CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-051

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review
FINAL
(February 26, 2007)

NDA: 22-051	**Date of Submission:** June 28, 2006
Generic Name	Fluticasone Furoate
Brand Name:	N/A
Formulations:	Nasal Spray
Route of Administration:	Nasal
Indication:	Seasonal and Perennial Allergic Rhinitis
Type of Submission:	New Formulation and Device
Sponsor:	Glaxo Smith Kline Pharmaceuticals Research Triangle Park, NC
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.

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1.0 Executive Summary

1.1 Recommendation:

From the clinical pharmacology perspective, this NDA is acceptable.

1.2 Phase 4 Commitment

From the clinical pharmacology perspective, no phase 4 commitment is applicable to this NDA.

1.3 Summary of Clinical Pharmacology Findings:

Fluticasone furoate (FF) is a new corticosteroid developed as an aqueous suspension to be delivered by a side-actuated nasal spray device. The drug is proposed to be used for the treatment of symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and children aged 2 years and older at a daily dose of 50 to 100 mcg per nostril.

The sponsor conducted an extensive clinical pharmacology program and conducted several safety and efficacy studies for the development of this product. The main focus of this review is on the clinical pharmacology program and on the effect on Hypothalamic Pituitary Adrenal (HPA) axis as characterized by the potential suppression of plasma or urine cortisol levels. Therefore, this summary is divided into the following three main sections:

1. Pharmacokinetics:

Several studies were conducted by the sponsor to establish the extent of systemic exposure after intranasal administration of FF after single and multiple doses in various groups of patients. In most of these studies the concentration of FF in the plasma was too low or below the assay's Lower Limit of Quantification (LLOQ) of 10 pg/mL. For example, out of 5574 blood samples obtained from 1868 subjects following FF doses of 50, 100, 200 or 400 QD only 500 (8.2%) blood samples had quantifiable levels of FF in 366 subjects (19.6%) on at least one occasion. The majority of the quantifiable concentrations were below 50 pg/mL. It appears that proportion of FF quantification increases with dose. However, this has not been consistent across doses.

The maximum dose administered intranasally in this program was 800 mcg TID x 10 doses (total = 2400 mcg/day). This dose is 8 times the daily dose being proposed (Study # FFR 10010). In this study, the absolute bioavailability of intranasal FF after being normalized to 250 mcg IV dose was only 0.55%. The mean Cmax was approximately 20 pg/mL which is just above the LLOQ of 10 pg/ml.

Similarly, in a dose escalating study at 50 to 800 mcg x 7 days, the maximum concentration achieved in this study was 37.8 pg/ml (Study # FFR 10001). The concentrations of FF in most of the samples were below the LLOQ. Based on a radio-labeled study 101% and 90% of the radioactivity was recovered in feces after oral (2 mg solution) and IV (250 mcg) administration, respectively (Study # FFR 10008). Based on this study, the oral bioavailability of FF was approximately 1.26 %. One metabolite, GW694301X, was identified after oral administration but

not after IV administration. Similarly in a single dose rising inhalation study ranging from 50 mcg to 4000 mcg this metabolite was not detected in any of the samples at all doses (Study # FFA 10001). This suggests that the metabolite is formed only after oral administration, possibly as a result of first pass metabolism. The primary isozyme responsible for the metabolism is CYP3A4.

Based on Study # FFA 10001, there was disproportional increase in FF exposure as the inhaled dose increased from 50 to 4000 mcg. For the Cmax it was less than proportional but for AUC it was more than proportional as the dose increase. In addition, the half life of FF increased from 2 hours to 27 hour as the dose increased from 50 mcg to 4000 mcg, suggesting non-linear PK.

Ketocontazole appears to minimally increase FF exposure following 200 mg daily doses for 7 days and 100 mcg intranasal FF QD X 7 days. The FF plasma level was quantifiable in only 6 subjects out of 20. The mean Cmax of FF after ketoconazole treatment was 18.74 pg/ml, just above the LLOQ of 10 pg/ml (Study # FFR 10013). The reduction in cortisol level in ketoconazole arm was approximately 5% compared to placebo. It should be noted that the ketoconazole dose used in this study was 200 mg, one-half the maximum recommended dose of 400 mg. In addition, the drug-drug interaction guidance for industry recommends the use of the maximum ketoconazole dose, 400 mg.

The exposure to FF after oral inhalation in patients with moderate liver impairment was increased by approximately 3 fold compared to healthy subjects following a single 400 mcg oral inhalation dose of FF. As expected from the increase in systemic exposure, there was noticeable reduction in plasma cortisol levels in hepatic impairment patients compared to healthy subjects. It is noteworthy that this data is obtained after a single dose. Thus, the exposure and the effect on cortisol would be expected to be higher had this study been conducted after multiple doses.

2. Pharmacodynamics (Evaluation of HPA Axis))

The sponsor conducted several studies to evaluate the effect of intranasal FF on HPA axis in adults and children. In these studies, serum or 24-hour urine cortisol measurement or both were performed. The duration of these studies varied widely from single dose, 7 days, 14 days, 6 weeks, and 52 weeks. In addition, in almost all the clinical pharmacology studies, the effect of FF on HPA axis was evaluated. Below is a summary of the main studies.

Following oral inhalation of single doses ranging from 50 mcg to 4000 mcg, FF demonstrated dose dependent effect on HPA axis as characterized by plasma cortisol, urine, and 6-beta hydroxyl cortisol levels (Study FFA 10001). In the dose escalation study at 50 to 800 mcg x 7days, there was no evidence of effect on cortisol plasma levels compared to placebo after a single dose on Day 1 and repeat doses on Day 7.

The 6 weeks study conducted after daily intranasal administration of 100 mcg doses of FF in perennial allergic rhinitis (PAR) patients 12 to 65 years of age showed no difference between plasma cortisol concentration-time profiles for active and placebo subjects (Study # FFR 20002).

The positive control, 10 mg oral prednisone, showed substantial suppression in plasma cortisol levels. However, the 24 hour urinary excretion data showed some reduction in cortisol excretion with a mean change from the baseline of -16.68. A similar 6 weeks study was also conducted in pediatric patients with PAR at ages of 2 to <12 years (Study # FFR 100012). The study was conducted in approximately 50 patients in each cohort. The data for both PK and PD were similar to those from Study # FFR 20002. FF was not measurable in all plasma samples (n=262) from all the 53 subjects after 6 weeks of treatments, except 4 subjects. In these four subjects the concentrations of FF ranged from10.5 pg/mL to 18.9 pg/mL. Therefore, no PK parameters were reported in this study. In terms of pharmacodynamic, there was no evidence of cortisol suppression in either plasma or urine levels at all time points during the 6 weeks of treatments.

Furthermore, in the 52 weeks study (Study # FFR 102123), no difference in urine excretion data was noted between active treatment of 100 mcg QD and placebo in PAR patients 12 years and older. However, in pediatric patients with seasonal allergic rhinitis (SAR) there was some difference between active treatment and placebo after 12 weeks of daily treatment with intranasal FF at 100 mcg doses (Study # FFR 30008). The mean change from baseline in this study was -12.67.

In terms of PK, there were 331 samples out of 2512 samples were with quantifiable levels between 10 pg/mL to >500 pg/mL (Study # FFR 102123). However, there were high levels of FF in 10 samples out of 2512 samples from 10 different subjects out of 578 subjects who completed the 52 weeks study. The highest concentration observed in one of these 10 subjects is 1430 pg/ml. These very high concentrations are unexplainable. Therefore, the reviewer conducted an independent analysis of the data to establish if there is a relationship between the high exposure and the corresponding 24-hour urine cortisol levels in these 10 subjects. These subjects and the corresponding cortisol levels were identified from SAS database with kind assistance from the Division's statistician, Dr. Feng Zhou. From the individual plots for the FF plasma levels and the corresponding 24 hour urine cortisol levels there was no obvious trend or relationship in all 10 subjects. It is noteworthy that these high levels were observed **only once** in each subjects during the five visits. Therefore, sample contamination or assay related problems could be the cause of these unusiually high FF concentrations.

In small Japanese study with 8 healthy subjects, serum cortisol level was significantly lower than placebo following 400 mcg intranasal doses for 7 days. However, the study lack of adequate power with 8 subjects receiving active treatment and 3 subjects on placebo after repeat doses. No effect on cortisol serum levels was observed after single doses.

3. Exposure-Response Relationship (PK/PD Relationship):

Since there was no adequate FF plasma level following intranasal administration, the analysis of the relationship between systemic exposure and cortisol levels was conducted following oral inhalation and IV administration of FF. Thus, this analysis may not be directly relevant to intranasal FF, but serves as guidance for labeling purposes.

A population PK/PD analysis was conducted by the sponsor using seven single and multiple dose studies following IV and oral inhalation. As expected, the analysis shows some relationship

between FF systemic exposure (AUC) and suppression of serum cortisol and urine levels (**Figure 1.3.1-2**).

Figure 1.3.1. Model Predicted and Individual FF AUC (0-24) and Serum Cortisol Data

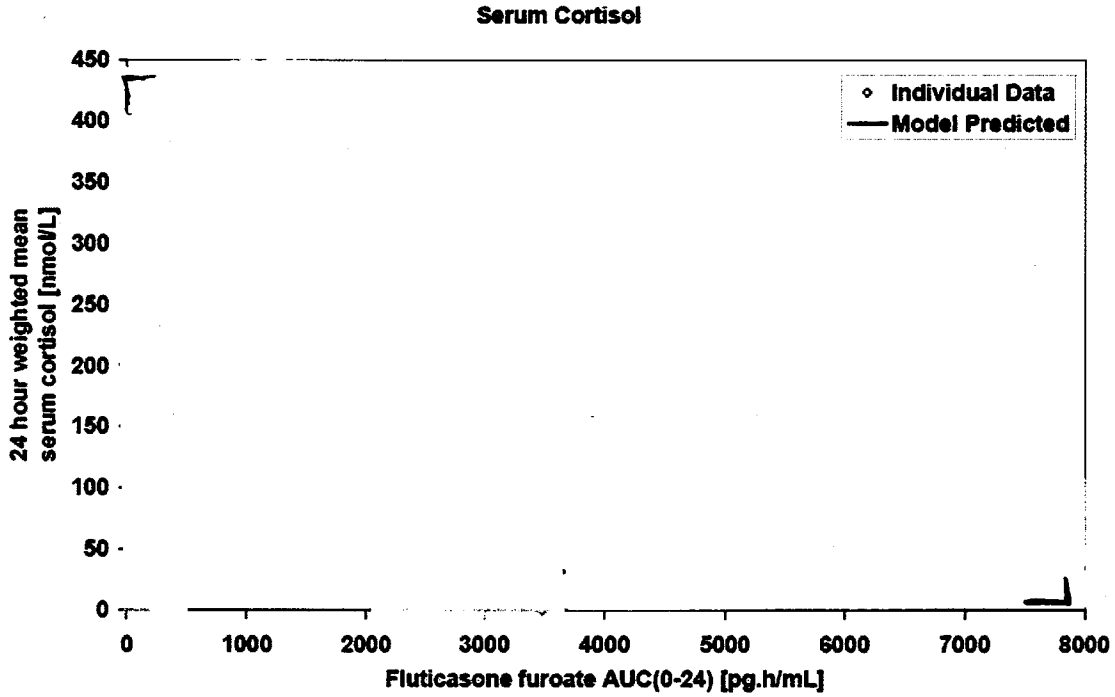
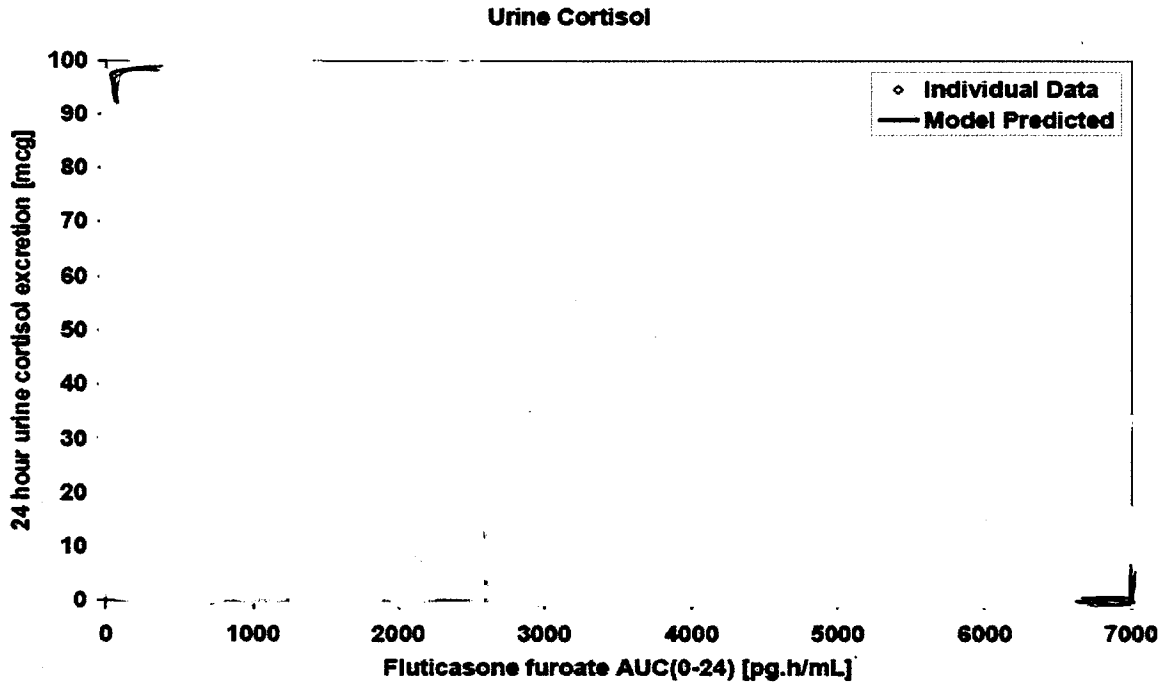


Figure 1.3.2. Model Predicted and Individual FF AUC (0-24) and Urine Cortisol Data



Effect on QTc:

The sponsor conducted study with the primary object to evaluate the effect of a single 4000 mcg orally inhaled dose of FF on QTc interval. This study is part of the COPD indication program. However, it was submitted with the 120 day safety update in this NDA. The study is currently pending review by Interdisciplinary Review Team (IRT). Briefly, the study was conducted in 40 healthy subjects as four-way crossover design as follows:

Period 1	Period 2	Period 3	Period 4
Fluticasone furoate 4000 mcg	Moxifloxacin 400 mg	COA 6.25 mg	Placebo
COA 6.25 mg	Fluticasone furoate 4000 mcg	Placebo	Moxifloxacin 400 mg
Placebo	COA 6.25 mg	Moxifloxacin 400 mg	Fluticasone furoate 4000 mcg
Moxifloxacin 400 mg	Placebo	Fluticasone furoate 4000 mcg	COA 6.25 mg

It should be noted that the positive control, moxifloxacin, was administered at the recommended dose per ICH E-14 QTc study guidance. Additional arm was included in this study to investigate the effect of cellobiose acta acetate (COA), an excipient used in dry powder formulation for FF inhalation on ECG parameters.

From the preliminary review and analysis of the data, moxifloxacin had substantial effect on the maximal mean change from baseline over 0-24 hours for QTcF and QTcB compared to FF and COA with placebo. The mean difference for FF was 0.788 msec and -0.074 msec for FF compared to 9.929 msec and 8.944 msec for moxifloxacin for QTcF and QtcB, respectively. The same trend was also seen for the weighted Mean Change from the Baseline. Moreover, there was no evidence of effect on the mean change from the baseline at each time points following FF and the exepient, COA.

No definitive conclusion can be made at this time until the IRT completes the review of the data. However, from the preliminary review of the data, it appears that FF and COA had minimal effect on QTc.

Conclusions:

From all these studies, the following conclusions can be made:

1) From the PK perspective, the exposure following intranasal FF is low, particularly following the proposed therapeutic doses. However, there appears to be unexplainable spikes of FF in plasma ranging from 20 pg/mLto 50 pg/mL in a few subjects and in some studies. These observed values were irrespective of dose or the duration of administration. Overall, these observed levels were inconsistent and unsustainable in any given subject or studies.

2) In addition, in terms of exposure, the major concern is with the isolated cases of extremely high plasma levels of FF that is ranging from approximately 500 to 1340 pg/mL in the 52 weeks study. These high values could not be validated with certainty at this time nor can be ignored. Therefore, appropriate language should be included in the labeling to reflect these observations.

3) From the PD perspective, it can be concluded that there appear to be some signals for HPA suppression after intranasal FF. In addition, the variability in the data was too high to completely rule out the lack of effect on HPA axis. Therefore, the label should be carefully worded to include standard precaution in the use of intranasal FF, particularly in pediatric patients.

Reviewer

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Office of Clinical Pharmacology
Division of Clinical Pharmacology 2
Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader----------

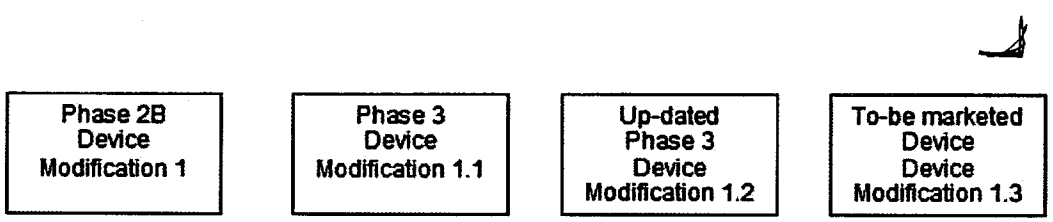
2. Question Based Review

2.1 General Attributes/Background:

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

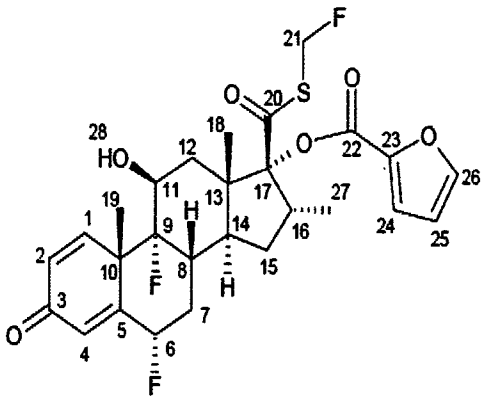
Fluticasone furoate or FF (GW685698X) is a new corticosteroid developed as an aqueous suspension in a side-actuated nasal spray device (**Figures 2.1.1.1**). The proposed indication is for once daily treatment for the symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and children aged 2 years and older.

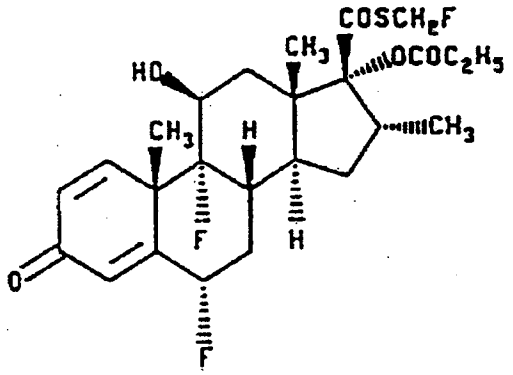
Figure 2.1.1.1. One Sided Spray Device



Structurally this is a typical corticosteroid. In other words, this is another salt for the widely marketed fluticasone products such as fluticasone propionate (**Figure 2.1.1.2**).

Figure 2.1.1.2 A and B. Structural Formula
A. Fluticasone Furoate **B. Fluticasone propionate.**





According to the sponsor, neither FF nor the currently marketed fluticasone propionate (FP) are metabolised to fluticasone in pre-clinical species or humans. The propionate and furoate esters are an integral part of the medicinal entity and remain covalently bound to the fluticasone steroid backbone.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

FF is typical corticosteroid acts as an anti- inflammatory agent (The detail of mechanism of action and other pharmacological activates will be discussed by the pharmacology and toxicology reviewer).

Briefly, based on *in vitro* receptor pharmacology data, the binding affinity to the glucocorticoid receptor (GR) was reduced by 30-fold when tested without furoate or propionate groups. The addition of the furoate was an improvement in the duration of pharmacological activities over fluticasone propionate (FP) to allow once daily administration. The reason for this longer duration of action is that FF binds more avidly with high affinity to GR than. The relative GR receptor affinities to dexamethsone is 2989 and 1775 for FF and FP, respectively. Therefore, this suggests that FF may be retained in human respiratory cells for a longer duration than FP.

It should be noted that the FF primary metabolite (GW694301X) virtually has no anti-inflammatory activity. The metabolite activity is about 6000-fold less than the parent compound, FF.

Indications:

The proposed indication for FF nasal spray is for the treatment of the symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in patients 2 years of age and older.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed starting dosage for adults and adolescents 12 years of age and older is 110mcg once daily (administered as two sprays in each nostril). Additionally, the sponsor proposed that when the maximum benefit has been achieved and symptoms have been controlled, the dose should be reduced to 55 mcg (one spray in each nostril) for maintenance treatment.

In children, the proposed starting dosage is 55mcg once daily (one spray pr nostril) with the option to increase the dosage to 110mcg once daily (2 sprays per nostril) in children not adequately responding to the lower dose. Once adequate control is achieved, the dosage may be decreased to 55mcg once daily.

2.1.4 What is the Core Studies Submitted in this NDA?

The development program consists of 22 Clinical Pharmacology studies in healthy volunteers and subjects with allergic rhinitis or asthma, and 12 Phase 2b/3 studies in adults, adolescents and children with SAR or PAR. A total of 3954 adult, adolescent, and pediatric subjects participated in the Phase 2b and Phase 3 clinical studies. Approximately 60% of these subjects (n=2359) exposed to doses of 50 mcg (n=369) and 100 mcg (n=1990).

From the PK perspective, the primary study is FFR10010 that was conducted at a supra-therapeutic intranasal dose of 800 mcg TID (i.e., 2400 mcg/day) x 10 doses in order to be able to detect FF concentration in plasma. Even after this dose, the plasma concentration of FF was just above LLQ of 10 pg/ml in most of the samples (**Figure 2.1.4.1 Table 2.1.4 .1**). The maximum concentration achieved in this study was 63 pg/ml. The absolute bioavailability of intranasal FF determined from this study was only 0.55% (**Table 2.1.4.2**).

Figure 2.1.4.1. Mean Plasma Concentration Time Profiles Following Intranasal and IV Administration in Day 1 and Day 4 (Study # FFR10010). (Reviewer's Generated Graphs)

A: Day 4 (Intranasal 800 mcg TID x 10 Doses) **B: Day 1 (Single 250 mcg IV)**

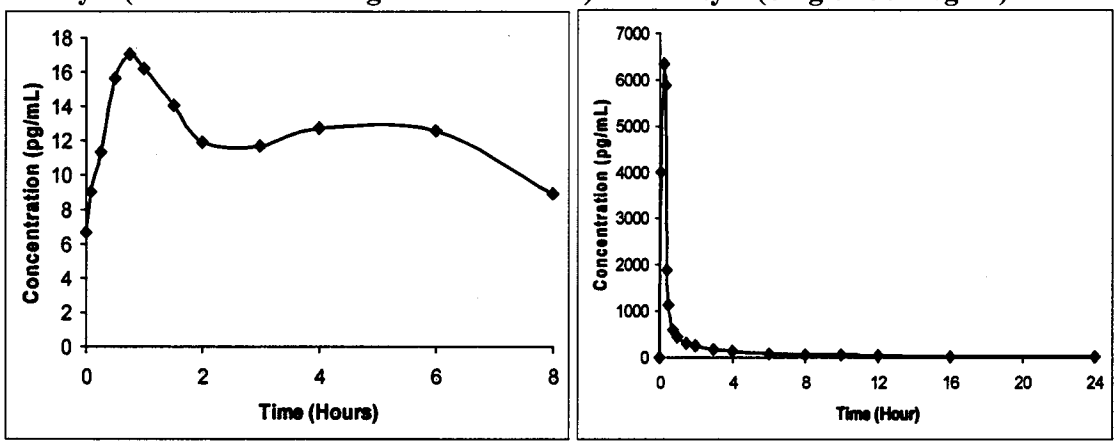


Table 2.1.4.11. Mean PK Parameters (Study # FFR 100010)

Parameter	IV			Intranasal		
	Mean	SD	Range	Mean	SD	Range
AUC (pg.h/mL)	4322.81	747.29	3108-5414	107.73	101.97	15.5-426.6
Cmax (pg/mL)	6844.49	1572.25	3834-8930	22.85	13.57	11.1-63.8
Tmax (h)	0.27	0.066	0.08-0.33	1.59	2.06	0.08-8.00
Half Life (h)	12.44	7.11	5.36-24.14	-	-	-

Table 2.1.4.2. Absolute Bioavailability of FF After Intranasal Administration (Study FFR10010).

Absolute bioavailability (%F)	90% CI
0.55	0.37–0.82

Other studies were conducted by the sponsor using various formulation and routes of administration as shown in the following **Tables 2.1.4 .3-4**. It should be noted that in all intranasal studies the final to be marketed micronized suspension was used, except in study FFR 10002 in which aqueous solution was used and in study FFR 10003 in which microfluidized (nanomilled) suspension was used. Therefore, these to latter studies (FFR 10002 and FFR 10003) are not relevant and will not be reviewed.

Table 2.1.4 .3. Completed Clinical Pharmacology Studies by Route and Population

	Route					Subjects	
Study	IN	IH	O (S)	CS	IV	Type	Dosed /Completed
FFR10001	X					Healthy	24 /21
FFR10002 [1]	X					Healthy	24 /23
FFR10003 [2]	X					Healthy	24 /22
FFR10005	X					Healthy Japanese	12 /11
FFR10006	X					Healthy	20 /20
FFR10007	X					Allergic Rhinitis	59 /55
FFR10008			X		X	Healthy	5 /5
FFR10010	X				X	Healthy	16 /16
FFR10013	X					Healthy	20 /20
FFA10001		X				Healthy	20 /19
FFA10002		X				Healthy	36 /35
FFA10003		X			X	Healthy	24 /23
FFA10004				X		Healthy	24 /24
FFA10007 [3,4]							
FFA10008 [3]							

Table 2.1.4.3 (continued). Completed Clinical Pharmacology Studies by Route and Population

	Route					Subjects	
Study	IN	IH	O (S)	CS	IV	Type	Dosed /Completed
FFA10009		X				Healthy	24 /24
FFA10013		X				Moderate hepatic impairment & Healthy	10 /10 10 /10
FFA10022		X				Asthmatic	40 /38
FFA10026 [3]							
FFA10027 [3]							
FFA10028		X				Asthmatic	28 /27
FFA103096		X				Healthy	44 /40
						Total	533 /494 (92.7%)

Route:
IN Intranasal (Nasally Inhaled)
IH Orally Inhaled
O (S) Oral (Swallowed)
CS Cutaneous
IV Intravenous

All of the nasal inhalation studies used the proposed marketed formulation (micronized suspension) except for [1] FFR10002 (solution) and [2] FFR10003 (microfluidized suspension).

[3] These studies do not provide relevant pharmacokinetic, pharmacodynamic or safety data for consideration of this intranasal product and are not discussed further. Clinical study reports for these studies are, however, available in Module 5.

[4] Study FFA10007 was discontinued:

Demographics:

All relevant clinical pharmacology studies were conducted in healthy subjects, except the following:

- FFA 10022 asthmatics
- FFA 10007 [redacted]
- FFA 10026 [redacted]
- FFA 10027 [redacted]
- FFA 10028 asthmatics
- FFR 10007 allergic rhinitis
- FFA 1003 Hepatic impairment and healthy
- FFR 1005 Healthy Japanese

Overall, the sponsor conducted extensive clinical pharmacology program for the development of of FF by different routes of administration. However, the focus of this review will be on the studies following intranasal administration (**Table 2.1.4.5**).

Table 2.1.4.4. Completed Clinical Efficacy and Safety Studies with PK Data

Study	Population	PK Sampling Approach	No. Subjects Randomised to FF	No. Subjects in PK Population
FFR20001	Adult/adolescent SAR	Sparse (n=3 /subject)	513	502
FFR20002	Adult/adolescent PAR	Extensive (n=8 /subject)	48	44
FFR102123	Adult/adolescent PAR	Sparse (n=5 /subject)	605	578
FFR100010	Pediatric SAR	Sparse (n=1 /subject)	368	349
FFR100012	Pediatric PAR	Extensive (n=5 /subject)	57	53
FFR30008	Pediatric PAR	Sparse (n=2 /subject)	370	342

FF = Fluticasone furoate
SAR = Seasonal Allergic Rhinitis; PAR = Perennial Allergic Rhinitis

The focus of this review will be on those studies related to intranasal administration and clinical studies with data evaluating the effect of FF on HPA axis.

As shown in the above list, the sponsor conducted an extensive clinical pharmacology program with the following nine core studies: FFR10001, 10002, 10003, 10005, 10006, 10007, 10008, 10010, and 10013]. The primary route of administration in eight of these studies was nasal inhalation; six studies used the final to-be-marketed formulation, a micronized suspension. Study # FFR10008 was conducted after IV administration of radio-labeled FF for ADME determination.

Since FF was negligibly detected in the plasma after a therapeutic dose, the relationship between the systemic exposure to FF and the effect on HPA axis was investigated after oral inhalation and IV administration in the following eight studies: FFA10001, FFA 10002, FFA 10003, FFA10009, FFA10013, FFA10022, FFA10028 and FFA103096. Nevertheless, the clinical significance of these studies may not directly be translated to intranasal route of administration. Similarly, four studies conducted for the orally inhaled FF clinical pharmacology program do not provide information relevant to the evaluation of nasally inhaled FF. These are: FFA10007 [redacted] FFA10008 ([redacted] FFA10026 [redacted] and FFA10027 ([redacted].

An intravenous solution of FF was also administered in three of the studies to provide information on intravenous pharmacokinetics, metabolism and absolute bioavailability (FFR10008, FFR10010 and FFA10003]. Study FFR10008 did not evaluate HPA axis effect and did not provide information relevant to the evaluation of nasally inhaled FF.

Table 2.1.4.5. Clinical Pharmacology Studies Conducted After Intranasal Administration

Study Number (Report No)	Objective	No. of Subjects Enrolled /Completed	Design	Route and Formulation	Doses Range & Duration of Treatment
FFR10001 (GM2002/00324/00)	Evaluate safety, tolerability, PK and PD	24/21 healthy males	Randomised, placebo controlled, double blind, ascending dose	Intranasal aqueous nasal spray of micronized suspension	50, 100, 200, 400 and 800mcg SD + 200 and 800mcg 7 days RD
FFR10002 (GM2002/00325/00)	Evaluate safety, tolerability, PK and PD	24/23 healthy males	Randomised placebo controlled, double blind, ascending dose	Intranasal aqueous nasal spray of solution	5, 10, 20, 40 and 80mcg SD
FFR10003 (GM2002/00326/00)	Evaluate safety, tolerability, PK and PD	24/22 healthy males	Randomised placebo controlled, double blind, ascending dose	Intranasal aqueous nasal spray of microfluidized suspension	50, 100, 200, 400 and 800mcg SD + 200 and 800mcg 7 days RD.
FFR10005 (JM2004/00008/00)	Safety, tolerability, PK and PD in Japanese subjects	12/11 healthy males	Double blind, randomised, placebo-controlled, single and multiple intranasal dose	Intranasal aqueous nasal spray micronized suspension	100, 200 and 400mcg SD + 400mcg 7 days RD
FFR10006 (GM2005/00247/00)	Investigate the nuclear translocation of the glucocorticoid receptor	20/20 healthy males	Randomised, single-blind, 2-period, crossover	Intranasal aqueous nasal spray of micronized suspension	400mcg SD
FFR10007 (GM2004/00170/00)	Evaluate efficacy following allergen challenge	59/55 male allergic rhinitis patients	Randomised, placebo controlled, single-blind, 2-period, crossover	Intranasal aqueous nasal spray of micronized suspension	200mcg 7 days RD
FFR10008 (GM2005/00081/00)	Radiolabel study	5/5 healthy males	Non-random, open, 2-period, cross-over	Oral solution (propylene glycol), IV infusion	2000mcg oral, 250mcg IV SD

Table 2.1.4.5 (Continued). Clinical Pharmacology Studies Conducted After Intranasal Administration

Study Number (Report No)	Objective	No. of Subjects Enrolled /Completed	Design	Route and Formulation	Doses Range & Duration of Treatment
FFR10010 (GM2005/00381/00)	Absolute Bioavailability	8/8 male, 8/8 female; healthy	Randomised, open, 2-period, cross-over	Intranasal aqueous nasal spray of micronized suspension, IV infusion	10 doses 800mcg intransal 8hr intervals, SD 250mcg IV infused over 20 min
FFR10013 (GM2005/00385/01)	Ketoconazole interaction on serum cortisol and PK	20/20 healthy males	Randomised, double-blind, 2-period, cross-over	Intranasal aqueous nasal spray of micronized suspension	100mcg 7 days RD

SD=Single Dose, RD=Once daily repeat dose

In addition, the effect on the HPA axis will be further evaluated from the following four clinical trails: FFR 20002, FFR 102123, FFR 100012, and FFR 30008 (see above **Table 2.1.5**). An extensive PK samples were collected in two of these studies (FFR 20002 and FFR 100012) and sparse sampling from other remaining two studies and one additional study (FFFR 20001). All other studies are to be considered supportive and will be referred as necessary.

2.2 General Clinical Pharmacology

The actual dose to be delivered by the device is 27.5 mcg/actuation, which is the proposed in the label. However, throughout the development program the spray content of the device has been approximated 25 mcg/actuation. The proposed label dose for the commercial product is the overall mean of the spray content database for clinical batches at release and long term stability (For more details, see CMC review). Based on the spray content assessment, the doses tested in the clinical program were actually 55 mcg, 110 mcg, 220 mcg, and 440 mcg rather than the 50 mcg, 100 mcg, 200 mcg, and 400 mcg as indicated in the study reports.

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

From the efficacy perspective, the total nasal symptom score (TNSS) and the total ocular symptom score (TOSS) are used to determine the efficacy of the intranasal FF. These will be discussed in more details by the Medical Officer.

From the clinical pharmacology perspective, the main safety endpoint is measurement of cortisol level in plasma and in urine. Corticosteroid are known to suppress HPA axis and hence suppress

cortisol production. Therefore, the focus of this review will be on dose-response relationship with respect to cortisol levels in plasma and urine.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The sponsor conducted ^{14}C radio-labeled FF solution administered orally at a single dose of 2 mg and IV dose of 250 mcg in healthy subjects (Study # FFR 10008). The data from this study is summarized in **Tables 2.2.2.1-4and Figures 2.2.2.1-3.**

Table 2.2.2.1. Summary of PK Parameters for the parent drug, FF (GW685698X), and the metabolite, GW694301X, and Radioactivity PK Parameters Following Oral and IV Administration (Study # FFR 10008)

Treatment	Parameter	Geometric Mean (95% CI) [1]		
		GW685698X	GW694301X	Radioactivity
2 mg oral (N=5)	AUC(0-t) (pg.h/mL)	404.6 (151.2, 1082.8)	83.26 (31.11, 222.85)	23197 (11238, 47883)
	AUC(0-∞) (pg.h/mL)	1082.6[a] (649.9, 1803.6)	105.20 (47.89, 231.09)	38129[b] (17606, 82575)
	Cmax (pg/mL)	153.7 (48.6, 486.0)	60.03 (25.95, 138.88)	1360 (1080, 1720)
	tmax (h)	0.50 (0.50-1.00)	0.75 (0.50-1.00)	0.75 (0.50-2.00)
	t1/2 (h)	3.89[a] (range: 2.91-5.19)	0.985 (0.643, 1.510)	20.421[b] (11.08, 37.63)
250 mcg i.v. (N=5)	AUC(0-t) (pg.h/mL)	3918.6 (2955.0, 5196.4)	ND	10158 (5266, 19594)
	AUC(0-∞) (pg.h/mL)	4352.2 (3446.0, 5496.6)	ND	16935[c] (4555, 62958)
	Cmax (pg/mL)	2806.5 (1739.6, 4527.8)	ND	4910 (3500, 6900)
	tmax (h)	0.50 (0.25,0.53)	ND	0.50 (0.50-0.53)
	t1/2 (h)	15.12 (11.82, 19.35)	ND	20.77[c] (2.60, 166.15)

Source Data: Table 10.11, Table 10.12 and Table 10.13

1. Geometric mean (95% CI) is presented for all parameters except tmax where median (range) is presented and t1/2 for GW685698X for the oral dose where geometric mean (range) is presented. n= xcept for: a: n=2; b: n=3; c: n=4.

ND = not determined, all concentrations below limit of quantitation.

