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APPLICATION NUMBER:

NDA 21-254

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA 21-254:	Submission Date: 12/07/05, 4/14/06
Brand Name:	Advair® HFA MDI (Inhalation Aerosol)
Generic Name:	Fluticasone propionate (FP)/Salmeterol (SALM)
Reviewer:	Shinja Kim, Ph.D.
Team Leader:	Emmanuel Fadiran, Ph. D.
OCP Division:	DCP 2
OND Division:	DPADP (HFD-570)
Sponsor:	GlaxoSmithKline, Inc.
Submission Type:	Supplement (SLR)
Formulation; Strength(s):	Inhalation Powder (FP/Sal), 45/21, 115/21, 230/21 mcg
Indication:	*Asthma*: Long-term, twice-daily, maintenance treatment of asthma in patients ≥ 12 years of age.

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Recommendation: The Office of Clinical Pharmacology has reviewed the information provided in NDA 21-254. OCP found this application acceptable.

1.2 Phase 4 Commitment: None

1.3 Summary of clinical Pharmacology Findings

This is a labeling supplement NDA. Revised labeling Pharmacokinetics section under CLINICAL PHARMACOLOGY is based on the data from Study SAS10007 as well as the sponsor's response to the comments provided in the Approvable Letter (dated October 16, 2002). Overall, the proposed labeling is adequate per OCP standpoint.

2. QUESTION BASED REVIEW

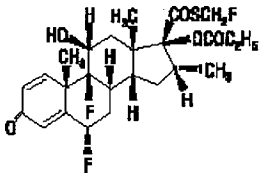
2.1 General Attribute of ADVAIR® HFA Inhalation Aerosol

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

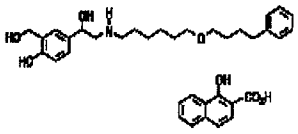
ADVAIR HFA is a combination of fluticasone propionate and salmeterol xinafoate.

Fluticasone propionate (FP) is a corticosteroid with a molecular weight of 500.6 and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

Salmeterol xinafoate (SALM) is a $beta_2$-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol with molecular weight of 603.8 and the empirical formula $C_{25}H_{37}NO_4 \bullet C_{11}H_8O_3$. It is freely soluble in methanol, slightly soluble in ethanol, chloroform, and isopropanol and sparingly soluble in water. Chemical structures for fluticasone (left panel) and salmeterol (right panel) are shown below;



Fluticasone Propionate



Salmeterol Xinofoate

ADVAIR HFA Inhalation Aerosol is pressurized, metered-dose aerosol units intended for oral inhalation only. Each unit contains a microcrystalline suspension of fluticasone propionate (micronized) and salmeterol xinafoate (micronized) in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

2.1.2. What are the proposed dosage(s), route(s) of administration, and indications?

ADVAIR HFA MDI should be administered by the orally inhaled route only in patients 12 years of age and older with asthma; two inhalations twice daily, titrate to the lowest effective strength after adequate asthma stability is achieved. ADVAIR HFA is available in 3 strengths, 45/21, 115/21, and 230/21 Inhalation Aerosol, containing 45, 115, and 230 mcg of fluticasone propionate, respectively, and 21 mcg of salmeterol per inhalation.

2.2. General Clinical Pharmacology

2.2.1. What is known About the General Clinical Pharmacology and PK and pharmacodynamic of FP and SALM?

Mechanism of Action: FP is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity and Salmeterol is a long-acting $beta_2$ -adrenergic agonist.

PK of FP: Oral systemic bioavailability of FP is negligible (<1%), primarily due to incomplete absorption and pre-systemic metabolism in the gut and liver. In contrast, the majority of the FP delivered to the lung is systemically absorbed.
FP is metabolized by CYP3A4. The major route of elimination is the feces. The renal excretion of FP is negligible (<0.02% of the dose) and less than 5% of the dose is excreted in the urine as metabolites. The terminal elimination half-life following intravenous or inhaled administration is about 6 - 8 hours.

Pharmacodynamics of FP: The systemic pharmacodynamic effects of corticosteroids are numerous and can affect almost all body systems. The most sensitive and most easily measured effects are on the hypothalamic-pituitary-adrenal (HPA) axis. Inhibition of the HPA axis by exogenous corticosteroids can be assessed by reductions in serum cortisol concentrations and urinary cortisol excretion.

PK of SALM: Peak plasma concentrations occur within 5 - 8 minutes. It is extensively metabolized by hydroxylation (CYP3A4 isoenzyme), with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces. The elimination half-life was estimated to be 5.5 hours.

Pharmacodynamics of SALM: The systemic circulation its extrapulmonary pharmacodynamic effects include dose-related increases in heart rate, QTc interval and blood glucose concentrations; and dose-related reductions in diastolic blood pressure and plasma potassium concentrations.

2.2.2. What are the rationales of this submission?

Approvable Letter (dated October 16, 2002) was sent out to the sponsor upon the review of the original NDA submission. The current submission is complete response to the approvable letter by revising the labeling. Thus, the current NDA involves the reviewing the proposed labeling. Revised labeling under CLINICAL PHARMACOLOGY is based on the data from Study SAS10007 as well as the sponsor's response to the comment (i.e., comment 20d) provided in the Approvable Letter. Since Study SAS10007 was not reviewed previously, it is reviewed in this NDA.

2.1.2. **What were the objective and the outcomes of the Study SAS10007?**

Objective: Characterize FP and SALM PK and pharmacodynamics in adult subjects with asthma.

Methodology: This was a randomized, multiple-dose, double-blind, placebo-controlled, 4-way crossover study in adult subjects with asthma aged 18 to 55 years (13 subjects completed). Each subject was randomized to receive 1 inhalation of the combination FP/SALM 250/50 mcg BID DISKUS, 2 inhalations of the combination FP/SALM 110/21 mcg BID HFA MDI, 2 inhalations of the individual FP 110 mcg BID HFA MDI, and matching DISKUS and HFA MDI placebo inhalers for 28 days after a 21-day screening period. Blood was sampled for the determination of FP and SALM concentrations on Day 28 relative to the time of the morning dose, at pre-dose, 5, 10, 30 min and 1, 2, 4, 8, 10 and 12 hours post-dose. The assay was performed using a LC-MS-MS method with a detection limit of 5 pg/mL for FP and 25 pg/mL for SALM. Also, serial blood sampling for the determination of cortisol concentrations were collected on Day 28 as follows: pre-morning-dose, 30 minutes and 1, 2, 4, 8, 10, and 12 hours post-dose. Additionally, 24-hour urine (Day 27-28) was collected for urinary cortisol and 6β-hydroycortisol determination. ECG data were used for the determination of QT interval and HR, and were collected within 5 minutes pre-evening-dose (time 0), and at 10, 30 minutes, and 1, 2, 4, 8, 10, and 12 hours post-dosing on Day 27.

Results:

Plasma concentrations: The median FP and SALM plasma concentration-time plots are presented in Figure 1 and Figure 2, respectively. For FP, 5% of samples from FP/SALM DISKUS, 10% from FP/SALM HFA, and 15% from FP HFA were blow the limit of quantitation (BLQ), respectively. All plasma concentrations were BLQ for 2 of the subjects (15%) who received FP/SALM DISKUS. For SALM, more than 50% samples were BLQ (52% for FP/SALM DISKUS and 53% for FP/SALM HFA).

Figure 1: Plot of Median plasma Fluticasone Propionate Time Linear Profile

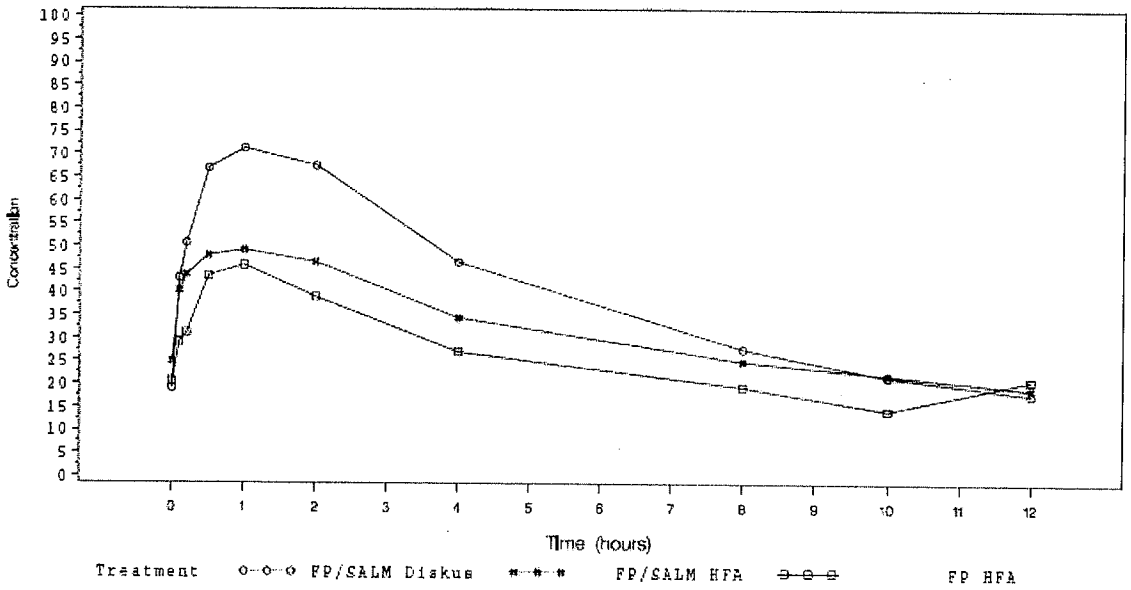
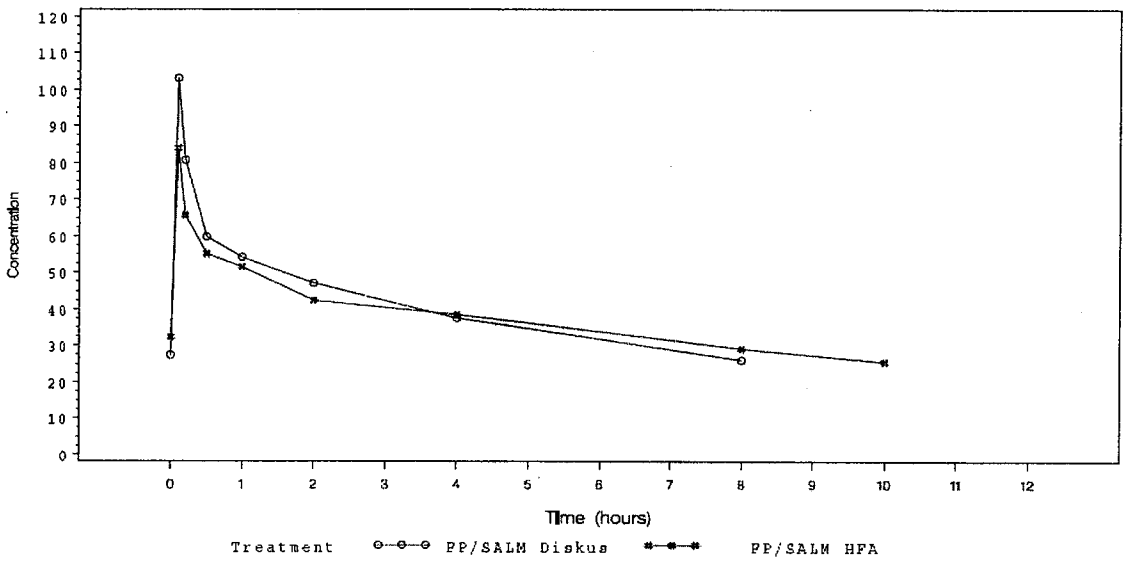


Figure 2: Plot of Median plasma SALM Time Linear Profile



PK Parameters:

Key PK parameters including 95% confidence intervals (CI) and treatment comparisons including 90% CI for FP and SALM are presented in Table 1 and 2 respectively.

Table 1. Key FP Pharmacokinetic Results

Parameter	Geometric Means and 95% Confidence Intervals		
	FP HFA	**FP/SALM DISKUS**	**FP/SALM HFA**
AUClast (pg·h/mL)	179 (75.2, 427)	338 (197, 581)	274 (150, 502)
Cmax (pg/mL)	34.5 (20.5, 57.9)	58.1 (38.3, 88.1)	43.2 (25.2, 73.8)
tmax (h)[a]	1.00 (0.50, 4.00)	1.00 (0.17, 4.00)	1.03 (0.08, 2.00)
	Ratio of Geometric LS Means and 90% Confidence Intervals		
	FP/SALM DISKUS / FP HFA	**FP/SALM MDI HFA / FP HFA**	**FP/SALM DISKUS / FP/SALM HFA**
AUClast (pg·h/mL)	2.05 (1.15, 3.65)	1.72 (0.96, 3.08)	1.19 (0.67, 2.13)
Cmax (pg/mL)	1.74 (1.10, 2.74)	1.35 (0.85, 2.14)	1.28 (0.81, 2.03)
tmax (h)b	-0.33 (-0.75, 0.01)	-0.42 (-0.88, 0.27)	-0.02 (-0.67, 0.68)

FP=fluticasone propionate; SALM=salmeterol; HFA=hydrofluoroalkane; MDI=metered dose inhaler

a. median and range for treatments

b. median difference and 90% confidence interval for comparison

Table 2. Key FP Pharmacokinetic Results

Parameter	Geometric Means and 95% CI		Geometric LS Mean Ratio and 90% CI
	FP/SALM DISKUS	FP/SALM HFA	DISKUS / HFA
AUClast (pg·h/mL)	70.0 (19.3, 254)	52.9 (17.0, 164)	1.30 (0.28, 6.05)
Cmax (pg/mL)	83.8 (45.8, 153)	75.4 (46.9, 121)	1.04 (0.53, 2.04)
tmax (h)a,b	0.08 (0.08, 1.00)	0.08 (0.08, 1.00)	0.00 (0.00, 0.01)

FP=fluticasone propionate; SALM=salmeterol; HFA=hydrofluoroalkane; CI=confidence interval

a. median and range for treatments

b. median difference and 90% confidence interval for comparison

PK Conclusions:

- FP AUC_{last}, Cmax and tmax from the combination DISKUS and HFA MDI inhalers were similar.
- Exposure from FP HFA MDI was lower compared with the combination inhalers and reached statistical significance with the DISKUS.
- SALM AUC_{last} and Cmax from the combination DISKUS and HFA MDI inhalers were similar. Median tmax was 5 minutes following both treatments.

Pharmacodynamics

FP: The mean linear serum cortisol concentration-time plot and key results for plasma and urinary cortisol and its metabolite are presented in Figure 3 and Tables 3-4, respectively.

Figure 3. Plot of Mean Serum Cortisol Time Linear Profile

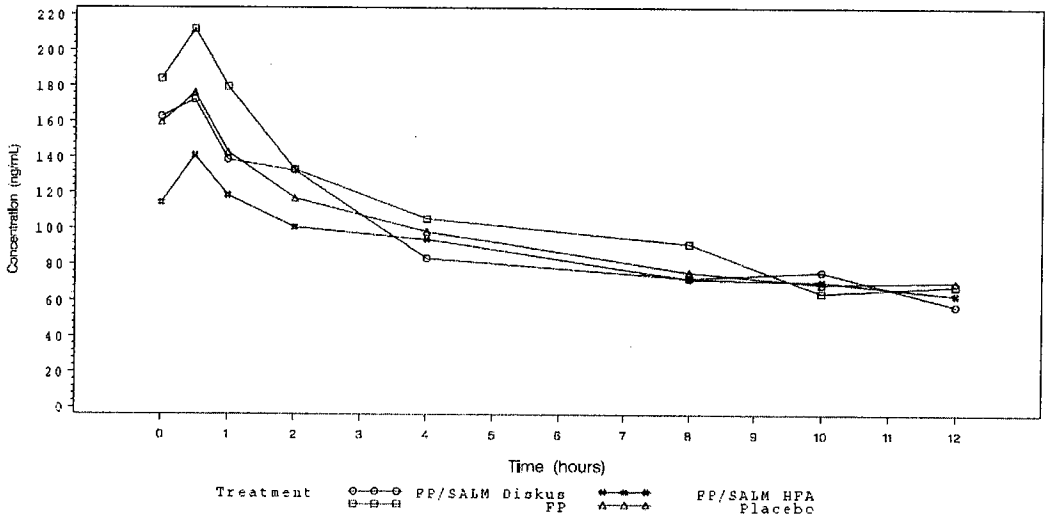


Table 3. Post-Treatment Cortisol Geometric Means and Treatment Comparisons

Parameter	PL N=13	FP HFA N=13	FP/SALM HFA N=13	FP/SALM DISKUS N=13
Serum AUC12 (ng*h/mL)				
Geometric Mean	1010.	1188.	903.8	1017.
95% CI	(738.4, 1382.)	(917.5, 1539.)	(647.0, 1262.)	(796.2, 1299.)
Ratio to Placebo		1.21	0.90	1.03
95% CI		(0.93, 1.57)	(0.69, 1.17)	(0.79, 1.34)
Ratio to **DISKUS**			0.87	
95% CI			(0.67, 1.13)	
Ratio to FP HFA			0.75	0.86
95% CI			(0.57, 0.97)	(0.66, 1.11)
Serum Cmin (ng/mL)				
Geometric Mean	41.5	43.8	33.3	37.4
95% CI	(26.2, 65.7)	(31.4, 61.0)	(21.1, 52.7)	(26.1, 53.6)
Ratio to Placebo		1.08	0.79	0.90
95% CI		(0.75, 1.57)	(0.54, 1.14)	(0.62, 1.31)
Ratio to **DISKUS**			0.88	
95% CI			(0.60, 1.27)	
Ratio to FP HFA			0.73	0.83
95% CI			(0.50, 1.06)	(0.57, 1.20)

PL=placebo; FP=fluticasone propionate; SALM=salmeterol; HFA=hydrofluoroalkane; CI=confidence interval
Source: Tables 10.7 and 10.8

Table 4. Geometric LS Mean and 95% Confidence Intervals for Treatment Comparisons

Comparison with Placebo	FP HFA N=13	FP/SALM HFA N=13	FP/SALM DISKUS N=13
Cortisol	0.86 (0.53, 1.39)	0.75 (0.46, 1.21)	0.49 (0.30, 0.80)
6-β-hydroxy	0.89 (0.52, 1.50)	0.80 (0.47, 1.35)	0.67 (0.39, 1.14)
Total	0.89 (0.55, 1.45)	0.80 (0.49, 1.30)	0.56 (0.34, 0.91)
Comparison with DISKUS			
Cortisol		1.52 (0.94, 2.45)	
6-β-hydroxy		1.19 (0.70, 2.04)	
Total		1.44 (0.89, 2.34)	
Comparison with FP HFA			
Cortisol		0.87 (0.54, 1.41)	0.57 (0.35, 0.93)
6-β-hydroxy		0.90 (0.53, 1.52)	0.75 (0.44, 1.29)
Total		0.90 (0.55, 1.47)	0.63 (0.38, 1.02)

PL=placebo; FP=fluticasone propionate; SALM=salmeterol; HFA=hydrofluoroalkane
Source: Tables 10.9, 10.10, and 10.11

Note: 14 urine collections (27%) were obtained outside the range 24±1 hour and 4 samples (8%) were obtained with 21 and 22 hrs. Additionally, 24-hr urine volumes were less than conventional minimum volume (e.g., 600 mL for female and 800 mL for males) in some of the subjects who received DISKUS.

