

CLINICAL PHARMACOLOGY REVIEW

NDA	205625/S-005 (SDN 234)
Submission Date	07/21/2017
Proposed Brand Name	ARNUITY ELLIPTA
Generic Name	Fluticasone furoate (FF) Inhalation Powder
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OCP Division	Clinical Pharmacology 2
OND Division	Pulmonary, Allergy, and Rheumatology Products
Applicant	GlaxoSmithKline (GSK)
Formulation; Strength(s)	Micronized FF and lactose monohydrate; administered via Ellipta® DPI device
Approved Indication	Treatment of asthma in patients aged 12 years and older
Approved Dosage Regimen	100 mcg or 200 mcg once daily via DPI
Proposed Indication	Treatment of asthma in patients aged 5 to younger than 12 years
Proposed Dosage Regimen	50 mcg once daily via Ellipta® DPI

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1 EXECUTIVE SUMMARY

GSK has submitted a pediatric supplement for NDA 205625 seeking approval of Fluticasone Furoate Inhalation Powder (ARNUITY ELLIPTA) for maintenance treatment of asthma as prophylactic therapy in patients aged 5 years and older.

Fluticasone Furoate Inhalation Powder (hereafter referred to as FF) is a corticosteroid for oral inhalation to be administered via the ELLIPTA inhaler (a dry powder inhaler [DPI]). FF was approved at doses of 100 mcg and 200 mcg administered once daily (QD) for the treatment of asthma in adults and adolescents aged 12 years and older on August 20, 2014. For the treatment of pediatric subjects with asthma, the proposed dosage is FF 50 mcg QD.

The Clinical Pharmacology information of this supplemental NDA consist of population pharmacokinetic (PK) data (from the single pivotal Phase IIb/III dose ranging and efficacy trial [HZA106855] and two Phase IIa PK/PD studies [(HZA 102942 and 112777)]; and a dedicated HPA-Axis study in patients with asthma aged 5 to 11 years (HZA107118). The pharmacokinetics of FF in pediatric subjects with asthma was consistent with previously observed in adults and adolescent asthma population. There was no relevant effect of age on the apparent clearance of FF. At the proposed dosage (i.e., FF 50 mcg QD), no clinically relevant changes in adrenal function, as measured by 24-hour serum cortisol profiles, were observed. No dose adjustment is recommended for any intrinsic factor in pediatric asthma population.

1.1 Recommendations

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

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

- FF systemic exposure in pediatric subjects with asthma (5 to 11 years old), in terms of AUC and C_{max} , was dose proportional and similar to adult and adolescent population with asthma (Original NDA).
- No dose adjustment for the proposed dosage, 50 mcg QD, is recommended for any intrinsic factors. Patient intrinsic factors including body weight, age (5 to 11 years old), gender, and race were not found to have a clinically meaningful effect on FF pharmacokinetics in pediatric subjects with asthma.
- There was no evidence of serum cortisol reduction at the proposed dosage of 50 mcg QD in subjects with asthma. A 6-week, double-blind, placebo- and active-controlled dedicated study in children 5 to 11 years of age evaluated the effect of the proposed dosage (i.e., 50 mcg QD) on the HPA axis (Study HZA107118). Following 6-week once daily oral inhalations of FF 50 mcg, the FF treatment group demonstrated to be non-inferior to placebo based on the primary endpoint of derived serum cortisol weighted mean (0-24 hour), as the lower limit of the 95% CI was greater than 0.80 (95% CI: 0.8096, 1.0620).

2 QUESTION-BASED REVIEW

2.1 What are the clinical studies submitted to support this supplemental NDA?

Three clinical and two clinical pharmacology studies have been completed as part of the pediatric asthma clinical development program. These studies are:

- HZA106855: Phase IIb/III pivotal, dose-ranging, parallel group efficacy and safety study in the target population (575 children uncontrolled on non-ICS asthma medication and/or low dose ICS) to support the selection of the FF dose for the pediatric development program.
- HZA107112: Two-way cross-over study of short-term lower leg growth;
- HZA107118: Placebo-controlled, parallel group study evaluating the effect of FF on the hypothalamic-pituitary-adrenocortical (HPA) axis.
- HZA102942 and HZA 112777: Phase IIa two-way cross-over, safety, tolerability, PD and PK clinical pharmacology studies. These two studies were submitted and reviewed as part of the original NDA.

There is also an ongoing Phase IV study HZA114971 which is a randomized, double-blind, placebo-controlled, parallel-group study investigating the effects of a 1-year regimen of orally inhaled FF 50 mcg on growth velocity in pre-pubertal, pediatric subjects with asthma.

This review will focus on the dedicated HPA-Axis study (HZA107118) and population PK analysis using the PK data from studies HZA106855, HZA102942 and HZA112777. A tabular listing of clinical studies conducted in support of this supplemental NDA is presented in Table 1.

Table 1. Overview of ARNUITY ELLIPTA Pediatric Clinical Development Program

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration) Dose in mcg unless otherwise specified	Total No. of Subjects by Group Entered ^{1/} / Completed
PK and Initial Tolerability Studies					
HZA102942 (YM2010/00094/01)	Safety, tolerability, PK, PD	R, DB, PC, XO	Pediatric subjects, 5 to 11 years of age, with asthma; PEF ≥80%.	FF 100 and Placebo; Once daily; IH; 14 days	27 randomized/ 22 completed
PD and PK/PD Studies					
HZA112777 (2011N127524_01)	Safety, tolerability, PK, PD	R, DB, XO	Pediatric subjects, 5 to 11 years of age, with asthma; PEF ≥75%.	FF/VI 100/25 and FF 100; Once daily; IH; 14 days	26 randomized/ 23 completed
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication					
HZA107112 (2016N270107_00)	Effect of FF on short-term growth in pediatric subjects	R, DB, PC, XO	Pediatric subjects, 5 to 11 years of age, with asthma; FEV ₁ ≥80%	FF 50 or Placebo; Once daily; IH, 14 days	FF 50: 60 randomized/ 58 completed Placebo: 60 randomized/ 60 completed
HZA107118 (2016N293062_00)	Effect of FF on HPA-axis system	R, DB, PC, PG	Pediatric subjects, 5 to 11 years of age, with asthma; cACT Score of >19	FF 50 or Placebo; Once daily, IH, 42 days	FF 50: 56 randomized/ 54 completed Placebo: 55 randomized/ 53 completed
HZA106855 (2013N185014_00)	Pediatric dose ranging, safety and efficacy	R, DB, DD, PC, AC, PG	Pediatric subjects, 5 to 11 years of age, with asthma; PEF 60 to 90%.	FF 25, 50, or 100 once daily, FP 100 twice daily or Placebo; IH; 84 days	FF 25: 118 randomized/ 94 completed FF 50: 120 randomized/ 87 completed FF 100: 118 randomized/ 85 completed FP 100: 118 randomized/ 89 completed Placebo: 119 randomized/ 66 completed
Ongoing Studies					
HZA114971 (NA)	Effect of FF on growth velocity	R, DB, PC, PG	Pediatric subjects, 5 to <9 years (males) or <8 years (females) of age, with asthma; FEV ₁ ≥60% to ≤95%; cACT >19	FF 50 or Placebo; IH; 365 days	FF 50: 225 planned Placebo: 225 planned

(Source: Module 2.7.6 Synopses of Individual Studies-Pediatric, Table 1)

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 is a small molecule drug with a molecular weight of 538.6 g/mol, and empirical formula of C₂₇H₂₉F₃O₆S. FF molecular structure is shown in Figure 1. FF is practically insoluble in water.