The units presented in this table for radioactivity AUC(0-t), AUC(0-∞) and Cmax are pg.h/mL and pg/mL for

Figure 2.2.2.1. Median Plasma Concentration-Time Profiles Following Oral Administration of FF (Study # FFR 10008)

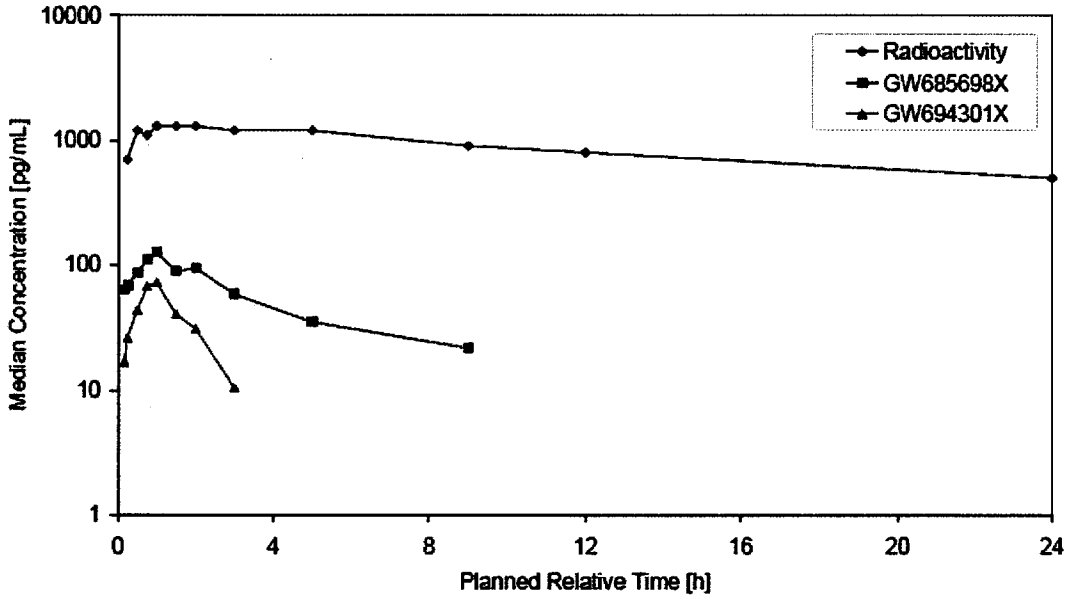


Figure 2.2.2.2 . Median Plasma Concentration-Time Profiles Following IV Administration of FF (Study # FFR 10008)

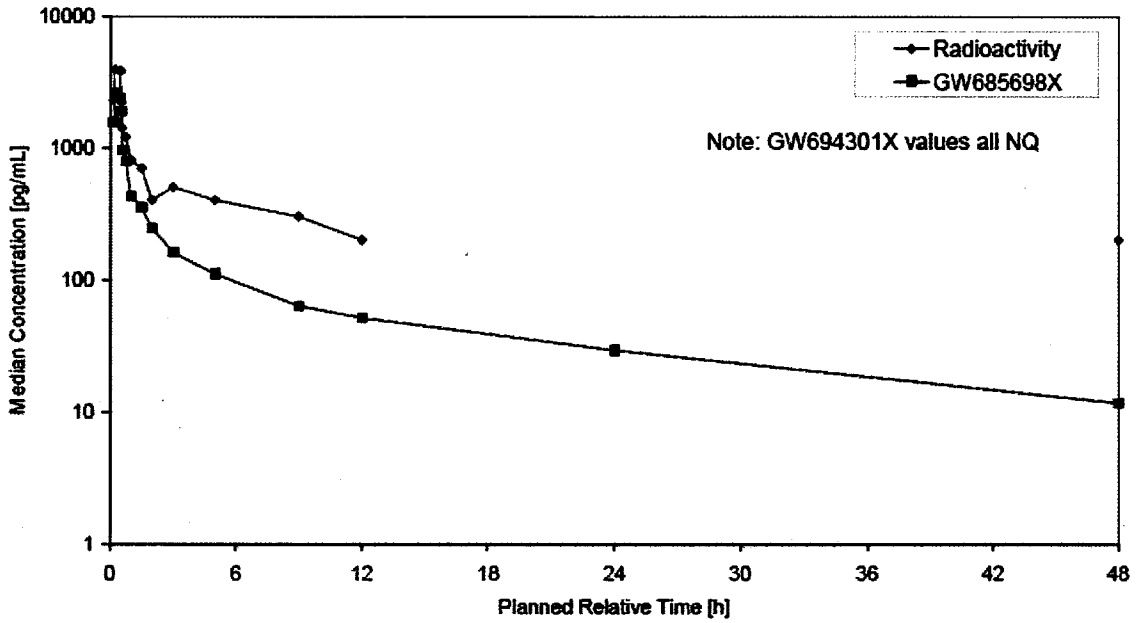


Table 2.2.2.2. Estimate of Percentage of Dose Absorbed

Subject	Treatment	AUC (0-t) [n.g.h/mL]	DN AUC (0-t)	Ratio DN AUC(0-t) [%]
1	250mcg IV	5.03	20.12	
	2mg Oral	10.71	5.355	27
2	250mcg IV	15.59	62.36	
	2mg Oral	46.19	23.095	37
3	250mcg IV	6.73	26.92	
	2mg Oral	16.59	8.295	31
4	250mcg IV	16.41	65.64	
	2mg Oral	23.12	11.56	18
5	250mcg IV	12.49	49.96	
	2mg Oral	35.4	17.7	35
Mean				30
Minimum				18
Maximum				37

Source Data: Table 10.14
DN AUC(0-t) – Dose normalised AUC(0-t) i.e. AUC(0-t)/nominal dose

Table 2.2.2.2. Mean of Radioactivity Exposure Following Oral and IV Administration (Study # FFR 10008)

Parameter	Treatment	N	n	Mean	95% CI (Lower,Upper)	SD	CVb (%)	Median	Min.	Max.
AUC(0-inf) ratio[1]	2mg Oral	5	5	102.236	(3.375,201.097)	79.6196	77.88	101.779	26.36	223.14
	250mcg IV	5	5	4.373	(0.911, 7.835)	2.7881	63.76	3.714	1.72	8.23
Cmax ratio	2mg Oral	5	5	11.472	(1.615, 21.329)	7.9384	69.20	11.914	3.14	21.37
	250mcg IV	5	5	1.867	(0.860, 2.873)	0.8106	43.43	1.569	1.19	3.24

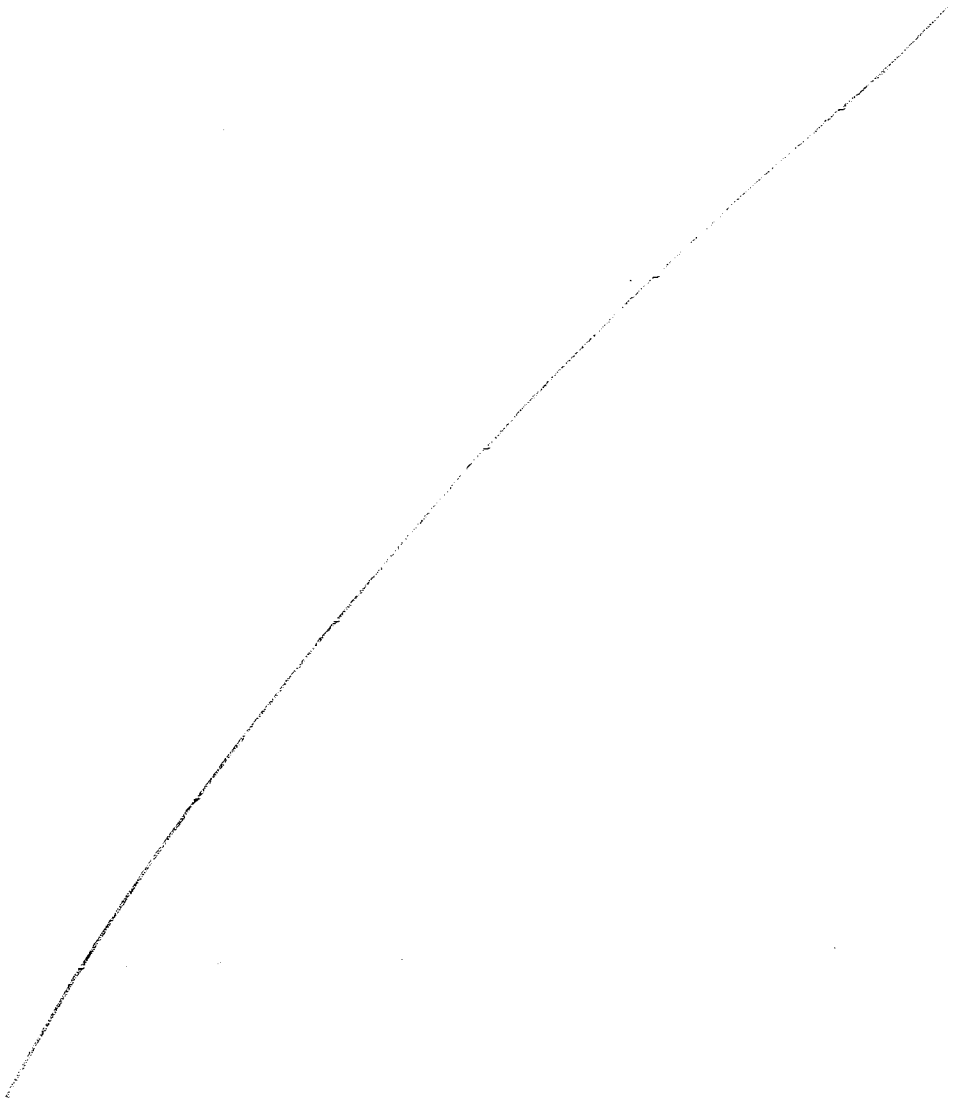
Parameter	Treatment	N	n	Geom. Mean	95% CI (Lower,Upper)	SD logs
AUC(0-inf) ratio[1]	2mg Oral	5	5	76.5737	(25.2239,232.459)	0.89433
	250mcg IV	5	5	3.6612	(1.5737, 8.5177)	0.68001
Cmax ratio	2mg Oral	5	5	8.8606	(3.0394,25.8311)	0.86172
	250mcg IV	5	5	1.7512	(1.0881, 2.8183)	0.38323

Table 2.2.2.3. Oral Bioavailability (Study # FFR 1008)

Parameter	N	n	Mean	95% CI (Lower,Upper)	SD	CVb (%)	Median	Min.	Max.
%F	10	5	1.585	(0.267, 2.902)	1.0610	66.95	1.517	0.48	2.82

Parameter	Treatment	N	n	Geom. Mean	95% CI (Lower,Upper)	SD logs
%F	Oral/IV	10	5	1.258	(0.463, 3.418)	0.8049

Figure 2.2.2.3. FF Metabolic Scheme in Animals and Human



Based on this study, most of the radioactivity was recovered in feces; accounting for approximately 101% after oral and 90% after IV administration. The high percentage of radioactivity in feces after IV administration suggests that the drug and or its metabolites are excreted via the bile and then to the feces. The total recovery in urine following either oral or IV administration was <2%.

One of the major metabolite, GW694301X, was detected in the plasma after oral administration only. This suggests that the drug undergoes extensive first pass metabolism after oral administration. Thus the absolute bioavailability of the oral solution based on AUCs was only 1.26%. Based on the AUC ratios, it appears that 30% of the oral dose was absorbed.

The scheme of the metabolic pathway in animals and human shows several other miner metabolites for FF. From this scheme it can be seen that the principle route of metabolism is hydrolysis of the S-fluoromethyl carbothioate group to form the carbocylic acid metabolite, GW694301X (M10). As shown in the scheme this metabolite undergoes further metabolism to several other minor metabolites.

Conclusions:

Although this study may be considered irrelevant to the intranasal administration, it provides useful information about the metabolism and excretion of the drug after oral and IV administration. Two major conclusions can be made from this study that can be relevant to intranasal administration. First, if the drug is swallowed after intranasal administration it is will undergo extensive first pass metabolism. Second, if it is absorbed it will be recycled back to the GI tract via the bile. Thus, the systemic exposure after intranasal administration would be expected to be low, regardless.

2.2.3 Exposure Response

2.2.3.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?

Since this is for intranasal administration for local action, minimal systemic exposure has been observed for this product. Also, the recommended dose for SAR and PAR treatment is within narrow range of 1 to 2 sprays per nostril (i.e., 50 to 100 mcg) per day. This will be further discussed in the Medical Officer's review.

2.2.3.2 What are the characteristics of the dose-systemic exposure relationships for safety?

From the clinical pharmacology and safety perspective, the sponsor conducted Pop PK analysis from selected studies after oral inhalation and IV administration to establish PK/PD relationship between exposure and cortisol levels. As expected, the analysis shows some relationship between FF systemic exposure (AUC) and suppression of serum cortisol and urine levels (**Figures 2.2.3.2.1-2**).

Figure 12.2.3.2.1. Model Predicted and Individual FF AUC (0-24) and Serum Cortisol Data

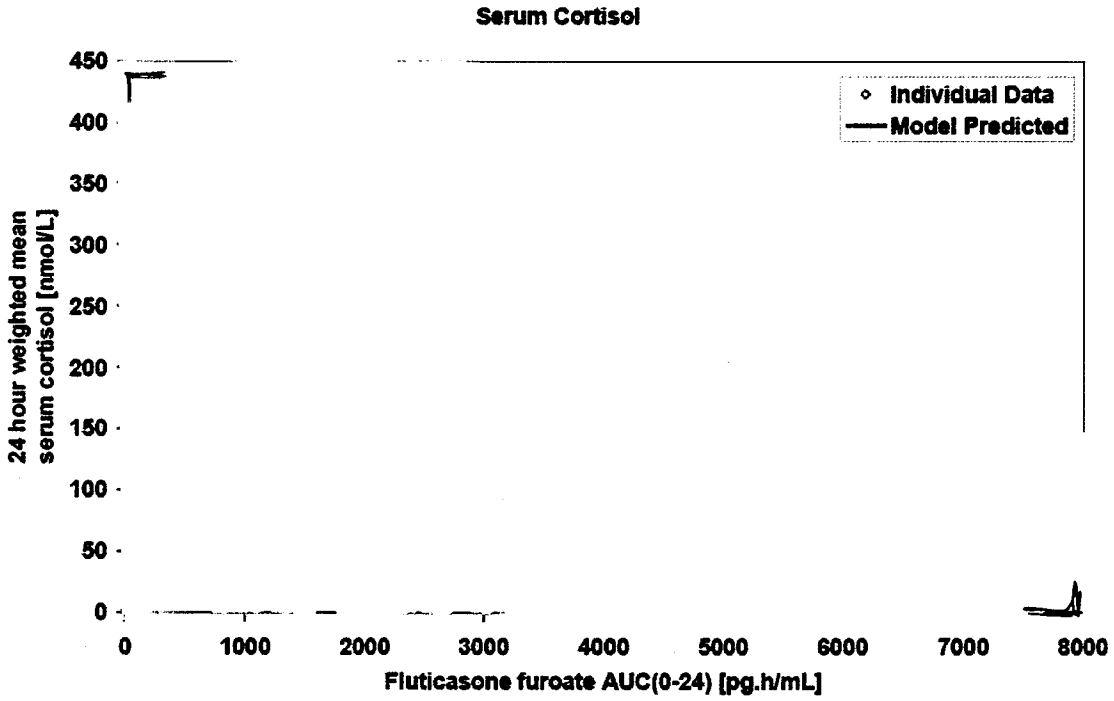
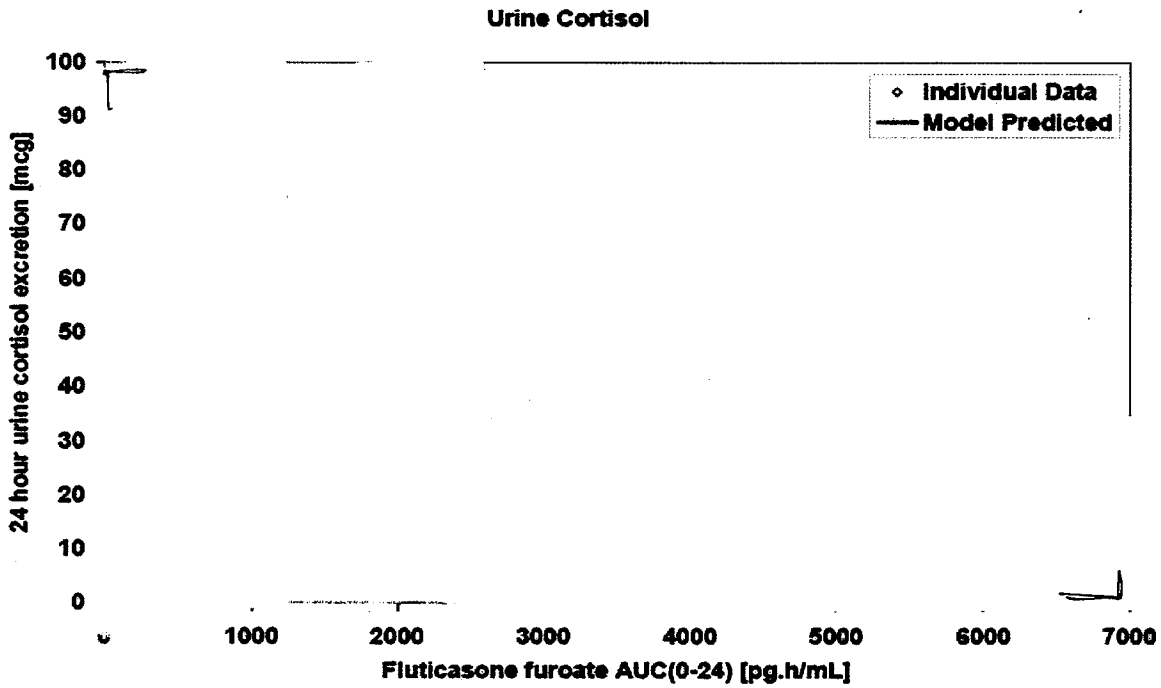


Figure 2.2.3.2.2. Model Predicted and Individual FF AUC (0-24) and Urine Cortisol Data



Several additional studies were conducted to determine the effect systemic exposure of FF on plasma or urine cortisol levels. In a study following oral inhalation of single doses ranging from 50 mcg to 4000 mcg, FF demonstrated dose dependent effect on HPA axis as characterized by plasma cortisol, urine, and 6-beta hydroxyl cortisol levels (Study FFA 10001, **Figures 2.2.3.2.3-5**).

Figure 2.2.3.2.3. Serum Cortisol Profiles Following Oral Inhalation of 50 to 4000 mcg Doses of FF (Study # FFA 10001, Reviewer's Generated Graph)
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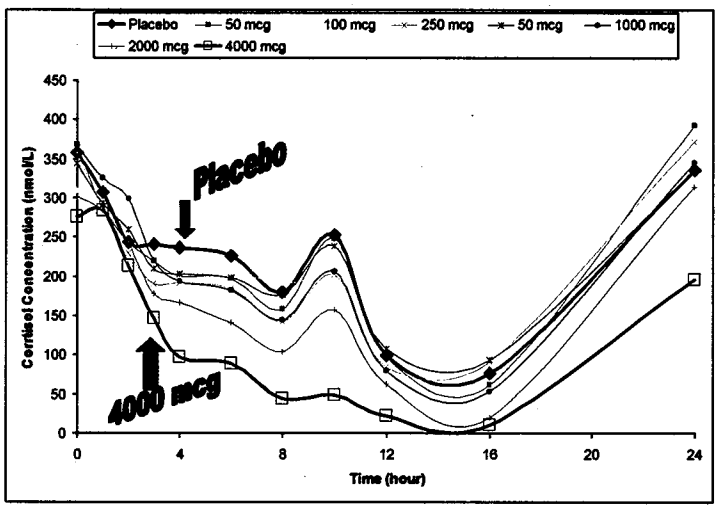


Figure 2.2.3.2.4. Individual Ratios of Total Urine Free Cortisol (24 h) With Mean Difference and 95% CI (Study # FFA 10001).

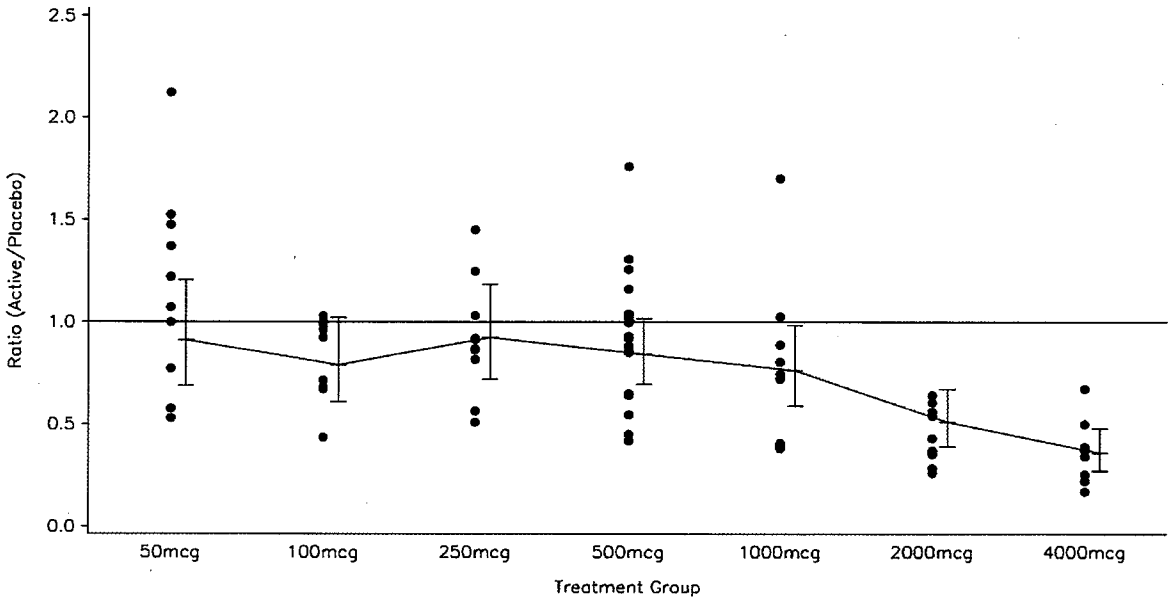
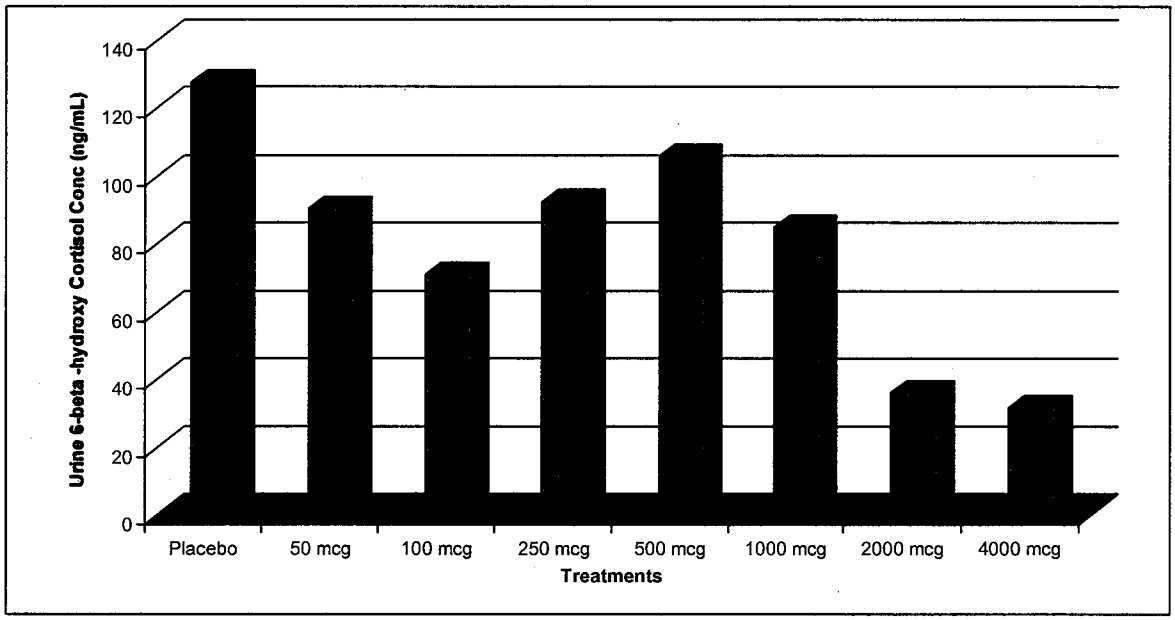


Figure 2.2.3.2.4.5.Mean 6-Beta Hydroxy Cortisol Levels (Study # FFA 10001, Reviewer's Generated Graphs, Source Table 13.6, Pages 295 to 303).



In the dose escalation study at 50 to 800 mcg x 7days, there was no evidence of effect on cortisol plasma levels compared to placebo after a single dose on Day 1 and repeat doses on Day 7 (**Figures 2.2.3.2.6-7**).

Figure 2.2.3.2.6. Mean Cortisol Plasma Concentration-Time profiles After Single Doses on Day 1 of Intranasal Administration of FF (Study # FFR 10001). (Reviewer's Generated Graphs)

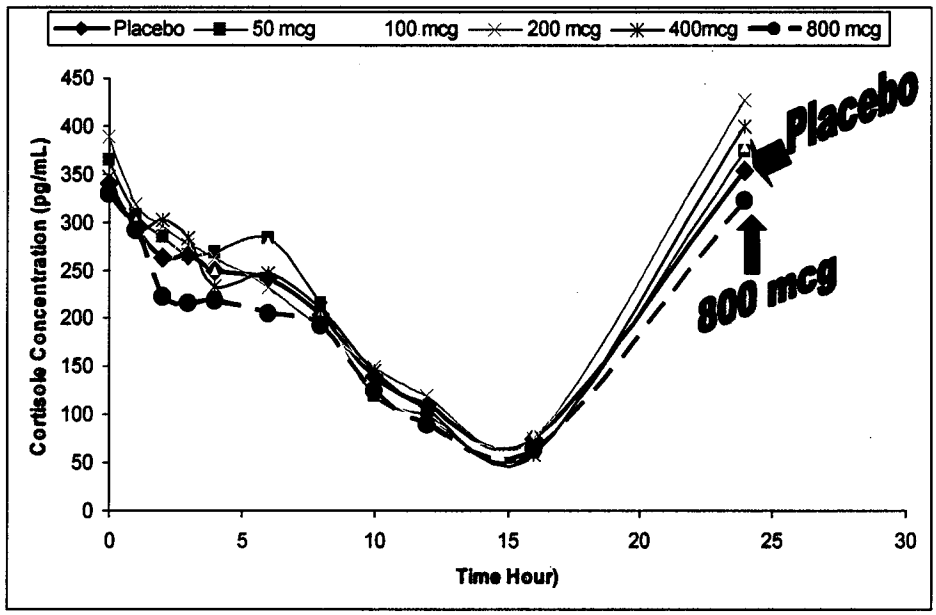
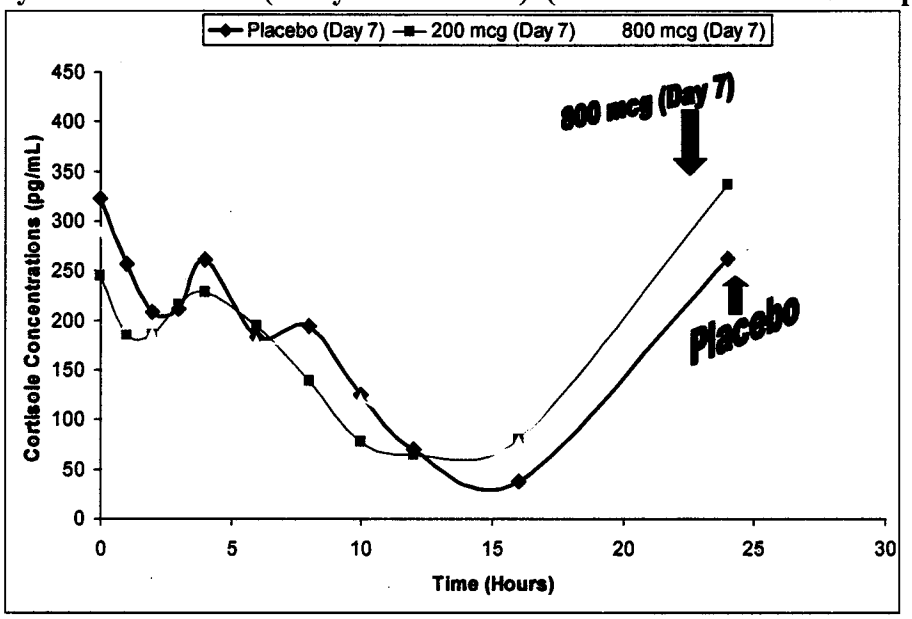
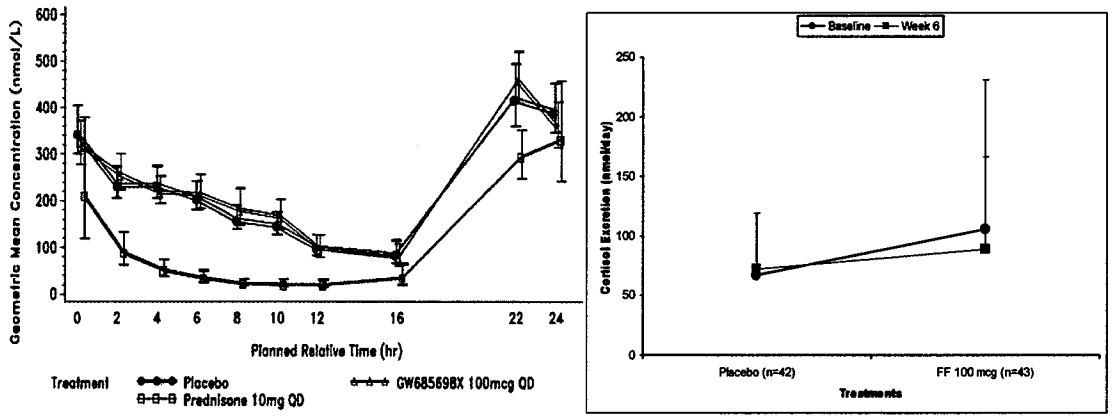


Figure 2.2.3.2.7. Mean Cortisol Plasma Concentration-Time profiles on DAY 7 After Repeat Daily Intranasal Doses (Study # FFR 10001). (Reviewer's Generated Graphs)



In the 6 weeks studies conducted after daily intranasal administration of 100 mcg doses of FF in perennial allergic rhinitis (PAR) patients 12 to 65 years of age show no difference between plasma cortisol concentration-time profiles for active and placebo subjects (Study # FFR 20002, **Figure 2.2.3.2.8 A & B**). The positive control, 10 mg oral prednisone, showed substantial suppression in plasma cortisol levels. However, the 24 hour urinary excretion data showed some reduction in cortisol excretion with a mean change from the baseline of -16.68 (**Figure 2.2.3.2.8 B**).

Figure 2.2.3.2.8. Plasma (A) and Urine (B) Cortisol At Week 6 (Study # FFR 20002)
A: Plasma **B: Urine (Reviewer's Generated Graphs)**

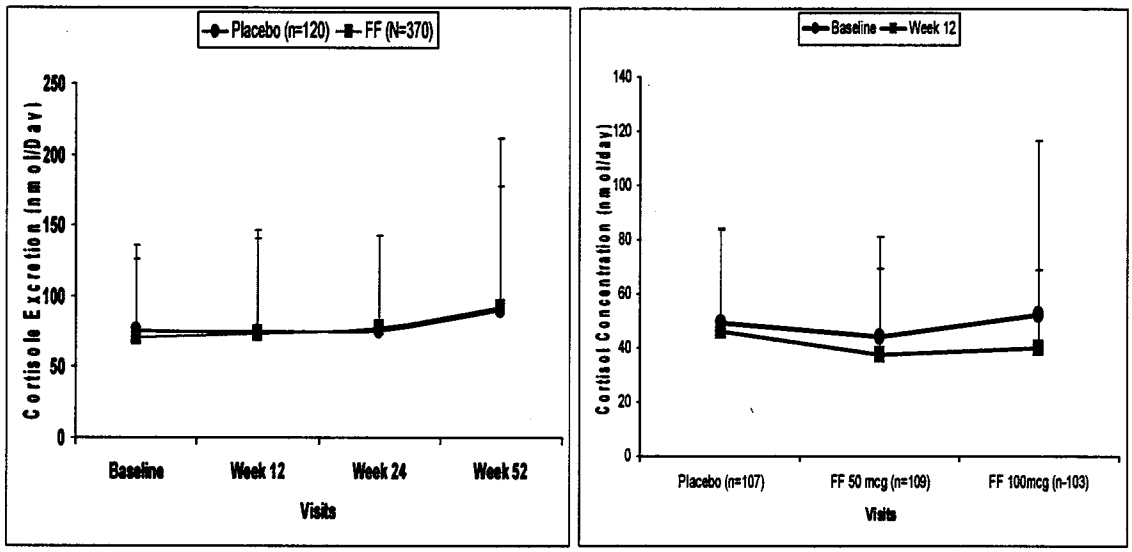


Finally, in the 52 weeks study (Study # FFR 102123), no difference in urine excretion data was noted between active treatment of 100 mcg QD and placebo in PAR patients 12 years and older (**Figure2.2.3.2.9 A & B**). However, in pediatric patients with seasonal allergic rhinitis (SAR) there was some difference between active treatment and placebo after 12 weeks of daily treatment with intranasal FF at 100 mcg doses (Study # FFR 30008, **Figure 1.3.13 B**). The mean change from baseline in this study was -12.67.

Figure 2.2.3.2.9. Mean (± SD) 24-Hour Urine Cortisol Excretion (Reviewer's Generated Graphs)

A: Week 52 in 12-65 Years (Study # FFR102123)

B: 12 Weeks in 2-12 Years (Study # FFR30008)



Conclusions:

From these data it can be concluded that there is a relationship between exposure and cortisol suppression following. However, following intranasal administration, the effect is minimal compared to placebo or oral inhalation.

2.2.3.3 Does this drug prolong the QT or QTc interval?

The sponsor conducted study with the primary object to evaluate the effect of a single 4000 mcg orally inhaled dose of FF on QTc interval. This study is part of the COPD indication program. However, it was submitted with the 120 day safety update in this NDA. The study is currently pending review by Interdisciplinary Review Team (IRT). Briefly, the study was conducted in 40 healthy subjects as four-way crossover design as follows:

Period 1	Period 2	Period 3	Period 4
Fluticasone furoate 4000 mcg	Moxifloxacin 400 mg	COA 6.25 mg	Placebo
COA 6.25 mg	Fluticasone furoate 4000 mcg	Placebo	Moxifloxacin 400 mg
Placebo	COA 6.25 mg	Moxifloxacin 400 mg	Fluticasone furoate 4000 mcg
Moxifloxacin 400 mg	Placebo	Fluticasone furoate 4000 mcg	COA 6.25 mg

It should be noted that the positive control was administered at the recommended dose per ICH E-14 QTc study guidance. Additional arm was included in this study to investigate the effect of cellobiose acta acetate (COA), an excipient used in dry powder formulation for FF inhalation on ECG parameters.

From the preliminary review and analysis of the data, moxifloxacin had substantial effect on the maximal mean change from baseline over 0-24 hours for QTcF and QTcB compared to FF and COA with placebo (**Figures 2.2.3.3.1).** The mean difference for FF was 0.788 msec and -0.074 msec for FF compared to 9.929 msec and 8.944 msec for moxifloxacin for QTcF and QtcB, respectively (**Tables 2.2.3.3.1 and 2.2.3.3.2). The same trend was also seen for** the weighted Mean Change from the Baseline. Moreover, there was no evidence of effect on the mean change from the baseline at each time points following FF and the exepient, COA (**Figure 2.2.3.3.2**).

Figure 2.2.3.3.1. Maximal Mean Change from Baseline (0-24 hour)

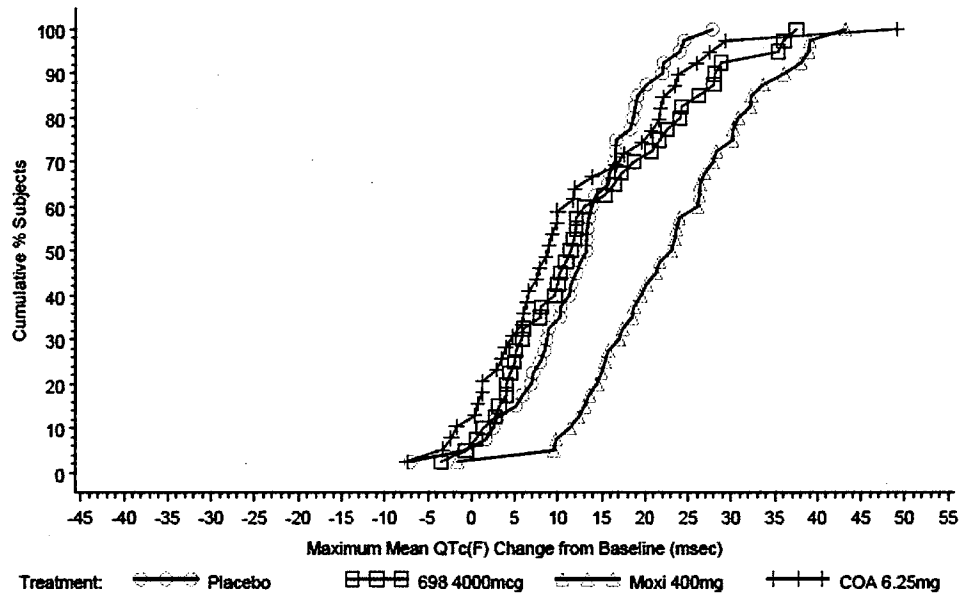


Table 2.2.3.3.1. Summary of Statistical Analysis of QTcF Maximal Mean Change from Baseline (0-24 h)

Comparison	Treatment Difference (msec)	90% Confidence Interval (msec)
Fluticasone furoate 4000 mcg – Placebo	-0.074	(-3.586,3.437)
Moxifloxacin 400 mg – Placebo	8.944	(5.433,12.455)
COA 6.25 mg – Placebo	-1.486	(-5.042, 2.070)

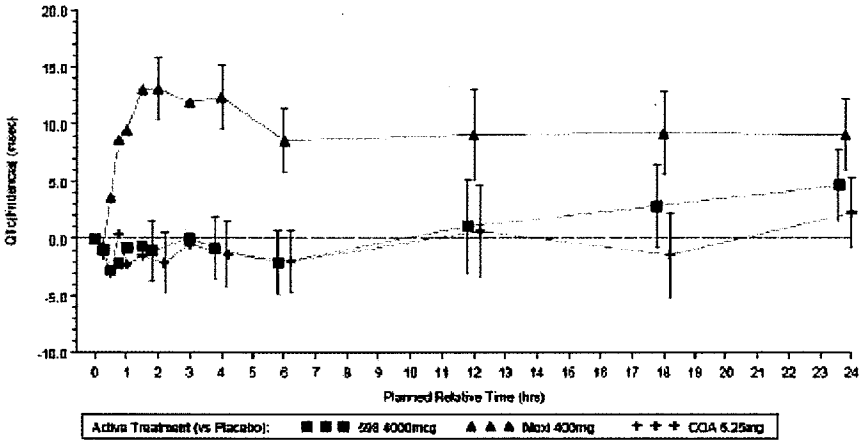
Data Source: Table 10.8
Note: N=40 for fluticasone furoate, moxifloxacin and placebo, N=39 for COA

Table 2.2.3.3.2. Summary of Statistical Analysis of QTcB Maximal Mean Change from Baseline (0-24 h)

Comparison	Treatment Difference (msec)	90% Confidence Interval (msec)
Fluticasone furoate 4000 mcg – Placebo	0.999	(-0.612, 2.610)
Moxifloxacin 400 mg – Placebo	9.295	(7.683, 10.906)
COA 6.25 mg – Placebo	-0.670	(-2.293, 0.953)

Source Table 10.9
Note: N=40 for fluticasone furoate, moxifloxacin and placebo, N=39 for COA

Figure 2.2.3.3.2.Mean Change From Baseline QTCF at Each Time Point Post Dose (0-24 h)



No definitive conclusion can be made at this time until the IRT comletes the review of the data. However, from the preliminary review of the data, it appears that FF and COA had minimal effect on QTc.

