Clinical Pharmacology and Biopharmaceutics Review
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1. **Executive Summary**

The active component of FLOVENT Inhalation Aerosol is fluticasone propionate (FP), a glucocorticoid that is approved for the maintenance treatment of asthma as prophylactic therapy. It is also indicated for patients requiring oral corticosteroid therapy for asthma. FLOVENT inhalation aerosol is pressurized, metered-dose aerosol unit intended for oral inhalation only.

This submission is part of the Agency's Written Request dated June 25, 1999 requesting submission of pediatric information for Flovent Inhalation Aerosol. A population pharmacokinetic (pop PK) approach was used to determine the PK of FP in pediatric population. The safety of Flovent Inhalation Aerosol delivered through either Optichamber® or Aerochamber® with a face mask to children was studied in 2 double-blind, parallel-group, placebo-controlled, 12-week clinical trials. The first study was in children of 24-47 months of ages (Study FMS30058) and the second study was in children with age group ranging from 6 months to 23 months (Study FMS30059). A single blood sample was withdrawn from each subject at a randomized sampling time point ranging from 0 to 11 hours post inhalation of morning doses of either 44 mcg or 88 mcg of Flovent Inhalation Aerosol.

FP was detected in 13 subjects who were treated with placebo. The FP plasma concentration in these thirteen placebo treated subjects ranged from 11.2 to 135 pg/ml with a mean concentration of 40.5 pg/ml. These concentrations are within the range observed in FP treated group. The sponsor did not provide an adequate explanation for this observation thus making the reliability of the PK data questionable.

FP plasma concentrations were below the detectable levels in 49% and 31% of samples collected after oral inhalation of 44 mcg and 88 mcg doses, respectively. Overall, FP concentrations following 88 mcg dose were higher than 44 mcg dose. Concentrations were highest at 2.5 hours post dose. There was a high variability in FP plasma concentration which ranged from approximately 10 pg/ml to 450 pg/ml following 44 mcg and 88 mcg doses. For comparison, according to the current Flovent label the FP plasma concentration in adult subjects following 880 mcg inhaled dose ranges from 100 pg/ml to 1000 pg/ml. Considering the differences in study design, doses, and methodology the concentration of FP in children is not greater than in adult.

The relationship between FP systemic exposure and FP pharmacodynamics (PD) in terms of FP efficacy (change in morning and evening asthma scores, use of albuterol, symptoms free days) and safety (growth as in change in height, urinary cortisol) was explored but no relationship was found. The main reason for lack of PK/PD relationship is that inhaled FP formulations deliver the drug directly to the site of action (lungs) where it exerts its local effect. While FP systemic exposure was found to increase with height, other measures of growth did not affect this exposure. Ethnicity was also found to be a covariate, but interpretation was limited due to the small number of individuals. (b) (4)

The collection of a single blood sample from each subject was not an optimal approach for Pop PK analysis. This approach did not allow for adequate determination of individual subject's PK parameters and subsequently for PK/PD analysis.

1.1 Comments to the Medical Officer:

1. The reliability of the PK data is questionable due to the fact that FP was detected in 13 subjects who were treated with placebo. The FP plasma concentration in these subjects ranged from 11.2 pg/ml to 135 pg/ml. The sponsor did not provide adequate explanation for this observation (fax dated may 15, 2003)
2. The population PK study is acceptable. Please note that only a single blood sample was collected from each subject over a dosing interval. This design prevented the estimation of individual subject's PK parameters which, if estimated, could be used in the subsequent PK/PD analysis.
3. Plasma FP concentrations following the 88 mcg dose were higher than corresponding concentrations following the 44 mcg dose. Concentrations were highest during the first 2.5 h after dosing and averaged 54.4 pg/mL after the 88 mcg dose and 35.8 pg/mL after the 44 mcg doses.
4. There was a high variability in FP plasma concentration following both doses (10 pg/ml to 450 pg/ml). This is similar to the variability found in adult. According to the current Flovent label the FP plasma concentration in adults ranges from 100 pg/ml to 1000 pg/ml following 880 mcg inhaled doses. This also demonstrates that concentration range in children from the current study is not greater than that of adults.
5. The sponsor attempted to establish the PK/PD relationship in both studies. However, due to the low drug exposure observed in this study, no conclusive PK/PD relationship was observed.

1.2 Comments to Sponsor:

- The sponsor is requested to investigate the reasons and provide explanation for the high FP plasma concentrations in 13 subjects who were treated with placebo. The FP plasma concentration in these subjects ranged from 11.2 pg/ml to 135 pg/ml. These concentrations are considered sufficiently very high to question the reliability of the entire PK data.
- In future studies, the sponsor is advised to collect at lease 2-3 blood samples from each subjects to facilitate the establishment of population PK models and to enable the analysis of PK/PD relationship of the drug.
- The sponsor is encouraged to conduct a simulation trial to prospectively design a Pop PK study that will meet the study objective(s).

1.3 RECOMMENDATION:

The clinical pharmacology section of the submission is unacceptable to the Office of Clinical Pharmacology and Biopharmaceutics because of the major Data Quality and Integrity issues observed in the study reports.

Reviewer

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cc: HFD-570, HFD-870 (Al Habet, Fadiran, and Malinowski), Drug file (Biopharm File, Central Document Room).

2. TABLE OF CONTENTS

3. Summary of Clinical Pharmacology and Biopharmaceutics Review

The concentration of FP in pediatric patients aged 6 months to 4 years following inhalation from Flovent inhalation Aerosol were obtained using a modified population pharmacokinetic (pop PK) approach was used together with a sparse sampling scheme in two studies. The first study was in children of 24-47 months of ages (Study FMS30058) and the second study was in children with age group ranging from 6 months to 23 months (Study FMS30059). A single blood sample was withdrawn from each subject at a randomized sampling time point ranging from 0 to 11 hours post inhalation of morning doses of either 44 mcg or 88 mcg of FP. Data from all subjects from both studies were combined for pop PK analysis. As an exploratory exercise, the relationship between FP systemic exposure and some of the clinical efficacy and safety endpoints was also investigated. In addition, subjects were randomized to receive treatments via Meter Dose Inhaler (MDI) with chlorofluorocarbon (CFC) propellants and either Aerochamber in Study FMS30058 and and Study FMS30059 or Optichamber with facemask in study FMS30058 only. Both studies were randomized, double blind, placebo controlled. The following conclusions can be made from the analysis of the data from both studies:

- FP was detected in the plasma of 13 placebo treated subjects. The FP plasma concentration in these subjects ranged from 11.2 pg/ml to 135 pg/ml. If patients were truly on placebo, then these high concentrations are not acceptable from both the analytical and the PK point view. However, if patients were not on placebo, then the quality of the clinical data becomes highly questionable. The sponsor was contacted and was unable to provide adequate and convincing explanation (fax dated May 15, 2003). The sponsor made the following statement in the fax dated May 15, 2003 “In summary, many possibilities were investigated to explain FP concentrations in plasma samples of placebo subjects, but none of them give the possible explanation for this observation”