Fluticasone furoate

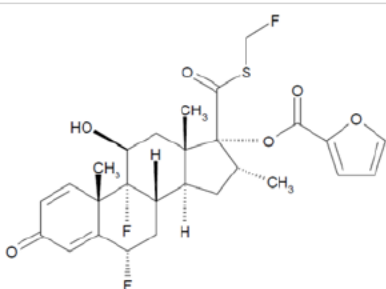


Figure 1: Molecular structure of fluticasone furoate

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 (commercial pack) or 14 (institutional pack) regularly distributed blisters, each containing a white powder, which is a blend of micronized FF and lactose monohydrate (Table 2). Upon actuation, the inhaler delivers the contents of one blister containing FF.

Table 2. Composition of Fluticasone Furoate Inhalation Powder

Inhalation Powder Strength	50 mcg	100 mcg	200 mcg	Function	Reference to Standard
Component	Quantity (Per 12.5 mg Blister ¹)				
Fluticasone furoate micronised ²	50 mcg	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 of up to (b) (4) of the dry powder blend may be included in the final product.
2. The quantity of drug may be adjusted to reflect the assigned purity of the input drug substance.
3. Details of the specification of the active ingredient are provided in 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 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). The proposed indication is “*maintenance treatment of asthma as prophylactic therapy in patients aged 5 years and older.*” FF is not indicated for relief of acute bronchospasm.

2.2.3 What are the proposed dosages and routes of administration?

For the treatment of pediatric subjects (5-11 years old) with asthma, the proposed dosage is 50 mcg once-daily, administered via oral inhalation from the Ellipta DPI device.

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?

Three FF doses of 25, 50, and 100 mcg were evaluated in pivotal Phase IIb/III study HZA106855. This study was a randomized, double blind, double-dummy, parallel-group, placebo- and active-controlled, dose-ranging, efficacy and safety study of inhaled FF in the target population (pediatric subjects aged 5 to less than 12 years uncontrolled on non-ICS asthma medication and/or low dose ICS).

These doses were selected based on the data generated from a phase IIb dose-ranging study in adults and adolescents (FFA109687) and from a phase IIa study in pediatrics (HZA102942):

- Study FFA109687 was an 8-week, randomized, double-blind, placebo- and active-controlled, parallel group study evaluating the PK, PD and safety of once daily administration of FF 25, 50, 100 and 200 mcg in adult and adolescent subjects (aged above 12 years) with asthma (reviewed at the original NDA205625);
- Study HZA102942 was a 14-day, randomized, 2-way crossover study in pediatric subjects (aged 5-11 years, n=27) with asthma evaluating the PK, PD and safety of once daily administration of FF 100 mcg.

It should be noted that two additional dose-ranging studies (FFA109685 and FFA109684) were conducted in adolescent and adult patients exploring once daily doses from 100 mcg to 800 mcg. Results from the three dose-ranging studies in this population showed a dose-response relationship for FF doses ranging from FF 25 mcg to 200 mcg QD, with no additional benefit for FF doses above 200 mcg QD (refer to the Clinical Pharmacology Review of Dr. Jianmeng Chen, DARRTS date 07/18/2014, Original NDA).

A population PK and PK-PD analyses of combined clinical data (Original NDA) estimated steady-state FF $AUC_{(0-24h)}$ to range between 181-241 pg.h/mL following FF 100 mcg QD, and indicated that an $AUC_{(0-24h)}$ of 1000 pg.h/mL would be required to reduce 24-hour serum cortisol by 20% in adults. These results allowed the conclusion that FF100 mcg once daily would be safe to be investigated in pediatrics (aged 5-11 years).

Further, FF 100 mcg QD represents the lowest approved dosage of FF inhalation powder for adults and adolescents. Hence, the 100 mcg dose and two lower doses, 50 mcg and 25 mcg, were selected for investigation in study HZA106855.

FF 50 mcg once daily is proposed as the FF dose in subjects with asthma based on efficacy and safety results of study HZA106855. In addition, FF 50 mcg QD dosage had no suppressive effect on HPA axis function (see section 2.4.3.1). Therefore, this dose has demonstrated clinical efficacy with a tolerable safety profile. Refer to the Clinical Review of Dr. Keith Hull and statistical review of Dr. Mingyu Xi for further information.

Details of the clinical/clinical pharmacology studies supporting this supplemental NDA and their design features are listed under section 2.1.

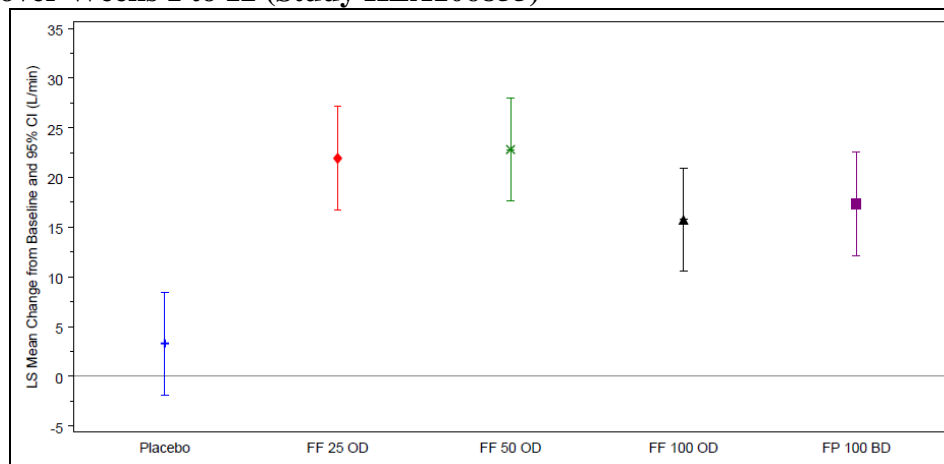
2.4 Dose/Exposure-Response

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

The systemic exposure of fluticasone propionate is not directly related to clinical response (FEV1). In asthma patients above 12 years of age, a dose-response relationship is observed, with an increasing effect with increasing dose (FF 25 mcg to 200 mcg), for all clinical endpoints evaluated (refer to the Clinical Pharmacology Review of Dr. Jianmeng Chen, DARRTS date 07/18/2014, Original NDA). In asthma patients 5 to 11 years of age, FF doses of 25, 50 and 100 mcg were investigated with no evidence of a dose-response relationship for the clinical endpoints (study HZA106855). As illustrated in plots of the geometric mean changes from baseline, no dose-ordering was apparent for the primary endpoint, morning peak respiratory flow (AM PEF) averaged over Weeks 1 to 12 (Figure 2); and for the secondary endpoint, evening trough FEV1 at Week 12 (Figure 3).

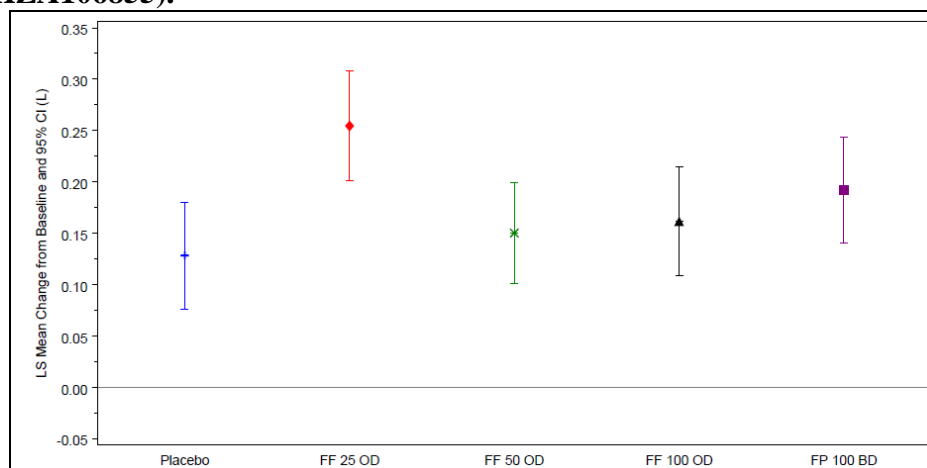
Refer to the clinical review of Dr. Keith Hull and statistical review of Dr. Mingyu Xi regarding the final risk/benefit assessment for the proposed dose for FF inhalation powder based on the efficacy and safety analyses of Phase IIb/III study.

