

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-077

CLINICAL PHARMACOLOGY and
BIOPHARMACEUTICS REVIEW(S)

JAN 19 2000

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

/S/

NDA: 21-077

Salmeterol Xinafoate/Fluticasone Propionate
50 µg /100 µg, 50 µg /250 µg, and 50 µg /500 µg
Combination Dry Powder Inhalation Products

SUBMISSION DATE:

03/24/99 (Serial No. N-000)
05/28/99 (Serial No. BB)
08/30/99 (Serial No. BL)
01/13/2000 (Serial No. BL)

BRAND NAME:

ADVAIR Diskus

SPONSOR: GlaxoWellcome

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION:

Original NDA for Approved Drugs in Combination Dry Powder
Dosage Form for Inhalation Code: 4S

TITLE:

"Review of Human Pharmacokinetics and Bioavailability (PK/Bio) Section of An
NDA"

SYNOPSIS:

Salmeterol (Sal) is reported as a long-acting β -adrenergic agonist (not an NME) and its products have been reviewed and approved under NDA 20-236 (Serevent Inhalation Aerosol) on 02/04/94 and under NDA 20-692 (Serevent Diskus Inhaler) on 09/19/97. Fluticasone propionate (FP) is a synthetic, trifluorinated corticosteroid reported to possess potent anti-inflammatory activity (not an NME) and its products have also been reviewed and approved under NDA 20-548 (Flovent Inhalation Aerosol) on 03/27/96. NDA 20-549 (Flovent Rotadisk Dry Powder Inhaler) was approved on 11/07/97 for adults and adolescents > 12 years old and NDA 20-770 was approved later for the use of Flovent Rotadisk in pediatric patients 4 to 11 years old.

On 03/24/99, GlaxoWellcome (GW) submitted an original NDA 21-077 (ADVAIR Diskus) for review. This is a combination DPI (dry powder inhalation) product of Sal/FP (SFC) which is designed to benefit the patients to produce a greater improvement in pulmonary function and symptom control than Sal or FP used alone at their recommended dosages. The combination product is indicated for the maintenance treatment of asthma _____ in patients 12 years of age and older by orally inhaled route only. The recommended dosing regimen is one inhalation BID. For starting dose and the highest recommended dose of ADVAIR Diskus based on prior antiasthma therapy, please see the proposed package insert (PI) in Attachment 1 for details. This product is NOT indicated for the relief of acute bronchospasm. The sponsor is seeking approval for three strengths, 50/100, 50/250, and 50/500 µg. ADVAIR Diskus contains Sal and FP in lactose. The only differences among the three strengths are the amounts of FP and _____

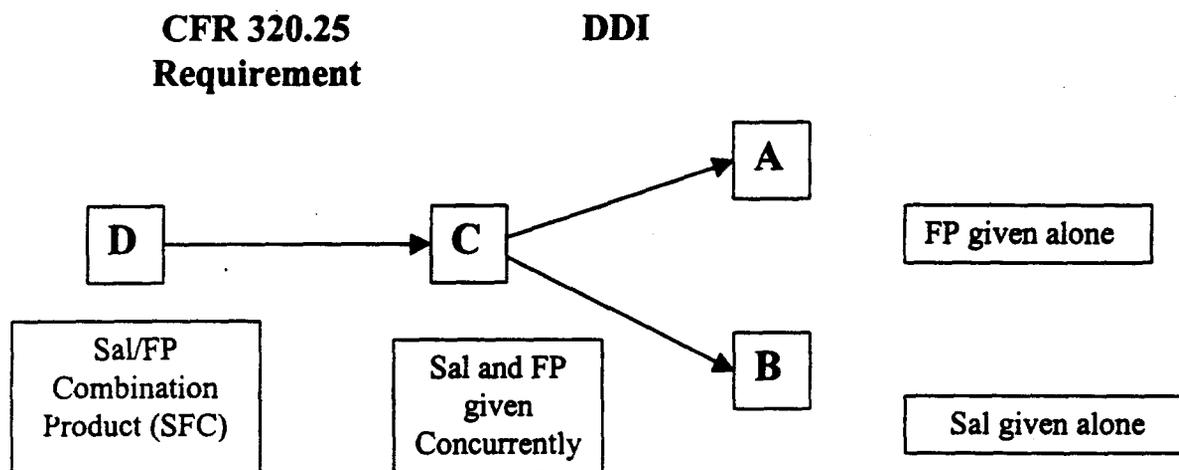
Submitted under human PK/Bio section were 6 PK studies. Three had been reviewed previously which included a single-dose study using ADVAIR Diskus 50/100 µg. Three new PK studies are therefore reviewed here and 4 PK study results related to the performance of ADVAIR Diskus

BEST POSSIBLE COPY

are presented in this review. The clinically tested formulations are the same as the to-be-marketed ones for ADVAIR Diskus and they were employed in the single-dose and multiple-dose PK studies and also in clinical trials. Finally, assay methods and the validation reports for plasma Sal and FP levels as well as for plasma and urinary cortisol levels were provided.

The following issues are addressed in the NDA submitted:

- 1). To determine whether the rate and extent of absorption of each active ingredient (or therapeutic moiety) in the combination drug product (SFC) is equivalent to that of each active ingredient administered concurrently in separate single-ingredient preparations (the requirements according to CFR 320.25 for combination products).
- 2). To assess drug-drug interaction (DDI) of Sal on FP mainly (Sal and FP administered concurrently vs. FP alone).



Note: Due to low plasma Sal levels (close to limit of quantitation, LOQ), only one PK study had a treatment arm of Sal alone employed in the study. Nevertheless, very limited plasma levels for Sal were obtained (10-30 min postdose) and analyzed for DDI of FP on Sal (C_{max} data mainly) from the above study.

- 3). To assess the FP dose proportionality through interstudy comparison for FP 100, 250, and 500 μg doses using the 3 combination products.
- 4). To evaluate the pharmacodynamic (PD) effects of Sal and FP (in most of the PK studies where available).

Also, the issue of gender differences is investigated.

APPEARS THIS WAY
ON ORIGINAL

I.	Summary of PK study.....	3
II.	Comments to the Medical Officer.....	15
III.	Recommendation.....	16
IV.	Labeling Comments (Need to be sent to the firm).....	16
	<u>Appendix 1: Package Insert (01/14/2000 Version).....</u>	21
	<u>Appendix 2: Individual Studies.....</u>	55

I. SUMMARY OF PHARMACOKINETICS AND PHARMACODYNAMICS:

The 4 PK studies are summarized below:

Table 1. Descriptions of Individual Studies

Study No. (Vol No.)	Comparison ^a	No. of Subjects (M/F)	Dosing Regimen	Strengths ^b (SAL/FP)	Total (or Daily) Dose (SAL/FP)	Assessments			
						FP PK	PD ^c	SAL PK	PD
SFCB ^d 1002 (Vol 1.37)	D vs. A Placebo	12M Healthy Volunteers	Single Dose	D: 50/100 A: 100	50/100 x 5 100 x 5	√	√	-	-
SFCB 1004 (Vol 1.38)	D vs. A or B Placebo	13M+15F Healthy Volunteers	Multiple Dose (10 days)	D: 50/250 A: 250 B: 50	50/250 x2 BID 250 x 2 BID 50 x 2 BID	√	√	√	√
SFCB 1005 (Vol 1.40)	D vs. C vs. A	8M+6F Healthy Volunteers	Single Dose	D: 50/500 C: SAL 50 & FP 500 A: 500	50/500 x 2 SAL 50 x 2 & FP 500 x 2 500 x2	√	√	√	√
SFCB ^e 3019 (Vol 1.41)	D vs. C vs. A	31M+14F Patients	Multiple Dose (12 wks)	D: 50/500 C: SAL 50 & FP 500 A: 500	50/500 BID SAL 50 BID & FP 500 BID 500 BID	√	√	-	-

^a D (SAL/FP combination product, SFC), C (SAL and FP given concurrently), B (SAL alone), and A (FP alone).

^b Combination products (D) are the to-be-marketed formulations.

^c PK and/or PD data analyzed.

^d Reviewed previously by OCPB.

^e A PK subset of a clinical trial.

BEST POSSIBLE COPY

Study No. **SFCB 1004** was a randomized, double-blind, placebo-controlled, four-treatment, three-period, cross-over study, using an incomplete block design. Each study period lasted 12 days, with a washout of at least 9 days. Any one subject received 3 of the 4 treatments: SFC (all subjects), SAL (all subjects), and then either FP (half the subjects) or placebo. A single dose of Sal which replaced the 19th placebo dose (Day 10) was given to half the subjects in the placebo group. On Day 10, after the 19th dose, PD effects of Sal on pulse rate, systolic and diastolic blood pressure, ECG (for QTc interval), serum potassium and glucose levels were monitored. PK of Sal (single- and multiple-doses) and FP were investigated. Plasma and urinary cortisol levels were also monitored. On Day 12, all subjects received cumulative doses of albuterol from metered-dose inhalers at intervals of 30 min (400, 400, 800 and 1600 µg, giving a total dose of 3200 µg).

Study No. **SFCB 1005** was a single dose, randomized, double-blind, 3-way cross-over design, with a washout period of at least 7 days (dose to dose) between periods. Each study period lasted 48 hr. In addition to FP PK data, the PD effects of Sal on pulse rate, systolic and diastolic blood pressure, ECG (for QTc interval), serum potassium and glucose levels were measured up to 4 hr post-dose. Plasma and urinary cortisol levels were also monitored.

