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RESEARCH**

APPLICATION NUMBER:

21-433

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-433
Generic name:	Fluticasone propionate
Brand Name:	Flovent [®] HFA
Dosage Strengths	44 mcg, 110 mcg, 220 mcg
Dosage Form:	Oral Inhalation Aerosol
Inhalation Device:	Hydrofluoroalkane (HFA) Metered-dose Inhaler (MDI)
Indication:	Maintenance treatment of asthma
Dosage and Administration: (Age 12 and older)	Starting doses based on prior asthma therapy Bronchodilators alone: 88 mcg twice daily Inhaled corticosteroids: 88- 220 mcg twice daily Oral corticosteroids - mcg twice daily
Applicant:	Glaxo Smith Kline
OND Clinical Division:	DPADP (HFD-570)
OCPB Division	DPEII (HFD-870)
Submission Type:	3S
Submission Date:	2/26/02
Review Date:	10/21/02
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Emmanuel O. Fadiran, Ph.D.

Executive Summary

Background: This new drug application is to provide information to demonstrate the safety and effectiveness of Flovent[®] HFA Inhalation Aerosol (Flovent[®] HFA) at three dosage strengths of 44 mcg, 110 mcg and 220 mcg. The active ingredient in Flovent is fluticasone propionate (FP). FP is a potent glucocorticoid used to treat asthma. It has a high therapeutic index with significant topical anti-inflammatory activity and is associated with low systemic (hypothalamic-pituitary-adrenal axis) suppressive activity. Pressurized metered dose inhalers (MDIs) are the most popular forms of portable treatment for respiratory disease. Chlorofluorocarbons (CFCs) have been used for many

years as medicinal aerosol propellants in MDIs because they are non-toxic, inert, and non-flammable. However, the environmental threat posed by the emission of CFCs to the atmosphere is now well recognized, necessitating the need for development of new propellants. The sponsor has developed a FP metered-dose inhaler (MDI) containing a nonchlorinated hydrofluoroalkane (HFA) to replace the currently marketed CFC propellants. Three dose strengths of FP CFC inhalation aerosol are available for use in the U.S.: 44 mcg, 110 mcg and 220 mcg.

The objectives of the clinical pharmacology program conducted to support this application were to 1) describe FP systemic exposure following single doses from different FP strength inhalers using HFA propellant in healthy adult volunteers 2) describe FP systemic exposure at steady state following multiple doses from different FP strength inhalers using HFA propellant in adolescent and adult with asthma 3) evaluate the effect of the HFA propellant on FP systemic exposure in

healthy adult volunteers and 4) evaluate the potential clinical significance of differences in FP systemic exposure between formulations by examining serum cortisol levels and urinary cortisol excretion in adolescent and adult patients with asthma.

The studies submitted demonstrated that in healthy volunteers, there was an increase in FP exposure with an increase in dose from 352 mcg to 1760 mcg. The increase was considered dose proportional for AUC, but not for Cmax. Following administration of FP 1760 mcg using the 220mcg HFA product in healthy volunteers, the exposures were 30% to 35% lower compared to the same dose administered from the approved 220 mcg FP CFC product. After multiple dosing in asthmatic patients, a dose-related increase in systemic exposure was observed when FP doses of 88, 220 and 440 mcg are administered via HFA propellant. However, the increase in systemic exposure was not proportional to dose. The effect of propellant on exposure was not adequately evaluated in the studies provided to support this submission. Cortisol levels decreased in all treatments compared to placebo. However, these decreases in cortisol were not dose-related. Generally, changes in urine cortisol were not statistically significant.

General Comments: There was not sufficient data in the application to completely assess the relative effect of changes in exposure of FP after administration with MDI via either HFA or CFC propellants on serum/urine cortisol levels in asthmatic patients. However, since there is clinical safety and efficacy data, this information may not be needed but may have been useful in understanding differences in safety in the two Flovent formulations. It is recommended that the sponsor evaluate the differences in exposure and cortisol levels in appropriate asthmatic patients after administration of Flovent CFC versus Flovent HFA if future studies are planned.

Recommendation: Based on the data submitted to the Human Pharmacokinetics and Bioavailability section of NDA 21-443 to fulfill section 320 and 201.5 of 21 CFR, the information on FP human pharmacokinetics support the approval of Flovent HFA from a clinical pharmacology and biopharmaceutics perspective.

Kofi A. Kumi, Ph.D.
Reviewer
Clinical Pharmacology and Biopharm.
OCPB

Concurrence

Emmanuel Fadiran, Ph.D.
Team Leader
Clinical Pharmacology and Biopharm.
HFD-570 Section
DPEII/OCPB

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Summary of Clinical Pharmacology and Biopharmaceutics Findings

Human pharmacokinetic and pharmacodynamic analyses to support this application were obtained from three new clinical studies (FAP 10001, FAP 30007 and FLTA3022) plus a report from a previous study (FLTB 1020) in healthy volunteers and asthmatic patients. Fluticasone propionate (FP) aerosol for oral inhalation was originally approved under NDA 20-548, 20-549. The approved product uses chlorofluorocarbon (CFC) propellants. A cross reference is made in this application to the pharmacokinetic studies submitted to NDA 20-548 and 20-549. All pharmacokinetic studies and reports submitted to this application were reviewed. The pharmacokinetic results of one study (FLTA 3022) at best was viewed as supportive information because of the design of the PK substudy (only a single trough concentration measured), the limited number of patients who participated in the pharmacokinetic studies and the significant number of patients with values below limit of quantitation (BLQ).

Dose proportionality was evaluated in a single dose study in healthy volunteers and in a multiple dose study in asthmatic patients using HFA propellants. In the pivotal single dose study, AUC_{last}, AUC_∞ and C_{max} increased following increasing single doses of 352, 880, and 1760 mcg in healthy volunteers administered from a 44, 110 and 220 mcg inhalers, respectively, containing HFA propellant. The increase was considered dose proportional for AUC, but not for C_{max}. Dose proportionality was also observed both in AUC and C_{max} in a supportive study using 8 inhalations FP strengths of 50, 125 and 250 mcg (doses of 400, 1000 and 2000 mcg), administered via HFA propellant marketed outside the United States. After multiple dosing in asthmatic patients, a dose-related increase in systemic exposure was observed when FP doses of 88, 220 and 440 mcg are administered via HFA propellant (Table 1). However, the increase in systemic exposure was not proportional to dose.

Table 1: Summary FP AUC_{last}, C_{max} and t_{max} in Asthmatic Patients after 4-week multiple dose administration.

FP Parameters	FP 88mcg HFA BID N=20	FP 220mcg HFA BID N=15	FP 440mcg HFA BID N=17	Ratio ^a 220:88	Ratio ^a 440:220
AUC _{last} (pg*h/mL)					
Geometric Mean	76.2	297.5	600.9		
95% CI	(33.2, 174.7)	(191.0, 463.6)	(430.7, 838.2)		
Geo LS Mean Ratio				1.56	1.01
90% CI				(0.77, 3.18)	(0.48,2.11)
C _{max} (pg/mL)					
Geometric Mean	25.2	60.8	103.1		
95% CI	(17.6, 36.1)	(45.8, 80.6)	(73.2, 145.1)		
Geo LS Mean Ratio				0.97	0.85
90% CI				(0.66, 1.42)	(0.57,1.26)
T _{max} (h)					
Median	1.03	1.00	1.00		
Range ^c	(0.50, 10.0)	(0.50, 7.6)	(0.00, 2.1)		
Mean Difference				-0.44	-0.51
90% CI				(-1.52, 0.64)	(-1.62,0.6)

^adata dose normalized and log transformed prior to statistical analysis except t_{max}

The effect of propellant on systemic exposure of FP was evaluated in healthy patients. Following administration of FP 1760mcg using the 220mcg HFA product, the geometric mean for AUC_{last} and C_{max} were 30% and 35%; respectively, lower compared to the same dose administered from the approved 220mcg CFC product.

Treatment	FP 220 mcg HFA	Ratio HFA/CFC	FP 220 mcg CFC
Total Dose	(1760 mcg)		(1760 mcg)
AUC _{last} (pg*h/mL)			
Geo. Mean	2495		3606
95% CI	(1945, 3200)		(2626, 4953)
Mean Ratio		0.696	
90% CI		(0.588, 0.823)	
AUC _∞ (pg*h/mL)			
Geo. Mean	2760		4442
95% CI	(2156, 3533)		(3552, 5556)
Mean Ratio		0.648	
90% CI		(0.571, 0.736)	
C _{max} (pg/mL)			
Geo. Mean	420.5		657.1
95% CI	(337.7, 523.6)		(498.3, 866.3)
Mean Ratio		0.646	
90% CI		(0.553, 0.755)	

The effect of FP on HPA axis was evaluated by examining the effect of FP on cortisol levels after administration of different doses of FP via HFA and CFC propellants in both healthy and asthmatic patients.

In healthy volunteers, significant dose-related decreases in serum cortisol (both AUC₂₄ and C_{min}) were observed following all HFA and CFC treatments compared to placebo. The decrease in serum cortisol was significantly greater with CFC compared to HFA propellant when tested using the 220 mcg strength at a dose of 1760 mcg. Significant decreases in urinary cortisol excretion were observed after the 880 and 1760 mcg doses but not with 352 mcg compared to placebo. Statistically significant decrease in urinary 6-beta-hydroxycortisol excretion was observed only at the 1760 mcg dose when the doses of FP administered were compared to placebo. When the effect of propellant was evaluated, statistically significant differences in urinary cortisol and in 6-beta-hydroxycortisol excretion were not observed when the 220 mcg HFA and CFC FP strength at a dose of 1760 mcg were compared.

The following table provides the effect of FP administered via HFA propellant on serum cortisol in asthmatic patients

Table 3: Key Pharmacodynamic Results for Serum Cortisol at Week 4

Serum Cortisol	Placebo HFA	FP 88 mcg HFA	FP 220 mcg	FP 440 mcg
Parameters	BID	BID	HFA BID	HFA BID
	N=13	N=20	N=15	N=17
AUC12 (ng*h/mL)				
Geometric Mean	903.09	955.74 ^b	670.44 ^a	779.93
Geometric LS Mean	934.42	886.50	687.84	811.60
Active/Placebo		0.95	0.74	0.87
95% CI		(0.74, 1.22)	(0.57, 0.96)	(0.67, 1.12)
Cmin (ng/mL)				
Geometric Mean	34.76	37.25	30.50	30.01
Geometric LS Mean	36.36	33.73	31.54	31.63
Active/Placebo		0.93	0.87	0.87
95% CI		(0.56, 1.54)	(0.51, 1.48)	(0.52, 1.46)

a Significantly different from placebo

b Significantly different from 220 mcg dose

Cortisol AUC12 and Cmin decreased in all treatments compared to placebo. However, these decreases in cortisol were not dose-related. Changes in serum cortisol and urine cortisol were not dose-related and generally not significant. Only serum cortisol AUC12 after the 220 mcg treatment was significantly different from placebo. There were no significant changes in the corresponding cortisol Cmin or urine cortisol excretion measurements at this dose.

No relationship was observed between FP systemic exposure and gender, pulmonary function and weight. There was a weak but significant relationship between FP systemic exposure and subject's age as illustrated in figure 1. However, no correlation was observed between serum cortisol and age. Therefore, the increase in exposure may not be clinically significant.

Fig. 1

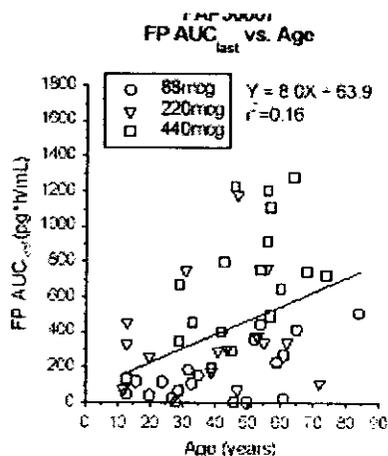
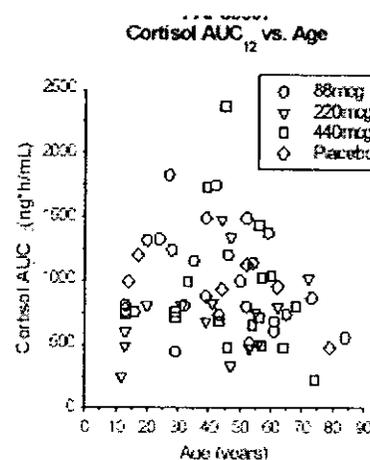


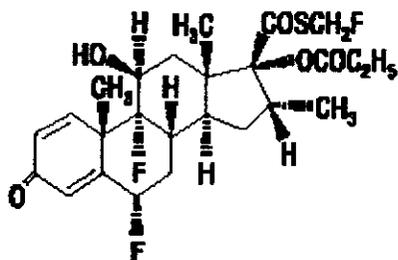
Fig 2



What are the general attributes of the approved Fluticasone Propionate (FP) CFC MDI?

FP is a long-acting, potent, synthetic trifluorinated glucocorticoid with topical anti-inflammatory activity. FP is a white to off-white powder with a molecular weight of 500.6. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide and slightly soluble in methanol and 95% ethanol. The following is the structure for FP

Fig 3



Inhaled FP is a potent corticosteroid that has negligible oral bioavailability due to incomplete absorption from the GI track. The absolute bioavailability of FP as a percentage of nominal dose after inhalation was 28.6% (90%CI 24.1 – 33.8%). Urinary cortisol excretion decreased on the average by 44% following 880 mcg inhaled FP and by 39% following 250 mcg intravenous FP. Flovent 44 mcg, 110 mcg, 220 mcg inhalation aerosol are pressurized, metered-dose aerosol units intended for oral inhalation. Each unit contains a microcrystalline suspension of FP (micronized) in a mixture of two chlorofluorocarbon propellants 11 and 12 (trichlorofluoromethane and dichlorodifluoromethane) with lecithin. The chlorofluorocarbon (CFC) formulation of FP, Flovent Inhalation Aerosol was approved in 1996. Three dose strengths of FP CFC were approved for use in U.S.: 44 mcg, 110 mcg and 220 mcg ex-actuator dose equivalent to 50 mcg, 125 mcg and 250 mcg ex-valve dose. The FP HFA formulation will also be available in similar strengths.

Is the FP concentration after administration via MDI HFA proportional to dose?

Dose proportionality of FP after administration with HFA propellant was evaluated in 2 pivotal studies in healthy volunteers and asthmatic patients and 1 supportive study conducted outside the U.S. in healthy volunteers. Dose proportionality was evaluated using power model analysis ®.

There is a proportional increase in plasma concentration when the dose of FP administered via HFA propellant to healthy volunteers is increased from 352 to 1760 mcg. However, in asthmatic patients administered doses between 88 and 440 mcg, via MDI with HFA propellant, the increase in concentration was not proportional to dose.

In healthy volunteers, AUC_{last}, AUC_∞ and C_{max} increased following increasing doses of 352, 880 and 1760mcg from the 44, 110 and 220mcg inhalers, respectively, containing HFA propellant. The increase was considered dose proportional for AUC, but not for C_{max}. Following administration of FP 1760mcg using the 220mcg HFA product, the geometric mean for AUC_{last} was 70% compared to the same dose administered from the 220mcg CFC product. The following tables contain the calculated pharmacokinetic parameter and the results of the power model analysis. A confidence interval of the slope that is within the range 0.78 - 1.22, indicates dose proportionality over the range tested. The adjusted mean slope (and 90% confidence interval) of the log transformed AUC_{last} was 1.02 (0.91, 1.13) and that of AUC was 0.95 (0.84, 1.06). The

corresponding results of the Cmax analysis were 0.75 (0.65, 0.85). Thus, the results indicated that there was dose proportional increase in AUClast and AUC across HFA strengths. A dose-related increase in Cmax was observed, but was not considered dose proportional. The increase in Cmax with increasing dose was smaller than the change in dose.

Table 4: Key PK Results for each Parameter by Treatment				
Treatment Total	8 X 44mcg HFA	8 X 110mcg HFA	8 X 220mcg HFA	8 X 220mcg CFC
Dose	(352mcg)	(880mcg)	(1760mcg)	(1760mcg)
AUClast (pg*h/mL)				
Geo. Mean	487.5	1283.7	2495	3606
95% C.I.	(361.9, 656.7)	(904.4, 1822.)	(1945, 3200)	(2626, 4953)
AUC ∞ (pg*h/mL)				
Geo. Mean	628.7	1595	2760	4442
95% C.I.	(480.7, 822.2)	(1254, 2029)	(2156, 3533)	(3552, 5556)
Cmax (pg/mL)				
Geo. Mean	126.3	254.1	420.5	657.1
95% C.I.	(108.0, 147.7)	(202.4, 318.9)	(337.7, 523.6)	(498.3, 866.3)
tmax (h)				
Median	1.00	1.02	1.00	0.67
Range	(0.17, 4.00)	(0.33, 2.00)	(0.33, 2.05)	(0.17, 2.02)
t1/2 (h)				
Geo. Mean	3.79	5.10	6.63	6.47
95% C.I.	(3.07, 4.68)	(4.57, 5.69)	(5.92, 7.42)	(5.89, 7.12)

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Results of FP PK Parameter Dose Proportionality using Power Model					
Parameters	Intercept	Slope	Standard Error	DF	90% CI
AUCinf (hr*pg/mL)	0.834	0.951	0.064	40	(0.843, 1.060)
AUClast (hr*pg/mL)	0.202	1.022	0.067	43	(0.909, 1.134)
Cmax (pg/mL)	0.455	0.748	0.061	43	(0.646, 0.851)

Table 5 (above)

Table 6 contains the calculated pharmacokinetic parameters obtained when FP was administered via HFA propellant in asthmatic patients.