Figure 2. Mean Change from Baseline in Morning Peak Respiratory Flow (AM PEF) Averaged over Weeks 1 to 12 (Study HZA106855)



(Source: CSR HZA106855, Figure 6.2)

Figure 3. Mean Change from Baseline in Evening Trough FEV1 at the PM Visit at Week 12 (Study HZA106855).



(Source: CSR HZA106855, Figure 6.13)

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

In the pivotal study HZA106855, there was no apparent dose-ordering between treatment groups (FF 25, 50 and 100 mcg once daily) in the overall incidence of subjects experiencing adverse events (AEs) during treatment, even though the incidence was slightly higher in the FF treatment groups (range: 32% to 36%) compared with the placebo group (29%). The overall incidence of AEs in the active control group, FP 100 BD, was 31%.

Similarly, there was no apparent dose-ordering in the incidence of the most frequent AEs during treatment. The highest incidence of on-treatment AEs occurred in the System Organ Class (SOC) of Infections and Infestations, and AEs in this class were reported for a similar proportion of subjects in the placebo (21%), FF treatment groups (range: 19% to 22%) and the active control group, FP 100 BD (16%). Refer to the clinical review of Dr. Keith Hull for overall safety evaluation.

In addition, there was no apparent trend of reduction in urinary cortisol level versus plasma FF exposure (predicted FF AUC_{0-24h}), indicating the lack of effect of FF exposure on urinary cortisol. Refer to the Pharmacometrics review in Appendix 4.1 for details.

2.4.3.1 Are there any concerns about impact on hypothalamic-pituitary-adrenal (HPA) axis function?

Hypothalamic pituitary-adrenal (HPA)-axis suppression is a known class effect of corticosteroids use. The safety of inhaled FF on the HPA axis of adult (>18 years of age) and adolescent (12-17 years of age) patients with asthma has been established (Original NDA, Study HZA106851 and meta-analysis 2011N130478_00). The risk of HPA-suppression in children (5-11 years of age) following chronic once daily administration of FF was investigated in the dedicated HPA-axis study HZA107118 submitted in support of this supplement.

Study 107118 was a randomized, double-blind, parallel-group, placebo-controlled, stratified, safety study. Randomization was stratified by age (5 to less than 8 years and 8 to less than 12

years). In this study, the proposed therapeutic dose of FF 50 mcg was selected to be investigated. FF 50 mcg was administered by once daily oral inhalation for 6 weeks to male and premenarchal female subjects aged 5 to 11 years with a diagnosis of asthma, who were receiving a SABA alone or in combination with a non-corticosteroid controller.

The effects of FF on the HPA axis were assessed primarily based on changes in serum cortisol levels from pre-dose to the end of the 6-week treatment period. The effects of FF on the HPA axis were also assessed based on changes in 24-hour urinary free cortisol levels from pre-dose to the end of the 6-week treatment period.

Subjects were randomly assigned in a 1:1 ratio to 1 of 2 treatment arms in a double-blind manner as follows:

- FF 50 mcg: one inhalation daily in the morning via ELLIPTA for 6 weeks
- Placebo: one inhalation daily in the morning via ELLIPTA for 6 weeks

Subjects had a baseline evaluation (visit 2, pre-dose) and attended up to 3 on-treatment visits at Weeks 2, 4 (optional), and 6.

At baseline (Visit 2, pre-dose), 24-hour serial blood sampling and urine collection, which served as a treatment-free control, were performed before the first treatment dose was administered. At the end of treatment (Visit 5, Day 42), serial blood sampling and urine collection over a 24-hour period were performed for cortisol determination. PK blood samples were collected for determination of serum concentrations of FF immediately prior to administration of the last study medication dose and at 0.5 hour post-dose.

Serum cortisol samples were assayed using a validated assay with the lower limit of quantification (LLOQ) of 1 µg/dL (28 nmol/L). Urine cortisol samples were assayed using a validated assay (Original NDA). Systemic levels of FF were quantified by a validated bioanalytical method with an LLOQ of 10 pg/mL (see section 2.8).

During the study, there was no evident decrease in the median value of derived cortisol weighted mean (0-24h) is summarized by treatment group in Table 3.

Table 3. Analysis of Derived Serum Cortisol Weighted Mean (0-24h) (nmol/L) and Ratio from Baseline (per protocol population)

	Placebo		FF	
	Value (nmol/L)	Ratio from baseline	Value (nmol/L)	Ratio from baseline
Baseline				
n	51		53	
Median	183.50		157.46	
Min	97.2		73.4	
Max	404.6		345.6	
End of Treatment (Week 6)				
n	50		52	
Median	175.63	1.02	151.21	1.01
Min	67.5	0.3	83.7	0.4
Max	538.7	3.8	519.1	4.1
LS mean	173.25	1.05	160.65	0.97
LS mean ratio FF/Placebo				0.93
95% CI				0.8096, 1.0620

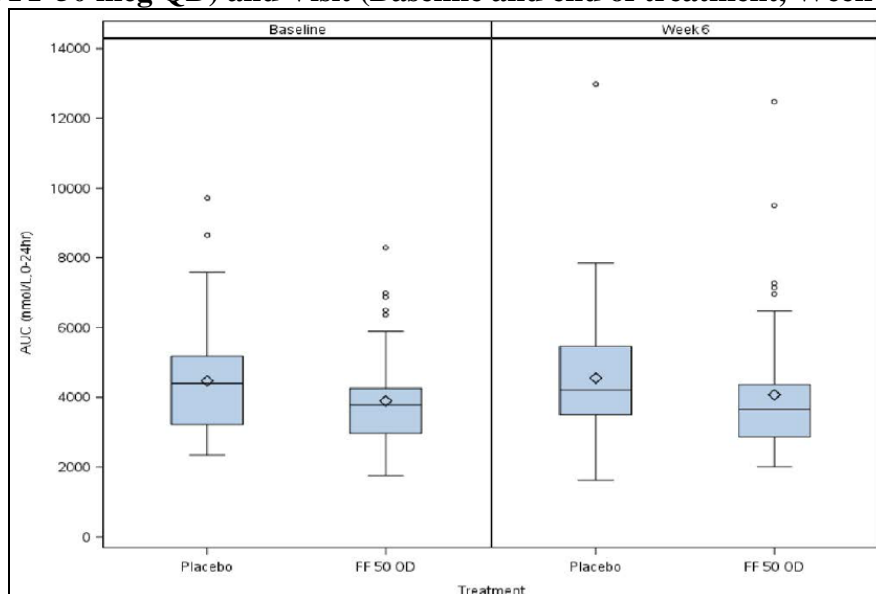
Abbreviations: n= number of subjects with value at the visit; LS = Least Square; CI = Confidence Interval (Source: CSR HZA107118, Tables 2.3 and 2.5).