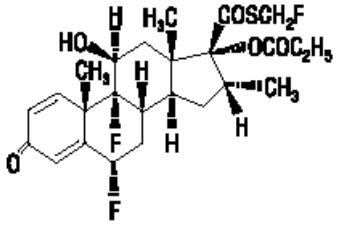
- There was no PK-PD relationship that was found in both studies. Inhaled FP formulations deliver drug directly to the site of action (lungs) when it exerts its local effects. It is therefore not surprising that a clear relationship between efficacy and systemic exposure was not observed.
- There was a high variability in the plasma concentrations among subjects in both studies. FP plasma concentrations were below the detectable levels in 49% of samples collected after 44 mcg dose and in 31 % of 88 mcg dose.
- The FP plasma concentration following both doses range from approximately 10 pg/ml to 450 pg/ml. In adults, however, the FP plasma concentration ranges from 100pg/ml to 1000 pg/ml following 880 mcg doses (current label). Therefore, considering the differences in study designs, doses, and methodology, the range of FP concentration found in children in the present study is not greater than that in adult.
- Overall, FP concentration following 88 mcg dose was higher than 44 mcg dose. Concentrations were highest during the first 2.5 h after dosing and averaged 54.4 pg/mL after the 88 mcg dose and 35.8 pg/mL after the 44 mcg doses.

- The collection of a single blood sample from each subject was not an optimal approach for Pop PK analysis. This approach did not allow for adequate determination of individual subject's PK parameters and subsequently for PK/PD analysis.
- It appears that the subject's heights and ethnic background could be important covariates. The interpretation of the ethnicity data was limited due to the small number of individual subjects in each ethnic group. (b) (4)
- There was a weak relationship between FP exposure (AUC) and several safety or efficacy scores and parameters.
- There was no relationship between exposure and cortisol level. This could be due to the low systemic drug exposure.

4. Question Based Review

4.1 What are the General Attribute of Flovent Inhalation Aerosol?

The active component of FLOVENT Inhalation Aerosol is FP, 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:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

FLOVENT inhalation aerosol is pressurized, metered-dose aerosol units intended for oral inhalation only. Each unit contains a microcrystalline suspension of fluticasone propionate (micronized) in a mixture of two chlorofluorocarbon propellants (trichlorofluoromethane and dichlorodifluoromethane) with lecithin.

4.2 What is known About the General Clinical Pharmacology and PK of FP?

This is a brief summary of the most relevant PK information to this submission. FP is a synthetic, trifluorinated glucocorticoid with potent anti-inflammatory activity. Inflammation is recognized as an important component in the pathogenesis of asthma. Glucocorticoids have been shown to inhibit multiple cell types and mediators that precipitate asthmatic symptoms. These anti-inflammatory actions of glucocorticoids may contribute to their efficacy in asthma.

Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of FP is negligible (<1%), primarily due to incomplete absorption and pre-systemic metabolism in the gut and liver. In contrast, the majority of the FP delivered to the lung is systemically absorbed. The systemic bioavailability of FP inhalation aerosol in healthy volunteers averaged about 30% of the dose delivered from the actuator. The drug is extensively metabolized with <5% of radioactivity dose excreted in urine and the remainder is excreted in feces as parent and metabolites. Most of these studies were conducted in adult healthy volunteers or patients.

4.3 What Are the Rationals of the Submission:

This submission is in reference to the Agency's Written Request dated June 25, 1999 and amended May 21, 2001and October 25, 2001 requesting submission of pediatric information for

FP (Flovent) pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act. The Written Request was for both Dermatology and pulmonary studies. In this review, the focus is only on the pulmonary studies.

The pulmonary portion of the Written Request consists of the following pediatric studies:

1) One safety study of fluticasone propionate nasal spray for the treatment of allergic rhinitis in children between the ages of >2 years and <4 years.

2) Two efficacy and safety studies (FMS30058 and FMS30059) of fluticasone propionate inhalation aerosol for the maintenance treatment of asthma as prophylactic therapy in two groups of children:

    a) Ages of >2 years and <4 years
    b) Ages >6 months and <2 years

3) *In vitro* study characterizing the dose delivery from two different US-marketed spacers (RD2000/02054/00).

4) Clinical Pharmacology/population pharmacokinetics (Pop PK) analysis report from all subjects who provided samples in the FMS30058 and FMS30059 clinical studies (Report # M2002/00318/00). For Pop PK analysis, the sponsor combined the data from both clinical studies.

(b) (4)

The current submission is considered by the sponsor as a final response which consists of the above mentioned two clinical studies, an *in vitro* study, and a population PK analysis report. Each study will be summarized below.

What are the Relevant Terminology/Abbreviations?

The following relevant definitions/abbreviations are to be used for all studies:

Intent-to-Treat (ITT) Population: Includes all subjects who were randomized, received at least one dose of study drug, but did not have any observations taken while receiving study drug.

Reduced intent-to-treat (RITT) population: This excluded from the ITT population at one of the sites, because of study conduct irregularities and also subjects at any investigative site for whom the treatment blind was broken. Following removal of PK subjects from those sites, RITT PK subset of total PK population was obtained.

Growth Population (GP): Defined as the ITT excluding subjects who had any one of the following:

1. Did not have growth assessments in at least three visits that included both baseline (Visit 2) and Week 12 (Visit 7).
2. Had a reduction in height measures from baseline to endpoint, i.e., the minimum of the triplicate height readings at baseline is larger than the maximum of the triplicate height readings at endpoint.
3. Received systemic (oral or injectable) corticosteroids or medium to high doses of inhaled corticosteroids within 8 weeks prior to any growth assessments.

The GP population was considered by the sponsor as the primary efficacy population for efficacy analysis of clinical data. Therefore, for all pharmacodynamic (PD) parameters to correlate with pharmacokinetics (PK) parameters, GP subset of all RITT PK subjects was used except for calculating urine cortisol (**UCP**) (see below). For calculating mean urine cortisol, the urine cortisol population (**UCP**) subset of all RITT PK subjects was used.

Urine Cortisol Population (UCP): This excludes those subjects from ITT population whose urine samples were considered to have confounding factors that would affect the interpretation of the results. Specifically, the UCP was defined as the ITT population but without subjects who had any one of the following:

1. Urine volume <80mL and a 12-hour creatinine excretion below the lower limit of threshold range of 6.5 mg/kg/12hrs, regardless of gender.
2. Had collection time intervals outside 12 ±2 hours.
3. Received systemic (oral or injectable) corticosteroids or medium to high doses of inhaled corticosteroids within 8 weeks prior to any start time of urine collection.
4. Used intranasal or topical corticosteroids (except □1% potency topical corticosteroids) within 30 days prior to any start time of urine collection.
5. Had been off study drug for more than one day at the start time of the post-baseline urine collection.