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters of FF and its metabolites? How do the PK parameters change with time following chronic dosing?

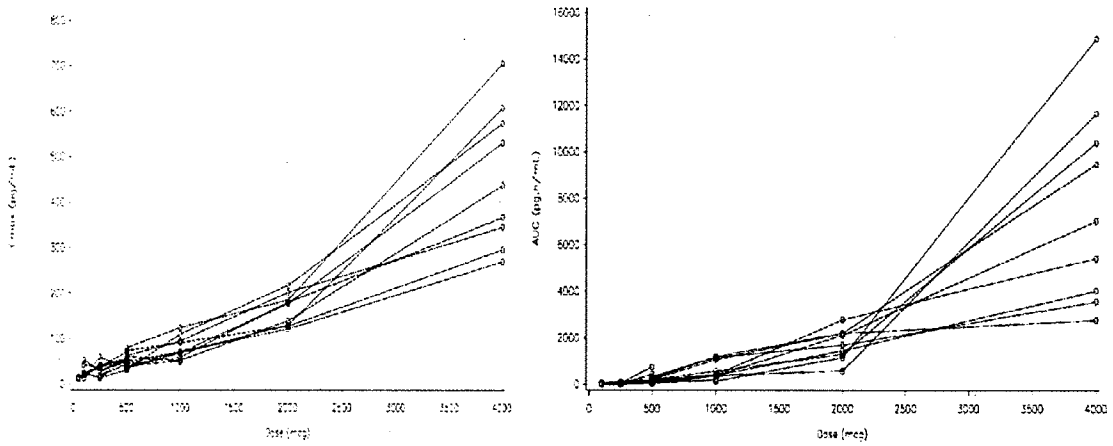
As stated previously, in most of the studies, FF was negligibly detected in most of the studies. This was regardless of the dose and duration. In almost all studies at the recommended dose of 100 mcg, the concentration was just above LLOQ of 10 pg/ml. Therefore, no information is

available to adequately describe the PK of FF and its metabolites following intranasal administration.

2.2.4.2 Are the PK of FF and its metabolites linear and dose-proportional?

Dose proportionality data is available only after oral inhalation. Thus, based on Study # FFA 10001, there was disproportional increase in FF exposure as the inhaled dose increase from 50 to 4000 mcg (**Figures 2.2.4.2.1**). For Cmax it was less than proportional but for AUC it was more than proportional as the dose increase. In addition, the half life of FF increased from 2 hours to 27 hour as the dose increased from 50 mcg to 4000 mcg, suggesting non-linear PK.

Figure 2.2.4.2.1. FF Exposure After Inhalation of 50 mcg to 4000 mcg (Study # FFA 10001)
A: Cmax **B. AUC**



2.2.4.3 What is the Extent of Systemic Exposure After Intranasal Administration?

As stated previously, in most of the studies conducted by the sponsor the concentration of FF in the plasma was too low or below the assay's Lower Limit of Quantification (LLOQ) of 10 pg/mL. For example, out of 5574 blood samples obtained from 1868 subjects following FF doses of 50, 100, 200 or 400 QD only 500 (8.2%) blood samples had quantifiable levels of FF in 366 subjects (19.6%) in at least one occasion (**Table 2.2.4.3.1 and Figures 2.2.4.3.1**). The majority of the quantifiable concentrations were below 50 pg/mL. It appears that proportion of FF detection increases with dose (**Figure 2.2.4.3.2**). However, this has not bee consistent across doses.

Table 2.2.4.3.1 . Percentage of Blood Samples with Quantifiable FF Concentration by Dose Group

Dose	Fluticasone Furoate Concentration Range [pg/mL]						
	10 to <20	20 to <30	30 to <50	50 to <100	100 to <200	200 to <500	≥500
50mcg [n=850]	2.24	0.71	0.12	0.12	0.24	0.12	0.00
100mcg [n=3979]	22.35	7.88	6.82	5.18	2.35	1.65	1.29
200mcg [n=375]	0.94	0.00	0.00	0.12	0.00	0.00	0.00
400mcg [n=370]	5.65	0.94	0.12	0.00	0.00	0.00	0.00
Overall [n=5574]	4.75	1.45	1.08	0.83	0.39	0.27	0.20

Bracketed values are total number of samples. Values are proportion of samples with quantifiable value expressed as a percentage of total

Figure 2.2.4.3.1. Proportion of Subjects With Quantifiable FF Concentration by Dose Group

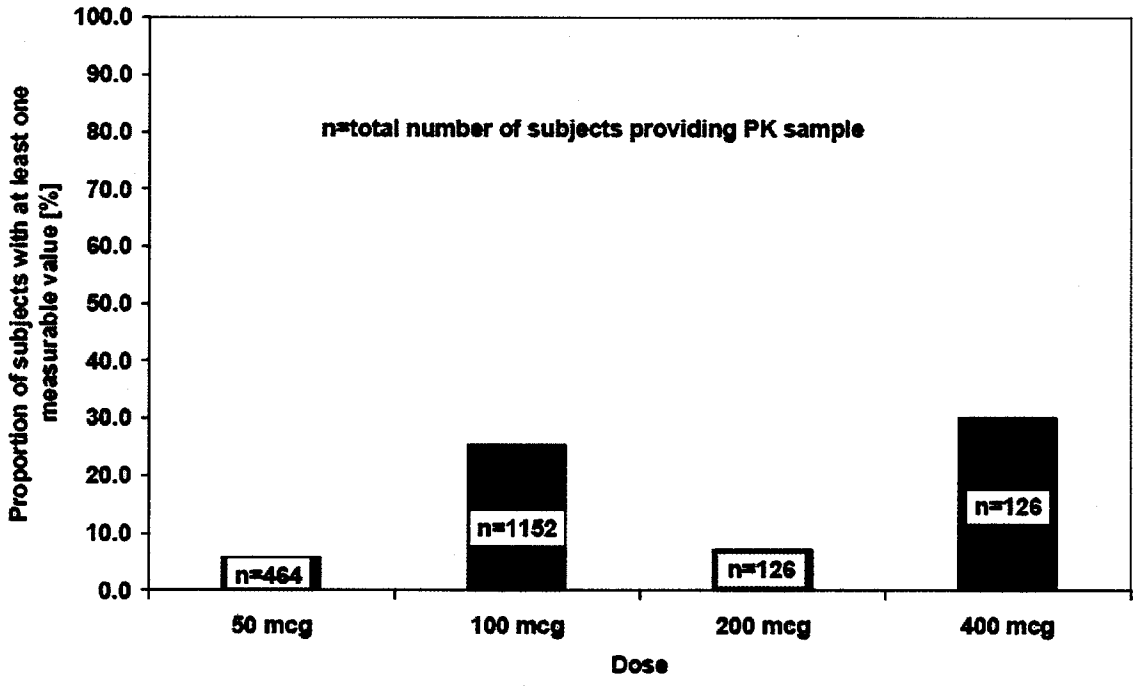
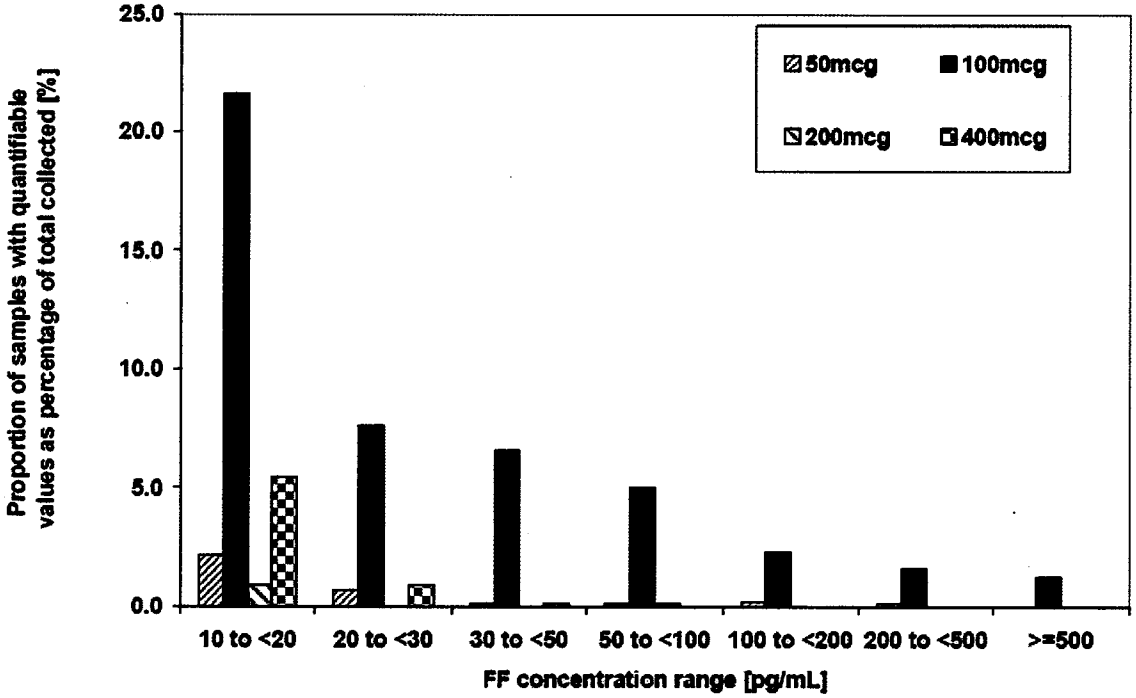
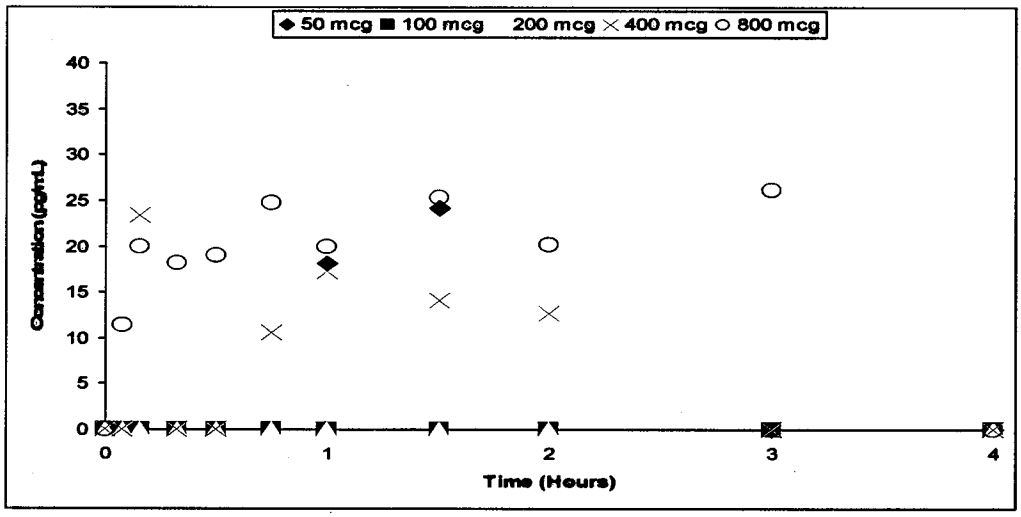


Figure 2.2.4.3.2. Proportion of Samples With Quantifiable FF Concentration by Dose Group



Similarly, in a dose escalating study at 50 to 800 mcg x 7 days, the maximum concentration achieved in this study was 37.8 pg/ml (Study # FFR 10001). The concentrations of FF in most of the samples were below the LLOQ (**Figure 2.2.4.3.3.**).

Figure 2.2.4.3.3. Scattered Plot of Mean FF Plasma Concentrations ((Reviewer's Generated Graph, Study # FFR 10001)



Furthermore, in the 52 weeks study (Study # FFR 102123) at 100 mcg daily doses, there were 331 samples out of 2512 samples were with quantifiable levels between 10 pg/mL to >500 pg/mL (**Table 2.2.4.3.2**).

Table 2.2.4.3.2. Summary of Samples with Quantifiable FF Concentration (Study # FFR 102123)

	10 to <20 pg/mL	20 to <30 pg/mL	30 to <50 pg/mL	50 to <100 pg/mL	100 to <200 pg/mL	200 to <500 pg/mL	≥500 pg/mL
No of quantifiable samples	139	58	53	39	18	14	10
% of quantifiable (n=331)	42%	17.5%	16.0%	11.8%	5.4%	4.2%	3.0%
% of total samples (n=2512)	5.5%	2.3%	2.1%	1.6%	0.7%	0.6%	0.4%

Source Data: Table 9.1

However, there were high levels of FF in 10 samples out of 2512 samples from 10 different subjects out of 578 subjects who completed the 52 weeks study (**Table 2.2.4.3.3**). The highest concentration observed in one of these 10 subjects is 1430 pg/ml (**Table 2.2.4.3.4**).

Table 2.2.4.3.2. FF Plasma Levels in the 10 Subjects with >500 pg/ml (Study # FFR 102123)

Subject	Visit 3	Visit 5	Visit 8	Visit 11	Visit 15
711	NQ	649 pg/ml	NQ	NQ	NQ
744	NQ	46.9 pg/mL	1430 pg/mL	NQ	65.5 pg/mL
751	NQ	NQ	NQ	1300 pg/mL	NQ
1216	NQ	17.8 pg/mL	18.8 pg/mL	65.8 pg/mL	796 pg/mL
1221	NQ	10.9 pg/mL	NQ	729 pg/mL	NQ
1225	12.7 pg/mL	NQ	NQ	729 pg/mL	12.7 pg/mL
1320	NQ	NQ	17.6 pg/mL	NQ	1340 pg/mL
1641	NQ	NQ	NQ	NQ	696 pg/mL
1783	NQ	744 pg/mL	NQ	NQ	NQ
1846	NQ	NQ	19.6 pg/mL	908 pg/mL	NQ

Source Data: Table 9.1

These very high concentrations are unexplainable. Therefore, the reviewer conducted an independent analysis of the data to establish if there is a relationship between the high exposure and the corresponding 24-hour urine cortisol levels in these 10 subjects (**Figures 2.2.4.3.4 A-C**). These subjects and the corresponding cortisol levels were identified from SAS database with kind assistance from the Division's statistician, Dr. Feng Zhou.

Figure 2.2.4.3.4 A-C. Relationship Between FF Levels and 24-Hour Cortisol Levels in 10 Subjects with High Plasma FF Levels (Study # FFR 102123)

Figure A. Visit 3 (Baseline)

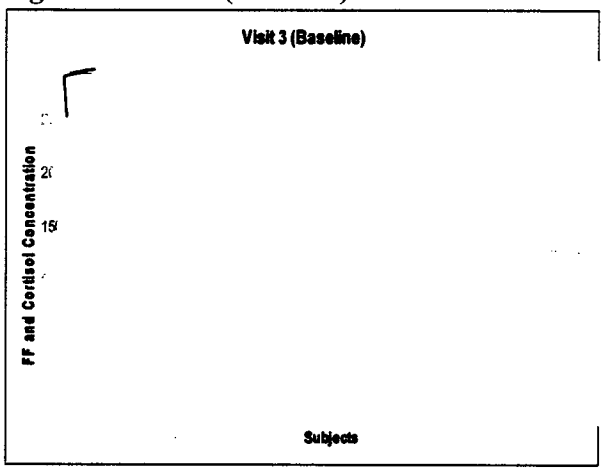


Figure B. Visit 5 (Week 12)

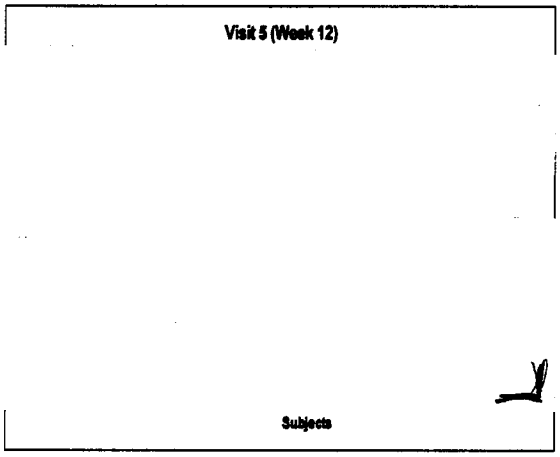


Figure C. Visit 8 (Week 24)

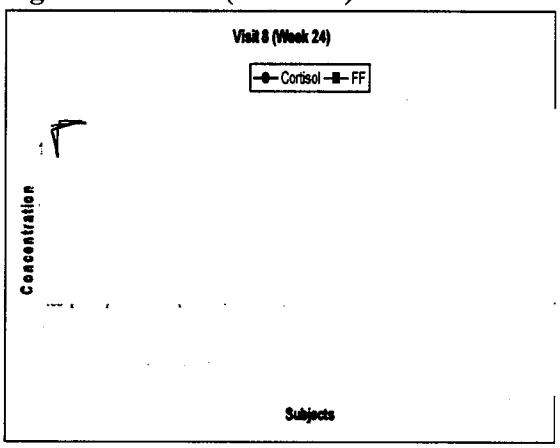
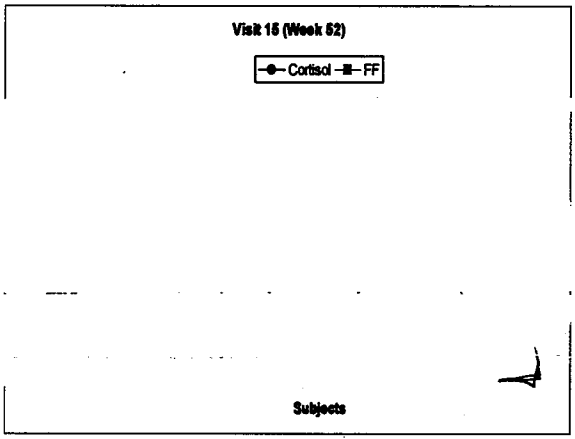


Figure D. Visit 15 (Week 52)



From the individual plots for the FF plasma levels and the corresponding 24 hour urine cortisol levels there appear no obvious trend or relationship in all 10 subjects. It is noteworthy that these high levels were observed **only once** in each subjects during the five visits. Therefore, sample contamination or assay related problems could be the cause of these unusual high concentrations.

Conclusions:

From all these observations, it appears there are inconstant and unexpected spikes of FF in plasma, regardless of the dose or duration of treatment. Therefore, these unusual levels could be associated with technical or assay issues.

2.3 Intrinsic factors

2.3.1 Does age, weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

There are several intrinsic factors that may affect the PK and PD performance of any drug. These include, but not limited to the following:

- Disease state such as hepatic and renal impairment
- Age
- Gender
- Weight
- Race
- Body Mass Index

There was no evidence of effect on any of these factors on the PK or PD performance of intranasal FF. No difference in PK or PD was noticed in this NDA in relation with age, gender, weight, race, or body mass. In addition, there was no difference in the PK or PD characteristics among healthy subjects, SAR or PAR patients.

2.3.2 Does renal impairment affect the PK of the drug? Is dosage regimen adjustment recommended?

As stated previously, the systemic exposure is minimal after intranasal administration. In addition, after IV or oral administration, the drug and its metabolites excreted mainly in feces (see radiolabel study discussed earlier). Therefore, renal impairment may not have effect on the PK of FF, especially after intranasal administration.

2.3.3 Does liver impairment affect the PK of the drug? Is dosage adjustment recommended?

The most significant finding in this NDA was the 3 fold increase in FF exposure in patients with hepatic impairment following oral inhalation of 400 mcg single dose of FF compared to healthy subjects (**Figures 2.3.3.1-2 and Tables 2.3.3.1-2** Study # FFA 10013).

Figure 2.3.3.1. FF Plasma Concentration-Time Profiles (Study # FFA 10013)

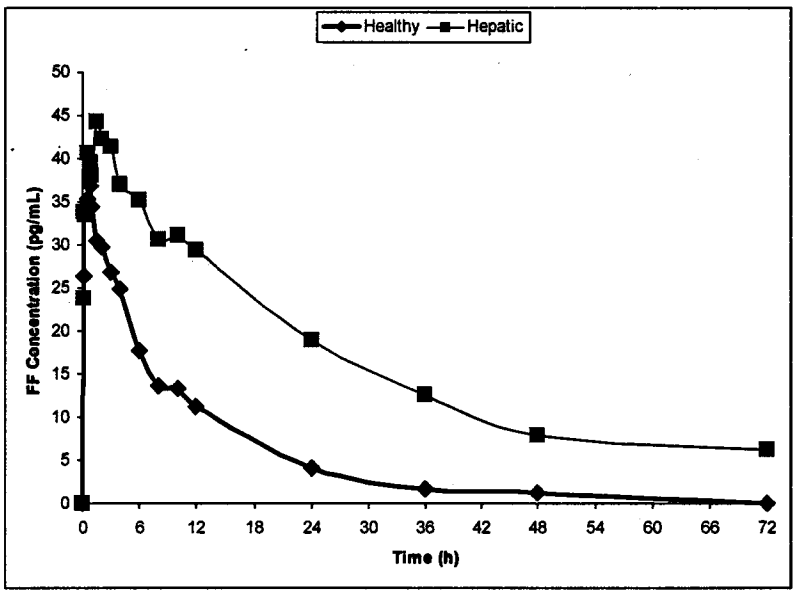


Table 2.3.3.1. Summary of PK Parameters in Healthy and Patients with Hepatic Impairment (Study # FFA 10013)

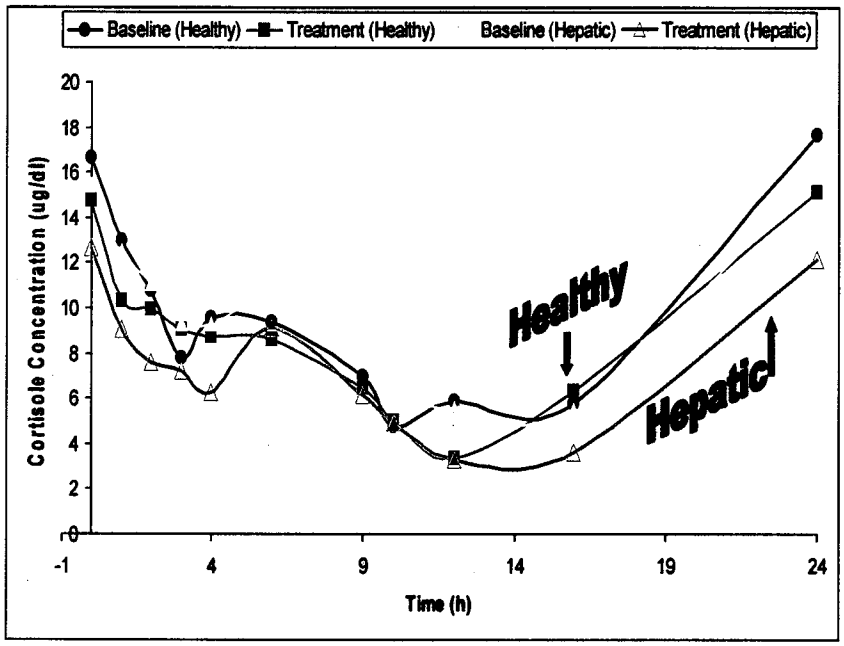
Parameter	Healthy N=10		Hepatic N=10	
	n		n	
AUC(0-∞) (pg·h/mL)	6	569 (155, 1193)	5	1942 (851.8, 3433)
AUC(0-t) (pg·h/mL)	10	235 (83.5, 590)	10	593 (83.5, 590.3)
Cmax (pg/mL)	10	38.2 (28.5, 52.7)	10	54.4 (40.7, 83.1)
Tmax (h)[2]	6	0.375 (0.17 – 1.0)	5	2.75 (0.75 – 10.1)
t½ (h)	6	10.5 (5.7, 17.3)	5	22.8 (10.1, 41.1)
Vss/F (L)	6	10648 (8310, 13643)	5	6791 (4291, 10748)
CL/F (L/h)	6	703 (377, 1312)	5	206 (110, 387)

Table 2.3.3.2. Summary of Statistical Analysis of PK Parameters in Healthy and Hepatic Impairment Patients (Study # FFA 10013)

Parameter	Adjusted Geom. Mean Hepatic	Adjusted Geom. Mean Healthy	Ratio (Hepatic/ Healthy)	90% Confidence Interval (Lower, Upper)
$AUC_{(0-\infty)}$ (pg.h/mL)	1816.1	667.1	2.72	(0.87, 8.49)
$AUC_{(0-t)}$ (pg.h/mL)	592.6	235.4	2.52	(1.02,6.19)
C_{max} (pg/mL)	54.38	38.22	1.42	(0.99, 2.04)
CL/F (L/h)	220.2	599.4	0.37	(0.12, 1.14)

Since the exposure was higher in hepatic impairment patients compared to healthy subjects, cortisol suppression was also greater in patients compared to healthy subjects (**Figure 2.3.3.2**). However, the magnitude of suppression is not as high as the increase in systemic exposure.

Figure 2.3.3.2. Serum Cortisol Profiles in Healthy Subjects and Patients with Liver Impairment (Study FFA 10013)



It is noteworthy that this study was conducted after a single dose. Therefore, the magnitude of exposure and the effect on cortisol level would be expected to be greater after multiple doses. Hence, appropriate language will be included in the label to describe the PK and PD of the drug in hepatic impairment patients, specifically after oral inhalation. However, no information is available on the effect of intranasal FF in hepatic impairment patients.

2.4 Extrinsic factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, diet, smoking and alcohol use were not evaluated.

2.4.2 Drug-Drug Interactions (DDI)

2.4.2.1 Is there an potential for drug-drug interactions with FF?

Ketoconazole appears to increase the systemic exposure of FF after intranasal administration. However, the magnitude of increase in exposure can not be determined due to the assay limitations. Only 6 subjects out of 20 subjects enrolled in this study had measurable FF plasma levels (**Table 2.4.2.1.1**).

Table 2.4.2.1.1 Mean PK Data of FF in 6 subjects with Measurable Plasma Levels.

Parameter	Treatment	N	n	Geometric mean	SD logs	95% CI of geometric mean
$AUC_{(0-t)}$ (pg.h/mL)	GW685698X 100 mcg + 200 mg ketoconazole	20	6	97.39	0.441	(61.29,154.74)
C_{max} (pg/mL)	GW685698X 100 mcg + 200 mg ketoconazole	20	6	18.74	0.217	(14.92,23.55)

In terms of effect on cortisol, there was approximately 5% reduction in 24 hour weighted mean plasma cortisol level after ketoconazole compared to placebo (**Table 2.4.2.1.2**)

Table 2.4.2.1.2. Summary of Statistical Analysis of Serum Cortisol Weighted Mean (0-24 h) Data (nmol/L) (Study # FFR 10013)

Adjusted Geometric Mean GW685698X + Ketoconazole [Test]	Adjusted Geometric Mean GW685698X + Placebo [Reference]	Treatment Ratio [Test / Reference]	90% CI (Lower, Upper)
145.76	154.06	0.95	0.86,1.04

This data was obtained from a study in 20 healthy subjects who received 100 mcg FF intranasal daily doses for 7 days with placebo or 200 mg ketoconazole in crossover design.
The effect could have been higher had the study been conducted using the maximum recommended ketoconazole dose (400 mg). Appropriate language will be included in the label to reflect the limitations of the study.

No other drug-drug interaction studies have been conducted by the sponsor in this NDA.

2.5 General Biopharmaceutics

2.5.1 What is the BCS Class classification for FF?

This information was not provided by the sponsor.

2.5.2 What is the effect of food on the BA of the drug?

No effect of food study was conducted in this NDA. As stated previously, there minimal absorption of the drug after intranasal administration. In addition, some the dose may be swallowed after intranasal administration the drug undergoes extensive first pass metabolism. Thus, the systemic exposure is minimal. Even if food enhances the absorption of the swallowed portion of the drug, the systemic exposure will still be minimal due to rapid first pass effect.

2.5.3 Was the to-be-marketed formulation used in the PK/clinical trials?

Yes. There were no changes in formulation between Phase 2 dose ranging study and Phase 3 clinical trials (**Tables 2.5.3.1-2**). Also, the absolute bioavailability was conducted with the same formulation (#FFR10010). Furthermore, the Phase 3 clinical trials and the absolute bioavailability study batches were manufactured at the proposed commercial scale.

Table 2.5.3.1. Phase I Formulation

Formulation Description	**Nasal Spray Solution**				
Clinical Trial Phase	1	1	1	1	1
Active component (% w/w)					
Fluticasone Furoate					
Inactive components (% w/w)					
Dextrose Anhydrous					
Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF					
Polysorbate 80					
Benzalkonium Chloride Solution [1]					
Edetate Disodium					
Purified Water					
Target unit fill weight					

Note:
1 Contains ~~% Benzalkonium Chloride

Table 2.5.3.1. Phase 2 and 3 Formulation

Formulation Description			
Clinical Trial Phase	2 and 3	2	2
Active component (% w/w)			
Fluticasone Furoate			
Inactive components (% w/w)			
Dextrose Anhydrous			
Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF			
Polysorbate 80			
Benzalkonium Chloride Solution [1]			
Edetate Disodium			
Purified Water			
Target unit fill weight			

Note:

1 Contains —% Benzalkonium Chloride

2.5.4 What are the Biopharmaceutical Characteristics of the Products?

The nasal spray device is intended for local delivery of FF. According to the sponsor, the nasal spray produces a droplet size distribution and disposition pattern within the nose that is dependent on the formulation and device characteristics. Therefore, the availability to the local site of action is a function of these device characteristics, dissolution of the drug and absorption across the mucosa. Accordingly, when used at the proposed recommended dose of 100 mcg QD, the plasma levels is negligibly low and close to the LLOQ (10pg/mL) of the assay. Since this product was designed to act locally in the nose the systemic exposure to FF may not be relevant for the efficacy. Nevertheless, for these reasons the sponsor did not conduct bioequivalence studies with FF nasal spray pump device. Therefore, the performance of the product would be based on the clinical endpoints that determine the safety and efficacy.

FF spray is a white suspension contained in an amber glass bottle. It is closed with a metering spray pump and incorporated into a plastic device with a dose indicator window and side actuated lever (**Figure 2.5.4.1**). This is designed for self-administration by children from the age of 7 years and older. **Table 2.5.4.1** shows the composition of the nasal spray.

Figure 2.5.4.1 Device Individual Components

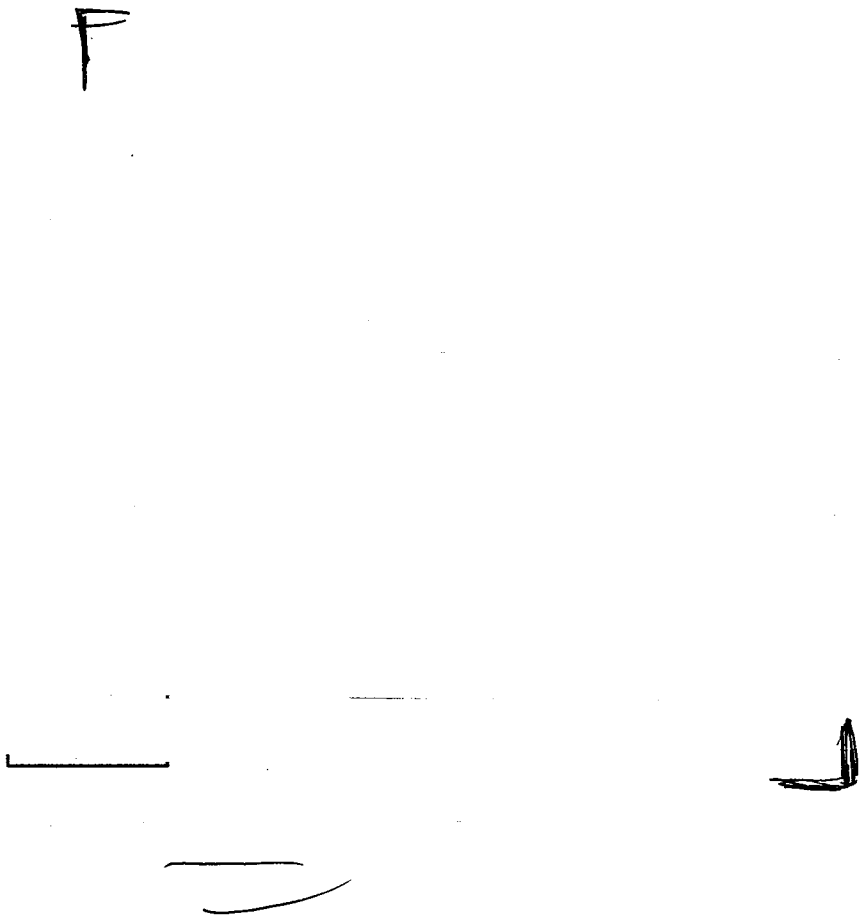


Table 2.5.4.1. Composition of Nasal Spray (27.5 mcg/spray)

Component	27.5 Micrograms/spray					
	Theoretical Quantity per Spray through Nozzle (mg)	(% w/w)	Amount per Container (mg)		Function	Reference to Standard
			120 Sprays	30 Sprays		
Active Ingredient						
Fluticasone Furoate (micronised)					Active	GlaxoSmithKline
Other Components						
Dextrose Anhydrous						USP
Microcrystalline Cellulose and Carboxymethylcellulose Sodium [1]						NF
Polysorbate 80						NF
Benzalkonium Chloride Solution [2]						NF
Edetate Disodium		0.015				USP
Purified Water						USP

Note:
1. % w/w carboxymethylcellulose sodium.
2. Contains benzalkonium chloride
3. Benzalkonium chloride equivalent to mg/spray and % w/w of

Details of the specification of the active ingredient are provided in m3.2.S.4.1, details of the specifications of the excipients are provided in m3.2.P.4.

As discussed earlier, the content of FF nasal spray has been approximately 25 mcg/actuation throughout the development program. Later it was confirmed that the actual dose delivered from the product is 27.5 mcg/actuation and this is proposed to be included in the label.

As stated earlier, the drug is intended for local delivery/action. Therefore, the delivery and release of the drug to the local site of action in the nasal mucosa and receptor would be rate limiting by the biopharmaceutical characteristics of the formulation and dissolution. Based on the PK data in this NDA, the systemic absorption after intra-nasal administration is negligible at the proposed doses. The plasma concentrations in most of the studies were just above or below the assay limit of quantification within the therapeutic doses.

2.5.5 Are the method and dissolution specifications supported by the data provided by the sponsor?

The *in vitro* dissolution methods and data analysis will be covered in more detail in the CMC review. Briefly, three main studies were conducted to assess the effect of certain physicochemical properties such as particle size, surface area, and crystallization on the *in vitro* dissolution profiles (**Table 2.5.5.1**).

Since FF is practically insoluble in water (0.001 mg/ml), a , such as Polysorbate 80 was added to the (**Table 2.5.5.1**). From these studies, it can be concluded that the dissolution is more affected by particle size than surface area (**Table 2.5.5.1**).

Table 2.5.5.1. Summary of In Vitro Dissolution Studies

Study	Drug Substance Attributes			Conditions	Mean % Dissolved at 30 minutes (range)
	Crystal habit	Particle Size (µm) $D_{(v0.1)}$ $D_{(v0.5)}$ $D_{(v0.9)}$	Specific Surface Area (m^2/g)		
1				Equipment: USP II Dissolution Bath with a media volume of 500mL, paddle speed of 50rpm, bath temperature of 37°C and a GxF/Glass filter. Media: (9:1 water:EtOH) + 0.9%w/v NaCl + 1.0%v/v Polysorbate 80 Sample Preparation: Approx 20mL of media was taken from each vessel and 10mL added to a vial containing 5mg of drug substance. This was swirled then added to the vessel at time zero. The remaining media was used to rinse the vial and the washings added to the vessel. Aliquots of 5mL were taken by syringe, 4mL filtered to waste, then 1mL added directly to a vial for analysis.	
2					
3					

Key:
Study 1
Study 2
Study 3

2.6 Analytical Section

The plasma concentrations of FF were determined by a validated high pressure liquid chromatography with ——— mass spectrometric detection coupled with solid phase extraction procedure ((SPE- HPLC-MS/MS). The analysis was performed at the Worldwide Bioanalysis (WWB) Department, Drug Metabolism and Pharmacokinetics (DMPK), GlaxoSmithKline (GSK), UK.

The method is highly sensitive with LLOQ of 10 pg/ml and a linear calibration ranging from10 to 1000 pg/ml. The reliability and precision of the assay are shown in the following **Tables 2.6.1-2.**

Table 2.6.1. Method Precision Within Run and Between Runs

Validation Report	Within-Run Precision (%CV)	Between-Run Precision (%CV)	Average Accuracy (% Bias)
FD2005/00013/00	———		-12.5% ≤ Bias ≤ 11.6%

Table 2.6.2. Quality Control Samples from Study FFR10010

Study FFR10010: Plasma concentrations of fluticasone furoate in QC samples			
	Nominal Concentrations		
	QC 40 pg/mL	QC 100 pg/mL	QC 800 pg/mL
Overall Mean	41.3	104.0	794.5
S.D. (within-run means)	6.5	10.3	47.4
Overall Precision (%CV)	15.7	9.9	6.0
Average Bias %	3.4	4.2	-0.8
n	16	17	17
Average Within-Run Precision (%)			
Between-Run Precision (%)			

21 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

4.2. Individual Study Review:

4.2.1.1 Study # FFR 10010 (Absolute Bioavailability)

Objectives: To determine the absolute bioavailability of FF after intranasal administration

Design: This was 2-way crossover study in 16 healthy subjects with washout period of 4-5 days between treatments as follows;

Treatment A (Intranasal): 800 mcg/spray (0.2% suspension) TID x 10 doses intranasally (Day 1 to Day 4). Total daily dose is 2400 mcg

Treatment B (IV): 250 mcg as single dose on Day 1 infused over 20 min.

PK blood samples were collected on Day 1 over 24 hours after IV and over 8 hours on Day 4 after intranasal administration. No blood samples were collected on Day 1 after intranasal administration.

Results:

Overall, the concentrations detected after 800 mcg/day intranasal doses was very low compared to 250 mcg single IV dose (**Figures 4.2.1.1.1-2**). The maximum concentration found in this study after intranasal administration was approximately 63 pg/ml (**Table 4.2.1.1**). However, the overall mean Cmax derived from this data was approximately 20 pg/mL and 6645 pg/ml after intranasal and IV administration, respectively. After normalizing the AUCs for the dose, the bioavailability after intranasal administration was only 0.55%.

Figure 4.2.1.1.1. Mean Plasma Concentration Time Profile Following Intranasal Administration in Day 4 (Study # FFR10010).