Salmeterol: PD parameters data are data are listed in Table 5. CIs were narrow indicating low intersubject variability. All ratios were close to 1.0 and most intervals contained unity indicating no major differences among the 3 treatments.

Table 5. Geometric LS Mean and 95% CIs for Treatment Comparisons of AUC HR and QTc Intervals

Comparison with Placebo	FP HFA N=13	FP/SALM HFA N=13	FP/SALM DISKUS N=13
HR	0.94 (0.89, 0.99)	1.02 (0.97, 1.08)	1.02 (0.96, 1.07)
QTcB	0.99 (0.98, 1.01)	1.00 (0.99, 1.02)	1.00 (0.99, 1.02)
QTcF	1.00 (0.99, 1.02)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Comparison with DISKUS			
HR		1.01 (0.96, 1.06)	
QTcB		1.00 (0.90, 1.02)	
QTcF		1.00 (0.99, 1.01)	
Comparison with FP HFA			
HR		1.09 (1.04, 1.15)	1.08 (1.03, 1.14)
QTcB		1.01 (1.00, 1.03)	1.01 (1.00, 1.03)
QTcF		1.00 (0.98, 1.01)	1.00 (0.98, 1.01)

HR=heart rate; PL=placebo; FP=fluticasone propionate; SALM=salmeterol; HFA=hydrofluoroalkane
Source: Tables 10.6

PD Conclusions:

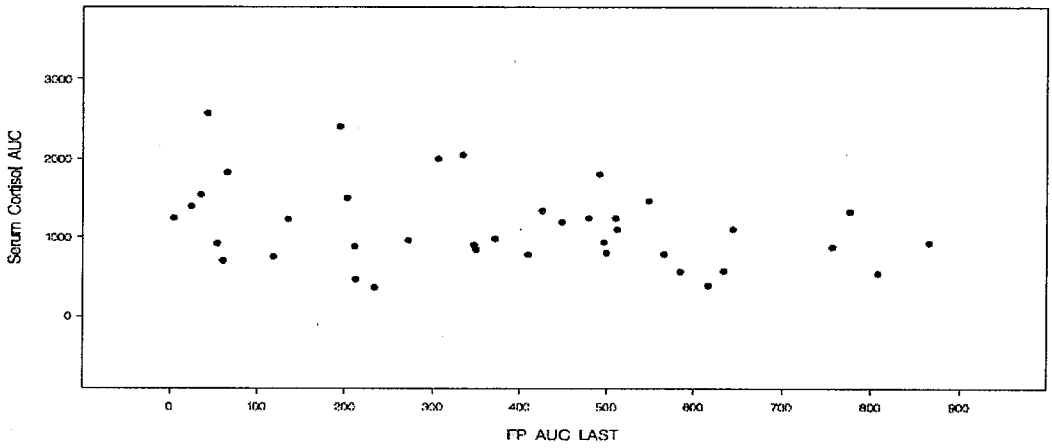
- No significant differences in serum cortisol AUC_{12} and Cmin across active treatments compared with placebo were observed. Mean AUC_{12} ratios comparing active treatment with placebo ranged from 0.90 to 1.21. Mean Cmin ratios comparing active treatments with placebo ranged from 0.79 to 1.08.
- Significant differences compared to placebo in cortisol and the sum of cortisol and 6-β-hydroxycortisol were observed following FP/SALM DISKUS administration (as opposed to not significant in serum cortisol). Sponsor stated, referring the article by Weinbrenner, 2002, serum cortisol is considered to be a more sensitive marker of drug effect (valid point). Also a significant difference between FP/SALM DISKUS and FP HFA was observed for cortisol, but not for 6- β-hydroxycortisol or the sum of the analytes. Thus, the sponsor concluded that urine cortisol and 6-beta-hydroxycortisol results generally agree with the serum cortisol results, but interpretation of the urine results was limited due to the urine collection and assay issues.

- No statistically significant increases in HR, QTcB, and QTcF were observed for any active treatment compared with placebo.

Pharmacokinetic/Pharmacodyamic Results

FP: A plot of serum cortisol AUC_{12} versus FP AUC_{last} showed no apparent relationship (Figure 4). Also, no apparent relationships were shown for serum cortisol Cmin *vs.* FP Cmax, 24-hour urine cortisol excretion *vs.* FP AUC_{last}, or 24-hour urine cortisol excretion *vs.* FP Cmax (not shown here). Therefore, per sponsor modeling was not performed.

Figure 4. Plot of Serum Cortisol AUC *vs.* FP AUC_{LAST} Correlation Coefficient = -0.3301



Salmeterol: Plots of HR AUC_{12} *vs.* SALM AUC_{last} (Figure 5) and QTcF AUC12 *vs.* SALM AUC_{last} (Figure 6) are shown below, and revealed no apparent relationships. Also no apparent relationships for QTcB AUC12 *vs.* SALM AUC_{last}, maximum HR *vs.* SALM Cmax, maximum QTcB *vs.* SALMCmax (not shown here).

Figure 5. Plot of HR AUC_{12} *vs.* SALM AUC_{LAST} Correlation Coefficient = 0.471

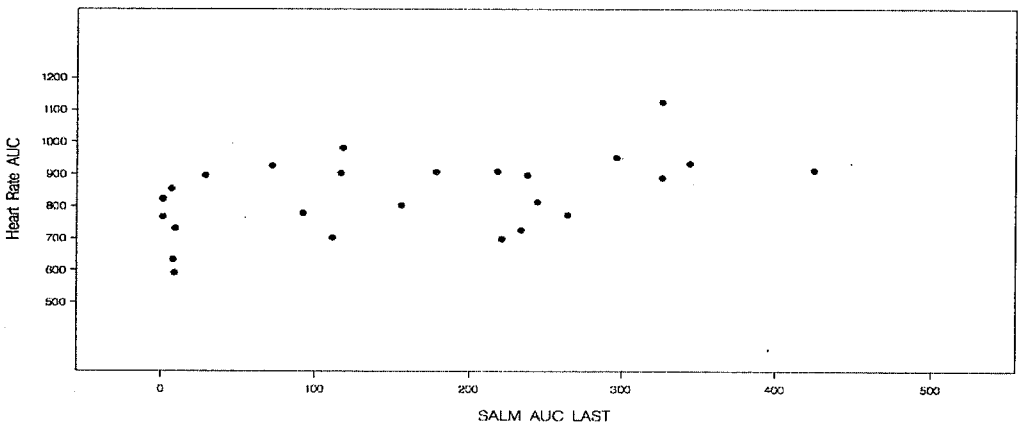
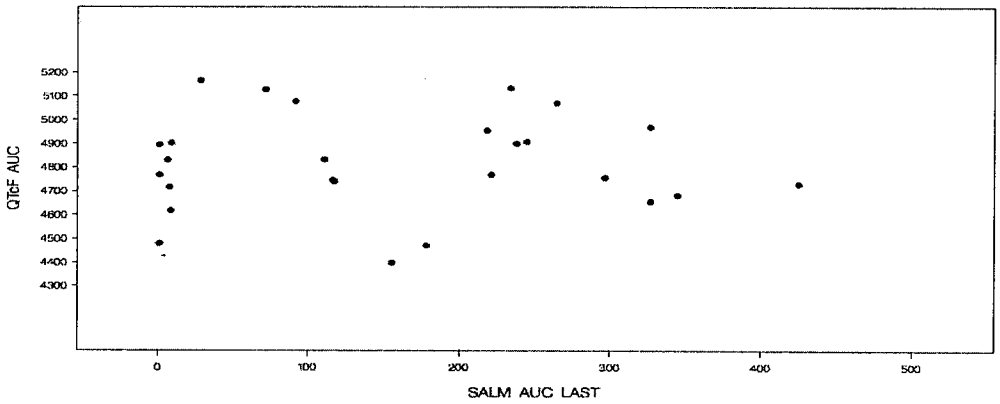


Figure 6. Plot of QTcF AUC_{12} *vs.* SALM AUC_{LAST} Correlation Coefficient = 0.0013



Therefore, it is concluded that no correlations between FP and SALM PD effects and exposure were found at these levels of exposure.

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/s/

Shinja Kim
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Emmanuel Fadiran
5/22/2006 11:12:29 AM
BIOPHARMACEUTICS
I concur

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-254 (000)	**Submission Date:** August 22, 2002
Name: ADVAIR™ HFA (fluticasone/salmeterol)	**Sponsor:** GlaxoSmithKline, PA
Type of Submission: Response	**Reviewer:** Shinja R. Kim, Ph.D.

Background: The subject of this New Drug Application, ADVAIR™ HFA Inhalation Aerosol, is an orally inhaled combination product containing fluticasone propionate (synthetic corticosteroid) and salmeterol xinafoate (long-acting β_2-adrenergic agonist) in the non-CFC propellant 1,1,1,2 -tetrafluoroethane. The inhalation aerosol is the first line extension to the approved product ADVAIR™ DISKUS®. Marketing approval is sought for three strengths, each containing a different amount of fluticasone propionate (44, 110 or 220 µg per actuation) and the same amount of salmeterol (21 µg per actuation), expressed as the ex-actuator amount.

Approvable Letter dated October 19, 2001 for this NDA was issued. In this letter, two CPB comments (#30 and #31) were included, and the sponsor was requested to respond to the comments/questions.

Gegeometric mean C_{max} and AUC_{last} of salmeterol in plasma following Advair™ HFA 8 inhalations of 44 µg fluticasone/21 µg salmeterol, 110 µg fluticasone/21 µg salmeterol, 220 µg fluticasone/21 µg salmeterol, from Study SAS10003, are shown in the table below.

Comparisons for salmeterol PK parameters

	44 µg/21 µg	110 µg /21 µg	220 µg /21 µg
AUC_{last} (pg•h/ml)	84	131	162
C_{max} (ng/ml)	0.22	0.38	0.47

As shown in the table, observed salmeterol plasma concentrations were different following the administration of the same dose. Therefore, the sponsor was asked to investigate cause(s) of this observation (i.e., Question #30). Similarly, plasma concentrations of salmeterol and especially fluticasone that were observed in Study SAS10005 were much higher compared to those from Study SAS10002. Thus, the sponsor was asked to explain this observation (i.e., Question #31)

The sponsor responded to questions #30 and 31 in the present submission, and they are summarized as follows:

Question #30

Investigate cause(s) of different salmeterol concentrations that were observed in Study SAS10003 following the same dose administration.

Response

Since systemic exposure following oral inhalation is often related to particles below —— in size, changes in C_{max} were compared to particle size distribution across strengths following cascade impactor analysis (Table 1).

Table 1. Mean Comparison of Salmeterol C_{max} (pg/mL) and Particle Size (µg) Across Strengths in SAS10003

	44/21	110/21	220/21
C_{max}	84	131	162

There was a trend for larger salmeterol particles [redacted] with fluticasone propionate (FP) strength, but these particle size differences did not correlate with the differences in systemic exposure between strengths and it is generally accepted that smaller, not larger, particles are more likely to be absorbed systemically. Smaller size particles within FPM [redacted] and in [redacted] did not correlate with the increase in systemic exposure observed. However, the differences in salmeterol systemic exposure observed in SAS10003 did not produce any significant differences in pharmacodynamic (e.g., heart rate and serum potassium) measurements.

Comment: Reviewing chemist was informed about the cascade impactor analysis (Table 1) and the systemic exposure of salmeterol. The sponsor stated that observed differences in the systemic exposure between strengths could not be explained by the particle size differences.

Question #31

Provide an explanation for the plasma concentrations for salmeterol and especially for fluticasone in Study SAS10005 being much higher than those observed in other studies (e.g., SAS10002).

Response

Differences in FP exposure in plasma were observed across studies (Table 2).

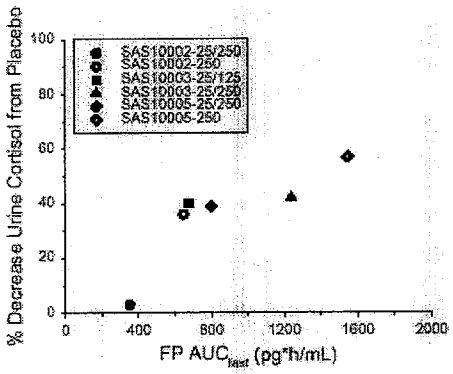
Table 2. Comparison of FP Systemic Exposure and FPM Following Combination and Individual FP Administration

	Combination 220/21 MDI	FP 220 MDI	Ratio Combo/FP (90% CI)
SAS10002 Geo LS Mean AUC_{last} (pg*h/mL)	341	645	0.53 (0.27, 1.04)
Geo LS Mean C_{max} (pg/mL)	84.8	119	0.71 (0.52, 0.96)
Mean FPM (mcg)	[redacted]		
SAS10005 Geo LS Mean AUC_{last} (pg*h/mL)	797.7	1528.8	0.52 (0.38, 0.72)
Geo LS Mean C_{max} (pg/mL)	187	304	0.62 (0.46, 0.82)
Mean FPM (mcg)	[redacted]		

FPM = Fine Particle Mass (Stages 3 - 5) following cascade impactor analysis testing

The effect of FP systemic exposure on urine cortisol excretion was examined across studies following administration of the combination and FP MDI devices.

Relationship between Cortisol and FP AUC_{last} across Studies



Differences in salmeterol plasma concentrations between studies were not so significant.

Comment: Differences in FP exposure between studies (i.e., Study SAS10002 and SAS10005) were significant, however, this difference in FP exposure became minimal if the FP exposure was compared between inhalers (see column 4 in Table 2). Still, the sponsor did not provide the reason(s) to why there was a significant differences in FP exposure between studies (design of these two studies were similar, employing healthy volunteers with similar age group and similar number of subjects). It was noted that batches that were used in these studies were different; Batches for combination HFA 220/21 MDI in Studies SAS10002 and SAS10005 were R10453/AX2846 and 9ZM0849, respectively. Batches for FP 220 MDI in Studies SAS10002 and SAS10005 were W0366NC and W0938CB, respectively.

Conclusion:

The sponsor responded to the comments #30 and 31 in the Approvable Letter for NDA 21-254 dated October 19, 2001. The sponsor could not provided an adequate explanation for the observed differences of salmeterol plasma concentrations in Study SAS10003 and fluticasone plasma concentrations in studies SAS10002 and SAS10005.

Shinja R. Kim, Ph.D., DPE II

Emmanuel Fadiran, Ph.D., Team Leader

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Shinja Kim
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Emmanuel Fadiran
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BIOPHARMACEUTICS
I concur

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-254 (000)
Drug Substance	Fluticasone propionate/Salmeterol xinafoate
Drug Product	ADVAIR™ HFA (fluticasone/salmeterol inhalation aerosol)
Strengths	44/21, 110/21 and 220/21 mcg (fluticasone/salmeterol)
Route of Administration	Oral Inhalation
Sponsor	GlaxoWellcome Inc.
Type of submission	Original NDA
Date of submission	12/20/2000
OCPB Division	DPE-II
Clinical Division	Pulmonary and Allergy Drug Products (HFD-570)
Reviewer	Shinja R. Kim, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D.

EXECUTIVE SUMMARY

The subject of this New Drug Application, ADVAIR™ HFA Inhalation Aerosol, is an orally inhaled combination product containing fluticasone propionate (synthetic corticosteroid) and salmeterol xinafoate (long-acting β_2-adrenergic agonist) in the non-CFC propellant 1,1,1,2 - tetrafluoroethane (Glaxo Wellcome code GR106642X). The inhalation aerosol is the first line extension to the approved product ADVAIR™ DISKUS®. Marketing approval is sought for three strengths, each containing a different amount of fluticasone propionate (44, 110 or 220 μg per actuation) and the same amount of salmeterol (21 μg per actuation), expressed as the ex-actuator amount. The product is designed to deliver 120 actuations providing a four-week supply of medication. ADVAIR™ HFA is proposed to be used for the long-term, 2 inhalations twice-daily maintenance treatment of asthma in patients 12 years of age and older. However, dose-response studies were not performed with ADVAIR™ HFA. The sponsor stated that dose selection for the ADVAIR™ HFA was based on previously established products, such as individual components of salmeterol (Serevent®) and fluticasone propionate (Flovent®) formulated as CFC inhalation aerosols or ADVAIR™ DISKUS®.

In support of this NDA, the clinical pharmacology program evaluated the pharmacokinetics and pharmacodynamics of salmeterol and fluticasone propionate using ADVAIR™ HFA (SFC HFA) MDI, Serevent®, Flovent® or ADVAIR™ DISKUS® products in four randomized, placebo-controlled, crossover studies in healthy volunteers (48 males and 20 females). The major findings from the studies are as follows; (1) systemic exposure of salmeterol and fluticasone from SFC HFA MDI were approximately half of that from individual CFC MDI, and corresponding pharmacodynamic effects were also reduced, except in a few pharmacodynamic measurements of salmeterol. (2) Pharmcokinetic and pharmacodynamic effects of fluticasone were similar from SFC HFA MDI and SFC DISKUS. On the other hand, systemic exposure for salmeterol from SFC HFA MDI was about 90% higher compared to the SFC DISKUS (causes not evaluated), and corresponding pharmacodynamic effects were less or comparable to each other. However how the systemic exposure, and further pharmacokinetic/pharmacodynamic data obtained only from the healthy volunteers, could interpolated into clinical efficacy is not clearly understood. Therefore, dose selections need to rely heavily on the results of clinical studies. The proposed labeling for pharmcokinetic section is reasonable with minor labeling recommendations (Page 20).

