F (Asthma)	-1.68 [-2.18, -1.18]	0.186 [0.113, 0.307]
Q2/F (L/h)	5.54 FIXED	254.7 FIXED
V2 /F(HVT) (L)	6.25 FIXED	518.0 FIXED
V2/F (Asthma) (L)	4.53 [4.34, 4.72]	92.8 [76.7, 112.2]
Q3/F (L/h)	4.91 FIXED	135.6 FIXED
V3/F (L/h)	7.73 FIXED	2275.6 FIXED
D1 (HVT) (h)	-2.52 [-2.65, -2.39]	0.08 [0.07, 0.09]
D1 (Asthma) (h)	-3.15 [-3.47, -2.83]	0.04 [0.03, 0.06]

CL/F=inhaled clearance; V1/F = volume of central compartment; Q2/F & Q3/F= intercompartmental clearances; V2/F & V3/F= volumes of peripheral compartment, D1=input duration , CI=confidence interval
Study1=HZA106851, Race2= East Asian, Japanese and South East Asian

(source: Table 15, pop PK report 2011N130480)

Figure 13. VPC for the Final VI Population PK Model. Points represent observed values while the black lines represent the model predicted median and corresponding 5th and 95th percentiles (black dashed lines). Observed median (solid red line) and 5th and 95th percentiles are in red dashed lines. The prediction intervals of the median, 5th and 95 percentiles are depicted in green shading.



Sponsor's Conclusions

The pharmacokinetics (PK) of FF was well described by a two-compartment model with 1st order absorption and 1st order elimination. The only covariate found to be significant was race (East Asian, Japanese and South Asian) on inhaled clearance (CL/F). Based on the final model, the population mean estimate for CL/F was 185 L/h for a subject with asthma. Estimates of FF AUC(0-24) for East Asian, Japanese and South Asian subjects were on average 33% to 53% higher compared with subjects in other racial groups. This finding is consistent with results seen previously in healthy subjects and COPD patients. 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.

The pharmacokinetics (PK) of VI was well described by a three-compartment model with zero-order absorption. Significant covariates were study (HZA106851) on VI inhaled clearance (CL/F) and volume of the central compartment (V1/F) and race (RACE1=2; East Asian, Japanese or South Asian heritage) on V1/F.

Based on the final model, the population estimate for VI V1/F is predicted to be lower

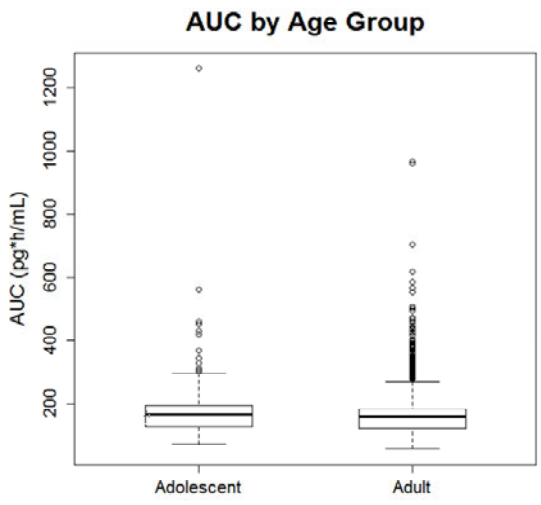
(81%) for those subjects with an Asian heritage compared with subjects with asthma from a non-Asian heritage. As a result, VI Cmax is predicted to be 220 to 287% higher and AUC(0-24) comparable for those subjects from an Asian heritage compared with subjects with asthma from a non-Asian heritage. However, there was no evidence that the higher VI C_{max} resulted in a greater effect on observed heart rate compared with subjects with asthma.

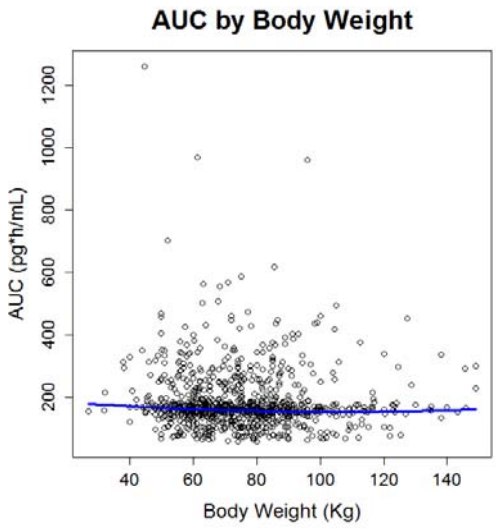
The typical value of VI CL/F in study HZA106851 (n=110 subjects; 13% of the VIPK population) is predicted to be 93% higher than the typical value for the other studies conducted in subjects with asthma (HZA106839, HZA106827 and HZA106829). The reason for this marked study difference is unclear. The may just reflect between-study variability

Reviewer's comments: *A rigorous analysis assessing the of the covariate effects on VI and FF exposure was performed using population PK methodology. 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 and VI resulted in similar results with similar parameter estimates. Therefore, the reviewer concludes the analysis, and the corresponding conclusions and interpretations, presented by the sponsor is reasonable.*

To address the safety concern of LABA use in pediatric patients, this reviewer assessed the impact of age and weight on systemic exposure of VI in asthmatic patients (Figure 14, exclude study 102936). There was no difference in systemic exposure to VI in adolescent (12-17 years) subjects with asthma compared with adult (≥18 years) subjects with asthma.