Table 6

FP Parameters	FP 88mcg HFA BID N=20	FP 220mcg HFA BID N=15	FP 440mcg HFA BID N=17	Ratio ^a 220:88	Ratio ^a 440:220	Ratio ^a 440:88
AUClast (pg*h/mL)						
Mean ± SD	176.8 ± 166.9	391.17 ± 300.45	707.2 ± 359.24			
Geometric Mean	76.2	297.5	600.9			
95% CI	(33.2, 174.7)	(191.0, 463.6)	(430.7, 838.2)			
Geo LS Mean Ratio				1.56	1.01	1.58
90% CI				(0.77, 3.18)	(0.48, 2.11)	(0.79, 3.13)
Cmax (pg/mL)						
Mean ± SD	32.8 ± 24.4	68.7 ± 38.0	125.0 ± 78.4			
Geometric Mean	25.2	60.8	103.1			
95% CI	(17.6, 36.1)	(45.8, 80.6)	(73.2, 145.1)			
Geo LS Mean Ratio				0.97	0.85	0.82
90% CI				(0.66, 1.42)	(0.57, 1.26)	(0.57, 1.19)
tmax (h)						
Mean ± SD	2.07 ± 2.53	1.63 ± 1.75	1.11 ± 0.74			
Median	1.03	1.00	1.00			
Range	(0.50, 10.0)	(0.50, 7.6)	(0.00, 2.1)			
Mean Difference				-0.44	-0.51	-0.96
90% CI				(-1.52, 0.64)	(-1.62, 0.60)	(-1.99, 0.09)

^aData dose normalized and log transformed prior to statistical analysis except for tmax

Ratio of geometric mean AUClast between 440 and 220 mcg treatments was 2.02 (dose normalized ratio was 1.01). The ratio between 220 and 88 mcg treatments was 3.9 (dose normalized ratio was 1.56). The ratio of geometric means for Cmax between 440 and 220 mcg treatments was 1.7 (dose normalized ratio was 0.85) and between 220 and 88 mcg treatments was

2.4 (dose normalized ratio was 0.97). None of the pairwise comparisons were statistically significant (90% confidence intervals contained 1.0) likely because of the small number of subjects that were examined.

Power model analysis for these 3 treatments showed that adjusted mean slope (and 90% CI) of the log transformed AUC_{last} was 1.30 (0.88, 1.72) and 0.88 (0.66, 1.11) for C_{max}. A confidence interval (CI) of the slope that is within the range 0.78 - 1.22, would indicate dose proportionality over the range tested. Ninety percent CI for slopes for both parameters were wider compared to the acceptance range indicating that increase in AUC_{last} and C_{max} across HFA strengths was dose-related, but could not be considered dose-proportional. Dose normalized pairwise comparison support the results from the power model analysis.

Dose proportionality was demonstrated in healthy volunteers but not in asthmatic patients. However, the range of doses studied were different with higher doses studied in healthy subjects and lower doses in asthmatic patients. The doses in asthmatic patients represent the therapeutic doses recommended. Hence, dose proportionality was not demonstrated between 88 and 440 mcg of FP when administered with HFA propellant.

Is the Exposure of FP different after administration of FP via MDI HFA versus CFC Inhalers?

Following administration of FP 1760 using the 220 mcg HFA product to healthy volunteers, the exposure to FP was higher after administration with MDI with CFC propellant compared to HFA propellant. Geometric mean for AUC_∞ after administration with HFA propellant was about 65% of the AUC_∞ of the same dose administered from the 220 mcg CFC product. A comparison of exposure after administration of FP via MDI with CFC or HFA in asthmatic patients was not adequately evaluated. Table 7 provides a comparison of exposures after administration of FP via MDI either with CFC or HFA to healthy volunteers

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Table 7: Key Results for Comparison between HFA and CFC Formulations			
Treatment	FP 220mcg HFA	Ratio HFA/CFC	FP 220mcg CFC
Total Dose	(1760mcg)		(1760mcg)
AUC _{last} (pg*h/mL)			
Geo. Mean	2495		3606
95% CI	(1945, 3200)		(2626, 4953)
Mean Ratio		0.696	
90% CI		(0.588, 0.823)	
AUC _∞ (pg*h/mL)			
Geo. Mean	2760		4442
95% CI	(2156, 3533)		(3552, 5556)
Mean Ratio		0.648	
90% CI		(0.571, 0.736)	
C _{max} (pg/mL)			
Geo. Mean	420.5		657.1
95% CI	(337.7, 523.6)		(498.3, 866.3)
Mean Ratio		0.646	
90% CI		(0.553, 0.755)	

Is the Effect of FP on cortisol levels different after administration via MDI with CFC propellant compared to MDI with HFA propellant?

The effect of FP on serum and urinary cortisol levels was compared after FP administration via MDI with either CFC or HFA in healthy volunteers. In asthmatic patients, the effect of FP on cortisol levels after FP administration via MDI with HFA propellant was compared to Placebo.

Significant decreases in serum cortisol (both AUC₂₄ and C_{min}) were observed following all HFA and CFC treatments compared to placebo in healthy volunteers and asthmatic patients. In healthy volunteers, the decrease in serum cortisol was significantly greater with CFC compared to HFA propellant when tested using the 220 mcg strength at a dose of 1760 mcg (Fig. 8, Table 8). Significant decreases in urinary cortisol excretion were observed at doses of 880 and 1760mcg but not with 352 mcg when compared to placebo in healthy volunteers. A comparison of the effect of the propellant used with MDI to deliver FP in asthmatic patients was not adequately evaluated.

The potential effect of FP on hypothalamic-pituitary-adrenal (HPA) axis in adolescents and adults with asthma provide physicians with information on the safety of FP. The effects in adolescents and adults on the HPA axis at doses less than 1000 mcg daily are reported to clinically not be significant when delivered either in a dry powder formulation or with the CFC propellant. The effect of FP when delivered via MDI with HFA propellant on the HPA axis was evaluated by measuring cortisol levels. Figure 4 and table 8 represent data obtained in the pivotal study in healthy volunteers

Linear Median Serum Cortisol Concentration—time

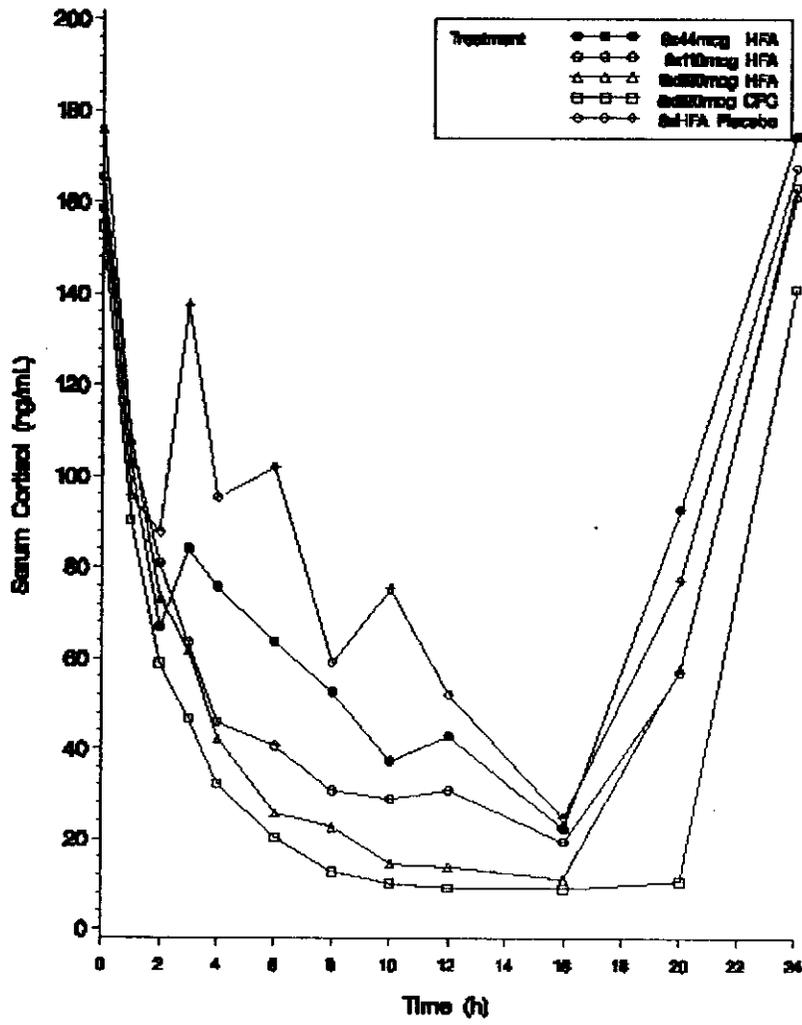


Fig. 4

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Table 8: Serum Cortisol Results in Healthy Volunteers					
		8x44mcg	8x110mcg	8x220mcg	8x220mcg
Treatment		HFA	HFA	HFA	CFC
Total Dose	Placebo	(352mcg)	(880mcg)	(1760mcg)	(1760mcg)
AUC24 (ng*h/mL)	2090	1815 ^{ab}	1504 ^a	1270 ^{abc}	1068 ^a
Geometric Mean					
% decrease compared to placebo		16	31	42	51
Cmin (ng/mL)					
Geometric Mean	25.79	21.58 ^{ab}	16.78 ^a	13.01 ^{abc}	10.11 ^a
% decrease compared to placebo		22	41	53	63

a Significantly different from placebo
b Significantly different from 880mcg dose
c Significantly different from 220mcg CFC

Statistically significant dose-related decreases in serum cortisol AUC24 and Cmin were observed in all treatments when compared to placebo in healthy volunteers (Table 8). Differences were observed between the HFA and CFC treatments for AUC24 and Cmin and were statistically different (Table 8). No statistically significant differences in urinary cortisol and in 6-beta-hydroxycortisol excretion were observed between the 220 mcg HFA and CFC FP strength at a dose of 1760 mcg.

The following figure (Fig. 5) provides serum cortisol-time profile in asthmatic patients

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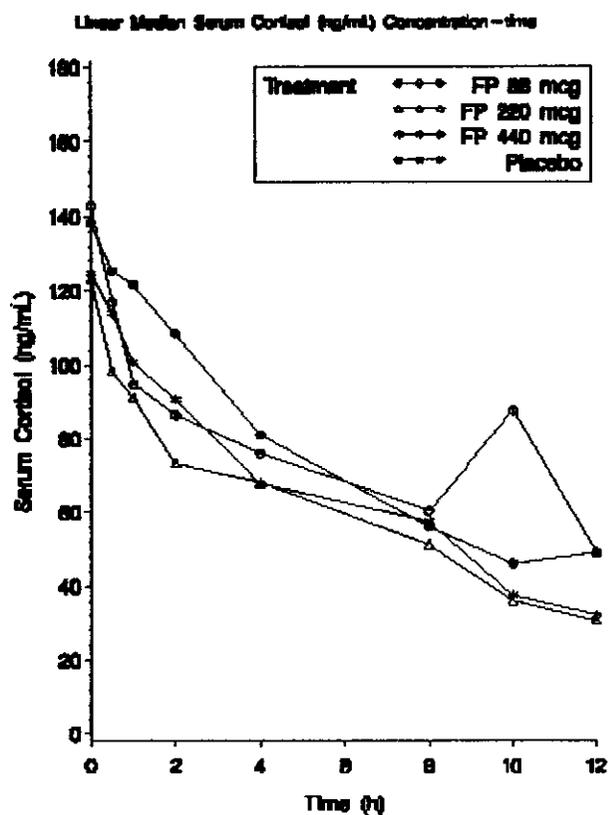


Fig. 5

Table 9: Key Pharmacodynamic Results for Serum Cortisol at Week 4 in Asthmatic Patients

Serum Cortisol Parameters	Placebo HFA N=13	FP 88mcg HFA N=20	FP 220mcg HFA BID N=15	FP 440mcg HFA BID N=17
AUC ₁₂ (ng*h/mL)				
Geometric Mean	903.09	955.74 ^b	670.44 ^a	779.93
Geometric LS Mean	934.42	886.50	687.84	811.60
Active/Placebo		0.95	0.74	0.87
95% CI		(0.74, 1.22)	(0.57, 0.96)	(0.67, 1.12)
C _{min} (ng/mL)				
Geometric Mean	34.76	37.25	30.50	30.01
Geometric LS Mean	36.36	33.73	31.54	31.63
Active/Placebo		0.93	0.87	0.87
95% CI		(0.56, 1.54)	(0.51, 1.48)	(0.52, 1.46)

a Significantly different from placebo

b Significantly different from 220mcg dose

Fig 6

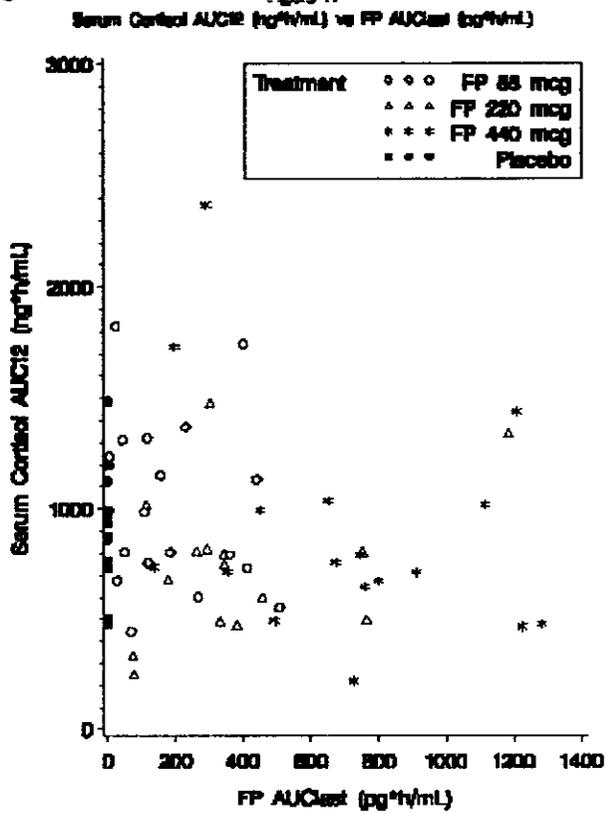
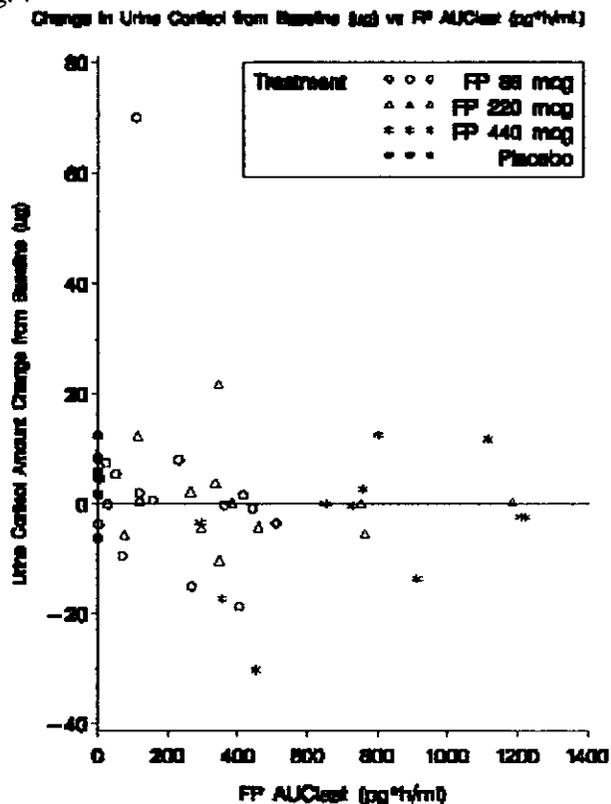


Table 10: Summary of Urine Cortisol Results in Asthmatic Patients

Urine Cortisol Excretion	Placebo	FP 88mcg HFA	FP 220mcg	FP 440mcg
	HFA BID	BID	HFA BID	HFA BID
	N=7	N=17	N=12	N=11
Baseline (mcg/24h)				
Mean	4.76	14.99	12.60	15.66
% CV	94	90	70	92
Median	4.00	11.69	13.75	14.52
Final (mcg/24h)				
Mean	9.90	17.93	13.57	11.88
% CV	50	144	95	123
Median	10.00	9.29	11.63	12.60
Change from Baseline (mcg)				
Mean	5.14	2.94	0.97	-3.77
% CV	116	637	898	331
Median	6.00	0.33	0.19	-2.16

In asthmatic patients, cortisol AUC₁₂ and C_{min} decreased for the higher dose strengths compared to placebo (Fig. 5, Table 9). Among the comparisons with placebo treatment, only the 220 mcg vs. placebo AUC₁₂ comparison was statistically significant with ratio (and 95% CI) of 0.74 (0.57, 0.96) (Table 9). Decrease in urine cortisol was observed for FP 440 mcg HFA BID treatment (Table 10). The re was considerable variability with baseline and final cortisol levels.

Fig. 7



The extent of systemic exposure and the effect on serum cortisol level after administration of FP via MDI with HFA compared to CFC propellant to asthmatic patients was not adequately established in the pharmacokinetic studies conducted to support this application. However, in a study in which single trough concentrations were taken from a limited number of asthmatic patients, there was a suggestion that when considering the potential effect of propellant, there was higher systemic exposure for the CFC formulation compared with the HFA formulation at a dose of 440mcg. This difference was not seen at a dose of 880mcg. . There was high variability in the trough concentrations, limited number of samples obtained during the study and large number of samples with values below limit of quantitation of the assay.

Is there any demographic differences in FP exposure after administration of FP via MDI with HFA propellant?

No relationship between FP systemic exposure and gender, weight and pulmonary function was observed in asthmatic patients. A weak correlation ($r^2 = 0.16$) was observed between FP exposure and age; there was a trend towards an increase in exposure with age. No correlation was observed between serum cortisol and age. Therefore, the clinical significance of the observed correlation between FP exposure and age in asthmatic patients is not clear.

FP AUClast was plotted against several demographic characteristics to examine the effect of baseline characteristics on FP systemic exposure in asthmatic patients. Linear regression of FP AUClast as a function of the demographic parameter at each dose was used to look for trends. The following plots show FP AUC vs. gender, pulmonary function (% of predicted normal FEV1), weight and age. There was no relationship between FP AUC and any of the parameters except age (p value = 0.003). There was no relationship observed between cortisol AUC12 and age for any dose.