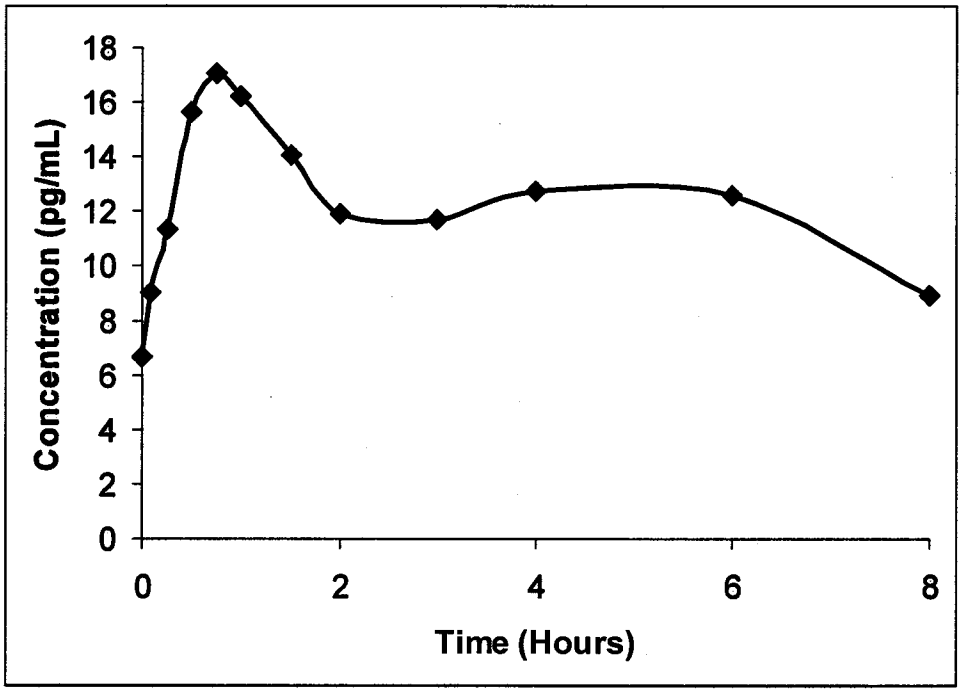


Figure 4.2.1.1.2. Mean Plasma Concentration Time Profile Following IV Administration in Day 1 (Study # FFR10010).

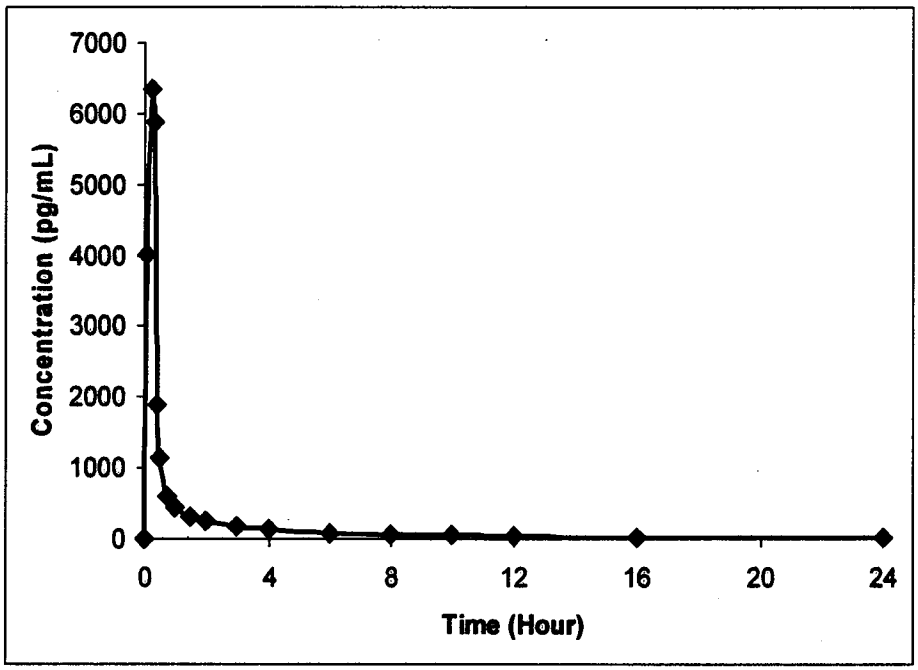


Table 4.2.1.1. Mathematical Mean PK Parameters (Study # FFR 100010)

Parameter	IV			Intranasal		
	Mean	SD	Range	Mean	SD	Range
AUC (pg.h/mL)	4322.81	747.29	3108-5414	107.73	101.97	15.5-426.6
Cmax (pg/mL)	6844.49	1572.25	3834-8930	22.85	13.57	11.1-63.8
Tmax (h)	0.27	0.066	0.08-0.33	1.59	2.06	0.08-8.00
Half Life (h)	12.44	7.11	5.36-24.14	-	-	-

Reviewers Comments:

Although the drug is formulated for local action, there is still some systemic exposure at high doses. However, the dose administered in this study is about 8 times higher than the therapeutic dose. Therefore, the systemic exposure would be minimal after the therapeutic dose. The maximum concentration found in this study is approximately 63 pg/ml. Thus, assuming dose proportionality, the concentration that would be expected after 100 mcg is approximately in the range of 10 to 20 pg/ml or lower. Based on these data, the systemic exposure would be minimal.

4.2.1.2 Study # FFR 10001 (Dose Escalation, 50-800 mcg X 7 days):

Objectives: To determine the PK after a single dose and seven day repeat intranasal doses of micronized suspension.

Design: This was double blind, placebo-controlled, crossover study in 24 healthy subjects (12 per cohort, 3 per sequence) at five dose levels (50, 100, 200, 400 and 800 mcg). In Period 1-4, Cohort A received 50, 100, ad 200 mcg doses and cohort B received 200, 400, and 800 mcg doses. All subjects received single doses in an escalating manner with a matching placebo. In period 5, subjects in Cohort A and B received repeated doses of 200 mcg and 800 mcg for 7 days, respectively. There was a 5-7 days washout period between each treatments period and sequence. The treatment sequence is detailed below:

COHORT A					
Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
1	Placebo	50	100	200	Repeat doses of 200 µg or placebo for 7 days
2	50	Placebo	100	200	
3	50	100	Placebo	200	
4	50	100	200	Placebo	

COHORT B					
Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
1	Placebo	200	400	800	Repeat doses of 800 µg or placebo for 7 days
2	200	Placebo	400	800	
3	200	400	Placebo	800	
4	200	400	800	Placebo	

Each actuation of spray was delivering a volume of 100 µl (100 mcg). A maximum of 800 µl in volume was administered to the nose (400 µl/nostril). Blood samples for PK and cortisol measurements were collected in at appropriate time intervals throughout the study (Day 1-7).

Results:

A. Pharmacokinetics:

The maximum observed Cmax in this study is 37.8 pg/ml at a dose of 200 mcg and only in one subject at this dose level (**Table 4.2.1.2.1**). At the 800 mcg dose, approximately half of the subjects (6 out 11) had detectable levels of FF in the plasma. The maximum observed concentration in this group was 26.2 pg/ml. There was no particular time to predict the appearance of the drug in the plasma. In particular, the time for Cmax would be largely unpredictable (**Figures 4.2.1.2.1-2.**). Therefore, the data reported by the sponsor for Tmax in this study is unreliable for this product.

Surprisingly, no plasma concentrations of FF were detectable in all subjects at all times points following single and once daily repeat dosing for 7 days. Thus, no PK parameters were available for analysis.

Table 4.2.1.1. Summary of PK Parameters After Single Doses Intranasal Administration of FF (Study # FFR 10001) (n=number of subjects with measurable levels).

Parameter [units]	Dose [µg]	n/N	Median	Range
C_{max} [pg/mL]	50	1/12	BLQ	BLQ to 24.2
	100	0/12	BLQ	BLQ to BLQ
	200	1/23	BLQ	BLQ to 37.8
	400	2/11	BLQ	BLQ to 23.3
	800	6/11	11.7	BLQ to 26.2
t_{max} [hours]	50	1/12	BLQ	BLQ to 1.50
	100	0/12	BLQ	BLQ to BLQ
	200	1/23	BLQ	BLQ to 3.02
	400	2/11	BLQ	BLQ to 1.00
	800	6/11	0.17	BLQ to 3.00
$AUC_{(0-t)}$ [pg.h/mL]	50	1/12	BLQ	BLQ to 12.84
	100	0/12	BLQ	BLQ to BLQ
	200	1/23	BLQ	BLQ to 18.90
	400	1/11	BLQ	BLQ to 19.33
	800	4/11	BLQ	BLQ to 63.27

BLQ – all concentrations below the LLOQ
n = number of subjects for whom parameter could be defined

Figure 4.2.1.2.1. Mean Plasma Profiles of FF For All Doses (Study # FFR 10001)

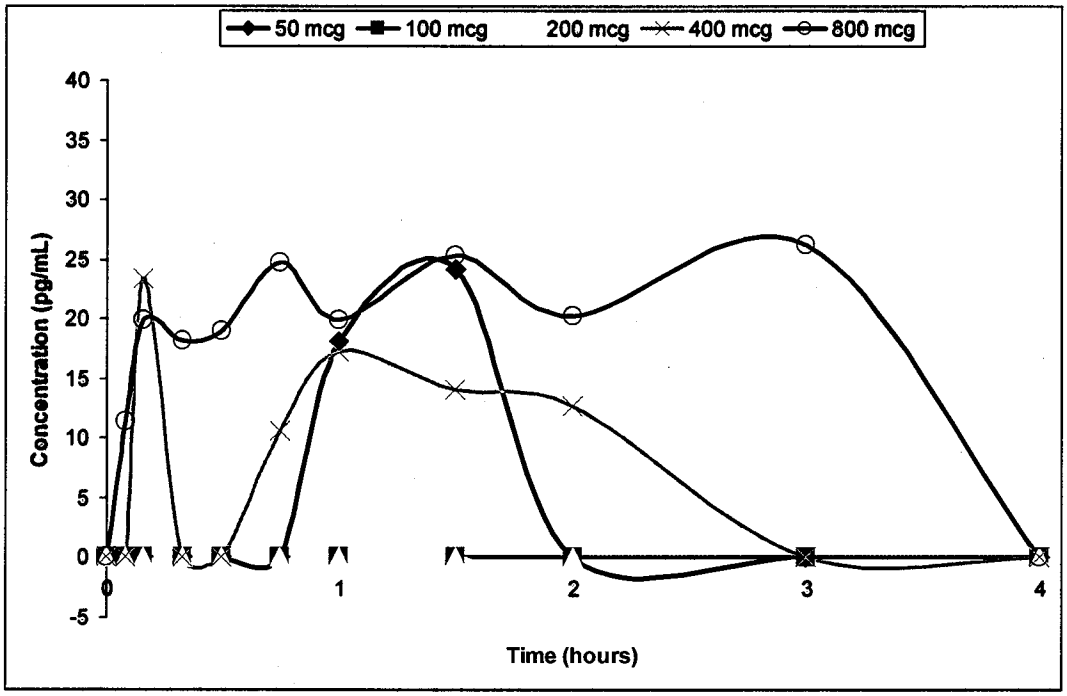
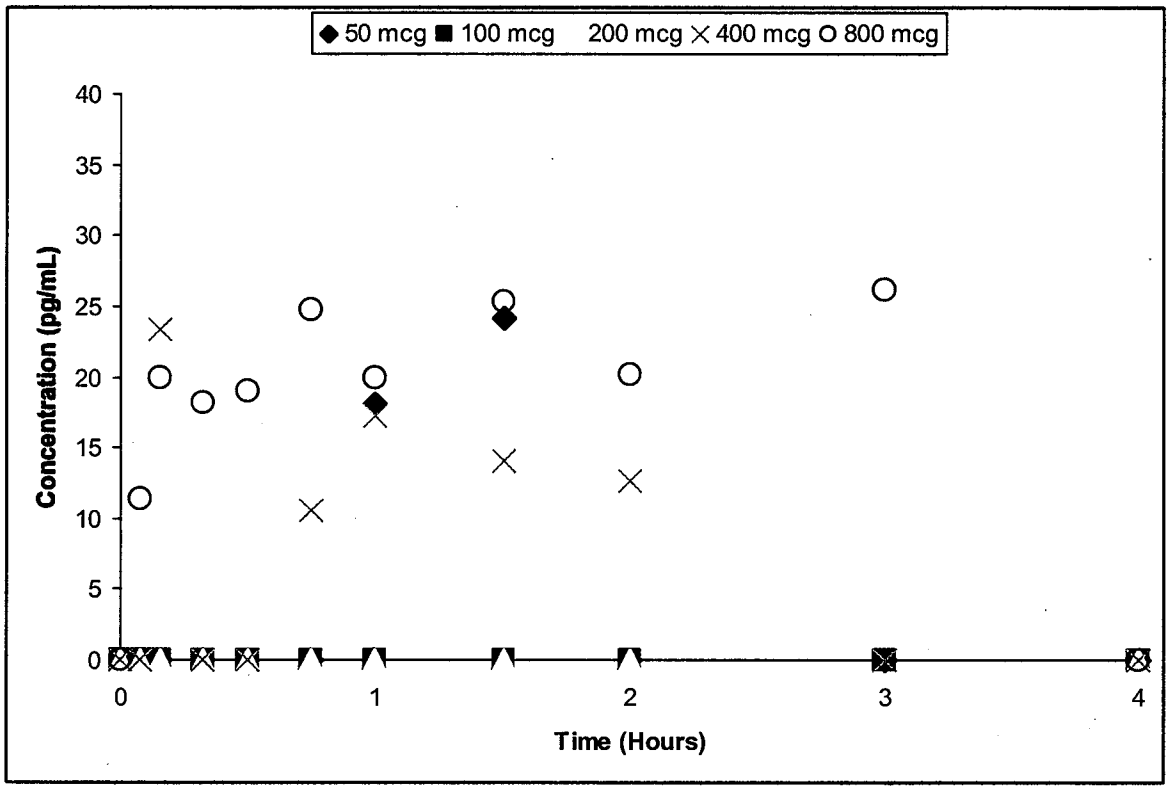


Figure 4.2.1.2.2. Scattered Plot (Unconnected Time Points) for the Plasma Mean FF Concentrations Presented in the Previous Graph (Study # FFR 10001)



B. Pharmacodynamics:

The effect of FF on 24 hours plasma cortisol levels after single and repeated administration are shown in **Figures 4.2.1.2.3-4** . From these plots, there was no obvious difference in the plasma cortisol concentration-time profiles among all treatments compared to placebo following either single doses (**Figure 4.2.1.2.3**) or repeat intranasal doses (**Figure 4.2.1.2.4**). Further analysis of the data shows that the estimates of the ratios for each of the active treatments (**Test**) compared to placebo (**Reference**) are close to unity following single doses (Period 1-4) and repeat doses (Period 5) of intranasal administration (**Table 4.2.1.2.1 and Figures 4.2.1.2.5-6**).

Figure 4.2.1.2.3. Mean Cortisol Plasma Concentration-Time profiles After Single Doses of Intranasal Administration of FF (Study # FFR 10001)

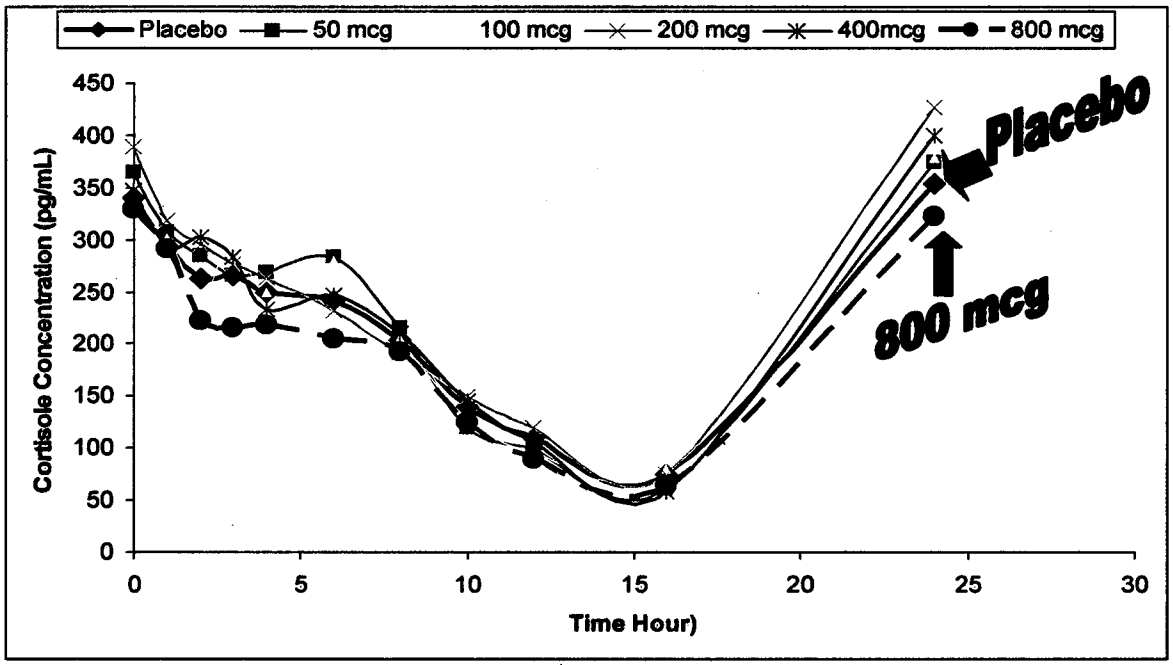


Figure 4.2.1.2.4. Mean Cortisol Plasma Concentration-Time profiles on DAY 7 After Repeat Daily Intranasal Doses (Study # FFR 10001)

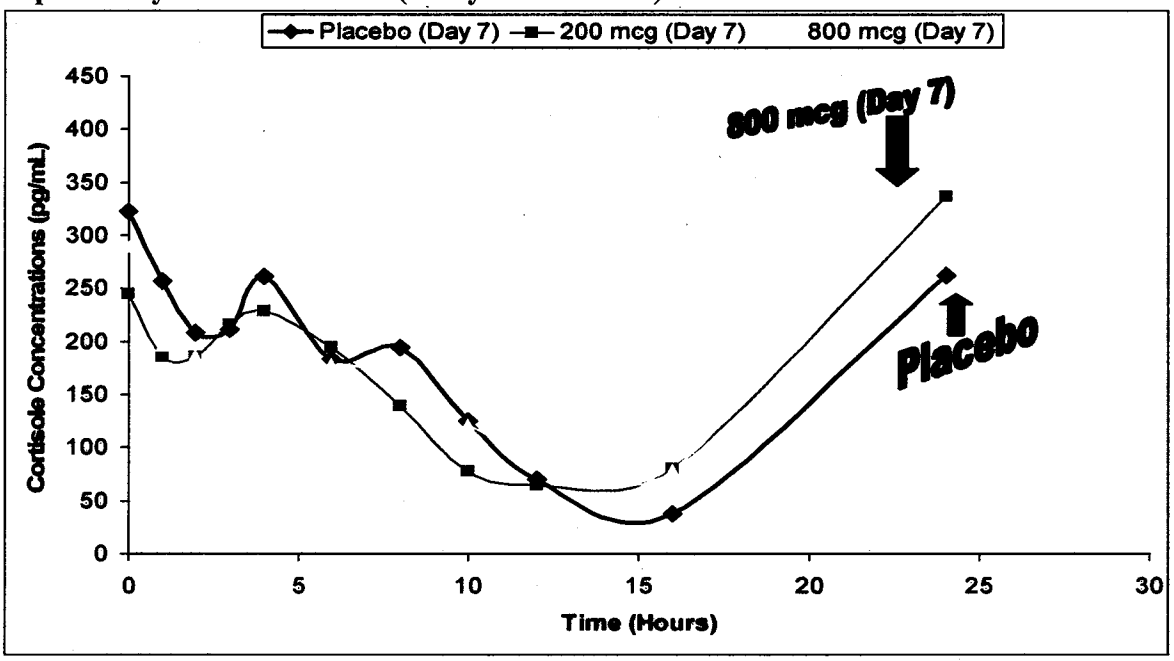


Table 4.2.1.2.1. Summary of Statistical Analysis of Serum Cortisol Weighted Means (nmol/L) Following Single Doses (Period 1-4) and repeat Doses (Period 5).

Comparison (test versus reference)	Adjusted mean			
	Test	Reference	Ratio	95% confidence intervals
Periods 1-4				
GW685698X 50 µg SD versus Placebo	194.75	194.50	1.001	(0.891,1.125)
GW685698X 100 µg SD versus Placebo	202.97	194.50	1.044	(0.937,1.163)
GW685698X 200 µg SD versus Placebo	203.28	194.50	1.045	(0.960,1.137)
GW685698X 400 µg SD versus Placebo	206.30	194.50	1.061	(0.949,1.186)
GW685698X 800 µg SD versus Placebo	178.86	194.50	0.920	(0.816,1.036)
Period 5 (Day 7)				
GW685698X 200 µg versus placebo RD	154.09	161.10	0.956	(0.774,1.182)
GW685698X 800 µg versus placebo RD	171.66	161.10	1.066	(0.861,1.318)

Figure 4.2.1.2.5. Adjusted Mean Ratio and 95% CI of Serum Cortisol Weighted Mean (Perido 1-4 (Single Doses, Study # FFR 10001)

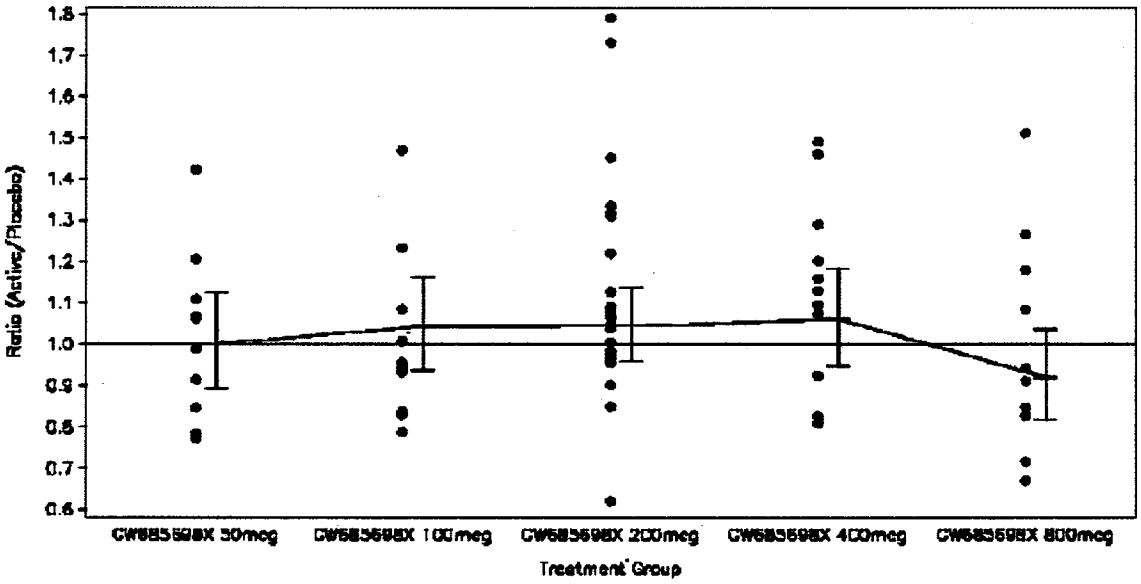
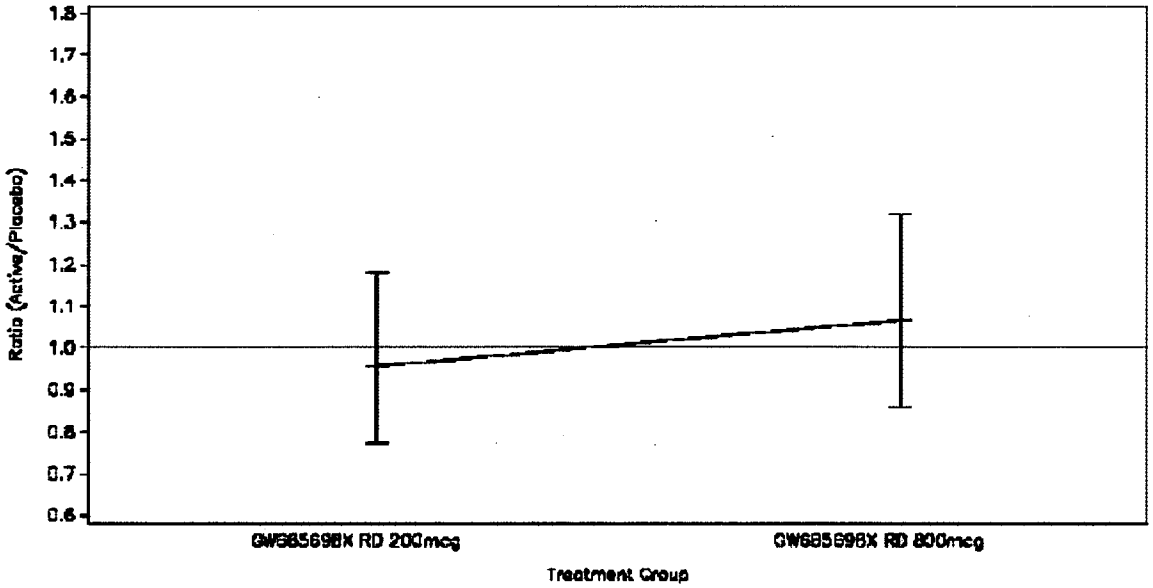


Figure 4.2.1.2.6 . Adjusted Mean Ratio and 95% CI of Serum Cortisol Weighted Mean (Perido 1-4 (Single Doses, Study # FFR 10001)



Reviewer's Comments:

The FF plasma levels were too low in this study considering the high doses administered intranasally (up to 800 mcg). It is noteworthy that there was a high variability in the plasma concentrations of FF and in particular the time point for the Cmax. Therefore, the data are unreliable to make adequate conclusions with respect to the disposition of the drug and the derived PK parameters such as Cmax.

Furthermore, the dose exposure (dose proportionality), can not adequately be established for this route of administration. Nevertheless, the 800 mcg dose appears to produce slightly higher and more consistent concentrations throughout the sampling time points than any other tested doses in this study.

In terms of the effect on HPA axis, this study did not show evidence of suppression of plasma cortisol levels. However, no conclusion on the effect of intranasal FF can be made from this study due to the study design limitation and in particular the short duration of the study (i.e., 7 days). Other studies to determine the effect of FF on HPA axis were conducted by the sponsor with at least 6 weeks treatment duration. These studies will be discussed in a separate section of the review and also in more details by the Medical Officer's review.

Conclusions:

From this study, the plasma concentration of FF was negligible in most of the time points. The concentration after 800 mcg was only slightly higher than other lower doses. Even with this 8 times of the proposed therapeutic dose (100 mcg QD, the concentration was just above the assay LLOQ.

Although there was no evidence of cortisol suppression found in this study, no conclusion can be made due to the limitation of the study design and the duration of treatments.

4.2.1.3 Study # FFR 10008 (^{14}C Radio-labeled Oral and IV Solution for Mass Balance)

Objectives:

The primary objective of this study was to evaluate the excretion (mass balance) after oral and IV administration of ^{14}C radio-labeled FF solution.

Design:

This was two-way crossover study in 5 healthy subjects with a washout period of approximately 4 weeks as follows:

Treatment A: 2 mg single **oral** dose of ^{14}C FF intravenous solution.
Treatment B: 250 mcg single IV infusion.

Blood, Urine and feces were collected at appropriate time points over duration of 7 days.

Results:

Most of the radioactivity was recovered in feces; accounting approximately 101% after oral and 90% after IV administration. The high percentage of radioactivity in feces after IV administration suggests that the drug and or its metabolites are excreted via the bile and then to the feces. The total recovery in urine following either oral or IV administration was <2%.
The Cmax in plasma occurred within 30 min to 2 hours following oral administration. The half life of the radioactivity (not the parent drug, FF) was approximately 20 hours following either oral or IV administration (**Table 4.2.1.3.1**).

Table 4.2.1.3.1. Summary of PK Parameters for the parent drug, FF (GW685698X), and the metabolite, GW694301X, and Radioactivity PK Parameters Following Oral and IV Administration (Study # FFR 10008)

Treatment	Parameter	Geometric Mean (95% CI) [1]		
		GW685698X	GW694301X	Radioactivity
2 mg oral (N=5)	AUC(0-t) (pg.h/mL)	404.6 (151.2, 1082.8)	83.26 (31.11, 222.85)	23197 (11238, 47883)
	AUC(0-∞) (pg.h/mL)	1082.6[a] (649.9, 1803.6)	105.20 (47.89, 231.09)	38129[b] (17606, 82575)
	Cmax (pg/mL)	153.7 (48.6, 486.0)	60.03 (25.95, 138.88)	1360 (1080, 1720)
	tmax (h)	0.50 (0.50-1.00)	0.75 (0.50-1.00)	0.75 (0.50-2.00)
	t1/2 (h)	3.89[a] (range: 2.91-5.19)	0.985 (0.643, 1.510)	20.421[b] (11.08, 37.63)
250 mcg i.v. (N=5)	AUC(0-t) (pg.h/mL)	3918.6 (2955.0, 5196.4)	ND	10158 (5266, 19594)
	AUC(0-∞) (pg.h/mL)	4352.2 (3446.0, 5496.6)	ND	16935[c] (4555, 62958)
	Cmax (pg/mL)	2806.5 (1739.6, 4527.8)	ND	4910 (3500, 6900)
	tmax (h)	0.50 (0.25,0.53)	ND	0.50 (0.50-0.53)
	t1/2 (h)	15.12 (11.82, 19.35)	ND	20.77[c] (2.60, 166.15)

Source Data: Table 10.11, Table 10.12 and Table 10.13

1. Geometric mean (95% CI) is presented for all parameters except tmax where median (range) is presented and t1/2 for GW685698X for the oral dose where geometric mean (range) is presented. n=5 except for: a: n=2; b: n=3; c: n=4.

ND = not determined, all concentrations below limit of quantitation.

The units presented in this table for radioactivity AUC(0-t), AUC(0-∞) and Cmax are pg.h/mL and pg/mL for

One of the major metabolite, GW694301X, was detected in the plasma after oral administration only (**Figures 4.2.1.3.1-2**). This suggests that the drug undergoes extensive first pass metabolism after oral administration. Thus the absolute bioavailability of the oral solution based on AUCs was only 1.26%. Based on the AUC ratios, it appears that 30% of the oral dose was absorbed (**Tables 4.2.1.3.2-4**).

Figure 4.2.1.3.1. Median Plasma Concentration-Time Profiles Following Oral Administration of FF (Study # FFR 10008)

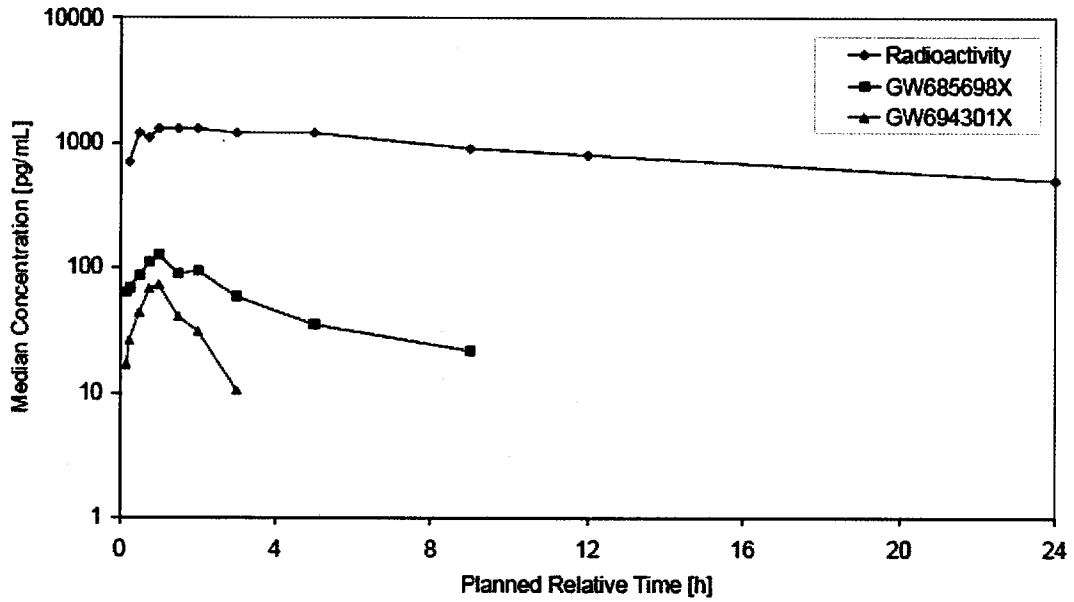


Figure 4.2.1.3.2 . Median Plasma Concentration-Time Profiles Following IV Administration of FF (Study # FFR 10008)

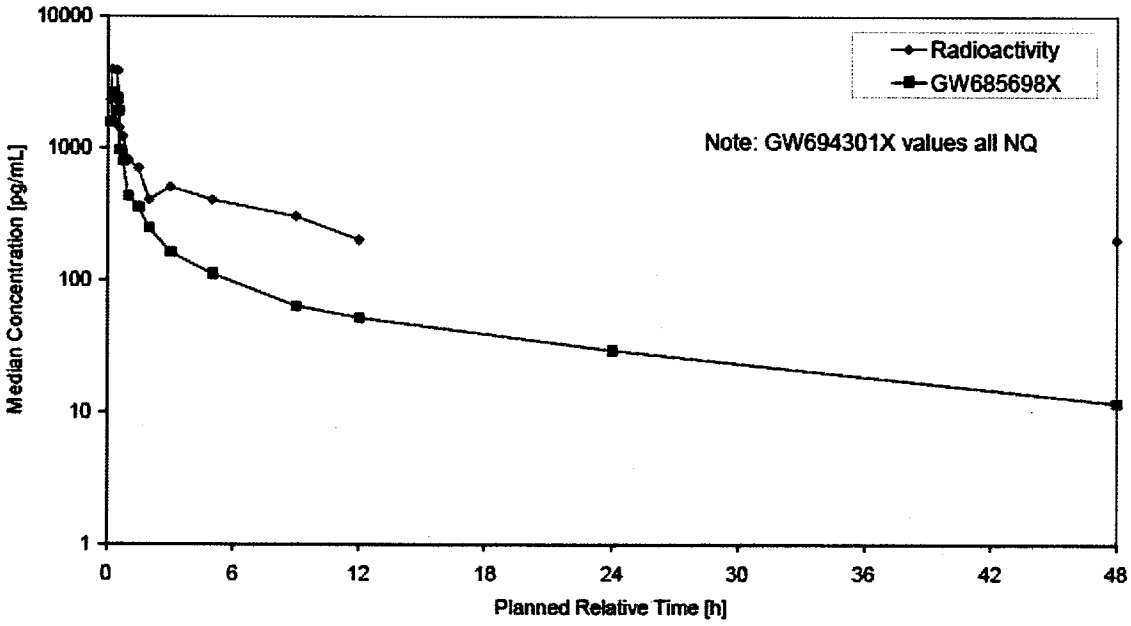


Table 4.2.1.3.2. Estimate of Percentage of Dose Absorbed

Subject	Treatment	AUC (0-t) [n.g.h/mL]	DN AUC (0-t)	Ratio DN AUC(0-t) [%]
1	250mcg IV	5.03	20.12	
	2mg Oral	10.71	5.355	27
2	250mcg IV	15.59	62.36	
	2mg Oral	46.19	23.095	37
3	250mcg IV	6.73	26.92	
	2mg Oral	16.59	8.295	31
4	250mcg IV	16.41	65.64	
	2mg Oral	23.12	11.56	18
5	250mcg IV	12.49	49.96	
	2mg Oral	35.4	17.7	35
Mean				30
Minimum				18
Maximum				37

Source Data: Table 10.14
DN AUC(0-t) – Dose normalised AUC(0-t) i.e. AUC(0-t)/nominal dose

Table 4.2.1.3.3. Mean of Radioactivity Exposure Following Oral and IV Administration (Study # FFR 10008)

Parameter	Treatment	N	n	Mean	95% CI (Lower,Upper)	SD	CVb (%)	Median	Min.	Max.
AUC(0-inf) ratio[1]	2mg Oral	5	5	102.236	(3.375,201.097)	79.6196	77.88	101.779	26.36	223.14
	250mcg IV	5	5	4.373	(0.911, 7.835)	2.7881	63.76	3.714	1.72	8.23
Cmax ratio	2mg Oral	5	5	11.472	(1.615, 21.329)	7.9384	69.20	11.914	3.14	21.37
	250mcg IV	5	5	1.867	(0.860, 2.873)	0.8106	43.43	1.569	1.19	3.24

Parameter	Treatment	N	n	Geom. Mean	95% CI (Lower,Upper)	SD logs
AUC(0-inf) ratio[1]	2mg Oral	5	5	76.5737	(25.2239,232.459)	0.89433
	250mcg IV	5	5	3.6612	(1.5737, 8.5177)	0.68001
Cmax ratio	2mg Oral	5	5	8.8606	(3.0394,25.8311)	0.86172
	250mcg IV	5	5	1.7512	(1.0881, 2.8183)	0.38323

Table 4.2.1.3.4. Oral Bioavailability (Study # FFR 1008)

Parameter	N	n	Mean	95% CI (Lower,Upper)	SD	CVb (%)	Median	Min.	Max.
%F	10	5	1.585	(0.267, 2.902)	1.0610	66.95	1.517	0.48	2.82

Parameter	Treatment	N	n	Geom. Mean	95% CI (Lower,Upper)	SD logs
%F	Oral/IV	10	5	1.258	(0.463, 3.418)	0.8049

The scheme of the metabolic pathway in animals and human shows several other miner metabolites for FF (**Figure 4.2.1.3.3**). From this scheme it can be seen that the principle route of metabolism is hydrolysis of the S-fluoromethyl carbothioate group to form the carbocylic acid metabolite, GW694301X (M10). As shown in the scheme this metabolite undergoes further metabolism to several other minor metabolites. It should be noted that based M10 metabolites virtually has very low pharmacological activities compare to the parent compound, FF (See also Pharmacology/Tox review).

Figure 4.2.1.3.3. FF Metabolic Scheme in Animals and Human

Reviewer's Comments:

Although this study may be considered irrelevant to the intranasal administration, it provides useful information about the metabolism and excretion of the drug after oral and IV administration. Two major conclusions can be made from this study that can be relevant to intranasal administration. First, if the drug is swallowed after intranasal administration it is will undergo extensive first pass metabolism. Second, if it is absorbed it will be recycled back to the GI tract via the bile. Thus, the systemic exposure after intranasal administration would be expected to be low, regardless.