Figure 14. VI AUC (at steady state) in asthmatic patients Left plot – AUC vs age, Right plot – AUC vs Body Weight (study HZA106827, HZA106829, HZA106839, HZA106851)





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2. FF/VI PK/PD in healthy Chinese subjects

Trial # HZA115199

Title: A randomized, double-blind, placebo-controlled, four-way crossover study to evaluate and compare the pharmacodynamics and pharmacokinetics of fluticasone furoate /vilanterol in different dose combinations (50/25mcg, 100/25mcg and 200/25mcg) after single and repeat dose administration from a Dry Powder Inhaler in healthy Chinese subjects

Objectives:

Primary objective: PD effects. To evaluate the systemic steroid pharmacodynamics (PD) effects (serum cortisol 24 hour weighted mean on Day 7) of fluticasone furoate (FF) and systemic β-adrenergic PD effects (ECG maximum QTcF 0-4h and whole blood potassium 0-4h on Day 1 and Day 7) of vilanterol (VI) after a single and repeat dose administration of FF/VI inhalation powder in different dose combinations in healthy Chinese subjects.

Secondary objective: PK effects

Study design and treatment schedule:

A single center, double-blind, placebo-controlled, four-way cross over, randomized, single and repeat dose study. Each of the 16 subjects participated in four treatment periods as described in Figure 1 and received the following treatments. Each treatment lasted for 7 days:

- FF/VI 50/25
- FF/VI 100/25
- FF/VI 200/25
- Placebo

- **Results**

PK results

The FF systemic exposure observed in healthy Chinese subjects in this study was similar to that observed in healthy Chinese subjects administered FF 200 mcg in the study HZA113477 conducted in Australia (Table 19). In the study HZA113477, following inhalation FF systemic exposure was higher in healthy East Asian than that in Caucasian subjects.

Table 19. Summary of FF Plasma Pharmacokinetic Parameters in two studies for Asian and Caucasian subjects

Study / Treatment	Population	N	Cmax (pg/mL)	AUCss[1] /AUC(0-24) (pg.h/mL)
HZA 115199 FF/VI 200/25	Chinese	15	55.5 (49.4, 62.3)	691 (620, 770)
HZA113477 FF 200	Chinese	20	66.9 (57.5, 77.9)	680[2] (603, 767)
	Korean	20	72.3 (65.9, 79.3)	629[3] (566, 698)
	Japanese	20	55.7 (46.6, 66.5)	561[4] (454, 694)
	Caucasian	19	41.1[2] (32.8, 51.5)	541[5] (440, 666)

CI = confidence interval;
1.AUCss represents AUC(0-24) in HZA115199.
2. n=18 3.n=19 4.n=16 5.n=9
(Source – Table 18, Study HZA115199 report)

The VI PK parameters observed for VI in these healthy Chinese subjects are similar to those seen in non-Chinese healthy subjects, including Japanese healthy subjects (Table 20), which indicated no PK differences in healthy Chinese subjects compared with non-Chinese healthy subjects studied in the global program. In healthy Chinese subjects there was no evidence for the difference in VI PK parameters across the three FF/VI treatments (FF/VI 50/25, 100/25 and 200/25 mcg). This finding is consistent to the VI equivalence demonstrated in healthy non-Chinese subjects across the same dose strengths [Allen, 2013a].

Table 20. Summary of VI Plasma Pharmacokinetic Parameters across studies in healthy subjects

Study / Treatment	Day	Population	N	Cmax (pg/mL)	AUC(0-t') (pg.h/mL)	t' (h)
HZA 115199						
FF/VI 50/25	7	Chinese	15	155 (136,178)	73.0 (65.4,81.4)	1.5
FF/VI 100/25			15	151 (132, 174)	66.4 (56.0, 78.8)	1.5
FF/VI 200/25			15	157 (136, 180)	72.6 (63.9, 82.6)	1.5
DB1112017 VI 25	7	Japanese	12	310 (276, 349)	123 (109, 140)	4
HZA111789 FF/VI 200/25	7	Caucasian	9	247 (195, 312)	306 (254, 369)	8
HZA113970 FF/VI 200/25	7	Caucasian	9	153 (56.4, 415)	190 (99, 368)	8
HZA105548 FF/VI 200/25	7	Western[1]	18	120 (91.5, 158)	76.1 (47.1, 123)	2
HZA102936 FF/VI 200/25	7	Western[2]	74	115 (102, 130)	85.0[3] (71.0, 102)	24
DB2114635[4] UMEC/VI 125/25	10	Western[5]	75	340[6] (307, 376)	131[6] (120, 143)	1
DB2113950[4] UMEC/VI 500/25	8	Western[7]	16	230[8] (175, 302)	78.3[8] (52.2, 118)	1