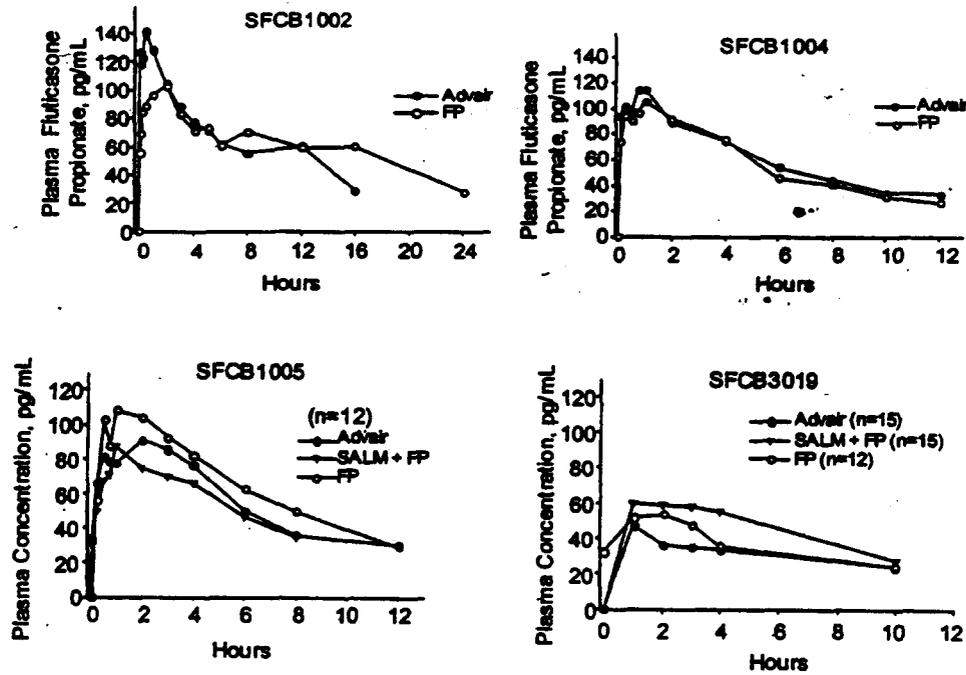
Study No. **SFCB 3019** was a randomized, double-blind, double-dummy, parallel-group design consisting of three stages: run-in, treatment and follow-up. This is in fact a PK subset of a pivotal clinical trial. The study period was 32 or 34 weeks: run-in was two weeks (or four if repeated), treatment was 28 weeks, and follow-up was two weeks. In addition to clinical efficacy and safety data, the PK of FP, plasma and urinary cortisol levels were also monitored in the subset of patients.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

Mean plasma FP profiles obtained from 4 PK studies are shown below:

Figures 1-4. Mean Plasma FP profiles



1. REQUIREMENT UNDER CFR 320.25:

The comparisons of FP PK between D and C are shown below:

Table 2. Fluticasone PK (D vs. C)

Study No.	Fluticasone PK Data				
	Total (Daily) Dose (µg)	Geo. LS Mean AUC (pg-hr/ml)	Geo. LS Mean C _{max} (pg/ml)	Median T _{max} (hr)	T _{1/2} (hr)
SFCB1005 Single Dose	D (SFC): 100/1000	AUC _{0-∞} 917 [CV 52%] ^a (78 - 131) ^b	107 [CV 41%] (95 - 113)	1.0	5.33
	C: SAL 100 & FP 1000	908 [CV 41%]	94.0 [CV 39%]	1.0	6.53
SFCB3019 Multiple Dose	D (SFC): 50/500 BID	AUC _{0-12, ss} 389 [CV 58%] (53 - 104)	57.3 [CV 44%] (64 - 96)	2.0	-----
	C: SAL 50 BID & FP 500 BID	521 [CV 40%]	72.9 [CV 27%]	2.0	-----

BEST POSSIBLE COPY

a. CV % (coefficient variation) of the mean.

b. 90% CI (confidence interval).

- The results of Study SFCB 3019 showed that the highest recommended dose of the combination product, SFC given BID (D) had lower mean AUC and C_{max} values when compared to Sal and FP given concurrently (C) to asthmatic patients.
- Trough plasma FP levels were also obtained from all the subjects enrolled in SFCB 3019. There were no significant differences found in their mean trough levels, D: 33.8 pg/ml (n=118), C: 36.9 pg/ml (n=127), and A: 37.3 pg/ml (n=114).
- Comments: The differences in the mean steady-state PK parameters obtained from SFCB 3019 are inconsistent with those obtained from Study SFCB 1005 which could be due to differences in study designs (single administration vs. BID dosing), dose levels, populations studied and/or PK sampling times (in SFCB 3019, the first sample was at 1hr postdose, so C_{max} may not be picked up if peak occurred before 1 hr).

The comparisons for Sal PK between D and C are shown below:

Table 3. Salmeterol PK (D vs. C)

Study No.	Salmeterol PK Data		
	Total (Daily) Dose (μ g)	Geo. LS Mean C_{max} (pg/ml)	Median T_{max} (hr)
SFCB1005 Single Dose	D (SFC): 100/1000	200. (33% ↑)* [CV 42%]	0.1
	C: SAL 100 & FP 1000	150. [CV 22%]	0.1

*. Statistically significant.

- The combination product (SFC; D) had significant increase in mean Sal C_{max} value when compared to concurrent administration of Sal with FP (C) to healthy volunteers in this single-dose PK study.
- Comments: Most of the C_{max} values obtained were close to LOQ and no AUC values were obtained for Sal due to assay limitations (LOQ being ———). Therefore, the differences in mean C_{max} values could not be further confirmed.

2. DRUG-DRUG INTERACTION:

Table 4. Fluticasone PK (C vs. A)

Study No.	Fluticasone PK Data				
	Total (Daily) Dose (μg)	Geo. LS Mean AUC (pg-hr/ml)	Geo. LS Mean C_{max} (pg/ml)	Median T_{max} (hr)	$T_{1/2}$ (hr)
SFCB1005 Single Dose	C: SAL 100 & FP 1000	AUC _{0-∞} 908 [CV 41%]	94.0 [CV 39%]	1.0	6.53
	A: FP 1000	954 [CV 56%]	120. [CV 35%]	1.0	5.30
SFCB3019 Multiple Dose	C: SAL 50 BID & FP 500 BID	AUC _{0-12,ss} 521 [CV 40%]	72.9 [CV 27%]	2.0	-----
	A: FP 500 BID	487 [CV 48%]	70.0 [CV 35%]	2.0	-----

- Comments: No major or consistent differences (for DDI) in FP PK were obtained from the above two studies, C (Sal and FP concurrently given BID) and A (FP given alone).

Additional comparisons for FP PK between D and A were conducted and the results are summarized below:

Table 5. Fluticasone PK (D vs. A)

Study No.	Fluticasone PK Data				
	Total (Daily) Dose (μg)	Geo. LS Mean AUC (pg-hr/ml)	Geo. LS Mean C_{max} (pg/ml)	Median T_{max} (hr)	$T_{1/2}$ (hr)
SFCB1002 Single Dose	D (SFC): 250/500	AUC _{0-12,ss} 889	146	0.21*	-----
	A: FP 500	1146	105	2.00	-----

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

SFCB1004	D (SFC): 100/500 BID	AUC _{0-12h} 723 [CV 18%]	112 [CV 22%]	1.0	7.65
Multiple Dose	A: FP 500 BID	668 [CV 20%]	107 [CV 25%]	0.75	6.91
SFCB1005	D (SFC): 100/1000	AUC _{0-12h} 917 [CV 52%]	107 [CV 41%]	1.0	5.33
Single Dose	A: FP 1000	954 [CV 56%]	120. [CV 35%]	1.0	5.30
SFCB3019	D (SFC): 50/500 BID	AUC _{0-12h} 389 [CV 58%]	57.3 [CV 44%]	2.0	-----
Multiple Dose	A: FP 500 BID	487 [CV 48%]	70.0 [CV 35%]	2.0	-----

- Comments: No major or consistent DDI was observed from the above comparisons for FP PK. The above results are complicated by different assay methods used for SFCB 1002 and _____ for SFCB 1004, 1005, and 3019). Also, interstudy comparisons show that asthmatic patients had lower mean AUC and C_{max} values (SFCB 3019) as compared to those obtained from healthy volunteers.

Similar analyses for Sal PK between D and B were also conducted and the results are summarized below:

Table 6. Salmeterol PK (D vs. B)

Study No.	Salmeterol PK Data		
	Total (Daily) Dose (µg)	Geo. LS Mean C _{max} (pg/ml)	Median T _{max} (hr)
SFCB1004			
Multiple Dose (Day 10)	D (SFC): 100/500 BID	229 (4% fl) [CV 27%]	0.083
	B: 100 BID	220. [CV 27%]	0.083
Single Dose (replaced 19 th placebo dose on Day 10)	B: 100	155 [CV 32%]	0.083

BEST POSSIBLE COPY

- Comments: Accumulation of Sal at steady state may occur after multiple-dose administration to healthy volunteers. No major differences in Sal PK were observed between the combination product (SFC) given BID (D) and Sal given alone (B). Again, it should be noted that Sal C_{max} levels are close to the LOQ. Nevertheless, plasma Sal levels were not monitored in asthmatic patients (SFCB 3019). Therefore, whether accumulation of Sal will occur upon BID dosing of ADVAIR DISKUS as compared to individual components given concurrently to this patient population could not be confirmed.