Conclusions:

Based on this study, the following conclusions can be made:

- No metabolites were observed after IV administration. The metabolite, GW694301X was observed after oral administration only.
- The oral bioavailability of FF is very low (~1.25%).
- The entire radioactivity accounted for after oral administration (101%) was recovered in feces.
- After IV administration, 90% of the radioactivity was excreted in feces. Thus, confirming billiary excretion.

4.2.3.4 Study # FFA 10001 (Single Rising Dose Inhalation, 50 mcg to 4000 mcg):

Objective: To Investigate the PK/PD after a singled inhaled doses of 50 mcg to 4000 mcg in healthy male subjects.

Design: Double-Blind, crossover single escalating dose in 24 healthy males subjects in two cohorts as follows:

COHORT 1					
Sequence	**Period 1**	**Period 2**	**Period 3**	**Period 4**	**Period 5**
1	Placebo (P)	50 µg	100 µg	250 µg	500 µg
2	50 µg	P	100 µg	250 µg	500 µg
3	50 µg	100 µg	P	250 µg	500 µg
4	50 µg	100 µg	250 µg	P	500 µg
5	50 µg	100 µg	250 µg	500 µg	P

COHORT 2					
Sequence	**Period 1**	**Period 2**	**Period 3**	**Period 4**	**Period 5**
1	Placebo (P)	500µg	1000 µg	2000 µg	4000 µg
2	500 µg	P	1000 µg	2000 µg	4000 µg
3	500 µg	1000µg	P	2000 µg	4000 µg
4	500 µg	1000µg	2000 µg	P	4000 µg
5	500 µg	1000µg	2000 µg	4000 µg	P

There was at least 7 days washout between treatments. The drug was administered via a multidose dry powder inhaler device (DISKHALER) with ROTADISK. The formulations/products and inhalers used in this study are summarized in the following table:

Property	**Study Drug**	
	GW685698X DISKHALER	**Matched placebo DISKHALER**
Formulation	GW685698X powder blended with lactose	Lactose powder
Dosage form	**ROTADISK** (4 blister)	**ROTADISK** (4 blister)
Unit dose strength	50 µg, 250 µg and 1000 µg / blister.	N/A
Physical Description	Dry white powder	Dry white powder
Manufacturer	GSK Ware	GSK Evreux
Route of administration	Inhaled via **DISKHALER**	Inhaled via **DISKHALER**

Blood was collected over 24 hours for the determination of the concentration of the parent drug (FF) and its metabolites and also cortisol levels. In addition, 24 hour urine was collected from subjects in Cohort 2 only for cortisol and 6-betahydxy cortisol measurements.

Results:

A. Pharmacokinetics:

The Cmax occurred within 20 to 50 min after inhalation after all doses (**Figure 4.2.1.3.1 and Table 4.2.1.3.1-2**). However, there was less than dose proportional increase in Cmax with increasing dose (**Figures 4.2.1.3.2-3 and Table 4.2.1.3.2**). By contrast, there was greater than dose proportional increase in AUC with dose (**Figure 4.2.1.3.3**). The half life increased from approximately 2 hours to 27 hours as the dose increased from 50 to 4000 mcg (**Table 4.2.1.3.2**). It should be noted that the metabolite, GW694301X was not detected in the plasma at all doses. The concentration in all samples was BLQ.

Figure 4.2.1.3.1. Mean Plasma Concentration-Time Profiles of FF Following Inhaled Doses (Study # FFA 10001)

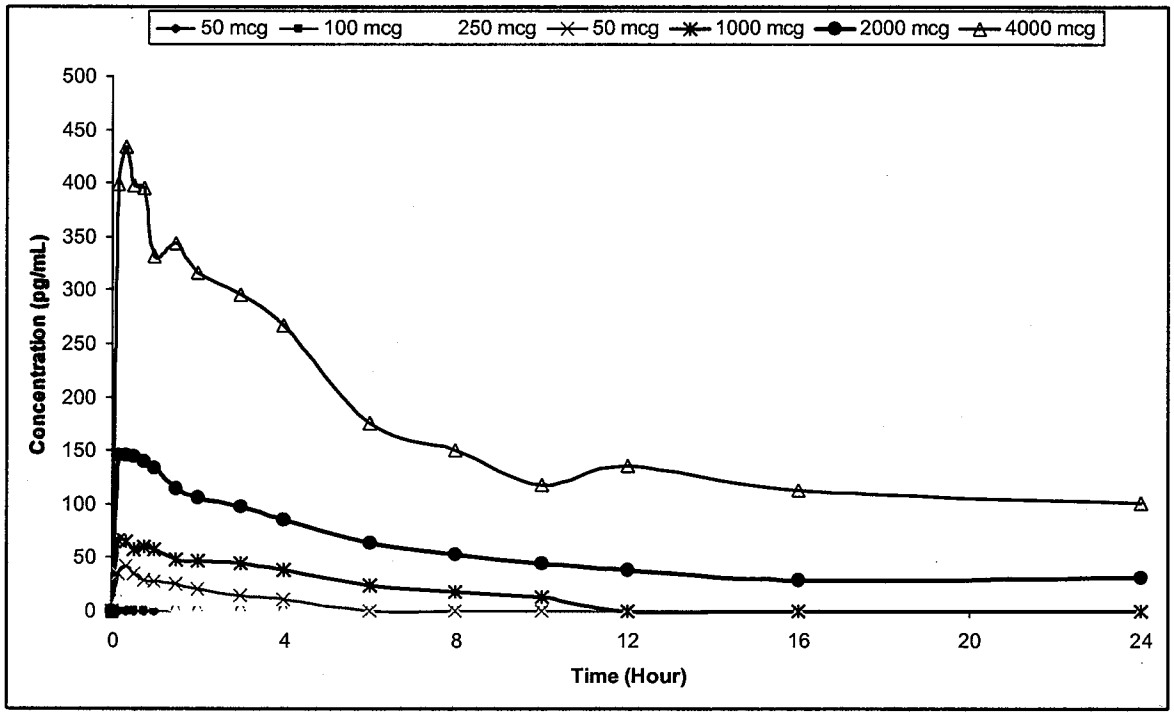


Table 4.2.1.3.1A. Summary of PK Parameters (Study # FFA 10001)

Parameter [units]	Dose [µg]	N	n	Geometric Mean	95% Confidence Interval
C_{max} [pg/mL]	50	10	4	13.02	11.08–15.31
	100	10	7	24.21	15.13–38.74
	250	10	10	28.74	20.35–40.58
	500	20	20	49.27	43.36–55.99
	1000	10	10	75.42	60.36–94.24
	2000	9	9	160.75	135.71–190.41
	4000	9	9	436.65	336.57–566.49
t_{max}[1] [h]	50	10	4	0.88	0.17–1.00
	100	10	7	0.75	0.17–4.03
	250	10	10	0.50	0.17–2.00
	500	20	20	0.33	0.17–1.00
	1000	10	10	0.75	0.17–1.50
	2000	9	9	0.50	0.17–4.00
	4000	9	9	0.50	0.17–1.50
AUC_{last} [pg.h/mL]	50	10	0	ND	ND
	100	10	5	22.1	8.8–55.5
	250	10	9	25.1	13.2–47.9
	500	20	20	105.4	77.8–142.9
	1000	10	10	355.0	231.2–545.0
	2000	9	9	1205.3	927.3–1566.7
	4000	9	9	3750.4	2974.4–4728.8

Table 4.2.1.3.2 B. Summary of PK Parameters (Study # FFA 10001)

Parameter [units]	Dose [µg]	N	n	Geometric Mean	95% CI
AUC_{∞} [pg.h/mL]	100	10	1	47.8[1]	ND
	250	10	4	51.8	22.7–118.4
	500	20	13	198.1	131.6–298.4
	1000	10	9	543.3	338–873.3
	2000	9	6	1750.2	974.4–3143.8
	4000	9	7	8125.8	5167.7–12777.3
$t_{½}$ [h]	100	10	1	1.800	ND
	250	10	4	1.498	0.837–2.684
	500	20	13	3.952	2.501–6.244
	1000	10	9	6.578	3.253–13.303
	2000	9	6	13.683	5.512–33.968
	4000	9	7	26.998	14.331–50.681

Figure 4.2.1.3.2. Mean FF Cmax at Individual Doses (Study # FFA 10001):

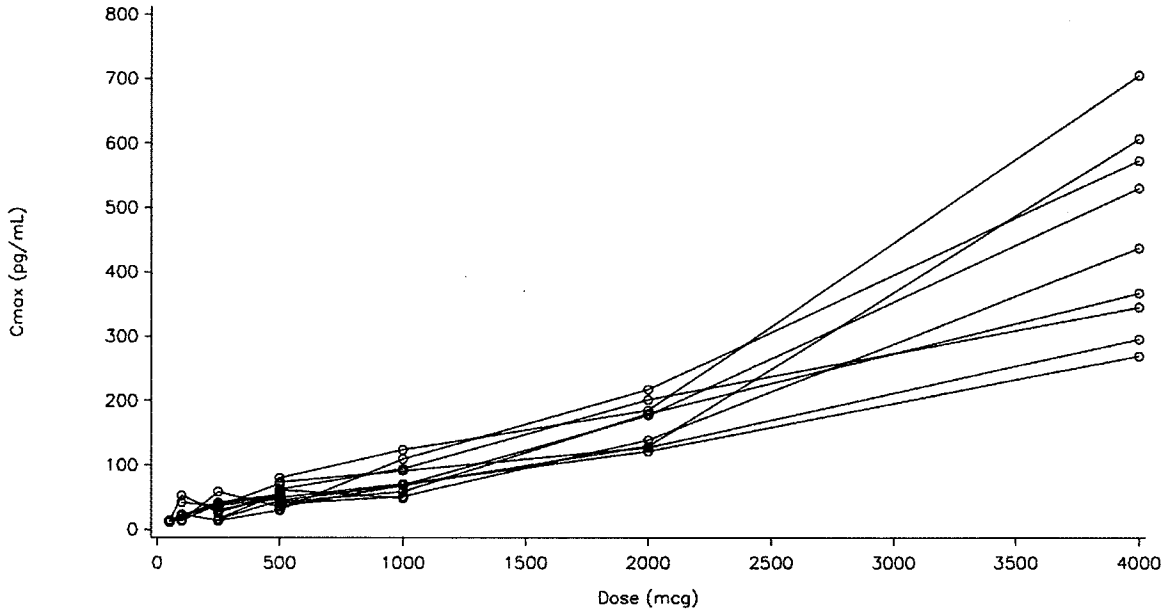
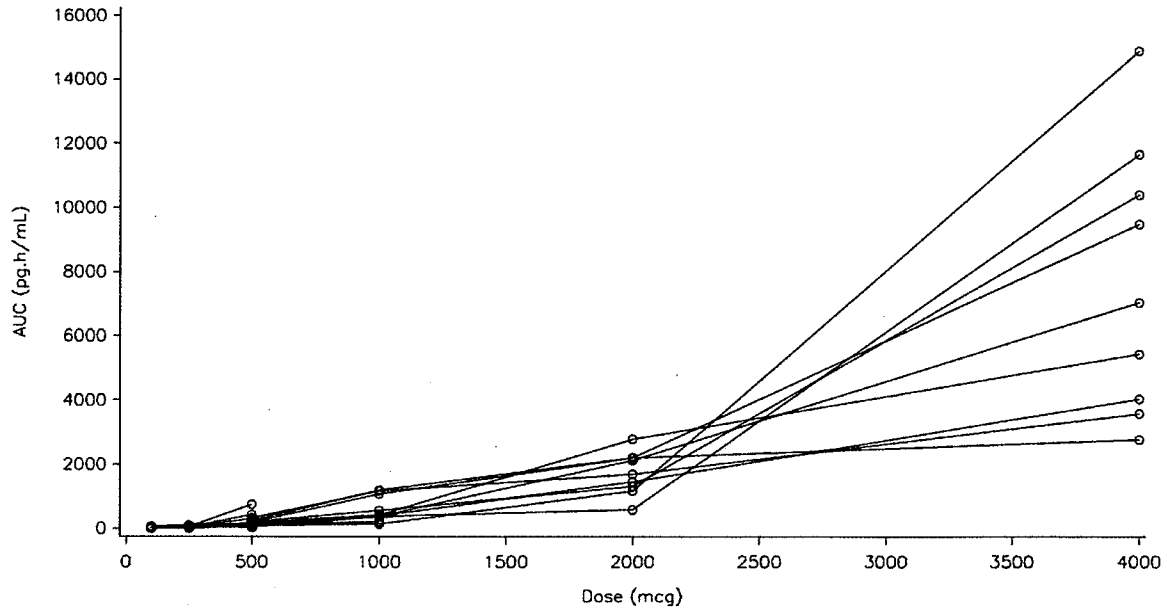


Figure 4.2.3.3. Mean FF AUC at Individual Doses (Study # FFA 10001):



B. Pharmacodynamic:

It is clearly that after inhalation, FF show substantial effect on plasma and urine cortisol levels (**Figures 4.2.1.3.4**). The effect is dose dependent and is more pronounced at the highest dose of 4000 mcg. The individual ratios of weighted mean 0-24 h serum cortisol relative to placebo following the all treatments decreased in dose-dependent manner (**Figures 4.2.1.3.5-8 and Table 4.2.1.3.3).** At the highest dose of 4000 mcg, the ratio dropped to below 0.5 (**Table 4.2.1.3.4.**). The same trend was observed in urine cortisol levels where the level of 6-beta hydroxyl cortisol was substantially reduced at the highest dose (**Figure 4.2.1.3.9**).

Figure 4.2.1.3.5. Serum Cortisol Profiles Following Oral Inhalation 50 to 4000 mcg Doses of FF (Study # FFA 10001).

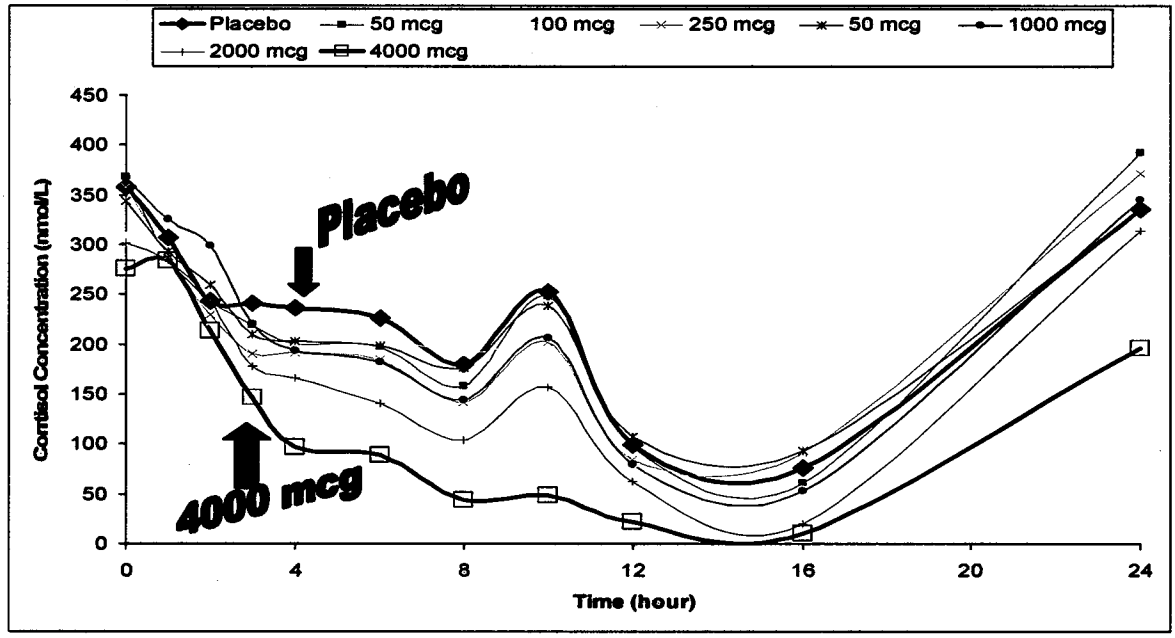


Figure 4.2.1.3.7. Individual Ratios of Serum Cortisol Weighted Mean (0-24 h) With Mean Difference and 95% CI (Study # FFA 10001).

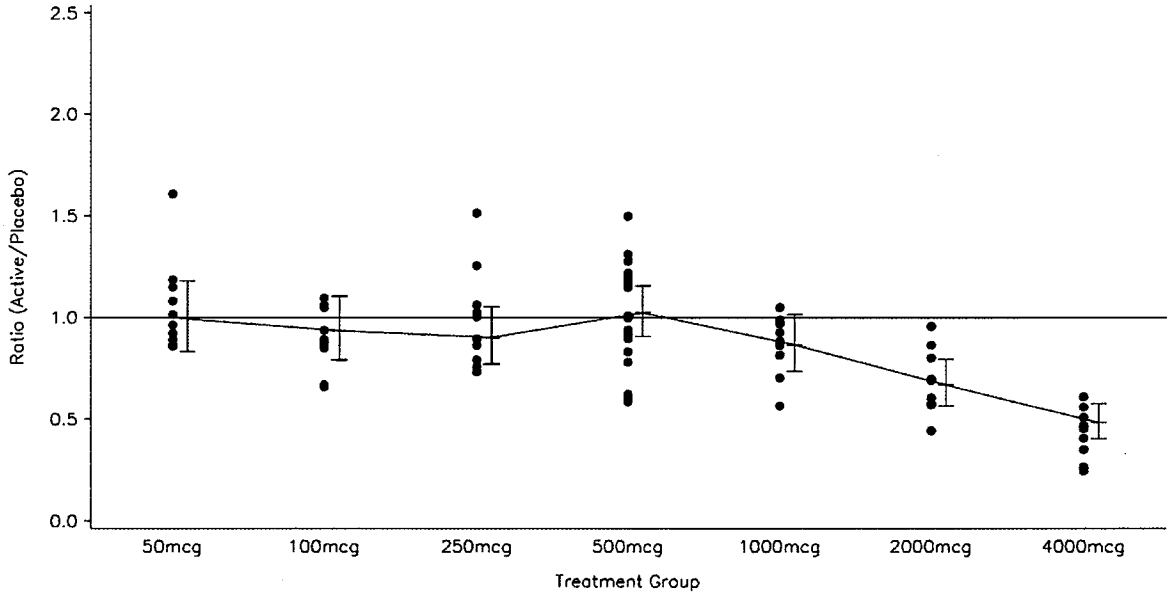


Figure 4.2.1.3.8. Individual Ratios of Total Urine Free Cortisol (24 h) With Mean Difference and 95% CI (Study # FFA 10001).

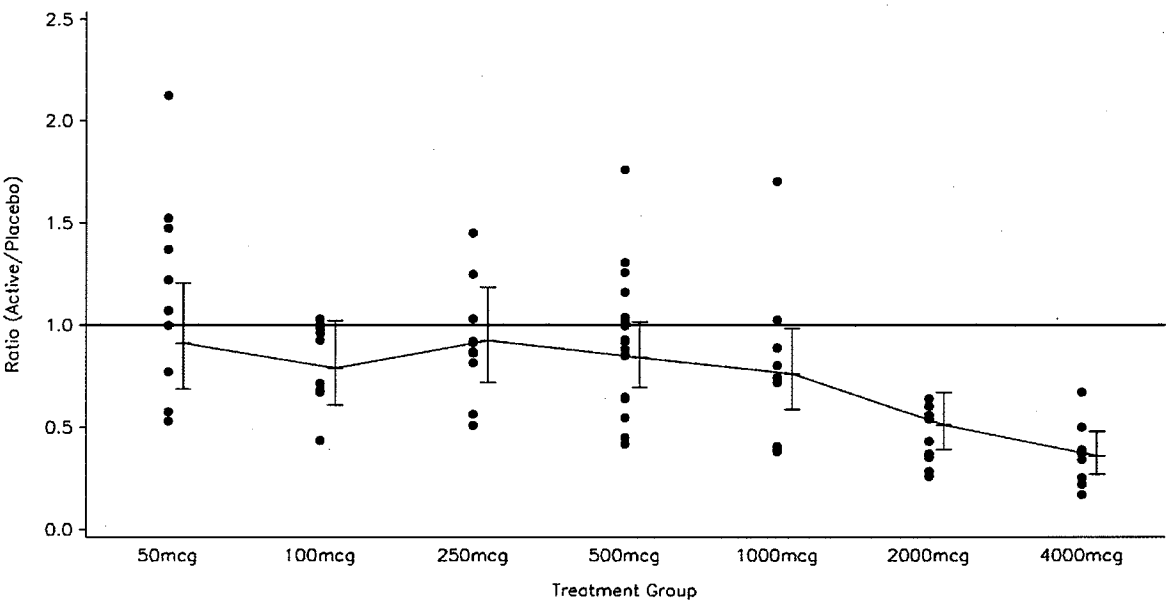
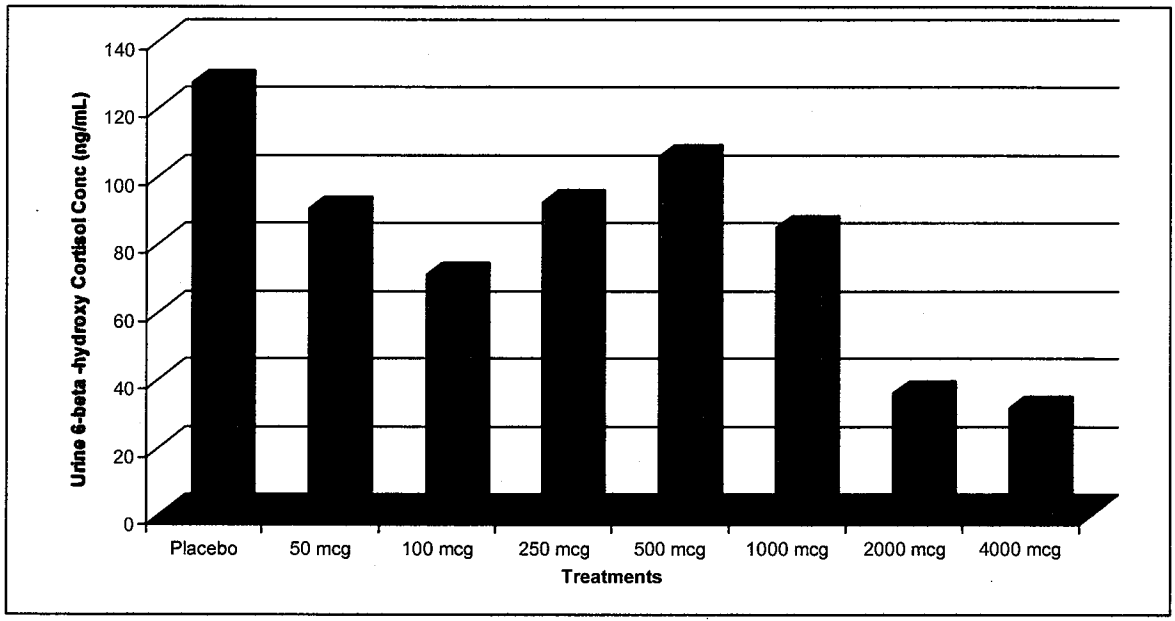


Table 4.2.1.3.4. Summary of Statistical Analysis of Serum Cortisol Weighted Mean 0-24 hour.

Comparison	Ratio (active/placebo)	95% Confidence Interval
50 µg vs. Placebo	0.99	0.83–1.18
100 µg vs. Placebo	0.93	0.79–1.10
250 µg vs. Placebo	0.90	0.77–1.05
500 µg vs. Placebo	1.03	0.91–1.16
1000 µg vs. Placebo	0.87	0.74–1.02
2000 µg vs. Placebo	0.67	0.57–0.79
4000 µg vs. Placebo	0.48	0.40–0.58

Figure 4.2.1.3.9. Mean 6-Beta Hydroxy Cortisol Levels (Study # FFA 10001, Source Table 13.6, Pages 295 to 303).



Reviewer's Comments:

It is not clear as to why there was less than dose proportional increase in Cmax with increasing dose whereas the there was greater than dose proportional increase in AUC with dose. The exposure for Cmax and AUC should be in the same direction. Nevertheless, the greater than proportional increase with dose for AUC is evidence of saturation in the metabolic and/or elimination pathways. The effect on cortisol is expected at such high doses.

Conclusions:

Overall, from the PK perspective, the exposure increases with dose. Similarly, the effect on HPA axis was dose dependent as evidence from the suppression effect on serum and urine cortisol levels.

4.2.1.5 Study # FFR 10013 (Effect of Ketoconazole on Cortisole Levels):

Objective:

The primary objective of this study is to investigate the effect of co-administration of ketoconazole with FF on cortisol level.

Design:

Double blind, placebo-controlled, 2-period crossover trail in 20 healthy subjects as follows:

Treatment A: 100 mcg FF intranasal PLUS Placebo QD x 7 days
Treatment B: 100 mcg FF intranasal PLUS 200 mcg ketoconazole QD x 7 days

Ketoconazole or placebo doses were given 1 hour before each of FF spray (**Table 4.2.1.5.1**).

Table 4.2.1.5.1.Treatment administration (Study # FFR 10013)

Drug	Dose/form/route	Frequency/duration	Batch number	Expiry date
GW685698X	100 mcg via aqueous nasal spray (0.05% w/w)	Once daily for 7 days in each of 2 trial periods	051064795	30 June 2006
Ketoconazole	200 mg overencapsulated[1] oral tablets	Once daily for 7 days in 1 of 2 trial periods	051070806	04 September 2005
Ketoconazole placebo	overencapsulated[1] oral tablets	Once daily for 7 days in 1 of 2 trial periods	031008918	04 September 2005

1. Enclosed in Swedish orange hard gelatine capsules, to make active and placebo treatments indistinguishable

Blood for serum cortisol measurement were collected over 24 hours on Day 1 and day 7. However, PK samples were collected over 24 hours on Day 7 only.

Results:

Pharmacokinetics:

When administered with placebo, the concentration of FF was below LLQ (<10 pg/mL) in all subject but one. However, when administered with ketoconazole, the FF concentration was measurable in 6 subjects, yet at low level (**Tables 4.2.1.5.2-3**).

Table 4.2.1.5.2. Number of Subjects with not quantifiable (NQ) Samples (Study # FFR 10013)

Timepoint	GW685698X 100 mcg + placebo (N=20)		GW685698X 100 mcg + 200 mg ketoconazole (N=20)	
	n	Frequency of NQ samples	n	Frequency of NQ samples
Pre-dose	19	19	20	20
30 min	20	20	20	19
45 min	20	19	20	15
60 min	20	19	20	15
2 hours	20	19	20	14
4 hours	19	19	20	14
6 hours	20	20	19	15
8 hours	19	19	20	16
12 hours	20	20	20	19
24 hours	20	20	20	20

Table 4.2.1.5.3. Mean PK Data of FF in 6 subjects with Measurable Plasma Levels.

Parameter	Treatment	N	n	Geometric mean	SD logs	95% CI of geometric mean
$AUC_{(0-t)}$ (pg.h/mL)	GW685698X 100 mcg + 200 mg ketoconazole	20	6	97.39	0.441	(61.29,154.74)
C_{max} (pg/mL)	GW685698X 100 mcg + 200 mg ketoconazole	20	6	18.74	0.217	(14.92,23.55)

Pharmacodynamics:

It appears that there was some reduction in 24 hour weighted mean cortisol levels after ketoconazole. However, the difference is approximately 5% (**Table 4.2.1.5.4**).

Table 4.2.1.5.4. Summary of Statistical Analysis of Serum Cortisol Weighted Mean (0-24 h) Data (nmol/L) (Study # FFR 10013)

Adjusted Geometric Mean GW685698X + Ketoconazole [Test]	Adjusted Geometric Mean GW685698X + Placebo [Reference]	Treatment Ratio [Test / Reference]	90% CI (Lower, Upper)
145.76	154.06	0.95	0.86,1.04

Reviewer's Comments:

The FF dose used in this study is rather small (100 mcg) to demonstrate any significant exposure as a result of co-administration with ketoconazole. For the study purpose, the sponsor should have used a higher dose for both FF. In addition, for the purpose of the study the sponsor should have used the maximum ketoconazole dose of 400 mg rather than 200 mg.

Overall, from the PK perspective, there was some evidence of increase in exposure when FF was co-administered with ketoconazole. The only evidence is that FF levels was mearurbale in more subjects (n=6) after ketoconazole than after placebo (n=1). However, the magnitude of the increase in exposure can not be determined from this study as the dose of FF used in this study is too small.

From the pharmacodynamic perspective, the effect of ketoconazole on cortisol level was approximately 5% compared to placebo. However, if the doses of FF and ketoconazole were higher, the effect would have been greater.

Conclusions:

Ketoconazole appears to increase the systemic exposure of FF. However, due to the limitation of the study design and in particular the dose of FF and the limitation of the assay for FF measurement, the magnitude of increase in exposure can not be determined from this study.

In terms of the effect on cortisol level, the increase in the systemic exposure of FF was evident by suppression of cortisl level compared to placebo. The magnitude of this suppression was only 5%. However, it could be higher if higher doses of both FF and ketoconazole were administered. Specific language will be included in the product label in reference to doses and level of exposure.

4.2.1.6 Study # FFA 10013 (Effect of inhaled FF on Cortisol in Hepatic Impairment):

Objective:

The primary objective of this study is to investigate the PK and PD (cortisol level) of inhaled FF in patients with liver impairment.

Design:

This was open label study in healthy subjects and patients with moderate hepatic impairment (Child-Pugh B) as follows:

Group A (Healthy Subjects, n = 10): 400 mcg single oral inhaled dose
Group B (Liver Impairment, n=10): 400 mcg single oral inhaled dose

Blood was collected over 24 hours and 72 hours PD (cortisol level) and PK, respectively.

Results:

Pharmacokinetics:

In this study there was marked increased in systemic exposure to FF in hepatic impaired patients compared to control. The magnitude is approximately 3 fold increase in AUC (~172%), but to less extent in Cmax (**Figure 4.2.1.6.1 and Tables 4.2.1.6.1-2**). The Tmax was also delayed in patients compared to healthy (23 min vs 2.75 hour). Furthermore, the half life was longer in patients (~23 h) compared to healthy subjects (~10 h).

Figure 4.2.1.6.1. FF Plasma Concentration-Time Profiles (Study # FFA 10013)

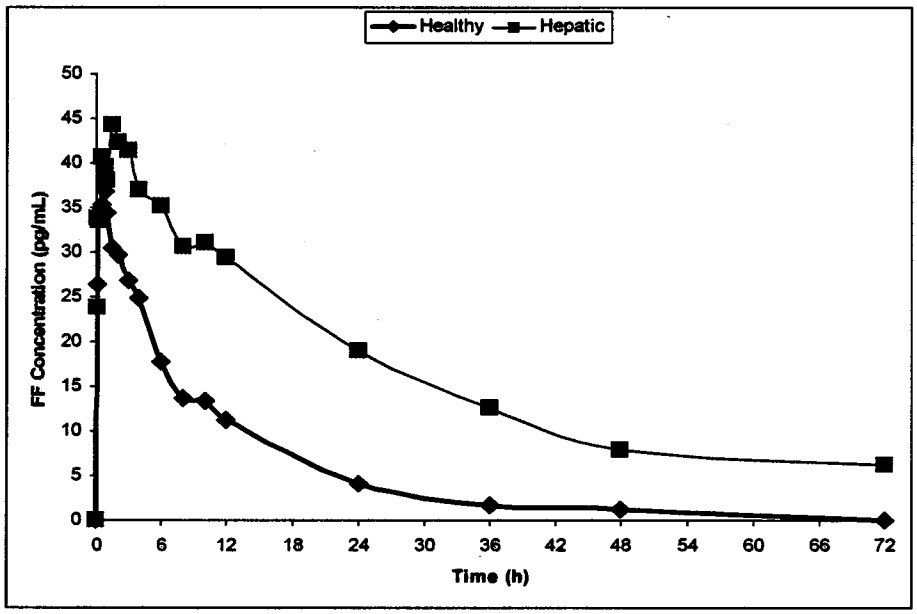


Table 4.2.1.6.1. Summary of PK Parameters (Study # FFA 10013)

Parameter	Healthy N=10		Hepatic N=10	
	n		n	
AUC(0-∞) (pg·h/mL)	6	569 (155, 1193)	5	1942 (851.8, 3433)
AUC(0-t) (pg·h/mL)	10	235 (83.5, 590)	10	593 (83.5, 590.3)
Cmax (pg/mL)	10	38.2 (28.5, 52.7)	10	54.4 (40.7, 83.1)
Tmax (h)[2]	6	0.375 (0.17 – 1.0)	5	2.75 (0.75 – 10.1)
t½ (h)	6	10.5 (5.7, 17.3)	5	22.8 (10.1, 41.1)
Vss/F (L)	6	10648 (8310, 13643)	5	6791 (4291, 10748)
CL/F (L/h)	6	703 (377, 1312)	5	206 (110, 387)

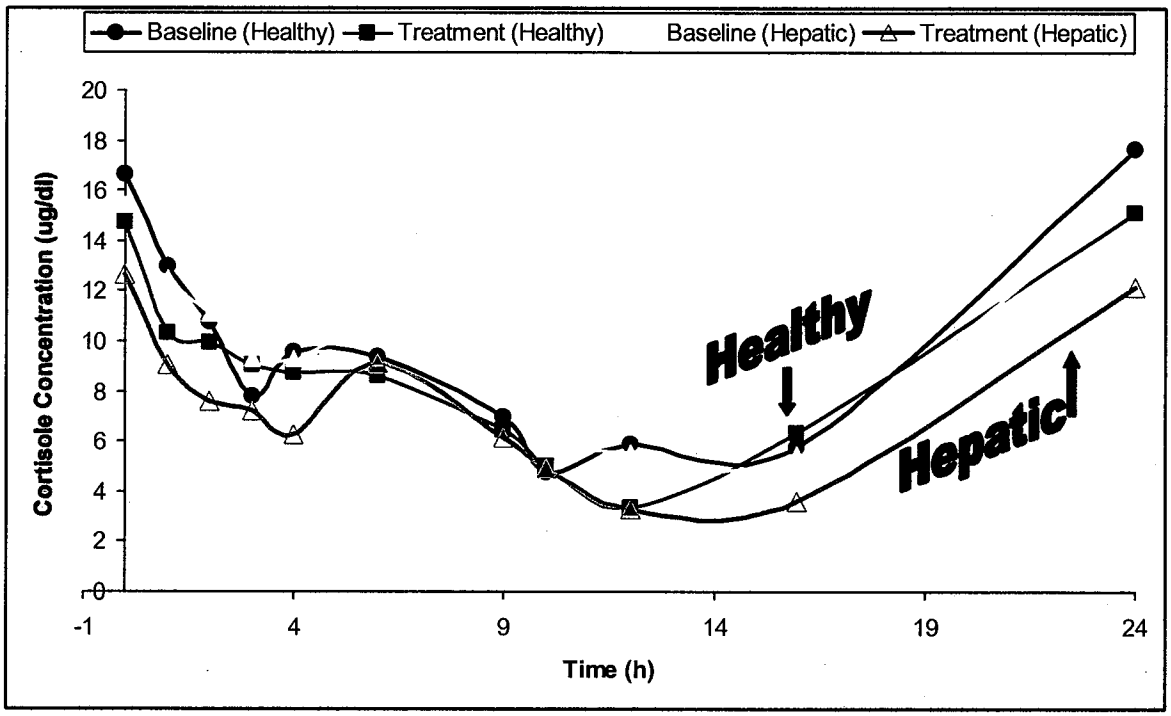
Table 4.2.1.6.2. Summary of Statistical Analysis of PK Parameters (Study # FFA 10013)

Parameter	Adjusted Geom. Mean Hepatic	Adjusted Geom. Mean Healthy	Ratio (Hepatic/ Healthy)	90% Confidence Interval (Lower, Upper)
$AUC_{(0-\infty)}$ (pg.h/mL)	1816.1	667.1	2.72	(0.87, 8.49)
$AUC_{(0-t)}$ (pg.h/mL)	592.6	235.4	2.52	(1.02,6.19)
C_{max} (pg/mL)	54.38	38.22	1.42	(0.99, 2.04)
CL/F (L/h)	220.2	599.4	0.37	(0.12, 1.14)

Pharmacodynamic:

As the exposure is higher in hepatic impairment patients compared to healthy subjects, cortisol suppression is also greater in patients compared to healthy subjects (**Figure 4.2.1.6.2**). However, the magnitude of suppression is not as high as the increase in systemic exposure.

Figure 4.2.1.6.2. Serum Cortisol Profiles (Study FFA 10013)



Reviewer's Comments:

This is very important study to characterize the PK profiles of FF in hepatic impairment patients. However, the study was conducted after inhalation of FF. Therefore, this data in some aspect would be extrapolated to intranasal route. It is noteworthy that this study was conducted after a single dose. Therefore, the magnitude of exposure and the effect on cortisol level would be expected to be greater after multiple doses. Hence, appropriate language will be included in the label to describe the PK and PD of the drug in hepatic impairment patients.

Conclusions:

The exposure to FF is approximately 3 fold higher in hepatic impairment patients compared to healthy subject. In line with increase in systemic exposure, there was greater effect on cortisol suppression in hepatic impairment patients compared to healthy subjects.

4.2.1.7 Study # FFR 10005 (Single and Repeat 400 mcg Intranasal Doses x 7 Days in Japanese Subjects):

Objective:

The primary objective of this study is to investigate the PK and PD of FF after intranasal administration of a single dose and repeat dose of 400 mcg in Japanese healthy male subjects.

Design:

This was double-blind, placebo controlled, ascending dose wit a single dn repeat intranasal dosing in 12 healthy male Japanese subject as follows:

Group (Number of subjects)	Single administration			Repeat administration (once daily in the morning for 7 days)
	Period 1	Period 2	Period 3	Period 4
A (4 subjects)	Placebo	200 µg	400 µg	400 µg
B (4 subjects)	100 µg	Placebo	400 µg	400 µg
C (4 subjects)	100 µg	200 µg	Placebo	Placebo

100 µg: 1 shot to each nostril using 0.05 % nasal spray
200 µg: 1 shot to each nostril using 0.1 % nasal spray
400 µg: 2 shots to each nostril using 0.1% nasal spray
Placebo: 1 or 2 shots to each nostril using placebo nasal spray

Each treatment was separated by at least 7 days. Blood samples for PK and cortisol measurement were collected over 24 in all periods. In addition, in period 4, blood was collected pre-dose on Days 1, 5, and 6.

