CLINICAL PHARMACOLOGY REVIEW

NDA:	21-433 (SLR-011) (Prior Approval, Labeling, Postmarketing Study Commitment: PREA)
Submission Type:	Pediatric safety information. The sponsor is not seeking an indication in children 6 months to 4 years of age.
Proprietary Drug Name:	FLOVENT® HFA®
Generic Name:	Fluticasone Propionate (FP) Inhalation Aerosol
Approved Indication:	Treatment of asthma in adults and children 4 years and older
Dosage Form:	Inhalation Aerosol
Strength evaluated:	44 mcg
Route of Administration:	Oral Inhalation
Dosage and administration evaluated:	**Children 6 months to < 4 yrs**: Two actuations (88 mcg) twice a day
Applicant:	GlaxoSmithKline, Inc.
Clinical Division:	DPAP (HFD-570)
Submission Date:	November 21, 2007; May 6, 2008; May 21, 2008
Date of Assignment:	March 5, 2008
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader (acting) :	Wei Qiu, Ph. D.

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1. EXECUTIVE SUMMARY

Flovent HFA MDI contains fluticasone propionate, an orally inhaled glucocorticoid. Flovent HFA MDI (44, 110, and 220 mcg) was approved on May 14, 2004 for the maintenance treatment of asthma as prophylactic in adults and adolescent patients 12 years and older. Flovent HFA MDI was approved for the same indication in children 4 to 11 years of age in February 2006.

In the present submission (supplement SLR-011), the sponsor included pediatric safety data in children 6 to <12 months of age (Study FAS106533) to fulfill the required postmarketing study commitment of the Pediatric Research Equity Act (PREA). The sponsor, GSK, stated that they are not proposing any changes to the currently approved product indications (i.e., Flovent HFA is indicated for patients 4 years and older) (b) (4)

This submission also includes revised labeling that incorporates the results from Study FAS106533 as well as the pharmacokinetic and pharmacodynamic results from Study FAS30030. Study FAS30030 was included in the April 28, 2005 submission to NDA 21-433 (SE5 004) and was reviewed by Drs. Shinja Kim and He Sun[1].

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology II (OCP / DCP-2) has reviewed the labeling supplement/post marketing study commitment (SLR011) submitted to NDA 21-433 on November 21, 2007, May 6, 2008, and May 21, 2008. This submission is acceptable from a Clinical Pharmacology point of view provided that a mutually satisfactory agreement can be reached between the sponsor and

[1] Clinical Pharmacology review for NDA 21-433 s004 submitted on April 28, 2005 and DFS'd by Dr. Shinja Kim on 12/9/2005.

the Agency regarding the language in the package insert. The labeling recommendations (page 16) should be conveyed to the sponsor as appropriate.

1.2 Comments to the Medical Team

1.2.1 PK part of Study SAS106533 (assessment of systemic exposure in children 6 to <12 months of age).

- The geometric mean (CV%) Cmax and $AUC_{0\text{-}12\ hrs}$ values of fluticasone propionate (FP) in children 6 to < 12 months of age were 24.6 pg/mL (172%) and 75.0 pg*hr/mL (289%), respectively. For certain subjects who had below limit of quantitation (BLQ) samples throughout the sampling interval, it is noted that $AUC_{0\text{-}12\ hrs}$ values as low as 8 pg*hr/mL were reported. In cases where a planned PK parameter could not be calculated (e.g., all concentrations are BLQ), the value for that parameter should be set to "Not Calculable".

- Due to the large variability in the PK parameters, there might be a substantial bias in reporting mean values as being proposed by the sponsor. Therefore, in addition to the geometric mean (95% CI), the label should include the range of PK parameters (e.g., the $AUC_{0\text{-}12\ hrs}$ ranged from Not Calculable to 671.74 pg*hr/mL and from Not Calculable to 332 pg*hr/mL in children 6 to < 12 months and children 4 to < 11 years of age, respectively).

1.2.2 PD part of Study SAS106533 (assessment of HPA Axis Suppression in children 6 to < 12 months of age.

- This reviewer acknowledges the ethical and technical difficulties in assessing the degree of HPA axis suppression in infants. In addition, given that the Division previously agreed with the sponsor on the design of the study used to assess the degree of cortisol suppression (one-way, single sequence study design, with no assessment of baseline and no wash-out period between treatments), the results of this study might be sufficient for the purpose of compliance with PREA requirements.
- The sponsor may need to further evaluate the potential effect on HPA axis in children 6 to < 12 months of age receiving multiple doses of Flovent HFA MDI if an indication is pursued in this pediatric population. This recommendation is based on the limitation of the study design for Study SAS106533 and the findings that the FP mean systemic exposure in children 6 to < 12 months of age is 2.7-times of that observed in children 4 to 11 years of age via cross-study comparison (geometric mean $AUC_{0\text{-}12\ hrs}$ values were 75 pg.hr/mL vs. 28 pg.hr/mL).

1.3 Summary of Clinical Pharmacology Findings

Study FAS106533 was an open-label, repeat dose, single-sequence, two session study. The open-label MDIs for this study contained either FLOVENT in the 44 mcg per actuation strength with propellant HFA or only HFA propellant (i.e., placebo). In Session 1, subjects received 2 inhalations of placebo HFA MDI twice daily for 14 days (placebo).

In Session 2, subjects received 2 inhalations of FP HFA MDI 44 mcg twice daily for 28 days (FP HFA). The objectives of this study were to determine the effect of administration of FP HFA MDI 88 mcg BID on 12 hour serum cortisol in pediatric subjects, ages 6 months to <12 months, who had experienced 2 or more wheezing episodes in the preceding 6 months, to determine the systemic exposure to FP, and to determine the safety and tolerability following administration of FP HFA MDI 88 mcg BID in this age group.

PK of FP in Children 6 to < 12 Months of Age

The geometric mean (CV%) Cmax and $AUC_{0\text{-}12\ hrs}$ of FP following multiple dose administration of Flovent HFA MDI 88 mcg BID for 28 days delivered via a valved holding chamber (AeroChamber Plus®) with infant face mask in children 6 to < 12 months of age were 24.6 pg/mL (172%) and 75.0 pg*hr/ml (289%) and, respectively. It is noted that AUC values as low as 8 pg*hr/mL were reported for some subjects who had BLQ samples throughout the sampling interval. Cmax values as low as 2 pg/mL were reported for some subjects. The FP Cmax values observed in children 6 to <12 months of age ranged from BLQ to 106 pg/mL. The $AUC_{0\text{-}12\ hrs}$ values ranged from Not Calculable (all samples were BLQ) to 671.74 pg*hr/mL.

A Cross-study comparison showed that the FP systemic exposure (geometric mean Cmax and $AUC_{0\text{-}12\ hrs}$) observed in children 6 to <12 months of age was similar to that observed in adults following multiple dose administration of Flovent HFA MDI 88 mcg BID (Table 1.3.1). The $AUC_{0\text{-}12\ hrs}$ in children 6 to < 12 months of age was about 2.7-times of and 50% lower than that in children 4 to 11 years of age and 1 to < 4 years of age, respectively. The $AUC_{0\text{-}12\ hrs}$ ranged from Not Calculable to 671.74 pg*hr/mL and from Not Calculable to 332 pg*hr/mL for children 6 to < 12 months and children 4 to < 11 years of age, respectively.

Table 1.3.1. Flovent HFA MDI Pharmacokinetic Parameters across ages

	Geometric Mean (CV%) [95% CI]	
	Cmax (pg/mL)	**AUC(0-12) (pg.hr/mL)**
Children 6 to <12 months (N=17)	24.6 (172) [13, 45]	75.0 (289) [34, 166]
Children 1 to <4 years[a] (N=13)	21.86 [21, 23]	141.39 [127, 156]
Children 4 to 11 years[b] (N=13)	15.1 [9,27]	28 [10,80]
Adults[b] (N=20)	25 [18, 36]	76 [33, 175]

[a] Data based on Pop PK analysis from NDA 21-433 review[1]. [b]Taken from approved Flovent HFA PI.

HPA Axis Effect in Children 6 to < 12 Months of Age

It appears that no significant reduction in serum cortisol levels was observed in children 6 to <12 months of age following multiple administration of FP HFA MDI 88

mcg BID as measured by the 12-h serum cortisol estimations (ratio of geometric means was 0.95 [95% CI 0.72, 1.27] (Table 1.3.2). It is noted that treatment comparisons give similar results whether using weighted mean (see question based review section for discussion on the use of both methods) or AUC over the same time interval.

Table 1.3.2. Summary of Statistical Analysis of Log Transformed Serum Cortisol $AUC_{0\text{-}12\ hrs}$ (nmol*hr/L) (Study FAS 106533)

Treatment	**Adjusted Geometric Mean**	**95% Confidence Interval of Geometric Means**
FP HFA (n=16) Placebo (n=18)	2465.4 2585.3	(1953.3, 3111.7) (2075.4, 3220.5)
Comparison	**Ratio of Geometric Means**	**95% Confidence Interval of Ratio**
FP / Placebo	0.95	(0.72, 1.27)

However, these results should be interpreted with caution. An open-label, one-way, single sequence study design (placebo followed by FP HFA treatments) with no assessment of baseline and no wash-out period between treatments was used for the assessment of HPA axis suppression. The potential period effect may be a confounding factor. The study design might not be ideal for this patient population due to the following reasons:

- Serum cortisol circadian rhythm is not well established before 2 years of age[2].
- Cortisol levels are highly dependent on stress levels and wake-sleep patterns which are predominant in infants.