3. DOSE PROPORTIONALITY:

No dose proportionality study for the 3 strengths (in terms of FP) was conducted in any PK studies. Upon previous agreement with the Agency (in the Agency's letter dated 12/02/97), an interstudy comparison of FP AUC and C_{max} was performed by the sponsor since demographic profiles of healthy subjects were similar for SFCB 1002, 1004 and 1005.

Several assumptions were made: 1) $AUC_{0-last} \approx AUC_{0-\infty} \approx AUC_{0-\tau}$, 2) small interassay variability for different assay methods used: SFCB 1002, _____ for SFCB 1004 and 1005), and 3) correction of mean steady-state C_{max} values (for accumulation ratio, Rac) to mean C_{max} value for single dose based on one-compartment model,

$$Rac = [1/(1-e^{-k\tau})]$$

- Both SFCB 1004 & 1005 used the same assay method and the assumption of $AUC_{0-\infty}$ for a single dose study $\approx AUC_{0-\tau}$ for a multiple dose study is logical based on linear kinetics.
- Assumption for $AUC_{last} \approx AUC_{0-\infty}$ might not be valid between two single-dose studies, SFCB 1002 and 1005 since different assay methods were used (SFCB 1002 used an _____ with an LOQ of _____ while SFCB 1005 used _____ with an LOQ of _____ Furthermore, the AUC extrapolation from the last time point to infinity was found to contribute 25 to 35% to the total $AUC_{0-\infty}$ in Study SFCB 1005.

The plots of dose-proportionality are shown below:

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Figure 5. Mean FP AUC vs. Doses Administered in 3 PK Studies

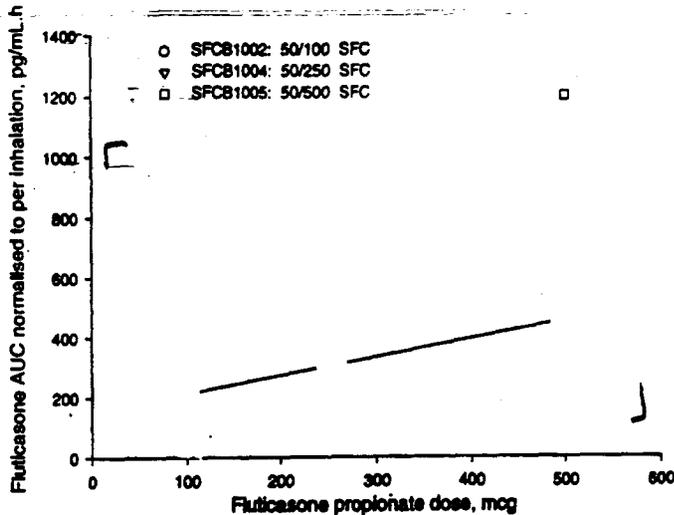
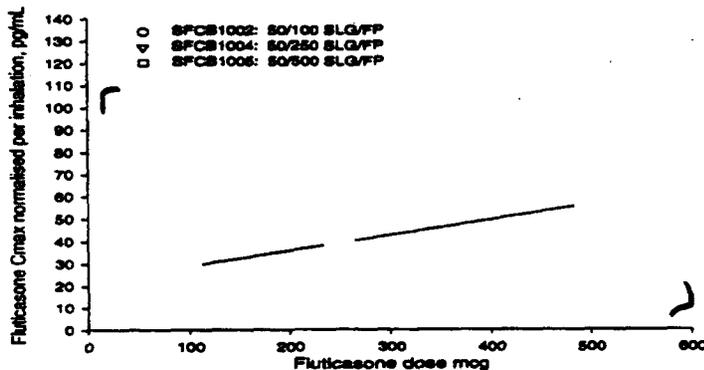


Figure 6. Mean FP C_{max} vs. Doses Administered in the 3 PK Studies



- Comments: A dose-related increase in systemic exposure to FP was found and the increase was less than dose-proportional. The sponsor's attempt to assess dose proportionality is less satisfactory (or less than ideal).

4. GENDER:

Significant gender differences were reported for Study SFCB 3019, i.e., male patients had about 40-45% lower mean FP AUC and C_{max} values than female patients for all 3 treatments, combination products, SFC (D, 9M/5F), concurrent administration of Sal and FP (C, 8M/6F), and FP alone (A, 10M/2F).

Table 7. Mean FP PK Parameters Obtained From Males and Females (SFCB 3019)

Study SFCB 3019	Arithmetic Mean AUC ₀₋₁₂ (pg·h/ml)		Arithmetic Mean C _{max} (pg/ml)	
	Male	Female	Male	Female
D	303 (181) ^a n=9	588 (219) n=5	48.1 (20.8) n=10	77.2 (23.5) n=5

BEST POSSIBLE COPY

C	421 (170) n=8	708 (152) n=6	65.9 (10.7) n=9	81.8 (17.0) n=6
A	406 (209) n=10	672 (80.) n=2	58.6 (19.7) n=10	92.3 (8.3) n=2

Standard deviation (SD).

- The above gender differences could be partly due to the differences in mean BW (male: 82.3 kg vs. female: 75.9 kg) and in bioavailability, apparent clearance and/or apparent volume of distribution.
- Comments: The above gender difference in FP PK is seemingly consistent with the mean FEV₁ (%) reported (male: 71.2% vs. female: 88.3%).

5. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

The PK and PD data were obtained, but no PK/PD relationships were analyzed. The effects of FP on plasma and urinary cortisol levels are shown below:

Table 8. Fluticasone PD

Mean Fluticasone PD Data			
Study No.	Total (Daily) Dose (µg)	Mean % Change in 24-hr Urinary Cortisol Excretion (Post- vs. Pre-treatment)	
SFCB1002 Single Dose	D (SFC): 250/500	4.4% ↓	
	A: FP 500	6.7% ↓	
	Placebo	2.1% ↓	
Study No.	Total (Daily) Dose (µg)	Mean % Change in Morning Plasma Cortisol vs. Placebo	Mean % Change in 24-hr Urinary Cortisol Excretion vs. Placebo
SFCB1004 Multiple Dose	D (SFC): 100/500 BID	19% ↓	53% ↓*
	B: 100 BID	0%	6% ↓
	A: FP 500 BID	20% ↓	52% ↓*
	Placebo	17.2 µg/dl	47.1 µg

BEST POSSIBLE COPY

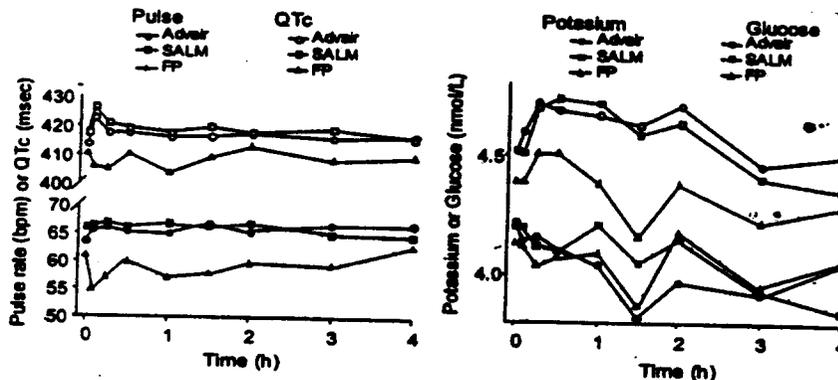
Study No.	Total (Daily) Dose (µg)	Mean % Change in Plasma Cortisol AUC ₀₋₁₀ from Baseline	Mean % Change in 24-hr Urinary Cortisol Excretion from Baseline
SFCB1005 Single Dose	D (SFC): 100/1000	25.3% ↓	27.0% ↓
	C: Sal 100 & FP 1000	20.7% ↓	- 25.7% ↓
	A: FP 1000	16.0% ↓	30.3% ↓
. . .			
Study No.	Total (Daily) Dose (µg)	Geo. LS Mean Plasma Cortisol AUC ₀₋₁₀ (nmol-h/l) (Visit 5)	Mean 24-hr Urinary Cortisol Excretion (nmol/24 hr)
SFCB3019 Multiple Dose	D (SFC): 50/500 BID	2472.1	223 (week 0), 210 (wk 12), & 223 (wk 28)
	C: Sal 50 BID & FP 500 BID	2897.8	201 (week 0), 221 (wk 12), & 220 (wk 28)
	A: FP 500 BID	2472.0	221 (week 0), 240 (wk 12), and 175 (wk 28)

- Sal given alone (B) had little effects on plasma and urinary cortisol levels, therefore, it would probably have little effects on plasma and urinary cortisol levels when given as the combination product (D) or given concurrently with FP (C).
- Single-dose administration of FP to healthy volunteers (using an even higher than the recommended dose for patients) had no significant effects on the reduction of plasma and/or urinary cortisol levels, although decreases are seemingly dose-related (SFCB 1002 & 1005). Multiple dosing seemingly had significant effects only on urinary (not plasma) cortisol levels (SFCB 1004) when FP was given to healthy volunteers.
- No significant differences in plasma and/or urinary cortisol levels among treatments were observed when the highest recommended was given BID to asthmatic patients (SFCB 3019).
- Comments: After multiple dosing of the same daily dose of FP (1000 µg), different PD effects on urinary cortisol suppression were observed in healthy volunteers and in asthmatic patients. The above difference in PD effects (cortisol suppression) may be related to lower systemic exposure of FP found in asthmatic patients.