COMMENTS TO THE SPONSOR

- Consider collecting pharmacokinetic data in patients from the [redacted]
- Investigate cause(s) of different salmeterol concentrations that were observed following the same dose administration (i.e., study SAS10003).
- Plasma concentrations for fluticasone and salmeterol that were observed in study SAS10005 were much higher compared to those from other studies (e.g., SAS10002). The sponsor needs to explain this observation.

COMMENTS TO THE MEDICAL OFFICER

- Systemic exposure (AUC_{last}) and C_{max} of fluticasone from the SFC HFA MDI were 53% and 71% respectively of those of fluticasone from the Flovent® MDI, and corresponding pharmacodynamic effects on serum and urinary cortisol were also reduced.
- Systemic exposure of fluticasone from the SFC HFA MDI and SFC DISKUS inhaler was similar and resulted in similar decreases in serum and urine cortisol.
- Systemic exposure (AUC_{last}) and C_{max} of salmeterol from the SFC HFA MDI were 42% and 34% respectively of those of salmeterol from the Serevent® MDI, and corresponding pharmacodynamic effects on heart rate, QTc interval, serum potassium and serum glucose was either comparable or reduced from the SFC HFA MDI.
- Systemic exposure of salmeterol from the SFC HFA MDI was 88% higher compared to the SFC DISKUS (317 vs. 169 pg•h/ml), and peak concentrations were 12% lower after SFC HFA MDI compared to the SFC DISKUS (196 vs. 223 pg/ml). Corresponding pharmacodynamic effects on heart rate, QTc interval, and serum potassium and glucose were either comparable or reduced from the SFC DISKUS compared to SFC HFA MDI.
- All four clinical pharmacology studies were conducted in healthy volunteers.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Human Pharmacokinetics and Bioavailability section and found that NDA 21-254 is acceptable from a CPB standpoint provided the sponsor accepts the above comments (to the sponsor) and labeling recommendations (page 20).

Shinja R. Kim, Ph.D., DPE II

Emmanuel Fadiran, Ph.D., Team Leader

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Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings

In support of this NDA four CPB studies were conducted. A brief description of the studies are presented below:

SAS10001: A three-way crossover, cumulative doses study in 12 healthy subjects to compare the systemic pharmacodynamic effects of salmeterol administered from the combination HFA MDI (total dose 336/1760 mcg of salmeterol/fluticasone) or the individual salmeterol formulated with CFC propellants 11 and 12 MDI (total dose 336 mcg salmeterol).
SAS10002: Single-dose, four-way crossover design in 20 healthy subjects to compared the pharmacokinetics and pharmacodynamics of salmeterol and fluticasone following four inhalations from the combination 21/220mcg HFA MDI, salmeterol 21mcg CFC MDI, fluticasone propionate 220mcg CFC MDI, and placebo MDI.
SAS10003: Single-dose, four-way crossover design in 21 healthy subjects, examined salmeterol and fluticasone propionate pharmacokinetics and pharmacodynamics following eight inhalations from the combination 21/44mcg (total dose 168/352), 21/110mcg (168/880mcg), and 21/220mcg (total dose 168/1760mcg) HFA MDI strengths.
SAS10005: Single-dose, five-way cross-over design in 15 healthy subjects. The study compared fluticasone pharmacokinetics and pharmacodynamics from the 4 inhalations of combination HFA MDI, 2 inhalations of combination DISKUS, 4 inhalations of individual fluticasone propionate CFC MDI 220 mcg, and intravenously administered fluticasone propionate. Also, salmeterol pharmacokinetics and pharmacodynamics was compared between the combination HFA MDI and combination DISKUS products.

The following summarized pharmacokinetic and pharmacodynamic properties of fluticasone and salmeterol were derived from these 4 studies:

Fluticasone Propionate:

- Systemic exposure from the combination (SFC) HFA MDI was significantly lower (e.g., AUC_{last} from the SFC was 53% of the AUC_{last} from Flovent® MDI compared to the individual

inhaler, and corresponding pharmacodynamic effects on serum and urinary cortisol were also reduced. The sponsor did not give explanation for the differences in the bioavailability of the formulations, SFC HFA MDI vs. fluticasone CFC inhaler, however, the sponsor indicated that drug-drug interaction between salmeterol and fluticasone can be ruled out based on earlier work with SFC DISKUS. The sponsor speculated that the reduction in the number of finer particles in SFC might have resulted in lower systemic exposure for the SFC HFA MDI.

- T_{max} were similar from the SFC HFA, SFC DISKUS and individual inhalers and occurred in 0.33 – 1.5 hours.
- Systemic exposure (AUC_{last}) from the SFC HFA MDI was not influenced by gender, however, it is not sufficiently validated due to the small number of subject (12 male and 9 female from SAS10003).
- Plasma fluticasone concentrations increased proportionally with strength suggesting lung deposition was dose proportional. These changes resulted in treatment-related decreases in urinary cortisol.
- Systemic exposure of fluticasone propionate from the SFC HFA MDI and SFC DISKUS inhaler was similar and resulted in similar decreases in serum and urine cortisol.

Salmeterol:

- Systemic exposure from the combination HFA MDI was significantly lower compared to the individual inhaler (salmeterol $AUC_{0\text{-}30min}$ from the combination inhaler was 42% of the value from the salmeterol CFC inhaler), and corresponding pharmacodynamic effects on heart rate, QTc interval, serum potassium and serum glucose was either comparable or reduced from the SFC inhaler (SAS10002).
- Systemic exposure of salmeterol from the SFC HFA MDI was 88% higher compared to the SFC DISKUS (317 vs. 169 pg•h/ml), and peak concentrations were 12% lower after SFC HFA MDI compared to the SFC DISKUS (196 vs. 223 pg/ml). Based on the 90% confidence intervals for the AUC_{last} and C_{max} parameters, SFC HFA MDI and SFC DISKUS formulations were not comparable for salmeterol (cause(s) were not evaluated). Changes in serum potassium and serum glucose were similar between SFC HFA MDI and SFC DISKUS, but, most assessments of ECG changes from SFC DISKUS were not different from placebo, while these changes from SFC HFA MDI were different compared to placebo (SAS10005).
- Following a single dose, peak plasma salmeterol concentrations occurred in 5 - 10 minutes from the SFC HFA MDI, SFC DISKUS and individual inhaler (SAS10005).
- C_{max} of salmeterol was not influenced by gender, however, the number of subjects was too small to be validated for this claim (SAS10003).
- Plasma salmeterol concentrations were not identical from the three strengths. The sponsor stated that the difference in plasma salmeterol concentrations was not explained by differences in salmeterol fine particle mass, nor by Cascade impactor data, and further examination would require the co-administration of separate inhalers containing the individual drugs in GR106642X propellant,
  However, pharmacodynamic effects of salmeterol on heart rate and serum potassium were similar across 3 strengths used in study SAS10003.

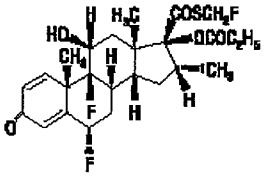
Basic PK properties of salmeterol and fluticasone propionate were not evaluated and the information in the proposed Package Insert are from the currently approved products.

BACKGROUND: The following information was provided by the sponsor (from package inserts and/or previous work).

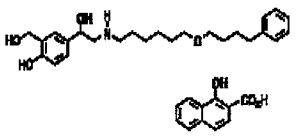
Chemistry: ADVAIR HFA Inhalation Aerosol is a combination of fluticasone propionate and salmeterol xinafoate. This product does not contain any chlorofluorocarbon (CFC) as the propellant. and intended for oral inhalation only.

Fluticasone propionate is a corticosteroid with a molecular weight of 500.6 and the empirical formula is $C_{25}H_{31}F_3O_5S$. Chemical structure for fluticasone (left panel) is shown below.

Salmeterol xinafoate is a highly selective beta$_2$-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol with molecular weight of 603.8 and the empirical formula $C_{25}H_{37}NO_4 \bullet C_{11}H_8O_3$. Chemical structure for salmeterol (right panel) is shown below;



Fluticasone Propionate



Salmeterol Xinofoate

Pharmacokinetics of Fluticasone Propionate: Absorption is rapid with peak plasma concentrations in most subjects occurring within one hour. The major portion of the inhaled dose is swallowed regardless of inhalation device; but does not contribute significantly to the systemic exposure. Oral bioavailability is less than 1 % due to a combination of incomplete absorption and high first pass metabolism by the gut wall and liver. The volume of distribution at steady state is 4.2 L/kg. Plasma protein binding averages 91%. Plasma clearance is high averaging 1.1 L/min. The terminal elimination half-life following intravenous or inhaled administration is about 6 - 8 hours. Metabolism to an inactive carboxylic acid metabolite (GR36264) occurs by the cytochrome P450 isoenzyme, CYP3A4. The major route of elimination is the feces. The renal excretion of fluticasone propionate is negligible (<0.02% of the dose) and less than 5% of the dose is excreted in the urine as metabolites. In asthma patients the systemic exposure to fluticasone propionate following inhalation is about half that found in healthy subjects and is likely due to airflow obstruction. The elimination kinetics appears to be unaltered in asthmatic subjects. This is illustrated by the similarity of the accumulation ratio following multiple dosing in patients (1.7) and healthy subjects (1.5). Fluticasone propionate does not affect the metabolism of other drugs metabolized by the CYP3A4 enzyme system. Drugs that act as a substrate for (terfenadine) or as a moderate inhibitor (erythromycin) of the CYP3A4 system do not significantly alter the systemic exposure of fluticasone propionate. Ketoconazole increased the systemic exposure of fluticasone propionate, and thus a similar potential exists for other strong inhibitors of the CYP3A4 enzyme system such as ritonavir.

Pharmacodynamics of Fluticasone Propionate: Fluticasone propionate is a glucocorticosteroid. As with salmeterol, its principal site of action is locally in the lung, but systemic absorption can lead to extrapulmonary effects. The systemic pharmacodynamic effects of corticosteroids are numerous and can affect almost all body systems. The most sensitive and most easily measured effects are on the hypothalamic-pituitary-adrenal (HPA) axis. Inhibition of the HPA axis by exogenous corticosteroids can be assessed by reductions in serum cortisol concentrations and urinary cortisol excretion. Previous data from individual dry powder and

metered dose inhaler formulations demonstrated that daily doses of 500mcg twice daily were at the threshold for producing systemic effects on the HPA axis. The relationship between systemic exposure and serum cortisol concentrations and urinary cortisol excretion (i.e., PK-PD) were modeled, and the model demonstrated that exposure expected from single doses of 1000mcg fluticasone propionate, or repeat doses of 500mcg twice daily, associated with significant reductions in these measures.

Pharmacokinetics of Salmeterol Xinafoate: Salmeterol xinafoate is an ionic salt, which freely dissociates in solution releasing the salmeterol and 1-hydroxy-2-naphthoic acid moieties. These components are subsequently absorbed, distributed, metabolized and excreted independently. The salmeterol dose is expressed as the free base. Salmeterol hydroxynaphthoate is highly lipophilic and has very poor aqueous solubility. Plasma protein binding is 96% and involves both alpha1-acid glycoprotein and albumin. Peak plasma concentrations occur within 5 - 8 minutes regardless of the inhalation device used. The pharmacokinetics of salmeterol is essentially unchanged from the combination DISKUS compared to salmeterol DISKUS. Elimination of salmeterol is primarily by cytochrome P450-mediated metabolism involving the CYP3A4 isoenzyme. The major pathway in man is aliphatic oxidation to generate an alpha hydroxyl metabolite (GR127433). A minor product is the O-dealkylated derivative (GR72438). Excretion is by metabolic clearance and fecal excretion of the metabolites. No parent drug was detected in the urine or feces. The elimination half-life, based on limited plasma concentration-time data from one subject using radiolabelled drug, was estimated to be 5.5 hours.

Pharmacodynamics of Salmeterol: The principal site of action for salmeterol is locally in the lung. However, in common with other $beta_2$-agonists, once absorbed into the systemic circulation its extrapulmonary pharmacodynamic effects include dose-related increases in heart rate, QTc interval and blood glucose concentrations; and dose-related reductions in diastolic blood pressure and plasma potassium concentrations. Such effects are typically not seen at the recommended dose of salmeterol, 50mcg twice daily. The systemic pharmacodynamic effects of salmeterol were evaluated in order to assess the potential for pharmacodynamic interactions between salmeterol and fluticasone propionate. They were also used to compare exposure from different salmeterol-containing products, because the complete definition of salmeterol pharmacokinetics has not been possible due to the low and transient plasma concentrations achieved after inhalation of clinically effective doses, and the limits of the assay.

Indications and Usage: ADVAIR HFA is indicated for the long-term, twice-daily maintenance treatment of asthma in patients 12 years of age and older. ADVAIR HFA is NOT indicated for the relief of acute bronchospasm.

Question Based Review

Is the pharmacokinetics of the proposed product different compared to that from the currently marketed product(s)?

FLUTICASONE PHARMACOKINETICS

Note: (1) The sponsor indicated that $AUC_{0-\infty}$ estimates were often not estimated or involved using extrapolated areas comprising greater than 20% of this value in many subjects, therefore, AUC_{last} (i.e., time zero to the quantitation limit of the assay), is considered a better parameter to describe systemic exposure (Thus, AUC_{last} was used for systemic exposure comparison in all PK studies). (2) For comparative purposes the 90% confidence intervals for the treatment ratios were plotted with the range 0.7-1.43 and used to describe a 30% difference between drug products (per the sponsor).

1. Comparison to Individual Inhaler (SAS10002)

Relative bioavailability was obtained and conclusions derived from this study are presented in Table 1:

Table 1. PK of fluticasone and treatment comparisons

	SFC	SFC/FP	FP
AUC_{last} (pg*h/mL) Geometric Mean 95% CI Mean Ratio 90% CI	350.7 (195.0, 630.8)	 0.53 (0.27, 1.04)	647.3 (341.2, 1227.7)
C_{max} (pg/mL) Geometric Mean 95% CI Mean Ratio 90% CI	85.7 (66.6, 110.3)	 0.71 (0.52, 0.96)	120.3 (82.6, 175.4)
t_{max} (h) Median Range Median Difference 90% CI	1.00 (0.50, 3.00)	 -0.25 (-0.5, 0.0)	1.50 (0.50, 2.05)

SFC = salmeterol/fluticasone propionate combination inhaler 21/220mcg [total dose 84/880mcg], FP = fluticasone propionate inhaler 220mcg [total dose 880mcg]

- Fluticasone propionate concentrations were appreciably lower from SFC resulting in significantly lower $AUC_{last=0-8h}$ (53% of FP CFC) and C_{max} (71% of FP CFC) estimates compared to FP (i.e., Flovent® MDI). The 90% CI for the AUC_{last} and C_{max} parameters was considerably outside the range 0.7 – 1.43 (30% difference) indicating that the PK for the two formulations was not comparable. The sponsor did not give explanation for the differences in the bioavailability of the formulations, SFC HFA MDI vs. fluticasone CFC inhaler, however, the sponsor indicated that drug-drug interaction between salmeterol and fluticasone can be ruled out based on earlier work with SFC DISKUS. The sponsor speculated that the reduction in the number of finer particles in SFC might have resulted in lower systemic exposure.
- T_{max} was similar following both treatments.
- Terminal $t_{1/2}$ was similar from the SFC and fluticasone CFC inhalers averaging 6.2 and 5.8 hrs, respectively (Table 1, page 27).

2. Comparison with Combination DISKUS, Individual Inhaler and Intravenous Dose (SAS10005)

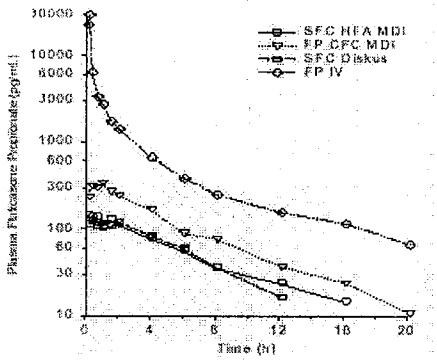
The pharmacokinetic parameters are summarized in Table 2 and the plasma concentration-time profiles are shown in Figure 1. AUClast and Cmax after intravenous dose were 15.7 ng•h/mL and 29.7 ng/mL respectively (Table 1, page 36).

Table 2. Comparisons following inhalation administration

Parameter	SFC MDI 4 x 21/220	SFC Disk 2 x 50/500	FP MDI 4 x 220	SFC MDI/ SFC Disk	SFC MDI/ FP MDI	SFC Disk/ FP MDI
AUC_{last} (pg*h/mL) Geo. Mean	799	832	1543			
95% CI	484, 1318	663, 1044	1156, 2061			
Ratio				0.96	0.52	0.55
90% CI				0.69, 1.34	0.38, 0.72	0.39, 0.76
C_{max} (pg/mL) Geo. Mean	186	182	307			
95% CI	136, 255	150, 222	233, 404			
Ratio				1.02	0.62	0.60
90% CI				0.77, 1.37	0.46, 0.82	0.45, 0.80
t_{max} (h) Median	0.33	0.83	0.67			
Range	0.17, 1.5	0.17, 2.0	0.33, 4.0			
Median Diff.				-0.33	-0.17	0.25
90% CI				-0.67, 0.00	-0.42, 0.17	-0.33, 0.67

SFC MDI = salmeterol/fluticasone inhalation aerosol 21/220mcg [total dose 84/880mcg], SFC Diskus = salmeterol/fluticasone Diskus 50/500mcg [total dose 100/1000mcg],
FP MDI = marketed fluticasone propionate inhalation aerosol 220mcg [total dose 880mcg]

Figure 1. Median fluticasone concentration-time profiles following each treatment



Absolute bioavailability: Absolute BA estimates for the two SFC combination treatments based on AUC are show in Table 3 (the sponsor also estimated for AUC_{∞} for comparison).