4.4 Study FMS30058 (or for short study 58):

What are the Objectives of the study?

The objective of this study was to evaluate the efficacy and safety of FP 44 mcg twice daily and 88 mcg BID versus placebo delivered via Meter Dose Inhaler (MDI) with chlorofluorocarbon (CFC) propellants 11/12 plus either the Aerochamber with a facemask in the treatment of asthma in pediatric patients with asthma between ages of 6-23 months.

How Was the Study Designed?

This was a 12-week, randomized, double-blind, parallel group, placebo-controlled multicenter study. It consists of two periods: screening period of 2-4 weeks and a treatment period of 12 weeks. At the end of the Screening Period, eligible subjects were randomized to receive one of the following in conjunction with either an Aerochamber or Optichamber valved holding chamber with attached facemask for the duration of the 12-week Treatment Period:

Fluticasone propionate chlorofluorocarbon (CFC) 44 mcg BID
Fluticasone propionate chlorofluorocarbon (CFC) 88 mcg BID
Placebo CFC BID

All double-blind treatment medication were delivered via MDI with CFC propellants 11/12. At each of Visits 2, 5 and 6 (Day 1/Randomization, Week 4, and Week 8, respectively), two inhalers (Inhaler A and Inhaler B) from the assigned double-blind treatment pack were dispensed to each randomized subject for use over approximately four weeks. Subjects inhaled one puff from Inhaler A and one puff from Inhaler B twice daily, approximately twelve hours apart using either an Aerochamber or Optichamber valved holding chamber with facemask.

In addition, subjects were dispensed albuterol inhalation aerosol (MDI) and/or nebules for use in relieving asthma symptoms as needed. Subjects could use either or both albuterol MDI and nebules. The number of puffs and/ or nebules of albuterol used per day was required to be documented on the daily record card by the parent/guardian. A separate valved holding chamber, other than that supplied with the study drug was used to administer albuterol if needed.

The primary efficacy endpoint was the average change from baseline in daytime and nighttime (daily) asthma symptom scores during the last two weeks of diary data prior to end of study, asthma exacerbation, or study withdrawal. Daily asthma symptom score was defined as the average of daytime and nighttime (composite) asthma symptom scores. Asthma symptom four points score system (0 to 3) was used to assess symptoms of wheeze, cough and shortness of breath. Scores were recorded by the parents or guardians. Other safety and efficacy parameters were recorded.

PK Blood Samples:

Sparse blood samples were collected 12 weeks after treatments for the determination of the plasma concentration of FP and for population PK analysis as detailed later in the next section.

Briefly, subjects were randomized to one of four particular sampling time intervals and a single blood sample of approximately 5mL was collected. If subjects were unable to provide a sample at their randomized time interval, their sample was allocated to another interval. The sampling time interval ranged from -1.0 to 0.0 hours (pre-dose), 0.25 to 2.5, 3 to 8, or 9 to 11 hours post-dose relative to the morning dose administered at Visit 7 (Week 12). Data from all subjects providing a sample in this study were combined with data from subjects in FMS30059, a similar study in subjects aged 6-23 months.

4.5 Study FMS30059 (or for short study 59):

The study objective and design is similar to that of study FMS30058. The main difference is with the children's ages, which range from 6 to 23 months in this study. Briefly, this was also 12-week, randomized, double-blind, parallel group, placebo-controlled multicenter study. The study had two periods; a Screening Period of 2-4 weeks and a Treatment Period of 12 weeks. During the Treatment Period subjects attended clinic visits at Weeks 1, 2, 4, 8, and 12 (Weeks 6 and 10 were phone contacts only). At the end of the Screening Period, eligible subjects were randomized to receive one of the following in conjunction with an Aerochamber valved holding chamber with attached facemask for the duration of the 12-week Treatment Period:

- Fluticasone propionate CFC 44 mcg BID
- Fluticasone propionate CFC 88 mcg BID
- Placebo CFC BID

As described in study FMS30058, subjects inhaled one puff from Inhaler A and one puff from Inhaler B twice daily, approximately twelve hours apart using the Aerochamber with facemask. Albuterol inhaler was also supplied and used as in study FMS30058. The primary efficacy endpoint was the average change from baseline in daytime and nighttime (daily) asthma symptom scores during the last two weeks of diary data prior to end of study, asthma exacerbation, or study withdrawal. Sparse blood samples were collected at the same time intervals as in study FMS30058. Data from all subjects providing a sample in this study were combined with data from subjects in study FMS30058.

Clinical Results:

The safety and efficacy data for both studies are discussed in the Medical Officer's review. For details, please refer to the Medical Officer's review.

4.6 Population Analysis

4.6.1 Methodology

What Were the Methodology and Study Design?

This report is based on the PK data obtained from the above described studies #58 and 59. The objectives of the analysis were:

- To describe the population pharmacokinetics (pop PK) and identify influential covariates on the PK of FP in pediatric patients with asthma
- To explore the relationship between FP systemic exposure and FP pharmacodynamics (PD) in terms of FP efficacy (change in morning and evening asthma scores etc.) and safety (growth as in change in height, urinary cortisol) parameters.

As stated above, subjects were randomized to receive FP via MDI using either an Aerochamber (Study FMS30058 and #59) or Optichamber (Study FMS30058 only) valved holding chamber with a facemask (**Table 1**).

Table 1. Distribution of Subjects By treatments

Distribution of Subjects by Treatments			
Treatment	**FMS 30058**	**FMS 30059**	**Total**
Placebo CFC	60	47	107
FP 44 CFC	70	46	116
FP 88 CFC	66	39	105
Total	196	132	328

At each site, the treatments were stratified by age as follows:

- Study FMS30059: 6-12 months and 12-23 months
- Study FMS30058: 24-36 months and 36-47 months

What Was the Number of PK Blood Samples Collected?
What is the Distribution of Blood Sampleing Times?

Subjects were randomized to a particular sampling time interval -1.0 to 0.0 (pre-dose), 0.25 to 2.5, 3 to 8, or 9 to 11 hours post-dose relative to the morning dose. **A single** blood sample was collected from **each** subject for the determination of FP concentration in plasma.

A total of 354 subjects provided blood samples for pharmacokinetic (PK) analysis. Of these, 213 samples were from study FMS30058 and 141 were from study FMS30059 (**Table 2)**. The final dataset consisted of a total of 328 samples, 196 from study FMS30058 and 132 from study

FMS30059 (**Table 1**). However, 221 samples were from subjects who have received active treatments (136 from study FMS30058 and 85 from study FMS30059).