BEST POSSIBLE COPY

The PD effects of Sal [on pulse rate, systolic and diastolic blood pressure, ECG (for QTc interval), serum potassium and glucose levels] were monitored and the results are shown below in Figures 7 and 8 (Study SFCB 1004):

Figures 7-8: Mean PD Data/Profiles Obtained from Study No. SFCB1004 (D vs. B)



The above data show that FP did not have major effects on pulse, QTc, potassium and/or glucose and no major differences were observed in PD between combination product (D) and individual component of Sal (B). The PD data in SFCB 3019 will be reviewed thoroughly by the reviewing medical officer.

6. FORMULATIONS, DOSAGE, AND DRUG ADMINISTRATION:

The composition for the 3 strengths of ADVAIR is shown below in Table 9:

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Table 9. Composition of 3 Strengths of ADVAIR DISKUS

Component	Grade	Sal/FP Content		
		(µg per 12.5 mg powder mix)		
		50/100	50/250	50/500
Active Ingredient				
Salmeterol Xinafoate	Glaxo Wellcome	72.5	72.5	72.5
Fluticasone Propionate	Glaxo Wellcome	100	250	500
Other Ingredient				
Lactose	Glaxo Wellcome			

7. ASSAY:

- For plasma FP and Sal levels, the same assay methods were employed which had been reviewed previously (SFCB 1002 used an _____ with LOQ of _____ and SFCB 1004, 1005, 3019 used an _____ with an LOQ of _____ Their performance and assay validation reports were submitted and summarized below:

BEST POSSIBLE COPY

- For plasma and urinary cortisol levels using an _____ the performance and the assay method validation reports were submitted in most of the studies.
- Comments: The above assay methods are found overall acceptable.

II. COMMENTS TO THE MEDICAL OFFICER:

1. The FP PK data obtained from Study SFCB 3019 that was conducted in asthmatic patients (a PK subset of a clinical trial) show that the combination product (SFC) had lower ($\approx 25\%$) mean AUC and C_{max} values for FP as compared to those when Sal and FP were given concurrently. Regarding drug interactions for Sal on FP (concurrent vs. FP alone), no major differences in PK were observed since the magnitude of interactions were low. The systemic PD data follow the same trend.
2. The above FP PK data obtained from asthmatic patients (SFCB 3019) are lower than those obtained from healthy subjects (SFCB 1002, 1004, and 1005) which is seemingly perceivable due to disease status.
3. When given to healthy volunteers as the combination product or given alone (SFCB 1004) FP caused significant decrease in mean 24-hr urinary cortisol excretion but not in mean plasma cortisol levels. However, the above trend was not observed in asthmatic patients. Further, no major differences in patients were observed between baseline and FP when given alone, concurrently with Sal, or as the combination product.
4. Significant gender differences were reported for Study SFCB 3019, i.e., male patients had lower mean FP AUC (40-48% \Downarrow) and C_{max} (21-38% \Downarrow) values than female patients. The above gender differences in FP PK are consistent with the mean FEV₁ (%) reported (male: 71.2% vs. female: 88.3%). However, no gender

BEST POSSIBLE COPY

differences in plasma or urinary cortisol levels were reported. Therefore, it is to ~~bring to the attention of the reviewing medical officer to see whether the similar trend with female patients having higher FEV₁ than male patients, is observed in clinical trials with respect to systemic safety and efficacy.~~

5. ~~The dose proportionality of FP among 3 ADVAIR strengths was assessed by the sponsor via interstudy comparison (with several assumptions). The results showed that a dose-related increase in systemic exposure to FP was found and the increase was less than dose proportional. The sponsor's attempt to assess dose proportionality, however, is less satisfactory (or less than ideal). The reviewing medical officer should pay attention to safety outcome if unusual incidents occurred with increasing dose in other clinical trials. . . .~~
6. The Sal PK data obtained from a single-dose study SFCB 1005 show that the combination product (SFC) had significantly higher mean C_{max} values for Sal as compared to the treatment where Sal was given concurrently with FP (D vs. C). However, the above data is inconsistent with those obtained from a multiple-dose study SFCB 1004 (D vs. B). Furthermore, Study SFCB 1004 show that Sal may accumulate after multiple dosing to healthy volunteers. However, no plasma Sal levels in asthmatic patients were obtained from study SFCB 3019 to confirm the accumulation issue. It should be noted that the Sal plasma C_{max} values obtained were close to assay limits. Therefore, these data should be viewed with caution.

III. RECOMMENDATION:

ADVAIR DISKUS (Sal/FP combination 50/100 µg, 50/250 µg, 50/500 µg) dry powder inhaler that was submitted under NDA 21-077 on 03/25/99 by GW has been reviewed by the OCPB/DPE II. OCPB is of the opinion that the NDA is acceptable for supporting the 3 strengths of ADVAIR DISKUS. The following Labeling Comments on PK subsection as appropriate should be conveyed to the sponsor. The Labeling Comments on PD subsection should be referred to the reviewing medical officer.

IV. LABELING COMMENTS: (Need to be sent to the sponsor)

NOTE: Upon Agency's request, the sponsor submitted on 01/13/2000 the revised Advair's PI to standardize the CLINICAL PHARMACOLOGY Pharmacokinetics and Pharmacodynamics subsection.

1. The following is the Agency's version of package insert for Pharmacokinetics subsection under clinical Pharmacology section:

Salmeterol Xinafoate Pharmacokinetics:

Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and

BEST POSSIBLE COPY

independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Absorption: Because of the small therapeutic dose, systemic levels

Distribution: Binding of salmeterol to human plasma proteins averages 96% in vitro over the concentration range from 8 to 7722 ng/ml of salmeterol base,

Metabolism: Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

Elimination: In 2 healthy subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabel was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

Special Populations:

The xinafoate moiety has no apparent pharmacologic activity, is highly protein bound (>99%), and has a long elimination half-life of 11 days.

Fluticasone Propionate Pharmacokinetics:

Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate from the DISKUS device in healthy volunteers averaged about 18%.

Distribution: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg. The percentage of fluticasone propionate bound to human plasma proteins averaged 91%.

Fluticasone propionate is weakly and reversibly bound to erythrocytes. is not significantly bound to human transcortin.

Metabolism: The only circulating metabolite detected in man is the 17 β -carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4

BEST POSSIBLE COPY

pathway. This metabolite had ~~less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies.~~ Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Elimination:

Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations:

Formal pharmacokinetic studies using fluticasone propionate were not carried out

Drug-Drug Interaction: In a multiple-dose drug interaction study, coadministration of fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg three times daily) did not affect fluticasone propionate pharmacokinetics. In a drug interaction study, coadministration of fluticasone propionate (1000 mcg) and ketoconazole (200 mg once daily) resulted in increased fluticasone propionate concentrations, plasma cortisol no effect of urinary excretion of cortisol. Since fluticasone is a substrate of CYP3A4, caution should be exercised when CYP3A4 inhibitors (e.g., ritonavir, ketoconazole) are co-administered with fluticasone as this could result in increased plasma concentrations of fluticasone.

ADVAIR DISKUS Pharmacokinetics:

Following administration of ADVAIR DISKUS to healthy peak plasma concentrations of salmeterol were achieved in about 5 minutes and those for fluticasone were achieved in 1 to 2 hours.

In a single-dose study, a higher than the recommended dose of ADVAIR DISKUS was administered to 14 healthy volunteers

Mean peak plasma concentrations of salmeterol averaged 200 pg/mL and 150 pg/mL fluticasone averaged 107 and 94 pg/ml, respectively, indicating no changes in systemic exposures of salmeterol and fluticasone propionate.

In a repeat-dose study, the highest recommended dose of ADVAIR DISKUS was administered to 45 asthmatic patients

Mean peak steady-state plasma concentrations of fluticasone averaged respectively, indicating no changes in systemic exposure of fluticasone propionate. No plasma concentrations of salmeterol were measured in this repeat-dose study.

No changes in excretion of salmeterol or fluticasone were observed. The terminal half-life of fluticasone averaged 5.33 to 7.65 hours when ADVAIR DISKUS was administered which

BEST POSSIBLE COPY

is similar to that reported. _____ when fluticasone propionate was given concurrently with salmeterol or when fluticasone propionate was given alone. No terminal half-life of salmeterol was reported upon ADVAIR DISKUS administration or salmeterol given concurrently with fluticasone propionate.

Special Populations:

[
Formal pharmacokinetic studies using ADVAIR DISKUS were not _____
populations, such as elderly patients or patients with hepatic or renal impairment.