Analysis was also conducted with the intent-to-treat (ITT) population (N=111), which was a supporting population and considered with equal weighting to the per protocol population (serum cortisol) for the primary endpoint. The findings for the ITT population were similar to those for the per protocol population (weighted mean at baseline: 172.45 nmol/L for placebo and 151.71 nmol/L for FF 50 mcg; Week 6: 177.00 nmol/L for placebo and 156.47 nmol/L for FF 50 mcg; treatment ratio for FF 50 mcg vs. placebo of derived serum cortisol weighted mean (ratio from baseline) was 0.92 (95% CI: 0.80, 1.05).

Three subjects (752, 753, and 1364) were considered as extreme outliers (by assessment of both statistical studentised residuals and clinical data) which prompted a sensitivity analysis to assess the impact of removing these subjects from the primary analysis. After exclusion of these subjects from the per protocol population, the treatment ratio for FF 50 mcg vs. placebo of derived serum cortisol weighted ratio from baseline was 0.91 (95% CI: 0.80, 1.02).

The secondary endpoint was the change from baseline in serum cortisol AUC_(0-24h). At the end of 6 weeks of treatment, the change from baseline in serum cortisol AUC_(0-24h) were 1.06 and 0.97 for placebo and FF, respectively. The treatment ratio for FF 50 mcg vs. placebo was 0.93 (95% CI: 0.81, 1.06). Graphical representation of serum cortisol AUC_(0-24h) by treatment group and visit for the protocol population is presented in Figure 4.

Figure 4. Effect of FF on serum cortisol AUC_(0-24h) (nmol.h/L) by Treatment Group (Placebo and FF 50 mcg QD) and Visit (Baseline and end of treatment, Week 6)



(Source: HZA107118 CSR, Figure 2.19)

Overall, the 24-hour serum cortisol data indicate that FF 50 mcg once daily via ELLIPTA had no suppressive effect on the HPA axis in the 5 to 11 years old age group.

Change from baseline at Week 6 in 24-hour urinary free cortisol excretion and its metabolite, 6-beta hydroxycortisol, were also analyzed as secondary endpoints. The urinary free cortisol (treatment ratio 0.79 [95% CI: 0.61, 1.03]) and metabolite (treatment ratio 0.88 [95% CI: 0.72, 1.07]) results indicated that the FF 50 mcg treatment group had numerically lower values compared with placebo group. The sensitivity analysis (excluding outliers) had a treatment ratio of 0.75 (95% CI: 0.59, 0.95) for urine cortisol excretion. It should be noted that non-inferiority criteria were not set for the secondary endpoint, urine cortisol.

A positive control oral corticosteroid (such as prednisolone) was not included in the study due to ethical concerns of administering corticosteroids to children younger than 12 years old in doses high enough to cause HPA axis suppression. This is consistent with other similar trials of ICS and intranasal corticosteroids in children. A 6-week treatment duration was previously used in the adult and adolescent HPA axis study for FF (HZA106851, Original NDA) and was considered a sufficient duration to show any possible differences in serum cortisol levels. Overall, the study design is considered robust and acceptable with a significant number of subjects in each group, as well as robust endpoints such as measurement of changes in serum cortisol.

Altogether, the results indicate that 6-weeks of treatment with FF 50 mcg once daily did not show any clinically significant effect on the HPA axis function.

Plasma concentrations of FF were quantifiable in only 4 out of the 52 subjects (92% NQ) at pre-dose (trough concentration at Week 6) and in 35 out of 52 subjects (33% NQ) at 0.5 hour post-

dose. Median concentration was 12.1 pg/mL at 0.5 hour post-dose and ranged from 0-41.7 pg/mL with variance of 88% suggesting high variability in the data.

2.5 PK Characteristics of the Drug

2.5.1 What are the PK parameters of fluticasone propionate in pediatric patients?

The systemic exposure to FF in pediatric subjects with asthma (5-11 years old), in terms of AUC and C_{max} , was dose proportional (Table 4).

The systemic exposure to FF at steady-state in pediatrics was comparable to that observed in adolescents and adults following FF 100 mcg once daily dosing (Table 4). The geometric mean $AUC_{(0-24h)}$ following 100 FF in children aged 5 to 11 years (196 pg.h/mL) was comparable to that in adults and adolescents in (181 pg.h/mL) [Study FFA114496, Original NDA]. Geometric mean C_{max} was also similar in pediatrics, and adults and adolescents (22 pg/mL and 27 pg/mL, respectively).

Table 4. Comparison of FF Steady-State Systemic Exposure in Pediatrics, Adolescents and Adult Subjects with Asthma following Repeat Dosing with FF

Population	Study	Dose	N	C_{max} (pg/mL)	95% CI	$AUC_{(0-24h)}$ (pg.h/mL)	95% CI
5-<12 y	HZA106855	25	92	5.7	5.1-6.4	47	41-54
		50	85	11.6	10.6-12.7	98	87-110
		100	77	22.4	19.9-25.3	196	167-230
5-<12 y	HZA102942	100	26	23.6	20.8-26.8	171	142-205
5-<12 y	HZA112777	100	26	20.3	17.1-24.2	158	127-196
≥12 y	FFA114496	100	116	27.0	15.4-50.3	181	118-292
		200	115	55.1	32.6-98.2	395	194-918

Data are population PK model predicted C_{max} and $AUC_{(0-24h)}$ values (Geometric Mean, 95% confidence interval) following repeat administration of FF 25 mcg, 50 mcg, 100 mcg or 200 mcg once daily in pediatric, adolescents and adults with asthma by study.

(Source: Population Pharmacokinetic Report 2013N162904_02, Table MA10; and Population Pharmacokinetic Report 2015N233663_00, Table MA6).

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC , C_{max} , C_{min}) and how much of the variability is explained by the identified covariates?

A population PK analysis was conducted to describe the FF systemic exposure in pediatric subjects with asthma aged 5 to 11 years. There is no effect of age, weight, gender or race on exposure to FF in pediatric subjects with asthma. Refer to the Pharmacometrics review in Appendix 4.1 for additional details.

2.7 General Biopharmaceutics

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

FF is delivered via an ELLIPTA DPI as a single strip inhaler in the to-be-marketed product. The PK/PD studies HZA102942 and HZA 112777 were conducted using the DPI two blister configuration. One blister contained FF formulated with lactose in the first strip and a second strip containing lactose (b) (4) (these excipients comprise placebo to match the vilanterol strip in the FF/VI combination product).

The efficacy/safety study (HZA106855), the HPA-axis (HZA107118), the short (HZA107112) and long-term growth (HZA114971) clinical studies were conducted using the one strip configuration. Therefore, the pivotal studies used the same single strip formulation as the proposed commercial product.

2.7.2 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 inhaled FF was not assessed. It is unlikely the PK of inhaled FF is affected by food because the oral bioavailability of FF is minimal.

2.8 Analytical Section

2.8.1 What are the analytical methods used to measure fluticasone propionate in plasma and other matrices?

The method 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 of FF (original NDA). The analytical methods used in the clinical studies conducted in support of this application are listed in Table 5.

Table 5. Summary of analytical methods for analysis of FF in clinical trials

Validation Report	WD2010/00145/00
Clinical Studies Supported	HZA112777 HZA102942
Method Description	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.
Method Performance	
Validated Range	10.0 to 1000 pg/mL
Intra-run Precision (%CV)	≤13.1%
Inter-run Precision (%)	≤7.5%
Inter-run Accuracy (%Bias)	-11.0% ≤ bias ≤3.5%
Validation Report	2012N153939_00; WD2002/01057/00; WD2006/01727/00; 2013N159391_00; 2012N152308_00
Clinical Studies Supported	HZA107118 HZA106855
Method Description	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 an APCI interface and multiple reaction monitoring.
Method Performance	
Validated Range	10.0 to 1000 pg/mL
Intra-run Precision (%CV)	≤10.2%
Inter-run Precision (%)	≤9.8%
Inter-run Accuracy (%Bias)	≤8.0%

(Source: Adapted from Appendix Table 1, Summary of Clinical Pharmacology Studies)

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

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

2.8.3 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 quantification of FF in plasma ranged from 10 to 1000 pg/mL. A linear regression model, with weighting factor of 1/concentration² was used for the curve fitting for FF.