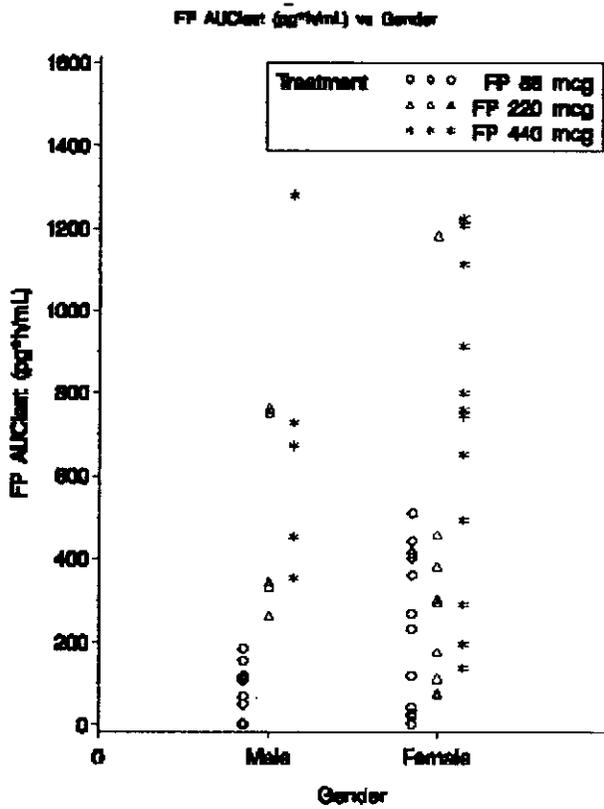


Fig 8

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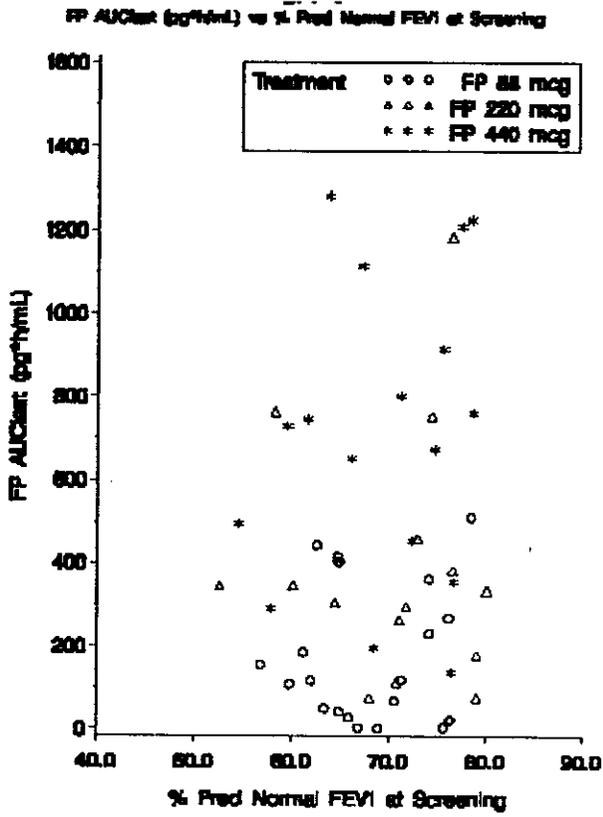
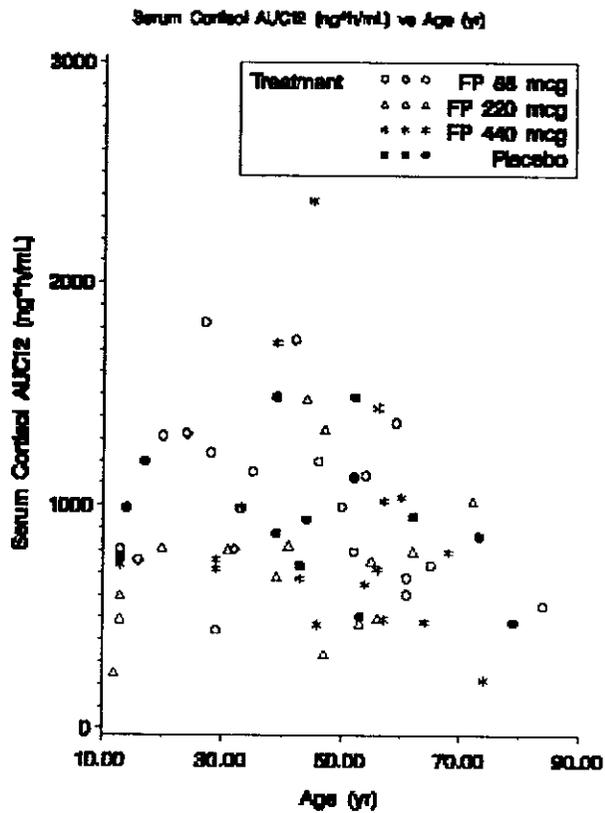


Fig. 10



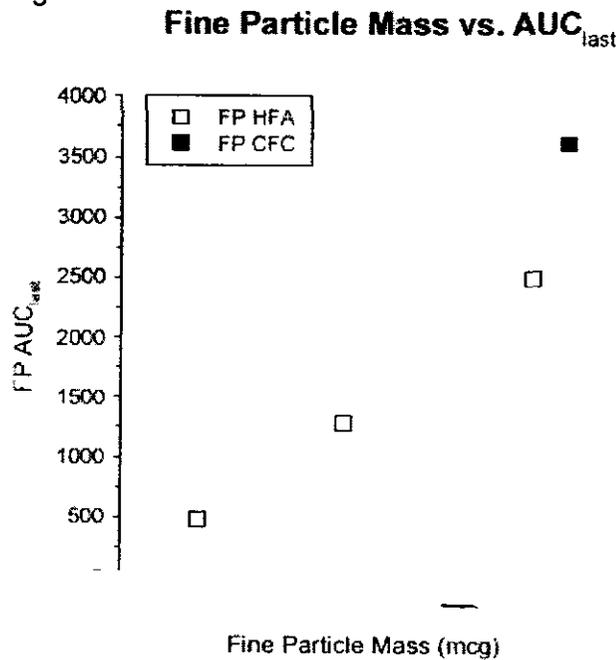
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Does particle size have an effect on systemic exposure after administration of FP via MDI with either HFA or CFC?

Fine particle mass dose correlated with systemic exposure to fluticasone propionate for the HFA inhalers.

The relationship between particle size and systemic exposure was examined in the single dose study in healthy volunteers. Systemic exposure from the 220mcg HFA inhaler was significantly lower compared to the 220mcg CFC inhaler (Fig. 11). Differences in particle size distribution could potentially affect lung deposition and the rate of absorption from the lung. The in vitro delivery characteristics of the batches used in these studies were assessed via Anderson cascade impactor. Fine particle mass (FP) values are plotted versus FP AUC_{last}.

Fig 11



Differences in systemic exposure observed between HFA and CFC inhalers may be partially explained by differences in fine particle mass. Additional factors such as oropharyngeal deposition may also contribute to these differences.

What are the attributes of the analytical methods used to determine FP concentrations?

Fluticasone propionate concentrations were determined using an HPLC method. The calibration range was 0.5 to 100 ng/ml. The limit of quantitation was 0.5 ng/ml. The bias in the assay was 1.5%. The intra-assay CV was 2.5% and interassay CV was 3.5%. The recovery was determined to be 100%. The method was re-validated and the limit of quantitation lowered to 0.1 ng/ml. The re-validated method was linear from 0.1 to 100 ng/ml. For this re-validated method, the bias was 1.5% and the intra-assay CV was 2.5%.

— The revalidated method was used to determine FP concentrations in the pivotal single dose study in healthy volunteers and the pivotal multiple dose study in asthmatic patients. The analytical method was adequate and acceptable.

What is the formulation for Flovent HFA ?

The drug substance, fluticasone propionate (micronised), used in FLOVENT HFA is the same as that used in the approved 50 µg and FLOVENT (fluticasone propionate) Inhalation Aerosol

Table 11: Composition of FLOVENT HFA per Actuation Delivered through the Valve

Component	Theoretical Quantity per Actuation Through the Valve ^{1,2}			Function	Reference to Standard
	44 µg, 120 Actuation	110 µg, 60 & 120 Actuation	220 µg, 120 Actuation		
Active Ingredient:					
Fluticasone Propionate (micronised)	50 µg	125 µg	250 µg	Active	GSK
Other Component:					
GR106642X	--	---		Propellant	GSK

1. The target quantity of fluticasone propionate delivered per actuation delivered through the valve is 50 µg, 125 µg and 250 µg for the 44 µg, 110 µg and 220 µg strength products, respectively.
 2. 60 mg per actuation is the nominal weight of suspension delivered by the metering valve for the 44 µg strength product and 75 mg per actuation is the nominal weight of suspension delivered by the metering valve for the 110 µg and 220 µg strength products.
- GSK=GlaxoSmithKline

Table 12: Composition of FLOVENT HFA per Canister and Suspension Concentration

Component	Theoretical Quantity per Canister ¹ (Suspension Concentration)			Function	Reference to Standard
	44 µg, 120 Actuation ^{2,3}	110 µg, 120 Actuation ^{2,4}	220 µg, 120 Actuation ^{2,5}		
Active Ingredient: Fluticasone Propionate (micronised)	/	/	/	Active	GSK
Other Component: GR106642X	/	/	/	Propellant	GSK

- 3.
- 4.
- 5.
- 6.



GSK=GlaxoSmithKline

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 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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Appendices

A. Proposed Label

B. Individual Study Reports

C. OCPB Filing Form

Proposed Package Insert (label)

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Individual Study Reports

Title: Pharmacokinetics and pharmacodynamics following increasing fluticasone propionate doses using different strengths in HFA propellant and comparison with the marketed product in CFC propellant (Protocol FAP10001)

Objectives: The primary study objectives were to describe the increase in fluticasone propionate (FP) systemic exposure following increasing doses from different FP strength inhalers using HFA propellant; to evaluate the effect of propellant on FP pharmacokinetics and to evaluate the potential clinical significance of pharmacokinetic differences by examining serum and urinary cortisol excretion.

Subjects: Twenty-four healthy subjects enrolled and completed the study. There were thirteen female and eleven male subjects. The mean \pm SD (range) age and weight were 30.8 ± 7.7 (21-45) years and 23.8 ± 2.25 (27.8 – 19.6) kg, respectively.

Study Design: This was an open-label, randomized, five-way crossover study. The subjects were randomly assigned to receive each of the following treatments as a single dose, separated by a 5-7 day washout period between treatment sequences:

- 8 x 44 mcg FP from HFA-containing inhaler (total ex-actuator dose = 352 mcg)
- 8 x 110 mcg FP from a HFA-containing inhaler (total ex-actuator dose = 880 mcg)
- 8 x 220 mcg FP from a HFA-containing inhaler (total ex-actuator dose = 1760 mcg)
- 8 x 220 mcg FP from a CFC containing inhaler [FLOVENT] (total ex-actuator dose = 1760 mcg)
- 8 x HFA-containing placebo inhaler

The FP dose in each treatment is expressed as total ex-actuator dose. Inhalations were given at 30sec intervals over a 3.5min period. Subjects rinsed their mouths with 50mL of water at the end of inhaler administration. The water was not swallowed.

The FP/GR106642X inhaler and the FP/CFC inhaler were pressurized metered-dose inhalers for oral inhalation. Each inhaler consisted of a white to off-white suspension of FP (micronized) in a liquefied HFA propellant (GlaxoSmithKline Inhalation Grade GR106642X) or CFC propellant, which was contained in an aluminum can sealed with a metering valve. The canisters were presented in a plastic actuator fitted with a dust cap.

Table 1

Study Drug/Dose	Batch Number	Expiration/Review Date
FP 44mcg MDI	AX4462/003	31 May 2002
	(filled as R11165/003)	
FP 110mcg MDI	AX4461/001	28 February 2002
	(filled as R11137/001)	
FP 220mcg MDI	AX4460/001	28 February 2002
	(filled as R11138/001)	
FLOVENT 220mcg MDI	OZP0910	31 January 2002
Placebo HFA MDI	AX4462/001	28 February 2002
	(filled as R11142/001)	

Safety Measurements: Adverse events, vital signs, concurrent medications, and pregnancy testing

Data Analysis:

Pharmacokinetic measurements:

Sixteen serial five-milliliter blood samples were collected into the _____ tubes provided at the following time points: predose, 10, 20, 40 minutes post dose and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours post dose for determination of FP concentrations (80 mL PK blood per treatment period, 400 mL PK blood total for study).

PK plasma was analyzed for FP concentrations at each time point using _____

_____ The method required _____ of plasma and has been validated over the range _____

Pharmacokinetic parameters were derived for each subject from the plasma fluticasone concentration data as well as metabolite concentration data using standard non-compartmental technique.

Pharmacodynamic measurements:

Twelve serial two-and-one-half-milliliter blood samples were collected into the tubes provided at the following time points: predose, and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours from the beginning of dosing for determination of serum cortisol concentrations (30mL pharmacodynamic (PD) blood per treatment period, 150 mL total for PD blood for the study). Serum samples were analyzed for cortisol levels using _____

For the determination of urinary cortisol excretion following administration of all five treatments was collected for 24 hours post-dose. Cortisol levels were determined by _____

Pharmacodynamic measurements were serum cortisol over 24h for AUC24 and Cmin, urine cortisol excretion over 24h

Statistical methods:

The power model analysis of AUClast, AUC, and Cmax was performed. The power model using the equation $y = e^{a * \text{dose}^b}$ was used to examine increases in FP systemic exposure, where y was the quantity (AUClast, AUC or Cmax) before log transformation. A value of b (slope) close to unity would indicate a proportionality of doses. The analyses were performed using SAS PROC MIXED procedure with dose level and period as fixed effect and subject as random effect after log transformation of AUClast, AUC and Cmax.

In addition to the power model, ratio $R = X_B / X_A$, and its 90% confidence interval were also estimated for all adjacent pairs of doses, where X_B and X_A are AUC, AUClast, Cmax, tmax, t1/2, and λ_z from treatment B and A (44mcg, 110mcg or 220mcg HFA).

Comparability of the HFA and CFC data was examined by a pairwise ANOVA comparison using the CFC inhaler as the reference population. To evaluate the effect of propellant on FP pharmacokinetics, the ratio ($R_{\text{prop}} = \text{AUC}(\text{HFA}) / \text{AUC}(\text{CFC})$), and its 90% confidence interval were also estimated, where AUC(HFA) and AUC(CFC) are AUC or AUClast from 220mcg HFA and CFC, respectively. Ratios for Cmax were also calculated.

Absolute values of serum cortisol data were listed by subject, treatment and time. The area under the serum cortisol concentration versus time curve 24 hours after dosing (AUC24) was calculated using the linear trapezoidal area method.

The ANOVA approach was also used for the log transformed data except for tmax to examine increases in FP systemic exposure following dose normalization of the data and was planned to be a secondary analysis unless the power model was shown not to be adequate. ANOVA was used to analyze tmax. Comparability of the HFA and CFC data was performed by similar analysis. The CFC data was utilized as the reference population.

Serum cortisol was analyzed by calculating AUC24 for 24h after each dose using the linear trapezoidal area method. The minimum concentration over 24h, Cmin, was also calculated. Urinary free cortisol concentration was converted to amount excreted in 24h. Analysis of variance (ANOVA), adjusted for the fixed effects of period and treatment group and random effect of subject was performed on log-transformed data. Comparisons of serum and urinary cortisol after each active treatment were made against placebo and between the 352 and 880mcg doses and 1760 and 880mcg doses. An ANOVA comparison between the high strength FP HFA and CFC products was also made.

Serum 6- β -hydroxycortisol, a metabolite of cortisol, was analyzed. Serum 6- β -hydroxycortisol concentrations were below the limit of quantitation (BQL) for most of the subjects, and, therefore, were not analyzed statistically. However, the urine data were analyzed.

RESULTS

Bioanalytical: Concentrations of FP in human serum were determined by — Accuracy and precision were calculated using —

Table 2

Analyte	Sample size (n)	Accuracy (% BIAS)	Precision (% CV)	Calibration Range
Fluticasone Propionate		/		

Concentrations of Cortisol and 6- β -Hydroxycortisol in human serum were determined by — Accuracy and precision were calculated

Table 3

Analyte	Accuracy (% BIAS)	Precision (% CV)	Calibration Range
Cortisol		/	
6- β -Hydroxycortisol			

The analytical methods are acceptable.

Pharmacokinetic: Comparative semi-log plots of individual AUClast, AUC and Cmax are shown in figures 1-3. Median tmax was about 1h for the 3 HFA treatments whereas for 220 mcg CFC treatment it was 40 min.