Drug-Drug Interaction: In the repeated-dose or single-dose studies, _____
]

2. The following is the Agency's version of package insert for Pharmacodynamic subsection for Advair Diskus subsection under clinical Pharmacology section:

ADVAIR DISKUS: Since _____ pharmacodynamic effects of salmeterol are seen at the therapeutic dose, higher doses were used to produce measurable effects. _____

[
In clinical studies with ADVAIR DISKUS in patients with asthma, no significant differences were observed in the pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given alone or as ADVAIR DISKUS. In 72 adolescent and adult patients with asthma given either ADVAIR DISKUS _____ or ADVAIR DISKUS _____ continuous 24-hour electrocardiographic monitoring was performed after the first dose and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

BEST POSSIBLE COPY

In a 28-week study in patients with asthma, ADVAIR DISKUS — twice daily was compared with the concurrent use of salmeterol powder 50 mcg plus fluticasone propionate powder 500 mcg from separate inhalers or fluticasone propionate powder 500 mcg alone. No significant differences across treatments were observed in plasma cortisol AUC after 12 weeks of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

In a 12-week study in patients with asthma, ADVAIR DISKUS — twice daily was compared with fluticasone propionate powder 250 mcg alone, salmeterol powder 50 mcg alone and placebo. For most patients, the ability to increase cortisol production in response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with ADVAIR DISKUS. One patient (3%) who received ADVAIR DISKUS — had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing, compared with 2 patients (6%) who received placebo, 2 patients (6%) who received fluticasone propionate 250 mcg, and no patients who received salmeterol.

NOTE: CPB Briefing on 11/09/99: Drs. M.L. Chen, R. Uppoor, and S. Johnson (MO) and Mr. J. Hunt

ISI

11/19/2000

11/02/99

Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Ramana Uppoor, Ph.D.

RU 11/03/99

FT initialed by Ramana Uppoor, Ph.D.

ISI

11/19/2000

cc: NDA 21-677, HFD-570 (Johnson, Jani), HFD-870 (S.M. Huang, R. Uppoor, T.M. Chen), CDR (B. Murphy).

BEST POSSIBLE COPY

NDA 21-077 for ADVAIR Diskus

**(Salmeterol/Fluticasone Propionate 50/100 µg, 50/250 µg,
50/500 µg) Serial No. N-000**

Appendix 1

**APPEARS THIS WAY
ON ORIGINAL**

Sponsor's Proposed Package Insert (01/14/2000 version)

WITHHOLD 27 PAGE (S)

Draft labeling

BEST POSSIBLE COPY

NDA 21-077 for ADVAIR Diskus

**(Salmeterol/Fluticasone Propionate 50/100 μ g, 50/250 μ g,
50/500 μ g) Serial No. N-000**

Appendix 2

**APPEARS THIS WAY
ON ORIGINAL**

Summary of Individual Study Reports

SUMMARY OF STUDY No. SFCB1004 (Vol. 1.38)

TITLE

The systemic pharmacodynamic effects and pharmacokinetics of salmeterol and fluticasone propionate when given alone and in combination, after repeat dosing from Diskus™ inhalers in healthy volunteers.

OBJECTIVES

- To investigate whether the salmeterol/fluticasone (SLG/FP) combination has acceptable safety and tolerability after repeat doses.
- To investigate whether the systemic pharmacodynamic effects after repeat doses and after cumulative salbutamol (AL) doses and pharmacokinetics after repeat doses of SLG and FP show any significant interaction when the two drugs are administered together.

DESIGN

This was a randomised, double-blind, placebo-controlled, four-treatment, three-period, cross-over study, using an incomplete block design.

Any one subject received 3 of the 4 treatments:

- SLG/FP (all subjects)
- SLG (all subjects)
and then either
- FP (half the subjects) or
- Placebo except for a single dose of SLG (SLG SD) which replaced the 19th dose (half the subjects)

Each study period lasted 12 days, with a washout of at least 9 days. Treatment for the first 11 days was twice daily (12 hourly) from Diskus™ Inhalers. On Day 10, after the 19th dose, pharmacodynamic effects and pharmacokinetics of SLG and FP were investigated. On Day 12, all subjects received cumulative doses of SAL from metered-dose inhalers. This was to investigate tachyphylaxis to the systemic pharmacodynamic effects of SLG, (a β -agonist like SAL) and see whether this was affected by the presence of FP during the period of dosing with SLG.

SETTING/STUDY DATES

The study took place in the Clinical Pharmacology Unit at Glaxo Wellcome SpA., Verona, Italy, between 04May96 and 08Aug96.

APPEARS THIS WAY
ON ORIGINAL

SUBJECTS

The design called for 24 healthy male and female subjects; 28 subjects participated, including withdrawals. There were 13 males and 15 females, average age 27.0y (range 21 - 48y), average weight 65.9kg (range 50 - 88kg), all from the Volunteer Panel of the Glaxo Wellcome Clinical Pharmacology Unit, Verona, Italy.

TREATMENTS

Treatment for the first 11 days was twice daily (at 12 hour intervals) from Diskus™ Inhalers, 2 inhalations per dose of either:

- SLG 50mcg/FP 250mcg, (23 subjects)
- SLG 50mcg, (24 subjects)
- FP 250mcg, (13 subjects) or
- placebo (12 subjects).

For the placebo group only, the 19th dose only was replaced by a single dose of 2 inhalations of 50mcg SLG. This enabled comparison of the pharmacodynamic effects and pharmacokinetics of SLG after a single dose with those at steady state.

On Day 12, subjects on all treatments received cumulative doses of SAL from metered-dose inhalers at intervals of 30min, (400, 400, 800 and 1600mcg, giving a total dose of 3200mcg).

The design called for 24 subjects, with all subjects receiving the first two treatments, half of them receiving the FP alone treatment and the other half receiving the placebo. In practice, 28 subjects participated in the study to some extent, and the numbers of subjects providing data on Day 10 are shown above (in brackets) for each treatment.

MEASUREMENTS

Pharmacodynamics:

Pharmacodynamic effects of SLG (pulse rate, blood pressure, QTc from ECG, potassium and glucose) were evaluated for 4h after the 19th dose (Day 10), determining the mean across the 4h period and the maximum (or minimum) value. The effects of SLG after a single dose were compared to those after repeat dosing, and the effects of SLG alone after repeat dosing were compared with those when concomitant FP was also given. On Day 12, the same pharmacodynamic measures were made pre-dose and 25 min after each dose of SAL in the cumulative series. Dose-response curves were constructed, and responses summarised as the slope of the response against the dose and the final value reached after the last dose. Comparisons of these responses to SAL were used to evaluate the development of tachyphylaxis to SLG, and whether this was affected by concomitant FP.

β_2 -adrenoceptors on lymphocytes were measured at various points in the study. For some subjects, the genetic polymorphisms present at loci 16 and 27 in the β_2 -adrenoceptor gene were also determined, as they may be related to the development or otherwise of tachyphylaxis to the systemic effects of β_2 -agonists.

Pharmacodynamic effects of FP (morning plasma cortisol levels and 24h urinary cortisol excretion) were evaluated prior to the 19th dose, on Day 10. Comparisons were made between the effects of FP given alone or in combination with SLG.

Pharmacokinetics:

Blood samples of 6mL for FP determination in plasma were taken after the morning dose on day 10 of each treatment period pre-dose (within 5 minutes of dosing) and at 5, 15, 30, 45min and 1, 2, 4, 6, 8, 10 and 12 h. Blood samples of 6mL for determination of SLG were collected after the morning dose on day 10 of each treatment period

BEST POSSIBLE COPY

pre-dose (within 5min of dosing) and at 2, 5, 10, 20 and 30min. Time points were related to the start of inhalation. FP and SLG were assayed in plasma _____, respectively, with quantification limits of _____, respectively. Pharmacokinetic parameters were determined by non compartmental analysis.

Safety:

Adverse events were recorded throughout and laboratory safety data obtained pre- and post-study.

RESULTS

Pharmacodynamics:

APPEARS THIS WAY
ON ORIGINAL

SLG

The systemic effects after 19 doses SLG were compared with those after a single dose of SLG: the only comparison to show a significant difference was the mean pulse rate over 4h (2.5bpm, 95% CI 0.2, 4.8, $p = 0.034$). There were differences in the baseline pulse rate (i.e. before the 19th dose on Day 10): the mean for the repeat SLG group was 66bpm while that in the placebo group (before the single dose of SLG) was 58.5bpm. After the single dose of SLG, the pulse rate rose almost to the baseline levels seen in the repeat SLG group.

Comparison of the effects of repeat SLG with repeat SLG/FP found no statistically significant differences for any of the parameters, either in the weighted means or in the maximum (pulse rate, systolic blood pressure, QTc and glucose) or minimum (diastolic blood pressure and potassium) values. The effects of SLG were unchanged by concomitant FP.

The responses to salbutamol on Day 12 showed that tachyphylaxis had developed to the systemic effects of β -agonists (on pulse rate, QTc, potassium and glucose) following treatment with SLG. Comparison of the (repeat) SLG group with placebo group showed statistically significant differences for pulse rate and QTc in baseline, final value and slope (change per 100mcg salbutamol), and for potassium and glucose in final value and slope.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Statistical comparisons of responses to SAL on Day 12, after prior treatment with SLG compared to placebo

Parameter	Difference (95% CI) and p value		
	Baseline	Final value	Slope (per 100mcg increase)
Pulse rate (bpm)	3.6 (-0.1, 7.1), 0.046	-6.2 (-11.4, -1.0), 0.02	-0.29 (-0.47, -0.11), 0.002
QTc (msec)	7.8 (0.8, 14.8), 0.029	-8.4 (-15.3, -1.5), 0.018	-0.5 (-0.79, -0.20), 0.001
Potassium (mmol/L)*	0.97 (0.92, 1.02), 0.178	1.10 (1.04, 1.17), 0.003	1.004 (1.002, 1.006) <0.001
Glucose (mmol/L)*	1.02 (0.98, 1.06), 0.253	0.92 (0.87, 0.97), 0.001	0.997 (0.995, 0.998), <0.001

* Ratio and slope as ratio

Similar results were seen when SLG/FP was compared with placebo.