This reviewer acknowledges the ethical and technical difficulties in assessing the degree of HPA axis suppression in infants and given that the Division previously agreed with the sponsor on the design, the results of this study (based on the ratio of geometric means) might be sufficient for the purpose of compliance with PREA requirements.

The sponsor may need to further evaluate the potential effect on HPA axis in children 6 to < 12 months of age receiving multiple doses of Flovent HFA MDI if an indication is pursued in this pediatric population. This recommendation is based on the limitations mentioned above with regards to study design and the findings that the FP mean systemic exposure ($AUC_{0\text{-}12\ hrs}$) in children 6 to < 12 months of age may be 2.7 times of that observed in children 4 to 11 years of age via cross study comparison.

PK of FP and HPA Axis Effect in Children 1 to < 4 Years of Age

Study FAS30030 was included in SE5-004 submission dated April 28, 2005 and reviewed by Drs. Shinja Kim and He Sun[1]. Study FAS30030 was a randomized, stratified, double-blind, parallel-group, placebo-controlled, and 12-week trial. Pediatric asthma patients (1 to < 4 years of age) received Flovent HFA MDI 88mcg BID or Placebo

[2] **Knutsson, U. et al. (1997) Circadian Cortisol Rhythms in Healthy Boys and Girls: Relationship with Age, Growth, Body Composition, and Pubertal Developmenta1. J. Clin. Endoc & Met. Vol. 82:2, 536-540**

HFA delivered via an MDI and a Valved Holding Chamber with facemask. The objectives of this study were to evaluate the efficacy and safety of FP HFA 88mcg BID delivered via an MDI and a valved holding chamber with facemask in the treatment of asthma in pediatric subjects aged 1 to <4 years, to characterize the systemic exposure of FP HFA after 12 weeks of treatment, and to assess parental nighttime awakenings due to the child's asthma, and parental satisfaction with treatment.

This study included a population PK analysis. The geometric means of some PK parameters were estimated using individual post-hoc values. The geometric mean (95% CI) Cmax and AUC values in children 1 to < 4 years of age were 21.86 pg/mL (20.74, 22.98) and 141.30 pg.hr/mL (127.15, 155.63), respectively. It was concluded that the systemic exposure (geometric mean AUC=141. 30 pg*hr/mL) estimated in this pediatric population was about 4-fold higher than that observed in children 4 to 11 years of age (geometric mean AUC = 28 pg*hr/mL). In addition, the population PK analysis demonstrated that none of the demographic (e.g., age, weight, height, BMI, gender, ethnicity) had an effect on FP PK.

As part of Study FAS30030, timed 12-hour overnight urine for the analysis of cortisol and creatinine levels was collected within 2 evenings prior to Randomization Visit and within 2 evenings prior to the subjects' last visit (Week 12 or Premature discontinuation). The mean 12-hour urine cortisol excretion change from baseline was -0.5 and -0.4 mcg for placebo HFA (N = 42) and the Flovent HFA 88mcg (n = 73) treatment groups, respectively. The median 12-hour urine cortisol excretion change from baseline was -0.2 and -0.5 mcg for placebo HFA (N = 42) and the Flovent HFA 88mcg (n = 73) treatment groups, respectively.

2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Flovent HFA MDI (44, 110, and 220 mcg) was approved on May 14, 2004 for the maintenance treatment of asthma as prophylactic in adolescents and adults patients 12 years and older. In the approval letter for the May 14, 2004 submission, the Agency advised the sponsor to conduct pediatric studies in children 6 to <12 months of age as a postmarketing study commitment. Flovent HFA MDI in children 4 to11 years of age was submitted on April 28, 2005 and approved in February 2006. Data from studies conducted in children 1 to <4 years of age were also included in the submission; however the results from studies in children 1 to < 4 years of age were not included in the approved labeling at that time since the submission was approved only for children 4 years and older. In the approval letter dated February 2006, the Agency issued a revised commitment to submit pediatric studies in children 6 months to < 4 years of age. The present submission fulfills the final aspect of the postmarketing study commitment requirement with a study (Study FAS106533) in children 6 to < 12 months of age. Study FAS106533 is entitled "A repeat-dose, open-label, 2-session study to assess the systemic exposure to, and pharmacodynamics of, FP HFA inhalation aerosol 88 mcg administered twice-daily for 28 days delivered via an MDI and valved holding chamber with infant face mask to

subjects ages 6 months to <12 months who have experienced 2 or more wheezing episodes in the preceding 6 months".

The present submission includes revised labeling that incorporates the results from Study FAS106533 (PK, PD, and safety information in children 6 to < 12 months of age) and Study FAS30030 (PK, PD, and safety data in children 1 to < 4 years of age) by cross-reference. Study FAS30030 was included in the April 28, 2005 submission to NDA 21-433 (s004). Study FAS30030 was a randomized, stratified, double-blind, parallel-group, placebo-controlled, 12- week, trial of Flovent HFA MDI 88mcg BID versus Placebo HFA delivered via an MDI and a Valved Holding Chamber with facemask in pediatric subjects 1 to <4 Years of age with asthma. This study included a population PK analysis reviewed by Drs. Shinja Kim and He Sun[1].

2.1.2 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Drug Substance

The active component of Flovent Inhalation Aerosol is Fluticasone propionate , a glucocorticoid having the chemical name S-(fluoromethyl)6 ,9-difluoro-11 ,17-dihydroxy- 6 -methyl-3- oxoandrosta-1,4-diene-17 -carbothioate, 17-propionate and the following chemical structure:

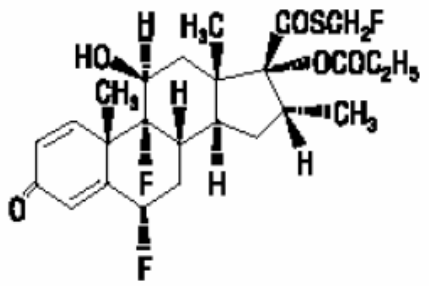

Figure 2.1.2.1. Structural formula of FP
Molecular formula: $C_{25}H_{31}F_3O_5S$
Molecular weight: 500.6
Solubility: FP is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

Drug Product

Flovent HFA inhalation aerosol is pressurized, metered-dose aerosol unit intended for oral inhalation only. Each unit contains a microcrystalline suspension of FP (micronized) in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients. It is available as Flovent HFA 44, 110 and 220 mcg inhalation Aerosol.

2.1.3 What are the approved therapeutic indication(s), dosage and administration?

INDICATION, DOSAGE AND ADMINISTRATION (as per proposed labeling)

Flovent HFA MDI is indicated for maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. The recommended starting dosage and the highest recommended dosage of Flovent HFA, based on prior asthma therapy, are listed in Table below.

Flovent HFA is not approved in children < 4 years of age.

Table 2. Recommended Dosages of FLOVENT HFA
NOTE: In all patients, it is desirable to titrate to the lowest effective dosage once asthma stability is achieved.

Previous Therapy	Recommended Starting Dosage	Highest Recommended Dosage
Adolescent and adult patients (≥12 years)		
Bronchodilators alone	88 mcg twice daily	440 mcg twice daily
Inhaled corticosteroids	88–220 mcg twice daily*	440 mcg twice daily
Oral corticosteroids†	440 mcg twice daily	880 mcg twice daily
Pediatric patients (4 to 11 years)‡	88 mcg twice daily	88 mcg twice daily

*For Patients Currently Receiving Inhaled Corticosteroid Therapy: Starting dosages above 88 mcg twice daily may be considered for patients with poorer asthma control or those who have previously required doses of inhaled corticosteroids that are in the higher range for that specific agent.

†For Patients Currently Receiving Chronic Oral Corticosteroid Therapy: Prednisone should be reduced no faster than 2.5 to 5 mg/day on a weekly basis, beginning after at least 1 week of therapy with FLOVENT HFA. Patients should be carefully monitored for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency (see WARNINGS). Once prednisone reduction is complete, the dosage of fluticasone propionate HFA should be reduced to the lowest effective dosage.

‡Recommended pediatric dosage is 88 mcg twice daily regardless of prior therapy.

2.2 General Clinical Pharmacology

2.2.1 What is the systemic exposure of FP in children 6 to < 12 months of age following multiple administration of Flovent HFA MDI 88 mcg BID?

The PK of FP in asthmatic children 6 to < 12 months of age was evaluated in an open-label, repeat dose, single-sequence, two session study. In Session 1, subjects received 2 inhalations of placebo HFA MDI twice daily for 14 days. In Session 2, subjects received 2 inhalations of Flovent HFA MDI 88 mcg twice daily for 28 days. Blood samples for analysis of FP concentrations were collected at 1 h post-dose following the morning dose on Day 14 (Session 1) and at 0, 1, 4, 8, and 12 h post-dose on Day 28 (Session 2). Plasma concentrations of FP for Session 1 Day 14 were listed to ensure that data from subjects with FP exposure before Session 2 were not used in the analysis. Twenty three subjects were enrolled in the study and 17 of them were included in the PK statistical analysis. Table 2.2.1.1 summarizes the key PK parameters. Figure 2.2.1.1 shows the mean (min, max) FP plasma concentration time profile following multiple administration of Flovent HFA MDI.