The analytical runs for the clinical studies with pharmacokinetic assessment met the pre-defined acceptance criteria. The inter-run accuracy and precision of QC samples for clinical studies HZA112777, HZA102942, HZA107118, and HZA106855 is listed in Table 6 below.

Table 6. Inter-run Accuracy and Precision of Quality Control (QC) Samples

Study	Total number of QC samples	Precision (\leq %CV range)	Accuracy (%Bias range)
HZA112777 (2012N145011)	24	5.1-15	-1.9 to 4.3
HZA102942 (2011N113755)	58	6.0-15	-8.4 to 3.9
HZA107118 (2015N241664)	24	4.0-7.1	-3.7 to 1.0
HZA106855 (2014N219805)	66	6.7-11.6	-2.3 to 1.0

(Source: Module 5.3.1.4 Appendix Table 2- Bioanalytical Reports 2012N145011, 2011N113755, 2015N241664, 2014N219805).

2.8.5 What is the result for the re-analysis of the incurred samples?

Pharmacokinetics samples from the clinical studies HZA112777, HZA102942, HZA107118, and HZA106855 were re-analyzed for FF as part of the incurred sample reproducibility assessment. Results for HZA112777, HZA107118 and HZA106855 met the acceptance criteria of $> (b)(4)\%$ of the incurred sample results being within 20% of the original result. For HZA102942, however, the acceptance criterion was not met with only $(b)(4)\%$ of the incurred sample results being within 20% of the original result; $(b)(4)\%$ were above the +20% limit and $(b)(4)\%$ were below the -20% limit. The applicant conducted a thorough investigation and concluded the assay was reproducible and original study data were acceptable.

2.8.6 What is the stability of FF under conditions used in the studies?

Pharmacokinetic samples from the clinical studies HZA112777, HZA102942, HZA107118, and HZA106855 were stored and analyzed within the validated storage stability period and conditions for FF.

For the bioanalytical methods, stability of FF was demonstrated under different conditions: FF was stable in human whole blood at 37°C and ambient temperature for at least 4 hours, in human plasma for at least 24 hours at room temperature, at least 18 months stored at -20°C, at least 6 months at -80°C in human plasma after 5 freeze-thaw cycles from -80°C or -20°C to room temperature. Stability of processed samples (auto sampler reinjection and reproducibility) under ambient conditions (bench-top) for at least 72 hours was also established.

3 LABELING RECOMMENDATIONS

Labeling discussions are ongoing. The reader is referred to the approved label for final recommendations.

4 APPENDIX

4.1 Pharmacometrics Review

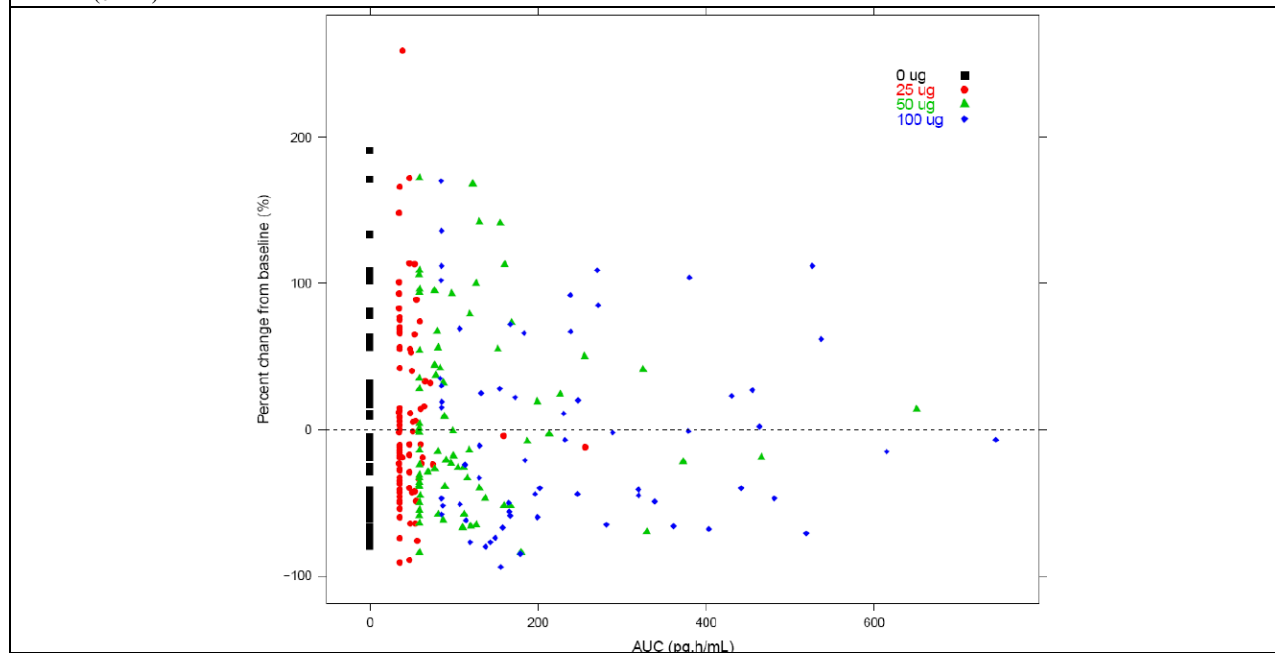
1 KEY REVIEW QUESTIONS

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

1.1 What are the characteristics of exposure-response relationships for efficacy and safety?

There was a flat relationship between plasma fluticasone furoate (FF) exposure and urinary cortisol. Sponsor's graphical exploration of percent change from baseline urinary cortisol versus predicted FF $AUC_{(0-24h)}$ showed no apparent trend of reduction in urinary cortisol level in HZA106855, the pivotal Phase IIb study in pediatric patients, with 61 on placebo, 86, 81 and 73 subjects on FF 25, 50 and 100 ug, respectively (**Figure 5**). No apparent correlation or trend was observed from **Figure 5**, indicating the lack of effect of FF exposure on urinary cortisol.

Figure 5: Percentage Change from Baseline Urinary Cortisol versus Systemic Exposure $AUC_{(0-24h)}$



Source: Figure MA9 of applicant's population pharmacokinetics report for pediatric asthma patients dated 31Mar2015.