(Source – Table 19, Study HZA115199 report)

PD results

In healthy Chinese subjects there was no statistically significant effect of FF/VI 50/25 mcg on 24 hour weighted mean serum cortisol compared with placebo while statistically significant decreases of 15% and 25% were seen with FF/VI 100/25 and 200/25 mcg, respectively (Table 21).

Table 21. Analysis of Serum Cortisol Weighted Mean 0–24 h (ng/mL) on Day 7

Treatment Comparison **TEST** vs **REF**	Adjusted Geometric Mean **TEST**	Adjusted Geometric Mean **REF**	Ratio of Adjusted Geometric Mean (90% CI)
FF/VI 50/25 vs Placebo	39.455	41.260	0.956 (0.890, 1.028)
FF/VI 100/25 vs Placebo	34.970	41.260	0.848 (0.789, 0.911)
FF/VI 200/25 vs Placebo	30.989	41.260	0.751 (0.699, 0.807)

(Source – Table 14, Study HZA115199 report)

In some of the comparisons with placebo, slight increases in QTcF (Table 22) and slight decreases in whole blood potassium (Table 23) were seen with active FF/VI treatments in healthy Chinese subjects.

Table 22. Analysis of Maximum QTcF 0-4 h (msec)

Treatment Comparison **TEST** vs **REF**	Day	Adjusted Mean **TEST**	Adjusted Mean **REF**	Differences in Adjusted Means (90% CI)
FF/VI 50/25 vs Placebo	1	411.0	409.6	1.42 (-1.88, 4.72)
	7	411.9	408.2	3.69 (0.60, 6.78)
FF/VI 100/25 vs Placebo	1	412.8	409.6	3.25 (-0.05, 6.55)
	7	413.5	408.2	5.25 (2.16, 8.35)
FF/VI 200/25 vs Placebo	1	410.0	409.6	0.46 (-2.84, 3.76)
	7	409.8	408.2	1.53 (-1.56, 4.62)

(Source – Table 15, Study HZA115199 report)

Table 23. Analysis of Whole Blood Potassium Weighted Mean 0-4 h (mmol/L)

Treatment Comparison **TEST** vs **REF**	Day	Adjusted Mean **TEST**	Adjusted Mean **REF**	Differences in Adjusted Means (90% CI)
FF/VI 50/25 vs Placebo	1	3.845	3.963	-0.118 (-0.192, -0.043)
	7	3.888	3.975	-0.087 (-0.159, -0.015)
FF/VI 100/25 vs Placebo	1	3.939	3.963	-0.024 (-0.099, 0.050)
	7	3.934	3.975	-0.041 (-0.114, 0.031)
FF/VI 200/25 vs Placebo	1	3.905	3.963	-0.058 (-0.133, 0.017)
	7	3.887	3.975	-0.088 (-0.160, -0.015)

(Source – Table 16, Study HZA115199 report)

- **Conclusions**

The exposure of FF is higher in Chinese population compared to Caucasian population.

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

NDA/BLA Number	**204275/S001**	**Brand Name**	**BREO ELLIPTA**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Fluticasone Furoate/Vilanterol Inhalation Powder**
Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**ICS/Inhaled 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 NDPI**
Pharmacometrics Reviewer/Team Leader	**Jianmeng Chen MD, Ph. D/ Liang Zhao Ph.D**	**Dosing Regimen**	**FF/VI (100/25 mcg, 200/25 mcg)**
Date of Submission	**6/30/2014**	**Route of Administration**	**Inhalation**
Estimated Due Date of OCP Review	**3/26/2015**	**Sponsor**	**GSK**
PDUFA Due Date	**4/30/2015**	**Priority Classification**	**Standard**

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**			**Updated based on pop PK report in asthma patients**
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Transporter specificity:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**2**		(b) (4) HZA115199, Healthy Chinese subjects (HPA axis)
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**X**	**1**		pop PK report in asthma patients
II. Biopharmaceutics				
Absolute bioavailability				
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				
Genotype/phenotype studies				
QT studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		

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/s/

JIANMENG CHEN
03/26/2015

YANING WANG
03/26/2015

SURESH DODDAPANENI
03/26/2015