Table 2.2.1.1. Flovent HFA MDI Pharmacokinetic in children 6 to <12 months of age

	Geometric Mean (CV%) [95% CI]	
	Cmax (pg/mL)	**AUC(0-t) (pg hr/mL)**
Children 6 to <12 months (N=17)	24.6 (172) [13, 45]	75.0 (289) [34, 166]

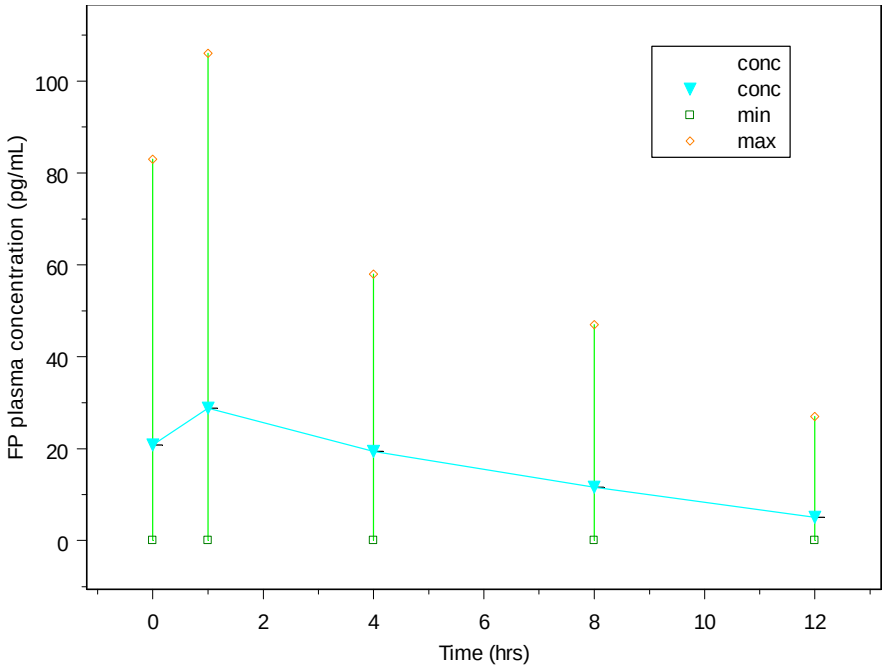

Figure 2.2.1.1. Mean (min, max) FP plasma concentration following multiple administration of Flovent 88 mcg BID administered via the HFA MDI to children 6 to < 12 months of age using the valved holding chamber with face mask (data taken from study FAS106533).

It is noted that AUC values as low as 8 pg*hr/mL were reported for some subjects who had BLQ samples throughout the sampling interval. The elimination of these subjects and others that had AUC calculated based on one or two sample-times from the AUC statistical analysis gave an arithmetic mean AUC of about 267.2 pg*hr/mL (compared to 70.5 pg*hr/mL for the 4 to 11 years old). Cmax values as low as 2 pg/mL were reported for some subjects. According to the sponsor (submission dated May 21, 2008), since NQ (non-quantifiable) data provides valuable information, values BLQ of the assay were handled as follows:

- If no concentrations were measurable, then the pre-dose concentration was set to zero and the next two data points were imputed with 1/2 BLQ (1/2 BLQ for FP was 2.5 pg/mL).
- If only one concentration was measurable at a time point other than pre-dose, then pre-dose concentration was set to zero and the subsequent NQ concentration was imputed with 1/2 BLQ.
- If only the pre-dose concentration was measurable, then the next two concentrations were imputed with 1/2 BLQ.
- If two concentrations including the pre-dose were measurable, then the subsequent NQ concentration was imputed with 1/2 BLQ.

The sponsor stated that these procedures are part of a GSK guidance document (non-compartmental analysis of pharmacokinetic data) named GUI-CPK-3001 v01 which was not included in the original submission.

It is noted that the sponsor did not follow this guidance in the calculation of PK parameters since under section 4.2 of the GSK guidance (Pharmacokinetic parameters) it

is stated the following "In cases where a planned PK parameter could not be calculated (e.g., all concentrations are non-measurable), the cell for that parameter should be set to "NC" meaning "Not Calculable".

The FP Cmax values observed in children 6 to <12 months of age ranged from BLQ to 106 pg/mL. The $AUC_{0\text{-}12\ hrs}$ values ranged from Not Calculable (all samples were BLQ) to 671.74 pg*hr/mL. Consequently, there might be a substantial bias in reporting mean values in the pK parameters, as being proposed by the sponsor. This reviewer is of the opinion that the label should reflect the range in pK parameters in addition to the geometric means.

2.2.2 How does the systemic exposure of Flovent HFA MDI in children 6 to < 12 months of age compared to that observed in older children and adults?

A cross-study comparison based on geometric mean values showed that the Cmax (24.6 pg/mL) and AUC (75 pg*hr/mL) in children 6 to < 12 months of age was similar to that observed in adults receiving the same dose of Flovent HFA MDI (88 mcg BID). Compared to older children, the AUC in children 6 to < 12 months of age was about 2.7-times of and 50% lower than that in children 4 to 11 years of age and 1 to <4 years of age, respectively) (Table 2.2.2.1) (Figure 2.2.2.1). The $AUC_{0\text{-}12\ hrs}$ ranged from Not Calculable to 671.74 pg*hr/mL and from Not Calculable to 332 pg*hr/mL for children 6 to < 12 months and children 4 to < 11 years of age, respectively.

It is noted that the mean AUC in children 1 to < 4 years of age was about 5-times of that observed in children 4 to 11 yeas of age (Table 2.2.2.1 and Figure 2.2.2.2). It is also noted that data from another study (FAS10002 submitted under NDA 21-433 s004 on Apr 28, 2005) showed that the systemic exposure in children 1 to < 4 years of age is similar to that observed in children 6 to < 12 months of age (Figure 2.2.2.3).

As mentioned before, since there might be a substantial bias in reporting mean values in the pK parameters as being proposed by the sponsor, the label should reflect the range in pK parameters in addition to the geometric means.

Table 2.2.2.1. Flovent HFA MDI Pharmacokinetic Parameters across ages

	Geometric Mean (CV%) [95% CI]	
	Cmax (pg/mL)	**AUC(0-12h) (pg hr/mL)**
Children 6 to <12 months (N=17)	24.6 (172) [13, 45]	75.0 (289) [34, 166]
Children 1 to <4 years[a] (N=13)	21.86 [21, 23]	141.39 [127, 156]
Children 4 to 11 years[b] (N=13)	15.1 [9,27]	28 [10,80]
Adults[b] (N=20)	25 [18, 36]	76 [33, 175]

[a] Data from NDA 21-433 review based on Pop PK analysis [1]. [b]Taken from approved Flovent HFA PI.

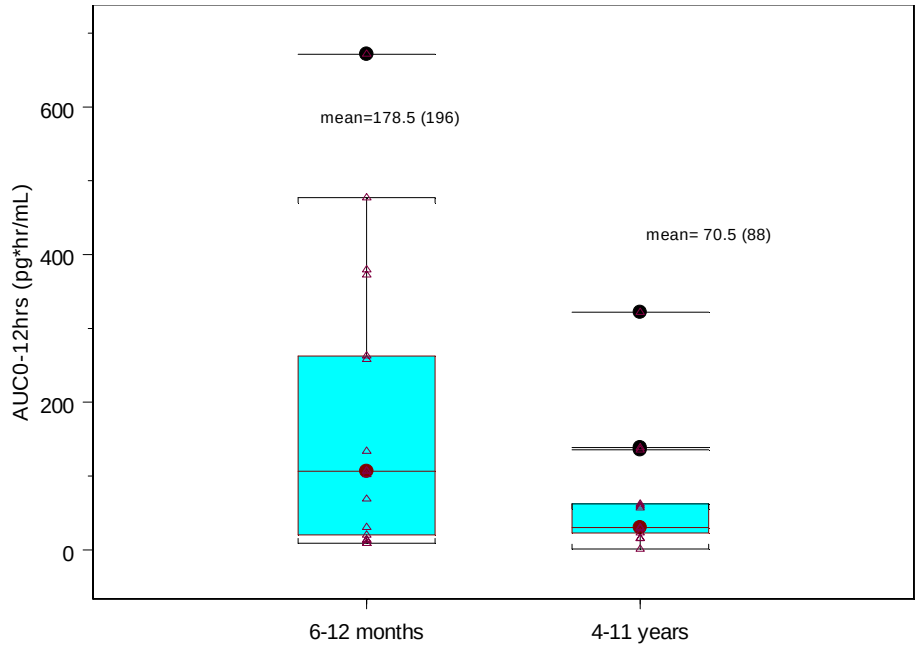

Figure 2.2.2.1. FP AUCt box plot following multiple administration of Flovent HFA 88 mcg BID to children 6 to < 12 months of age (N=18) (data from study FAS106533) and to children 4 to 11 years of age (N=13) (data from study FAP19058 submitted under NDA 21-433 s004 on Apr 28, 2005).

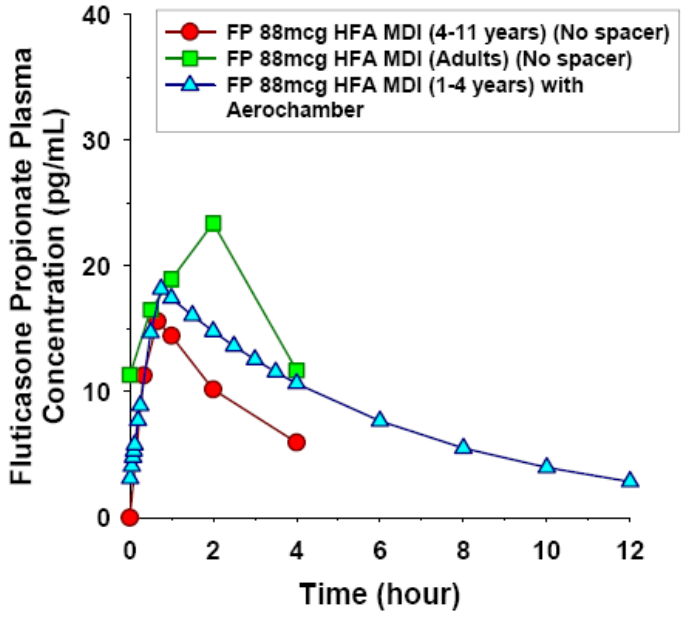

Figure 2.2.2.2 Steady-state plasma FP concentration – time profiles following Flovent HFA MDI 88mcg with Aerochamber Plus Spacer in 1-4 years old and without Spacer in 4-11 years old Asthmatic children compared to that in adults (graph taken from study S30030).