Table 2. Summary of Eliminated Samples from the Satabase

Summary of Sample Incorporation into Population Pharmacokinetic Database				
		FMS 30058	FMS 30059	Total
1.	Total No. of analyzed samples	213	141	354
2.	Samples removed due to missing information in CRF	17	9	26
3.	Placebo Treatment	60	47	107
4.	Insufficient sample for assay	-	2	2
5.	Not reported due to problems in analysis	4	1	5
6.	Samples stored for > 15 months prior to assay	5	3	8
7.	Samples with BQL[a] concentrations	49	37	86
8.	Samples with missing body mass index data	2	1	3
9.	Sample with missing baseline asthma data	1	-	1
10.	Total no. of eliminated samples (sum of rows 2 to 9)	138	100	238
11.	Total no. of samples used for analysis (row 1 minus row 10)	75	41	116
[a] Below Quantitation Limit				

In Study FMS30058, approximately 50% of the sites distributed the Aerochamber device and 50% distributed the Optichamber device with the double-blind study drug. Neither the subject nor the investigator were blinded to the valved holding chamber device. In study FMS30059, all sites distributed the Aerochamber device.

As discussed above in Studies FMS30058 and FMS30059, subjects were dispensed albuterol inhalation aerosol (MDI) and/or nebules for use in relieving asthma symptoms as needed. Subjects could use either or both albuterol MDI and Nebules. The number of puffs and/ or nebules of albuterol used per day was required to be documented on the daily record card by the parent/guardian. A separate valved holding chamber, other than that supplied with the study drug was used to administer albuterol, if needed.

Furthermore, following removal of subjects on placebo treatment, those subjects with missing covariate documentation and those with FP concentrations below the limit of quantitation, the final dataset for PK analysis contained 116 subjects (75 from study FMS30058 and 41 from study FMS30059). Of these 50 subjects received FP44 mcg treatment and 66 subjects received the FP88 mcg treatment (**Table 3**).

Table 3. Distribution of PK Subjects By Study Population

Distribution of PK Subjects by Types of Study Population									
	FMS30058			FMS30059			Total		
	44	88	Total	44	88	Total	44	88	Total
Subjects included in the final pop PK analysis	31	44	75	19	22	41	50	66	116
RITT[a] population	31	43	74	19	22	41	50	65	115
Not in RITT population	---	1	1	---	---	---	---	1	1
Growth population	25	35	60	16	19	35	41	54	95
Not in growth population	6	9	15	3	3	6	9	12	21
Urine cortisol population	9	13	22	2	3	5	11	16	27
Not in urine cortisol population	22	31	53	17	19	37	39	50	89
[a] Reduced Intent-to-treat									

The above table shows that among 116 subjects used for pop PK analysis, 1 subject was not included in the Reduced intent-to-treat (RITT) population. Eighty-two percent (95/116) of subjects belonged to the growth population (GP) and were used in the PK-PD analysis for all PD parameters except urine cortisol. Some samples were not analyzed due to insufficient volume and assay problems. Those subjects with missing data were excluded from the urine cortisol population (UCP). Only 23% (27/116) of subjects were included in the PK-PD analysis for UCP.

4.6.2 What Was the Analytical Assay?

The plasma concentration of FP was determined using a validated LC-MS-MS method with a detection limit of 10 pg/mL. Overall, the inter and intra assay precision as measured by %CV was <10% and not more than 15% for the low and high concentration of control plasma samples. The calibration curve is linear over a range of 10 to 1500 pg/ml. Overall, this analytical assay is acceptable.

4.6.3 How Was the Data Analyzed? What PK Model Was Used?

Several NONMEM models were evaluated. Concentrations of FP in plasma were best described by a zero-order input, one-compartment model first-order elimination and an additive error model. Demographic and baseline characteristics (weight, height, age, gender), and other covariates (type of spacer, dose) were tested as covariates to evaluate their effect on PK parameters. Estimated primary parameters by the model were elimination constant *(*K) and apparent volume of (*V*/F). Individual AUC obtained from demographic and dose differences were plotted against efficacy and safety parameters to explore PK/PD relationship.

4.7 Results

- Samples from subjects who received placebo were below quantification level (BQL) of <10 pg/mL in 94 of 107 subjects. The remaining 13 samples in the placebo group (10 samples from Study FMS30058 and 3 samples from Study FMS30059) had measurable FP concentrations.
- In the 13 subjects from the placebo group the plasma concentrations ranged between 11.2 to 135 pg/mL with the mean concentration of 40.5 pg/mL. The sponsor could not explain the reason for this high FP concentration in the placebo group (fax dated May 15, 2003). From the analytical point of view, these high concentrations must be real, considering the sensitivity and specificity of the analytical method used in this study. Many other reasons could be used to explain these high FP concentrations in the placebo group. Therefore, it is up to the sponsor to provide adequate investigation and convincing explanation for the Agency to accept these data. At this point, the entire data are considered unreliable and unacceptable.
- Summary statistics for plasma FP concentration data are shown in **Table 4**.
- A scatter plot of individual subject's plasma FP concentration vs. time relative to morning dose is shown in **Figure 1**.
- There was a high variability in FP plasma concentration which ranged from approximately 10 pg/ml to 450 pg/ml following 44 mcg and 88 mcg doses. For comparison, according to the current Flovent label the FP plasma concentration in adult subjects following 880 mcg inhaled dose ranges from 100 pg/ml to 1000 pg/ml. Overall, considering the differences study design, doses, and methodology the concentration of FP in children is not greater than in adult.
- Many subjects in both treatments had FP concentrations BQL with approximately 50% of BQL data are from the lower dose (i.e., 44 mcg).
- The sponsor included the BQL data in the PK analysis and summary statistics as zero values.
- Overall, FP concentrations were consistently higher after the 88 mcg dose, compared to the 44 mcg dose. The ratios of geometric mean concentration between the 2 treatments (88 mcg / 44 mcg) were 1.29, 1.52, 1.10 and 1.47 for (pre-dose), (0h-2.5h), (>2.5h-8h), (>8h-< 12h) time intervals, respectively (**Table 4 and Figure 1**). The relationship between FP exposure (i.e., AUC) and various asthma scores and demographics are shown in **Figures 2-8.**
- There was no relationship between drug exposure and morning or evening asthma scores (**Figures 2, 3**). However, the slope of the line for the evening scores was slightly different from that of the morning (R^2=0.0008 vs R^2=0.0104). No difference was noted in the relationship between exposure and daily symptoms scores **(Figure 4**). The relationship between exposure and the use of albuterol to control asthma was variable and inconclusive (**Figure 5**). Similarly, there was no strong relationship between exposure and symptoms free days (**Figure 6**). In terms of the relationship with children's height, the data was also variable and inconclusive (**Figure 7**) and similarly for urine cortisol levels as a measure of children's growth (**Figure 8**).
- Apparent clearance (CL) and AUC were calculated for different ethnic backgrounds as shown in **Table 5**. From the data, it appears that the clearance is approximately 31% to 59% lower in Hispanics and Asians compared to Whites and Blacks.