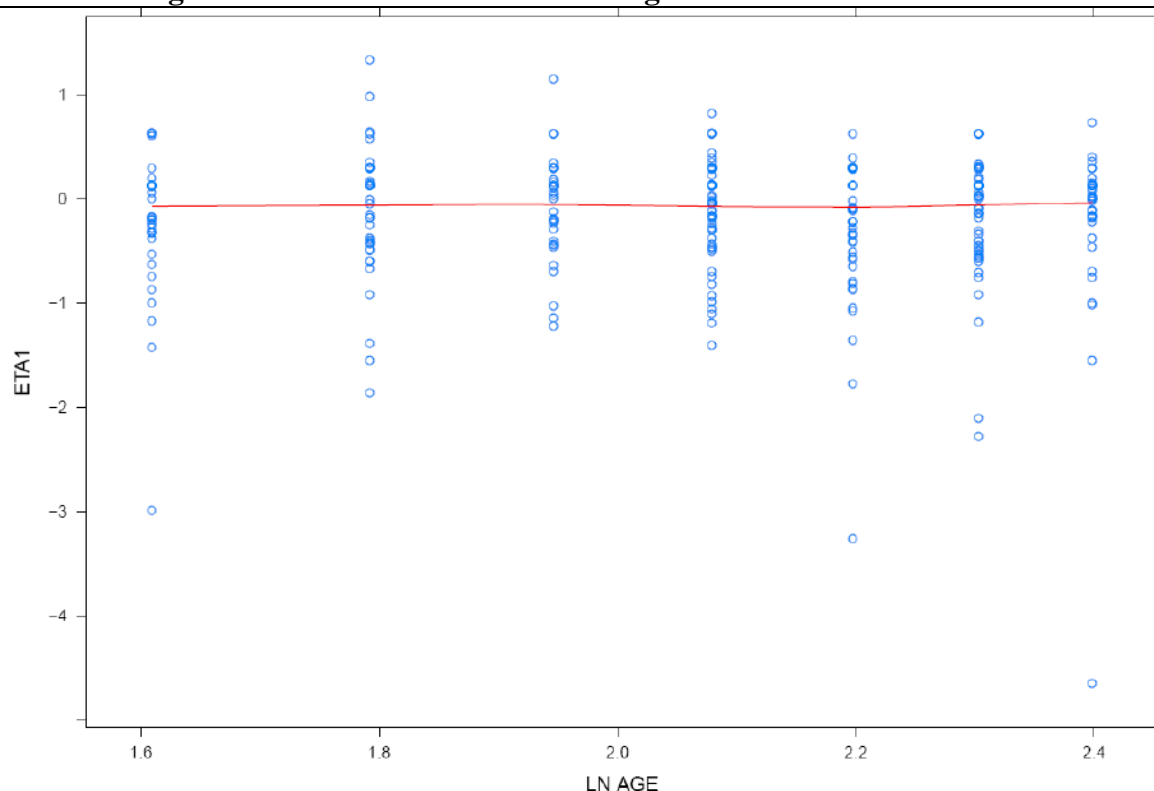
There was no ER analysis for FF efficacy as the drug is an inhalation product, for which the local action of FF could be more relevant to the effect than the FF concentration in the blood circulation.

1.2 Is the steady-state exposure of FF in pediatric patients with asthma aged 5 to less than 12 years comparable to that observed in adult and adolescent subjects following fluticasone furoate 100 mcg monotherapy?

Yes, the steady-state exposure for FF in pediatric asthma patients aged 5 to less than 12 years is comparable to that observed in adult and adolescent subjects following FF 100 mcg monotherapy, based on applicant's population pharmacokinetics report for pediatric asthma patients.

None of the covariates evaluated (age, weight, BMI, sex, ethnicity and race) were significant on FF pharmacokinetic parameters. As shown in **Figure 6**, the relationship is flat between Age and ETA of FF clearance, suggesting no age effect on FF exposure after the administration of FF doses in pediatric asthma patients.

Figure 6: Individual Inter-Subject Variability of FF Clearance (ETA1) versus Log Transformed Age for Pediatric Asthma Patients Aged 5-12 Years



Source: Figure MA6 of applicant's population pharmacokinetics report for pediatric asthma patients dated 31Mar2015.

2 APPLICANT'S POPULATION PHARMACOKINETICS ANALYSIS

2.1 Data

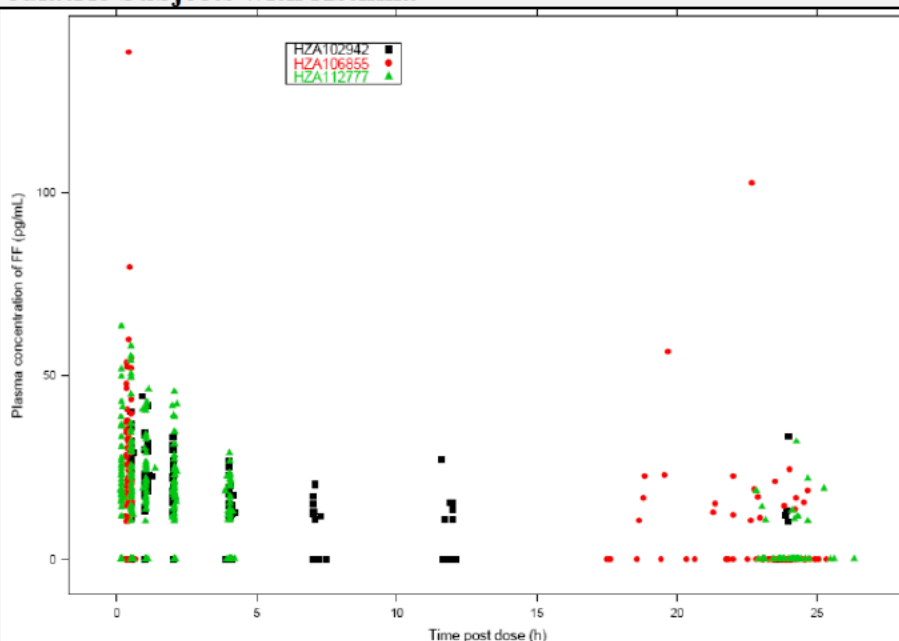
The study included a sparse sampling approach (peak and trough) for PK evaluation. It was planned to conduct population PK analysis for all treatments. Given the sparse nature of the sampling and the high proportion of records reporting FF concentrations below the lower limit of quantification (LLQ; 10 pg/mL), addition of more extensively sampled concentration-time data from the Phase IIa studies (HZA102942 and HZA112777) was required to achieve an

appropriate structural model to describe the data.

Studies HZA106855, HZA102942 and HZA112777 were included in the population PK dataset. FF concentration-time data for the following treatments were included: 25 mcg, 50 mcg and 100 mcg FF, and FF/VI 100/25 mcg. The samples from all three studies were analyzed for FF plasma concentrations using similar methodology with the same lower limit of quantification (LLQ) of 10 pg/mL. The NONMEM dataset was constructed using R code from individual study datasets. Steady-state was assumed with a dosing interval of 24 hours.

There were two records commented out using R-script for exclusion from the analysis because the concentration at ca. 24 hours was notably higher than that for those in the first hour post-dose, one record excluded due to very high concentration post dose. Subject 56157 did not have dosing record, therefore the subject was excluded from the analysis.

Figure 7: FF concentrations Relative to Time of Last Dose Following FF100 or FF/VI (100/25) to Pediatric Subjects with Asthma



Source: Figure 1 of applicant's population pharmacokinetics report for pediatric asthma patients dated 31Mar2015.

2.2 Methods

As consequence of the large extent of non-quantifiable data in the dataset it was necessary to use methodology that maximized the likelihood for all the data, treating those data below the LLQ as censored. The data were analyzed using the methodology referred to as M3 and requires the use of the F FLAG option and PHI function available in NONMEM v7 ([Ahn, 2008](#)).

In a previous population PK analysis of FF concentration-time data in adult/adolescent subjects with asthma the final structural model was a two-compartment model with 1st order absorption and 1st order elimination with additive error [GlaxoSmithKline Document Number [2011N130480 00](#)]. The model building started with the base model from that analysis.