AUClast (pg^h/mL) Comparative Semi-log Plot between Treatments

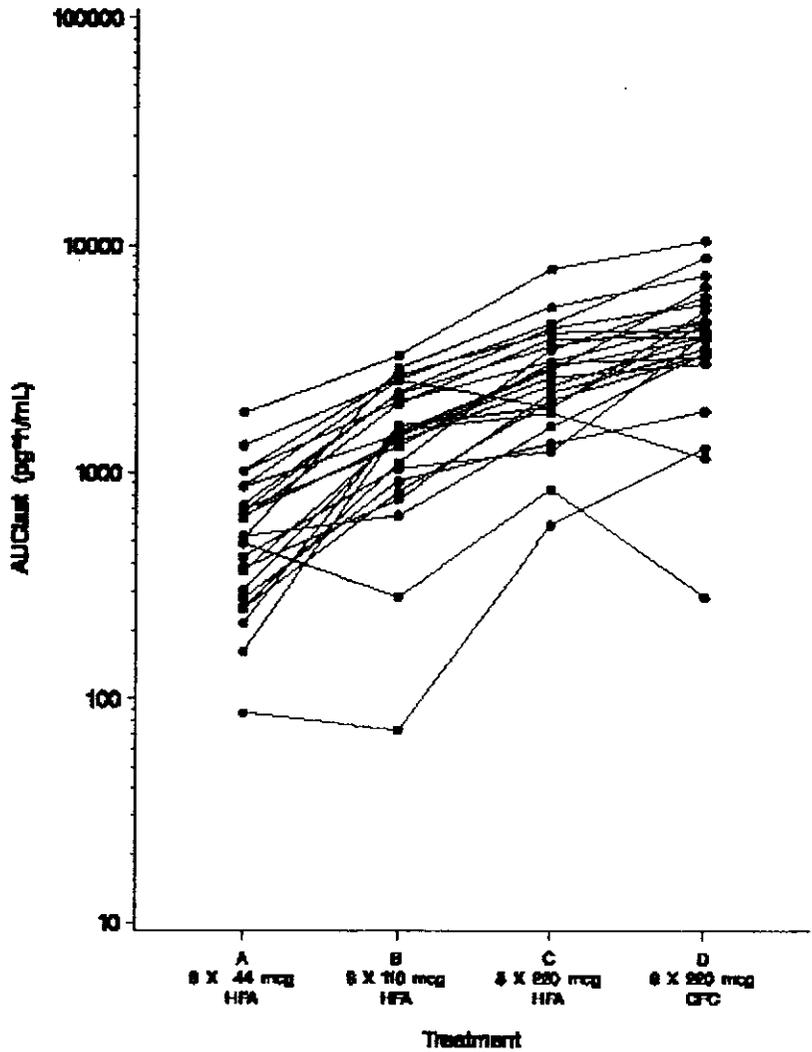


Fig 1

AUCinf (pg*hr/mL) Comparative Semi-log Plot between Treatments

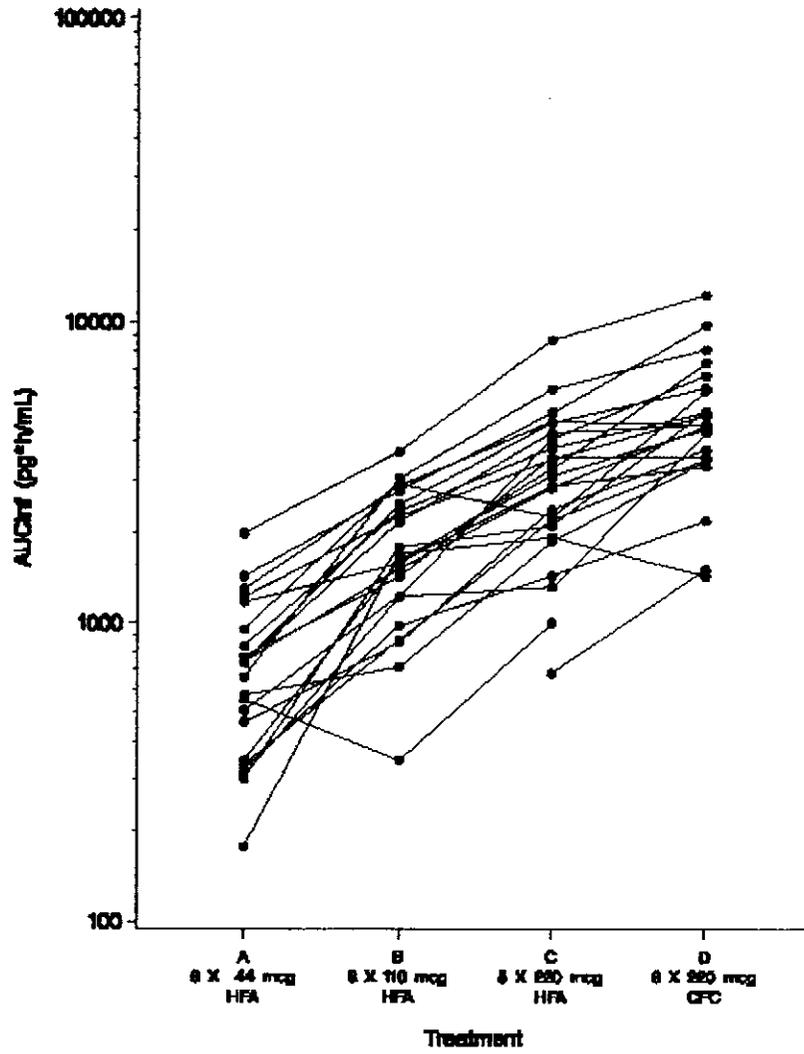


Fig 2

C_{max} (pg/mL) Comparative Semi-log Plot between Treatments

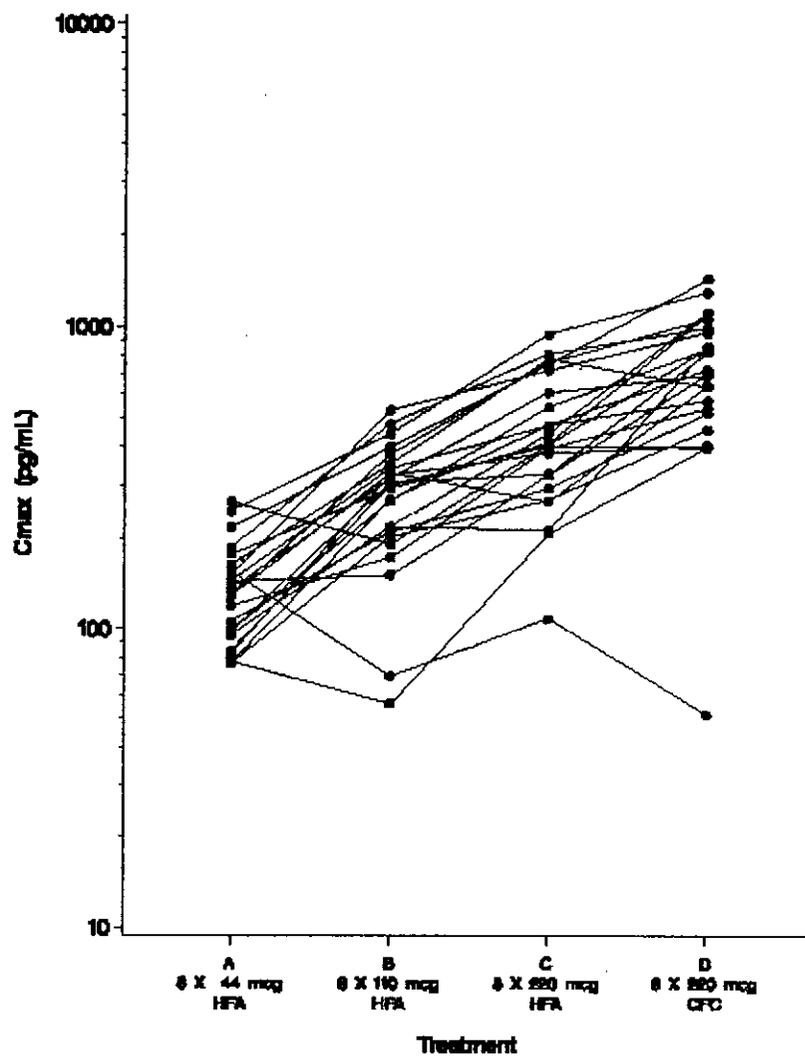


Fig 3

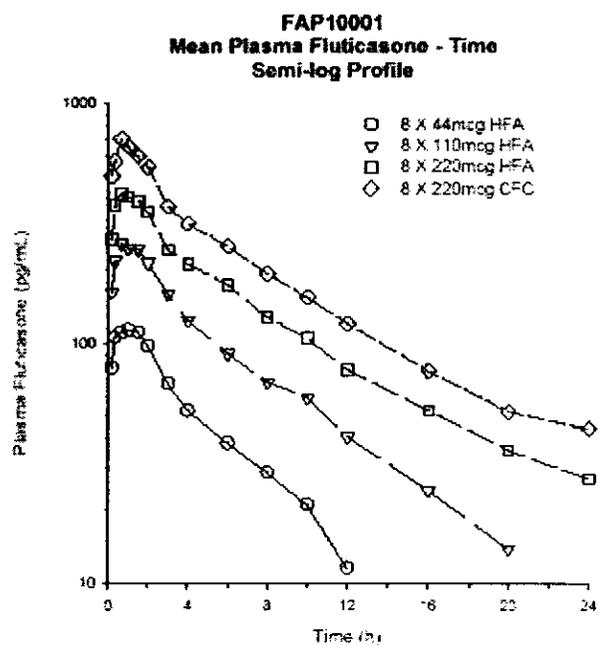


Fig 4

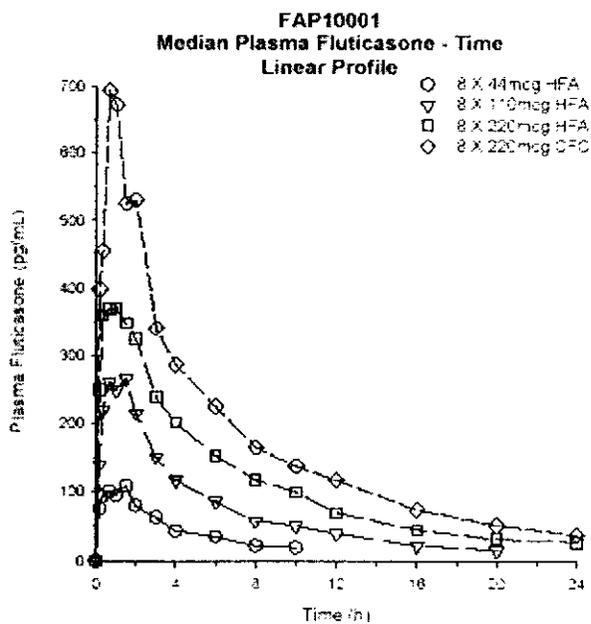


Fig 5

Table 4 provides summary pharmacokinetic parameters after the various treatments.

Table 4

	Key PK Results for each Parameter by Treatment			
Treatment Total	8 X 44mcg HFA	8 X 110mcg HFA	8 X 220mcg HFA	8 X 220mcg CFC
Dose	(352mcg)	(880mcg)	(1760mcg)	(1760mcg)
AUClast (pg*h/mL) Geo. Mean	487.5	1283.7	2495	3606
95% C.I.	(361.9, 656.7)	(904.4, 1822)	(1945, 3200)	(2626, 4953)
AUC ∞ (pg*h/mL) Geo. Mean	628.7	1595	2760	4442
95% C.I.	(480.7, 822.2)	(1254, 2029)	(2156, 3533)	(3552, 5556)
Cmax (pg/mL) Geo. Mean	126.3	254.1	420.5	657.1
95% C.I.	(108.0, 147.7)	(202.4, 318.9)	(337.7, 523.6)	(498.3, 866.3)
Tmax (h) Median	1.00	1.02	1.00	0.67
Range	(0.17, 4.00)	(0.33, 2.00)	(0.33, 2.05)	(0.17, 2.02)
t1/2 (h) Geo. Mean	3.79	5.10	6.63	6.47
95% C.I.	(3.07, 4.68)	(4.57, 5.69)	(5.92, 7.42)	(5.89, 7.12)

AUClast, AUC ∞ and Cmax for the 3 HFA-containing treatments showed increases with increasing dose. Table 5 presents the results of the power model analysis. A confidence interval of the slope that is within the range 0.78 - 1.22, indicates dose proportionality over the range tested. The adjusted mean slope (and 90% confidence interval) of the log transformed AUClast was 1.02 (0.91, 1.13) and that of AUC was 0.95 (0.84, 1.06). The corresponding results of the Cmax analysis were 0.75 (0.65, 0.85). Thus, the results indicated that there was dose proportional increase in AUClast and AUC across HFA strengths. A dose-related increase in Cmax was observed, but was not considered dose proportional. Increase in Cmax with increasing dose was smaller than the change in dose.

Table 5

Results of FP PK Parameter Dose Proportionality using Power Model					
Parameters	Intercept	Slope	Standard Error	DF	90% CI
AUCinf (hr*pg/mL)	0.834	0.951	0.064	40	(0.843, 1.060)
AUClast (hr*pg/mL)	0.202	1.022	0.067	43	(0.909, 1.134)
Cmax (pg/mL)	0.455	0.748	0.061	43	(0.646, 0.851)

Effect of propellant on FP pharmacokinetics was evaluated by estimating ratio (and 90% confidence interval) of HFA/CFC at a dose of 1760mcg (8x220mcg) using the 220mcg HFA product for the primary PK endpoints. The following table provides the comparison of the HFA and CFC Flovent 220 mcg.

Table 6

Key Results for Comparison between HFA and CFC Formulations			
Treatment	FP 220mcg HFA	Ratio HFA/CFC	FP 220mcg CFC
Total Dose	(1760mcg)		(1760mcg)
AUClast (pg*h/mL)			
Geo. Mean	2495		3606
95% CI	(1945, 3200)		(2626, 4953)
Mean Ratio		0.696	
90% CI		(0.588, 0.823)	
AUC∞ (pg*h/mL)			
Geo. Mean	2760		4442
95% CI	(2156, 3533)		(3552, 5556)
Mean Ratio		0.648	
90% CI		(0.571, 0.736)	
Cmax (pg/mL)			
Geo. Mean	420.5		657.1
95% CI	(337.7, 523.6)		(498.3, 866.3)
Mean Ratio		0.646	
90% CI		(0.553, 0.755)	

Geometric mean AUClast for the HFA inhaler was about 70% compared to the CFC inhaler and that of Cmax was about 65% compared to the CFC inhaler. The results indicate that 220mcg HFA product at a dose of 1760mcg was not comparable to the 220mcg CFC product at the same dose.

Pharmacodynamic: The mean cortisol-concentration time profile for all treatments is presented in figure 6. Key results for cortisol PD parameters are presented below:

Table 7: Serum Cortisol Results					
		8x44mcg	8x110mcg	8x220mcg	8x220mcg
Treatment		HFA	HFA	HFA	CFC
Total Dose	Placebo	(352mcg)	(880mcg)	(1760mcg)	(1760mcg)
AUC24 (ng*h/mL)	2090	1815 ^{ab}	1504 ^a	1270 ^{abc}	1068 ^a
Geometric Mean					
% decrease compared to placebo		16	31	42	51
Cmin (ng/mL)					
Geometric Mean	25.79	21.58 ^{ab}	16.78 ^a	13.01 ^{abc}	10.11 ^a
% decrease compared to placebo		22	41	53	63

a Significantly different from placebo
 b Significantly different from 880mcg dose
 c Significantly different from 220mcg CFC

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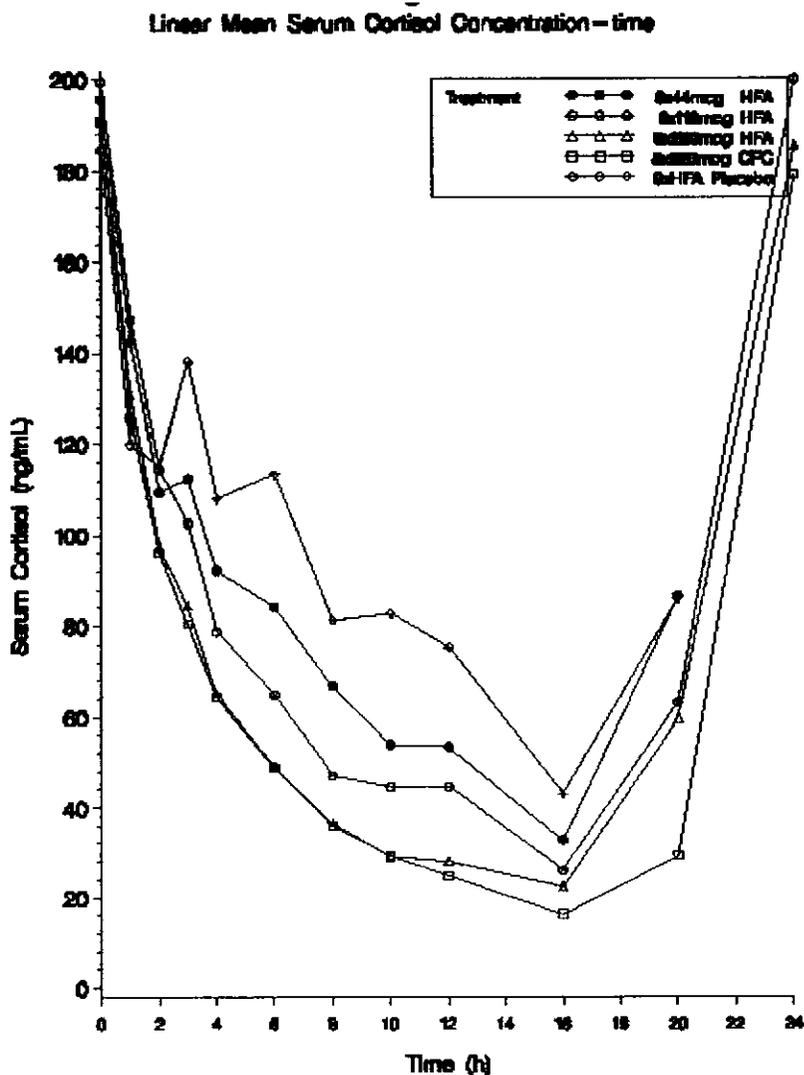


Fig 6

Statistically significant dose-related decreases in cortisol AUC₂₄ and cortisol C_{min} were observed in all treatments compared to placebo. Differences were observed between the 8 x 220mcg HFA and CFC treatments for AUC₂₄ and C_{min} and were statistically different. 6-B-hydroxycortisol levels for most subjects were BQL and were not analyzed.

While cortisol and 6-beta-hydroxycortisol trended lower following the 8 X 220mcg CFC treatment, the differences with 8 X 220mcg HFA were not statistically significant. Geometric LS mean ratios (with associated 95% confidence intervals) for 8 X 220mcg HFA/CFC comparison were 1.32 (0.91, 1.92) for cortisol and 1.21 (0.91, 1.62) for the 6-beta-hydroxycortisol. Figures 7-10 and table 7 contain urinary cortisol and 6-beta-hydroxycortisol information.