Results:

The maximum FF plasma concentration observed at all doses in all 8 subjects who completed this study was 14.6 pg/ml (**Table 4.2.1.7.1**). Only one had a measurable level after a single and three subjects after repeat dose on Day 7.

Table 4.2.1.7.1. Summary of PK Parameters after a Single and Repeat 400 mcg Intranasal Doses of FF in Eight Japanese Healthy Male Subjects (Study # FFR 10005).

Parameter [unit]	Dose	Number of subjects available for calculation /total number	Median	Range (minimum – maximum)
C_{max} [pg/mL]	400 µg, single	1/8	12	–
	400 µg, Day 7	3/8	11.9	10.7 – 14.6
t_{max} [hours]	400 µg, single	1/8	2	–
	400 µg, Day 7	3/8	0.75	0.5 – 0.75
AUC_{last} [pg.hr/mL]	400 µg, single	1/8	36.65	–
	400 µg, Day 7	3/8	13.77	7.97 – 22.77

Pharmacodynamics:

In this study there was statistically significant effect on cortisol level after repeat administration of 400 mcg doses on Days 7, but not after single doses (**Tables 4.2.1.7.2-3 and Figures 4.2.1.7.1-9**). The adjusted mean ratio to placebo was 0.6544 after repeat dosing comparing to approximately 0.95 after all single doses (**Table 4.2.1.7.1 and Figure 4.2.1.7.1**). There was high variability in the data following all treatments (**Figures 4.2.1.7.2-9**).

Table 4.2.1.7.2. Summary of Statistical of Serum Cortisol Levels After Single Dose in Eight Japanese Subjects (Study # FFR 10005)

Ratio (test product vs comparator)	Adjusted mean (test product)	Adjusted mean (comparator)	Ratio	95 %CI
Single administration				
GW685698 100 µg vs placebo	7.707	7.902	0.9754	(0.7817, 1.2171)
GW685698 200 µg vs placebo	7.710	7.902	0.9757	(0.7822, 1.2172)
GW685698 400 µg vs placebo	7.427	7.902	0.9399	(0.7596, 1.1630)
Repeat administration				
GW685698 400 µg vs placebo	5.849	8.937	0.6544	(0.4794, 0.8935)

Figure 4.2.1.7.1. Adjusted Mean Ratio and 95% CI of Serum Cortisol Weighted Means after Single Dose in Eight Japanese Subjects (Study # FFR 10005)

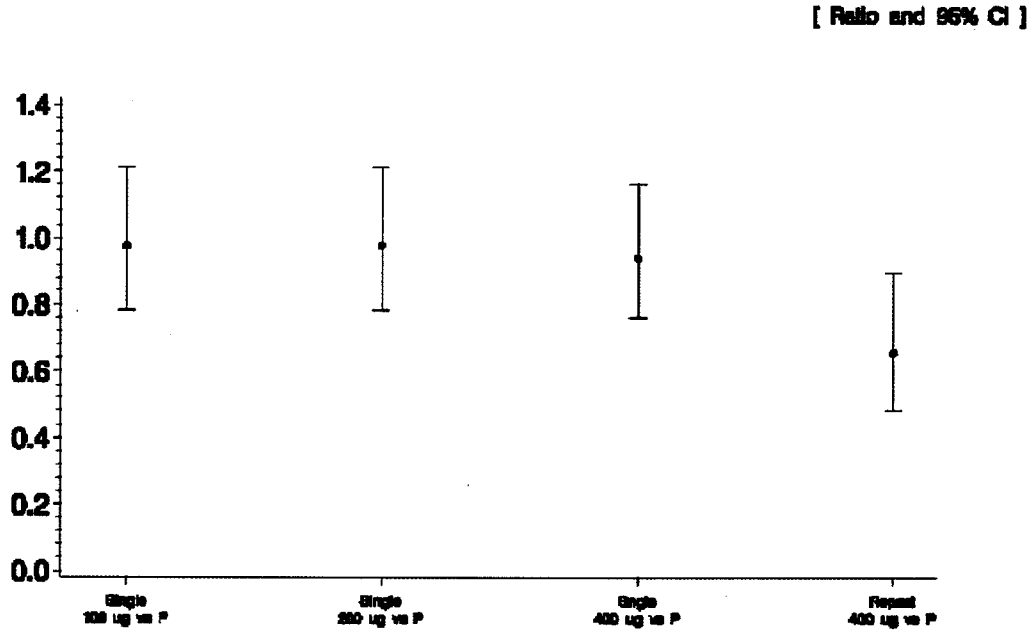


Figure 4.2.1.7.2 . Mean Serum Cortisol Levels after Single Dose in Eight Japanese Subjects (Study # FFR 10005)

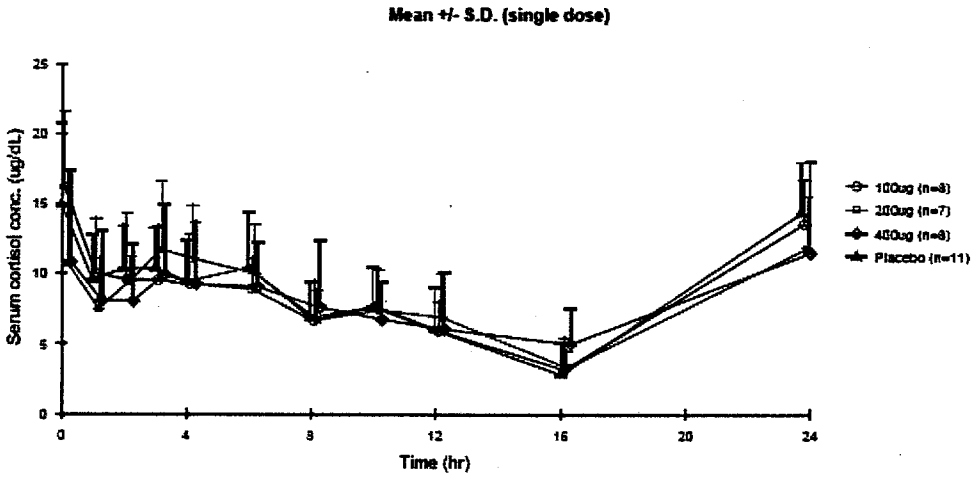


Figure 4.2.1.7.3. Individual Serum Cortisol Levels after <u>PLACEBO</u> Single Dose in Eight Japanese Subjects (Study # FFR 10005)

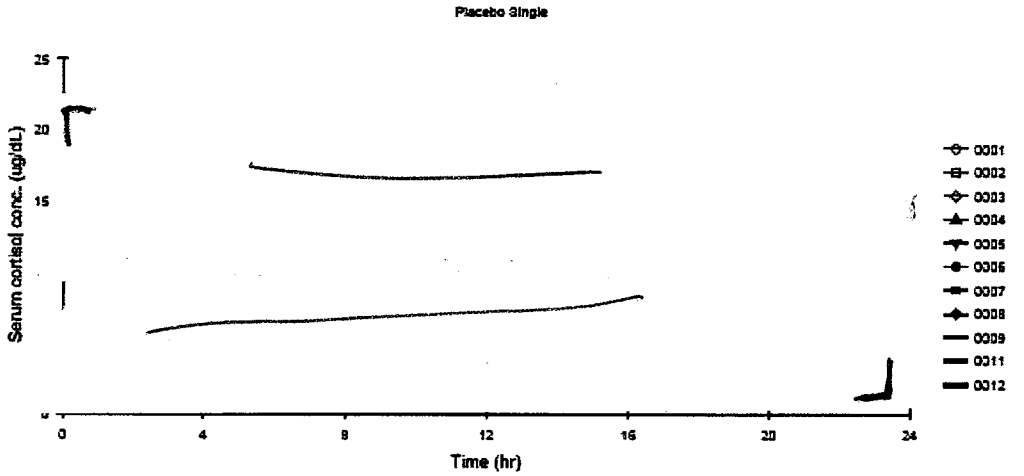


Figure 4.2.1.7.4. Individual Serum Cortisol Levels after <u>100 mcg</u> Single Dose in Eight Japanese Subjects (Study # FFR 10005)

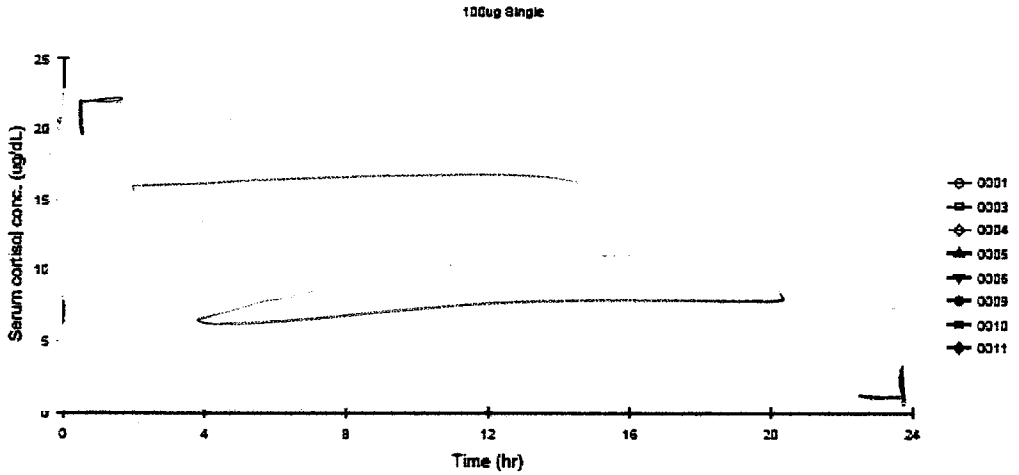


Figure 4.2.1.7.5. Individual Serum Cortisol Levels after 200 mcg Single Dose in Eight Japanese Subjects (Study # FFR 10005)

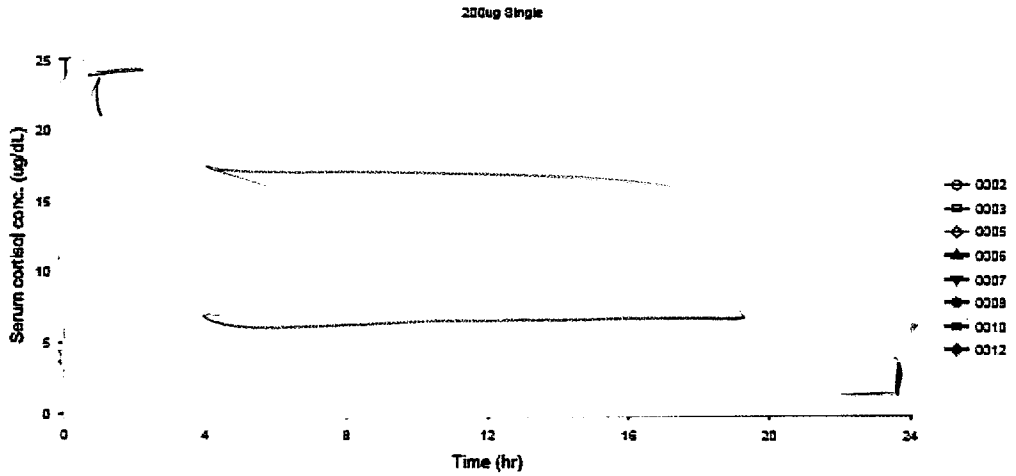


Figure 4.2.1.7.6. Individual Serum Cortisol Levels after 400 mcg Single Dose in Eight Japanese Subjects (Study # FFR 10005)

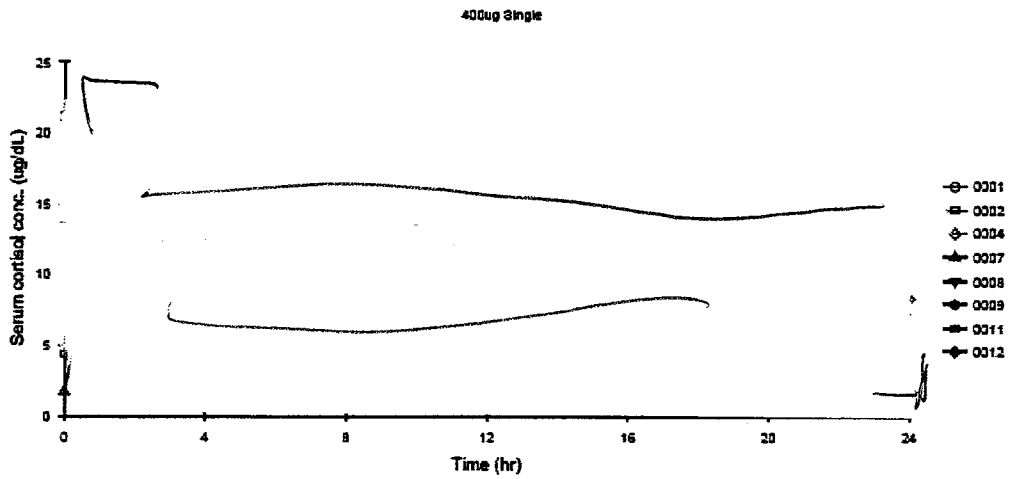


Figure 4.2.1.7.7. Mean Serum Cortisol Profiles after 400 mcg Repeat Dose in Eight Japanese Subjects (Study # FFR 10005)

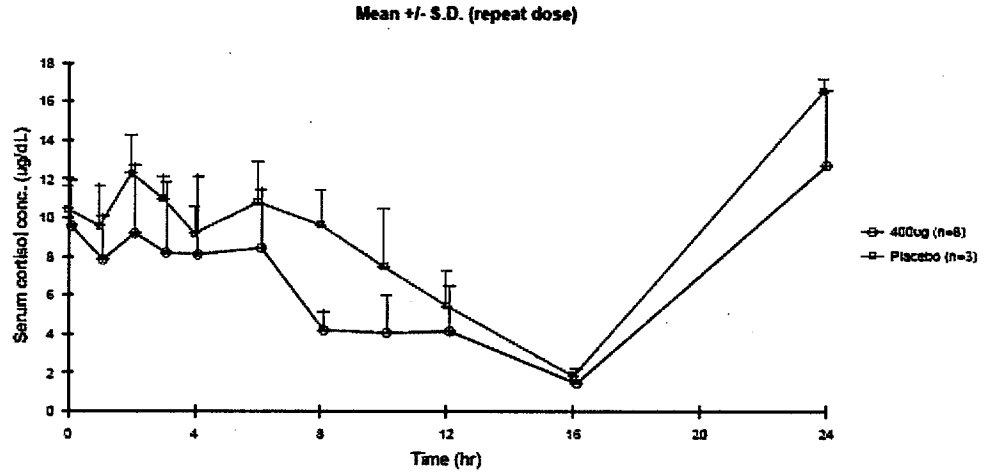


Figure 4.2.1.7.8. Individual Serum Cortisol Profiles after PACEBO Repeat Dose in Three Japanese Subjects (Study # FFR 10005)

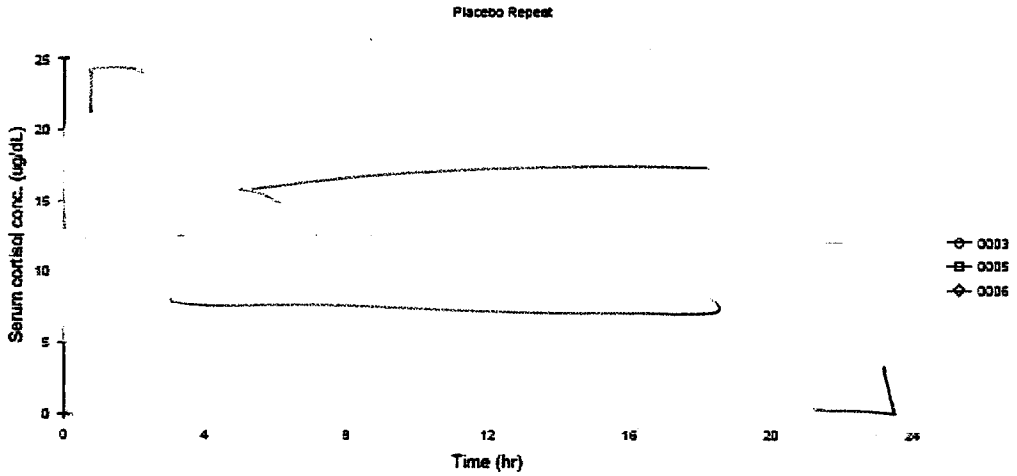
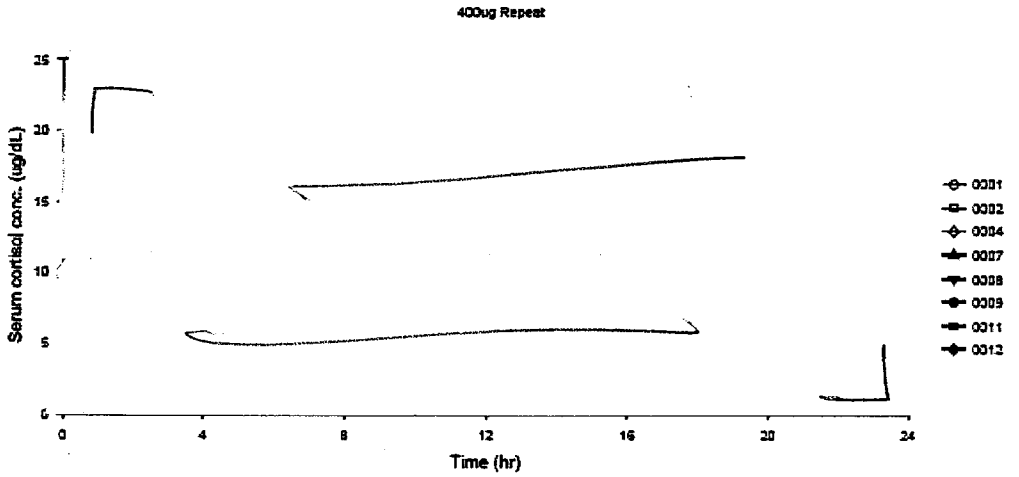


Figure 4.2.1.7.9. Individual Serum Cortisol Profiles after 400 mcg Repeat Dose in Eight Japanese Subjects (Study # FFR 10005)



Reviewer's Comments:

As expected form other studies, FF concentration in plasma was negligible. In terms of the effect of cortisol level, the study lacks of power as it was conducted in only 8 subjects. In addition, only 3 subjects received placebo after multiple doses. Therefore, the observed data for cortisol levels following active treatments compared to placebo is questionable, considering the high variability in the data.

Conclusions:

From this study three conclusions can be made:

- FF was quantifiable in only 1 subject and in 3 subjects out of 8 subjects following single doses and repeat doses, respectively.
- There appears some signal for cortisol suppression after multiple doses compared to placebo.
- The study lacks of power with high variability (n=8).

Based on the low power in the study, the data is questionable.

4.2.1.7.10. Study # FFR 10003 (Dose Escalation of 50 to 800 mcg x 7 days of nanomilled Suspension):

Objective:

The primary objective of this study is to investigate the PK of single and 7 days repeat intranasal administration of nanomilled aqueous suspension in healthy subjects.

Design:

This was a placebo-controlled, double-blind, crossover, single and repeat dose escalating study in 2 cohorts of 12 healthy young men. The study was conducted at five dose level: 50, 100, 200, 400, and 800 mcg administered intrnasally. In Period 5, the maximum well tolerated single dose in each cohort (or matching placebo) was administered once daily for 7 days as follows:

COHORT A					
Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
1	Placebo	50 µg	100 µg	200 µg	Repeat Dose 200 µg or placebo for 7 days
2	50 µg	Placebo	100 µg	200 µg	
3	50 µg	100 µg	Placebo	200 µg	
4	50 µg	100 µg	200 µg	Placebo	

COHORT B					
Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
1	Placebo	200 µg	400 µg	800 µg	Repeat Dose 800 µg or placebo for 7 days
2	200 µg	Placebo	400 µg	800 µg	
3	200 µg	400 µg	Placebo	800 µg	
4	200 µg	400 µg	800 µg	Placebo	

PK blood samples were collected over 24 hours on Days 1 and 7, whereas .for cortisol measurement blood was collected over 24 hours on Day 7 only.

Results:

As in other studies, the FF concentration was unquantifiable in most of the subjects at all doses. The maximum concentration observed in this study after both single and multiple doses was 28.0 pg/ml (**Table 4.2.1.7.10.1-2**).

Table 4.2.1.7.10.1. Summary of PK Parameters After Intranasal Single Doses (Study FFR 10003)

Parameter (units)	Dose (µg)	N	Evaluable subjects[1]	Median[2]	Range
C_{max} (pg/mL)	100	12	1	BLQ	BLQ to 18.7
	200	24	3	BLQ	BLQ to 31.2
	400	12	10	21.6	BLQ to 33.0
	800	12	8	14.0	BLQ to 28.0
t_{max} (h)	100	12	1	BLQ	BLQ to 3.00
	200	24	3	BLQ	BLQ to 1.00
	400	12	10	0.75	BLQ to 3.00
	800	12	8	0.54	BLQ to 1.50
$AUC_{(0-t)}$ (pg.h/mL)	100	12	1	BLQ	BLQ to 35.86
	200	24	3	BLQ	BLQ to 68.33
	400	12	8	10.83	BLQ to 104.41
	800	12	6	2.33	BLQ to 63.88

Data Source: Table 18.19

BLQ – all concentrations below the LLQ; all parameters for the 50 µg dose were BLQ

1. number of subjects with enough measurable data to calculate each PK parameter
2. for the calculation of median, BLQ was set to 0

Table 4.2.1.7.10.2. Summary of PK Parameters After Intranasal Multiple Doses (Study FFR 10003)

Parameter (units)	Dose (µg)		N	Evaluable subjects[1]	Median[2]	Range
C_{max} (pg/mL)	200	Day 1	9	7	16.4	BLQ to 30.7
		Day 7	9	4	BLQ	BLQ to 23.4
	800	Day 1	8	7	18.9	BLQ to 22.3
		Day 7	8	6	17.3	BLQ to 27.4
t_{max} (h)	200	Day 1	9	7	1.50	BLQ to 3.00
		Day 7	9	4	BLQ	BLQ to 0.50
	800	Day 1	8	7	0.46	BLQ to 1.50
		Day 7	8	6	0.73	BLQ to 1.50
$AUC_{(0-t)}$ (pg.h/mL)	200	Day 1	9	2	BLQ	BLQ to 65.92
		Day 7	9	1	BLQ	BLQ to 11.91
	800	Day 1	8	4	2.24	BLQ to 17.40
		Day 7	8	5	5.31	BLQ to 71.45

Data Source: Table 18.20

BLQ – all concentrations below the LLQ

1. number of subjects with enough measurable data to calculate each PK parameter
2. for the calculation of median, BLQ was set to 0

In terms of effect on cortisol, there was little difference between active an placebo treatments at all doses.

Figure 4.2.1.7.10.1. Mean Cortisol Plasma Profiles Intranasal Single Doses (Study FFR 10003)

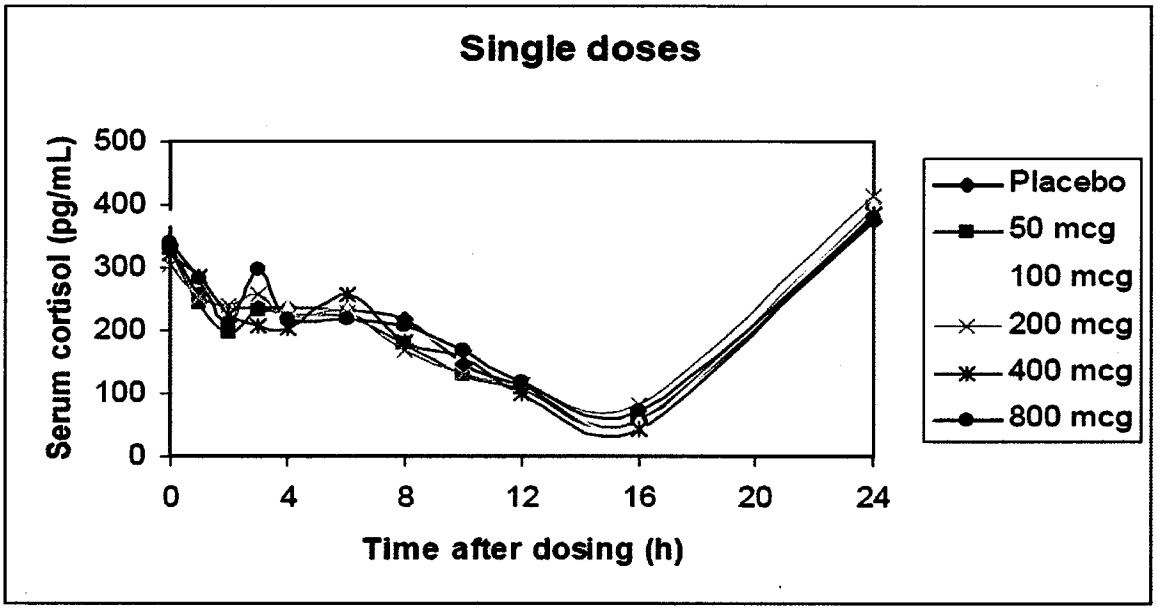
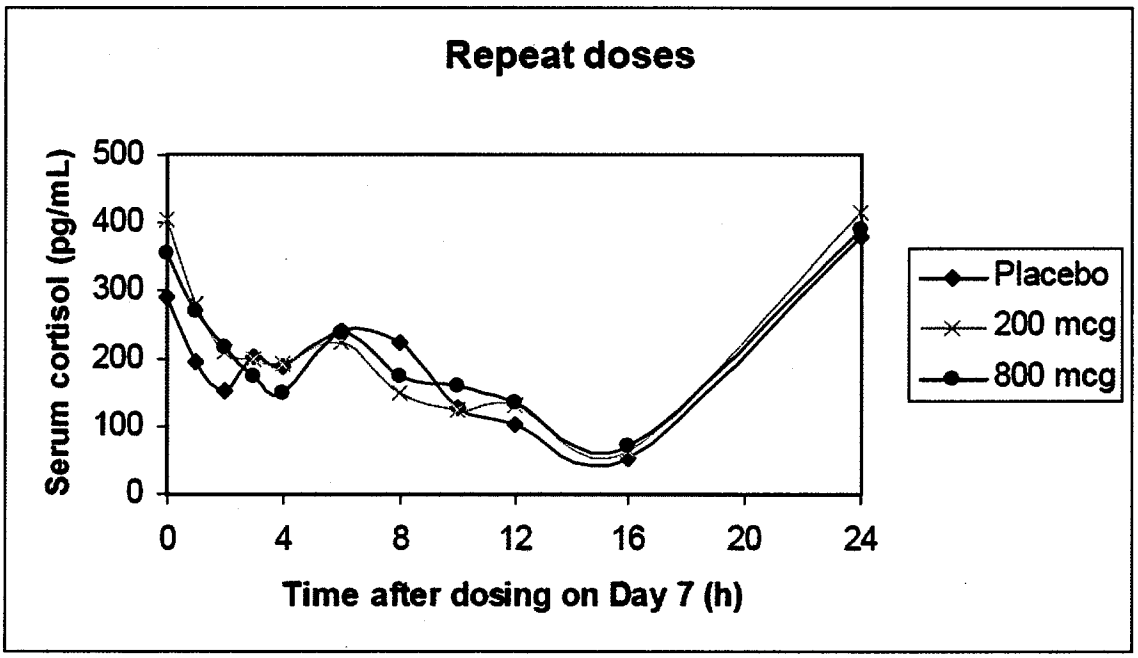


Figure 4.2.1.7.10.1. Mean Cortisol Plasma Profiles Intranasal Single Doses (Study FFR 10003)



Reviewer's Comments:

The PK and PD data from this study in is similar to other studies after intranasal administration. Therefore, it can be concluded that the FF was minimally detected in the plasma in most of the subjects with the highest concentration of 28 pg/ml. No statistical difference was noted on the effect on cortisol plasma levels compared to placebo.

4.2.2. Clinical Studies With HPA Axis Data

4.2.2.1 Study # FFR 20002 (6 Weeks Study in 12 to 65 Years Old PAR Patients):

Objective:

The primary objective of this study was to evaluate the 6 weeks intranasal once daily of 100 mcg of FF on HPA axis compared to placebo in subjects aged from 12 to 65 years of age with perennial allergic rhinitis (PAR).

Design:

This was double-blind, placebo controlled, and parallel group, 6 weeks treatment as follows:

Treatment A: 100 mcg QD aqueous nasal spray (2 sprays of 50 mcg in each nostril) x 42 days PLUS **placebo capsule** x 7 days

Treatment B: Placebo aqueous nasal spray (2 sprays of 50 mcg in each nostril) QD x 42 days **PLUS placebo capsule** x 7 days

Treatment C: Placebo aqueous nasal spray nasal (2 sprays of 50 mcg in each nostril) QD x 42 days **PLUS prednisone 10 mg** (over encapsulated tablet) QD x the last 7 days. The distribution of the study population in each arm of the study is shown in the following table.

	Placebo	GW685698X 100mcg QD	Prednisone 10mg QD
Planned, N	40	40	10
Randomized (N)	51 (100)	48 (100)	13 (100)
Completed, n (%)	44 (86)	44 (92)	12 (92)
Total Number Subjects Withdrawn, n (%)	7 (14)	4 (8)	1 (8)
Withdrawn due to Adverse Event, n (%)	2 (4)	0	0
Withdrawn due to Withdrawal of Consent, n (%)	1 (2)	3 (6)	1 (8)
Withdrawn for Other Reasons, n (%)	4 (8)	1 (2)	0

HPA axis was evaluated during 24 hour domiciled visits, at the end of screening and treatment periods. This includes 24 hour plasma and urine collection. In addition, PK samples were collected at appropriate time points.

Results:

Pharmacokinetics:

In this study, there was no measurable FF concentrations over 24 hours after 6 weeks of treatments in all plasma samples (n=351) from all the 44 subjects participated in this study. Therefore, no PK parameters are reported in this study.

Pharmacodynamics:

There was no difference in means serum cortisol concentration-time profiles or ratios from baseline at Week 6 between FF and placebo (**Figure 4.2.2.1.1 and Tables 4.2.2.1.1-2**). However, the positive control, prednisone, showed significant suppression compared to placebo, baseline and FF treatment.

Figure 4.2.2.1.1. Mean (95% CI) Serum Cortisol Concentration-Time Profiles At Week 6 (Study # FFR 20002)

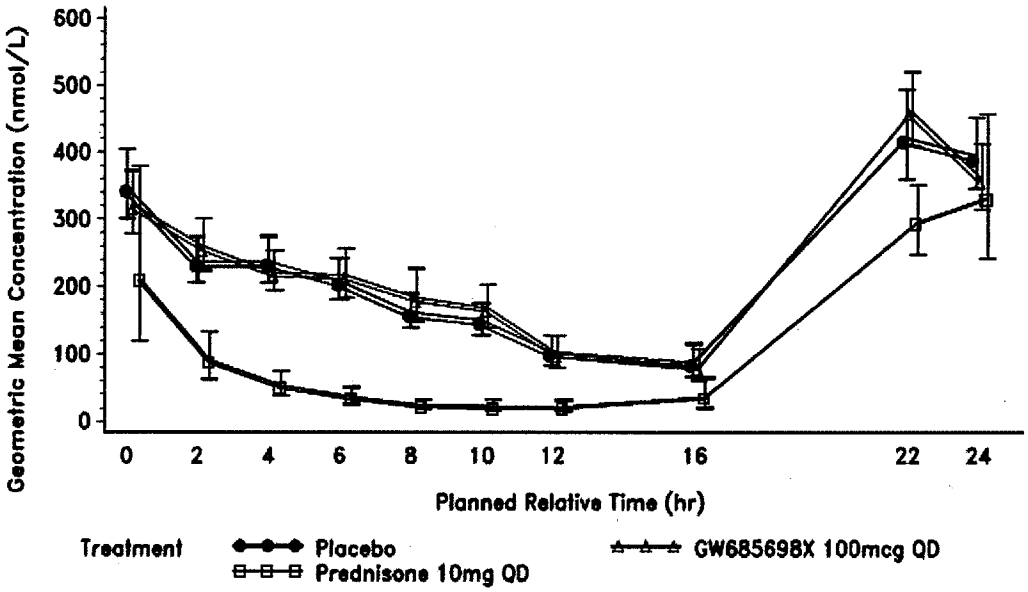


Table 4.2.2.1.1. Summary of Serum Cortisol Weighted mean (0-24 H) (nmol/L) (Study # FFR 20002)

	Placebo N=44	GW685698X 100mcg QD N=43	Prednisone 10mg QD N=12
Baseline			
n	44	43	12
Geometric Mean	238.21	248.70	237.36
95% CI for Geometric Mean	220.57, 257.27	223.59, 276.62	213.27, 264.18
Median	231.43	242.29	231.02
Min - Max	158.0 – 488.5	152.4 – 777.0	184.9 – 324.0
Week 6			
n	44	42	12
Geometric Mean	236.85	236.26	115.93
95% CI for Geometric Mean	214.35, 261.71	215.35, 259.20	97.13, 138.37
Median	222.97	228.35	129.87
Min - Max	78.7 – 661.0	144.5 – 565.5	70.0 – 154.9
Ratio from Baseline			
n[a]	44	42[a]	12
Geometric Mean	0.99	0.97	0.49
95% CI for Geometric Mean	0.92, 1.07	0.90, 1.04	0.42, 0.56
Median	1.00	1.01	0.50
Min - Max	0.49 – 2.06	0.61 – 1.49	0.34 – 0.67

a. Ratios were not calculated if the first (0 hr) or last (24 hr) samples were missing.

Table 4.2.2.1.2. Summary of Statistical Analysis of Derived Serum Cortisol Weighted Mean (0-24 H) (Ratio from Baseline) (Study # FFR 20002)

Treatment Comparison	Least Square Means		Treatment Ratio	95% CI
	Active	Placebo		
GW685698X 100mcg QD vs. Placebo[a]	**0.97**	**0.99**	**0.98**	**0.89, 1.07[b]**
Prednisone 10mg QD vs. Placebo	0.49	0.99	0.49	0.43, 0.57

a. Primary study comparison adjusted for center and log transformed baseline weighted mean
b. The non-inferiority margin of the CI was 0.80

In terms of urine data, there was some reduction in 24 hour cortisol urine excretion with FF compared to baseline and placebo after 6 weeks of treatments (**Figure 4.2.2.1.2 Table 4.2.2.1.2**). It should be noted that due to assay interference, no urine data were reported for prednisone arm of the study.

Table 4.2.2.1.2. Mean 24 Hours Urinary Cortisol Excretion (nmol/Day) (Study # FFR 20002)

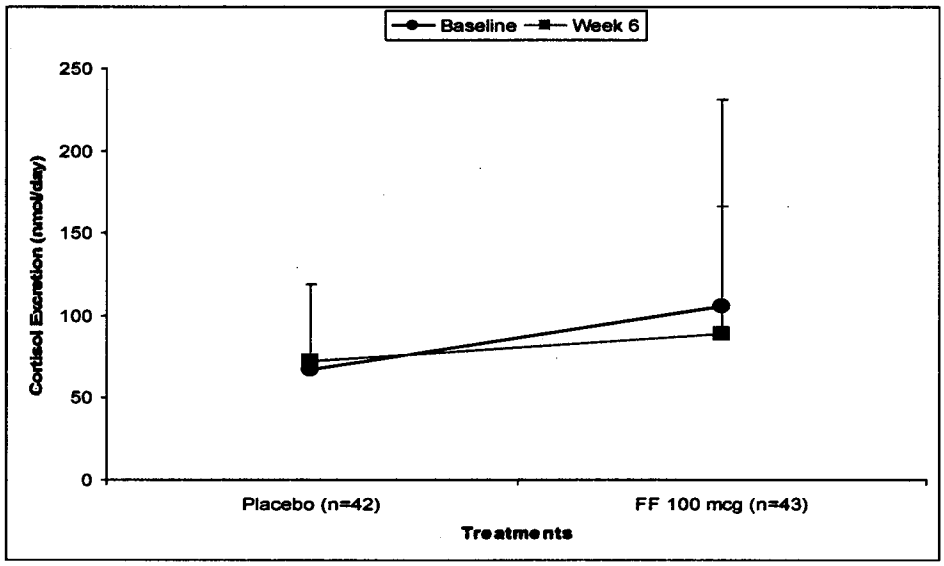


Table 4.2.2.1.2. Summary of 24 Hours Urinary Cortisol Excretion (nmol/Day) (Study # FFR 20002)

	Placebo **N=42**	**GW685698X 100mcg QD** **N=43**
Baseline		
Geometric Mean	54.42	73.13
Mean (SD)	67.38 (51.366)	105.95 (125.247)
Median	56.90	60.00
Min - Max	17.9 – 259.9	16.0 – 650.9
Week 6		
Geometric Mean	58.40	65.14
Mean (SD)	72.41 (46.670)	89.27 (76.925)
Median	62.05	60.00
Min - Max	6.4 – 238.0	7.9 – 402.6
Change from Baseline		
Mean (SD)	5.03 (47.159)	-16.68 (116.400)
Median	6.15	-1.10
Min - Max	-103.9 - 139.6	-504.8 – 157.6
Ratio from Baseline		
Geometric Mean	1.07	0.89
Median	1.19	0.99

Reviewer's Comments:

This study lacks of positive control for urine data. According to the sponsor, there was interference in the assay that prevents reporting cortisol urinary excretion data after prednisone treatment.

It appears that the observed difference in urine cortisol levels could, in part, have been due to two outliers. These two subjects had abnormally high values at both baseline (650.9 and 572.7 nmol/24h) and endpoints (146.1 and 116.8 nmol/24h). The serum cortisol weighted mean ratio (week 6/baseline) for these two subjects were 0.77 and 0.72. However, it should be noted that the variability in the urine data was tremendous for all values, including baseline. For example, the mean urinary cortisol excretion at baseline in the FF arm of the study was 105.95 (± 125.25 SD) which is ranging from 16 to 650.9 nmol/day. That's means the CV is 118%.

Overall, based on this study and its limitations, the observed effect in urine excretion data is real. However, the clinical impact of this difference is questionable.

Conclusions:

The drug was not quantifiable in all samples after 6 weeks of daily intranasal administration of 100 mcg doses. The lack of systemic exposure of FF is in line with the lack of observed differences in the plasma-concentration time profiles between FF arm and placebo arm. However, there was noticeable yet small difference in 24 h urinary excretion data after 6 weeks treatment with FF compared to placebo. The clinical impact of this difference in urinary cortisol excretion is questionable.