Table 3. Fluticasone absolute bioavailability Estimates (%)

Parameter	SFC MDI	SFC Diskus	FP MDI
AUC_{last} Geo. mean	5.3	5.5	10.3
95% CI	3.6, 7.9	3.6, 7.9	6.9, 15.3
AUC_{∞} (pg*h/mL) Geo. mean	6.3	6.0	12.5
95% CI	4.7, 8.5	4.5, 8.1	9.4, 16.5

Conclusions:

- Fluticasone propionate systemic exposure (AUC_{last}) from the combination inhaler was 52% of the value from the FP CFC inhaler. C_{max} for both combination inhalers were approximately 60% of C_{max} for the FP CFC MDI (Table 2). Therefore, formulations for the combination products and Individual inhaler were not comparable.
- The 90% CI for the estimated ratios of AUC_{last} and C_{max} parameters for SFC HFA MDI and SFC DISKUS were within or almost within the range 0.7 – 1.43, therefore, the sponsor concluded that SFC HFA MDI and SFC DISKUS were comparable. However, these two formulations were not comparable by applying bioequivalence criteria of 20% difference, 0.8 – 1.25 range (Table 2).
- Absolute bioavailability estimates for the two SFC combination treatments using AUC_{last} were approximately half of the value for FP CFC MDI (Table 3).
- Mean terminal half-life estimates for the 4 treatments were similar and ranged from 4.3 – 5.6 hours (Table 1, page 36).
- The relative bioavailability estimate comparing SFC HFA MDI to FP CFC MDI in this study (52%) confirmed the estimate observed in study SAS10002 (53%).

SALMETEROL PHARMACOKINETICS

3. Comparison to Individual Inhaler (SAS10002)

Pharmacokinetic parameters are summarized in Table 4 and conclusions derived from the study are presented below:

Table 4. PK of salmeterol and Treatment comparisons

	SFC	SFC/SALM	SALM
AUC_{last} (pg*h/mL) Geometric Mean 95% CI Mean Ratio 90% CI	64 (48, 84)	 0.42 (0.36, 0.48)	150 (120, 190)
C_{max} (pg/mL) Geometric Mean 95% CI Mean Ratio 90% CI	170 (120, 230)	 0.34 (0.28, 0.41)	510 (380, 680)
t_{max} (h) Median Range Median Difference 90% CI	0.083 (0.033, 0.58)	 -0.07 (-0.17,0.0)	0.083 (0.033, 0.33)

SFC = salmeterol/fluticasone propionate combination 21/220mcg inhaler (total dose 84/880mcg)
SALM = salmeterol 21mcg inhaler (total dose 84mcg)

- Salmeterol systemic exposure from the combination HFA MDI was significantly lower compared to the individual inhaler, i.e. mean AUC_{last} ($AUC_{0-0.5h}$) and C_{max} for SFC were 42% and 34% respectively of those of salmeterol CFC MDI (SALM). Therefore, the two formulations (SFC and SALM) were not comparable.
- T_{max} occurred within a few minutes (5 min) from the combination HFA MDI and individual salmeterol MDI.

4. Comparison with Combination DISKUS product (SAS10005)

Results are summarized in Figure 2 and Table 5:

Figure 2. Median plasma concentration-time plots

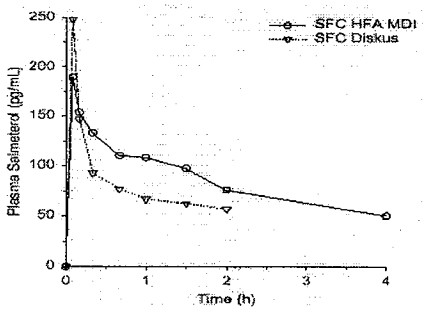


Table 5. PK of salmeterol and Treatment Comparisons

	SFC MDI	MDI/Diskus	SFC Diskus
AUC_{last} (pg*h/mL) Geometric Mean 95% CI Mean Ratio 90% CI	317 (221, 454)	 1.82 (1.27, 2.60)	169 (121, 237)
C_{max} (pg/mL) Geometric Mean 95% CI Mean Ratio 90% CI	196 (140, 276)	 0.86 (0.61, 1.20)	223 (161, 309)
t_{max} (h) Median Range Median Difference 90% CI	0.08 (0.08, 1.02)	 0.045 (0.000, 0.460)	0.08 (0.08, 1.00)

SFC MDI = salmeterol/fluticasone propionate combination 21/220mcg inhalation aerosol [total dose 84/880mcg]
SFC Diskus = salmeterol/fluticasone propionate combination 50/500mcg dry powder Diskus inhaler [total dose 100/1000mcg]

- Salmeterol AUC_{last} was 82% higher following SFC HFA MDI (317 pg•h/mL) compared to SFC DISKUS (169 pg•h/mL). Mean C_{max} was 12% lower after SFC HFA MDI (196 pg/mL) compared to after SFC DISKUS (223 pg/mL). The 95% CI for the AUC_{last} and C_{max} parameters for SFC HFA MDI and SFC DISKUS were not within the range 0.70 - 1.43, therefore, the pharmacokinetics for the two formulations were not comparable.
- Peak concentrations were observed at 5min in most subjects following both treatments with median values of 0.08h (5min) for both SFC HFA MDI and SFC DISKUS.

What is the dose-systemic exposure relationship following the proposed product, SFC HFA MDI?

Study SAS10003 was conducted with the purpose of showing dose proportionality.

Comparison across strengths for fluticasone: Utilized doses were eight inhalations from the combination 21/44, 21/110 and 21/220mcg SFC HFA MDI strengths; total dose of 352, 880 and 1760 mcg of fluticasone, respectively and 168mch of salmeterol. PK comparisons and the plasma concentration-time profiles are shown in Table 6 and Figure 3 respectively.

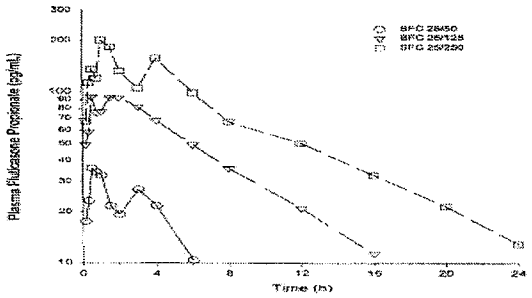
Table 6. Comparisons for the fluticasone PK parameters (geometric mean; median for t_{max})

	Treatment A: SFC 25/50 (400mcg)	Dose Normalized A/B	Treatment B: SFC 25/125 (1000mcg)	Dose Normalized C/B	Treatment C: SFC 25/250 (2000mcg)
AUC_{last} (pg*h/mL) Geometric Mean	80.4		675.8		1239.0
Mean Ratio		0.29		0.91	
90% CI		(0.16, 0.51)		(0.52, 1.60)	
C_{max} (pg/mL) Geometric Mean	41.4		107.9		172.5
Mean Ratio		0.93		0.81	
90% CI		(0.73, 1.18)		(0.64, 1.03)	
t_{max} (h) Median	1.00		1.50		1.50
Median Difference		-0.38		0.16	
90% CI		(-0.81, 0.00)		(-0.11, 0.50)	

Note: AUC_{last} and C_{max} treatment comparisons were performed following dose-normalization and log transformation. Treatment means were not dose-normalized.

Note: 25/50 µg, 25/125 µg, and 25/250 µg are expressed as ex-valve doses, and corresponding ex-actuator doses are 21/44 µg, 21/110 µg, and 21/220 µg, respectively.

Figure 3. Median plasma fluticasone concentration-time profiles.



A determination of dose proportionality was examined using a power model approach, and the results are presented in Table 7. The sponsor indicated that the measurable concentrations were observed in most samples taken through 24h following the 880mcg and 1760mcg doses. Conversely, concentrations following the 352mcg dose in most subjects was below the quantitation limit of 10pg/mL after 6h, which may result in under-estimations of AUC following 352-mcg dose. Therefore $AUC_{0\text{-}6h}$ was also constructed to support dose proportionality across strengths.

Table 7. PK and Dose Proportionality of Fluticasone from Three Strengths of Combination HFA MDI (Geometric mean)

	n	SALM/FP (mcg)			Dose Proportionality*
Strength/actuation Total dose		21/44 168/352	21/110 168/880	21/220 168/1760	Adjusted Mean Slope (90% CI)
FP C_{max} (pg/mL)	19-20	41.4	107.9	172.5	0.93 (0.80, 1.05)
FP AUC_0 (pg.h/mL)	10	233.6	701.4	1207.6	1.03 (0.88, 1.18)
FP AUC_{last} (pg.h/mL)	19-20	80.4	675.8	1239.0	1.75 (1.43, 2.07)

* A confidence interval within the range 0.78 – 1.22 indicated dose proportionality

Note: 21/44 and 21/220 (n=19); 21/110 (n=20)

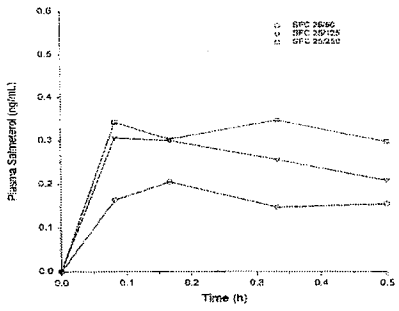
Comparison across strengths for salmeterol: Results are presented in Table 8 and Figure 4.

Table 8. PK of Salmeterol and Treatment Comparisons from each Strength after an administered Dose of 168mcg

	A: SFC 21/44	A/B	B: SFC 21/110	C/B	C: SFC 21/220
AUC_{last} (pg*h/mL)					
Geo. Mean	84		131		182
95% CI	(68, 104)		(99, 174)		(118, 222)
Mean Ratio		0.65		1.24	
90% CI		(0.52, 0.80)		(1.00, 1.53)	
C_{max} (pg/mL)					
Geo. Mean	220		380		470
95% CI	(180, 280)		(280, 530)		(340, 660)
Mean Ratio		0.59		1.23	
90% CI		(0.45, 0.77)		(0.94, 1.61)	
t_{max} (h)					
Median	0.167		0.150		0.167
Range	(0.083, 0.500)		(0.083, 0.517)		(0.083, 0.500)
Median Diff.		0.071		0.008	
90% CI		(0.00, 0.158)		(-.042, 0.084)	

SFC = salmeterol/fluticasone combination inhalers, SAL = salmeterol (total dose was 8 inhalations)

Figure 4. Median plasma salmeterol concentrations-time profile.



Although the same salmeterol dose (168 mcg) was administered in this study, differences in systemic exposure were observed across strengths. The sponsor stated that the difference in plasma salmeterol concentrations was not explained by differences in salmeterol 'fine particle mass' dose for the batches used in this study, nor by 'Cascade impactor' data. Further examination would require the co-administration of separate inhalers containing the individual drugs in GR106642X propellant.

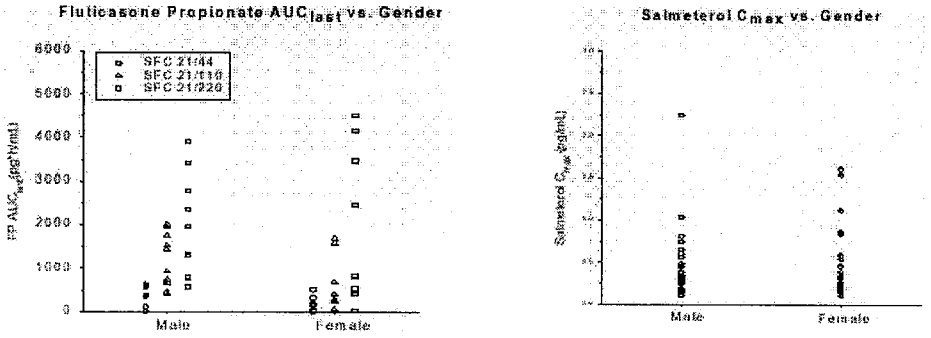
Conclusions:

- According to the sponsor, dose proportionality was achieved for C_{max}. AUC_{last} was proportional between the 880mcg (SFC 21/110) and 1760mcg (SFC 21/220) fluticasone doses, but could not be concluded for the 352mcg (SFC 21/44) fluticasone dose. The sponsor suggested that this was likely due to assay limitations at the lowest dose that prevented adequate estimation of this parameter. On the other hand, dose normalized C/B ratios for AUC_{last} and C_{max} (Table 7) were out side of the range of 0.8-1.25, therefore, dose proportional was not established for AUC_{last} and C_{max} even after 21/220 and 21/110 doses, by applying the bioequivalence criteria of 0.8-1.25. However, which cut off point (i.e., 20 or 30% difference) should be used is complicated considering variances and the sample size used in the data analysis.
- The systemic exposure to salmeterol was not identical for the three strengths of inhalers, and the sponsor has not offered any explanation for these observations (Table 8).
- t_{max} was similar for both fluticasone and salmeterol across strengths (Table 7 and 8).

How do the pharmacokinetics of the proposed product compare between males and females?

The effect of gender on the PK of fluticasone and salmeterol following SFC HFA MDI administration was examined in study SAS10003 (Figure 5). It appears that there were no gender-related differences, however, the number of subjects is too small for confirmation (12M, 9F):

Figure 5. Comparisons were based on data from SAS10003



How do the pharmacokinetics of the proposed product compare in asthmatic patients and healthy volunteers?

The pharmacokinetics of SFC HFA MDI has not been assessed in patients, but only in healthy volunteers (the sponsor indicated that a direct link between clinical efficacy and systemic exposure has not been established for fluticasone or salmeterol). However, six clinical studies (including non-USA studies) were carried out to provide an assessment of the effectiveness and safety of the proposed product. In addition, the sponsor indicated that Phase IIIb-IV studies have been planned with the HFA MDI (intention is not clear) combination product in adolescent and adult patients with asthma (may obtain PK data in patients from the . Regarding pediatric program, the sponsor plans

What are the basic pharmacokinetic (ADME) characteristics as well as intrinsic and extrinsic factors that influence exposure or response of the proposed product?

Since both active components, fluticasone propionate and salmeterol, in the proposed product are currently on the market as an Individual CFC MDI or DISKUS, or combination DISKUS, the information above were not assessed. The above information was obtained (borrowed) from currently marketed products for SFC HFA MDI Package Insert.

What were the pharmacodynamic effects measured following fluticasone and salmeterol administration? Were the pharmacodynamic effects following the proposed product different compared to the currently marketed products?

PHARMACODYNAMICS of FLUTICASONE

Urinary cortisol excretion and/or serum cortisol measurements were assessed to describe the effect of systemic fluticasone on HPA axis (e.g., cortisol level decreases following fluticasone administration).

1. Comparison to individual inhaler (SAS10002)

Each subject received SFC HFA MDI (84/880mcg), fluticasone CFC 220mcg (880mcg) and salmeterol 21mcg (total dose 84mcg). The results showed that SFC HFA MDI administration did not affect urinary cortisol excretion as compared to fluticasone CFC MDI administration that produced significant decrease in urinary cortisol; post treatment geometric means of urine cortisol following SFC HFA MDI, salmeterol CFC MDI and Placebo ranged between 26.3 – 28.3mcg , i.e., no difference in urine cortisol from these 3 treatment compared to 18.5mcg for fluticasone CFC MDI (Table 3, page 28). This difference (i.e., FP inhaler vs. SFC) may be due to higher systemic exposure found after FP inhaler.

2. Comparison with SFC DISKUS, Individual inhaler and Intravenous Dose (SAS10005)

Each subject received SFC HFA MDI (84/880mcg), SFC DISKUS (100/1000mcg), fluticasone CFC 220mcg (880mcg) inhalation aerosol (FP), intravenous fluticasone 1010mcg or placebo. Results are summarized in Table 9 and conclusions derived from this study are presented below.

Table 9. Post treatment Cortisol Geometric means and Treatment comparisons

Parameter	Placebo DISKUS	SFC HFA MDI	SFC DISKUS	FP CFC MDI	FP IV
Serum AUC_{24} (pmol*h/mL)	6231.8	4821.8[ab]	5357.7[abc]	4483.2[ab]	2604.1[a]
Serum C_{min} (pmol/mL)	58.1	38.3[ab]	42.0[b]	31.5[ab]	13.9[a]
Urine Excretion (mcg)	32.1	19.9[ab]	21.8[abc]	13.7[ab]	9.4[a]

a statistically different from placebo (confidence interval did not contain 1.0)
b statistically different from IV (confidence interval did not contain 1.0)
c statistically different from FP CFC MDI (confidence interval did not contain 1.0)

- Mean serum AUC_{24} for all active treatments were lower compared to placebo.
- Serum AUC_{24} from SFC DISKUS was statistically different compared to FP CFC MDI with ratio of 1.2, while AUC_{24} for SFC HFA MDI was not different from FP CFC MDI with a ratio of 1.03. However, serum AUC_{24} between SFC HFA MDI and SFC DISKUS was not statistically different based on 95% CI.
- Serum C_{min} for SFC DISKUS and placebo was not statistically different, but different for SFC HFA MDI and FP CFC MDI compared to placebo. However, C_{min} comparison between SFC HFA MDI and SFC DISKUS was not statistically different based on 95% CI.
- Urinary cortisol excretion for all inhaled treatments were lower compared to placebo.

- Urinary cortisol excretion for SFC HFA MDI and SFC DISKUS were similar (based on 95% CI) but higher than from FP CFC MDI.
- Decreases in serum C_{min} and urine cortisol were significantly less following 1mg fluticasone inhaled doses from SFC HFA MDI, SFC DISKUS and FP CFC MDI compared to a 1mg IV dose.
- This study suggested that the presence of salmeterol in the combination inhaler did not influence on the pharmacodynamics of fluticasone.

3. Comparisons across Strengths (SAS10003)

Urinary cortisol excretion following fluticasone propionate doses of 352, 880, and 1760mcg from 21/44, 21/110, and 21/220 SFC HFA MDIs, were reduced by 18%, 40%, and 42%, respectively, compared to placebo. The reductions from 21/110 and 21/220 were significantly higher compared to placebo, but not between 21/44 and placebo. However, differences between strengths did not reach statistical significance based on 95% CI; 21/44 *vs.* 21/110 = 0.92-2.08; 21/220 *vs.* 21/110 = 0.65-1.47 (Figure 3, page 33).

PHARMACODYNAMICS of SALMETEROL

A number of physiological biochemical parameters were used to measure systemic salmeterol pharmacodynamics because of the limited ability to measure systemic exposure to salmeterol. The parameters measured in each study are described below.