Figure 2.2.2.3. Individual plasma concentrations of FP following multiple administration of FP 88 mcg or placebo (big red triangles) administered via the HFA MDI in: children 6 to < 12 months of age (data from study FAS106533) and in children 1 to <4 years of age (data from study FAS10002 submitted under NDA 21-433 s004 on Apr 28, 2005). Subject 203 (big red triangle was not included in the PK Concentration Population due to a detectable FP concentration at Session 1 Day 14 (placebo).

2.2.3 What is the effect of FP on the HPA axis in children 6 to < 12 months of age following multiple administration of Flovent HFA MDI 88 mcg BID?

The PD (HPA axis suppression) of FP in asthmatic children 6 to < 12 months of age was evaluated in Study FAS106533. As mentioned before, this study was an open-label, repeat dose, single-sequence, two session study. In Session 1, subjects received 2 inhalations of placebo HFA MDI twice daily for 14 days. In Session 2, subjects received 2 inhalations of Flovent HFA MDI 88 mcg twice daily for 28 days. Blood samples (approximately 2 mL) for serum cortisol analysis were collected at 0, 2, 4, 8, and 12 h post-dose following the morning dose on Day 14 (Session 1) and on Day 28 (Session 2).

Figures 2.2.3.1 and 2.2.3.2 show no apparent evidence for a reduction in serum cortisol levels with Flovent HFA 88mcg as measured by the 12-h serum cortisol estimations in children 6 to <12 months of age following multiple administration of Flovent HFA MDI 88 mcg BID. The serum cortisol levels following multiple administration of Flovent HFA MDI was similar to that after placebo treatment. In addition, the estimates and 95% confidence intervals for the geometric means for both Flovent HFA and placebo were similar (Table 2.2.3.1).

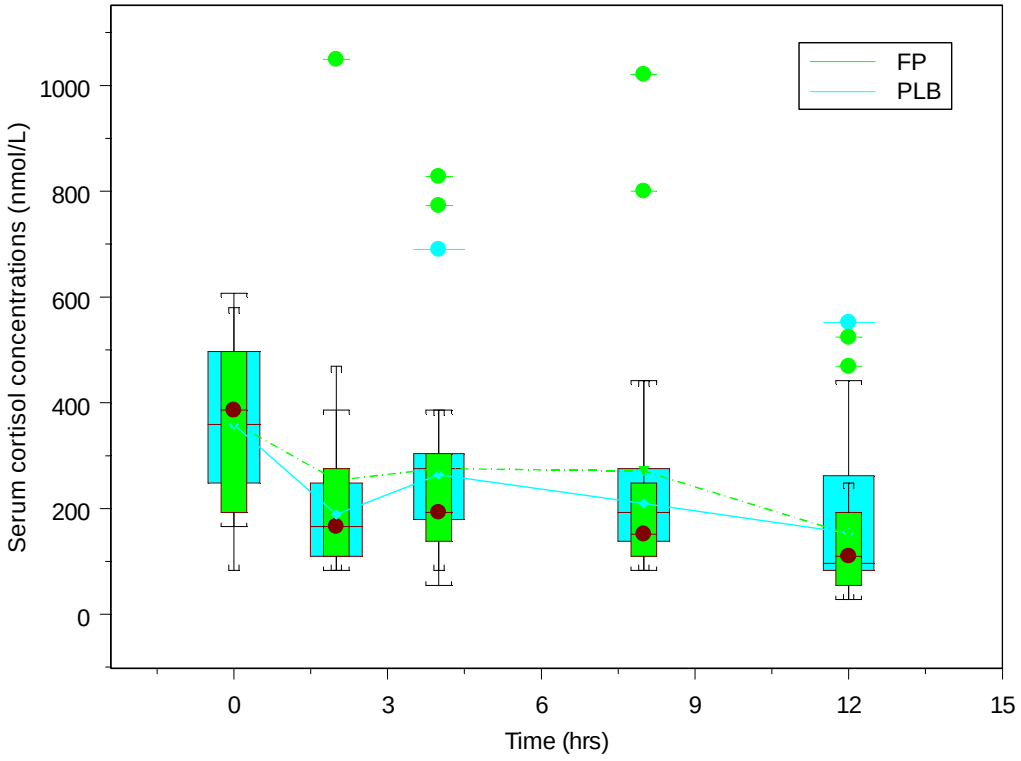

Figure 2.2.3.1. Serum cortisol Box plot and mean (arithmetic) serum cortisol concentrations over a 12 hour interval following multiple administration of the treatments (PLB:days 1-14; Flovent HFA MDI: days 15-43.

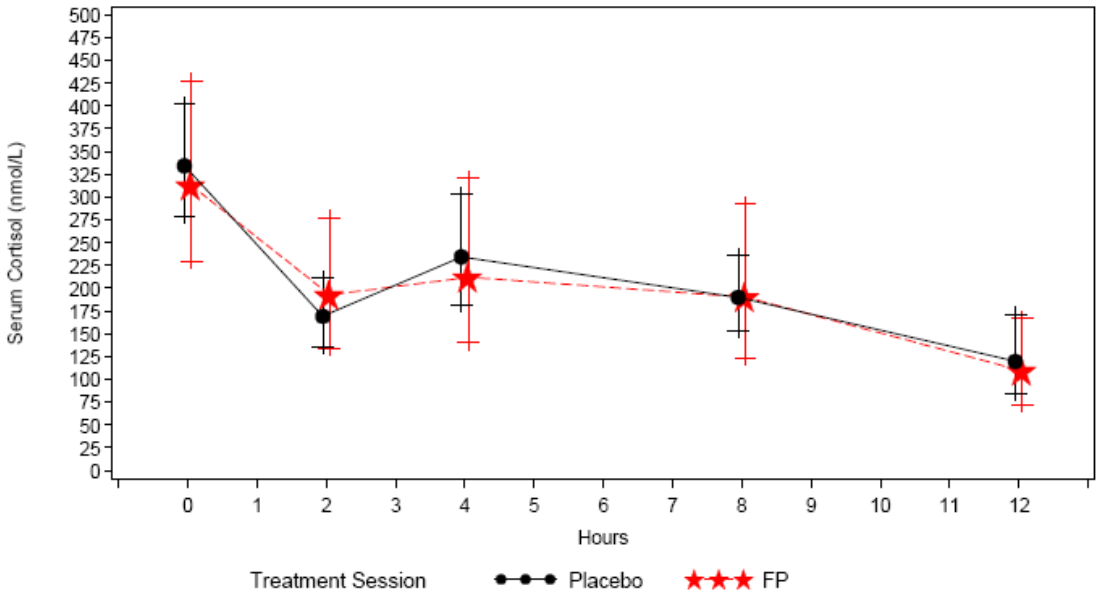

Figure 2.2.3.2. Geometric Mean (95% CI) serum cortisol over time (Study FAS106533) (data reported by sponsor).

Table 2.2.3.1. Serum Cortisol Results for Weighted Mean (0-12h) from Repeated Measures Analysis (Study FAS106533)

Treatment	**Geometric Mean (nmol/L)**	**95% Confidence Interval of Geometric Means**
Flovent HFA Placebo	184.58 191.65	(144.59, 235.64) (153.66, 239.03)
Comparison	**Ratio of Geometric Means**	**95% Confidence Interval of Ratio**
Flovent HFA / Placebo	0.96	(0.71, 1.31)

Initially, no individual estimates of cortisol AUC were reported in this study. The statistical analysis used to compare the treatments was the weighted means over the periods 0-12 hrs. Weighted geometric means were computed by the sponsor to maximize the use of the data since some subjects have some missing samples. Since the use of use of weighted geometric means (0-12h) for serum cortisol levels for the comparison between placebo and Flovent HFA treatments (instead of serum cortisol $AUC_{0\text{-}12\ hrs}$) may not be appropriate, the sponsor was requested to report the mean difference (95% CI) between treatments based on serum cortisol $AUC_{0\text{-}12\ hrs}$ excluding those subjects whose AUC could not be calculated.