- Simulated plasma FP concentrations vs. time data were also analyzed for both 44 mcg and 88 mcg dose using non-compartmental analysis (WinNonLin Software PK Program). **Table 6** shows the results for different ethnic backgrounds. The AUC values were also higher in Hispanics and Asians as compared to Whites and Blacks. This is in agreement with the above observation on apparent clearance (since clearance is derived from AUC).

Table 4. Summary of FP Plasma Concentration Used in the Pop PK Analysis:

Variable	Time Interval	Statistic or Category	Treatment Group: FP 44mg bid	Treatment Group: FP 88mg bid
FP Concentration (pg/mL)	Pre-dose	n	8	18
		Mean	24.94	39.67
		SD	22.50	53.76
		CV%	90	136
		Median	16.40	24.25
		Min.	11.6	10.3
		Max.	77.6	233.0
		SD logs	0.66	0.85
		Geo. Mean	19.69	25.43
		95% CI - L	11.30	16.68
		95% CI - U	34.30	38.77
	0 - 2.5 hrs	n	21	22
		Mean	59.10	68.78
		SD	94.75	51.19
		CV%	160	74
		Median	31.50	55.65
		Min.	12.0	13.2
		Max.	452.0	225.0
		SD logs	0.87	0.70
		Geo. Mean	35.80	54.41
		95% CI - L	24.10	39.83
		95% CI - U	53.18	74.33

Variable	Time Interval	Statistic or Category	Treatment Group: FP 44mg bid	Treatment Group: FP 88mg bid
FP Concentration (pg/mL)	2.5 - 8 hrs	n	18	12
		Mean	27.52	33.18
		SD	13.93	23.41
		CV%	51	71
		Median	22.05	25.50
		Min.	11.0	10.3
		Max.	54.5	80.5
		SD logs	0.50	0.67
		Geo. Mean	24.40	26.85
		95% CI - L	18.99	17.51
		95% CI - U	31.36	41.17
	8 - 12 hrs	n	3	14
		Mean	19.00	36.59
		SD	1.30	30.43
		CV%	7	83
		Median	19.70	30.70
		Min.	17.5	11.1
		Max.	19.8	122.0
		SD logs	0.07	0.75
		Geo. Mean	18.97	27.95
		95% CI - L	15.95	18.15
		95% CI - U	22.57	43.06