Salmeterol Pharmacodynamic Measurements

Parameter	SAS10001	SAS10002	SAS10003	SAS10005
Blood Pressure	✓	✓		
Heart Rate	✓	✓	✓	
QT Interval	✓	✓		✓
Potassium	✓	✓	✓	✓
Glucose	✓	✓		✓

4. Comparison to individual inhaler (SAS10001 and SAS10002)

SAS10001: Subjects received cumulative (42 – 336mcg) doses to assure adequate sensitivity for treatment comparisons. The results are summarized in Table 10 and conclusions are shown below (consulted with the medical reviewer):

Table 10. Mean salmeterol PD Parameters after a Cumulative Dose of 336mcg.

	SFC[a] (n=12)	SALM[a] (n=11)	Placebo (n=11)
Systolic Blood Pressure (mmHg)	122.38[cd]	125.91[b]	120.05
Diastolic Blood Pressure (mmHg)	65.75[bd]	67.23[b]	71.55
Heart Rate (bpm)	77.50[bc]	84.09[b]	62.55
QTcB (msec)	448.75[b]	450.45[b]	402.00
Potassium (mmol/L)	3.354[bc]	3.227[b]	3.772
Glucose (mmol/L)	6.043[b]	6.243[b]	4.902

a Doses of 42/220, 42/220, 84/440 and 168/880mcg of salmeterol/fluticasone propionate (SFC) or 42, 42, 84 and 168mcg salmeterol (SALM) were given at 60min intervals;
b statistically different from placebo;
c statistically different from SALM;
d slope statistically different from SALM

The effects on blood pressure from the combination inhaler were less than or comparable to salmeterol alone. The increase in HR following salmeterol administration from the combination inhaler was less than salmeterol alone, but the slopes of the increases were comparable. Increases in QTcB (QT interval corrected using Bazett's method) interval from the combination inhaler and salmeterol alone were similar. The effect of salmeterol on decreasing plasma potassium from the combination inhaler was less than salmeterol alone, but the slopes were comparable. The effect of salmeterol on the increase in plasma glucose from the two inhalers was comparable.

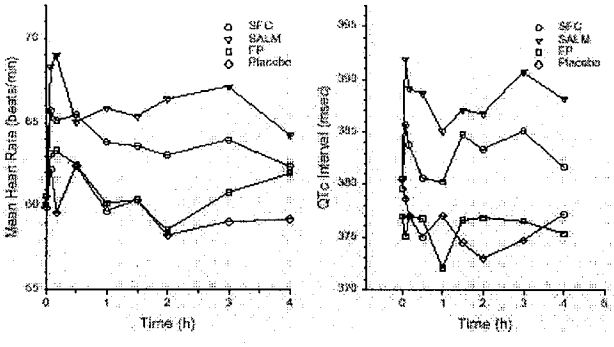
SAS10002: Subjects received a total dose of salmeterol 84mcg and/or fluticasone propionate 880mcg in each active treatment leg, and the results from this study are summarized in Table 11 and Figure 5 followed by conclusions below. Note: Weighted mean was calculated by dividing the area under the effect-time curve by the sampling interval to express the value in units of measure.

Table 11. Mean Salmeterol PD parameters (n = 20)

	SFC	SALM	FP	Placebo
Systolic Blood Pressure (mmHg)				
Weighted mean	116.9	118.1	115.3	115.9
Maximum	124.5	127.7	123.1	124.6
Diastolic Blood Pressure (mmHg)				
Weighted mean	71.2	72.1	72.8	72.9
Minimum	65.1	66.0	67.3	65.2
Heart Rate (bpm)				
Weighted mean	64.0[ab]	66.1[a]	60.7	59.6
Maximum	69.7[b]	74.1[a]	68.6	67.2
QTcB (msec)				
Weighted mean	383.1[ab]	388.1[a]	375.9[b]	375.2
Maximum	397.9[a]	401.0[a]	391.7	391.3
Potassium (mEq/L)[c]				
Weighted mean	4.2	4.2	4.4	4.3
Minimum	3.9	3.9	4.0	4.0
Glucose (mg/dL)[c]				
Weighted mean	99.9[a]	101.4[a]	94.9	94.6
Maximum	104.0	108.4	98.8	98.6

a statistically different from placebo
b statistically different from SALM
c geometric means used for this parameter

Figure 5. Comparison of Mean Heat Rate (left) and QTcB (right)



- While blood pressure and serum potassium were unaffected, there were significant changes in heart rate, QTc, and serum glucose following SFC and salmeterol CFC MDI (SALM) compared to placebo.
- SFC and SALM produced similar changes in serum glucose and maximum QTc, but SALM produced larger changes in heart rate and weighted QTc compared to SFC.

- Blood pressure, heart rate, serum potassium and serum glucose were unaffected by fluticasone CFC MDI (FP) administration. Weighted mean QTc was marginally, but significantly higher following FP, but maximum QTc was unaffected.

5. Comparison with Combination DISKUS (SAS10005)

Pharmacodynamic effects were compared among SFC HFA MDI, SFC DISKUS and placebo, and the results are summarized in Table 12.

Table 12. PD of Salmeterol (n = 15)

Parameter	SFC MDI	SFC Diskus	Placebo
Potassium (mEq/L)[a]			
Weighted mean	3.92[c]	3.95[c]	4.05
Minimum	3.78[c]	3.83[c]	3.92
Glucose (mg/dL)[a]			
Weighted mean	5.10[c]	5.03[c]	4.77
Maximum	5.29[c]	5.21[c]	4.97
Uncorrected QT (msec)[b]			
Weighted mean	414[c]	412[c]	420
Minimum	402[c]	402	406
QTcB (msec)[b]			
Weighted mean	414[cd]	407[c]	400
Maximum	424[c]	420[c]	410
QTcF (msec)[b]			
Weighted mean	413[c]	408	406
Maximum	422[c]	418	413

SFC MDI = salmeterol/fluticasone propionate combination 21/220mcg inhalation aerosol
SFC Diskus = salmeterol/fluticasone propionate combination 50/500mcg dry powder DISKUS inhaler
a geometric means,
b arithmetic means
c statistically different from placebo
d statistically different from SFC DISKUS

- Statistically significant increases in serum glucose and decreases in serum potassium concentrations were observed following SFC HFA MDI and SFC DISKUS compared to placebo.
- Minimum Uncorrected QT interval and Weighted mean and Maximum QTcF following the combination DISKUS did not change significantly compared to placebo.
- Weighted mean of QTcB following SFC HFA MDI was significantly higher compared to SFC DISKUS.
- It is noticed that where combination treatments were not statistically different, pharmacodynamic responses following SFC HFA MDI were greater compared to SFC DISKUS. This may be due to higher systemic exposure from SFC HFA MDI than that from SFC DISKUS.

6. Comparison across Strengths (SAS10003)

Subjects received a total dose of 168mcg salmeterol in each active treatment leg. The results are presented in Table 13, and conclusions derived from this study are shown below:

Table 13. PD of salmeterol[a] (n = 20)

	SFC 21/44 (n=19)	SFC 21/110 (n=20)	SFC 21/220 (n=19)	Placebo (n=20)
Heart Rate (bpm)				
Weighted mean[bc]	74.5	74.7	74.6	65.4
Maximum[bc]	81.7	84.5	83.6	73.1
Potassium (mEq/L)				
Weighted mean[bc]	4.0	4.0	4.0	4.3
Minimum[bc]	3.7	3.8	3.7	4.1

a arithmetic mean for heart rate and geometric mean for potassium
b all active treatments were statistically different from placebo
c SFC 21/44 and SFC 21/220 were not statistically different from SFC 21/110

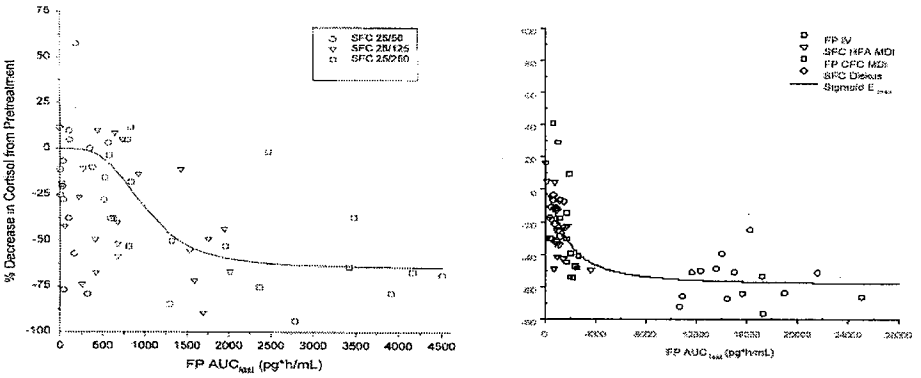
- Mean heart rates following each strength increased over placebo but the magnitude of increase was similar across strengths.
- Mean serum potassium values following each strength decreased over placebo but the magnitude of decrease was similar across strengths.
- While plasma salmeterol concentrations were not identical from the three strengths, pharmacodynamic effects on heart rate and serum potassium were similar.

Is there a systemic exposure-response relationship?

The sponsor examined exposure-response relationship in SAS10005 and SAS10003 as follows:

Figure 6 shows the relationship between the decrease in urinary cortisol excretion (left panel) or serum cortisol AUC_{24h} (right panel) as a function of fluticasone AUC_{last} using a Sigmoid E_{max} model. Estimated values of E_{max} and EC_{50} were -65% and 1000pg*h/mL respectively for urinary cortisol excretion *vs.* AUC_{last} fluticasone. Similarly, estimated values of E_{max} and EC_{50} were -59% and 1663pg*h/mL respectively between serum cortisol AUC_{24h} and fluticasone AUC_{last} relationship.

Figure 6. % decrease cortisol excretion (left) or Cortisol AUC_{24} (right) vs. FP AUC_{last}

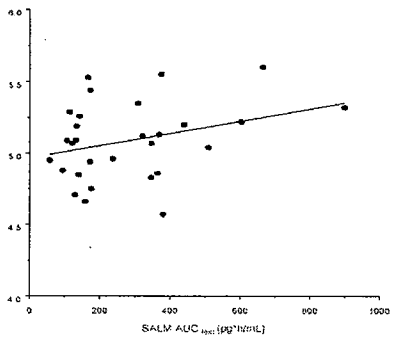


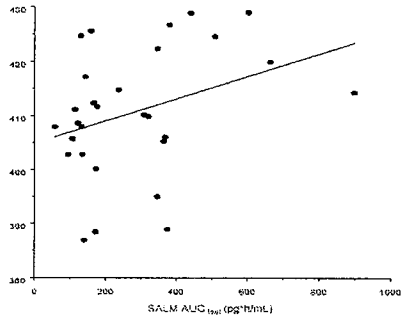
Equation for fitted line: % decrease = $(-65.0*AUC_{last}^{3.6})/(AUC_{last}^{3.6} + 999.9^{3.6})$

% decrease = $(-58.8*AUC_{last}^{1.51})/(AUC_{last}^{1.51} + 1663^{1.51})$,

The sponsor reported that meaningful ($p < 0.05$) exposure-response relationship for salmeterol was found only for serum cortisol and QTcB using linear regression (Figure 7);

Figure 7. Weighted mean glucose (left panel, p = 0.043) and weighted mean QTcB (right panel, p = 0.048) versus salmeterol AUC_{last}.





Line of regression ($r^2 = 0.10$)
Serum glucose = 4.9 + 0.0005 * AUC_{last}

QTcB = 405 + 0.021 * AUC_{last}
$r^2 = 0.12$

Were the analytical procedures used to determine fluticasone and salmeterol, glucose, potassium, urine and serum cortisol concentrations in this NDA acceptable?

The assays are acceptable. Fluticasone and salmeterol were determined by LC/MS/MS. Glucose and potassium concentrations were determined by [redacted] or [redacted] Urine and serum cortisol was determined by Immunoassay. The methods had adequate linearity, sensitivity, precision and accuracy. The sponsor provided adequate documentation of methods validation and in-study validation.

Is the clinical trial formulation the same as the to-be marketed?

Yes, This is verified with the CMC reviewer (in detail, the overage was not identical between batches). In addition, the formulation used for the clinical pharmacology and clinical trials is the same, except that the batch used for SAS10005 (9ZM0849) was not used in any clinical trials.

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APPENDICES

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Notation: Doses 25/50, 25/125 and 25/250 µg are expressed Ex-Valve doses (salmeterol/fluticasone), and corresponding Ex-Actuator doses are 21/44, 21/110 and 21/220 µg respectively [e.g., 25 µg (salmeterol)/250 µg (fluticasone) = 21 µg (salmeterol)/220 µg (fluticasone)].

Protocol SAS 10001

Study Type: PD effects of salmeterol

Title: Systemic pharmacodynamic effects of salmeterol, delivered over 3 hours in a cumulative dosing series, from salmeterol/fluticasone propionate/GR106642X metered-dose inhaler (MDI) to total dose 400/2000 µg, in comparison with salmeterol/P 11/12 MDI to total dose 400 µg, and placebo, in a randomised, double-blind, placebo-controlled, three-way cross-over study in healthy subjects.

Volume: Electronic submission

Clinical Investigators:

Objective: To compare the systemic PD effects of salmeterol administered via the SFC HFA MDI, SALMETEROL CFC MDI and placebo MDI formulated with HFA.

Methodology: A randomised, double-blind, placebo-controlled, 3-way crossover. Each treatment period comprised of a series of 4 cumulative inhaled doses given at 60-min intervals from either SFC HFA MDI, salmeterol CFC MDI or placebo.

Subjects: 12 healthy male (#8) and female (#4) subjects aged 19 - 30 years.

Study Drugs:

Test product: SFC HFA MDI, 25/125 µg per actuation, 2 puffs/dose, total dose 400/2000 µg, batch no: (R10452/004)

Reference products: (1) salmeterol CFC MDI (Serevent®), 25 µg per actuation, total dose 400 µg, batch no: 10461818. (2) Placebo HFA MDI, batch no: 8ZX011A.

Criteria for evaluation

PD: Ventricular heart rate, QTcB interval, Diastolic BP, systolic BP, plasma glucose and potassium.

Sampling times:

Blood samples: 0, 30 and 55 min after each dose in the cumulative series for potassium and glucose.

(other) PD: baseline before the 1st dose, and at 30 and 55min after each dose in the series.

Analytical Methodology:

Assay Method: Glucose and potassium were measured on the . Plasma glucose concentrations were determined using a colorimetric assay. Plasma potassium concentrations were determined using a Ion Selective Electrode (ISE).

Assay Sensitivity: Validation ranged for glucose and potassium was 0-42.0 and 1.5-10 nmol/L, respectively.

Accuracy and Precision: For glucose, assay variation of 1% with no bias against target mean. For potassium, assay variation was 1.2% and a negative bias of 0.3% against target mean.

Results: Analysis of final value and slope parameters for ventricular HR, QTcB, BPs, glucose and potassium are shown in Table 1 as well as in Table 2. Pharmacodynamic effects vs. log cumulative dose profiles are shown in Figure 1.

Note: There were 4 escalating doses: Dose 1 = 50/250 µg; Dose 2 = 100/500 µg; Dose 3 = 200/1000µg; Dose 4 = 400/2000µg, expressed as Ex-valve doses.

Table 1. Mean salmeterol PD parameters after a cumulative dose of 336 µg

	SFC[a] (n=12)	SALM[a] (n=11)	Placebo (n=11)
Systolic Blood Pressure (mmHg)	122.38[cd]	125.91[b]	120.05
Diastolic Blood Pressure (mmHg)	65.75[bd]	67.23[b]	71.55
Heart Rate (bpm)	77.50[bc]	84.09[b]	62.55
QTcB (msec)	448.75[b]	450.45[b]	402.00
Potassium (mmol/L)	3.354[bc]	3.227[b]	3.772
Glucose (mmol/L)	6.043[b]	6.243[b]	4.902

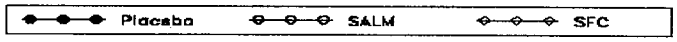
a Doses of 42/220, 42/220, 84/440 and 168/880mcg of salmeterol/fluticasone propionate (SFC) or 42, 42, 84 and 168mcg salmeterol (SALM) were given at 60min intervals;
b statistically different from placebo;
c statistically different from SALM;
d slope statistically different from SALM

Table 2. Analysis of final value and slope parameters

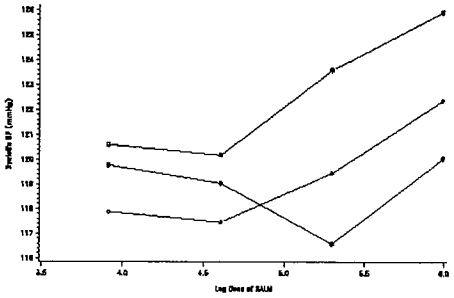
Variable	Treatment Comparison	Final value		Slope parameter	
		LS mean difference	95% CI	LS mean difference	95% CI
Systolic BP	SFC-SALM	-10.6	-16.4, -4.75	-4.15	-7.51, -0.79
	SFC-Placebo	0.76	-5.02, 6.53	1.24	-1.81, 4.29
	SALM-Placebo	11.33	6.07, 16.6	5.39	2.02, 8.75
Diastolic BP	SFC-SALM	-1.73	- 4.21, 0.75	-2.34	-3.61, -1.08
	SFC-Placebo	-5.23	- 7.66, -2.8	-2.19	-3.46, -0.93
	SALM-Placebo	-3.50	-6.02, -0.99	0.15	-1.12, 1.42
Heart Rate	SFC-SALM	-6.40	-11.7, -1.08	-2.65	-5.53, 0.23
	SFC-Placebo	15.58	10.5, 20.63	6.91	4.03, 9.79
	SALM-Placebo	21.97	16.6, 27.35	9.56	6.68, 12.44
QTcB interval	SFC-SALME	0.29	-34.8, 35.4	0.04	-16.0, 16.1
	SFC-Placebo	48.90	14.8, 83.01	20.47	4.41, 36.53
	SALM-Placebo	48.61	17.01, 80.2	20.43	4.37, 36.49
Glucose	SFC-SALM	-0.27	- 0.64, 0.09	-0.18	-0.42, 0.05
	SFC-Placebo	1.02	0.63, 1.40	0.20	-0.01, 0.42
	SALM-Placebo	1.29	0.91, 1.67	0.38	0.15, 0.62
Potassium	SFC-SALM	0.14	0.03, 0.26	0.08	-0.00, 0.15
	SFC-Placebo	-0.40	-0.52, -0.28	-0.21	0.28, -0.13
	SALM-Placebo	-0.54	-0.66, -0.43	-0.28	-0.36, -0.21

Note: Final value = Mean of the final 30 and 55 min. measurements. Slope = a linear regression of the mean of the 30 minute and 55 min measurements after each cumulative dose against the log cumulative dose. The slope parameter was derived provided that there was graphical evidence of a linear relationship between response and log cumulative dose.