In response to the this deficiency, the sponsor submitted the following statistical analysis for the serum cortisol $AUC_{0\text{-}12\ hrs}$ on May 21, 2008:

Table 2.2.3.2. Summary of Statistical Analysis of Log Transformed Serum Cortisol $AUC_{0\text{-}12\ hrs}$ (nmol*hr/L)

Treatment	**Adjusted Geometric Mean**	**95% Confidence Interval of Geometric Means**
FP HFA (n=16) Placebo (n=18)	2465.4 2585.3	(1953.3, 3111.7) (2075.4, 3220.5)
Comparison	**Ratio of Geometric Means**	**95% Confidence Interval of Ratio**
FP / Placebo	0.95	(0.72, 1.27)

Table 2.2.3.3. Summary of Statistical Analysis of Untransformed Serum Cortisol $AUC_{0\text{-}12\ hrs}$ (nmol*hr/mL)

Treatment	**Adjusted Mean (SE)**	**95% Confidence Interval of Geometric Means**
FP HFA (n=16) Placebo (n=18)	3036.0 (442.56) 2666.7 (416.35)	(2134.4, 3937.6) (1818.2, 3515.1)
Comparison	**Difference of adjusted Means (SD)**	**95% Confidence Interval of Ratio**
FP - Placebo	369.3 (553.48)	(-784.9, 1523.5)

It is noted that treatment comparisons give similar results whether using weighted mean or AUC over the same time interval. Nevertheless, the sponsor may require a more thorough comparison of the use of weighted geometric means of serum cortisol as a method for evaluating the degree of cortisol suppression. This could be accomplished by applying both methods (weighed means vs. AUC) to serum cortisol data from previous HPA axis studies. If it is demonstrated that the outcome of the analysis is the same regardless of the method used, we may consider the weighted geometric means of serum cortisol as an alternative to serum cortisol AUC.

It is noted that when the difference in treatments is computed (FP-PLB), a positive value (369.3 nmol*hr/L) is obtained. It suggested greater effect for the placebo treatment on cortisol levels. In this specific case, in which no baseline was determined, the values of the geometric mean ratio between FP HFA and placebo may be more appropriate than the difference in treatments. The accuracy of these results (either based on computing the difference or the ratio of geometric means) and therefore, the "true" outcome of the study is difficult to determine due to limitations in the study design. An open-label, one-way, single sequence study design (placebo followed by FP HFA treatments) with no assessment of baseline and no wash-out period between treatments was used for the assessment of HPA axis suppression. In such a design, the potential for period effect is confounded and might not be ideal for this patient population due to the following reasons:

- Serum cortisol circadian rhythm is well established by 2 years of age.
- Cortisol levels are highly dependent on stress levels and wake-sleep patters which are predominant in babies.

This reviewer acknowledges the ethical and technical difficulties in assessing the degree of HPA axis suppression in babies and given that the Agency previously agreed with the sponsor on the design, the results of this study (based on the ratio of geometric means) might be sufficient for the purpose of compliance with PREA requirements.

The sponsor may need to further evaluate the potential effect on HPA axis in children 6 to < 12 months of age receiving multiple doses of Flovent HFA MD if an indication is pursued in this children population. This recommendation is based on the limitations mentioned above and the findings that the FP mean systemic exposure ($AUC_{0\text{-}12\ hrs}$) in children 6 to < 12 months of age may be more than 2-fold higher than that observed in children 4 to 11 years of age (75 pg.hr/mL vs 28 pg.hr/mL).

2.2.4. Did the sponsor send all the appropriate information to support the suitability of the analytical method?

Concentrations of FP in human plasma were determined by solid phase extraction using [$^{13}C_3$]-FP as internal standard. Extracts were analyzed by HPLC-MS/MS using a TurboIonSpray™ interface and multiple reaction monitoring. This method has a lower limit of quantification (LLQ) of 5 pg/mL using a 500µL aliquot of human plasma.

Bias and precision were calculated using interpolated concentrations of quality control samples at three concentration levels (see Table below).

Analyte	Concentration (pg/mL)	Number of data points (n)	Inter-assay precision (%CV)	Inter-assay bias (%)	Calibration range (pg/mL)
Fluticasone propionate	16	8	17.1	-1.3	5 to 500 (r^2 ranged from 0.992 to 0.997)
	250	8	3.9	-6.4	
	400	8	4.5	-2.3	

V. LABELING COMMENTS

The sponsor's proposed changes (blue text for addition) to the PRECAUTIONS, Pediatric Use section of the labeling are shown below. This reviewer's comments are in underlined and red font for addition and a single crossover (red) for deletion.

(b) (4)

Reviewer's Remarks,

The above paragraph was found acceptable by Dr. Shinja Kim (Refer to Clinical Pharmacology review of NDA 21-433 submitted on April 28, 2005). This reviewer's comments are in red.

(b) (4)

Reviewer's Remarks,
The above paragraph is acceptable based on the results of study SAS106533 included in the present submission.

(b) (4)

Reviewer's Remarks,
The above paragraph was found acceptable by Dr. Shinja Kim (Refer to Clinical Pharmacology review of NDA 21-433 submitted on April 28, 2005).

(b) (4)

Reviewer's Remarks
The above text was found acceptable by Dr. Shinja Kim (review of Study SAS 30030 submitted under NDA 21-433 on April 28, 2005). This reviewer's comments are in red. The ratio and 95% CI of urine cortisol over 24 hours following fluticasone propionate HFA versus placebo (for the urine cortisol population) should be reported. The sponsor will be inquired to include this information in this portion of the labeling.

(b) (4)

Reviewer's Remarks

The above paragraph is acceptable based on the results of study SAS106533 included in the present submission.

4. Appendix
4.1 Individual Study Reports

"A repeat-dose, open-label, 2-session study to assess the systemic exposure to, and pharmacodynamics of, fluticasone propionate HFA inhalation aerosol 88 mcg administered twice-daily for 28 days delivered via an MDI and valved holding chamber with infant face mask to subjects ages 6 months to <12 months who have experienced 2 or more wheezing episodes in the preceding 6 months"

Document Number:	ZM2007/00094/00
Protocol No.	FAS106533
Phase:	IV
Initiation Date:	Aug 22, 2006
Completion Date:	Apr 13, 2007
Date of Report:	Oct 24, 2007

OBJECTIVE

Primary

- To determine the effect of administration of Flovent HFA MDI 88 mcg BID on 12 hour serum cortisol in pediatric subjects, ages 6 months to <12 months, who had experienced 2 or more wheezing episodes in the preceding 6 months.

Secondary

- To determine the systemic exposure to FP.
- To determine the safety and tolerability following administration of FP HFA MDI 88 mcg BID in this age group.

STUDY DESIGN AND TREATMENT ADMINISTRATION

This study was an open-label, repeat dose, single-sequence, two session study. The open-label MDIs for this study contained either FLOVENT in the 88 mcg per actuation strength with propellant HFA or only HFA propellant (i.e., placebo). In Session 1, subjects received 2 inhalations of placebo HFA MDI twice daily for 14 days (placebo). In Session 2, subjects received 2 inhalations of Flovent HFA MDI 88 mcg twice daily for 28 days (FP HFA).

In Session 1, subjects and their parents/guardians returned to the clinical facility on Day 14 for dosing and collection of PK and PD samples (if there was a scheduling conflict, the subject could return to the unit on either Day 13 or 15 to provide samples).

In Session 2, subjects and their parents/guardians returned to the clinical facility on Day 28 for dosing and collection of PK and PD samples (if there was a scheduling conflict, the subject could return to the unit on either Day 27 or 29 to provide samples). If a subject and his/her parent/guardian were unable to return to the clinical facility (due to

logistical issues) for PK and PD collection, the subject could continue to receive investigational product (at the discretion of the Investigator/Sponsor) until the subject and his/her parent were able to complete the final visit for PK and PD collection.

TREATMENT ADMINISTRATION

The open-label metered-dose inhalers for this study contained either FLOVENT in the 88 mcg per actuation strength with propellant HFA or only HFA propellant (placebo). Study drug was administered on an outpatient basis.

Table 1. Dosing Regimen

Session 1	two inhalations of placebo HFA MDI twice daily	Days 1-14
Session 2	two inhalations of Flovent HFA MDI 88 mcg twice daily	Days 1- 28

Table 2. Batch Information for Study FAS106533

Treatment	**Drug**	**Dose/Form/Route**	**Frequency/ Duration**	**Batch Number**
Placebo	Placebo HFA	Placebo/aerosol/ inhalation	2 inhalations BID for 14 days	0005
Flovent HFA	Fluticasone Propionate HFA	44 mcg/aerosol/ inhalation	2 inhalations BID for 28 days	0163

Doses were given at about the same time of day approximately 12 hours apart. Individual inhalations of placebo and Flovent HFA MDI were given about 30 seconds apart.
The valved holding chamber AeroChamber Plus with face mask was used with the MDI to administer study drug.

Pharmacodynamic Assessments

Collection and Preparation of Samples

Blood samples (approximately 2 mL) for serum cortisol analysis were collected at 0, 2, 4, 8, and 12 h post-dose following the morning dose on Day 14 (Session 1) and on Day 28 (Session 2). If sample collections for serum cortisol measurements and plasma FP were scheduled concurrently, then collection for serum cortisol measurements occurred first followed by collection for plasma FP concentrations. Table 3 shows all planned blood collections for both PD and PK assessments.

Pharmacokinetic Assessments

Collection and Preparation of Samples

Blood samples (approximately 3 mL) for analysis of FP concentrations were collected at 1 h post-dose following the morning dose on Day 14 (Session 1) and at 0, 1, 4, 8, and 12 h post-dose on Day 28 (Session 2). Plasma concentrations of FP for Session 1 Day 14 were listed to ensure that data from subjects with FP exposure before Session 2 were not used in the analysis.

Assay methods

Plasma samples were analyzed for FP using a validated method based on solid phase extraction followed by HPLC/MS/MS analysis. The lower limit of quantification (LLQ) for plasma FP was 5 pg/mL, using a 500 µL aliquot of human plasma with a higher limit of quantification (HLQ) of 500 pg/mL.

DATA ANALYSIS

Analysis populations

The Safety Population included all subjects who received at least one dose of placebo in Session 1.