4.2.2.2 Study # FFR 100012 (6 Weeks in Children 2 to <12 years PAR Patients):

Objective:

The primary objective of this study was to evaluate the 6 weeks intranasal once daily of 100 mcg of FF on HPA axis compared to placebo in children 2 to <12 years of age with perennial allergic rhinitis (PAR).

Design:

This study was similar in design as the previous study in adolescent and adults, except that no active control arm, prednisone, was included. For ethical concern, prednisone arm was not included in this pediatric study. Briefly, the study was designed as double-blind, placebo controlled, parallel group as follows:

Treatment A: 100 mcg QD aqueous nasal spray (2 sprays of 50 mcg in each nostril) x **42 days**

Treatment B: Placebo aqueous nasal spray (2 sprays of 50 mcg in each nostril) QD x **42 days**

The distribution of the study population in each arm of the study is shown in the following table.

	Placebo	GW685698X 100mcg QD
Planned, N	40	40
Randomized, n (%)	55 (100)	57 (100)
Completed, n (%)	52 (95)	53 (93)
Total Number Subjects Withdrawn, n (%)	3 (5)	4 (7)
Withdrawn due to Adverse Event, n (%)	1 (2)	1 (2)
Withdrawn due to Protocol Violation, n (%)	0 (0)	2 (4)
Withdrawn for Other Reasons, n (%)	2 (4)	1 (2)

HPA axis was evaluated during 24 hour domiciled visits, at the end of screening and treatment periods. This includes 24 hour plasma and urine collection. In addition, PK samples were collected at appropriate time points.

Results:

Pharmacokinetics:

In this study, there was no measurable FF concentrations over 24 hours after 6 weeks of treatments in all plasma samples (n=262) from all the 53 subjects participated in this study, except 4 subjects. The plasma level in all these four subjects ranged from 10.5 to 18.9 pg/ml (LLOQ = 10 pg/mL). Therefore, no PK parameters are reported in this study.

Pharmacodynamics:

Similar to that observed in the adolescent and adults study (Study # FFR 20002), there was no difference in means serum cortisol concentration-time profiles or ratios from baseline at week 6 between FF and placebo (**Figure 4.2.2.1 and Tables 4.2.2.1-2**).

Figure 4.2.2.1 . Mean Serum Cortisol Concentration-Time Profiles At Week 6 (Study # FFR 100012)

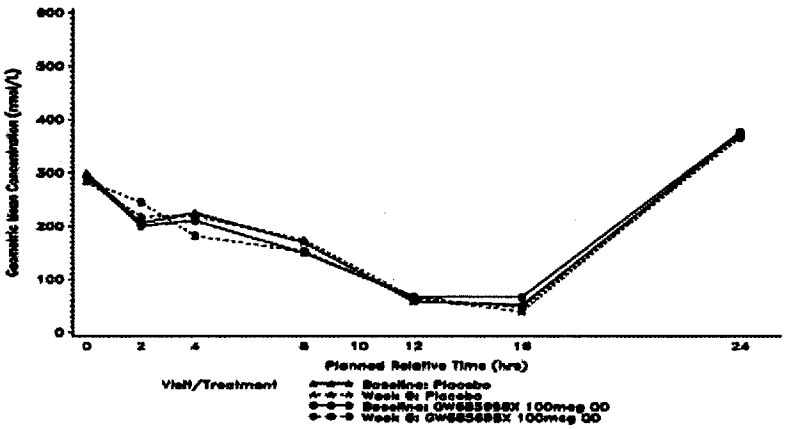


Table 4.2.2.1. Summary of Serum Cortisol Weighted mean (0-24 H) (nmol/L) (Study # FFR 100012)

	Placebo N=49	GW685698X 100mcg N=52
Baseline		
n	48	50
Geometric Mean	185.04	189.88
95% CI for Geometric Mean	171.06, 200.17	175.06, 205.96
Median	176.79	193.76
Min - Max	103.8 – 408.5	107.7 – 346.9
Week 6		
n	48	50
Geometric Mean	181.58	181.55
95% CI for Geometric Mean	168.50, 195.68	166.88, 197.50
Median	181.70	171.27
Min - Max	101.0 – 414.5	104.0 – 493.3
Ratio from Baseline		
n[a]	47[a]	48[a]
Geometric Mean	0.979	0.935
95% CI for Geometric Mean	0.912, 1.052	0.860, 1.017
Median	0.972	0.989
Min - Max	0.52 – 1.66	0.56 – 1.86

Table 4.2.2.2. Summary of Statistical Analysis of Derived Serum Cortisol Weighted Mean (0-24 H) (Ratio from Baseline) (Study # FFR 20002)

Treatment Comparison	Least Square Mean		Treatment Ratio	95% CI
	Active	Placebo		
GW685698X 100mcg vs. Placebo	0.94	0.97	0.97	0.88, 1.07[a]

Unlike the urinary excretion data observed in the previous adolescent and adult study, there was no obvious suppression in 24 hour cortisol urine excretion with FF compared to baseline and placebo after 6 weeks of treatments (**Table**).

Table . Summary of 24 Hours Urinary Cortisol Excretion (nmol/Day) (Study # FFR 100012)

	Placebo N=41	GW685698X 100mcg N=43
Baseline		
Geometric Mean	22.35	25.06
Mean (SD)	30.99 (27.125)	33.64 (28.829)
Median	20.40	25.90
Min - Max	2.4 – 146.0	2.6 – 136.3
Week 6		
Geometric Mean	28.20	24.43
Mean (SD)	36.92 (26.771)	32.17 (25.470)
Median	27.60	29.60
Min – Max	6.5 – 105.7	2.8 – 147.5
Change from Baseline		
Mean (SD)	5.93 (26.012)	-1.47 (33.879)
Median	2.70	3.30
Min - Max	-93.3 – 67.5	-106.6 – 125.4
Ratio from Baseline		
Geometric Mean	1.26	0.97
Median	1.15	1.13

Reviewer's Comments:

The data from this study is less variable than the previous adolescent and adult study. However, there were three outliers in this study for urine data, one on placebo and two on active treatment. The three subjects had high baseline ranging from 116.6 to 146.0 nmol/24 h. The endpoint, however, was 23.4 and 29.7 nmol/24 h in two subjects, but was markedly high (147.5 nmol/24 h) in the third subject. The reasons for these abnormal values are unknown.

Overall, the cortisl data appears to be consistent with lack of systemic exposure after nasal administration.

Conclusions:

This study may be used as confirmatory to the data obtained in the previous adolescent and adult study (Study # FFR 20002). It confirms the lack of absorption of FF after intranasal administration and hence lack of effect on HPA axis. To summarize, there was no noticeable difference in serum cortisol plasma concentration-time profiles and urinary excretion of cortisol between FF and placebo treatment arms.

4.2.3. Study # FFR 102123 (100 mcg QD X 52 Weeks in 12 years and Older)

Objectives:

The primary object of this study was to evaluate the safety and efficacy 100 mcg of FF after 12 months (**52 weeks**) of daily intranasal administration in patients with PAR 12 years of age or older.

Design:

This was double blind, placebo controlled, parallel group in patients 12 years or older with PAR as follows:

Treatment A (n=525): 100 mcg QD aqueous nasal spray (2 sprays of 50 mcg in each nostril) x **52 weeks**

Treatment B (n=175): Placebo aqueous nasal spray (2 sprays of 50 mcg in each nostril) QD x **52 weeks.**

The study was conducted in 13 countries. The distribution of the patients in each arm of the study is shown in the following table:

	Placebo	FF 100mcg
Number of subjects planned, N	175	525
Randomised,[1] N	201	605
Completed, n (%)	144 (72%)	448 (74%)
Total Number Subjects Withdrawn, n (%)	57 (28%)	157 (26%)
Withdrawn due to Adverse Events, n (%)	7 (3%)	38 (6%)
Withdrawn due to Lack of Efficacy, n (%)	5 (2%)	6 (<1%)
Lost to follow-up	4 (2%)	9 (1%)
Withdrawn due to protocol violation	20 (10%)	49 (8%)
Subject decided to withdraw	15 (7%)	48 (8%)
Withdrawn for other reasons, n (%)	6 (3%)	7(1%)

1. Excludes 4 subjects who were randomised but did not receive any study treatment.

PK blood samples were collected at appropriate time points on weeks 4, 12, 24, 36, and 52 whereas the 24 hours urine collection for cortisol measurement was on week 0 (baseline), 12, 24, and 52.

Results:

Pharmacokinetics:

As in the previous studies, FF was not quantifiable in most of the samples after 52 weeks of daily treatment with 100 mcg intranasal FF. However, FF was quantified in 331 samples out of 2512 samples collected (13.2%). These measurable levels were found in 223 subjects out of 578 subjects treated with FF in ore than one occasion. In appears that no subjects had measurable levels in all five time points (i.e, Week 4, 12, 24, 36, and 52). The majority of the values (289 out of 331 samples) were below 100 pg/ml (**Table 4.2.3.1**).

Table 4.2.3.1. Summary of Samples with Quantifiable FF Concentration (Study # FFR 102123)

	10 to <20 pg/mL	20 to <30 pg/mL	30 to <50 pg/mL	50 to <100 pg/mL	100 to <200 pg/mL	200 to <500 pg/mL	≥500 pg/mL
No of quantifiable samples	139	58	53	39	18	14	10
% of quantifiable (n=331)	42%	17.5%	16.0%	11.8%	5.4%	4.2%	3.0%
% of total samples (n=2512)	5.5%	2.3%	2.1%	1.6%	0.7%	0.6%	0.4%

Source Data: Table 9.1

It is noteworthy that in 10 samples from 10 different subjects (3% of subjects or 0.4% of total PK samples) the FF levels were unexpectedly above the 500 pg/ml. However, the values above 500 pg/ml was observed only once in each subject during the five time points (**Table 4.2.3.1**). The highest observed concentration is 1430 pg/ml in subject # 744 in Visit 8 (Week 24).

Table 4.2.3.1. FF Plasma Levels in the 10 Subjects with >500 pg/ml (Study # FFR 102123)

Subject	Visit 3	Visit 5	Visit 8	Visit 11	Visit 15
	NQ	649 pg/ml	NQ	NQ	NQ
	NQ	46.9 pg/mL	1430 pg/mL	NQ	65.5 pg/mL
	NQ	NQ	NQ	1300 pg/mL	NQ
	NQ	17.8 pg/mL	18.8 pg/mL	65.8 pg/mL	796 pg/mL
	NQ	10.9 pg/mL	NQ	729 pg/mL	NQ
	12.7 pg/mL	NQ	NQ	729 pg/mL	12.7 pg/mL
	NQ	NQ	17.6 pg/mL	NQ	1340 pg/mL
	NQ	NQ	NQ	NQ	696 pg/mL
	NQ	744 pg/mL	NQ	NQ	NQ
	NQ	NQ	19.6 pg/mL	908 pg/mL	NQ

Source Data: Table 9.1

Further analysis of the data reported in the above table reveals no relationship exists between the high FF levels and the corresponding 24-hour cortisol levels in each subject (**Figures 4.2.3.1 A-C and Table 4.2.3.1**). This analysis was necessary to validate the high FF values reported from those 10 patients with high FF levels.

Figure 4.2.3.1 A-D. Relationship Between FF Levels and 24-Hour Cortisol Levels in 10 Subjects with High Plasma FF Levels (Study # FFR 102123)

Figure A. Visit 3 (Baseline)

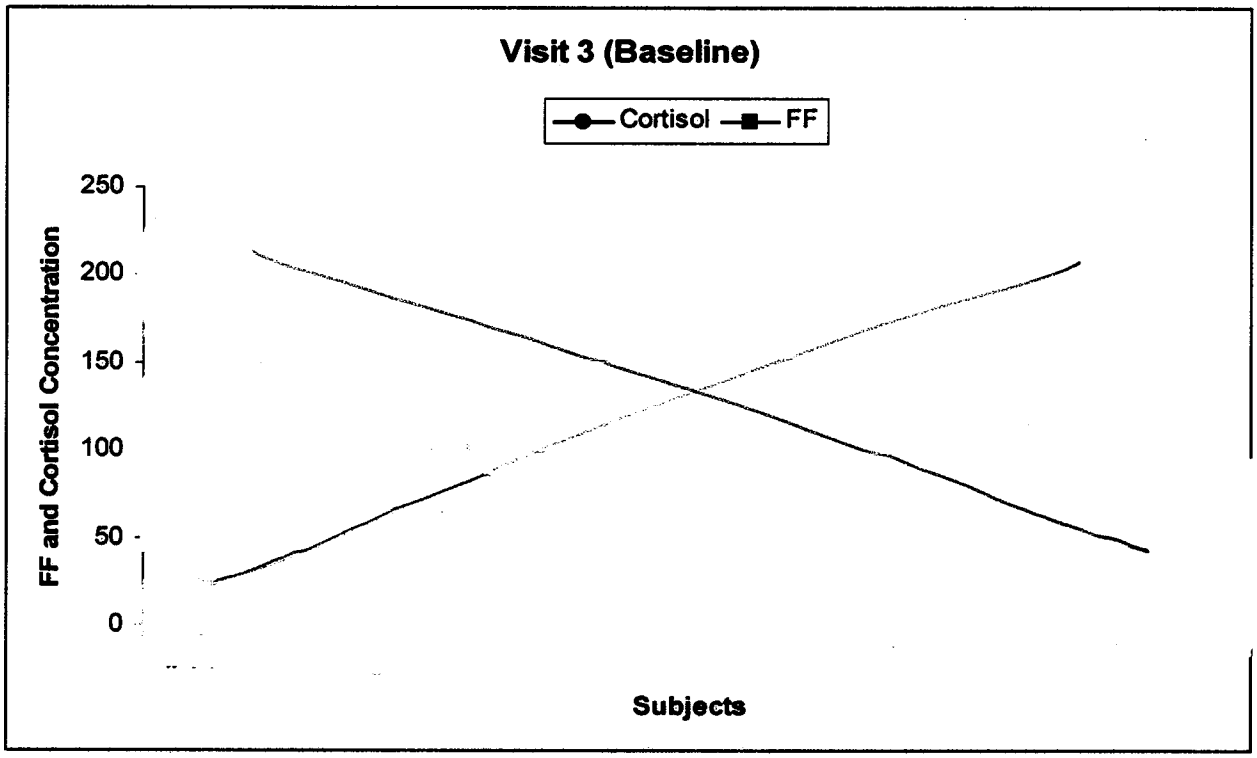


Figure 4.2.3.1 B. Visit 5 (Week 12)

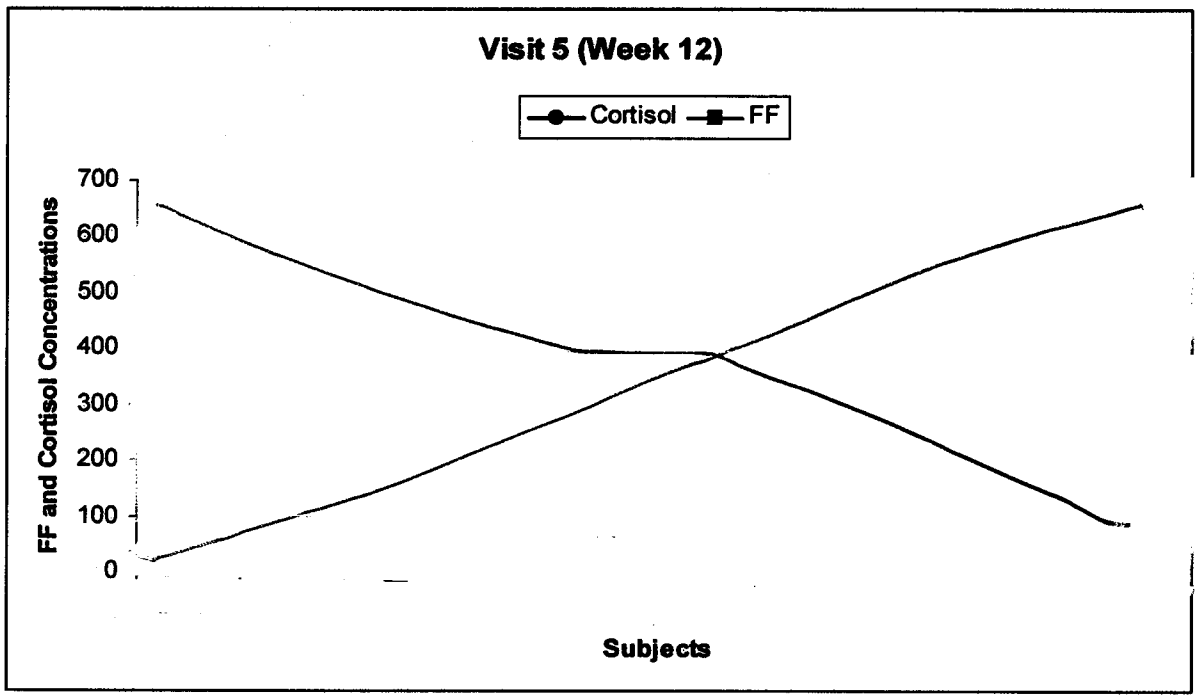


Figure 4.2.3.1 C. Visit 8 (Week 24)

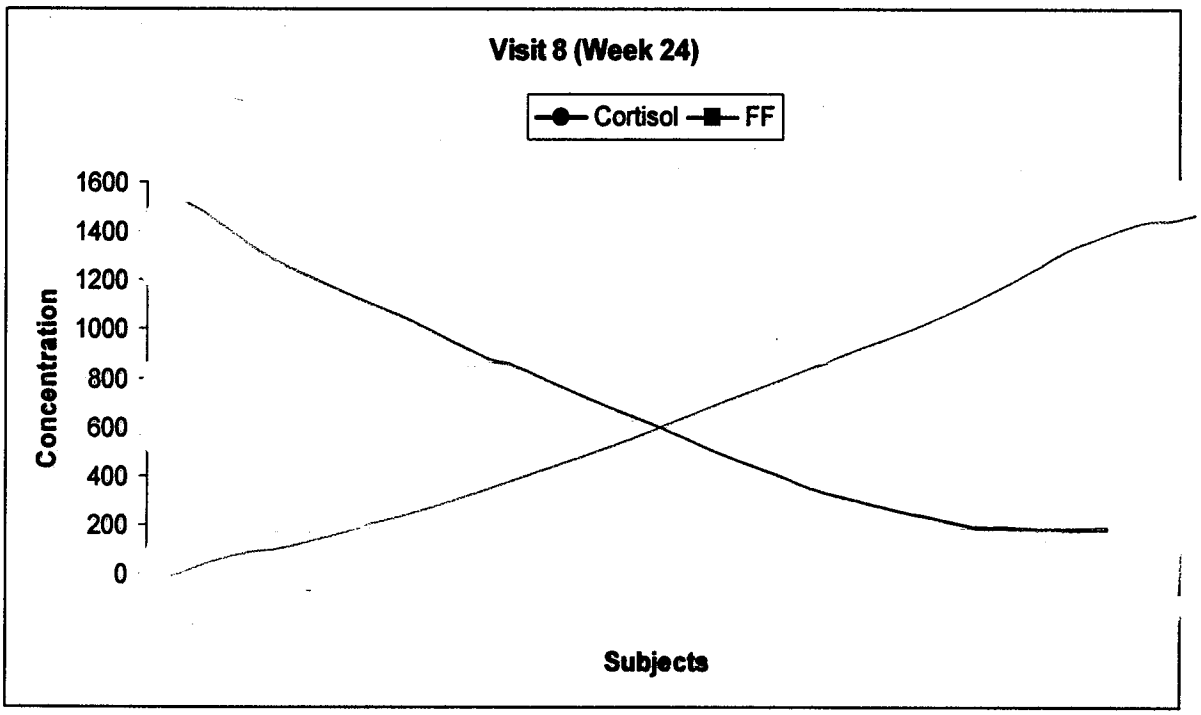


Figure 4.2.3.1 D. Visit 15 (Week 52)

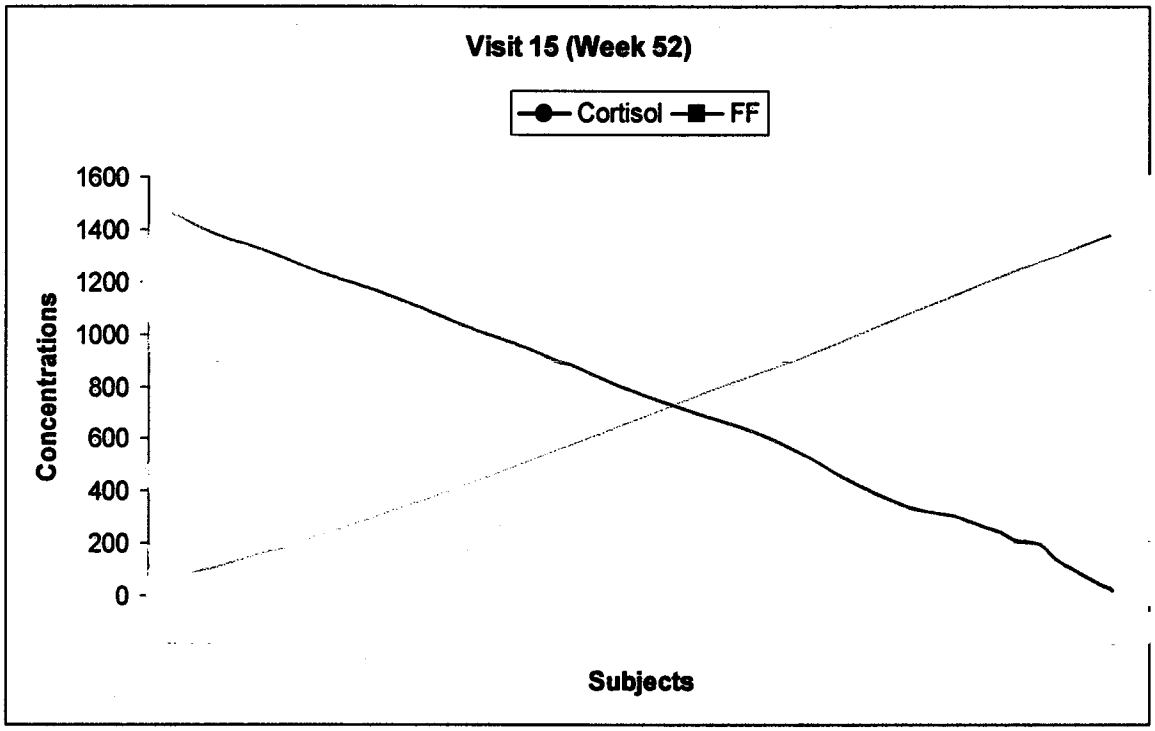


Table 4.2.3.1. Summary of FF Concentration (pg/mL) and 24-Hour Urine Excretion (nmol/day) in the 10 Subjects with High FF Levels (Study # FFR 102123)

Subjects	Visit 3 (Baseline)		Visit 5 (Week 12)		Visit 8 (Week 24)		Visit 11 (Week 36)		Visit 15 (Week 52)	
	Cort-isol	FF	Cort-isol	FF	Cort-isol	FF	Cort-isol	FF	Cort-isol	FF

Overall, due to the lack of adequate number of samples with sustained measurable FF levels, no further PK analysis was conducted by the sponsor to determine the standard PK parameters.

Pharmacodynamics (Urine Cortisol Data and Effect on HPA Axis):

The urinary excretion data in this study shows no evidence of cortisol suppression at any time points (**Figures 4.2.3.2-3 and Tables 4.2.3.2-3**). In actuality, the mean urinary cortisol excretion on week 52 (12 months) was even slightly higher than the baseline for both placebo and FF treatment arms. The figures and tables below were constructed in different format for clarity with and without SD. The main source of the raw data is in Table 7.40 in page 8140 of the study report. The box plot shows no change from the baseline for cortisol excretion data following FF or placebo at all time points (**Figure 4.2.3.4**). There was relatively reasonable, but scattered relationship, between baseline and Week 52 for individual 24 hour urine cortisol excretion (**Figure 4.2.3.5**).

Figure 4.2.3.2. Mean 24 Hour Urine Cortisol Excretion (Study # FFR 102123). Source of data Table 7.4 (Page 8140 of the Study Report)

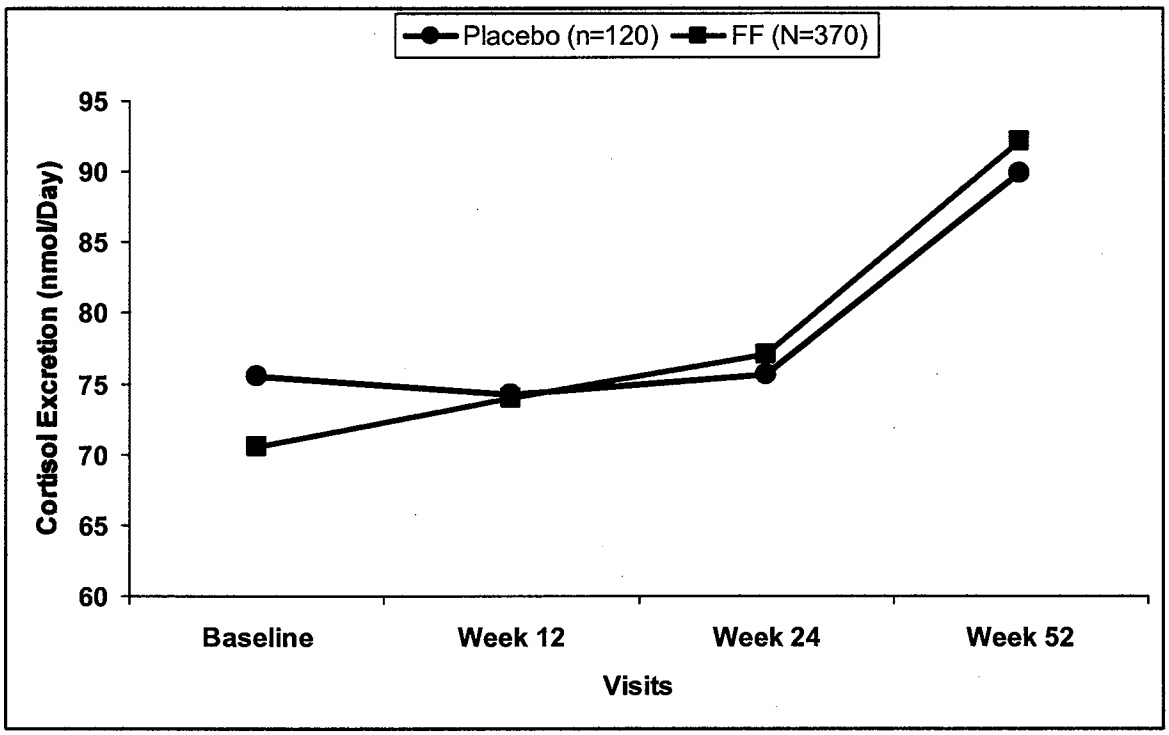


Figure . 4.2.3.2.3 Mean (± SD) 24 Hour Urine Cortisol Excretion (Study # FFR 102123). Source of data Table 7.4 (Page 8140 of the Study Report) (Note: this is the same graph as the above except SD was included).

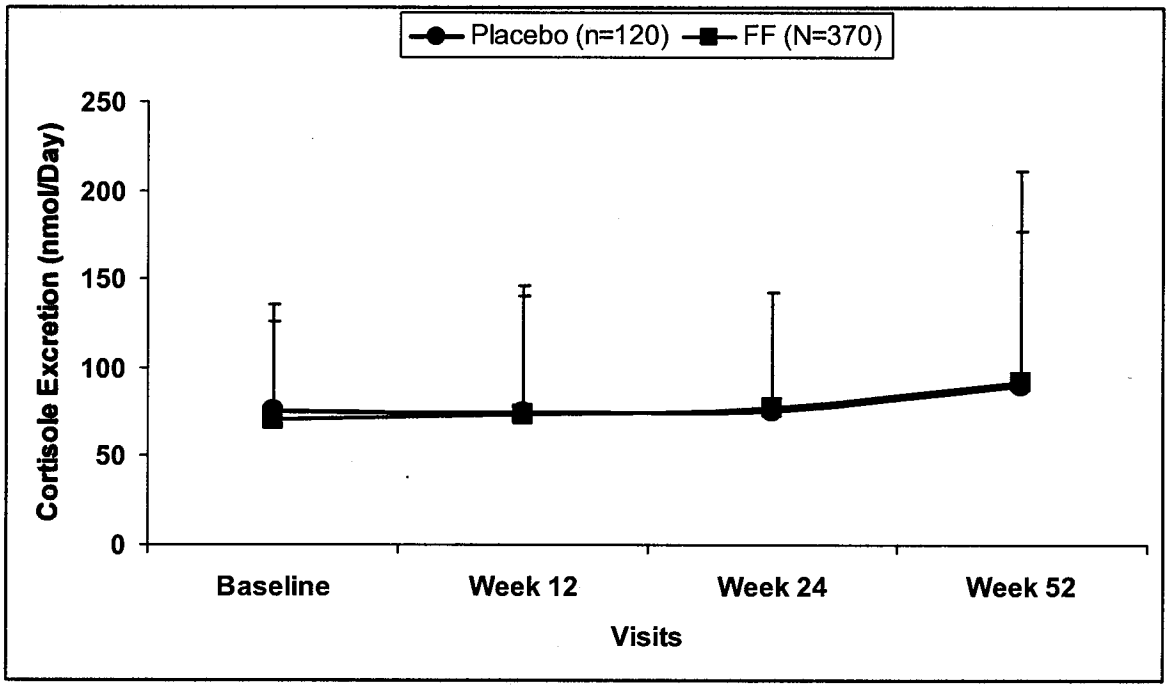


Table 4.2.3.2. Mean Urinary Cortisol Excretion Data (Source Table 7.40, Page 8140 of the Study Report # FFR 102123)

	Baseline	Week 12	Week 24	Week 52
Placebo (n=120)				
Mean (nmol/day)	75.56	74.19	75.66	89.89
SD (nmol/day)	60.4	72.2	67.19	87.42
CV (%)	79.9	97.3	88.8	97.2
Range (nmol/day)	3.6-441.7	4.7-675.8	5.0-481.3	9.1-680.0
FF (100 mcg) (n=370)				
Mean (nmol/day	70.58	77.11	77.11	92.10
SD (nmol/day	55.16	65.22	65.22	119.31
CV (%)	78.1	84.5	84.5	129.5
Range (nmol/day)	5.0-572.1	6.9-715.8	5.6-670.7	5.2-1247.1

Table 4.2.3.3. Summary of 24 Hour Urinary Cortisol Excretion (Study # FFR `102123)

	Placebo (N=120)	FF 100mcg (N=370)
Baseline		
Geometric mean	58.27	57.06
Mean (SD)	75.56 (60.460)	70.58 (55.161)
Median	60.00	57.00
Min - Max	3.6 - 441.7	5.0 - 572.1
Change from Baseline		
Week 12		
Mean (SD)	-1.37 (74.744)	3.39 (70.095)
Median	-4.15	1.35
Min - Max	-330.3 - 456.2	-435.8 - 601.0
Week 24 (n)		
Mean (SD)	0.10 (76.909)	6.54 (72.784)
Median	-0.95	2.45
Min - Max	-341.2 - 428.5	-505.8 - 434.7
Week 52 (n)		
Mean (SD)	14.33 (94.613)	21.53 (111.020)
Median	4.90	5.75
Min - Max	-370.9 - 573.7	-483.7 - 1160.2
Ratio to Baseline		
Week 12 (n)		
Geometric mean	0.99	1.01
Median	0.94	1.03
Week 24 (n)		
Geometric mean	0.96	1.05
Median	0.98	1.06
Week 52 (n)		
Geometric mean	1.13	1.14
Median	1.08	1.12

Figure 4.2.3.4. Box Plot of Change from Baseline for 24 hour Urine Cortisol Excretion(Study FFR 102123).

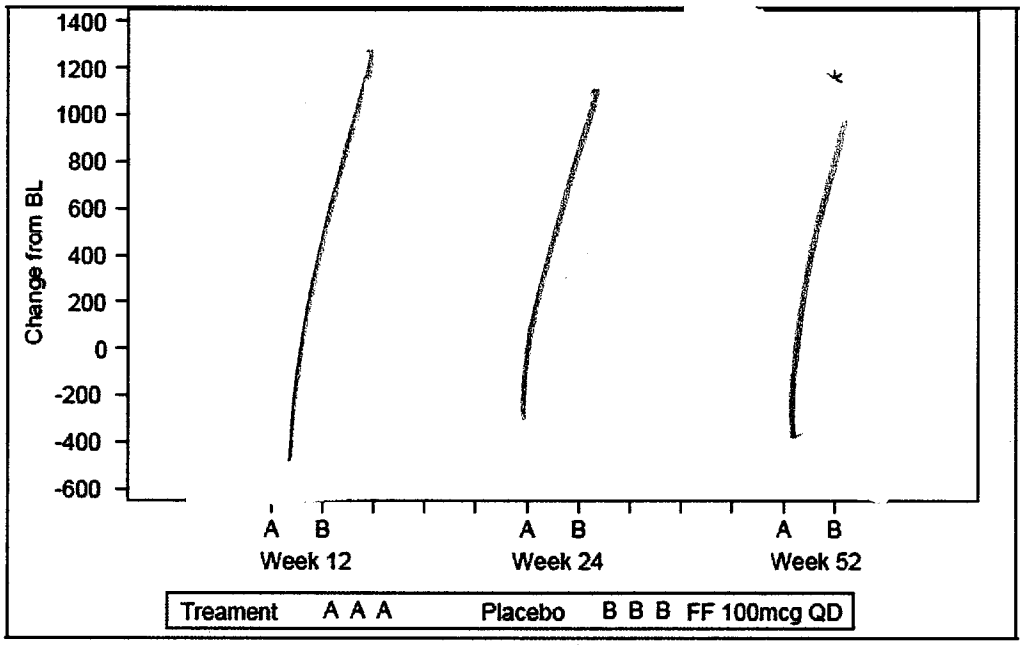
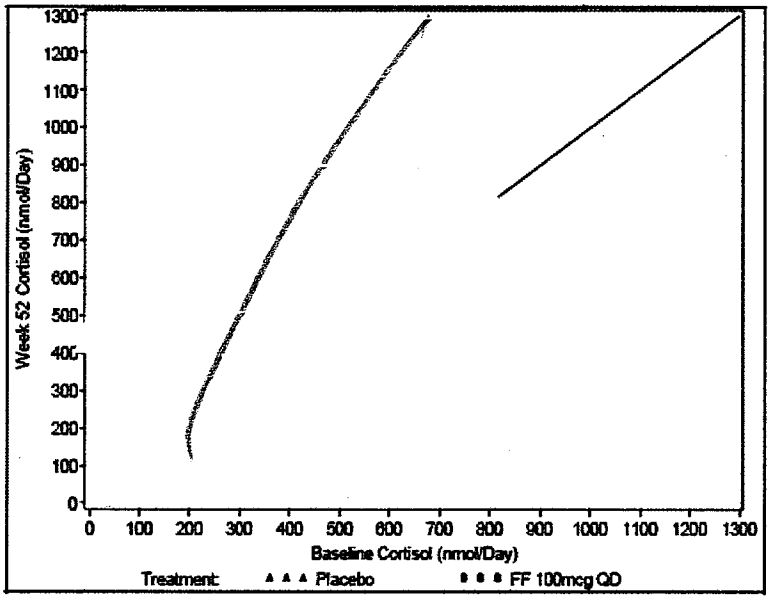


Figure 4.2.3.5 .Scattered Plot for 24-Hour Urine Cortisol Excretion at Baseline and Week 52 (Study # FFR 102123).



Reviewer's Comments:

From the pharmacodynamic perspective, this study may rule out the potential effect of intranasal administration of FF on HPA axis. The 24 hour cortisol excretion data were comparable to placebo and in some instances is higher than the baseline after 52 weeks of daily administration. However, there was wide variability in the data as shown in the above tables with CV >100% in some situation. Nevertheless, the overall assessment is conclusive to state that the effect on HPA axis is unlikely with this product at 100 mcg dose.

However, the PK data is a little concerning due to the fact that some subjects had concentrations above 500 pg/mL. In addition, the greater concern is that three subjects had levels higher than 1000 pg/ml. No adequate explanation was provided by the sponsor on those subjects. Thus, one may suspect three possible reasons:

1. Analytical or any other technical issues
2. Samples contamination and/or concomitant administration of other products containing other corticosteroid by the patients
3. Real data

The sponsor ruled out any possible demographic reasons to be associated with these high values (**Table 4.2.3.3**).

Table 4.2.3.3. Summary of Demographic Characteristics in Subjects With and Without Quantifiable Levels of FF (Study # FFR 102123)

	Subjects with at least one quantifiable level	Subjects without any quantifiable levels
n	223	352
Age [yrs] – mean (range)	30.7 (12 – 66)	33.4 (12 – 73)
Height [cm] - mean (range)	170.3 (138 – 195)	170.4 (143 – 205)
Weight [kg] - mean (range)	71.1 (30.0 – 124.0)	72.2 (33 – 134)
BMI [kg/m^2] - mean (range)	24.4 (15.8 – 42.4)	24.7 (14.7 – 40.6)
Gender - % male :% female	53% : 47%	48% : 52%
Race - % White : % American Hispanic : % Other	91% : 8% : <1%	85% : 13% : 2%

The most reasonable explanation is associated with technical and/or samples contamination rather than physiological or demographic factors associated with subjects characteristics. If the latter is true, a sustained high concentration would be expected throughout the sampling periods.

Conclusions:

The study showed no potential effect on HPA axis after 52 weeks of treatment with daily intranasal administration of 100 mcg in patients with PAR.

From the PK perspective, it can be stated that the FF plasma level was generally unquantifiable. However, some subjects had high levels of FF and in particular 10 subjects with level >500 pg/mL. Of a major concern is the level in three subjects was >1000 pg/mL. The reasons of these high concentrations are unknown at this time.

4.2.4.4. Study # FFR 30008 (50 mcg and 100 mcg QD X 12 Weeks in 2 to <12 Years of Age):

Objectives:

The primary object of this study was to evaluate the safety and efficacy 50 mcg and 100 mcg of FF after 12 weeks of daily intranasal administration in pediatric patients 2 to <12 years of age with PAR. The secondary objective is to characterize the systemic exposure of FF after intranasal administration of 50 and 100 mcg for 12 weeks.