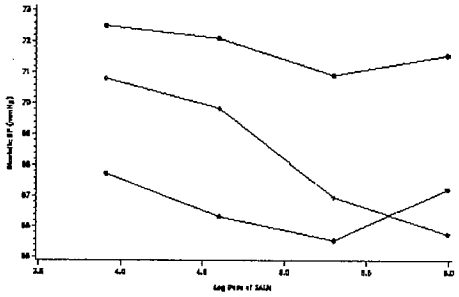
Figure 1. Pharmacodynamic effects vs. log cumulative dose



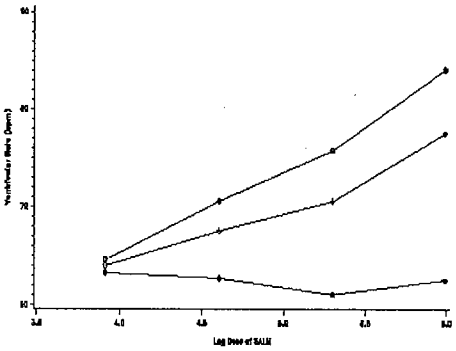
Systolic BP



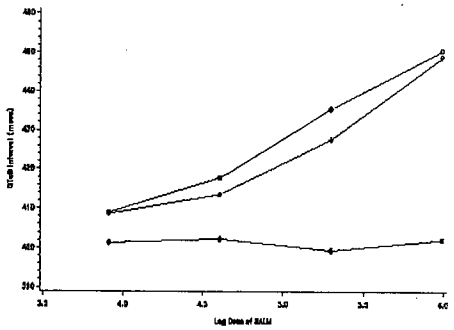
Diastolic BP



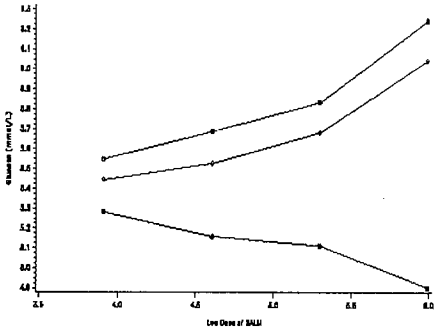
Heart Rate



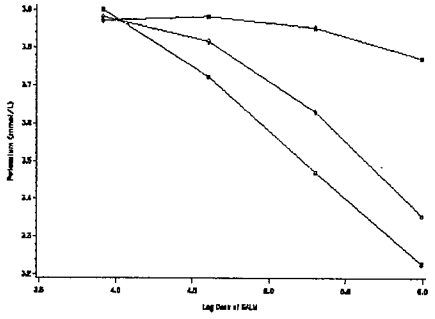
QTcB



Glucose



Potassium



Results in Table 1 and 2 (and figure 1) can be concluded as follows;

- The administration of both salmeterol alone and combination MDI at these high doses resulted in dose-related increases in systolic blood pressure, ventricular heart rate, QTcB interval and plasma glucose concentrations compared to placebo. Similarly, salmeterol alone and combination administration resulted in dose-related reductions in diastolic blood pressure and plasma potassium concentrations compared to placebo.
- The effects on blood pressure from the combination (SFC) inhaler were less compared to salmeterol alone (Serevent® CFC MDI = SALM).
- The increase in heart rate following salmeterol administration from the combination inhaler was less than salmeterol alone. The differences in slop parameters for salmeterol alone and combination compared to placebo were 9.56 (95% CI: 6.68-12.44) and 6.91 (4.03-9.79) respectively (Table 2).
- Increases in QTcB interval from the combination inhaler and salmeterol alone were similar.
- The effect of salmeterol on decreasing plasma potassium from the combination inhaler was less than salmeterol alone, but the slopes were comparable (pg 30, Table 2).
- The effect of salmeterol on the increase in plasma glucose from the two inhalers was comparable.

Overall conclusions:

- In general, the estimate of the true differences (SFC-PLAC and SALM-PLAC) for the pharmacodynamic variables indicated that cumulative doses of salmeterol (total dose 336mcg) and salmeterol/fluticasone combination (total dose 336/1760mcg) had systemic pharmacodynamic effects which differed from placebo.
- Most often, pharmacodynamic parameters measured were less from SFC HFA MDI than salmeterol alone.

Labeling Claim: Comparable or lower effects were observed for ADVAIR HFA compared to salmeterol alone.

Comment: Labeling claim made by the sponsor is reasonable.

Protocol SAS 10002

Study Type: Single dose PK and PD (HFA MDI *vs.* individual salmeterol and fluticasone)

Title: A Four-Period Crossover, Placebo Controlled Study to Investigate the Pharmacokinetic and Pharmacodynamic Effects of Salmeterol/Fluticasone Propionate/GR106642X via MDI in Combination Compared With Salmeteroleterol/P11/12 and Fluticasone Propionate/P11/12 via MDI Administered Individually.

Volume: Electronic submission

Clinical Investigator: [redacted]

Objective: To compare the PK and systemic PD of salmeterol and fluticasone in the combination product in GR106642X propellant to each compound administered individually as the currently marketed products in CFC propellant.

Methodology: single-dose, randomized, double-blind, placebo-controlled, four-way crossover design. Inhalations were given at 30-second intervals over 1.5 minutes:

- Treatment A (SFC): 4 actuations x salmeterol 25 µg /FP 250 µg HFA MDI.
- Treatment B (SALM): 4 actuations x SEREVENT® CFC MDI, 25 µg/actuation.
- Treatment C (FP): 4 actuations x FLOVENT® CFC MDI, 250 µg/actuation
- Treatment D (Placebo): 4 actuations from a placebo HFA MDI.

Subjects: 20 healthy male (#17) and female (#3) subjects aged 20 - 50 years.

Study Drugs:

Test product: SFC HFA 25/250 µg, batch #R10453/AX2846.

Reference products: (1) Serevent® P11/12 containing 25 µg/inhalation salmeterol, batch # 8ZM0407A. (2) Flovent® P11/12 containing 250 µg/inhalation, batch #W0366NC. (3) Placebo inhaler containing GR106642X propellant alone, batch #8ZX011A.

Criteria for evaluation

PK: Plasma salmeterol and fluticasone.

PD: Urinary cortisol, QTc interval, heart rate, BP, serum potassium and glucose.

Sampling times:

Blood samples: (1) before dosing, and at 2, 5, 10, 20 and 30 minutes after each dose for the determination of plasma salmeterol concentrations. (2) predose, and at 10, 20, 30, and 45min and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20 and 24 hours after dose for the determination of plasma FP concentrations.

PD: Urine was collected for 24 hours pre-dose and for 24 hours post-dose for cortisol determination. Heart rate, systolic and diastolic BP, 12-lead ECG (for QTc interval), and blood samples for serum potassium and glucose were collected pre-dose and post dose at 5, 10, 30 minutes and at 1, 1.5, 2, 3, and 4 hrs.

Analytical Methodology:

Assay Method: LC/MS/MS (fluticasone/salmeterol), Immunoassay (free cortisol in urin) and [redacted] (glucose/potassium).

Assay Sensitivity: Validated calibration ranges for fluticasone, salmeterol, cortisol, glucose and potassium were 20-1520 pg/mL, 0.05-1.0 ng/mL, 6-2069 nmol/L, 0-450 mg/dl and 1-15.0 nmol/L, respectively.

Accuracy and Precision: Between run assay precision and accuracy was ≤ 9.9%/ and ≤ ±5.5%, and ≤ 8.6% and ≤ ±8.2% for fluticasone and salmeterol respectively. Overall analytical runs for cortisol, glucose and potassium was acceptable.

Results: The results are presented in Tables 1-4, and Figures 1-2.

Table 1. Fluticasone pharmacokinetics and treatment comparisons

	Fluticasone Propionate (mean± SD)		
	SFC	**FP**	**90% CI[d]**
AUC_{last} (pg•h/ml)[a]	577 ± 499	1099.6 ± 872	
AUC_{inf} (pg•h/ml)[a]	997 ± 582	1638 ± 846	
C_{max} (pg/ml)[a]	98 ± 56	152 ± 89	
t_{max} (h)[b]	1.2 ± 0.6	1.5 ± 0.5	
AUC_{last}(pg•h/ml)[c]	350.7	647.3	0.27-1.04
AUC_{inf} (pg•h/ml)[c]	847.5	1437.6	0.43-0.77
C_{max} (pg/ml)[c]	85.7	120.3	0.52-0.96
$t_{1/2}$ (h)[c]	6.2	5.9	0.85-1.32

[a]Mean±SD [b]Median t_{max} [c]Geometric mean [d]Median difference $AUC_{last} = AUC_{0\text{-}8h}$

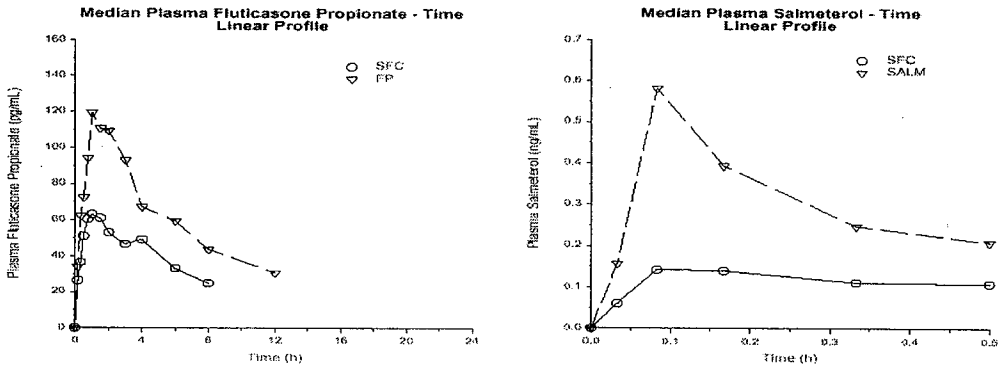
Table 2. Salmeterol pharmacokinetics and treatment comparisons

	Salmeterol (mean± SD)		
	SFC	**SALM**	**90% CI[d]**
AUC_{last} (ng•h/ml)[a]	0.076 ± 0.05	0.17 ± 0.08	
C_{max} (ng/ml)[a]	0.22 ± 0.18	0.60 ± 0.29	
t_{max} (h)[b]	0.083	0.083	
AUC_{last}(ng•h/ml)[c]	0.064	0.15	0.36-0.48
C_{max} (ng/ml)[c]	0.17	0.51	0.28-0.41

[a]Mean±SD [b]Median t_{max} [c]Geometric mean [d]Median difference $AUC_{last} = AUC_{0\text{-}0.5h}$

Note: The sponsor indicated that $AUC_{0\text{-}\infty}$ estimates were often not estimated or involved using extrapolated areas comprising greater than 20% of this value in many subjects, therefore, AUC_{last} (i.e., time zero to the quantitation limit of the assay, BQL), is considered a better parameter to describe systemic exposure. Thus, time up to 8 hrs and 0.5 hrs as AUC_{last} for FP and SLG, respectively.

Figure 1. Median Concentration-time profiles



PHARMACODYNAMICS: Urinary cortisol from each fluticasone treatment and pharmacodynamic effects of salmeterol are presented in Table 3 and 4, respectively. Figure 2 shows the mean Heat Rate (left) and QTcB (right) profiles.

Table 3. Urinary cortisol treatment comparisons

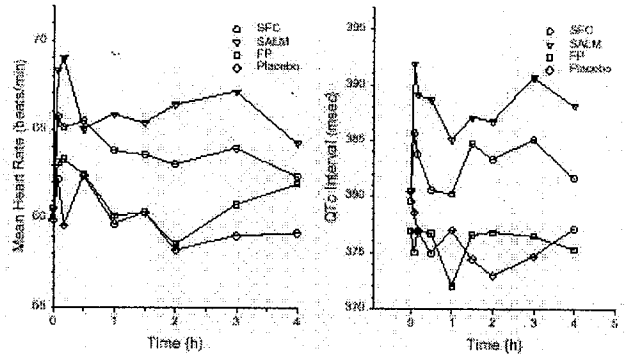
Treatment	Geometric Mean Pre	Geometric Mean Post	Geometric LSMean	Comparison	Ratio	95% CI
SALM	29.66	28.15	26.64	SFC vs FP	1.52	(1.05,2.22)
SFC	28.51	26.33	27.17	SFC vs Pla	0.97	(0.67,1.40)
FP	34.45	18.47	17.80	SALM vs Pla	1.02	(0.71,1.46)
Placebo	32.13	28.34	26.01	FP vs Pla	0.64	(0.44,0.92)

Table 4. Mean salmeterol pharmacodynamic parameters

	SFC	SALM	FP	Placebo
Systolic Blood Pressure (mmHg)				
Weighted mean	116.9	118.1	115.3	115.9
Maximum	124.5	127.7	123.1	124.6
Diastolic Blood Pressure (mmHg)				
Weighted mean	71.2	72.1	72.8	72.9
Minimum	65.1	66.0	67.3	65.2
Heart Rate (bpm)				
Weighted mean	64.0[ab]	66.1[a]	60.7	59.6
Maximum	69.7[b]	74.1[a]	66.6	67.2
QTcB (msec)				
Weighted mean	383.1[ab]	388.1[a]	375.9[a]	375.2
Maximum	397.9[a]	401.0[a]	391.7	391.3
Potassium (mEq/L)[c]				
Weighted mean	4.2	4.2	4.4	4.3
Minimum	3.9	3.9	4.0	4.0
Glucose (mg/dL)[c]				
Weighted mean	99.9[a]	101.4[a]	94.9	94.6
Maximum	104.0	106.4	98.8	98.6

a statistically different from placebo
b statistically different from SALM
c geometric means used for this parameter

Figure 2. Comparison of Mean Heat Rate (left) and QTcB (right)



No significant differences were observed with blood pressure between any treatments. Weighted mean heart rate increased 4.4-6.5 beats/min over placebo following SFC inhaler and SALM inhaler administration, but not following the FP inhaler. Mean heart rate following the SALM inhaler was higher than SFC inhaler. Maximum heart rate gave similar results except that the difference between SFC inhaler and placebo was not significant. Weighted mean QTcB for the SFC, FP, and SALMETEROL inhalers increased over placebo. QTcB following the SALM inhaler was higher than after SFC inhaler. Maximum QTcB for SFC and SALM inhalers were

higher than placebo, but the difference between SFC and SAL inhalers was not significant. Weighted mean and minimum serum potassium concentrations were similar across treatments. Weighted mean and maximum serum glucose for SFC and SALM inhalers were similar and higher than placebo, respectively but not following the FP inhaler. Overall pharmacodynamic effects on heart rate, QTc interval, serum potassium and serum glucose was either comparable or reduced from the combination inhaler.

Relationship between response and drug dose or drug concentration: The sponsor stated that PK-PD relationship was thought, but it was not meaningful since the single dose produced limited data.

Overall Conclusions:

- For the fluticasone, AUC_{last} from the SFC was 53% of the AUC_{last} from Flovent® MDI (Table 1). While a significant reduction (36%) in urinary cortisol excretion was seen following the FP inhaler, cortisol excretion following SFC product was unchanged (Table 3).
- With respect to plasma salmeterol concentrations, AUC_{last} from the SFC formulation was 42% of that from the Serevent® MDI resulting in less effect on heart rate and QTc interval from the SFC product compared to Salmeterol alone. However, changes in serum glucose and maximum QTc from placebo were comparable. Blood pressure and serum potassium were unaffected by any treatments (Table 2 and 4).
- Formulations for SFC HFA MDI and Flovent® MDI were not comparable each other, nor for SFC HFA MDI and Serevent® MDI. The sponsor could not explain the cause(s), but stated that it is not due to drug-drug interaction between fluticasone and salmeterol based on previous work with ADVAIR DISKUS.

Labeling Claims: S

Comment: Underline text and strikethrough represent modification and deletion, respectively.

Protocol SAS 10003

Study Type: Dose proportionality and pharmacodynamics

Title: A double-blind, placebo-controlled four way crossover study to evaluate the PK and PD of fluticasone propionate and salmeterol with increasing dose strengths of the fluticasone propionate/salmeteroleterol/GR106642X MDI combination product.

Volume: Electronic submission

Clinical Investigators: [redacted]

Objective: (1) To examine the increase in systemic exposure to fluticasone over the range of fluticasone strengths available in the combination product. (2) To characterize changes in urinary free cortisol excretion and salmeterol PK and PD with increasing strengths of fluticasone in the combination product formulated with GR106642X propellant.

Methodology: single-dose, randomized, double-blind, placebo-controlled, four-way crossover design in 21 healthy male (#12) and female (#9) subjects aged 20 - 49 years. Each subject received the following treatments randomly. Inhalations were given at 30-second intervals over 3.5 minutes;

- *Treatment A* (SFC 25/50) - 8 actuations x salmeterol 25 µg/FP 50 µg MDI (200/400 µg total dose), batch R10451/AX2845
- *Treatment B* (SFC 25/125) - 8 actuations x salmeterol 25 µg/FP 125 µg MDI (200/1000 µg total dose), batch R10452/AX2847
- *Treatment C* (SFC 25/250) - 8 actuations x salmeterol 25 µg/FP 250 µg MDI (200/2000 µg total dose), batch R10453/AX2846
- *Treatment D* (Placebo) - 8 actuations from a placebo MDI, batch 8ZX011A.

This study used all three strengths of SFC developed in the GR106642X MDI: 25/50 µg, 25/125 µg, and 25/250 µg . Corresponding ex-actuator doses are: 21/44 µg, 21/110 µg, and 21/220 µg.

Criteria for evaluation

PK: Plasma fluticasone and salmeterol.

PD: Urinary cortisol, QTc interval, heart rate, blood pressure, serum potassium.