Statistical comparisons of responses to SAL on Day 12, after prior treatment with SLG/FP compared to placebo

Parameter	Difference (95% CI) and p value		
	Baseline	Final value	Slope (per 100mcg increase)
Pulse rate (bpm)	1.7 (-1.7, 5.2), 0.317	-9.1 (-14.2, -4.0) <0.001	-0.34 (-0.52, -0.16) <0.001
QTc (msec)	1.2 (-5.6, 8.0), 0.724	-5.6 (-12.3, 1.1), 0.101	-0.18 (-0.47, 0.11), 0.212
Potassium (mmol/L)*	0.96 (0.92, 1.00), 0.069	1.10 (1.04, 1.17) 0.002	1.004 (1.002, 1.006) <0.001
Glucose (mmol/L)*	1.01 (0.98, 1.05), 0.481	0.91 (0.87, 0.96) <0.001	0.996 (0.995, 0.998) <0.001

* Ratio and slope as ratio

Tachyphylaxis to effects on blood pressure was not observed.

Statistical comparison of the responses to SAL after SLG/FP with those after SLG showed statistically significant differences only for QTc baseline (-6.6msec, 95%CI -11.9, -1.3, p = 0.016) and slope (0.32msec per 100mcg, 95%CI 0.09, 0.54, p = 0.007). The development of tachyphylaxis to the systemic effects of SLG was not affected by concomitant FP.

Genotyping of 21 individuals was performed, but genotype could not be correlated with development of tachyphylaxis.

β_2 -adrenoceptors on lymphocytes were measured but the variability was such that no conclusions as to treatment effects could be drawn.

FP

Treatment with FP reduced the 24h urinary cortisol excretion: the ratio for the FP group compared to placebo was 0.49 (95%CI 0.35, 0.67), p <0.001. The corresponding ratio for SLG/FP was 0.47 (95%CI 0.37, 0.60), p <0.001. Direct comparison of SLG/FP with FP gave a ratio of 0.97, p = 0.806, so the effect of FP was unchanged by concomitant SLG.

Morning plasma cortisol levels fell in the presence of FP, but not by a statistically significant amount; the ratio of the mean level in the FP group to that in the placebo group was 0.79, p = 0.130. No effect of concomitant SLG was discernible (the ratio for the SLG/FP group compared to the FP alone group was 1.02, p = 0.857).

Pharmacokinetics:

Pharmacokinetics of SLG

Except for one subject during SLG/FP treatment, C_{max} values for SLG for all three SLG treatments (SLG/FP, SLG, SLG SD) were reached within 5 min after dosing.

Comparison of SLG/FP and SLG treatments to assess the potential interaction with FP: Geometric LS mean C_{max} values of SLG were 0.229 ng/mL and 0.220 ng/mL (n=22) for SLG/FP and SLG treatments, respectively: they were not statistically different.

Parameter	Treatment	Geometric	95% CI	Ratio	Estimate	90% CI	p-value
LS mean	of LS mean		(%)				
C_{max}	SLG/FP (n=22)	0.229	0.205-0.256	SLG/FP / SLG	104	(92-118)	0.5948
(Ng/mL)	SLG (n=22)	0.220	0.197-0.245				

Influence of repeat dosing on SLG C_{max} : Statistical analysis of SLG C_{max} values of the 11 subjects who received both SLG and SLG SD treatments demonstrated that the C_{max} after SLG was significantly higher (1.3 fold) compared to SLG SD (p=0.0001).

Parameter	Treatment	Geometric	95% CI	Ratio	Estimate	90% CI	p-value
		LS mean	of LS mean		(%)		
C_{max}	SLG (n=11)	0.202	0.190-0.215	SLG / SLG SD	130	(122-140)	0.0001
(Ng/mL)	SLG SD (n=11)	0.155	0.146-0.165				

Period effect on SLG C_{max} : SLG C_{max} after SLG SD treatment was lower during study periods 2 and 3 compared to the first period. Such a period effect could not be explained, and was not observed after SLG treatment.

Treatment	SLG		SLG SD	
Period	Subjects	mean C_{max} (ng/mL)	Subjects	mean C_{max} (ng/mL)
1	n=4	0.2188	n=4	0.1920
2	n=4	0.2070	n=3	0.1493
3	n=3	0.2073	n=4	0.1473

Pharmacokinetics of FP

Statistical analysis of the FP data obtained from subjects who received both SLG/FP and FP showed a statistically significantly higher FP AUC_t after SLG/FP compared to FP alone. However the increase was small (8%; 90% CI of the estimate=103-113%) and not considered to be clinically relevant. Geometric LSmean values for FP C_{max} were 111.9 pg/mL for SLG/FP and 107.1 pg/mL for FP alone. The t_{max} of FP had a median value of 1.00 h for SLG/FP and 0.75 h for FP. These parameters were not different for the different treatments.

Parameter	Treatment	Geometric	95% CI	Ratio	Estimate ^c	90% CI	p-value
		LSmean ^a	of LSmean ^b		(%)		
AUC_t	SLG/FP (n=11)	722.7	694.2-752.4	SLG/FP / FP	108	(103 - 113)	0.0135
(pg.h/mL)	FP (n=11)	668.4	642.1-695.9				
C_{max}	SLG/FP (n=11)	111.9	105.2-119.1	SLG/FP / FP	104	(97 - 112)	0.2830
(pg/mL)	FP (n=11)	107.1	100.6-113.9				
C_t	SLG/FP (n=11)	35.64	25.69-57.67	SLG/FP - FP	5.86	(0.25 - 10.9)	0.0830

BEST POSSIBLE COPY

(ng/mL)	FP	(n=11)	29.75	25.15-50.28				
t _{1/2}	SLG/FP	(n=11)	7.65	7.01-8.31	SLG/FP / FP	111	(101 - 122)	0.0780
(h)	FP	(n=11)	6.91	6.36-7.50				
t _{max}	SLG/FP	(n=11)	1.00	0.50-1.00	SLG/FP - FP	0.23	(0.00 -0.50)	0.2344
(h)	FP	(n=11)	0.75	0.083-1.00				

* median for C_t and t_{max}

^b (min-max) for C_t and t_{max}

^c median difference for C_t and t_{max}

Adverse Events and Subject Withdrawals:

There were no serious adverse events. There were 6 withdrawals: one subject was withdrawn due to a drug-related adverse effect (tremor) after 9 doses of the SLG/FP combination; three subjects withdrew because of intercurrent illness, two with fever and one with bronchitis; two withdrew for personal reasons.

Of the 91 adverse events, most (67) were of types to be expected after high doses of β₂-agonists: tremor (39), palpitations (6) and headache (22). More episodes of tremor were reported in the SLG alone group. However, this may be misleading, as the total duration for which tremor was experienced was similar in the SLG and SLG/FP groups. There was nothing noteworthy about the occurrence or distribution of the other adverse events.

Laboratory Safety Screening:

There was one laboratory result within the range of potentially clinically relevant values (a low serum albumin), but this appeared to be of no clinical significance.

CONCLUSIONS

- All treatments were safe and well tolerated. There was no excess of adverse events in the SLG/FP group compared to the other groups. A greater number of reports of tremor, (but not a greater duration of tremor) was recorded prior to Day 12 for the group receiving repeat SLG.
- The effects of SLG, both the systemic pharmacodynamic effects after repeat dosing and its effects on the pharmacodynamic responses to cumulative SAL, were not altered in the presence of FP.
- The pharmacodynamic effects of FP, as seen in a reduction in 24h urinary cortisol excretion, were not affected by the presence of SLG.
- Addition of FP to SLG did not result in an altered plasma profile of SLG when compared to SLG treatment alone
- Addition of SLG to FP slightly (8%; 90% CI 103-113) increased the systemic exposure to FP when compared to administration of FP alone. This increase was within accepted bioequivalence limits and was not considered to be clinically relevant.
- The C_{max} of SLG following twice daily inhaled administration was significantly increased (1.3 fold) compared to single dosing, indicating some accumulation.

APPEARS THIS WAY
ON ORIGINAL

SUMMARY OF Study No. SFCB1005 (Vol. 1.40)

TITLE

The systemic pharmacodynamic effects and pharmacokinetics of salmeterol and fluticasone propionate when given together, from either a single or two separate Diskus™ Inhalers, in single doses.

OBJECTIVES

1. To show that the systemic pharmacodynamic (PD) effects and pharmacokinetics (PK) of either drug are comparable, whether they are administered from one Diskus™ Inhaler or two separate Inhalers.
2. To obtain data on the PK and PD of fluticasone propionate (FP) from the salmeterol (SLG) 50mcg/FP 500mcg strength of the combination product in the Diskus™ Inhaler, for use with data from other studies in an evaluation of the proportionality of FP systemic exposure to dose across the three strengths of the combination product.
3. To show that the highest strength of the combination product, with the highest ratio of FP to SLG, has acceptable safety and tolerability in single doses, even when administered at twice the normal therapeutic dose.

DESIGN

Single dose, randomised, double-blind, 3-way cross-over design, with a wash-out of at least 7 days (dose to dose) between periods.