Design:

This was double blind, placebo controlled, parallel group enrolled 808 pediatric patients 2 to <12 years with PAR as follows:

Treatment A (n=185): 50 mcg QD aqueous nasal spray (1 sprays of 50 mcg in one nostril and a second spray of placebo in the second nostril) x **12 weeks**

Treatment B (n=185): 100 mcg QD aqueous nasal spray (1 sprays of 50 mcg in each nostril) x **12 weeks**

Treatment B (n=188): Placebo aqueous nasal spray (2 sprays of 50 mcg in each nostril) QD x **12 weeks.**

PK plasma samples were collected on Weeks 6 and 12, whereas 24-hour urine for cortisol measurement was collected at baseline and on week 12.

Results:

Pharmacokinetics:

Out 342 subjects, 56 subjects had quantifiable levels (15.4% of the PK subjects) in whom there were only 60 samples with quantifiable levels (8.9% of total samples). Only 5 samples had concentration >100 pg/mL. The majority of the concentrations (73.3%) were <30 pg/ml (**Table 4.2.4.4.1**). In all samples with quantifiable levels the concentration ranged from 10.1 to 693.3 pg/mL.

Table 4.2.4.4.1. Number of Samples With Quantifiable FF Concentration (Study # FFR 30008)

Fluticasone furoate 50mcg				Fluticasone furoate 100mcg			
Age	10 to <20 pg/mL	20 to <30 pg/mL	>= 30 pg/mL	Age	10 to <20 pg/mL	20 to <30 pg/mL	>= 30 pg/mL
2 to <6 yrs n=73	4 (5.5%)	1 (1.4%)	1 (1.4%)	2 to <6 yrs n=76	7 (9.2%)	2 (2.6%)	2 (2.6%)
6 to <12 yrs n=260	10 (3.8%)	3 (1.2%)	4 (1.5%)	6 to <12 yrs n=263	13 (4.9%)	4 (1.5%)	9 (3.5%)

It should be noted, however, these detections were erratic, inconsistent, and unsustainable throughout. In other words, those subjects with detectable levels >30 pg/mL there was no detection or the concentrations were >30 pg/ml in the other visits. Furthermore, like the previous study (Study # FFR 102123), there was no consistent pattern associated with the demographic characteristics of the patients and the detection of FF concentrations.

Overall, due to the limited number of samples with sustained FF levels, no further PK analysis was conducted by the sponsor to determine any of the PK parameters.

Pharmacodynamics:

In this study, it appears that there was some suppression in 24 hour urine cortisol levels (**Figures 4.2.4.4.1-2 and Table 4.2.4.4.2**). There was consistent change from baseline in all treatments, including placebo (**Table 4.2.4.4.3**). Although there was high variability in the data, the effect is clearly dose dependent (i.e., greater at 100 mcg than 50 mcg dose or placebo).

Figure 4.2.4.4.1. Mean (± SD) 24 Hour Urine Cortisol Excretion (Study # FFR 30008).

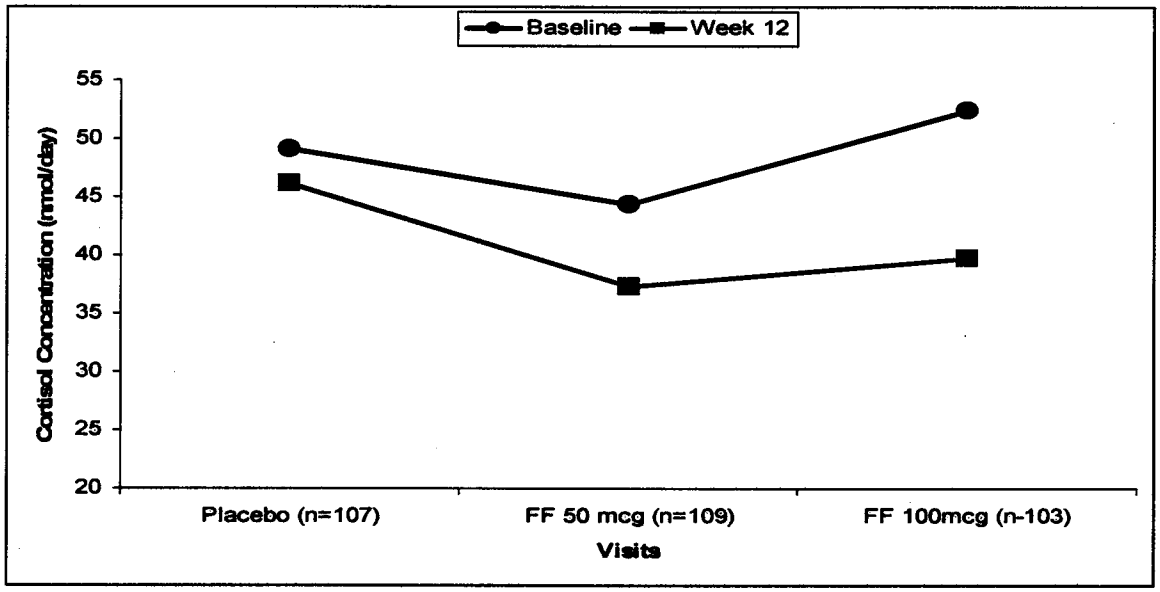


Figure 4.2.4.4.2. Mean (± SD) 24 Hour Urine Cortisol Excretion (Study # FFR 30008). (Note: this is the same graph as the above except SD was included).

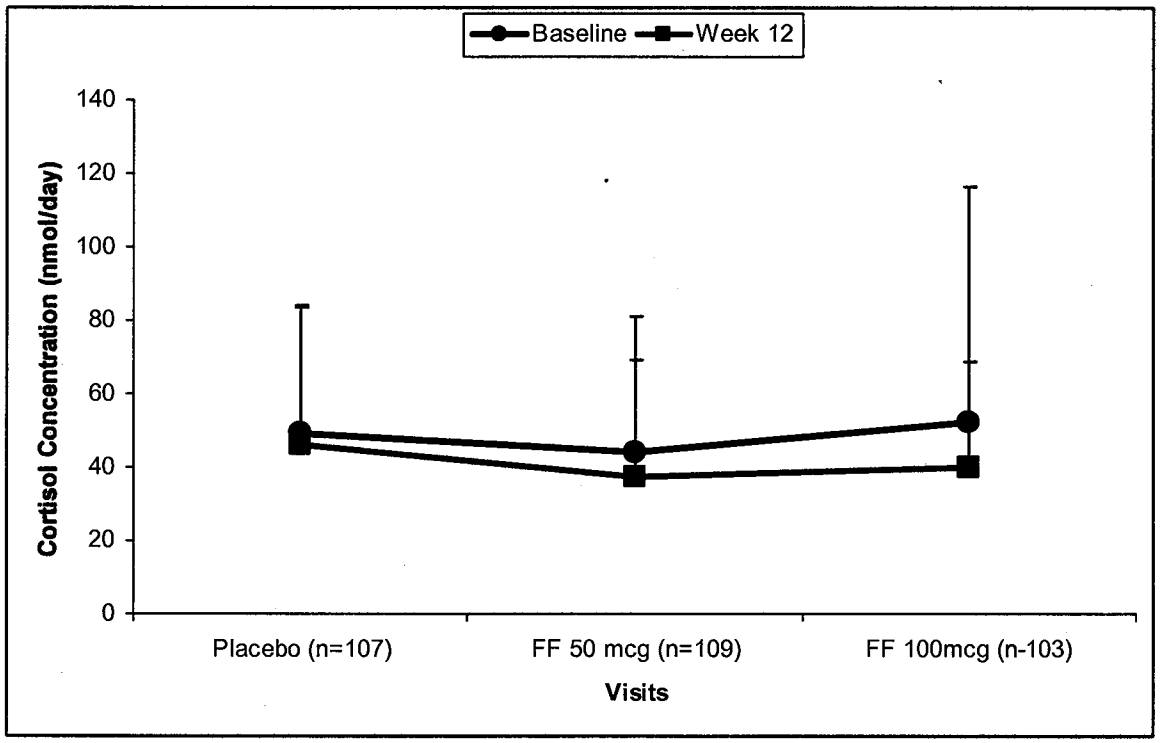


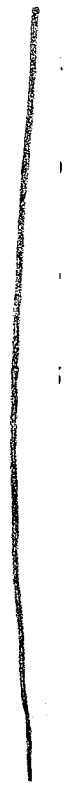
Table 4.2.4.4.2 Summary of 24 Hour Cortisol Excretion Data (Study # FFR 30008)

Cortisol Concentration (nmol/24 hr)	Placebo N=107	Fluticasone furoate 50mcg N=109	Fluticasone furoate 100mcg N=103
Baseline, n	107	109	103
Mean (SD)	49.15 (34.717)	44.33 (36.569)	52.43 (63.947)
Median	40.60	34.80	38.20
Geometric mean	39.98	34.70	38.91
Min-Max	9.7 – 195.0	3.9 – 231.7	4.1 – 568.1
Week 12, n	107	109	103
Mean (SD)	46.21 (37.565)	37.37 (32.064)	39.76 (29.061)
Median	34.20	30.70	30.60
Geometric mean	35.81	29.03	30.59
Min-Max	5.3 - 249.8	3.3 - 253.4	3.0 - 182.4
Change from Baseline, n	107	109	103
Mean (SD)	-2.94 (47.430)	-6.95 (45.481)	-12.67 (67.476)
Median	-2.80	-0.60	-5.00
Min-Max	-161.4 – 204.3	-214.5 – 222.5	-546.0 – 154.6
Ratio of Week 12 to Baseline, n	107	109	103
Median	0.91	0.97	0.88
Geometric mean	0.90	0.84	0.79

Reviewer's Comments:

From the PK perspective, the observed FF levels were much lower than that seen in the above study in adolescents and adults (Study # FFR 102123). However, the two studies showed erratic and inconsistent, but unsustainable FF levels in some patients. In this study, only 5 subjects had concentrations >100 pg/mL. Examining the individual data in Pages 7392-7424 (Table 9.1) of the sponsor's study report it was noted that almost all subjects with the level greater than 50 pg/ml were observed in the first sampling period, except subject # 920 as listed below:

Subject	Center	Dose (mcg)	Week	Time (h)	Concentration (pg/mL)
1276	12268	50	6	0.5	
1276	12268	50	12	2	
1404	13327	50	6	3.25	
1404	13327	50	12	1.67	
1397	13327	50	6	0.4	
1397	13327	50	12	1.17	
1285	12268	100	6	2	
1285	12268	100	12	1	
1303	12268	100	6	1.5	
1303	12268	100	12	1	
1400	13327	100	6	0.5	
1400	13327	10	12	1	
1401	13327	100	6	3.17	
1401	13327	100	12	1	
1256	12268	100	6	2	
1256	12268	100	12	1	
920	12556	100	6	3.13	
920	12556	100	12	0.4	



From the Pharmacodynamic perspective, the study showed some effect on the HPA axis at week 12. No cortisol data was collected at 6 weeks in this study to confirm the finding at week 12. The clinical significance of this suppression is questionable.

Conclusions:

From this study, the following conclusions can be made:

1) In general, the FF was undetectable in most of the subjects. However, in a few subjects the FF level was >100 pg/ml and was mainly observed in the first time period (i.e., Week 6).
2) There was some noticeable effect on HPA axis in this study at Week 12.
3) The clinical significance of these finding is questionable at this time.

4.2.4.5. Study # FFR 20001 (50, 100, 200, 400 mcg QD X 14 Days in 12 Years of Age older SAR Patients):

Objectives:

The primary object of this study was to evaluate the safety and efficacy 50, 100, 200, and 400 mcg of FF after 14 days daily intranasal administration in adolescent and adults 12 years of age and older with SAR. The secondary objective is to characterize the systemic exposure of FF after intranasal administration of 50 and 100 mcg for 12 weeks.

Design:

This was double blind, placebo controlled, parallel group in enrolled 641 patients 12 years of age and older with SAR. All subjects received a total of **four sprays** as one spray in each nostril from each Spray A and B devices as shown below:

Dose	Treatment Bottle	Dosing Regimen	Suspension Concentration
Placebo	Spray A	2 x placebo	Placebo
	Spray B	2 x placebo	Placebo
50 mcg	Spray A	2 x placebo	Placebo
	Spray B	2 x 25 mcg	0.05%
100 mcg	Spray A	2 x 25 mcg	0.05%
	Spray B	2 x 25 mcg	0.05%
200 mcg	Spray A	2 x 50 mcg	0.10%
	Spray B	2 x 50 mcg	0.10%
400 mcg	Spray A	2 x 100 mcg	0.20%
	Spray B	2 x 100 mcg	0.20%

Sparse PK blood samples were collected at Visit 3 (Day 8) and Visit 4 (Day 14) after treatments. 24-hour urine was collected on Visit 2 (baseline) and Visit 4 (Day 14).

Results:

Pharmacokinetics:

In this study 1476 samples were analyzed in this study collected form 502 patients. In general, the majority of the concentration in the majority of the samples was below LLOQ (<10 pg/mL). Out of 1476 samples, only 78 (5.3%) samples had measurable levels with a maximum concentration of not greater than 30 pg/mL (**Tables 4.2.4.5.1-2**). Only two subjects had a concentration of 50.7 and 114 pg/mL in one of their samples but in the remaining samples FF was not detectable.

Table 4.2.4.5.1. .Summary of the Systemic Exposure to FF (Study # FFR 20001)

	Samples			Patients		
Dose	With measurable value	Total	Percentage	With at least one measurable value	Total	Percentage
50 mcg	4	363	1.1%	4	124	3.2%
100 mcg	8	367	2.2%	8	126	6.4%
200 mcg	9	375	2.4%	9	126	7.1%
400 mcg	57	371	15.4%	38	126	30.2%
Overall	78	1476	5.3%	59	502	11.8%

Table 4.2.4.5.2. Mean FF Concentration Relative to Dose (Study # FFR 20001)

Dose	Geomean (pg/ml)	95% CI
50 mcg	15.1	(8.48, 26.7)
100 mcg	17.2	(8.98, 33.1)
200 mcg	14.4	(9.75, 21.2)
400 mcg	13.9	(12.8, 15.0)
Overall	14.3	(13.1, 15.6)

Pharmacodynamic:

In this study, no evidence of cortisol suppression based on 24-hour urinary excretion was observed (**Table 4.2.4.5.3.**). Cortisol level was similar at baseline and after 14 days of treatment at all doses, including placebo.

Table 4.2.4.5.3. Summary of Urinary Cortisol Excretion (mcg/24 h) (Study # FFR 20001)

UC		Placebo	GW685698X 50 mcg	GW685698X 100 mcg	GW685698X 200 mcg	GW685698X 400 mcg
		N = 117	N = 116	N= 118	N = 122	N =120
Baseline (n)		117	116	118	121	120
Mean (SD)		20.0 (14.32)	21.9 (18.04)	21.3 (21.79)	22.4 (15.50)	20.4 (12.35)
> Normal		8 (7%)	13 (11%)	15 (13%)	12 (10%)	8 (7%)
< Normal		1 (1%)	0	5 (4%)	0	0
Week 2 (n)		117	116	118	122	120
Mean (SD)		20.9 (18.73)	23.9 (23.09)	20.8 (18.25)	21.3 (16.35)	20.9 (14.92)
> Normal		11 (9%)	15 (13%)	9 (8%)	16 (13%)	9 (8%)
< Normal		1 (1%)	1 (1%)	2 (2%)	1 (1%)	1 (1%)
Change		0.9 (20.02)	2.0 (26.28)	-0.5 (25.23)	-1.2 (19.51)[a]	0.6 (17.81)
Shift	to Low	1 (1%)	1 (1%)	2 (2%)	1 (1%)	1 (1%)
	to Nml or NC	107 (91%)	104 (90%)	111 (94%)	108 (89%)	112 (93%)
	To High	9 (8%)	11 (9%)	5 (4%)	13 (11%)	7 (6%)

Reviewer's Comments:

The duration of this study is only 14 days, hence the cortisol data obtained from this study is considered supportive to the large studies conducted in this NDA with longer duration of treatment.

Conclusions:

This study provided supportive and confirmatory information on the PK and PD characteristic of FF intranasal product. No new information was learned from this study except that the PK and PD characteristics of FF intranasal product in SAR patients would be expected to be similar.

From this study it can be concluded that the majority of the samples were below the LLOQ and there was no evidence of HPA axis suppression in this 14 days study.

4.2.4.6. Study FFR 101888 (Effect on QTc of Single Dose Oral Inhalation):

Objectives:

The primary object of this study was to evaluate the effect of a single 4000 mcg orally inhaled dose of FF on QTc interval compared to placebo and a positive control of 400 mg single dose of moxifloxacin in healthy subjects. The secondary objective is to investigate the effect of cellobiose acta acetate (COA), an excipient used in dry powder formulation for FF inhalation on ECG parameters.

Design:

This was placebo-controlled, four-way crossover study in 40 healthy subjects as follows:

Treatment Sequence:

Period 1	Period 2	Period 3	Period 4
Fluticasone furoate 4000 mcg	Moxifloxacin 400 mg	COA 6.25 mg	Placebo
COA 6.25 mg	Fluticasone furoate 4000 mcg	Placebo	Moxifloxacin 400 mg
Placebo	COA 6.25 mg	Moxifloxacin 400 mg	Fluticasone furoate 4000 mcg
Moxifloxacin 400 mg	Placebo	Fluticasone furoate 4000 mcg	COA 6.25 mg

Subjects received one of the following treatments: 4000 mcg by oral inhalation dry powder formulated with COA and lactonse, 6.25 mg of COA alone, placebo, or 400 mg single dose of moxifloxacin. In each arm appropriate placebo was also administered as shown below:

Blinding: Active and Placebo Treatments:

Treatment	Oral inhaled – DISKUS device	Oral Tablet
Fluticasone furoate 4000 mcg	4000 mcg fluticasone furoate (with 5.625 mg COA and lactose)	Placebo tablet
COA 6.25 mg	6.25 mg COA (with lactose)	Placebo tablet
Placebo	Placebo (lactose)	Placebo tablet
Moxifloxacin 400 mg	Placebo (lactose)	400 mg moxifloxacin tablet

The primary end point was the mean change from baseline in QTcF over the 24 hours post dose for FF and placebo arms. Lack of effect on QTcF derived from the manually read ECG data was included if the upper limit of the two-sided 90% CI for the maximal mean change from baseline

was less than or equal to 7.5 msec. In addition, the lack of effect on QTcF was included if the upper limit of the two-sided 90% CI for the mean change from baseline at each post-dose time point was less than 10 msec. ECG was monitored over 24 hours. In addition, a total of 28 sparse PK sampling were collected form each subjects over 24 hour period.

Results:

The maximum mean change from baseline over 0-24 hours for QRcF and QTcB show substantial effect of moxifloxacin, the positive control, compared to FF and COA with placebo (**Figures 4.2.4.6.1-2 and Tables 4.2.4.6.1-2).** The mean difference for FF was 0.788 msec and -0.074 msec for FF compared to 9.929 msec and 8.944 msec for moxifloxacin for QTcF and QtcB, respectively (**Tables 4.2.4.6.1-2 and Figure 4.2.4.6.3).**

Figure 4.2.4.6.1. Maximal Mean Change from Baseline (0-24 hour)

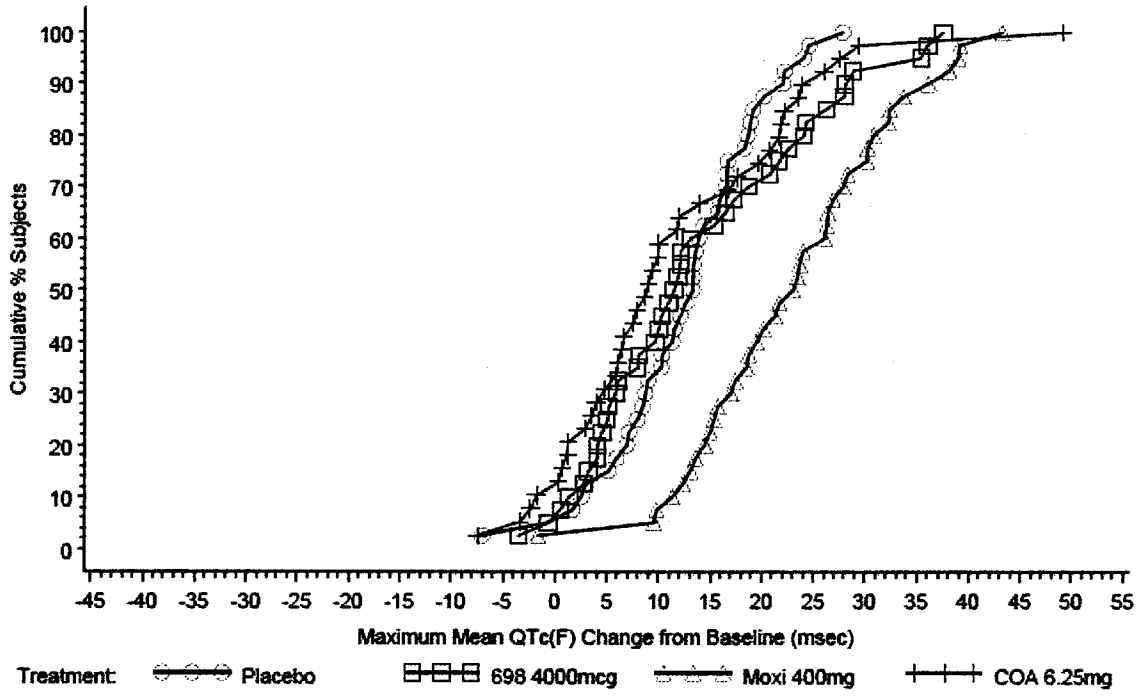


Figure 4.2.4.6.2. Weighted Mean Change From baseline (0-24 hour)

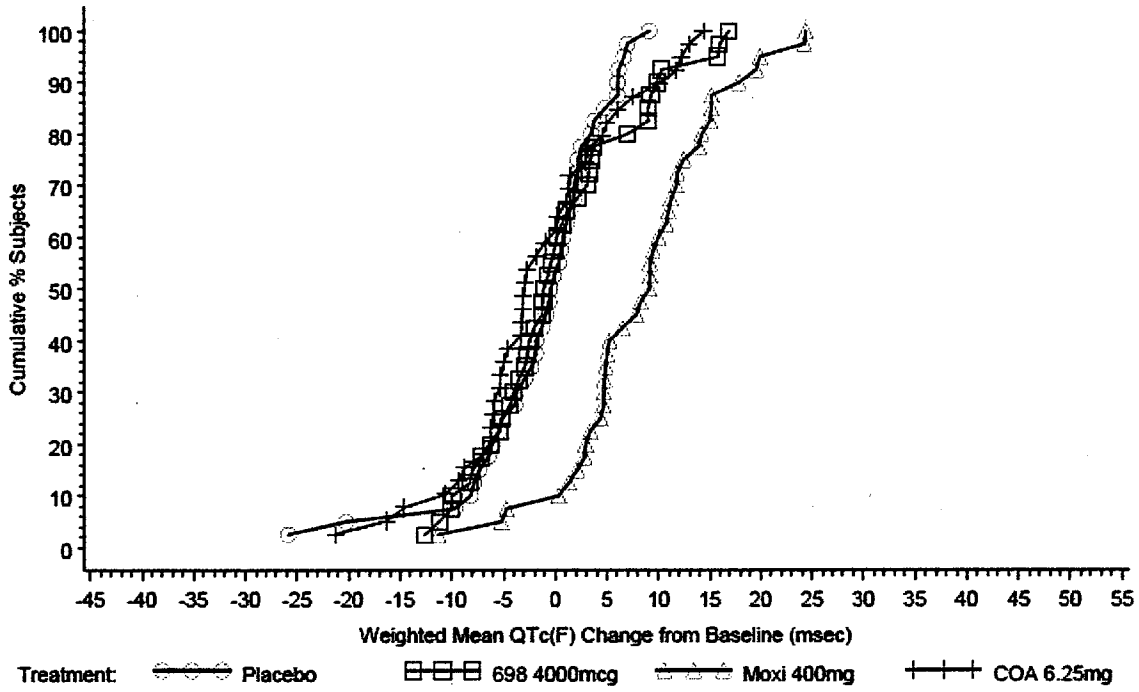


Table 4.2.4.6.2. Summary of Statistical Analysis of QTcF Maximal Mean Change from Baseline (0-24 h)

Comparison	Treatment Difference (msec)	90% Confidence Interval (msec)
Fluticasone furoate 4000 mcg – Placebo	-0.074	(-3.586,3.437)
Moxifloxacin 400 mg – Placebo	8.944	(5.433,12.455)
COA 6.25 mg – Placebo	-1.486	(-5.042, 2.070)

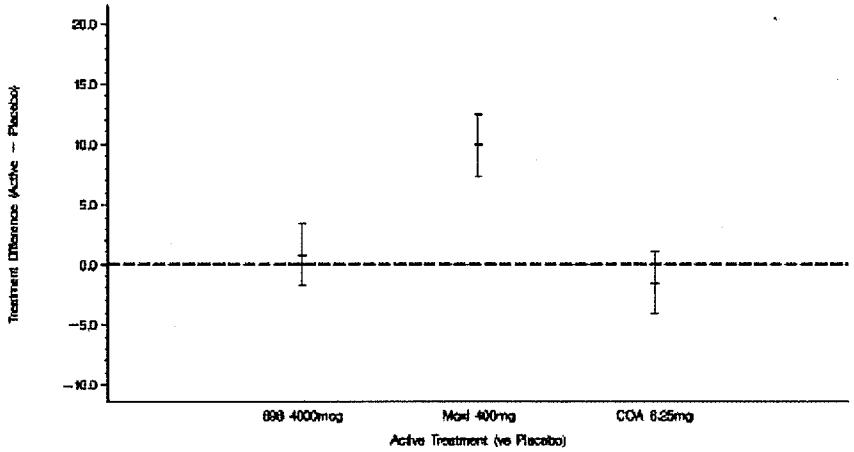
Data Source: Table 10.8
Note: N=40 for fluticasone furoate, moxifloxacin and placebo, N=39 for COA

Table 4.2.4.6.2. Summary of Statistical Analysis of QTcB Maximal Mean Change from Baseline (0-24 h)

Comparison	Treatment Difference (msec)	90% Confidence Interval (msec)
Fluticasone furoate 4000 mcg – Placebo	0.999	(-0.612, 2.610)
Moxifloxacin 400 mg – Placebo	9.295	(7.683, 10.906)
COA 6.25 mg – Placebo	-0.670	(-2.293, 0.953)

Source Table 10.9
Note: N=40 for fluticasone furoate, moxifloxacin and placebo, N=39 for COA

Figure 4.2.4.6.3. Treatment Difference for Maximal Mean Cahnge from Baseline (0-24 h) in QTcF (msec)



Similarly, Weighted Mean Change from the Baseline show lack of effect with FF and COA (**Figure 4.2.4.6.4 and Tables 4.2.4.6.3-4**).

Figure 4.2.4.6.4. Weighted Mean Change From Baseline (0-24 h) for QTcF.

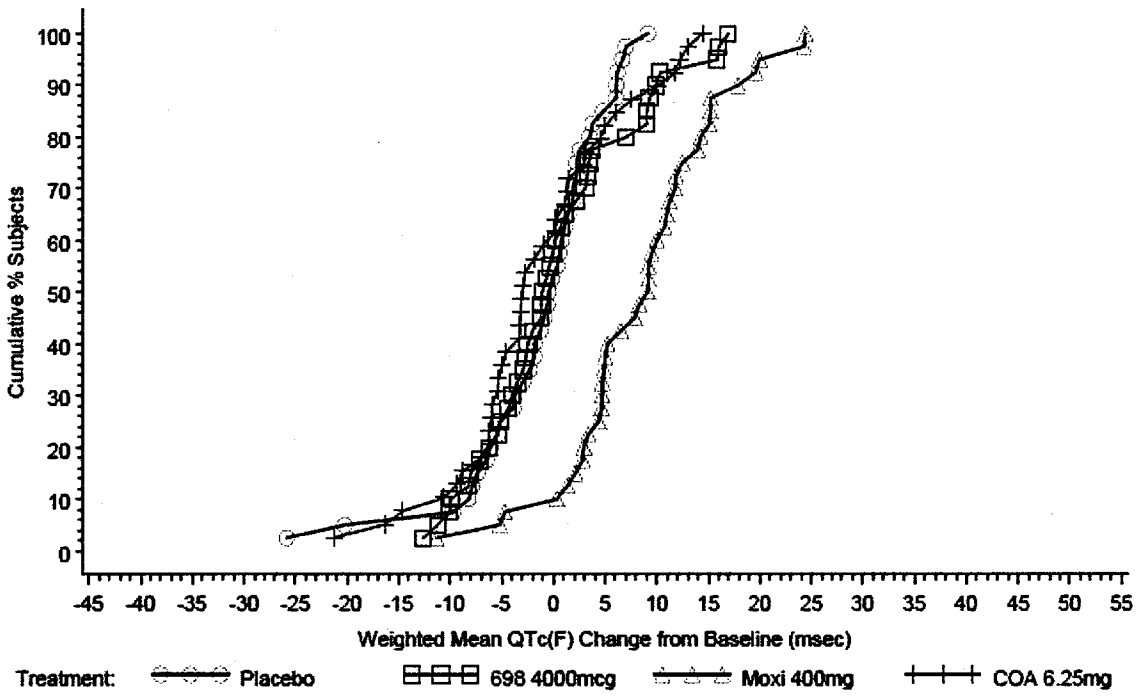


Table 4.2.4.6.3. Summary of Statistical Analysis of QTcF Weighted Mean Change from Baseline (0-24 h)

Comparison	Treatment Difference (msec)	90% Confidence Interval (msec)
Fluticasone furoate 4000 mcg – Placebo	0.999	(-0.612, 2.610)
Moxifloxacin 400 mg – Placebo	9.295	(7.683, 10.906)
COA 6.25 mg – Placebo	-0.670	(-2.293, 0.953)

Source Table 10.9
Note: N=40 for fluticasone furoate, moxifloxacin and placebo, N=39 for COA

Table 4.2.4.6.4. Summary of Statistical Analysis of QTcB Weighted Mean Change from Baseline (0-24 h)

Comparison	Treatment Difference (msec)	90% Confidence Interval (msec)
Fluticasone furoate 4000 mcg – Placebo	1.718	(-0.122, 3.559)
Moxifloxacin 400 mg – Placebo	10.180	(8.339, 12.020)
COA 6.25 mg – Placebo	-0.562	(-2.431, 1.308)

Source Table 10.9
Note: N=40 for fluticasone furoate, moxifloxacin and placebo, N=39 for COA

Moreover, there was no evidence of effect on the mean change from the baseline at each time points following FF and the exepient, COA (**Figure 4.2.4.6.5. and Tables 4.2.4.6.5-6**).

Figure 4.2.4.6.5.Mean Change From Baseline QTCF at Each Time Point Post Dose (0-24 h)

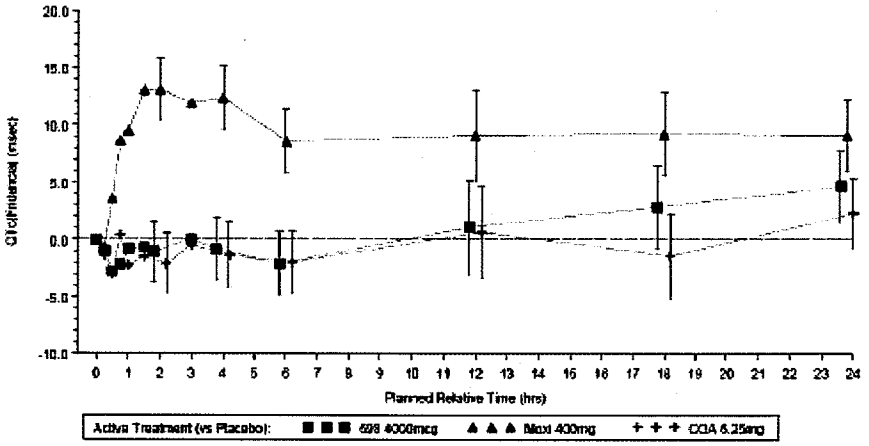


Table 4.2.4.6.5. Summary of Statistical Analysis of QTcF Mean Change from Baseline at Each Time Point Post dose (0-24 h)

Time Point (h)	Fluticasone furoate 4000 mcg – Placebo		Moxifloxacin 400 mg – Placebo		COA 6.25 mg – Placebo	
	Treatment Difference (msec)	90% Confidence Interval (msec)	Treatment Difference (msec)	90% Confidence Interval (msec)	Treatment Difference (msec)	90% Confidence Interval (msec)
0.25	-0.952	(-3.560, 1.656)	-0.641	(-3.250, 1.967)	-1.417	(-4.042, 1.208)
0.5	-2.769	(-5.044, -0.493)	3.615	(1.340, 5.891)	- 3.016	(-5.307, -0.725)
0.75	-2.182	(-5.088, 0.724)	8.648	(5.742, 11.554)	0.412	(-2.513, 3.337)
1	-0.771	(-3.397, 1.855)	9.510	(6.883, 12.136)	-2.274	(-4.917, 0.369)
1.5	-0.634	(-3.224, 1.956)	13.056	(10.466, 15.647)	-1.496	(-4.103, 1.111)
2	-1.084	(-3.727, 1.558)	13.090	(10.447, 15.733)	-2.113	(-4.773, 0.547)
3	0.074	(-3.248, 3.397)	11.901	(8.579, 15.224)	-0.493	(-3.837, 2.851)
4	-0.857	(-3.660, 1.945)	12.348	(9.545, 15.150)	-1.373	(-4.193, 1.447)
6	-2.103	(-4.810, 0.604)	8.584	(5.877, 11.292)	-1.978	(-4.703, 0.746)
12	1.091	(-2.938, 5.120)	9.098	(5.069, 13.127)	0.652	(-3.384, 4.688)
18	2.858	(-0.772, 6.488)	9.202	(5.572, 12.832)	-1.418	(-5.072, 2.236)
24	4.659	(1.621, 7.697	9.083	(6.045, 12.122)	2.265	(-0.793, 5.323)

Source Table 10.10
Note: N=40 for fluticasone furoate, moxifloxacin and placebo, N=39 for COA

Table 4.2.4.6.6. Summary of Statistical Analysis of QTcB Mean Change from Baseline at each Time Point Post dose (0-24 h)

Time Point (h)	Fluticasone furoate 4000 mcg – Placebo		Moxifloxacin 400 mg – Placebo		COA 6.25 mg – Placebo	
	Treatment Difference (msec)	90% Confidence Interval (msec)	Treatment Difference (msec)	90% Confidence Interval (msec)	Treatment Difference (msec)	90% Confidence Interval (msec)
0.25	0.465	(-3.151, 4.081)	-0.077	(-3.693, 3.539)	-0.502	(-4.149, 3.145)
0.5	-2.269	(-5.595, 1.058)	5.487	(2.161, 8.813)	-2.539	(-5.894, 0.817)
0.75	-0.903	(-5.051, 3.245)	11.855	(7.707, 16.003)	3.177	(-1.004, 7.358)
1	0.592	(-3.250, 4.435)	11.238	(7.396, 15.081)	-1.190	(-5.064, 2.684)
1.5	0.928	(-2.690, 4.546)	14.914	(11.296, 18.532)	-0.480	(-4.128, 3.168)
2	0.332	(-3.309, 3.973)	15.054	(11.413, 18.695)	-1.058	(-4.730, 2.614)
3	2.150	(-2.217, 6.517)	12.255	(7.888, 16.622)	0.027	(-4.374, 4.428)
4	1.970	(-1.782, 5.721)	14.036	(10.284, 17.787)	-1.067	(-4.849, 2.715)
6	-0.605	(-3.767, 2.557)	9.687	(6.525, 12.849)	-1.937	(-5.128, 1.254)
12	1.955	(-2.191, 6.100)	9.055	(4.909, 13.200)	-0.195	(-4.346, 3.955)
18	1.847	(-1.700, 5.394)	10.063	(6.517, 13.610)	-1.884	(-5.461, 1.693)
24	5.121	(1.530, 8.712)	9.978	(6.387, 13.568)	3.303	(-0.318, 6.924)

Source Table 10.10
Note: N=40 for fluticasone furoate, moxifloxacin and placebo, N=39 for COA

Since there was no noticeable effect on ECG (QTc), no PK/PD analysis was necessary to be performed.

Reviewer's Comments:

This study was specifically conducted for the COPD program for FF oral inhalation. It was submitted as additional safety information in the 120 day safety update to this NDA. Although, this may not directly be related to intranasal route, some of the information may be useful for labeling.

It should be noted that this study will be further reviewed by OCP when oral inhalation NDA is submitted. In addition, a consult for this study was sent to QTc review group within the Agency. The analysis and the review of this group is pending. However, the summary of this study is included in this review and may be amended as necessary when the final assessment of the QTc group is received.

From the preliminary review and analysis of the data, it appears that FF and COA had minimal effect on QTc.

Conclusion:

No conclusion can be made until the data is further analyzed and reviewed by the QTc assessment group. However, from the preliminary review of the data, it appears that FF and COA had minimal effect on QTc.

APPEARS THIS WAY ON ORIGINAL

4.3 Consult Review (Pharmacometric Review)

No pharmacometric consult was needed for this NDA.

4.4 Filing Memo:

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-051**	**Brand Name**	**N/A**
OCP (I, II, III)	**II**	**Generic Name**	**Fluticasone Furoate**
Medical Division	**DPADP**	**Drug Class**	Glucocorticoid
OCPB Reviewer	Sayed (Sam) Al Habet, RP.h, Ph.D.	**Indication(s)**	Seasonal and Perennial Rhinitis
OCPB Team Leader	**Emmanuel (Tayo) Fadiran, RP.h., Ph.D.**	**Dosage Form**	**Nasal Spray**
PM Reviewer		**Dosing Regimen**	**2 sprays (110 mcg) per nostril daily. Maintenance dose: 55 mcg QD one spray per nostril.**
Date of Submission	**June 28, 2006**	**Route of Administration**	**Nasal**
Estimated Due Date of OCP Review	**January 28, 2007**	**Sponsor**	**GSK**
PDUFA Due Date	**April 29, 2007**	**Priority Classification**	Standard
Division's Due Date	February 28, 2007		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

Healthy Volunteers-				
single dose:	x	8	8	
multiple dose:	x	6	6	
Patients-				
single dose:	x	2	2	
multiple dose:		4	4	
Dose proportionality -				
fasting / non-fasting single dose:	x	2	2	
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:	x	6	6	
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	7	5	
Population Analyses -				
Data rich:				
Data sparse:				
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		48	33	
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 ?	**No Comments at this time.**	Comments have been sent to firm (or attachment included). FDA letter date if applicable. NONE at this time
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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
2/26/2007 04:25:40 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
2/27/2007 03:12:17 PM
BIOPHARMACEUTICS
I concur.