Urine Cortisol Amount (ug) Semi-log Comparative for All Treatments

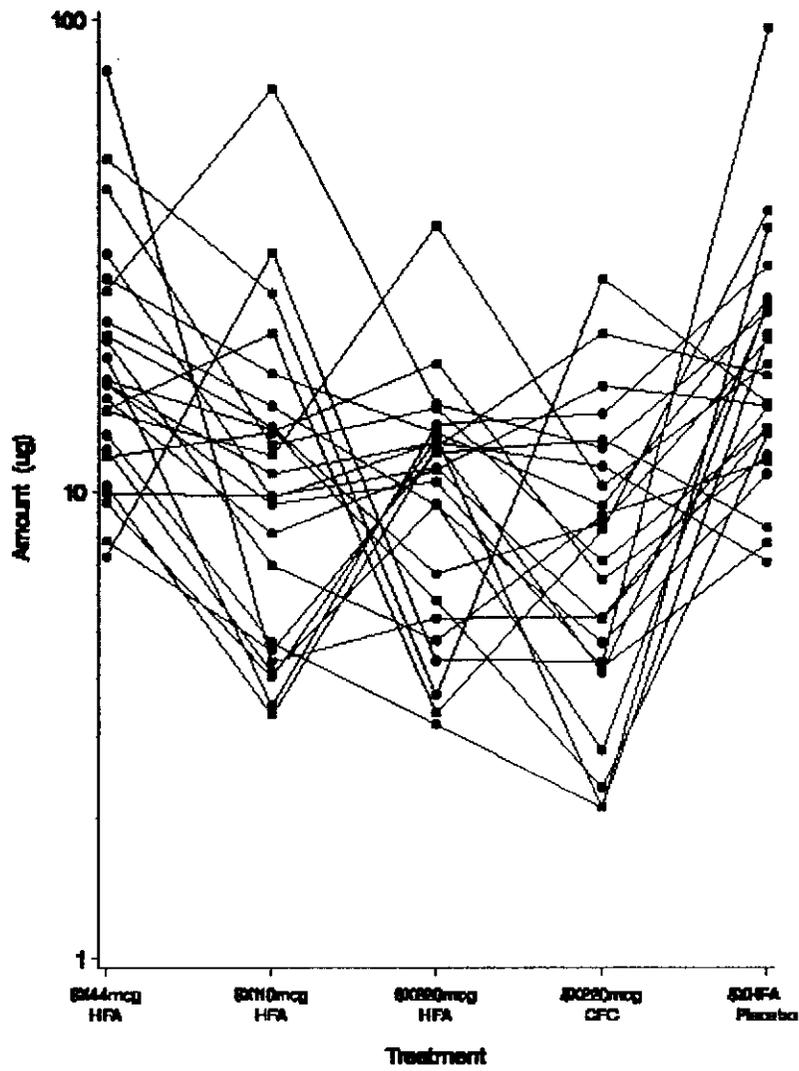


Fig 7

6-B-Hydroxyprogesterone Urine Cortisol Amount (μg) Semi-log Comparative for All Treatments

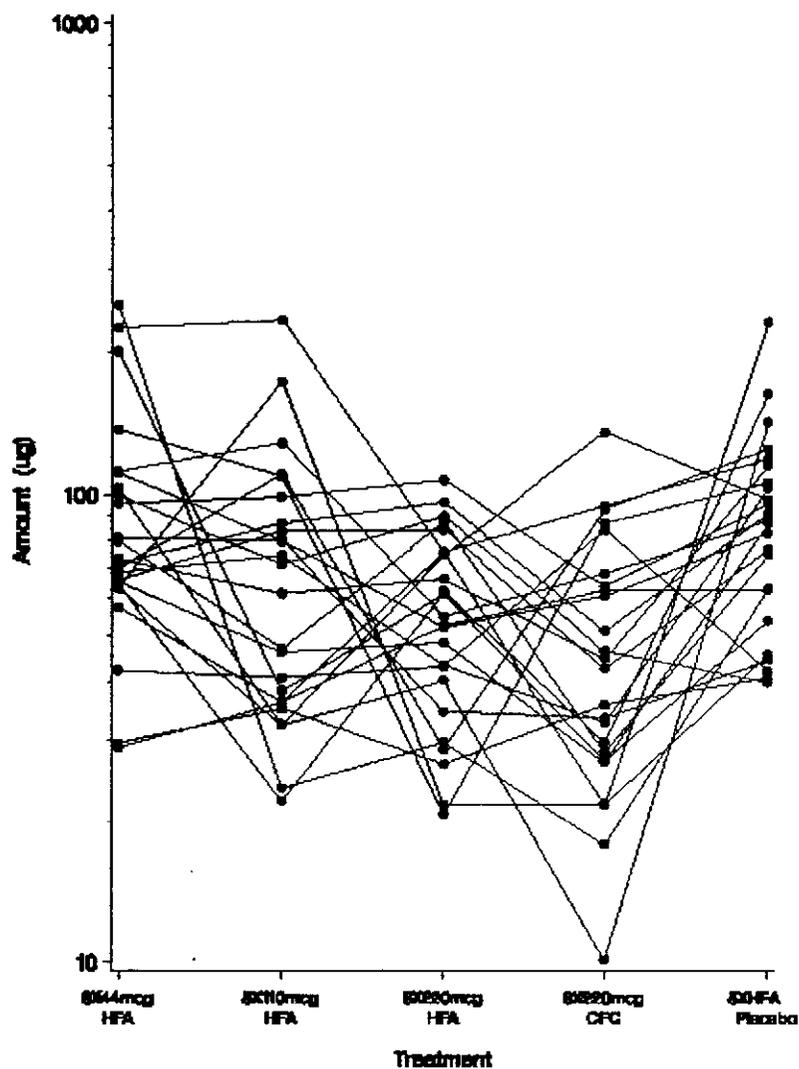


Fig 8

Table 8: Urine Cortisol and 6-β-Hydroxycortisol Results					
Treatment		8x44mcg HFA	8x110mcg HFA	8x220mcg HFA	8x220mcg CFC
Total Dose	Placebo	(352mcg)	(880mcg)	(1760mcg)	(1760mcg)
Cortisol (mcg) Geometric Mean	18.02	18.09 ^b	10.11 ^a	9.32 ^a	7.05 ^a
% decrease compared to placebo		1	44	48	61
6-β-Hydroxy (mcg) Geometric Mean	82.03	81.39	61.24	51.75 ^a	42.66 ^a
% decrease compared to placebo		2	25	37	48

a Significantly different from placebo

b Significantly different from 880mcg dose

Serum cortisol AUC₂₄ decrease with an increase in FP AUC_{last}. The relationship between the decrease in urine cortisol compared to placebo with increase in FP AUC_{last} is the depicted in the figure 10.

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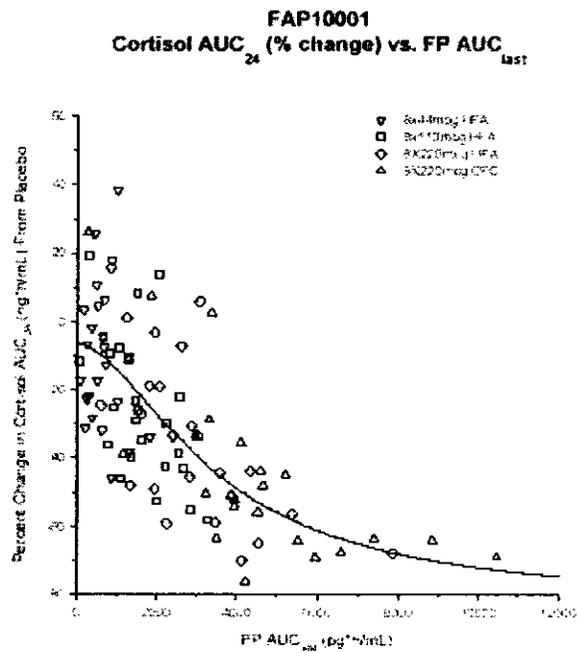


Fig 9

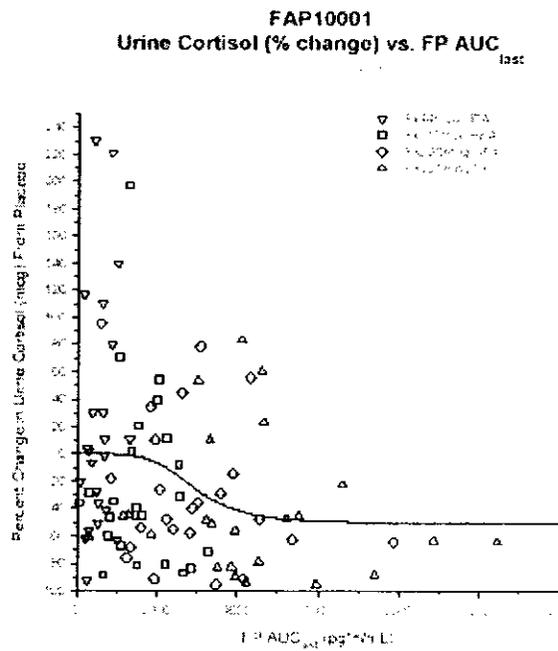


Fig 10

Significant decreases in urinary cortisol excretion were observed with 880 and 1760mcg doses but not with 352mcg HFA compared to placebo. Decreases in urinary 6-beta-hydroxycortisol excretion reached statistical significance compared to placebo only with 1760mcg doses but not with the 880mcg or 352mcg doses. No statistically significant differences in urinary cortisol and in 6-beta-hydroxycortisol excretion were observed between the 220mcg HFA and CFC FP strength.

SAFETY :

The sponsor reported that a total of 33 AEs were reported in 15 subjects throughout the study. None of the AEs were considered as treatment-related in the opinion of the investigator. Most AEs were mild to moderate in intensity. All resolved by the end of the study. The most common adverse event was headache. The sponsor reported that clinical laboratory results were all within normal limits, as determined by the investigator.

CONCLUSIONS:

AUClast, AUC ∞ and Cmax increased following increasing doses of 352, 880, and 1760mcg from the 44, 110 and 220mcg inhalers, respectively, containing HFA propellant. The increase was considered dose proportional for AUC, but not for Cmax. Following administration of FP 1760mcg using the 220mcg HFA product, the geometric mean for AUClast was 70% compared to the same dose administered from the 220mcg CFC product.

Significant dose-related decreases in serum cortisol (both AUC24 and Cmin) were observed following all HFA and CFC treatments compared to placebo. The decrease in serum cortisol was significantly greater with CFC compared to HFA propellant when tested a dose of 1760mcg. Significant decreases in urinary cortisol excretion were observed after the 880 and 1760mcg doses when compared to placebo. No statistically significant differences in urinary cortisol and in 6-beta-hydroxycortisol excretion were observed between HFA and CFC FP at a dose of 1760mcg.

REVIEWER'S COMMENTS:

Pharmacokinetics: Based on the power analysis model and the 90% confidence interval (CI) of 0.78 to 1.22 set a priori for the slope, dose proportionality was demonstrated when AUC was used as the PK parameter for the three FP HFA doses tested. When Cmax was used, dose proportionality was not demonstrated. Evaluation of dose-normalized AUCs support dose proportionality but there is less than proportional increase in Cmax when the HFA FP doses are increased from 352 to 1760 mcg. This may not be clinically significant since Cmax is usually associated with safety. There was large variability in the PK data and dose proportionality was not demonstrated in all the patients. Concentrations after administration of 1760 mcg FP with CFC propellant were usually higher than that measured after a similar dose via HFA propellant.

Pharmacodynamic: Reviewer agrees with sponsor conclusions. Serum cortisol levels were decreased to a greater extent after administration of 1760 mcg FP with CFC compared to HFA. However, no statistically significant differences in urinary cortisol and 6-beta-hydroxycortisol excretion were observed between the HFA and CFC FP strength at a dose of 1760mcg.

Title (FAP 30007): Pharmacokinetic Report: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial of Inhaled Fluticasone Propionate 88mcg BID, 220mcg BID and 440mcg BID versus Placebo in Propellant GR106642X in Adolescent and Adult Subjects with Asthma who are Maintained on Inhaled Corticosteroid Therapy.

Objective: The primary clinical pharmacology objective of the study was to describe the steady-state fluticasone propionate (FP) pharmacokinetics (PK) and pharmacodynamics (PD) in adolescent and adult subjects with asthma who were maintained on inhaled corticosteroid (ICS) therapy following FP 88mcg, 220mcg, and 440mcg HFA BID and relate FP systemic exposure to serum cortisol.

Study Design: This multi-center, randomized, double-blind, parallel-group, placebo-controlled trial was designed to assess the efficacy and safety of 12 weeks of treatment with FP 88 mcg, 220 mcg and 440 mcg HFA BID versus Placebo HFA via the MDI in adolescent and adult subjects (12 years of age or older) with asthma who were maintained on inhaled corticosteroid (ICS) therapy. All subjects demonstrated a morning pre-bronchodilator FEV₁ of 45-80% of predicted and >12% reversibility.

After 4 weeks of dosing, selected investigative sites assessed the PK and PD of double-blind study medication. Sixty-six subjects (14 placebo; 20 FP88 mcg HFA BID; 15 FP 220 mcg HFA BID; 17 FP 440 mcg HFA BID) participated in the PK/PD portion of the study. Subjects were randomly assigned at Treatment Day 0 to one of four double-blind study medications twice daily for the 12-week treatment period:

1. 2 x FP 44 mcg/actuation in propellant GR106642X (FP 88mcg HFA BID)
2. 2 x FP 110 mcg/actuation in propellant GR106642X (FP 220mcg HFA BID)
3. 2 x FP 220 mcg/actuation in propellant GR106642X (FP 440mcg HFA BID)
4. 2 x Placebo in propellant GR106642X (Placebo HFA BID)

Subjects were instructed to inhale two actuations (puffs) from the MDI inhaler each morning and evening, approximately 12 hours apart. Serial plasma FP and serum cortisol concentrations were obtained from a subset of subjects to compare systemic absorption of FP in subjects with inhaled corticosteroid-dependent asthma. Samples were collected immediately prior to dosing and at 0.5, 1, 2, 4, 8, 10 and 12 hours post-dose. Serial serum cortisol concentrations were also obtained for correlation with FP plasma concentrations. Samples were collected immediately prior to dosing and at 0.5, 1, 2, 4, 8, 10 and 12 hours post-dose. Twenty-four hour urine samples for cortisol excretion were collected beginning on the day prior to Visits 2 and 9. Collection of 24-hour urine sample for measurement of urinary cortisol and creatinine excretion was completed the day before the Randomization and Week 12 visits. If a 24-hour urine cortisol measurement was abnormal at Week 12, the investigator repeated the test as medically indicated.

Test product, dose and mode of administration, batch no.: FP in propellant GR 106642X (HFA), 44mcg/actuation (ex-actuator) via inhalation, 2 puffs twice daily, batch numbers AX4462/001, AX4462/003; FP 110mcg/actuation (ex-actuator) via inhalation, 2 puffs twice daily, batch number AX4461/001; FP in propellant GR106642X (HFA), 220mcg/actuation (ex-actuator) via inhalation, 2 puffs twice daily, batch number AX4460/001.

Reference therapy, dose and mode of administration, batch no.: Placebo in propellant GR106642X (HFA), 2 puffs twice daily, batch number AX4463/001.

Analytical Methods: Pharmacokinetic plasma was analyzed for FP concentrations at each time point using [redacted]. The method required [redacted] of plasma and has been validated over the range [redacted]. Serum cortisol levels were determined using [redacted] the method has been validated to a limit of quantitation of [redacted]. Urine free cortisol levels were analyzed by [redacted] the method required [redacted] of urine and has a validated limit of quantitation of [redacted].

Data Analysis: Pharmacokinetic parameters were derived for each subject from the plasma FP concentration data using standard non-compartmental techniques. For parametric analysis, a subject with all plasma concentrations below the LOQ, AUClast and Cmax were assigned a value of [redacted], respectively. The same analysis was also performed while setting the values to missing to ensure that results were similar.

To examine the increase in systemic exposure of FP over the range of FP strengths, the power model analysis of AUClast and Cmax was performed. The power model using the equation $y = e^a * \text{dose}^b$ was used to examine increases in FP systemic exposure, y was the quantity (AUClast and Cmax) before log transformation. A value of b (slope) close to unity would indicate a proportionality of doses. The adequacy of the power model was checked using suitable diagnostic techniques such as plotting residuals against log dose.

Systemic exposure of FP was evaluated using the ratio R,

$$R = \frac{AUC_B}{AUC_A}$$

and its 90% confidence interval, where AUC_B and AUC_A are dose normalized AUClast for each comparison. Ratios for Cmax were also calculated. Both AUClast and Cmax were dose normalized to 220 mcg. Comparison was performed with and without log transformation. Tmax was analyzed without transformation. Analysis of variance was used to compare treatments. A similar analysis was done on dose normalized AUClast and Cmax. Serum cortisol concentration at each sampling time point was summarized by treatment using mean, SD, median, maximum, and minimum and plotted by median and mean.

The following variables were calculated for each subject in the pharmacodynamic population:

Table 1

Variable Name	Description
AUC12	The area under the serum cortisol concentration versus time curve
Cmin	The minimum serum cortisol concentration over 12 hours post dose
Amount 24 (baseline)	The amount of cortisol in urine collected over 24 hours prior to visit 2
Amount 24 (final)	The amount of cortisol in urine collected over 24 hours prior to visit 9
Change from baseline in urine cortisol	Change in urine cortisol between baseline and 12 weeks

Serum cortisol AUC12 was plotted as a function of FP AUClast to determine whether there were any obvious relationships between the two parameters. Likewise, serum cortisol Cmin was plotted versus FP Cmax. Also, change in urine cortisol from baseline was plotted vs. FP AUClast. Linear regression was used to help determine if there was any relationship between these parameters.

Pharmacokinetic Results: The median age of subjects in this population across treatment groups ranged from 38.5 years to 54.0 years. Most subjects were female (57-71%) and most subjects were white (82-100%). The median height across treatment groups ranged from 168.0 cm to 173.0 cm and the median weight across treatment groups ranged from 72.2 kg to 79.4 kg. In the active treatment groups, in the 88 mcg treatment group 39% of the samples were BQL. In the FP 220 mcg treatment group, 7% samples were BQL and in 440 mcg treatment group 4% samples were BQL.

Median semi-log plasma FP concentration versus time is provided in figure 1 below. Plasma FP concentrations increased with dose.

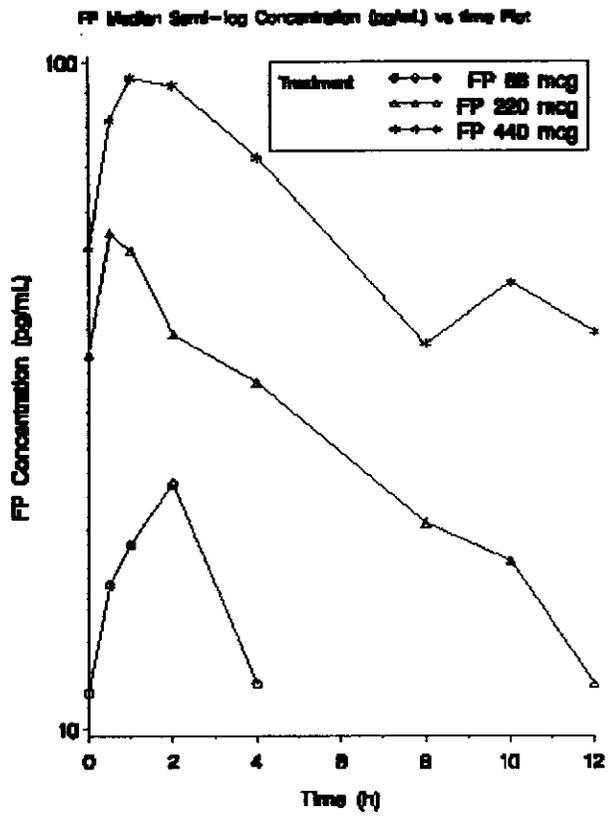


Fig. 1

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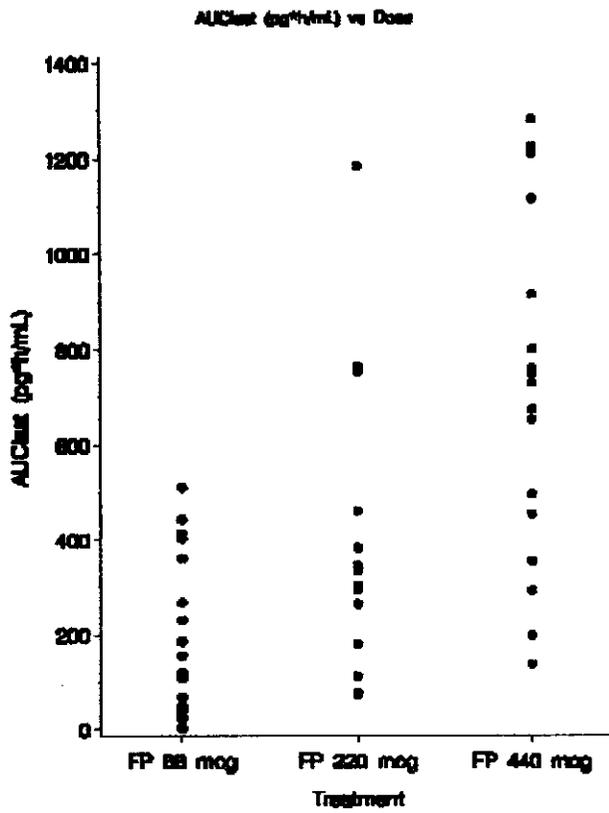
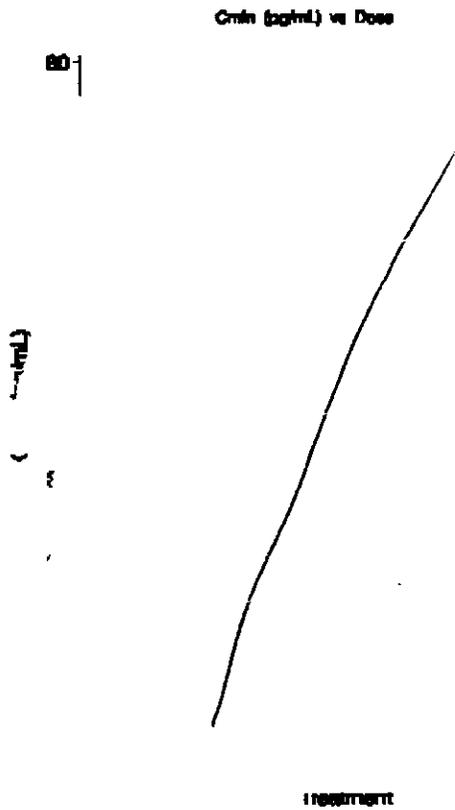


Fig 2 (above)
Fig. 3 (below)



Summary FP AUClast, Cmax and tmax are provided in table 2. Both AUClast and Cmax for the 3 treatments showed increases with increasing dose.