Figure 1. Individual Plasma FP Concentration

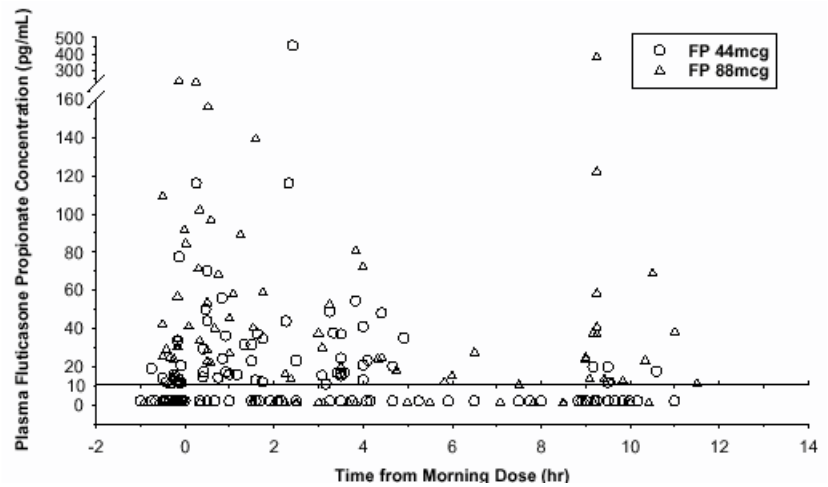


Figure 2. Relationship Between Individual FP AUC and Morning Asthma Scores

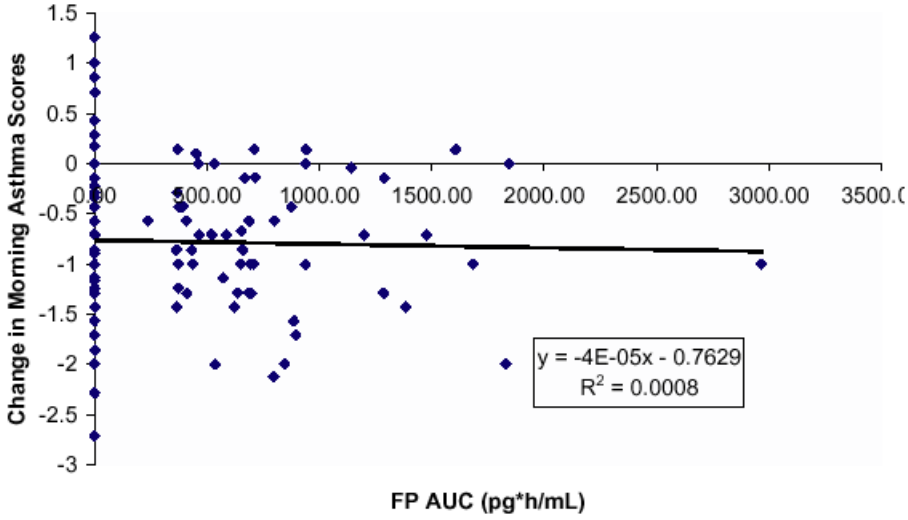


Figure 3. Relationship Between Individual FP AUC and Evening Asthma Scores

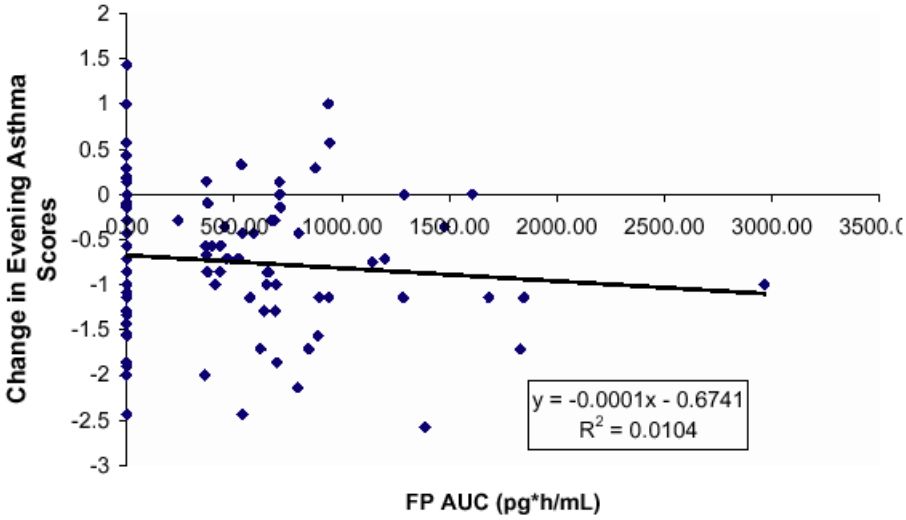


Figure 4. Relationship Between Individual FP AUC and Daily Asthma Scores

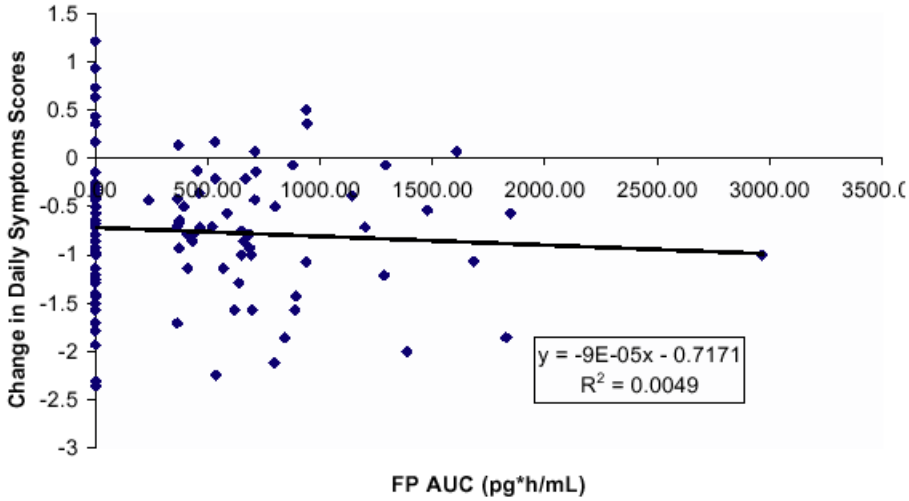


Figure 5. Relationship Between Individual FP AUC and Symptoms-Free and Albuterol-Free Days

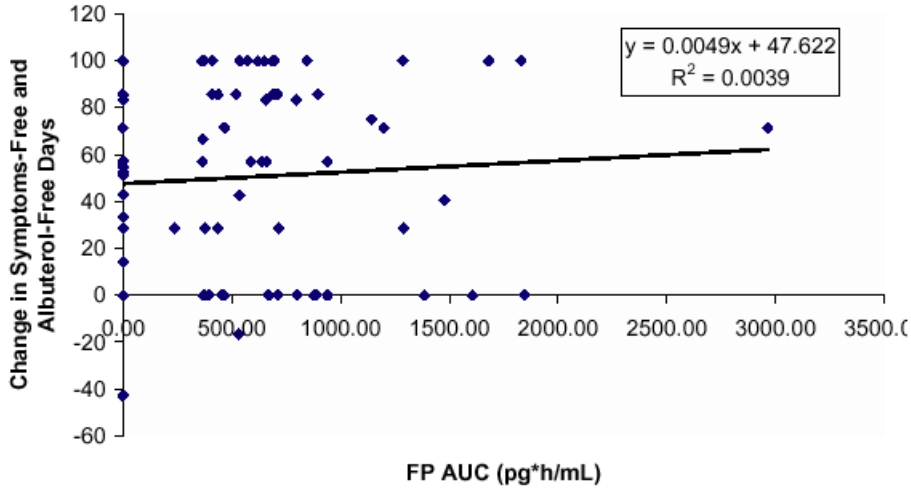


Figure 6. Relationship Between Individual FP AUC and Symptoms-Free Days

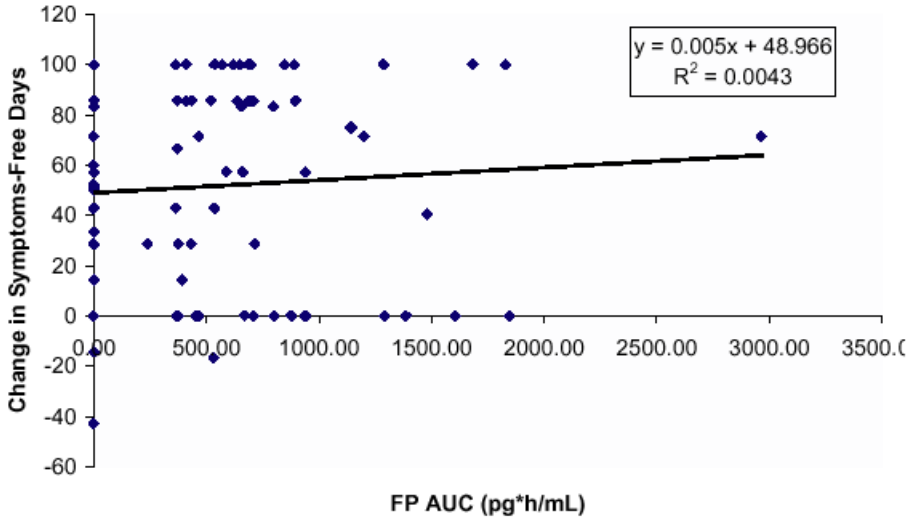


Figure 7. Relationship Between Individual FP AUC and Height as a Measure of Growth

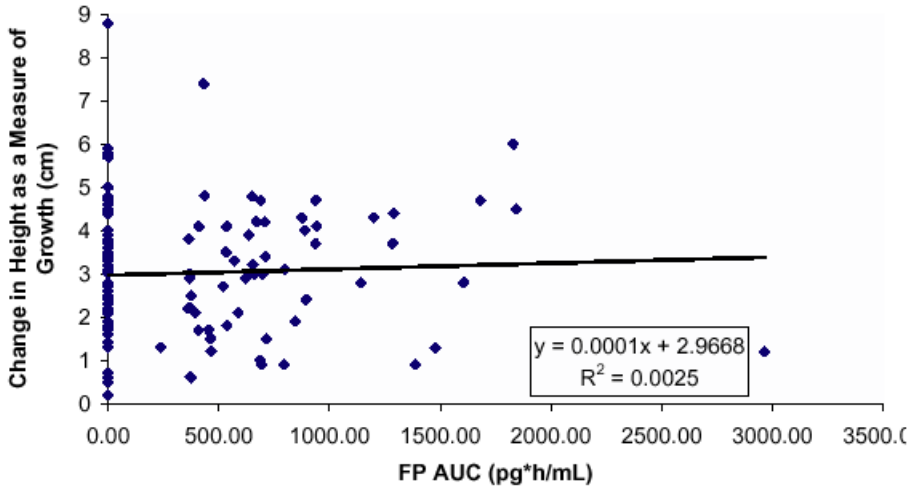


Figure 8. Relationship Between Individual FP AUC and Urine Cortisol as a Measure of Growth