The PD Population included all subjects in the Safety Population who had serum cortisol results for Session 1 Day 14 or Session 2 Day 28 with the exception of subjects who had a detectable FP level in Session 1. The PK Concentration Population included all subjects in the Safety Population who had PK results for Session 1 Day 14 or Session 2 Day 28 with the exception of subjects who had a detectable FP level in Session 1.
The PK Parameter Population included all subjects in the PK Concentration Population who had derived PK parameters for Session 2 Day 28. All available data for all subjects for whom there was sufficient information to estimate at least one PK parameter were included.

Treatment comparisons

The primary comparison was for serum cortisol weighted mean$_{(0\text{-}12h)}$ between treatments after 28 days of FP compared with 14 days of placebo (obtained from the repeated measures analysis). For the secondary endpoint of serum cortisol Cmin, the comparison was also between treatments after 28 days of FP compared with 14 days of placebo.

Pharmacodynamic analyses

A geometric mean plot of the serum cortisol concentrations over time was also plotted. The minimum serum cortisol concentration (Cmin), was derived for each session for each subject from the 0, 2, 4, 8 and 12 h concentrations. If a subject had a missing value for one of the time points within a session, Cmin was not derived for that session. The derived minimum measured serum cortisol concentrations (Cmin) were listed and summarized.

All serum cortisol concentrations were $\log_e$ transformed prior to analysis. The available concentrations at 0, 2, 4, 8 and 12 h were analyzed using a mixed model with treatment, planned relative time, and treatment by time interaction fitted as fixed effects and subject as a random effect. From this analysis, estimates of the weighted mean$_{(0\text{-}12h)}$ and corresponding 95% confidence intervals were presented for each treatment group as well as the estimate of the treatment difference and associated 95% confidence interval. These were obtained by exponentiating the estimates and 95% confidence intervals obtained using estimate statements that weight the timepoints in the same way as when using the trapezoidal rule to calculate the area under the curve.

Analysis of Serum Cortisol Cmin

The serum cortisol Cmin was analyzed using a mixed effects model on a $\log_e$ scale. Treatment was fitted as a fixed effect and subject as a random effect, using the Variance. Components structure for the G matrix. From this analysis, the adjusted geometric means for each treatment were presented, along with 95% confidence intervals. An estimate of the treatment ratio for FP versus placebo was calculated by exponentiating the difference between the adjusted means. The corresponding 95% confidence interval of the ratio was also presented.

Pharmacokinetic analyses

Pharmacokinetic analysis was carried using a non-compartment analysis. The non-compartmental analysis was performed using the analysis program WinNonlin Professional Edition version 4.0.1.

Plasma concentration-time data for FP were listed and plotted for each subject for whom concentrations were quantifiable. Individual plasma concentration-time profiles and median plasma concentration-time profiles were plotted. For each subject, the following PK parameters were derived from the plasma concentration-time data of FP:

- AUC(0-t): area under the plasma FP concentration-time curve from zero up to the last quantifiable plasma concentration
- Cmax: maximum observed plasma FP concentration
- tmax: the time of the sample in which Cmax was first measured

For each of the derived parameters, except tmax, the following descriptive statistics were calculated: n, arithmetic mean, 95% confidence intervals (CI) for the arithmetic mean, standard deviation, median, minimum, maximum, geometric mean, 95% CI for the geometric mean, standard deviation of the logarithmically transformed data and the coefficient of variation. For tmax, the arithmetic mean, 95% CI for the arithmetic mean, standard deviation, median, minimum and maximum were calculated.

RESULTS

Disposition of Subjects

Twenty-three subjects were enrolled in the study and received at least one dose of placebo. Twenty-one subjects received at least one dose of Flovent HFA. Eighteen (78%) subjects completed the study. Five (22%) subjects withdrew early. The reasons for subject withdrawal were:

- Adverse event (one subject receiving Flovent HFA withdrew due to varicella infection)
- Lost to follow-up (one subject receiving placebo)
- Parent decision (one subject receiving placebo and one subject receiving Flovent HF
- Other (one subject receiving Flovent HFA withdrew because medication was not administered due to an inability to obtain venous access for PK/PD sampling).

Subject disposition is summarized in Table 4.

The PD Population (N=21 for placebo, N=20 for FP HFA) included all subjects in the Safety Population who had serum cortisol results for Session 1 Day 14 or Session 2 Day 28 with the exception of any subject having a detectable FP concentration at Session 1 Day 14. Subject 503 (withdrawn from study while receiving placebo) was not included in the PD population. Subject 104 (lost to follow up before Session 2) was in the PD population for Session 1 but was removed from the PD population for Session 2. Subject 203 was not included in the PD Population due to a detectable FP concentration at Session 1 Day 14 (placebo). Subjects 209, 101 and 504 were also withdrawn from the study but are included in the PD population as they provided cortisol samples either in Session 1 or 2.

The PK Concentration Population (N=21 for placebo, N=17 for FP HFA) included all subjects in the Safety Population who had PK results for Session 1 Day 14 or Session 2 Day 28. Subject 503 was withdrawn before samples were collected on Session 1 Day 14. Subject 203 was not included in the PK Concentration Population due to a detectable FP concentration at Session 1 Day 14 (placebo).

The PK Parameter Population (N=17 for placebo, N=17 for Flovent HFA) included all subjects in the PK Concentration Population who had derived PK parameters for Session 2 Day 28. Subjects 209, 504, 101, and 104 were withdrawn from the study before samples were collected at Session 2 Day 28. Subject 203 was not included in the PK parameter descriptive statistics as any subject with a detectable FP level in the placebo period was excluded.

Demographic characteristics of all subjects enrolled in the study are provided in Table 5. Ages ranged from 6 to 11 months, with a mean of 9.4 months. Weight ranged from 7 to 11 kg, with a mean of 9.3 kg. More male subjects were enrolled than female subjects (78% compared with 22%, respectively).

Table 4. Subject Accountability: End of Study (FAS106533)

Number of Subjects	**Placebo Session 1**	**FP HFA Session 2**	**Total**
Planned, a N	16	16	16
Entered, N	23	21	23
Completed, n (%)	21 (91)	18 (86)	18 (78)
Total Withdrawn (any reason), n (%)	2 (9)	3 (14)	5 (22)
Withdrawn due to Serious Adverse Event, n (%)	0	0	0
Withdrawn due to Adverse Events, n (%)	0	1 (5)	1 (4)
Withdrawn due to other, n (%)	2 (9)	2 (10)	4 (17)
Lost to follow-up, n (%)	1 (4)	0	1 (4)
Subject decided to withdraw from study, n (%)	1 (4)	1 (5)	2 (9)
Other[b] n (%)	0	1 (5)	1 (4)

a. A sufficient number of subjects were planned for enrolment to ensure that at least 16 subjects completed the study (i.e., completed both treatment sessions).

b. Medication (FP HFA) not administered due to an inability to obtain venous access for PK/PD sampling.

Table 5. Demographic Characteristics of Study Population (Study FAS106533)

	n (%)
Age	
Pediatrics (6 to <12 months):	23
Mean Age (SD)	9.4 (1.59)
Age: Min, Max (months)	6, 11
Sex	
Female:	5 (22)
Male:	18 (78)
Ethnicity	
Hispanic or Latino:	7 (30)
Not Hispanic or Latino:	16 (70)
Race	
African American/African Heritage:	8 (35)
White – Arabic/North African Heritage:	1 (4)
White – White/Caucasian/European Heritage:	12 (52)
African American/African Heritage and White:	2 (9)
Weight (kg)	
Mean (SD):	9.3 (1.03)
Range: Min, Max (kg)	7, 11

Analytical Method

Plasma samples were analyzed for FP using a validated method based on solid phase extraction followed by HPLC/MS/MS analysis. The lower limit of quantification (LLQ) for plasma FP was 5 pg/mL, using a 500 µL aliquot of human plasma with a higher limit of quantification (HLQ) of 500 pg/mL. In study validation report was not provided.

Pharmacokinetic Results

Of the 85 samples following FP HFA treatment, 40% of the samples were NQ for the bioanalytical assay with a lower limit of quantification of 5 pg/mL. No detectable concentrations of FP were observed for Subjects 207 and 603. Figure 1 shows the mean (min, max) plasma concentration of FP following multiple administration (Day 28) of FP HFA MDI 88 mcg BID to children 6 to < 12 months of age. Figure 2 shows the individual plasma concentration of FP following multiple administration (Day 28) of FP HFA MDI 88 mcg BID to children 6 to < 12 months of age. Key results for FP HFA MDI PK parameter are across ages is presented in Table 6. Figure 3 shows a comparative FP plasma concentration of FP following multiple administration of FP 88 mcg or placebo administered via the HFA MDI to children 6 to < 12 months of age using the valved holding chamber with face mask and to children 1 to <4 years of age using the valved holding chambers, aerochamber plus and Babyhaler with face masks in children (data from study FAS10002 submitted under NDA 21-433 s004 on Apr 28, 2005).