Table 2

FP Parameters	FP 88mcg	FP 220mcg	FP 440mcg	Ratio ^a	Ratio ^a
	HFA BID	HFA BID	HFA BID	220:88	440:220
	N=20	N=15	N=17		
AUClast (pg*h/mL)					
Mean ± SD	176.8 ± 166.9	391.17 ± 300.45	707.2 ± 359.24		
Geometric Mean	76.2	297.5	600.9		
95% CI	(33.2, 174.7)	(191.0, 463.6)	(430.7, 838.2)		
Geo LS Mean Ratio				1.56	1.01
90% CI				(0.77, 3.18)	(0.48, 2.11)
Cmax (pg/mL)					
Mean ± SD	32.8 ± 24.4	68.7 ± 38.0	125.0 ± 78.4		
Geometric Mean	25.2	60.8	103.1		
95% CI	(17.6, 36.1)	(45.8, 80.6)	(73.2, 145.1)		
Geo LS Mean Ratio				0.97	0.85
90% CI				(0.66, 1.42)	(0.57, 1.26)
tmax (h)					
Mean ± SD	2.07 ± 2.53	1.63 ± 1.75	1.11 ± 0.74		
Median	1.03	1.00	1.00		
Range	(0.50, 10.0)	(0.50, 7.6)	(0.00, 2.1)		
Mean Difference				-0.44	-0.51
90% CI				(-1.52, 0.64)	(-1.62, 0.60)

^aData dose normalized and log transformed prior to statistical analysis except for tmax

Ratio of geometric mean AUClast between 440mcg and 220mcg treatments was 2.02 (dose normalized ratio was 1.01). The ratio between 220mcg and 88mcg treatments was 3.9 (dose normalized ratio was 1.56). The ratio of geometric means for Cmax between 440 mcg and 220 mcg treatments was 1.7 (dose normalized ratio was 0.85) and between 220mcg and 88mcg treatments was 2.4 (dose normalized ratio was 0.97). None of the pairwise comparisons were statistically significant (90% confidence intervals contained 1.0) likely because of the small number of subjects that were examined.

Reviewer's comments: There was large variability in the data and the 90% confidence interval around the ratio of geometric means was not contained within the usual 80% - 125%.

Power model analysis for these 3 treatments showed that adjusted mean slope (and 90% CI) of the log transformed AUClast was 1.30 (0.88, 1.72) and 0.88 (0.66, 1.11) for Cmax. A confidence interval (CI) of the slope that is within the range 0.78 - 1.22, would indicate dose proportionality over the range tested. Ninety percent CI for slopes for both parameters were wider compared to the acceptance range indicating that increase in AUClast and Cmax across HFA strengths was dose-related, but could not be considered dose-proportional. Overall tmax values were variable, but essentially unchanged with median value of 1h following all 3 treatments.

Median values for C_{min} were 0, 11.7 and 25.6pg/mL following the 88, 220 and 440mcg BID doses, respectively. This parameter (C_{min}) was difficult to measure due to the substantial number of instances where this value was below the LOQ. Mean \pm SD t_{1/2} was 5.3 \pm 1.8 h, 5.66 \pm 2.4 h and 6.44 \pm 1.93 h for 88mcg, 220mcg and 440mcg treatments, respectively. A dose-related increase in systemic exposure was observed. Mean FP AUC_{last} following FP 440mcg was about twice that following FP 220mcg. Mean FP AUC_{last} following FP 88mcg was lower than predicted.

Reviewer's comments: *Evaluation of the mean AUC and C_{max} data for dose proportionality indicated that increases in FP concentration after administration of increasing doses was less than proportional to the dose administered. This is consistent with the results of the power analysis which suggested that dose proportionality was not demonstrated in these asthmatic patients*

Pharmacodynamic Results: Pharmacodynamic parameters were estimated in 65 subjects. Thirteen of these subjects received placebo HFA BID, 20 received FP 88 mcg HFA BID, 15 received FP 220 mcg HFA BID, and 17 received FP 440 mcg HFA BID. The mean linear serum cortisol concentration -time plot is presented in figure 4.

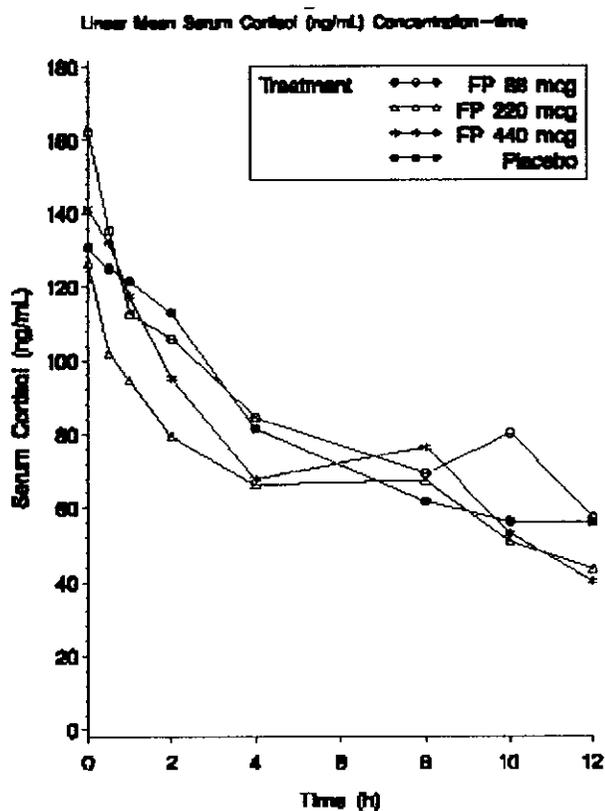


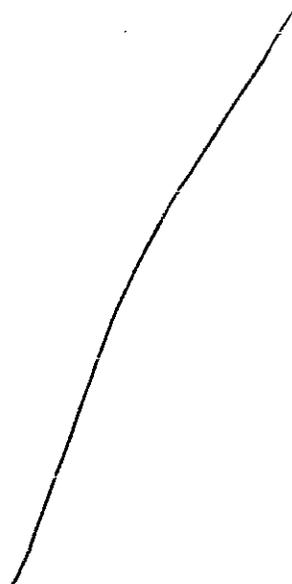
Fig 4

Figures 5 and 6 are scatter plots of cortisol AUC₁₂ and cortisol C_{min} for each treatment where each point on the plot represents an individual subject. Most cortisol values after both active treatments were within the range observed in placebo subjects. Inter-subject variability was high.

Percent CV for both cortisol AUC12 and Cmin increased with dose with values ranging from 33 to 58% for cortisol AUC12 and from 48 to 86% for cortisol Cmin.

Fig. 5

Serum Cortisol Cmin (ng/mL) vs Dose



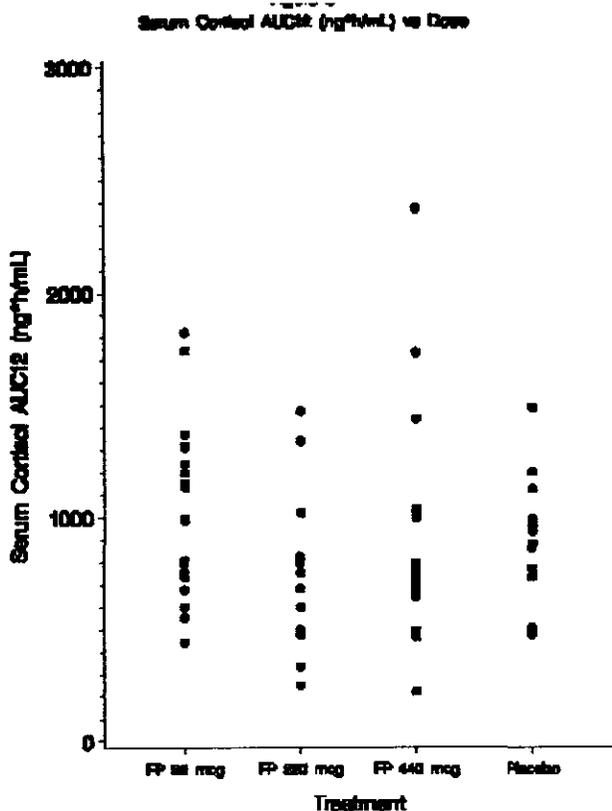


Fig. 6

Table 3 contains geometric least square (LS) mean serum cortisol AUC12 and Cmin values. These values were obtained by adjusting treatment as the main effect and the pre-dose measurement as the covariate.

Table 3: Key Pharmacodynamic Results for Serum Cortisol at Week 4

Serum Cortisol	Placebo HFA	FP 88mcg HFA	FP 220mcg	FP 440mcg
Parameters	BID	BID	HFA BID	HFA BID
	N=13	N=20	N=15	N=17
AUC12 (ng*h/mL)				
Geometric Mean	903.09	955.74 ^b	670.44 ^a	779.93
Geometric LS Mean	934.42	886.50	687.84	811.60
Active/Placebo		0.95	0.74	0.87
95% CI		(0.74, 1.22)	(0.57, 0.96)	(0.67, 1.12)
Cmin (ng/mL)				
Geometric Mean	34.76	37.25	30.50	30.01
Geometric LS Mean	36.36	33.73	31.54	31.63
Active/Placebo		0.93	0.87	0.87
95% CI		(0.56, 1.54)	(0.51, 1.48)	(0.52, 1.46)

a Significantly different from placebo

b Significantly different from 220mcg dose

Cortisol AUC₁₂ and C_{min} decreased in all treatments compared to placebo. However, these decreases in cortisol were not dose-related. Among the comparisons with placebo treatment, only the 220 vs. placebo AUC₁₂ comparison was statistically significant (confidence interval for the ratios did not contain 1.0) with ratio (and 95% CI) of 0.74 (0.57, 0.96). Among pairwise comparisons between active treatments, the difference between the FP 220mcg and 88mcg treatments for cortisol AUC₁₂ was the only comparison which reached statistical significance.

Table 4 and Figure 7 show baseline and final urine cortisol amount for individual subjects in each treatment group. Figure 7 indicates there was a trend for higher post-treatment values after placebo treatment. However, there does not appear to be clear trend observed after active treatment at any dose.

Urine Cortisol Amount (µg) vs Dose

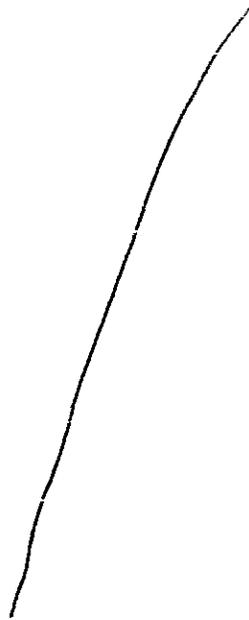


Fig. 7

Table 4: Summary of Urine Cortisol Results

Urine Cortisol Excretion	Placebo	FP 88mcg HFA	FP 220mcg	FP 440mcg
	HFA BID	BID	HFA BID	HFA BID
	N=7	N=17	N=12	N=11
Baseline (mcg)				
Mean	4.76	14.99	12.60	15.66
% CV	94	90	70	92
Median	4.00	11.69	13.75	14.52
Final (mcg)				
Mean	9.90	17.93	13.57	11.88
% CV	50	144	95	123
Median	10.00	9.29	11.63	12.60
Change from Baseline (mcg)				
Mean	5.14	2.94	0.97	-3.77
% CV	116	637	898	331
Median	6.00	0.33	0.19	-2.16

There was considerable variability with baseline and final % CV ranging from 50-144%. The sponsor stated that the variability in the baseline data across treatments may likely be due to the fact that subjects were taking a range of doses of different steroid therapy up until one day prior to dosing. Mean urine cortisol data at baseline and after 12 weeks of treatment for FP 88 mcg and 220 mcg treatments were similar and showed small increases over baseline. A small decrease in cortisol was observed after the 440 mcg treatment. Results from comparisons with placebo showed that differences in urine cortisol were greatest for FP 440 mcg HFA BID treatment but were not significant.

Figures 7 – 9 are plots of FP AUClast and cortisol AUC12 and cortisol Cmin vs. FP Cmax and urine cortisol vs FP AUClast. Although dose-related increases in systemic exposure were seen following three active treatments, there was no apparent relationship observed.

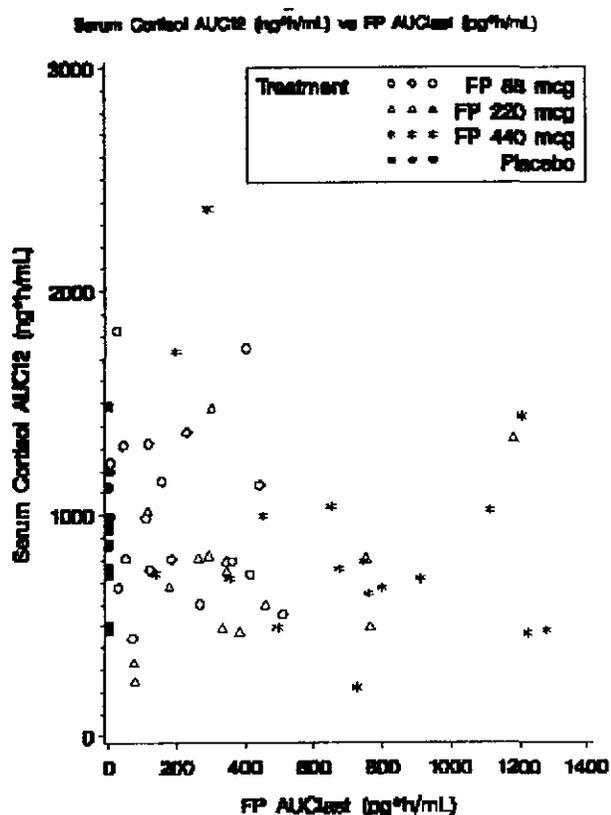
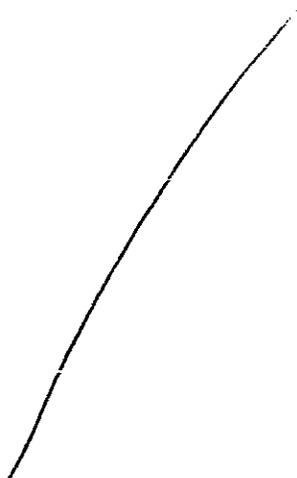


Fig 8

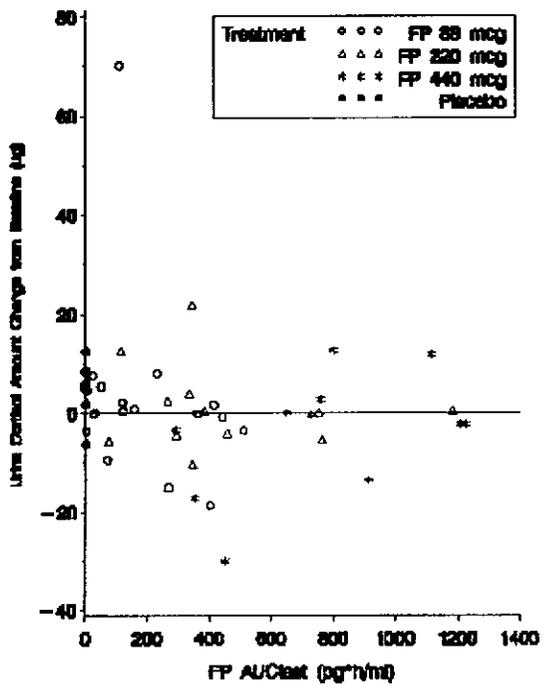
Serum Cortisol C_{max} (ng/ml) vs FP C_{max} (pg/ml)



FP C_{max} (pg/ml)

Fig 9

Change in Urine Cortisol from Baseline (ug) vs FP AUC₀₋₁₂ (pg*hr/ml)



FP AUClast was plotted against several demographic characteristics to examine the effect of baseline characteristics on FP systemic exposure in these subjects. Linear regression of FP AUClast as a function of the demographic parameter at each dose was used to look for trends. Figures 10 – 12 show FP AUC vs. gender, pulmonary function (% of predicted normal FEV1), and age. There was no apparent relationship between FP AUC and any of the parameters except age (p value = 0.003). There was no relationship observed between cortisol AUC12 and age for any dose.