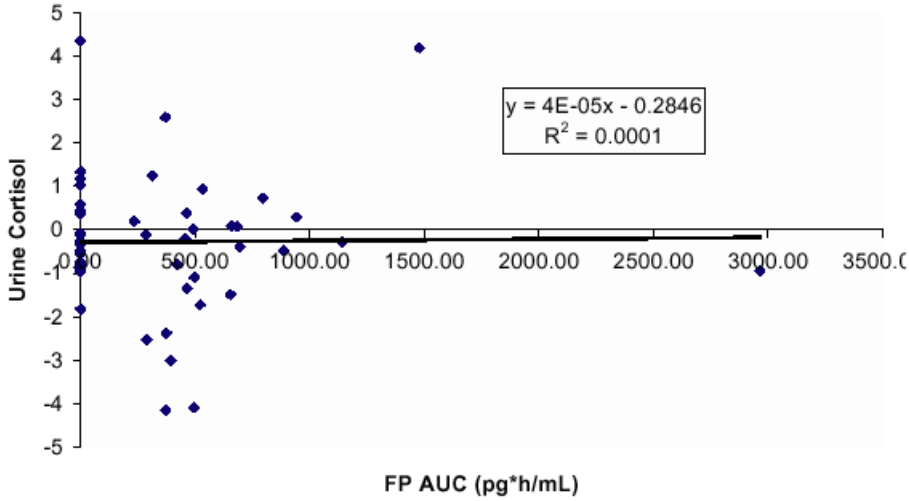


Table 5. Estimated Clearance and AUC in Different Ethnic Backgrounds

Estimation* of Clearance (*CL*) and Area under the Curve (AUC)						
Ethnicity	**N**	**Estimate of *V/d*[e] from model 90**	***V/F*[d] (Liters)[a]**	***CL* (Liters/h)[b]**	***AUC* for 44mcg CFC dose[c] (pg*h/mL)**	***AUC* for 88mcg CFC dose[c] (pg*h/mL)**
White	72	1.26	1260	137.34	320.37	640.75
Black	10	1.7	1700	185.30	237.45	474.91
Asian	3	0.869	869	94.72	464.52	929.04
Hispanic	26	0.736	736	80.22	548.46	1096.93
Other	5	0.777	777	84.69	519.52	1039.05

* All parameters were estimated without inclusion of BQL data.

a Since amount was in mcg and concentration in pg/mL, units were adjusted

b Using Clearance = (*V/F* * *K*) using *K* for a subject with average height (*K* = 0.109)

c Using *AUC* = Dose/ *CL* = (Dose*10^6)pg/(*CL**10^3)mL

d Apparent Volume of Distribution

Table 6. Simulated PK Parameters in Different Ethnic Background

Estimates* of PK Parameters using Non-compartmental Analysis of Simulated Data								
Ethnicity	**FP44mcg CFC**				**FP88mcg CFC**			
	N	**Tmax**	**Cmax**	**AUClast**	**N**	**Tmax**	**Cmax**	**AUClast**
White	26	0.25	46.57	314.39	46	0.25	93.15	628.78
Black	4	0.25	34.52	233.02	6	0.25	69.04	466.04
Asian	2	0.25	67.53	455.85	1	0.25	135.06	911.70
Hispanic	16	0.25	79.73	538.22	10	0.25	159.46	1076.45
Other	2	0.25	75.53	509.82	3	0.25	151.05	1019.65

* Not including BQL values

4.9 General Comments:

- Due to the fact that a high FP concentrations were detected in 13 placebo treated subject, the integrity of the data is highly questionable at this time. Therefore, the sponsor is highly encouraged to further investigate the issue and provide acceptable justification and explanation. In the fax dated May 15, 2003 the sponsor stated the following: "Since every effort to resolve this issue was made at the time of these findings were identified and samples are routinely disposed of after the report is written, no additional investigation is planned".
- A single blood sample was collected from each subject. Therefore, the sponsor used the naïve "pooled" population modeling approach by considering that all data are obtained from a single subject. Using this approach, the data were best described by a zero-order absorption, one-compartment model with first-order elimination. A limitation of this approach is that, post-hoc Bayesian estimates for individual subject's PK parameters could not be obtained.

- According to the population PK analysis, there were some differences in the PK of FP in different ethnicity. However, these differences may not be of a major clinical significance.

- While systemic levels were low and well below the concentrations usually associated with significant decreases in cortisol, these exposure estimates ma be overestimated because they do not include the large number of samples that were below the limit of the assay. As indicated earlier, about 50% of the samples following the 44 mcg dose and 30% of the samples following the 88 mcg dose were not measurable. If samples with concentrations below assay sensitivity (10 pg/mL) are assigned a value of zero and are included, median concentrations for most time intervals drop considerably lower with values being near or below assay sensitivity.

- A subject's height and ethnic background were found to be significant covariates. However, these findings could not be adequately validated.

- The decrease in change in height as a function of exposure is weak. Also, other parameters related to growth such as, weight, age and BMI, were not significant covariates. The safety concern related to the relationship between children's heights and exposure to FP can not be ruled out.

4.10 Overall Conclusions:

- The detection of the high concentration of FP in 13 placebo treated subjects signaling a lot of doubt about the entire PK data in one hand and the quality of the clinical data in the other hand. Therefore, the integrity of the entire PK and the clinical data is highly questionable.

- Plasma FP concentrations following the 88 mcg dose were higher than corresponding concentrations following the 44 mcg dose. Concentrations were highest during the first 2.5h after dosing and averaged 54.4 pg/mL after the 88 mcg CFC dose and 35.8 pg/mL after the 44 mcg dose.

- While FP concentrations are low and agree with the lack of effect on cortisol observed following both doses, they may be overestimates of the true exposure because of the large number of samples containing concentrations that could not be detected.

- While FP systemic exposure was found to increase with height, other measures of growth did not affect this exposure. Ethnicity was also found to be a covariate, but interpretation was limited due to the sparse amount of data in individual ethnic categories.

- The low drug exposure observed in this study did not correlate with any of the measured pharmacodynamic parameters.

- There was a high variability in FP plasma concentration following both doses (10 pg/ml to 450 pg/ml). This is similar to the variability found in adult. According to the current Flovent label the FP plasma concentration in adults ranges from 100 pg/ml to 1000 pg/ml following 880 mcg inhaled doses. This also demonstrates that concentration range in children from the current study is not greater than that of adults.

- A large number of samples were below detectable level.