Covariate analysis was performed to explore measurable sources of variability in FF PK. The covariate analysis was a step-wise process consisting of a forward and a backward selection procedure. The following covariates were prospectively identified to be evaluated for their

potential impact on the population PK of FF (in no particular order) through a step-wise approach: Continuous covariates (Age, weight height, BMI); Categorical covariates (sex, ethnicity [hispanic or latino/ non-hispanic or latino], race).

2.3 Results

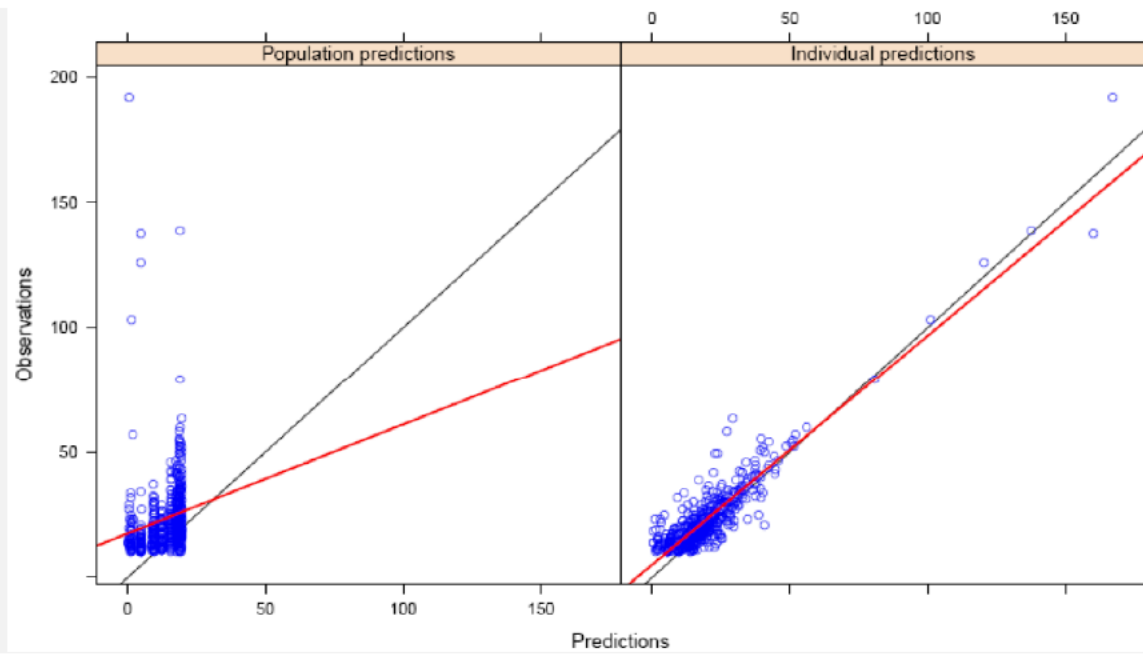
The population PK analysis dataset comprised 306 pediatric subjects with asthma. Total 301 subjects, (five subjects had not provided plasma samples for PK) provided a total of 940 sample records of which majority of the samples were following the 100 mcg dose. Of all the data, about 51% were reported as NQ ($<LLQ$ 10 pg/mL) overall, while the percent of -BLQ data was 77%, 64% and 39% for 25 mcg, 50 mcg and 100 mcg, respectively. It was noted that majority of data were immediately after the dosing and at trough, only very small amount of data were taken after 4 h post dose in the pediatric population due to the sampling schemes of individual studies.

A one compartment model with first absorption first order elimination was used to fit the data. Potential covariate-parameter relationships were explored graphically using the individual inter-individual variabilities (ETAs) from the base model (Run7wetablock, DMP19910-1.7). Apart from race, none of the other covariates assessed (age, ethnicity, sex, age, body weight, body mass index) showed potential to affect the estimate of inter-individual variabilities (ETAs) of CL/F, V/F, or KA. Although graphically there appeared a slight difference in ETA1 (on CL/F) with Asian population relative to others, there were very few subjects (11/306) in this group. The effect of race on CL/F was further assessed by incorporating this covariate into the base model (Run8, DMP19977-1.1). The result indicated non-significance of RACE as a covariate in the model.

Since there was no covariate that had any significant impact on any of the PK parameters, the final population PK model for FF in this population was the same as the base model.

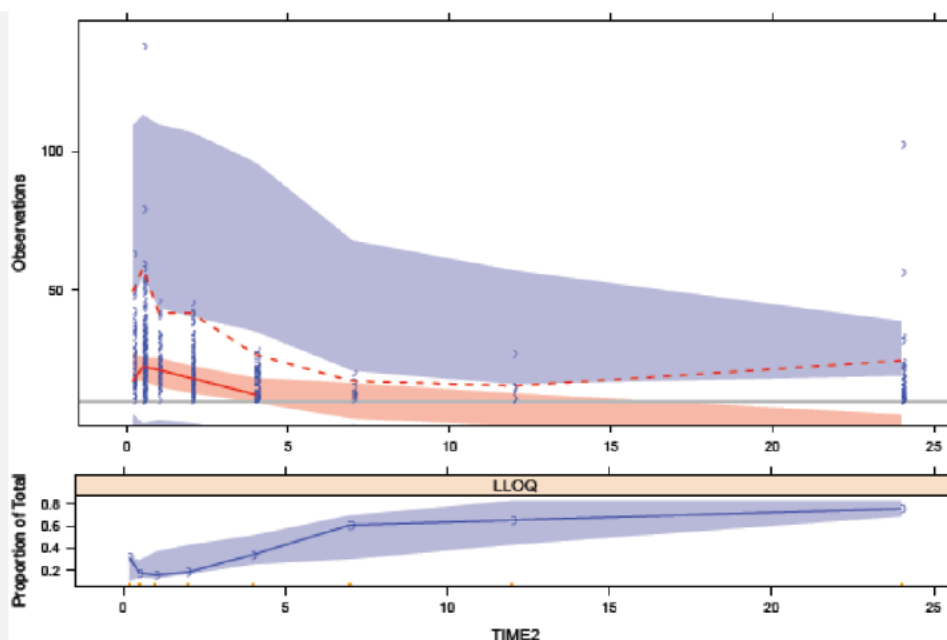
Figure 8 shows the scatter plot of individual and population predictions versus observed data (data above LLQ). However, due to large proportion of -BLQ data in the datasets, the frequently used goodness-of-fit plots, e.g. individual and population predictions versus observed data plots, conditional weighted residuals, were not appropriate to assess the model validity. VPC is more useful. The VPC plot is presented in **Figure 9**, where FF 100 mcg QD is taken as example. The upper panel showed that majority of the data is captured in the prediction interval encompassing 95% of the population as indicated by the 2.5th and 97.5th percentile boundary, indicating that the model was reasonable for this asthma dataset. The model also described the proportion (%) -BLQ data well for all doses studied in this dataset (bottom panel). These results indicated good fit of the one compartment model to the data that were above the LLQ and the proportion of data below the LLQ.

Figure 8: Observed versus Predicted FF Concentration of the Final Population PK Model



Source: Figure MA7 of applicant's population pharmacokinetics report for pediatric asthma patients dated 31Mar2015.

Figure 9: VPC Plot for FF 100 mcg OD



Source: Figure MA5 of applicant's population pharmacokinetics report for pediatric asthma patients dated 31Mar2015.

Table 7: Parameter Estimates of the Final Population Pharmacokinetics Model

	Estimate	95%CI Low	95% CI High
CL/F (L/h)	633	493	812
V/F (L)	1.2	1	2
KA (1/h)	0.12	0.09	0.16

Source: Table 3 of applicant's population pharmacokinetics report for pediatric asthma patients dated 31Mar2015.