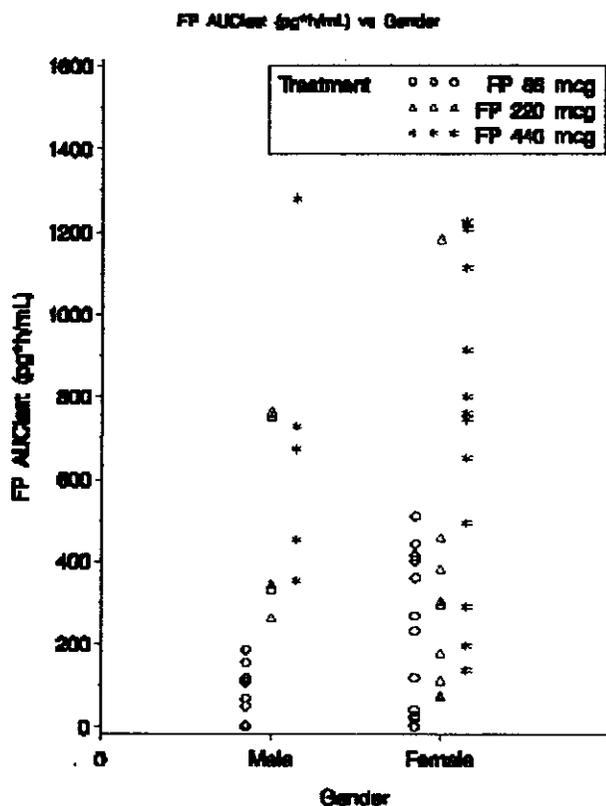


Fig. 10

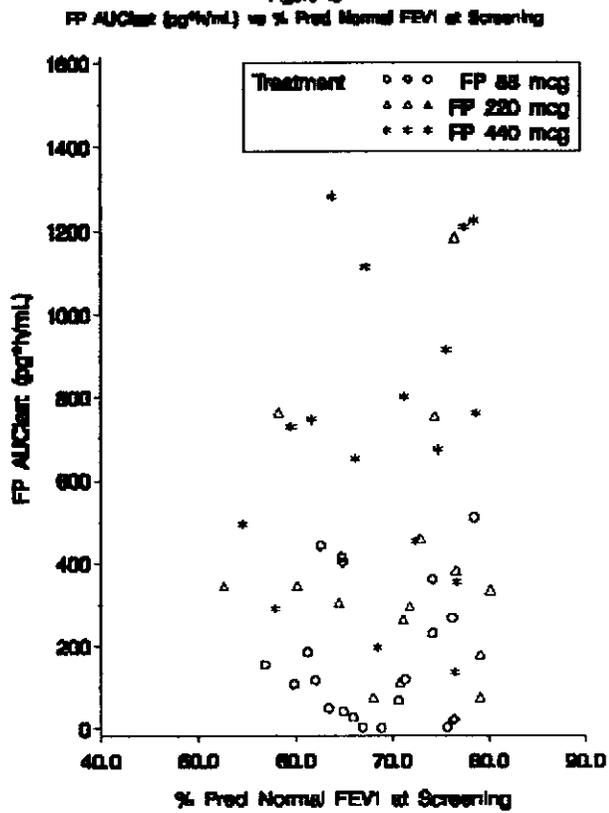
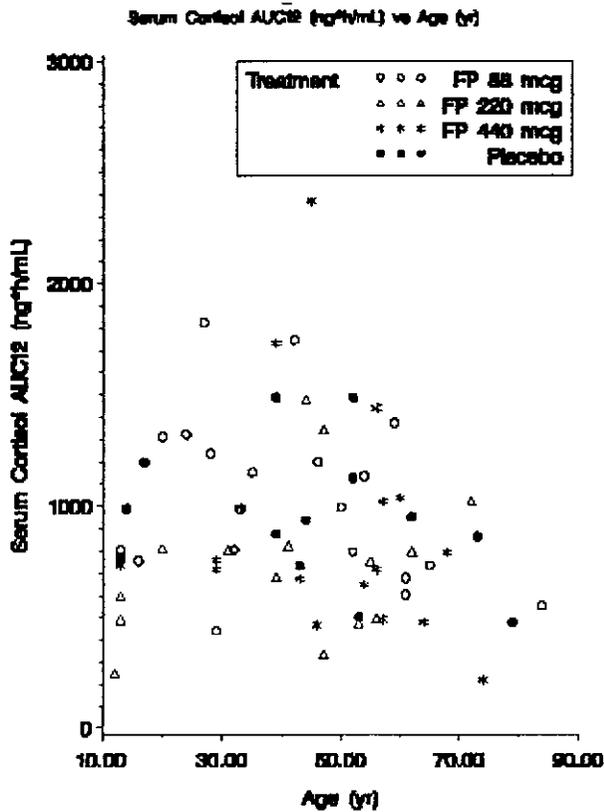


Fig. 11 (above)
Fig. 12 (below)



Safety Conclusions: Adverse Events related to ear, nose and throat and GI systems were somewhat higher in the three FP groups compared to the placebo group. Some of the AEs reported in the ear, nose and throat body system (e.g., throat irritation) and the GI body system (e.g. candidiasis mouth/throat) are predictable side effects of ICS.

Conclusion

A dose-related increase in systemic exposure was observed; however, the increase in systemic exposure was not proportional to dose. Mean FP AUC_{last} following FP 440mcg was about twice that following FP 220mcg. Mean FP AUC_{last} following FP 88mcg was lower than predicted probability due to bioanalytical limitations at this low dose. The rate of absorption into the systemic circulation was similar after each dose.

Changes in serum cortisol and urine cortisol were not dose-related and generally not significant. Only serum cortisol AUC₁₂ after the 220mcg treatment was significantly different from placebo. There were no significant changes in the corresponding cortisol C_{min} or urine cortisol excretion measurements at this dose. No relationship was observed between FP systemic exposure and gender, pulmonary function and weight. There was a significant relationship between FP systemic exposure and subject's age. However, no correlation was observed between serum cortisol and age; hence, the relationship between FP and systemic exposure is likely not to be of clinical significance.

Reviewer's comments: The reviewer agrees with the sponsor's conclusions. It must be noted that the variability in the data was large. The study was intended to evaluate patients 12 years and older, but there was not adequate representation of 12 year olds in the pharmacokinetic study.

Title (Protocol: FLTA3022): A randomized, double blind, placebo controlled comparative trial of fluticasone propionate 440µg BID or 880µg BID versus placebo administered via metered dose inhaler in propellant 11/12 or GR106642X in adolescent and adult oral corticosteroid dependent asthmatics: Pharmacokinetic Report

Objective: The primary objectives of the analysis were to: 1) To determine trough values of fluticasone (FP) plasma concentrations. 2) To compare systemic absorption across the treatment groups in terms of the trough FP concentrations.

Study Design: This study was of a multicenter, randomized, double-blind, parallel-group design to compare the dose related efficacy and safety of FP 440mcg BID and FP 880 mcg BID administered by metered-dose inhalers propelled by CFC propellants 11/12 or HFA propellant GR106642X. Male and female outpatients of at least 12 years of age, with a diagnosis of asthma (ATS definition) and a FEV1 40-85% predicted were screened for the study. Subjects were eligible if they had been shown to be oral corticosteroid-dependent for the past 6 months and it had been established that they were on their minimum effective dose of oral corticosteroid.

Subjects were randomly assigned to one of five treatment groups for 16 weeks at Clinic Visit 2 (Day 0).

- FP 440mcg BID - GR106642X
2 puffs BID of 220mcg FP - GR106642X (canister A) and 2 puffs BID of placebo - GR106642X (canister B)
- FP 880mcg BID - GR106642X
2 puffs BID of 220mcg FP - GR106642X (canister A) and 2 puffs BID of 220mcg FP - GR106642X (canister B)
- FP 440mcg BID - P11/12
2 puffs BID of 220mcg FP - P11/12 (canister A) and 2 puffs BID of placebo - P11/12 (canister B)
- FP 880mcg BID - P11/12
2 puffs BID of 220mcg FP - P11/12 (canister A) and 2 puffs BID of 220mcg FP - P11/12 (canister B)
- Placebo \in GR106642X
2 puffs BID of placebo - GR106642X (canister A) and 2 puffs BID of placebo - GR106642X (canister B)

Subjects were instructed to administer the assigned medication twice daily approximately 12 hours apart at 8:00AM and 8:00PM. Blood samples for measurement of plasma FP were obtained from 63 patients attending selected sites following two weeks of treatment. The assessment of FP plasma concentrations was made after two weeks of double blind treatment. A single blood sample was obtained 12 ours post-dose in order to determine the trough concentrations.

Analytical Method: Concentrations of FP in human plasma were determined by —

Table 1

	Accuracy	Precision	Calibration Range
Fluticasone propionate	—	—	—

Data Analysis: Plasma FP concentrations were summarized by treatment group at Week 2 for assessment of trough levels. Descriptive statistics were provided, comprising median, minimum and maximum. Means and standard deviations were considered inappropriate for those groups with many BQLs, and of marginal value for the rest. Transformation of concentrations to natural logarithms was carried out before statistical analysis. ANOVA was performed on log-transformed data with the model: dose + propellant + (dose * propellant interaction).

The log(trough concentration) values were subjected to analysis of variance to examine:

1. whether systemic exposure differed between the two propellants, and
2. whether there was an interaction between dose and propellant, and
3. whether systemic exposure was dose-proportional.

The limit of quantitation (LOQ) for FP in this study was \sim μ /ml. The values μ /ml were substituted for the below quantitation limit (BQL) values and the data reanalyzed for each substitution.

Results: Summary median trough concentrations are provided in table 2 below

Table 2

Summary of Fluticasone Propionate Trough Concentrations, (pg/mL)

Statistic	Treatment			
	FP 440mcg CFC BID	FP 440mcg HFA BID	FP 880mcg CFC BID	FP 880mcg HFA BID
N Obs	18	18	14	17
n	14	6	12	16
# Missing	4	8	2	1
Median	47.280	27.286	52.870	58.976
Min.	23.15	21.35	22.95	21.00
Max.	162.11	351.21	113.59	223.05

Results of comparative analysis following the assignment of non-zero values to BQL samples, to permit log transformation prior to analysis, are summarized in the tables 3-5.

Geometric LS Means of Fluticasone Propionate Trough Concentrations, (pg/mL)

Dose (mcg)	Propellant	20 pg/mL substituted			10 pg/mL substituted			1 pg/mL substituted		
		Geometric LS Mean	95% CI		Geometric LS Mean	95% CI		Geometric LS Mean	95% CI	
			lower	upper		lower	upper		lower	upper
440		35.4	28.0	44.8	26.9	19.9	38.3	13.8	6.0	19.4
880		49.7	39.1	63.0	46.3	34.1	62.8	36.7	20.3	66.5
	CFC	44.6	35.2	56.4	39.3	29.1	53.1	25.8	14.4	46.4
	HFA	39.4	31.1	50.0	31.7	23.4	43.0	15.3	8.5	27.8
440	CFC	43.9	32.2	59.9	37.5	25.3	56.0	22.6	10.4	49.0
440	HFA	28.5	20.0	40.6	19.2	12.2	30.1	5.1	2.1	12.4
880	CFC	45.3	31.8	64.4	41.9	26.1	64.4	29.5	12.2	71.2
880	HFA	54.5	39.5	75.0	52.3	34.7	78.8	45.7	20.5	102

Table 3 (above)

Ratios of Geometric LS Means of Fluticasone Propionate Trough Concentrations, (pg/mL)

Dose (mcg)	Propellant	Dose (mcg)	Propellant	20 pg/mL substituted			10 pg/mL substituted				
				Ratio	95% CI		Ratio	95% CI			
					lower	upper		p	lower	upper	p
440		880		0.71	0.51	1.03	0.047	0.38	0.36	0.60	0.014
	CFC		HFA	1.13	0.81	1.58	0.464	1.24	0.81	1.90	0.319
440	CFC	440	HFA	1.54	0.95	2.46	0.072	1.06	1.07	3.38	0.029
440	CFC	880	CFC	0.97	0.61	1.55	0.895	0.72	0.56	1.68	0.776
440	CFC	880	HFA	0.81	0.52	1.24	0.338	0.72	0.41	1.27	0.254
440	HFA	880	CFC	0.63	0.38	1.04	0.069	0.47	0.25	0.83	0.021
440	HFA	880	HFA	0.52	0.33	0.84	0.009	0.37	0.20	0.69	0.001
880	CFC	880	HFA	0.83	0.52	1.34	0.441	0.78	0.43	1.44	0.428

Table 4 (above)

Ratios of Geometric LS Means of Fluticasone Propionate Trough Concentrations, (pg/mL)

Dose (mcg)	Propellant	Dose (mcg)	Propellant	1 pg/mL substituted			
				Ratio	95% CI		
					lower	upper	p
440		880		0.29	0.13	0.68	0.005
	CFC		HFA	1.68	0.73	3.88	0.017
440	CFC	440	HFA	4.38	1.35	14.2	0.015
440	CFC	880	CFC	0.76	0.24	2.47	0.049
440	CFC	880	HFA	0.49	0.16	1.50	0.010
440	HFA	880	CFC	0.17	0.05	0.61	0.007
440	HFA	880	HFA	0.11	0.03	0.37	0.001
880	CFC	880	HFA	0.65	0.20	2.12	0.465

Table 5 (above)

It was noted that the dose main effect varied substantially with choice of substitute value. When considering the potential effect of propellant, there was higher systemic exposure for the CFC formulation compared with the HFA formulation at the 440mcg dose. However, this difference was not reflected at the 880 mcg dose. For the HFA formulation, a doubling in dose resulted in increased systemic exposure. In the case of the CFC formulation trough concentrations were similar at both dose levels. These conclusions can be drawn regardless of the non-zero value assigned to BQL samples.

Conclusion: In this study, a difference between HFA and CFC inhalers was observed at the lower dose but not at the higher dose. For the HFA formulation a doubling of dose resulted in increased systemic exposure but for the CFC formulation trough concentrations were similar at both dose levels. Due to the high variability observed in these trough concentrations, the limited number of samples obtained during the study and the large number of samples found to be below the limit of quantification of the assay (22% and 50% of the samples in the 440 mcg BID HFA and CFC groups, respectively) robust conclusions cannot be made.

Reviewer's comments: Eight out of 13 patients in the HFA 440 mcg had values below the LOQ; hence, comparison with this group is difficult. Determining exposures using a single trough concentration is problematic. Their variability in the data was large. The patients in the study were reported to generally have severe asthma which might have contributed to the high variability observed. Despite these shortcomings about the pharmacokinetic data, the trend observed that exposure as determined by trough concentrations after administration of FP via HFA propellant is generally lower than that seen when FP administration is via CFC propellant. The reviewer agrees generally with the sponsor's conclusions from this study.

APPEARS THIS WAY
ON ORIGINAL

Title (Report #: FLTB 1020): A Dose Proportionality Study of Fluticasone Propionate from 50, 125 and 250mcg HFA Inhalers and Comparability to 125 and 250 mcg CFC inhalers

Objective: 1) To examine dose proportionality of fluticasone (FP) over the range 400 – 2000 mcg using the available HFA alternate propellant strengths: 50, 125 and 250 mcg 2) The effect of the propellant on drug delivery at the 125 and 250 mcg strengths (HFA vs CFC)

Study Design: This was a single center, open-label, randomized, 5-way crossover study. Twenty-three healthy volunteers were randomly assigned to receive each of the single dose treatments but only twenty completed the study per protocol. The volunteers had to have a body mass index within the range 19 – 29 kg/m², with weight range of 55- 95 kg for males and 50 – 90 kg for females. Volunteers received one of the following single doses at each of the 5 treatment periods.

8 oral inhalations x 50 mcg FP from a HFA-containing inhaler (total dose = 400 mcg)
8 oral inhalations x 125 mcg FP from a HFA-containing inhaler (total dose = 1000 mcg)
8 oral inhalations x 125 mcg FP from a CFC-containing inhaler (total dose = 1000 mcg)
8 oral inhalations x 250 mcg FP from a HFA-containing inhaler (total dose = 2000 mcg)
8 oral inhalations x 250 mcg FP from a CFC-containing inhaler (total dose = 2000 mcg)

The total FP dose in each treatment represents the amount leaving the valve. Drug was administered as one inhalation every 30 seconds. The elapsed time from the first to the last inhalation was 3.5 minutes. There was at least a 5-day washout period between doses.

The FP HFA inhaler is a pressurized MDI for oral inhalation. Each inhaler consists of a white to off-white suspension of fluticasone propionate (micronized) in a liquefied hydrofluoroalkane propellant (Glaxo Wellcome Inhalation Grade GR 106642X) which is contained in an aluminum can sealed with a metering valve. The canister is presented in a plastic actuator fitted with a dust cap. The FP CFC inhaler is a pressurized MDI for oral inhalation. Each inhaler consists of a white to off-white suspension of FP (micronized) in a liquefied P11/12 propellant combination which is contained in an aluminum can sealed with a metering valve. The canister is presented in a plastic actuator fitted with a dust cap.

All study drug strengths were manufactured and packaged in the United Kingdom.

Blood samples (5 mL) were collected at predose, 10, 20, 40, 60 and 90 minutes and at 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours from the beginning of dosing for the determination of FP concentrations. Twenty-four hour urine samples were collected before and after each dose.

Analytical Method: Plasma samples were analyzed for FP using a validated method. The method required 1 mL of plasma and was validated over the range 0.1 – 100 ng/mL. Urine samples were analyzed for free cortisol for 24 hours. Cortisol levels were determined using liquid extraction followed by radioimmunoassay. The method required 1 mL of urine and was validated over the range 0.1 – 100 ng/mL.

Data Analysis: Pharmacokinetic parameters were determined using noncompartmental methods. AUC_∞, AUC_{last}, C_{max} and t_{1/2} obtained after administration of the HFA inhalers were log-transformed and tested for dose proportionality. The power model was fitted and a mean slope was estimated together with the associated 90% confidence intervals. As a secondary analysis, analyses of variance allowing for effects due to subjects, periods and treatments of log-

transformed dose-normalized AUC_{∞} , AUC_{last} and C_{max} and non dose-normalized $t_{1/2}$ were also performed. Estimates of the ratios of 50 mcg and 250 mcg to the reference dose 125 mg were calculated, together with the associated 90% CI. Tests of significance were performed at the 5% level. For acceptance criteria for comparability of inhaler formulations, CI outside the range of 0.75 – 1.33 were identified.

Comparability of the 125 mcg FP-HFA and 250 mcg FP-HFA to the CFC data was performed using analysis of variance allowing for effects due to subjects, periods and treatments. Estimates of the ratios of HFA to the corresponding CFC dose were calculated, together with the associated 90% CI.