5. (b) (4)

(b) (4)

6. APPENDICES

Appendix I

6.1 Pharmacometric Consult

Pharmacometrics Consult Comments

He Sun, Ph.D.
DPE 2

Feb. 19, 2003

Pharmacometrics reviewer's general comments/discussions:

1. The sponsor's effort to explore the population pharmacokinetics of FLOVENT is appreciated. One of the specific goals of this population analysis was to examine FP systemic exposure in pediatric asthmatic patients (6 months - 4 years). Due to only a single blood sample was obtained from each subject over a dosing interval at the end of the study, the naive pool approach was used, with which the post-hoc, Bayesian estimates for individual subject's PK parameters could not be obtained. While systemic levels were low and well below the concentrations usually associated with significant decreases in cortisol, these exposure estimates may be overestimated because they do not include a large number of samples that were below the limit of the assay (49% of the samples following the 44 mcg CFC dose and 31% of the samples following the 88 mcg CFC dose were not measurable).

2. A subject's height and ethnic background were found to be significant covariates. However, these findings could not be validated due to the absence of a validation dataset. As shown in Figure 21 of the submission, the decrease in exposure as a function of change in height is weak. Also, other parameters related to growth such as, weight, age and BMI, were not significant covariates. While it is of interest to know if height is a true covariate of exposure, it is clear that there is no safety concern, i.e. exposure does not increase as the height decreases.

3. The effect of ethnicity on V/F was modeled, however, due to the small number of subjects in each of the non-white ethnic groups are small (10 subjects were Black, 3 Asian and 5 classified as 'Other'), the results are pending future validation.

4. There is no PK-PD relationship found from this trial. Inhaled FP formulations deliver drug directly to the site of action (lungs) where it exerts its pharmacological action. Thus, it is not surprising that a clear relationship between efficacy and systemic exposure was not observed.

Pharmacometrics review conclusions (to be conveyed to medical officer)

1. The population PK study is acceptable. Due to only a single blood sample was obtained from each subject over a dosing interval at the end of the study and the naive pool approach was used, the post-hoc Bayesian estimates for individual subject's PK parameters could not be obtained. Plasma FP concentrations following the 88 mcg CFC dose were higher than corresponding concentrations following the 44 mcg CFC dose. Concentrations were highest during the first 2.5h after dosing and averaged 54.4 pg/mL after the 88 mcg CFC dose and 35.8 pg/mL after the 44 mcg CFC doses.

2. While FP systemic exposure was found to increase with height, other measures of growth did not affect this exposure. Ethnicity was also found to be a covariate, but interpretation was limited due to the small number of individual ethnic subjects. Moreover, these findings could not be validated due to the absence of a validation dataset. (b) (4)

3. The attempt to correlate pharmacodynamic parameters (both efficacy and safety parameters) with observed systemic concentration is highly encouraged. However, the low drug exposure observed in this study did not correlate with any of the measured pharmacodynamic parameters.

Pharmacometrics comments to the sponsor:

- The sponsor's efforts to explore the population pharmacokinetics of FLOVENT, and effort to correlate the efficacy and safety pharmacodynamic parameters with the observed systemic exposure are appreciated. However, the single random sample per subject design placed restrictions on the best use of the study results.

- It is understood that this study is a clinical add-on trial and the frequency of blood samples is limited. However, the "single random sample per subject" design should be avoided in the future. The sponsor is encouraged to conduct a simulation trial to prospectively design a PopPK study that will meet the study objective(s).

(b) (4)

Appendix II

6.2 (b) (4)

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Appendix III

6.3 Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**20-548**	**Brand Name**	**Flovent Inhalation Aerosol**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Fluticasone Propionate**
Medical Division	**DPADP**	**Drug Class**	**Corticosteroid**
OCPB Reviewer	**Sandra Suarez-Sharp**	**Indication(s)**	**Treatment of Asthma**
OCPB Team Leader	**Emmanuel Fadiran**	**Dosage Form**	**Inhalation aerosol**
PM Reviewer		**Dosing Regimen**	Adolescent and Adults 12 years and older: 88 mcg to 880 mcg twice daily depending on previous therapy and severity of symtoms
Date of Submission	**December 6, 2002**	**Route of Administration**	**Oral inhalation**
Estimated Due Date of OCPB Review	**April, 2002**	**Sponsor**	**GlaxoSmithKline**
PDUFA Due Date	**Jun 4, 2003**	**Priority Classification**	**Standard**
Division Due Date	**May 19, 2003**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
(b) (4)	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**X**	**2**		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**2**		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**X**	Comments have been sent to firm (or attachment included). FDA letter date if applicable. 1. Provide data files (ID, TIME, CONC, HT, WT, SURFACE AREA, AGE, GENDER, RACE etc.) in SAS transport format from protocol study FMS30058 and FMS30059. 2. Provide data for the validation of the analytical method (calibration curve statistics, graphs, QC statistics) used in studies FMS30058 and FMS30059
QBR questions (key issues to be considered)	**1. Does the PK data provide supporting information to the safety of the drug in children 6 months to 2 years of age?**	
Other comments or information not included above	**This reviewer will review the population PK study with the guidance of He Sun (PM reviewer).**	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 20-548, HFD-870 (Electronic Entry or Lee), HFD-570 (Jafari), HFD-870 (Fadiran, Sun, Hunt, Malinowski)), CDR (B. Murphy)

NDA 20-548 Fluticasone Propionate-WR
OBJECTIVES:

- To describe the population pharmacokinetics (pop PK) and identify influential covariates on the PK of FP in pediatric patients with asthma
- To explore the relationship between FP systemic exposure and FP pharmacodynamics (PD) in terms of FP efficacy (change in morning and evening asthma scores etc.) and safety (growth as in change in height, urinary cortisol) parameters.

PK STUDIES SUBMITTED TO THE NDA

Study Title/Description	Tabular listing/PK summary	Analytical method	PK parameters	Statistical analysis	Written request compliance
RM2002/00318/00: Analysis of PK samples	**X**	**X**		**X**	
Study Number: FMS30058 and FMS30059 Population pharmacokinetic analysis of fluticasone propionate delivered via CFC MDI and a valved holding chamber (Aerochamber or Optichamber) plus facemask in pre-school children with asthma for studies FMS30058 and FMS30059.	√		Population PK analysis	√	√

CONCLUSION: Submission is filable.

COMMENTS TO SPONSOR:

3. Provide data files (ID, TIME, CONC, HT, WT, SURFACE AREA, AGE, GENDER, RACE etc.) in SAS transport format from protocol study FMS30058 and FMS30059.
4. Provide "in-study" validation data for the analytical method (calibration curve statistics, graphs, QC statistics) used in studies FMS30058 and FMS30059

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

/s/

Sayed Al-Habet
5/30/03 10:19:09 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
5/30/03 10:35:09 AM
BIOPHARMACEUTICS
I concur