SETTING/STUDY DATES

The study took place in the Clinical Pharmacology Unit at Glaxo Wellcome SpA., Verona, Italy, between 31 October 1996 and 04 December 1996.

SUBJECTS

14 healthy subjects; 8 male and 6 female, mean age 27.4y (range 21.0 - 35.0y), mean weight 67.1kg (range 55.0 - 89.0kg), were recruited from the Glaxo Wellcome SpA Clinical Pharmacology Unit panel. Twelve subjects completed the study and two participated in part of the study.

TREATMENTS

Treatments, all from a dry powder formulation using the Diskus™ Inhalers, were :

- Salmeterol (SLG) 100mcg/FP1000mcg as combination (given as 2 inhalations from a placebo inhaler followed by 2 inhalations from SLG/FP inhaler at 50/500 per inhalation);
- SLG 100mcg and FP 1000mcg from separate inhalers (given as 2 inhalations from FP inhaler at 500mcg per inhalation followed by 2 inhalations from SLG inhaler at 50mcg per inhalation);
- FP 1000mcg alone plus placebo (given as 2 inhalations from a placebo inhaler followed by 2 inhalations from FP inhaler at 500mcg per inhalation).

Each study period lasted 48h, with the dose given after 24h at approximately 09.00.

MEASUREMENTS

Pharmacodynamics:

The effects of SLG on pulse rate, systolic and diastolic blood pressure, ECG (for QTc interval), serum potassium and glucose levels were measured at the following times: pre-dose, at 6, 16, 31 min and at 1, 1.5, 2, 3, and 4h post-dose. The means across the 4h time period were calculated for each treatment group, and the maximum values for pulse rate, systolic blood pressure, QTc interval and glucose and the minimum values for diastolic blood pressure and potassium were determined.

The effects of FP on cortisol production were evaluated by measuring urinary cortisol excretion for 24h before and after the dose, in 12h aliquots. Cortisol levels in plasma were measured at frequent intervals for 24h before and after the dose (at 24, 22, 20, 18, 16, 14, 12, 8, 4h, and 5min pre-dose and at 2, 4, 6, 8, 10, 12, 16, 20 and 24h post-dose), and the areas under the concentration-time curves for the 24h periods before and after each dose were calculated.

Pharmacokinetics:

Salmeterol concentrations in plasma were assayed using an _____ in samples obtained pre-dose and for 30min after the dose (at 3, 6, 11, 21 and 31 min).

FP concentrations in plasma were assayed using an _____ in samples obtained pre-dose and for 24h post-dose (at 6, 16, 31, and 45min and 1, 2, 4, 6, 8, 10, 12, 16 and 24h).

Pharmacokinetic parameters $AUC_{0-\infty}$, C_{max} , t_{max} and $t_{1/2}$ were determined by non-compartmental analysis.

Safety:

Medical screening, including medical history and examination, was performed within 3 weeks of the first study day. Laboratory safety screens (haematology, clinical chemistry and urinalysis) were performed within 3 weeks pre-study and within 14 days post-study. For female subjects, pregnancy tests were required pre-study, on Day 1 of each treatment period and post-study.

All adverse events reported during the study were recorded in the CRF.

RESULTS

Pharmacodynamics:

There were no statistically significant differences between SLG and FP as the combination product (from one inhaler) and concurrently (from 2 separate inhalers), for any of the effects measured. When the SLG/FP treatment was compared to the FP alone treatment, statistically significant differences were seen for pulse rate, QTc interval, potassium and glucose. When the SLG and FP concurrently treatment was compared to FP alone, statistically significant differences were seen for pulse rate and glucose.

Pharmacokinetics:

Insufficient data were available to characterise the plasma profile of SLG fully. The mean C_{max} of SLG was higher for SLG/FP from a single inhaler relative to SLG and FP concurrently: ratio 1.29, 90%CI 1.07, 1.56, $p=0.033$.

Comparison of the PK parameters for FP across the three treatments showed no statistically significant differences except for C_{max} following SLG and FP concurrently compared to FP alone. The corresponding ratio (SLG + FP to FP) of the C_{max} was 0.78, 90% CI 0.65, 0.94, $p=0.031$.

Adverse Events and Subject Withdrawals:

There were no deaths or serious adverse events. Two subjects were withdrawn but not due to a drug-related effect. Subject No. 4298 reported herpes genitalis which required medication and was withdrawn because of intercurrent illness, and Subject No. 4301 failed to complete for personal reasons.

A total of 13 minor adverse events were reported in five subjects. Only one (headache) was thought to be possibly drug related. All the adverse events were mild to moderate in severity.

Laboratory Safety Screening:

Laboratory safety screens were performed pre- and post-study. There were no abnormalities considered clinically significant.

CONCLUSIONS

- The systemic pharmacodynamic effects of SLG were not significantly different whether SLG was given together with FP in the combination product or concurrently with FP.
- The systemic pharmacodynamic effects of FP were not significantly different whether FP was given as a single agent, or together with SLG in the combination product or concurrently with SLG.
- The SLG C_{max} was 29% higher after the combination product compared to when the two drugs were given concurrently.
- The systemic exposure to FP was not significantly altered by SLG, after either the combination product or after concurrent administration.
- The FP C_{max} value was 22% lower when FP and SLG were given concurrently compared to FP alone. This was not observed for the combination product.
- All doses appeared safe and were well-tolerated.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

Summary of Study No. SFCB3019 (Vol. 1.41)

Title: A Multicentre, Randomised, Double-Blind, Double-Dummy, Parallel-Group Comparison of the Salmeterol/Fluticasone Propionate Combination Product (50/500mcg strength) BD via one DISKUS/ACCUHALER Inhaler with Salmeterol 50mcg BD via one DISKUS/ACCUHALER Inhaler and Fluticasone propionate 500mcg BD via another DISKUS/ACCUHALER Inhaler and with Fluticasone propionate 500mcg BD via one DISKUS/ACCUHALER Inhaler in adolescents and adults with reversible airways obstruction.

Investigator(s): Multicentre study

Study centre(s): 55 centres in three countries: _____

Publication(s): Not Applicable

Study period: 31st May 1996 - 10th Nov 1997 **Clinical phase:** III

Objectives: (1) To demonstrate the equivalence of the salmeterol/fluticasone propionate combination product (50/500mcg strength) bd delivered via a single DISKUS/ACCUHALER inhaler with its two constituents salmeterol 50mcg and fluticasone propionate 500mcg via two separate DISKUS/ACCUHALER inhalers bd over the first twelve weeks of the twenty-eight week treatment period. (2) To demonstrate superior efficacy of the salmeterol/fluticasone propionate combination product (50/500mcg strength) bd delivered via the DISKUS/ACCUHALER inhaler to fluticasone propionate 500mcg delivered alone via the DISKUS/ACCUHALER inhaler over the first twelve weeks of the twenty eight week treatment period. (3) To demonstrate the safety of the salmeterol/fluticasone propionate combination product (50/500mcg strength) in long-term use (28 week treatment period). (4) To document the use of resources and humanistic impacts with each treatment.

Methodology: This study was a randomised, double-blind, double-dummy, parallel-group design consisting of three stages: run-in, treatment and follow-up. Patients entered a two week run-in period and used their usual inhaled corticosteroid, with VENTOLIN as a rescue medication. Patients were then randomised to receive a 28 week regimen of either salmeterol/fluticasone propionate combination product (50/500mcg strength) bd or salmeterol 50mcg bd and fluticasone propionate 500mcg bd (concurrent therapy) or fluticasone propionate 500mcg bd delivered via DISKUS/ACCUHALER inhalers. During the two weeks of follow-up, patients received appropriate asthma medication. Eight Clinic Visits (including weeks 2, 4, 12, 20 and 28 on treatment) were scheduled, or nine if run-in was repeated.

Number of subjects: A total of 659 patients were screened, 503 received treatment, and 403 completed the study. The target number of patients in each treatment group was 150.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

A total of 167 patients were randomised to receive the combination product of whom 136 completed the study; 171 patients were randomised to receive concurrent therapy of whom 143 completed the study; 165 patients were randomised to receive fluticasone propionate alone of whom 124 completed the study.

Diagnosis and criteria for inclusion: Males or females 12 years of age or older, with a documented clinical history of reversible airways obstruction were included. Patients had also used inhaled corticosteroids continuously for at least 12 weeks before start of the run-in, and must have used beclomethasone dipropionate or budesonide at a dose of 1500-2000mcg/day*, or fluticasone propionate at a dose of 750-1000mcg/day* for at least four weeks before start of run-in. They were symptomatic on this treatment. Patients taking long-acting β_2 -agonists were excluded.

Test product, dose and mode of administration, batch no.: Salmeterol/fluticasone propionate 50/500mcg strength 60 blisters/strip (batch numbers U96/014E, U96/018E) administered via a DISKUS/ACCUHALER inhaler. Placebo, 60 blister/strip (batch number WP1ME1), administered via a DISKUS/ACCUHALER inhaler.

Duration of treatment: The study period was 32 or 34 weeks: run-in was two weeks (or four if repeated), treatment was 28 weeks, and follow-up was two weeks.

Reference therapy, dose and mode of administration, batch no.: Salmeterol 50mcg, 60 blisters/strip (batch number WP1W85) and fluticasone propionate 500mcg, 60 blister/strip (batch numbers WP1R2K, WP1W84 and WP298X), administered via DISKUS/ACCUHALER inhalers.