Individual $AUC_{(0-24h)}$ values, derived from individual post-hoc estimates of CL/F and C_{max} values obtained from simulation are summarized by study and dose administered in **Table 8**. The results revealed no obvious difference in C_{max} and $AUC_{(0-24h)}$ among the three studies.

Table 8: Model Predicted FF Cmax and AUC_(0-24h) (Geometric Mean [95% CI]) following administration of FF 25 mcg, 50 mcg and 100 mcg in Pediatric Subjects with Asthma by Study

Parameter (Units)	Study	Dose (mcg)	N	Geometric Mean	Lower 95% CI	Upper 95% CI
Cmax (pg/mL)	HZA106855	25	92	5.7	5.1	6.4
		50	85	11.6	10.6	12.7
		100	77	22.4	19.9	25.3
	HZA102942	100	26	23.6	20.8	26.8
	HZA112777	100	26	20.3	17.1	24.2
AUC _(0-24h) (pg.h/mL)	HZA106855	25	92	47	41	54
		50	85	98	87	110
		100	77	196	167	230
		100	26	171	142	205
		100	26	158	127	196

Source: Table 4 of applicant's population pharmacokinetics report for pediatric asthma patients dated 31Mar2015.

Discussion and Conclusion: The purpose of this meta-analysis was to characterize the FF population pharmacokinetics (population PK) in pediatric subjects with asthma. One Phase IIb (HZA106855) and two Phase IIa (HZA102942 and HZA112777) studies were included in the analysis. The FF concentration-time data was described by a one compartment linear model with first order absorption and first order elimination with an additive error model. None of the demographic covariates evaluated (age, weight, BMI, sex, ethnicity and race) were shown to be significant on FF pharmacokinetic parameters. The plot for the VPC indicated that the model was reasonable for this asthma dataset for both the observed data (data above LLQ) and the proportion (%) BQL. The estimated average FF Cmax for pediatric subjects with asthma in Study HZA106855 following 100 mcg FF [22 pg/mL (95% CI 20-25)] in the present study is within the range estimated using non-compartmental analysis method previously reported for the two Phase IIa studies following FF alone or in combination with VI (GlaxoSmithKline Document Number YM2010/00094/01, GlaxoSmithKline Document Number 2011N127524 01). In addition, model predicted AUC_(0-24h) for 100 mcg FF in the three studies was comparable. AUC_(0-24h) was not reported in the Phase IIa studies due to the relatively sparse blood sampling in these pediatric studies, hence AUC_(0-24h) could not be calculated using the non-compartmental analysis. Population PK modeling approach, in particular when pooling data from different studies, is a powerful tool to integrate data in order to adequately characterize the PK profiles and quantify the total systemic exposure following repeated dosing of FF in pediatric population.

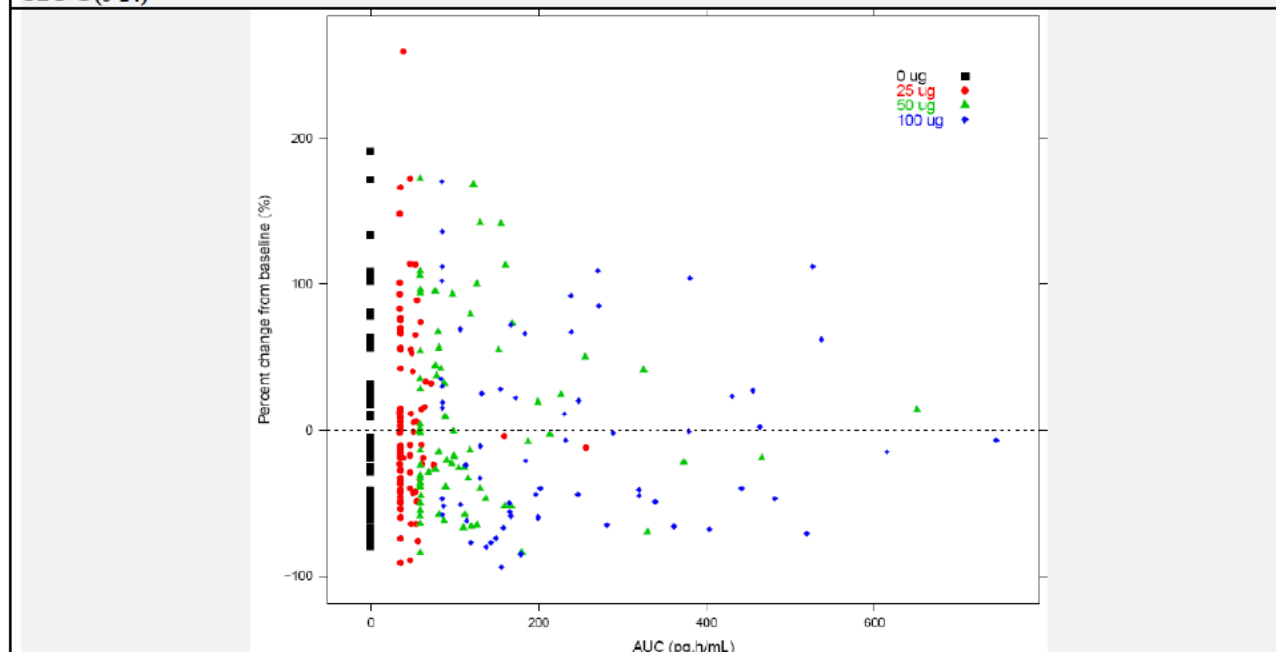
3 APPLICANT'S EXPOSURE-CORTISOL ANALYSIS

3.1 Data and Analysis

Data from all subjects who provided both quantifiable urinary cortisol data at baseline and post treatment in the ITT population, were merged with the model predicted AUC_(0-24h) for the PK/PD analysis. Total of 301 subjects (61 on placebo, 86, 81 and 73 subjects on FF 25, 50 and 100 mcg, respectively) were included in the following exploratory analysis. Scatter plot of percent change from baseline urinary cortisol versus AUC_(0-24h) is presented in **Figure 10**. No apparent correlation or trend was observed from these figures, indicating lack of effect of FF exposure on urinary cortisol. In addition, as the analysis of change from baseline 24 hour urinary cortisol

excretion were not statistically significant, there was no further exploration of correlation between systemic exposure of FF on cortisol.

Figure 10: Percentage Change from Baseline Urinary Cortisol versus Systemic Exposure $AUC_{(0-24)}$



Source: Figure MA 9 of applicant's population pharmacokinetics report for pediatric asthma patients dated 31Mar2015.

3.2 Discussion and Conclusion

Graphical exploration of percent change from baseline urinary cortisol versus predicted $AUC_{(0-24h)}$ showed no apparent trend of reduction in urinary cortisol level within the exposure range following the doses administered in this study. No further PK/PD analysis was considered necessary. Both the rate and extent of systemic exposure to FF at steady state in pediatrics were comparable to that observed in adolescents and adults following dosing with FF 100 mcg monotherapy. The average $AUC_{(0-24h)}$ following 100 mcg FF in pediatrics (196 pg.h/ml) was comparable to that in adults and adolescents in FFA114496 (181 pg.h/ml) (GlaxoSmithKline document number 2013n162904_02). Average C_{max} was also similar in pediatrics, and adults and adolescents (22 pg/ml and 27 pg.h/ml, respectively) (GlaxoSmithKline document number 2013n162904_02). In addition, the estimated FF $AUC_{(0-24h)}$ in pediatric subjects with asthma following 100 mcg FF QD is about 5-fold below the exposure value (1000 pg.h/ml) that is associated with about 20% decrease in 24-h serum or urine cortisol (Allen, 2013).

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