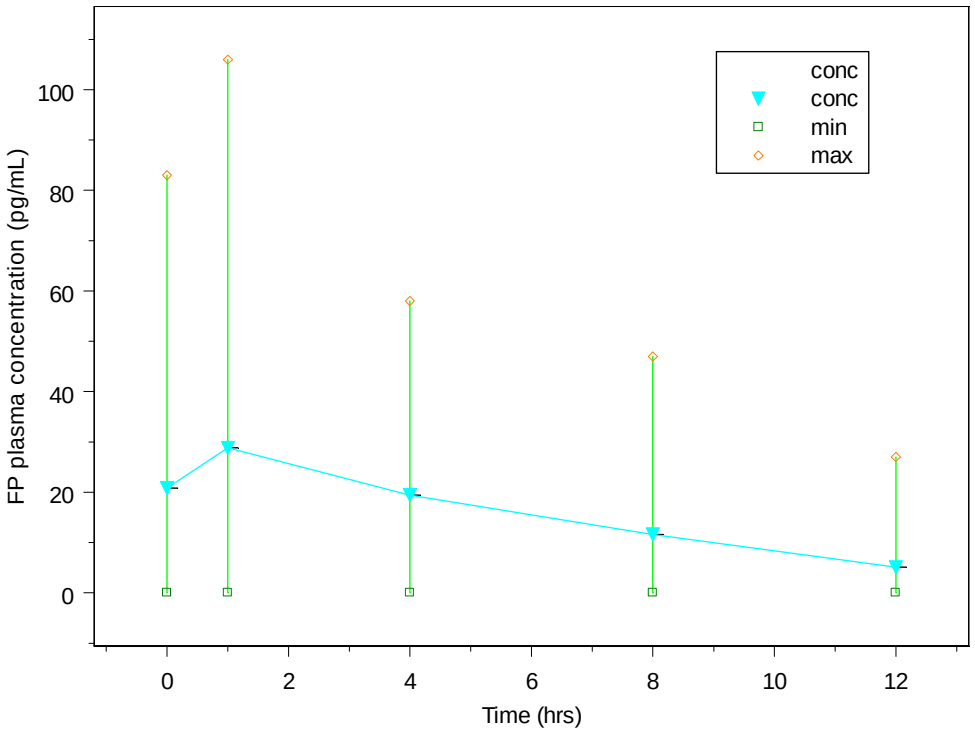

Figure 1. Mean (min, max) FP plasma concentration following multiple administration of FP 88 mcg BID administered via the HFA MDI to children 6 to < 12 months of age using the valved holding chamber with face mask (data from study FAS106533).

Figure 2. Individual fluticasone plasma concentration following multiple administration of FP 88 mcg or placebo (big red triangles) administered via the HFA MDI to children 6 to < 12 months of age using the valved holding chamber with face mask (data from study FAS106533).

Figure 3. Individual plasma concentration of fluticasone following multiple administration of FP 88 mcg or placebo (big red triangles) administered via the HFA MDI in: children 6 to < 12 months of age using the valved holding chamber with face mask (data from study FAS106533) and in children 1 to <4 years of age using the valved holding chambers, aerochamber plus and Babyhaler with face masks in children (data from study FAS10002 submitted under NDA 21-433 s004 on Apr 28, 2005).

Table 6. FP HFA MDI Pharmacokinetic Parameters across ages

	Geometric Mean (CV%) [95% CI]	
	Cmax (pg/mL)	**AUC(0-t) (pg.h/mL)**
Children 6 to <12 months (N=17)	24.6 (172) [13, 45]	75.0 (289) [34, 166]
Children 1 to <4 years[a] (N=13)	21.86 [21, 23]	141.39 [127, 156]
Children 4 to 11 years[b] (N=13)	15.1 [9,27]	28 [10,80]
Adults[b] (N=20)	25 [18, 36]	76 [33, 175]

[a] Data from NDA 21-433 review based on Pop PK analysis [3]. [b]Taken from approved Flovent HFA PI.

[3] ClinPharm review for NDA 21-433 s004 submitted on April 28, 2005 and DFS by Dr. Shinja Kim.

A closed review of the data revealed that AUC values as low as 8 pg*hr/mL were reported for some subjects who had BLQ samples throughout the sampling interval. The elimination of these subjects and others that had AUC calculated based on one or two sample-times from the AUC statistical analysis gave an arithmetic mean AUC of about 267.2 pg*hr/mL (compared to 70.5 pg*hr/mL for the 4 to 11 years old). Cmax values as low as 2 pg/mL were reported for some subjects. In addition, there are some discrepancies in the FP plasma concentration reported in the submission dated Nov 21, 2007, and those reported on May 8, 2008, (CRO Report number YAY/181) as part of the analytical method validation. For these reasons, on a letter dated May 15, 2008 the Division submitted the following comments to the sponsor:

- There are discrepancies in the fluticasone propionate (FP) plasma concentrations reported in your submission dated Nov 21, 2007, and those reported on May 8, 2008, (CRO Report number YAY/181). Specifically, the chromatograms (CRO Report number YAY/181, pages 24-25) showed that the FP plasma concentrations are 26.08 and 12.40 ng/mL for Subject 102 at pre-dose and 4 hr post dose at Period 2 Day 28, respectively. These values do not match those reported under study report FAS106533 (page 98). The reported FP concentrations in the study report were 25 and 11 pg/mL for Subject 102 at pre-dose and 4 hr post dose at Period 2 Day 28, respectively. Clarify these discrepancies.
- Submit a copy of all the individual plasma concentrations reported by the analytical site responsible for analyzing the FP concentrations from study FAS106533.

- An SOP for handling the FP plasma concentrations below the limit of quantitation (BLQ) was not included in the study report. It is noted that several low AUC 0-12hrs values were reported for some subjects whose FP concentrations were BLQ throughout the sampling interval. Explain the procedure you have used in calculating the AUC values for BLQ samples.

The sponsor responded to the above mentioned deficiencies on May 21, 2008 stating that the discrepancies identified in CRO report number YAY/181 were inadvertently included. It was mentioned that the correct plasma concentrations are those listed in the final study report FAS106533 which was submitted on November 21, 2007 and corroborated by the an amended for CRO Report YAY181. According to the sponsor, the chromatograms which were included in YAY/181 depicted the result which would be obtained if the data were acquired and processed using the proprietary software application (b) (4) However, the CRO, (b) (4), determined the FP concentrations from calibration plots using the (b) (4) software application.

According to the sponsor, since NQ (non-quantifiable) data provides valuable information, values BLQ of the assay were handled as follows:

- If no concentrations were measurable, then the pre-dose concentration was set to zero and the next two data points were imputed with 1/2 LLQ (1/2 LLQ for FP was 2.5 pg/mL).

- If only one concentration was measurable at a time point other than pre-dose, then pre-dose concentration was set to zero and the subsequent NQ concentration was imputed with 1/2 LLQ.
- If only the pre-dose concentration was measurable, then the next two concentrations were imputed with 1/2 LLQ.
- If two concentrations including the pre-dose were measurable, then the subsequent NQ concentration was imputed with 1/2 LLQ.

The sponsor stated that these procedures are part of a GSK guidance document (non-compartmental analysis of pharmacokinetic data) named GUI-CPK-3001 v01 which was not included in the original submission.

It is noted that the sponsor did not follow this guidance in the calculation of PK parameters since under section 4.2 (Pharmacokinetic parameters) it is stated the following "In cases where a planned PK parameter could not be calculated (e.g., all concentrations are non-measurable), the cell for that parameter should be set to "NC" meaning "Not Calculable".

AUC0-12hr values then ranged from Not Calculable (all samples were below the limit of quatitation) to 671.74 pg*hr/mL. Consequently, there might be a substantial bias in reporting mean values in the pK parameters, as being proposed by the sponsor. This reviewer is of the opinion that the label should reflect the range in pK parameters rather than the geometric mean.

Pharmacodynamic Results

Subject 601 had notable serum cortisol concentrations throughout the FP HFA dosing Session. At 0 hours, the concentration levels were 552 nmol/L; these levels increased to 1049 nmol/L by 2 hours postdose and remained high until 12 hours postdose when the levels returned to 524 nmol/L. According to the sponsor, no AE was reported in association with these slightly raised cortisol levels. FP levels for this subject at pre-dose were 9 pg/mL and not quantifiable (NQ) at 1, 4, 8, and 12 hours post dose.

Figure 4 shows the mean (arithmetic) serum cortisol concentrations over a 12 hour interval following multiple administration of the treatments (PLB:days 1-14; FP HFA MDI: days 15-28). Likewise, Figure 5 shows the individual serum cortisol concentration following multiple administration of the treatments. Figure 6 shows the mean serum cortisol concentrations over a 12 hour interval following multiple administration of the treatments (PLB:days 1-14; FP HFA MDI: days 15-28). Comparison of the estimate of the ratio of the geometric weighted mean$_{(0\text{-}12hrs)}$ for FP HFA compared to placebo is shown in Table 7. The estimates and 95% confidence intervals for the geometric means for both FP HFA and placebo were similar. Table 8 shows a comparison of FP HFA versus placebo for the minimum cortisol concentration over the interval 0 to 12 hours.

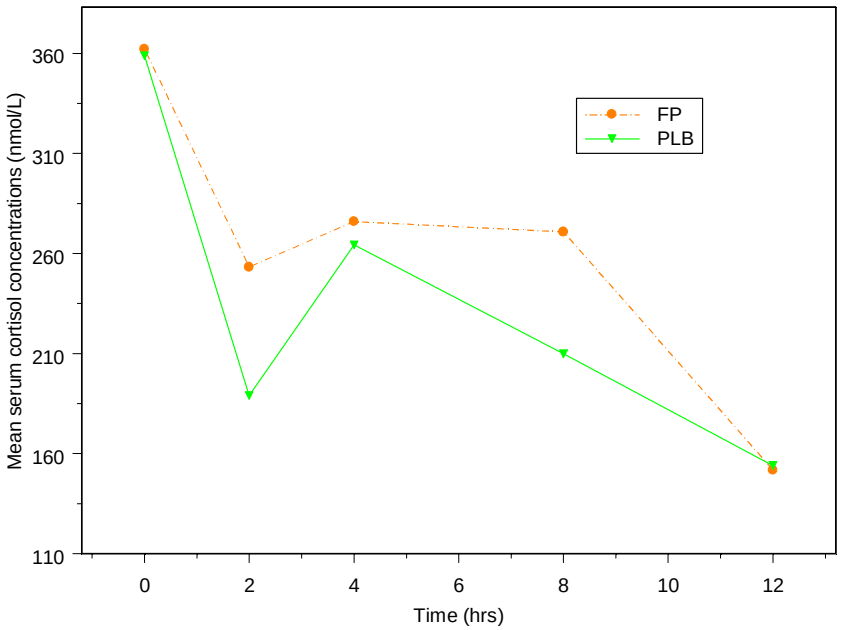

Figure 4. Mean (arithmetic) serum cortisol concentrations following over a 12 hour interval following multiple administration of the treatments (PLB:Days 1-14; FP HFA MDI: Days 15-43).