Criteria for evaluation: Primary efficacy assessments were based on treatment weeks 1-12 Daily Record Card data of morning PEFR as measured by the patient before taking any rescue or study medication. Secondary assessments were based on: i) Further analysis of morning PEFR, ii) Daily Record Card data of evening PEFR measured before taking any rescue and study medication, iii) recordings of the use of additional VENTOLIN rescue medication, iv) day-time and night-time asthma symptom scores, and v) Clinic Visit pulmonary function measurements of FEV₁ at all Clinic Visits except at follow-up.

Safety was assessed by monitoring adverse events, morning serum cortisol levels, haematology and biochemistry measurements, vital signs and ECGs and by performing physical and oropharyngeal exams. 24-hour urinary cortisol concentrations were measured in all patients in a sub-set of centres in _____ and the _____

Plasma cortisol and plasma fluticasone propionate levels were determined in a sub-set of patients in the _____ (Pharmacokinetic Sub-Group) in order to evaluate the relative absorption and systemic bioavailability of fluticasone propionate from the salmeterol/fluticasone propionate combination product compared with salmeterol and fluticasone propionate administered concurrently and fluticasone propionate alone.

Humanistic assessments were recorded by the patient in a patient questionnaire at the start of treatment, Clinic Visit 2/2A, and at Clinic Visit 7 or at withdrawal if earlier. Impact of asthma on daily activity was assessed at Clinic Visit 2/2A and during treatment on the Daily Record Card. Data on the use of medical resources were recorded by the investigator on the Unscheduled Healthcare Contacts Form in the CRF.

* All values are quoted as ex-valve doses

BEST POSSIBLE COPY

Statistical methods: The study was designed to include 450 evaluable patients, 150 per treatment group, to achieve 90% power to detect a treatment difference. Treatment groups were defined to be equivalent if the 90% confidence interval for the treatment difference was within ± 15 L/min. A further requirement was to detect a statistical difference ($p < 0.05$) between combination product and fluticasone propionate treatments. The primary assessment of efficacy was based on analysis of covariance of the mean morning PEF_R during the first 12 weeks of the treatment period with the Intent-To-Treat Population. Other variables were analysed using analysis of covariance or the van Elteren test, stratified by centre amalgamation. A subset of efficacy variables were also analysed using the Efficacy Population.

For each subject and treatment in the pharmacokinetic sub-group the following parameters were determined: plasma C_{max} , T_{max} and AUC steady state (AUC_{ss}). These parameters were analysed by analysis of variance or Wilcoxon Rank Sum.

Summary and Conclusions:

Efficacy: The primary efficacy measure was mean morning (AM) PEF_R for Weeks 1-12 with the Intent-to-Treat Population. The treatments were defined as equivalent for this endpoint if the 90% confidence limits for the treatment difference were within ± 15 L/min. Superiority was demonstrated by showing significance based on p-values. Additionally the 95% confidence limits were compared with the equivalence interval to assess clinical superiority. The 90% confidence limits of the treatment difference of concurrent therapy minus combination product were -10L/min, 4L/min over Weeks 1-12, indicating that the two treatments were equivalent. Equivalence was also demonstrated when the Efficacy Population was used in this analysis, and 95% confidence limits for both Intent-to-Treat and Efficacy Populations were within ± 15 L/min, again confirming equivalence. Salmeterol/fluticasone propionate combination product was significantly more efficacious than fluticasone propionate alone ($p < 0.001$). The 95% confidence limits for the treatment difference of fluticasone propionate minus salmeterol/fluticasone propionate were -29L/min, -12L/min, clearly outside the pre-defined equivalence interval. Similar results were seen for the Efficacy Population. Other time intervals analysed for mean morning PEF_R showed similar results to the results during Weeks 1-12, for both Intent-to-Treat and Efficacy Populations.

Results for other daily record card data (percent predicted mean morning PEF_R, mean evening PEF_R, percent predicted evening PEF_R, day-time symptom scores, symptom-free days and VENTOLIN usage) also showed significantly greater effects with the combination product than with fluticasone propionate alone. Effects of the combination product and concurrent therapy on these parameters were similar.

For Clinic Visit FEV₁ and percent predicted FEV₁, improvements were seen for all groups over the 28 week treatment period and were similar across all three treatment groups. In contrast to the daily record card data, no differences were observed between combination product and fluticasone propionate in either the Intent-to-Treat or Efficacy Populations.

Overall the efficacy results demonstrate that the combination product was effective in improving pulmonary function, reducing asthma symptom scores and decreasing VENTOLIN use in patients who were already receiving inhaled corticosteroids.

There were no differences between the groups for any of the humanistic measures assessed.

BEST POSSIBLE COPY

Safety: Overall, adverse events occurred with 71% of patients treated with the combination product, 73% treated with concurrent therapy and 70% treated with fluticasone propionate. The most commonly occurring adverse events were upper respiratory tract infections, viral respiratory infections, asthma, cough, bronchitis and headaches. Incidences of adverse events were similar between the three treatment groups. The adverse events experienced by patients in this study, were consistent with the asthmatic nature of the population and the known side effects of inhaled β_2 -agonists and corticosteroids. The incidence of drug-related adverse events was similar between treatment groups (17% of patients treated with combination product, 14% treated with concurrent therapy and 19% treated with fluticasone propionate). Events reported most frequently as drug-related were either events relating to the underlying disease and so possibly related to lack of efficacy of the medication (e.g. asthma, breathing disorders which included dyspnoea and shortness of breath, and cough), or those known to be associated with these classes of drug (e.g. hoarseness/dysphonia, throat irritation and headaches). None were reported with an incidence >3% with the exception of asthma and hoarseness, each of which was reported by 4% of patients in the concurrent therapy and fluticasone propionate groups respectively.

Two deaths were reported during this study; neither were considered by the investigator to be related to study medication. One patient, aged 72 years and treated with combination product, experienced status asthmaticus following surgery under local anaesthetic to remove a cataract. Study treatment was stopped on the day of surgery. The patient required ventilation and died 14 days later. The other patient, who was treated with concurrent therapy, had a bronchial carcinoma.

Twenty-three patients experienced serious adverse events during the study. Three were experienced by patients during the pre-treatment period, 4 were in association with combination product treatment, 9 in association with concurrent therapy and 7 in association with fluticasone propionate. No serious adverse events were considered drug related. Seven patients (3 treated with combination product and 4 treated with concurrent therapy) had serious adverse events which led to withdrawal. Fifty patients had non-serious adverse events which led to withdrawal of study drug; 14 patients treated with combination product, 13 treated with concurrent therapy and 23 patients treated with fluticasone propionate. The majority of withdrawals (65%) were due to asthma events or dyspnoea; 10 patients from the combination product group, nine patients from the concurrent therapy group and 14 patients from the fluticasone propionate group. There were no differences in the pattern of withdrawals between the treatment groups.

No differences were noted between treatments in patient profiles of cortisol concentrations either at Week 12 or at Week 28. The number of patients with cortisol values below the lower limit of the normal range was low in all treatment groups throughout the study. No patients reported events indicative of compromised HPA axis function. 24-Hour urinary cortisol excretion was measured in a sub-set of patients in the study. No differences between the groups were seen at either Week 12 or Week 28 and results on treatment with combination were similar to those seen at baseline.

No treatment related trends were evident in unfavourable laboratory changes, physical examinations, ECGs or vital signs. Oropharyngeal examinations revealed very low incidences of clinical evidence of oral candidiasis.

Pharmacokinetics: Overall, no differences were seen between the treatments in AUC, C_{max} , T_{max} for fluticasone propionate and there was no evidence from these data or from the trough fluticasone propionate concentrations that systemic exposure to fluticasone propionate was altered by administration

BEST POSSIBLE COPY

either as combination or concurrent therapy. There were no differences in serial plasma cortisol measures and no evidence of cortisol suppression in these patients.

Across the three treatment groups in the pharmacokinetic sub-group of patients, there was a significant sex related difference ($p < 0.001$) in fluticasone propionate exposure (AUC and C_{max}). There was, however, no sex by treatment interaction. This sex difference in fluticasone propionate exposure could arise from differences in pharmacokinetic parameters or in the deposition of drug in the lungs. The small numbers in this group and an imbalance in the male: female ratio (31 males: 14 females) may have contributed to this result.

Conclusions: The results of this study indicated that the combination product and concurrent therapy were equivalent for the primary end-point, mean morning PEFR for Weeks 1-12 in the Intent-to-Treat Population. Both treatments showed improvement in this and other efficacy endpoints. Combination product showed results similar to concurrent therapy for all other efficacy endpoints.

The combination product demonstrated superior efficacy when compared to fluticasone propionate for the primary endpoint, mean morning PEFR for Weeks 1-12 ($p < 0.001$). The combination product also showed significantly greater improvements than fluticasone propionate for percent predicted morning PEFR, evening PEFR, percent predicted evening PEFR, median daytime symptom score, percentage of symptom-free days and percentage of VENTOLIN-free days and nights.

No differences were seen between the treatments in health outcome measures.

The combination product was well tolerated over the twenty-eight week study period and had a comparable safety profile to that observed in both the fluticasone propionate and the concurrent therapy groups.

Date of Report: 1 April 1998

APPEARS THIS WAY
ON ORIGINAL