Sampling times:

Blood samples: (1) before dosing, and at 5, 10, 20 and 30 minutes after each dose for the determination of plasma salmeterol concentrations. (2) predose, and at 10, 20, 30, and 45min and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20 and 24 hours after dose for the determination of plasma FP conc.

PD: Urine was collected for 24 hours pre-dose and for 24 hours post-dose for cortisol determination. Heart rate, systolic and diastolic blood pressure, 12-lead ECG (for QTc interval), and blood samples for serum potassium and glucose were collected pre-dose and post dose at 5, 10, 30 minutes and at 1, 1.5, 2, 3, and 4 hrs.

Analytical Methodology:

Assay Method: LC/MS/MS (fluticasone/salmeterol), Immunochemiluminescence on the [redacted] for free cortisol in urine) and [redacted] (potassium).

Assay Sensitivity: Validated calibration ranges for fluticasone, salmeterol, cortisol and potassium were 10-1500 pg/mL, 0.05-1.0 ng/mL, 6-2069 nmol/L and 1-15.0 nmol/L, respectively.

Accuracy and Precision: Between run assay precision and accuracy was 7.3 – 5.7% and -4.4 – 8.6%, and 12.5 – 3.7% and -13.2 – 7.5% for fluticasone and salmeterol respectively. Overall analytical runs for cortisol and potassium were acceptable.

Results:

PK: Data from 20 subjects was used for the analysis. Results are presented in tables and figures below.

Figure 1. Median plasma fluticasone (left panel; semi-log) and salmeterol (right panel; linear) versus Time profiles.

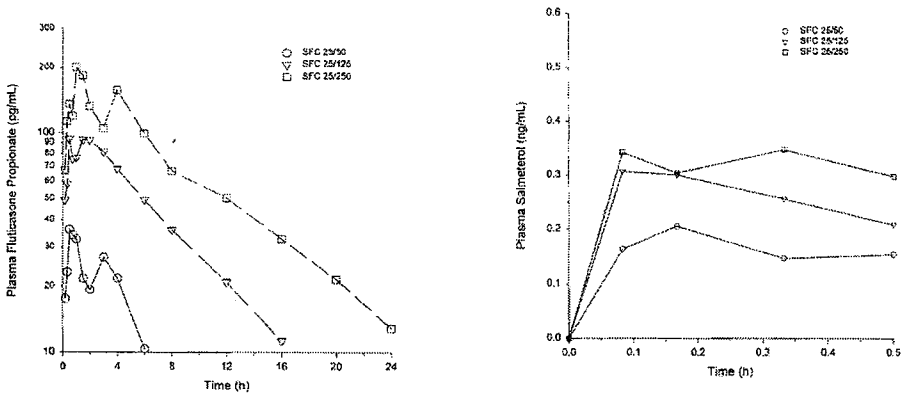


Table 1. Comparisons for fluticasone PK parameters

	Treatment A: SFC 25/50 (400mcg)	Dose Normalized A/B	Treatment B: SFC 25/125 (1000mcg)	Dose Normalized C/B	Treatment C: SFC 25/250 (2000mcg)
AUC_{last} (pg*h/mL) Geometric Mean	80.4		675.8		1239.0
Mean Ratio		0.29		0.91	
90% CI		(0.16, 0.51)		(0.52, 1.60)	
C_{max} (pg/mL) Geometric Mean	41.4		107.9		172.5
Mean Ratio		0.93		0.81	
90% CI		(0.73, 1.18)		(0.64, 1.03)	
t_{max} (h) Median	1.00		1.50		1.50
Median Difference		-0.38		0.16	
90% CI		(-0.81, 0.00)		(-0.11, 0.50)	

Table 2. Comparisons for salmeterol PK parameters

	Treatment A: SFC 25/50 (200mcg)	A/B	Treatment B: SFC 25/125 (200mcg)	C/B	Treatment C: SFC 25/250 (200mcg)
AUC_{last} (ng*h/mL) Geometric Mean	0.084		0.131		0.162
Mean Ratio		0.65		1.24	
90% CI		(0.52, 0.80)		(1.00, 1.53)	
C_{max} (ng/mL) Geometric Mean	0.22		0.38		0.47
Mean Ratio		0.59		1.23	
90% CI		(0.45, 0.77)		(0.94, 1.61)	
t_{max} (h) Mean	0.167		0.150		0.167
Median Difference		0.07		0.01	
90% CI		(0.00, 0.16)		(-.04, 0.08)	

There were differences in plasma salmeterol concentrations between the three strengths of inhaler (Figure 1, right and Table 2). The sponsor stated that the differences in plasma salmeterol concentrations was not explained by differences in salmeterol fine particle mass dose (— and —, for SFC 25/50, SFC 25/125 and SFC 25/250, respectively) for the batches used in this study, nor by Cascade impactor data. Further examination would require the co-

administration of separate inhalers containing the individual drugs in GR106642X propellant,

Dose proportionality: A determination of dose proportionality was examined using a power model approach (AUC or $C_{max} = e^a * (dose)^b$). The sponsor indicated that a confidence interval of the slope is within the range 0.78 – 1.22 is considered dose proportionality over the range tested. Table 3 shows that the mean slope (and 90% CI) for AUC_{last} and C_{max} were 1.75 (1.43 – 2.07) and 0.93 (0.8 – 1.05), respectively. Thus, dose proportionality was achieved for C_{max} but not AUC_{last}. The sponsor stated that due to low plasma levels of fluticasone after the 352 µg dose, AUC_{last} could not be accurately estimated for all subjects. Therefore, additional analysis was performed using $AUC_{0\text{-}6h}$ data, which supports dose proportionality across strengths.

Table 3. PK and Dose Proportionality of Fluticasone from Three Strengths of Combination HFA MDI (Geometric mean)

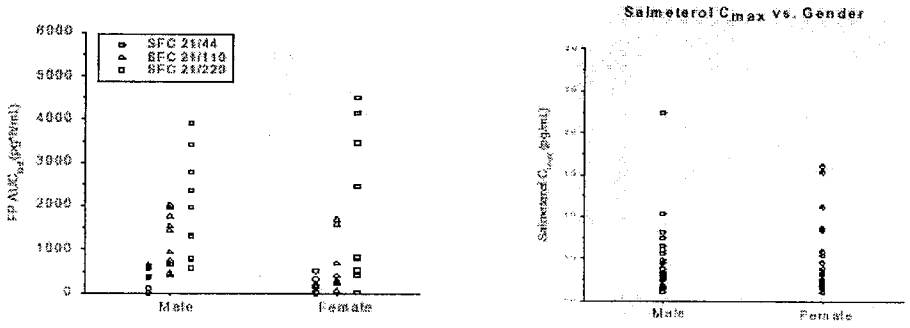
	n	SALM/FP (mcg)			Dose Proportionality*
Strength/actuation Total dose		**21/44 168/352**	**21/110 168/880**	**21/220 168/1760**	**Adjusted Mean Slope (90% CI)**
FP C_{max} (pg/mL)	19-20	41.4	107.9	172.5	0.93 (0.80, 1.05)
FP AUC_0 (pg.h/mL)	10	233.6	701.4	1207.6	1.03 (0.88, 1.18)
FP AUC_{last} (pg.h/mL)	19-20	80.4	675.8	1239.0	1.75 (1.43, 2.07)

* A confidence interval within the range 0.78 – 1.22 indicated dose proportionality

Note: 21/44 and 21/220 (n=19); 21/110 (n=20)

Gender effect: The effect of gender on fluticasone and salmeterol was examined, and no significant effects were observed based on AUC_{last} (Figure 2), however, the number of subjects is too small for confirmation (12M, 9F):

Figure 2. Comparisons AUC_{last} fluticasone (left) or salmeterol C_{max} (right) vs. Gender



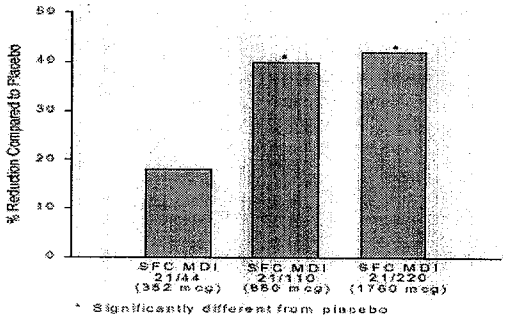
PK Conclusions:

- Fluticasone: (1) According to the sponsor, dose proportionality was achieved for C_{max}. AUC_{last} was proportional between the two highest doses (SFC 25/125 and SFC 25/250), but was not proportional for the low dose (SFC 25/50) due to possibly of assay limitations at the lowest dose that prevented adequate estimation of this parameter. However, dose proportionality was not achieved for AUC_{last} and C_{max} even between the two highest doses (SFC 25/125 and SFC 25/250) by applying the bioequivalence criteria of 0.8-1.25 (Table 1, 5th column, 90% CI). (2) t_{max} was similar across strengths.
- Salmeterol: (1) The systemic exposure to salmeterol was not identical for the three strengths of inhalers (cause(s) was not evaluated). (2) t_{max} was similar across strengths.

Pharmacodynamics

Urinary cortisone excretion: As shown in Figure 3, following fluticasone doses of 352, 880, and 1760 µg from 21/44, 21/110, and 21/220 SFC HFA inhalers, urinary cortisol excretion were reduced by 18%, 40%, and 42%, respectively, compared to placebo. However, differences between strengths did not reach statistical significance based on 95% CI; 21/44 *vs.* 21/110 = 0.92-2.08; 21/220 *vs.* 21/110 = 0.65-1.47.

Figure 3. Urinary cortisone excretion



Salmeterol: Mean heart rates or serum potassium values following each strength increased over placebo and its profiles were similar across strengths (Figure 4). Comparisons of these effects over time are presented in the Table 4.

Figure 4. Mean Heart rate (left) and Mean serum potassium (right) over time

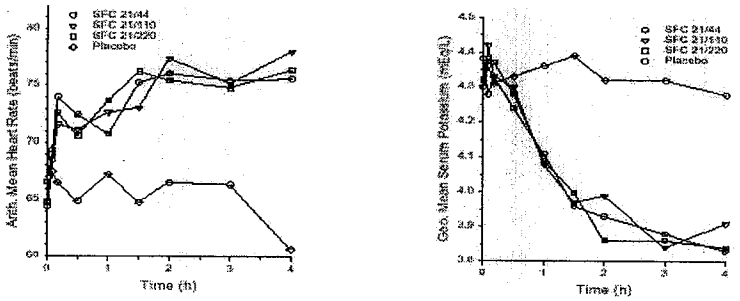


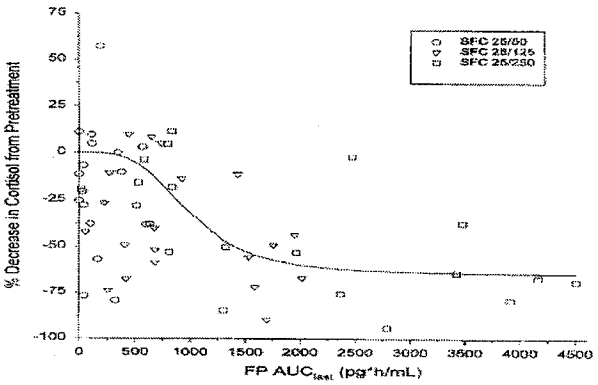
Table 4. Pharmacodynamics of salmeterol

	SFC 21/44 (n=19)	SFC 21/110 (n=20)	SFC 21/220 (n=19)	Placebo (n=20)
Heart Rate (bpm)				
Weighted mean[bc]	74.5	74.7	74.6	65.4
Maximum[bc]	81.7	84.5	83.6	73.1
Potassium (meq/L)				
Weighted mean[bc]	4.0	4.0	4.0	4.3
Maximum[bc]	3.7	3.8	3.7	4.1

[a] Arithmatic mean for heart rate and geometric mean for potassium
[b] All active treatments were statistically different from placebo
[c] SFC 21/44 and SFC 21/220 were not statistically different from SFC 21/110

Exposure-response relationship: Urinary cortisol excretion decreased as a function of fluticasone AUC_{last} was investigated using a Sigmoid E_{max} model, and results are shown in Figure 4. Estimated values of E_{max} and EC_{50} were -65% and 1000pg*h/mL, respectively.

Figure 4. % decrease Cortisol excretion *vs.* FP AUC_{last}



Equation for fitted line:
% decrease = $(-65.0*AUC_{last}^{3.6})/(AUC_{last}^{3.6} + 999.9^{3.6})$

The sponsor reported that exposure-response relationship for salmeterol could not be made due to high variability with the data.

PD conclusions:

- Fluticasone: Decreases in urinary cortisol excretion occurred with all strengths, but differences between strengths did not reach statistical significance.
- Salmeterol: Comparable increases in heart rate and decreases in serum potassium occurred following each active treatment.

Overall Conclusions:

- Plasma FP concentrations increased with strength resulting in treatment-related decreases in urinary cortisol excretion. Dose proportionally was shown in C_{max} (per the sponsor's analysis).
- The systemic exposure to salmeterol was not identical for the three strengths of inhalers, but these differences did not result in a differential effect on heart rate or serum potassium.

Labeling Claims: Peak plasma concentrations of fluticasone propionate were achieved in 0.33 to 1.5 hours and those of salmeterol were achieved in 5 to 10 minutes. Peak plasma concentrations of fluticasone propionate (n = 20 subjects) following 8 inhalations of ADVAIR HFA 44/21, ADVAIR HFA 110/21, and ADVAIR HFA 220/21 averaged 41, 108, and 173 pg/mL, respectively. Peak plasma salmeterol concentrations ranged from 220 to 470 pg/mL.

Comment: Labeling claim made by the sponsor is reasonable.

Protocol SAS 10005

Study Type: single dose PK, PD, absolute and relative bioavailability (BA).

Title: A part-randomized, single-blind, placebo-controlled, five-way crossover study to assess the absolute bioavailability, relative bioavailability and comparative pharmacodynamics of fluticasone propionate from ADVAIR HFA MDI, ADVAIR DISKUS, FP CFC MDI and intravenous FP and to assess the relative bioavailability and comparative pharmacodynamics of salmeterol from ADVAIR HFA MDI to ADVAIR DISKUS.

Volume: Electronic submission

Clinical Investigators: ———————

Primary objectives:

1. (a) Determine the absolute BA of FP from SFC HFA MDI, SFC DISKUS and the marketed FP CFC MDI by comparing systemic exposure to exposure after the intravenous (IV) FP formulation and (b) to determine the relative BA of inhaled formulations, i.e., SFC HFA MDI to SFC DISKUS, SFC HFA MDI to FP CFC MDI and SFC DISKUS to FP CFC MDI.
2. Compare 24h serum and urine cortisol changes from SFC HFA MDI, SFC DISKUS, FP CFC MDI and IV FP compared to placebo and to each other (SFC HFA MDI to SFC DISKUS, SFC HFA MDI to FP CFC MDI and SFC DISKUS to FP CFC MDI).

Secondary objectives:

1. Determine the relative BA of salmeterol in SFC HFA MDI to SFC DISKUS.
2. Compare the PD of salmeterol (QTC, serum glucose, serum potassium) in SFC HFA MDI to SFC DISKUS, SFC HFA MDI to placebo and SFC DISKUS to placebo.

Methodology: single-dose, randomized, single-blind, placebo-controlled, five-way crossover design in 15 healthy male (#11) and female (#4) subjects aged 21 - 40 years;

Treatment/drug Administration: Dose was given at approximately the same time for each subject participating in the study. Subjects received each of the following treatments as a single dose with at least 5 days between treatments. Inhalations were given at 30-second intervals and inhaled doses expressed as ex valve doses:

- IV fluticasone (500 µg/mL in propylene glycol, infused over 10min) (1010 µg total dose), batch number PDS2/BPR/6007
- SFC HFA MDI: 4 inhalations x salmeterol 25mcg/ fluticasone 250mcg MDI (100/1000 µg total dose), batch number 9ZM0849
- SFC DISKUS: 2 inhalations x salmeterol 50mcg/fluticasone 500mcg DISKUS Inhaler (100/1000 µg total dose), batch number B008226
- FP CFC MDI (Flovent®): 4 inhalations x fluticasone 250mcg CFC MDI (1000 µg total dose), batch number W0938CB
- Placebo: 2 inhalations placebo DISKUS Inhaler (to match SFC DISKUS), batch number WP31R9

Criteria for evaluation

PK: Plasma fluticasone and salmeterol.

PD: Serum cortisol, urine cortisol, ECG (for weighted means and maximum values of QTcB and QTcF and weighted mean and minimum for uncorrected QT interval), serum potassium and glucose (for weighted mean and minimum).

Sampling times:

Blood samples: (1) 0, 5, 10, 20, 40 min and 1, 1.5, 2 and 4 hrs post dose for the determination of plasma salmeterol concentrations. (2) 0, 5, 10, 20, 40min and 1, 1.5, 2, 4, 6, 8, 12, 16 and 20 hours after dose for the determination of plasma fluticasone conc.

PD: Blood samples were collected at 0, 1, 2, 4, 6, 8, 12, 16, 20 and 24 hrs post dose for the determination of serum cortisol concentrations. Urine was collected for 24 hrs post-dose for urinary cortisol determination.

Analytical Methodology:

Assay Method: LC/MS/MS (fluticasone /salmeterol), Immunoassay on a [redacted] serum cortisol), Immunochemiluminescence on the [redacted] for free cortisol in urine) and [redacted] (glucose and potassium).

Assay Sensitivity: Validated calibration ranges for fluticasone, salmeterol, cortisol and potassium were 10-1500 pg/mL, 0.05-1.0 ng/mL, 6-2069 nmol/L and 1-15.0 nmol/L, respectively.

Accuracy and Precision: Accuracy and precision of quality control samples at three concentration levels were ≤ ±6.3% and ≤ 10.6% for fluticasone, and ≤ ±15.2% and ≤ 10.4% for salmeterol, respectively. Overall analytical runs for cortisol, glucose and potassium were acceptable.

Results: The results, derived form the study, are shown in tables and figures below.