Results: Twenty three subjects were treated (12 male and 11 female; age range 19 –49 years, median 25 years; median weight 65 kg and median height 168 cm). All the participants were caucasians. Mean FP plasma concentration time plots are provided in figure 1

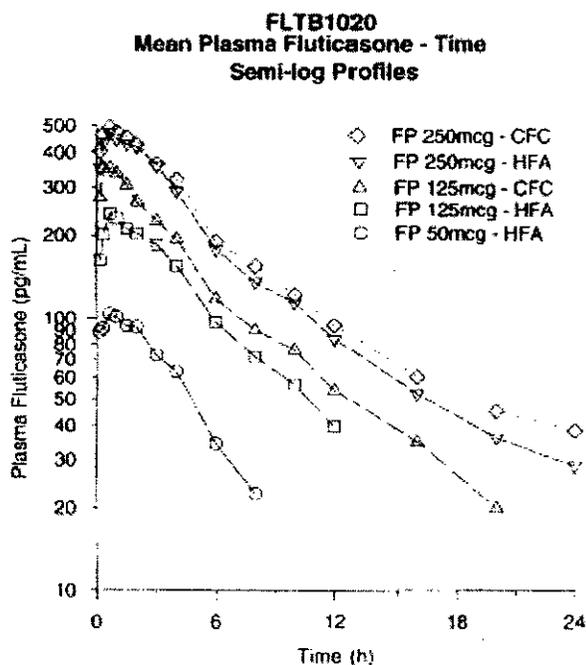


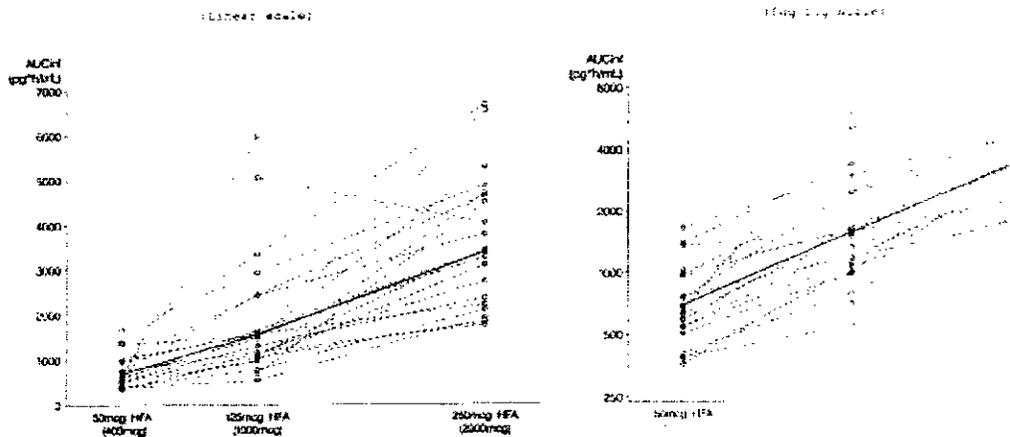
Fig 1

A biexponential curve was observed for the mean curves except may be for the FP 50 mcg HFA curve that appeared to be monoexponential. The FP 250CFC and 250 HFA curves appeared to be superimposable. Summary of statistical analysis is presented in the table 1.

Table 1

Treatment	FP 50-HFA	FP125-HFA	FP125CFC	FP250HFA	FP250CFC
Parameter	Mean ± SD (%CV)[n]				
AUC _{clast} (pg*h/mL)	555.7 ± 308.9 (55.58)[21]	1608.0±1243 (77.3)[21]	2184.5±812.2 (37.2)[22]	3279.5±1343 (40.9)[20]	3595.1±1341 (37.3)[21]
AUC _∞ (pg*h/mL)	767.8±375.2 (48.9)[19]	1894.7±1416 (74.7)[21]	2453.6±942.5 (38.4)[22]	3649±1492 (40.9)[20]	4092.7±1584 (38.8)[21]
C _{max} (pg/mL)	123.3±34.2 (27.7)[21]	265.5±133.4 (50.2)[21]	390.4±115.5 (29.6)[22]	531.7±179.9 (33.8)[20]	533.5±187.4 (35.1)[21]
T _{max} (h)	0.71 ± 0.39 (55.2)[21]	0.89 ± 67 (74.8)[21]	0.65 ± 0.39 (59.0)[22]	0.93 ± 0.69 (74.9)[20]	0.71 ± 0.48 (68.8)[21]
T _{1/2} (h)	4.4 ± 2.0 (43.9) [19]	5.8 ± 2.5 (43.5)[21]	6.4 ± 2.1 (33.2)[22]	6.5 ± 1.7 (26.7)[20]	7.1 ± 2.0 (28.7)[21]

Fig. 2



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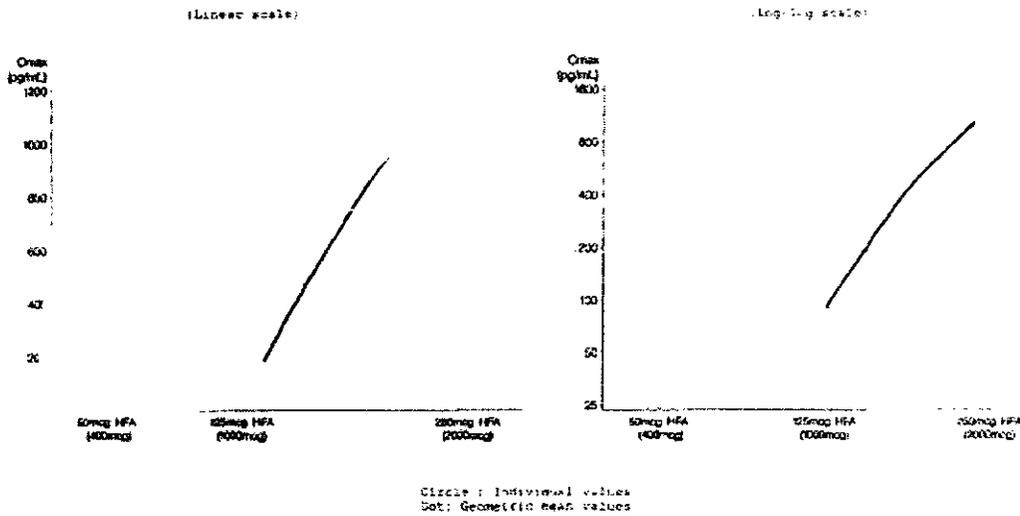


Fig. 3 (above)

The above are the linear and log-log plots of the individual AUC and Cmax data for the HFA strengths. Summary statistics on the dose proportionality of FP after administration from HFA propellant are presented in table 1.

Summary of statistical analysis on dose proportionality of HFA
log-transformed pharmacokinetic parameters through Power Model method
and Non-parametric analysis of tmax

Parameter	Adjusted mean slope	Standard error	df	90% CI
AUCinf	1.01	0.07	20	(0.89 , 1.14)
AUClast	1.15	0.07	20	(1.02 , 1.27)
Cmax	0.99	0.07	20	(0.79 , 1.31)
t-half	0.28	0.08	20	(0.15 , 0.41)

Parameter	Treatment Comparison	Estimate *	90% CI	p-value
tmax (h)	FP 50mcg - HFA - FP 125mcg - HFA	-0.08	(-0.50 , 0.08)	0.423
	FP 250mcg - HFA - FP 125mcg - HFA	0.00	(-0.33 , 0.42)	0.760

* Median difference for tmax

Table 2 (above)

The 90% CI of the slopes contain 1 and are contained within the 0.75 to 1.33 interval defined a priori as the acceptance range. Therefore, dose proportional is inferred based on the power analysis.

Summary of Statistical Analysis on dose proportionality of HFA
log-transformed dose-normalized AUC and C_{max} and non-normalized t-half through ANOVA method

Parameter	Treatment Comparison	Geometric LSmean Test treatment	Geometric LSmean Reference treatment	Ratio	90% CI	p-value
AUC ₀₋₁₂ (pg·h/mL)	FP 10mcg - HFA / FP 125mcg - HFA	664.6	1541.4	1.28	(0.98 , 1.32)	0.528
	FP 250mcg - HFA / FP 125mcg - HFA	1478.6	1541.4	1.11	(0.91 , 1.37)	0.301
C _{max} (pg/mL)	FP 10mcg - HFA / FP 125mcg - HFA	485.9	1282.6	0.95	(0.78 , 1.13)	0.635
	FP 250mcg - HFA / FP 125mcg - HFA	1143.4	1282.6	1.23	(1.01 , 1.49)	0.087
t _{1/2} (h)	FP 10mcg - HFA / FP 125mcg - HFA	118.41	238.26	1.24	(1.05 , 1.46)	0.041
	FP 250mcg - HFA / FP 125mcg - HFA	514.67	238.26	1.09	(0.91 , 1.29)	1.460
t _{max} (h)	FP 10mcg - HFA / FP 125mcg - HFA	4.026	5.202	0.77	(0.63 , 0.96)	0.069
	FP 250mcg - HFA / FP 125mcg - HFA	6.356	5.202	1.22	(0.99 , 1.53)	0.110

Note: LSmeans are expressed as non-normalized

ANOVA of dose normalized log-transformed and untransformed HFA data also indicated that dose proportionality might be inferred over the dose range tested.

However, a visual evaluation of the means did not support the inference of dose proportionality when the higher strengths are compared. The increase in FP concentration is less than proportional to the dose administered when the 1000 and 2000 mcg HFA doses are compared.

Table 4 provides a statistical comparison of FP concentrations after equal doses are administered via an HFA or CFC propellants.

Table 4 (below)

Summary of Statistical Analysis on Treatment Difference for pairwise comparisons
of 125 and 250mcg HFA/CFC Log-transformed Pharmacokinetic Parameters
and Non-parametric Analysis of t_{max}

Parameter	Treatment Comparison	Ratio *	90% CI	p-value
AUC ₀₋₁₂	FP 125mcg - HFA / FP 125mcg - CFC	0.67	(0.57 , 0.79)	<0.001
	FP 250mcg - HFA / FP 250mcg - CFC	0.88	(0.75 , 1.05)	0.226
AUC ₀₋₂₄	FP 125mcg - HFA / FP 125mcg - CFC	0.63	(0.53 , 0.74)	<0.001
	FP 250mcg - HFA / FP 250mcg - CFC	0.90	(0.76 , 1.08)	0.325
C _{max}	FP 125mcg - HFA / FP 125mcg - CFC	0.61	(0.54 , 0.74)	<0.001
	FP 250mcg - HFA / FP 250mcg - CFC	1.01	(0.86 , 1.18)	0.919
t _{1/2}	FP 125mcg - HFA / FP 125mcg - CFC	0.85	(0.71 , 1.01)	0.117
	FP 250mcg - HFA / FP 250mcg - CFC	0.91	(0.76 , 1.09)	0.387
t _{max}	FP 125mcg - HFA - FP 125mcg - CFC	0.17	(-0.08 , 0.42)	0.268
	FP 250mcg - HFA - FP 250mcg - CFC	0.25	(-0.08 , 0.50)	0.249

* Median difference for t_{max}

Table 5

Key results for the 125mcg strengths are summarized below:

	FP 125mcg - HFA	Ratio HFA/CFC	FP 125mcg - CFC
AUC ₀₋₁₂ (pg·h/mL)			
Geo. Mean	1547.1		2306.3
95% CI	(1165.6, 2053.5)		(1959.1, 2700.9)
Mean Ratio		0.67	
90% CI		(0.57, 0.79)	
p-value		<0.001	
C _{max} (pg/mL)			
Geo. Mean	237.69		375.46
95% CI	(190.93, 295.88)		(331.28, 425.53)
Mean Ratio		0.63	
90% CI		(0.54, 0.74)	
p-value		<0.001	
t _{max} (h)			
Median	0.667		0.667
Range	(0.167, 3.000)		(0.167, 1.500)
Median Difference (HFA-CFC)		0.17	
90% CI		(-0.08, 0.42)	
p-value		0.268	

Key results for the 250mcg strengths are summarized below:

	FP 250mcg - HFA	Ratio HFA/CFC	FP 250mcg - CFC
AUC₀₋₂₄ (pg*hr/mL)			
Geo. Mean	3365.4		3813.6
95% CI	(2767.8, 4092.0)		(3197.3, 4548.8)
Mean Ratio		0.88	
90% CI		(0.75, 1.05)	
p-value		0.226	
C_{max} (pg/mL)			
Geo. Mean	506.75		502.54
95% CI	(438.27, 585.92)		(426.49, 592.15)
Mean Ratio		1.01	
90% CI		(0.86, 1.18)	
p-value		0.919	
t_{1/2α} (h)			
Median	0.667		0.667
Range	(0.167, 3.000)		(0.167, 1.500)
Median Difference (HFA-CFC)		0.25	
90% CI		(-0.08, 0.50)	
p-value		0.249	

Table 6 (above)

The 90% CI for HFA/CFC comparison for AUC and C_{max} indicates that generally, FP exposure is less after administration 1000 mcg of FP via HFA propellant compared to CFC propellant. However, at the 2000 mcg dose, the exposures after administration via HFA or CFC formulations were similar.

Pharmacokinetic Conclusions:

Dose proportionality was established over the dose range of 400 – 2000 mcg using the HFA strengths. The 125 mcg HFA inhaler was not comparable to the CFC inhaler. The 250 mcg HFA inhaler was comparable to the CFC inhaler.

Reviewer comments: Generally, the reviewer agrees with the sponsor's conclusions from the evaluation of the pharmacokinetic data. However, after visual evaluation of the 1000 and 2000 mcg doses, dose proportionality may be questionable after administration via both the HFA and CFC propellants.

Pharmacodynamic Results:

Table 7 provides the summary of the statistical analysis of urine cortisol.

Table 7

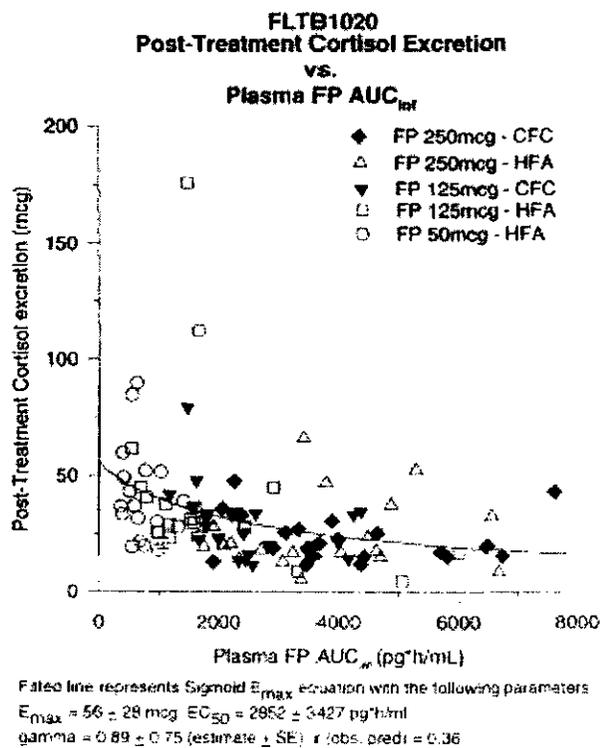
Summary of statistical analysis on log-transformed post-treatment urinary cortisol excretion

Treatment Comparison	Ratio	95% CI	p-value
FP 125mcg HFA / FP 125mcg CFC	1.04	(0.82, 1.32)	0.766
FP 250mcg HFA / FP 250mcg CFC	1.01	(0.79, 1.29)	0.938
FP 50mcg HFA / FP 125mcg HFA	1.43	(1.12, 1.83)	0.005
FP 250mcg HFA / FP 125mcg HFA	0.73	(0.57, 0.93)	0.012

Post treatment cortisol excretion decreased with dose. Geometric LS means were 41.04 mcg, 28.69 mcg and 20.96 mcg following the 400, 1000 and 2000 mcg doses containing HFA

propellant and were found to be significantly different. Propellant had no effect on cortisol excretion.

The relationship between cortisol excretion and FP AUC_∞ is provided in the following figure. Propellant had no effect on the relationship between urine cortisol excretion and FP exposure. Fig 4 below)



Safety: The sponsor reported that FP was proven safe and well tolerated up to 2000 mcg single dose, administered with CFC and with HFA propellants.

Conclusion: The increase in FP concentration occurred proportionally to dose after administration from the three HFA inhalers when dose proportionality was assessed using the power model. Decreases in urine excretion of cortisol after administration FP corresponded with dose. In this study, comparability of HFA and CFC propellants was examined by comparing systemic exposure of FP and urine cortisol. Comparable FP systemic exposure was observed for the 250 mcg HFA and CFC inhalers but not between the 125 mcg strength inhalers. FP exposure after administering equal doses of FP using the 125 HFA inhaler was about 33% lower compared to that seen after using the 125 CFC inhaler. The relationship between changes in urinary cortisol and FP systemic exposure was unaffected by propellant.

Reviewer's comments: The reviewer generally agrees with the sponsor's conclusions. Dose proportionality was demonstrated by all methods used between the 400 and 1000 mcg dose after administration of FP via HFA propellant. However, there is a suggestion from evaluation of the mean data dose proportionality may not exist when the 1000 mcg and 2000 mcg doses are compared. A less than proportional increase in FP concentration is observed when the dose is doubled from 1000 to 2000 mcg.

OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-433	Brand Name	Flovent HFA
OCPB Division (I, II, III)	II	Generic Name	Fluticasone propionate
Medical Division	DPADP	Drug Class	Glucocorticoid
OCPB Reviewer	Kofi Kumi	Indication(s)	Asthma
OCPB Team Leader	Emmanuel Fadiran	Dosage Form	Inhalation Aerosol
		Dosing Regimen	88 - 880 mcg BID
Date of Submission	2/26/02	Route of Administration	Oral inhalation
Estimated Due Date of OCPB Review	8/26/02	Sponsor	GlaxoSmithKline, Inc.
PDUFA Due Date	12/26/02	Priority Classification	Standard
Division Due Date			

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				
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	2	1	Study report only for I. Inhalers not marketed in U.S.
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	2	2	
Dose proportionality -				
fasting / non-fasting single dose:	x	2	2	Study report for I. Inhalers not marketed in U.S.
fasting / non-fasting multiple dose:	X	1	1	
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				

Phase 3:	X	2	2	
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1	1	
Phase 3 clinical trial:	X	1	1	
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		4	3	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included) FDA letter date if applicable		
QBR questions (key issues to be considered)	1. Is FP concentration after administration via MDI HFA proportional to dose? 1. Is the Exposure of FP different after administration via MDI HFA versus MDI CFC? 2. Is the effect of FP on serum cortisol different after administration via MDI HFA versus MDI CFC			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-433, HFD-850 (Electronic Entry or Lee), HFD-570 (Jafari), HFD-870 (Fadiran, Hunt, Malinowski), CDR (B. Murphy)

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

/s/

Kofi Kumi
12/5/02 01:18:15 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
12/5/02 01:29:26 PM
BIOPHARMACEUTICS
I concur