Figure 5. Individual serum cortisol concentration following multiple administration of the treatments.

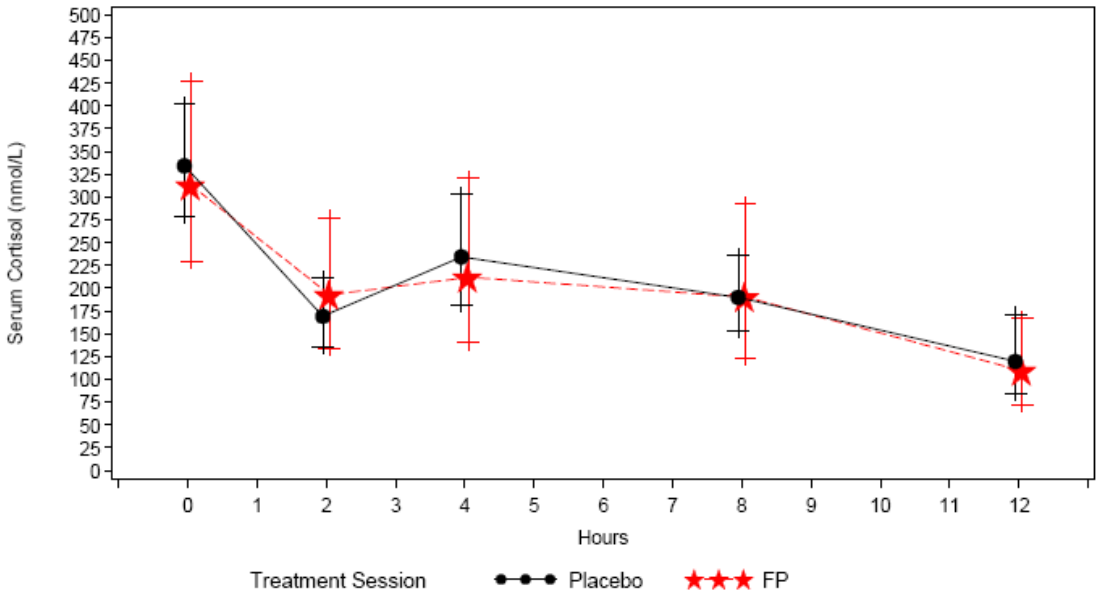

Figure 6. Geometric Mean (95% CI) serum cortisol over time (Study FAS106533) (data reported by sponsor).

Table 7. Serum Cortisol Results for Weighted Mean (0-12h) from Repeated Measures Analysis (Study FAS106533)

Treatment	**Geometric Mean**	**95% Confidence Interval of Geometric Means**
FP HFA Placebo	184.58 191.65	(144.59, 235.64) (153.66, 239.03)
Comparison	**Ratio of Geometric Means**	**95% Confidence Interval of Ratio**
FP HFA / Placebo	0.96	(0.71, 1.31)

Table 8. Minimum Serum Cortisol Results (Study FAS106533)

Treatment	**Geometric Mean**	**95% Confidence Interval of Geometric Means**
FP HFA Placebo	91.56 103.25	(64.00, 131.01) (74.47, 143.15)
Comparison	**Ratio of Geometric Means**	**95% Confidence Interval of Ratio**
FP / Placebo	0.887	(0.579, 1.359)

Reviewer's Remarks

Initially, no individual estimates of cortisol AUC were reported in this study. The statistical analysis used to compare the treatments was the weighted means over the periods 0-12 hrs which is not the typical way to assess for cortisol suppression: cortisol AUC change from baseline to endpoint compared to placebo treatment. In addition, the study design was also different in this study. Usually, PLB and drug under investigation are administered in a parallel design.

For these reasons, on a letter dated May 15, 2008 the Division submitted the following comment to the sponsor:

- The use of weighted geometric means (0-12h) for serum cortisol levels for the comparison between placebo and Flovent HFA treatments (Study FAS106533) instead of serum cortisol AUC (0-12hr) may not be appropriate. Report the mean difference (95% CI) between treatments based on serum cortisol $AUC_{0\text{-}12\ hrs}$ excluding those subjects whose AUC could not be calculated from study FAS106533.

In response to the this deficiency, the sponsor submitted the following statistical analysis for the serum cortisol $AUC_{0\text{-}12\ hrs}$ on May 21, 2008:

Table 9. Summary of Statistical Analysis of Log Transformed Serum Cortisol AUC (0-12h) (nmol.h/L)

Treatment	**Adjusted Geometric Mean**	**95% Confidence Interval of Geometric Means**
FP HFA (n=16) Placebo (n=18)	2465.4 2585.3	(1953.3, 3111.7) (2075.4, 3220.5)
Comparison	**Ratio of Geometric Means**	**95% Confidence Interval of Ratio**
FP / Placebo	0.95	(0.72, 1.27)

Table 10. Summary of Statistical Analysis of untransformed Serum Cortisol AUC (0-12h) (nmol*hr/mL)

Treatment	**Adjusted Mean (SE)**	**95% Confidence Interval of Geometric Means**
FP HFA (n=16) Placebo (n=18)	3036.0 (442.56) 2666.7 (416.35)	(2134.4, 3937.6) (1818.2, 3515.1)
Comparison	**Difference of adjusted Means (SD)**	**95% Confidence Interval of Ratio**
FP - Placebo	369.3 (553.48)	(-784.9, 1523.5)

It is noted that treatment comparisons give same results whether using weighted mean or AUC over the same time interval. Nevertheless, the sponsor will be advised that the acceptance of weighted means for future submission will require a more thorough comparison of the use of weighted geometric means of serum cortisol as a method for

evaluating the degree of cortisol suppression. This could be accomplished by applying both methods (weighed means vs. AUC) to serum cortisol data from previous HPA axis studies. If it is demonstrated that the outcome of the analysis is the same regardless of the method used, we may consider the weighted geometric means of serum cortisol as an alternative to serum cortisol AUC.

It is noted that when the difference in treatments is computed (FP-PLB), a positive value (369.3 nmol*hr/L) is obtained meaning higher effect for the placebo treatment on cortisol levels. In this specific case, in which no baseline was determined and therefore, the values are not reported as "change from baseline" computing the ratio may me more appropriate than the difference in treatments. The accuracy of these results (either based on computing the difference or the ratio of geometric means) and therefore, the "true" outcome of the study is difficult to determine due to flows in the study design. An open-label, one-way, single sequence study design (placebo followed by FP HFA treatments) with no assessment of baseline and no wash-out period between treatments was used for the assessment of HPA axis suppression. In such a design, the potential for period effect is confounded and might not be ideal for this patient population due to the following reasons:

- Serum cortisol circadian rhythm is well established by 2 years of age[4].
- Cortisol levels are highly dependent on stress levels and wake-sleep patters which are predominant in babies.

This reviewer acknowledges the ethical and technical difficulties in assessing the degree of HPA axis suppression in babies and given that the Agency previously agreed with the sponsor on the design, the results of this study might be sufficient for the purpose of compliance with PREA requirements.

The sponsor may need to conduct additional study (ies) to evaluate the potential effect on HPA axis in children 6 to < 12 months of age receiving multiple doses of Flovent HFA MD if an indication is pursued in this children population. This recommendation is based on the flaws mentioned above and the findings that the FP mean systemic exposure (AUC0-12 hrs) in children 6 to < 12 months of age may be more than 2-fold higher than that observed in children 4 to 11 years of age.

CONCLUSIONS

- The FP AUC 0-12 hrs values observed in children 6 to <12 months of age ranged from Not Calculable (all samples were below the limit of quatitation) to 671.74 pg*hr/mL.
- The FP Cmax values observed in children 6 to <12 months of age ranged from below the limit of quatitation (BLQ) to 106 pg/mL.
- The mean FP AUC0-12 hrs in children 6 to < 12 months of age may be more than 2-fold higher than that observed in children 4 to 11 years of age.

[4] **Knutsson, U. et al. (1997) Circadian Cortisol Rhythms in Healthy Boys and Girls: Relationship with Age, Growth, Body Composition, and Pubertal Developmenta1. J. Clin. Endoc & Met. Vol. 82:2, 536-540**

- It appears that no significant reduction in serum cortisol levels was observed in children 6 to <12 months of age following multiple administration of FP HFA MDI 88 mcg BID as measured by the 12-h serum cortisol estimations (ration of geometric means was 0.95 [CI 0.72, 1.27]. However, these results should be interpreted with caution. An open-label, one-way, single sequence study design (placebo followed by FP HFA treatments) with no assessment of baseline and no wash-out period between treatments was used for the assessment of HPA axis suppression. In such a design, the potential for period effect is confounded and might not be ideal for this patient population due to the following reasons:
    - Serum cortisol circadian rhythm is well established by 2 years of age.
    - Cortisol levels are highly dependent on stress levels and wake-sleep patters which are predominant in babies.
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