Figure 1. Median Plasma fluticasone (left panel; semi-log) and salmeterol (right panel; linear) Profiles

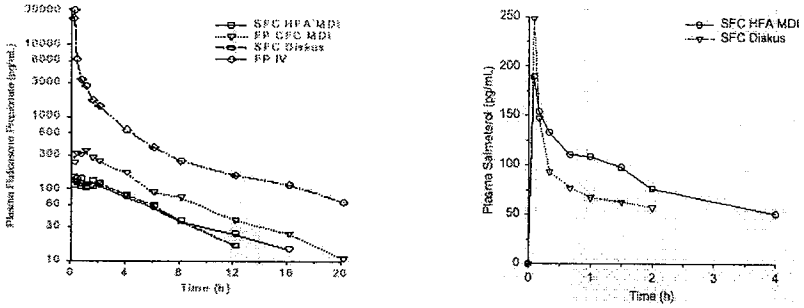


Table 1. PK of fluticasone following each treatment

Parameters	SFC MDI	SFC DISK	FP	IV
AUC_{last} (pg.h/ml)				
Geometric mean	799	832	1543	15722
95% CI	484, 1318	663, 1044	1156, 2061	13267, 17381
C_{max} (pg/ml)				
Geometric mean	186	182	307	29683
95% CI	136, 255	150, 222	233, 404	25262, 34878
T_{max} (h)				
Median	0.33	0.83	0.67	-
Range	0.17, 1.5	0.17, 2.0	0.33, 4.0	
$t_{1/2}$ (h)				
Geometric mean	5.5	4.3	5.6	5.0
95% CI	4.2, 7.1	3.4, 5.5	4.2, 7.5	4.1, 6.1

Table 2. PK of fluticasone following inhalation

Parameter	SFC MDI 4 x 21/220	SFC Disk 2 x 50/500	FP MDI 4 x 220	SFC MDI/ SFC Disk	SFC MDI/ FP MDI	SFC Disk/ FP MDI
AUC_{last} (pg*h/mL)						
Geo. Mean	799	832	1543			
95% CI	484, 1318	663, 1044	1156, 2061			
Ratio				0.96	0.52	0.55
90% CI				0.69, 1.34	0.38, 0.72	0.39, 0.76
C_{max} (pg/mL)						
Geo. Mean	188	182	307			
95% CI	136, 255	150, 222	233, 404			
Ratio				1.02	0.62	0.60
90% CI				0.77, 1.37	0.46, 0.82	0.45, 0.80
t_{max} (h)						
Median	0.33	0.83	0.67			
Range	0.17, 1.5	0.17, 2.0	0.33, 4.0			
Median Diff.				-0.33	-0.17	0.25
90% CI				-0.67, 0.00	-0.42, 0.17	-0.33, 0.67

Note: AUC_{last} is the AUC, time zero to the quantitation limit of the assay; $AUC_{0\text{-}16h}$ for SFC HFA and $AUC_{0\text{-}12h}$ for SFC Diskus. The sponsor stated that calculation of AUC_{∞} in all subjects was not possible because either half-life could not be accurately estimated or % extrapolated AUC was >20%, thus, AUC_{last} is considered better parameters for comparisons, including for BA estimation.

Fluticasone systemic exposure (AUC_{last}) from the combination inhaler was 52% of the value from the FP CFC inhaler. C_{max} for both combination inhalers were approximately 60% of C_{max} for the FP CFC MDI. Therefore, formulations for the combination products and Individual inhaler were not comparable (note: results are similar to the SAS10002). The sponsor stated that AUC_{last} to fluticasone was similar for the two combination inhalers based on 95% CI (30% difference), however, it is not similar based on bioequivalance criteria of 0.8-1.25 (20% difference). Mean terminal half-life estimates for the four treatments were similar and ranged from 4.3 – 5.6 hours.

Absolute bioavailability: Absolute BA estimates for the two combination inhalers were almost identical to each other and were about half of the value for FP inhaler (Table 3); the sponsor reported that estimation for bioavailability was carried out using AUC_{∞} and it was comparable to AUC_{last} estimates.

Table 3. Fluticasone absolute bioavailability Estimates (%)

Parameter	SFC MDI	SFC Diskus	FP MDI
AUC_{last}			
Geo. mean	5.3	5.5	10.3
95% CI	3.6, 7.9	3.6, 7.9	6.9, 15.3
AUC_{∞} (pg*h/mL)			
Geo. mean	6.3	6.0	12.5
95% CI	4.7, 8.5	4.5, 8.1	9.4, 16.5

Table 4. Treatment comparisons for salmeterol (n=14)

	SFC MDI	MDI/Diskus	SFC Diskus
AUC_{last} (pg*h/mL) Geometric Mean 95% CI Mean Ratio 90% CI	317 (221, 454)	1.82 (1.27, 2.60)	169 (121, 237)
C_{max} (pg/mL) Geometric Mean 95% CI Mean Ratio 90% CI	196 (140, 276)	0.86 (0.61, 1.20)	223 (161, 309)
t_{max} (h) Median Range Median Difference 90% CI	0.08 (0.08, 1.02)	0.045 (0.000, 0.480)	0.08 (0.08, 1.00)

The mean AUC_{last} following the SFC MDI was 82% higher than after the SFC DISKUS. The 90% CI for the AUC_{last} and C_{max} parameters for SFC HFA MDI and SFC DISKUS were not within the range 0.70 - 1.43 used to describe a 30% difference between treatments indicating that the PK for the two formulations were not comparable for salmeterol (causes not evaluated). t_{max} occurred at 5 minutes (0.08 hours) in most subjects following both treatments and it was not statistically different. (Note: estimated AUC_{∞} was approximately 0.42 ng•h/mL).

Pharmacodynamics:

Fluticasone: Serum cortisol and urinary cortisol measurements are summarized in Table 5.

Table 5

Post-Treatment Cortisol Geometric Means and Treatment Comparisons

Parameter	Placebo DISKUS	SFC HFA MDI	SFC DISKUS	FP CFC MDI	FP IV
Serum AUC_{24} (pmol*h/mL)	6231.8	4621.8[ab]	5357.7[abc]	4483.2[ab]	2604.1[a]
Serum C_{min} (pmol/mL)	58.1	38.3[ab]	42.0[b]	31.5[ab]	13.9[a]
Urine Excretion (mcg)	32.1	19.9[abc]	21.8[abc]	13.7[ab]	9.4[a]

a statistically different from placebo (confidence interval did not contain 1.0)
b statistically different from IV (confidence interval did not contain 1.0)
c statistically different from FP CFC MDI (confidence interval did not contain 1.0)

Significant differences in serum cortisol AUC_{24}, serum cortisol C_{min}, and urinary excretion ($Amount_{cort}$) for the inhalers were observed compared to intravenous FP. While cortisol levels were higher following both combination inhalers compared to FP MDI, the differences were only significant for 24-hr urine excretion with the SFC HFA MDI and for serum cortisol AUC_{24} and 24-hr urine excretion with the SFC DISKUS. No significant differences between the combination inhalers were observed for any parameter.

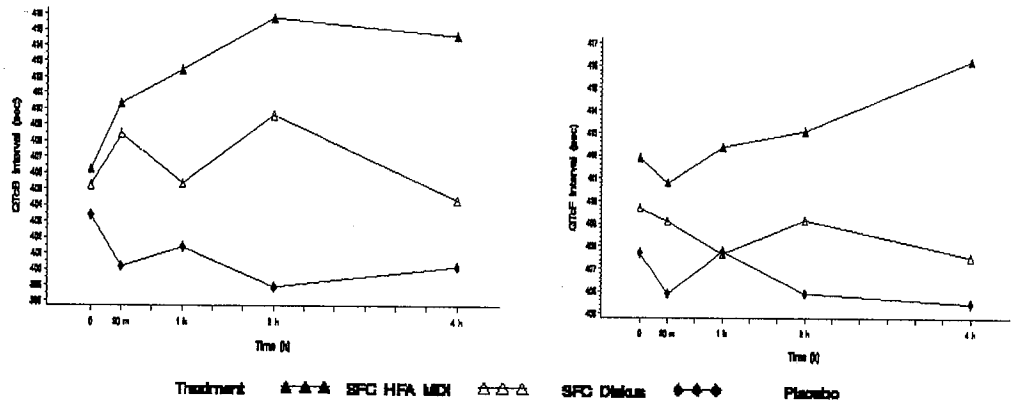
Salmeterol: Serum concentrations for PD analysis were obtained pre-dose and over four hours following the two combination and placebo inhalers for glucose, potassium and ECG measurements. Weighted mean was calculated by dividing the area under the effect-time curve by the sampling interval to express the value in units of measure. The results are summarized in Table 6 and Figure 2.

Table 6. PD of salmeterol (n = 15)

Parameter	SFC MDI	SFC Diskus	Placebo
Potassium (mEq/L)[a]			
Weighted mean	3.92[c]	3.95[c]	4.05
Minimum	3.78[c]	3.83[c]	3.92
Glucose (mg/dL)[a]			
Weighted mean	5.10[c]	5.03[c]	4.77
Maximum	5.29[c]	5.21[c]	4.97
Uncorrected QT (msec)[b]			
Weighted mean	414[c]	412[c]	420
Minimum	402[c]	402	406
QTcB (msec)[b]			
Weighted mean	414[cd]	407[c]	400
Maximum	424[c]	420[c]	410
QTcF (msec)[b]			
Weighted mean	413[c]	408	406
Maximum	422[c]	418	413

SFC MDI = salmeterol/fluticasone propionate combination 21/220mcg inhalation aerosol
SFC Diskus = salmeterol/fluticasone propionate combination 50/500mcg dry powder DISKUS inhaler
a geometric means,
b arithmetic means
c statistically different from placebo
d statistically different from SFC DISKUS

Figure 2. Linear mean QTcB (left) and QTcF (right) Interval (sec) – Time profiles



Small, but statistically significant increases in serum glucose and decreases in serum potassium concentrations compared to placebo that were similar in magnitude were observed following the combination inhalers. Small, but statistically significant changes in ECG measures were observed in the three QT parameters following the combination inhalers following most comparisons with placebo. Only minimum uncorrected QT interval following the DISKUS and weighted mean and maximum QTcF following the combination DISKUS did not change significantly. QT changes for the combination inhalers were all similar in magnitude except weighted mean QTcB that was significantly higher for the combination HFA MDI.

PD conclusions

Fluticasone:

- Decreases in serum and urine cortisol were significantly less following 1mg FP inhaled doses from SFC HFA MDI, SFC DISKUS and FP CFC MDI compared to a 1mg IV dose.
- Decreases in serum cortisol C_{min} and 24h urinary cortisol excretion were less from SFC HFA MDI and SFC DISKUS compared to FP CFC MDI, but did not reach statistical significance

for C_{min}. The decrease in serum cortisol AUC_{24} was significantly less from SFC DISKUS compared to FP CFC MDI, but not between SFC HFA MDI and FP CFC MDI.

- Decreases in serum and urine cortisol were similar from SFC HFA MDI and SFC DISKUS.

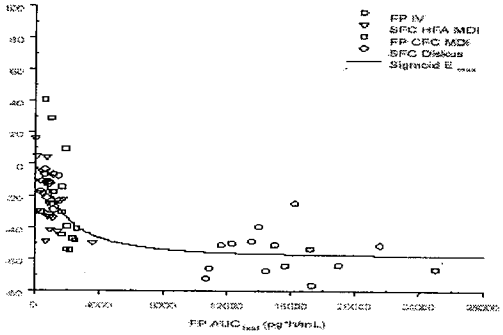
Salmeterol:

- Small, but statistically significant increases in serum glucose and decreases in serum potassium concentrations were observed following SFC HFA MDI and SFC DISKUS and were similar in magnitude.
- Except for the weighted mean of QTcB, all other QT measurements for both combination treatments were similar.

Relationship between response and drug dose or drug concentration

Figure 3 shows the relationship between the decrease in serum cortisol AUC_{24} with increase in fluticasone AUC_{last} using a sigmoid E_{max} model. Estimated values of E_{max} and EC_{50} were -59% and 1663pg•h/mL, respectively based on the model.

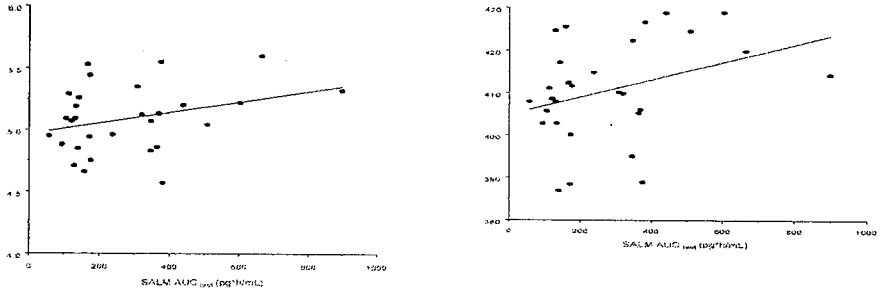
Figure 3. Cortisol AUC_{24} vs. AUC_{last}



Sigmoid E_{max} equation for fitted line:
% decrease = $(-58.8 \bullet AUC_{last}^{1.51})/(AUC_{last}^{1.51} + 1663^{1.51})$

Linear regression was used to screen for relationships between measures of salmeterol systemic exposure and response. Significant correlations were found only between salmeterol AUC_{last} and weighted mean glucose ($p = 0.043$) and salmeterol AUC_{last} and weighted mean QTcB ($p = 0.048$) (Figure 4).

Figure 4. Salmeterol AUC_{last} vs. Weighted mean glucose (left panel) or Weighted mean QTcB (right panel



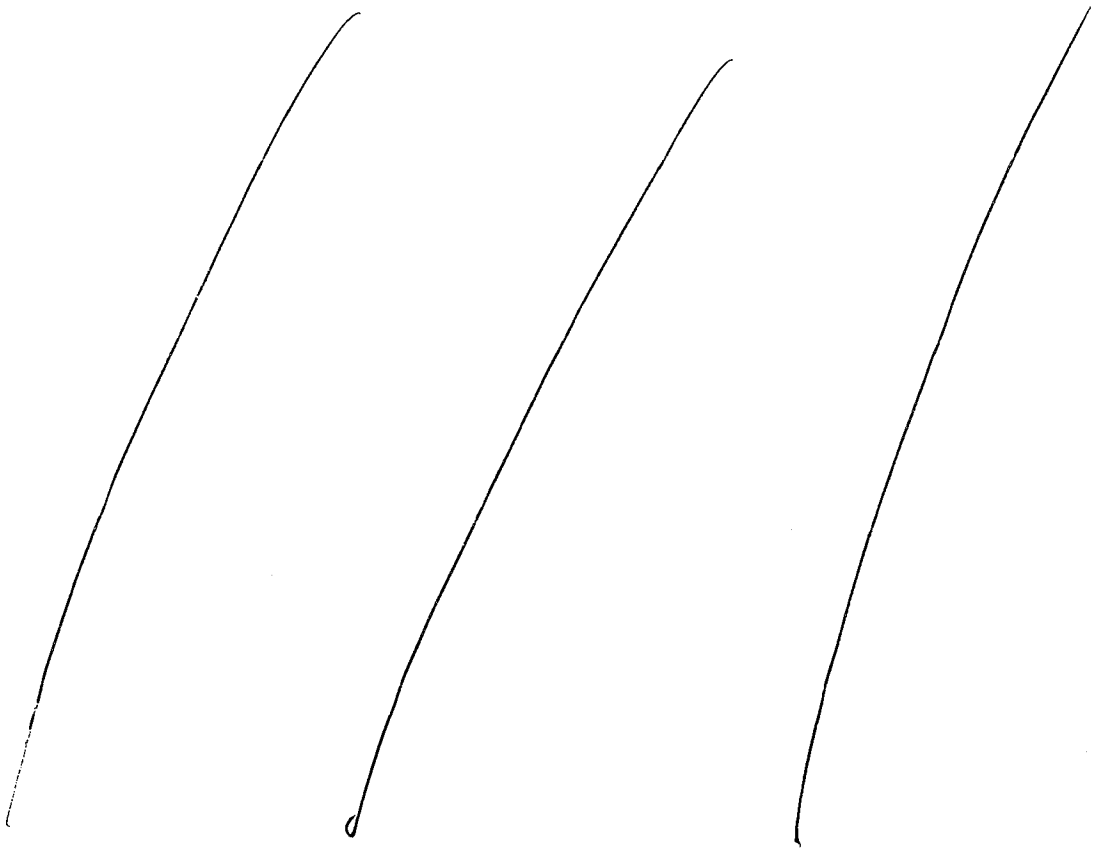
Line of regression ($r^2 = 0.10$)
Serum glucose = 4.9 + 0.0005 * AUC_{last}

QTcB = 405 + 0.021 * AUC_{last}
$r^2 = 0.12$

Overall conclusions:

- Fluticasone systemic exposures from the SFC HFA MDI and SFC DISKUS inhalers were similar and approximately half that observed following FP CFC MDI resulting in comparable and expected changes in serum and urinary cortisol for the combination products and a reduced effect on cortisol compared to FP CFC MDI (Table 1 and 4).
- Absolute BA was 5.3% for SFC HFA MDI, 5.5% for SFC DISKUS, and 10.3% for FP CFC MDI (Table 2).
- The times to peak FP plasma concentrations were similar from the combination HFA, combination DISKUS and individual inhalers and occurred in 0.33 – 1.5 hours (Table 1).
- Salmeterol systemic exposure was 82% higher from SFC HFA MDI compared to SFC DISKUS, but did not result in differences in serum glucose, serum potassium (Table 3 and 5).
- Except for the weighted mean of QTcB, all other QT measurements for both combination treatments were similar (Table 5).

Labeling Claims:



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Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-254	Brand Name	Advair™HFA MDI
OCPB Division (I, II, III)	DPE-II	Generic Name	Fluticasone/salmeterol
Medical Division	HFD-570	Drug Class	Anti-Asthma
OCPB Reviewer	Shinja Kim	Indication(s)	Asthma
OCPB Team Leader	Emmanuel Fadiran	Dosage Form	Inhalation Aerosol
		Dosing Regimen	2 inhaltions Bid
Date of Submission	12/20/00	Route of Administration	Oral Inhaltion
Estimated Due Date of OCPB Review	10/04/01	Sponsor	GlaxoWellcome
PDUFA Due Date	10/20/01	Priority Classification	S
Division Due Date	10/05/01		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3	3	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				

II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	4	4	

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/s/

Shinja Kim
10/5/01 01:34:21 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
10/5/01 03:29:52 PM
BIOPHARMACEUTICS
I concur