CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-833

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEC 7 1999

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-833
Fluticasone propionate
inhalation powder 50, 100, and 250 μg

SUBMISSION DATE:
09/13/99 (Serial No. BB)

BRAND NAME: Flovent Diskus

SPONSOR: GlaxoWellcome

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Responses to The Approvable Letter Code: 3S

TITLE: "Review of Responses To The Agency's Approvable Letter"

BACKGROUND:

Fluticasone propionate (FP) is a synthetic, trifluorinated corticosteroid developed by GlaxoWellcome (GW). Fluticasone reportedly possesses potent anti-inflammatory activity with negligible oral bioavailability. In the US, two FP drug products are currently available for oral inhalation for the treatment of asthma, Flovent Inhalation Aerosol and a dry powder inhaler (DPI), Flovent Rotadisk.

On 03/30/98, the sponsor submitted NDA 20-833 and was seeking approval for a second FP dry powder inhaler (DPI), Flovent Diskus. It is for the same indication as Flovent Rotadisk in adults and children 4 years and older. Diskus is a specially designed plastic device containing a double-foil strip with blisters of 50, 100, or 250 μg of —— FP —— with lactose to a total weight of 12.5 mg only. The NDA was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). The NDA was deemed approvable by HFD-570 and three general comments and one labeling comment from OCPB were sent to the sponsor on 06/16/99.

SYNOPSIS:

On 09/13/99, GW submitted **1)** their responses to the 3 OCPB comments and **2)** revised labeling (06/08/99 version). A teleconference was further held on 07/09/99 between OCPB and the sponsor to clarify and discuss the above 3 general comments. The above responses and labeling revision are reviewed and found acceptable. Please see Attachments 1 and 2 for details.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION:

GW's responses to 3 OCPB's general comments and the labeling comment that were submitted under NDA 20-833 (Serial No. BB) on 09/13/99 are found acceptable. No further action is needed.

COMMENT: (Needs NOT to be sent to the sponsor)

For certain PK information, e.g., Gender, Pediatric, Elderly, Renal and Hepatic Impairment, the statements should be included under Special Populations subsection under PK section of the PI.

APPEARS THIS WAY
ON ORIGINAL

/S/ 12/07/99
12/06/99

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

RD/FT initialed by Ramana Uppoor, Ph.D. /S/ 12/07/99

cc: NDA 20-833, HFD-570 (Purucker, Cobbs), HFD-870 (S.M. Huang, R. Uppoor, T.M. Chen), CDR (B. Murphy).

NDA 20-833: fluticasone propionate 50, 100, and 250 μg
(Flovent Diskus Dry Powder Inhaler)

ATTACHMENT 1

Three OCPB Comments and Their Responses

1. **In the drug-drug interaction analysis for study FLTA2001, the point estimates of the overall ratio of fluticasone propionate and placebo groups were reported as 0.55 and 0.49 (page 30, volume 1.19) indicating no greater systemic exposure of terfenadine when co-administered with fluticasone propionate. However, based on the raw data reported (pages 70 and 74, volume 1.19) the overall ratios of fluticasone propionate and placebo groups for terfenadine mean C_{max} and $AUC_{0\text{-last}}$ values were recalculated by the reviewer and determined to be 1.40 and 2.09, respectively. The recalculated ratios indicate that co-administration of fluticasone propionate and terfenadine increased the parent terfenadine plasma levels. Although it is less of a concern since terfenadine has been withdrawn from the market, it is recommended that the above discrepancies (in ratios) be addressed.**

Study FLTA2001 was a 3-arm, parallel-group study with treatment arms of placebo, fluticasone propionate (FP) Diskhaler 500mcg BID, and FP Diskus 500mcg BID in patients with mild to moderate asthma. Serial blood samples for analyses of terfenadine concentrations were taken at Visits 2 (first dose), 3 (Week 1) and 6 (Week 4). Subjects

were not randomized to terfenadine, however, it was allowed as a concomitant medication. Terfenadine concentrations could have been present at all 3 visits.

In the analyses of the terfenadine pharmacokinetic data, a technique similar to a backward stepwise regression method was used, in which all factors (treatment, visit and subject(treatment)) were entered into the model and then removed if they were not significant. Visit was not significant and since the results of the two FP treatments were not different they were combined into a common treatment group. The final model was as follows:

Log(PK Parameter) = subject within treatment + treatment (placebo or FP)

The combining of the data across visits and the FP groups optimized the statistical power to detect a difference (or equivalence) between the placebo and FP groups.

The AUC and C_{max} variables were log transformed prior to analyses since it is well known that the variance of PK data increases with increasing dose. A log transformation of these data helped stabilize the variance, which is important in that one of the underlying assumptions of an ANOVA is of a constant variance. This log transformation is also in line with current FDA guidelines for the analysis of PK data as outlined in the following guidance documents:

Guidance – Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design. U.S. Food and Drug Administration, Division of Bioequivalence, Office of Generic Drugs, July 1998

Guidance for Industry (draft, not for implementation) - Food-Effect Bioavailability and Bioequivalence (issued by the FDA, October 1997).

The comparison for a drug interaction study is basically similar to that of a bioequivalence trial, i.e. to show that PK parameters are equivalent after dosing with either a drug alone or a combination of drugs. The absence of a drug interaction is accepted if the confidence interval of the ratio of the 'combination/drug alone' contains 1 and is within a set boundary. We were not able to show equivalence in these comparisons, however, we did show that the ratios for C_{max} and AUC_{last} of FP + terfenadine / placebo + terfenadine were considerably less than 1. This would indicate no increase in terfenadine concentrations when terfenadine and FP were administered together.

A concern was expressed at the teleconference on July 9 that some individuals in the FP groups had higher concentrations than individuals in the placebo group. It is true that one

and has been validated with a lower limit of quantitation of — . A summary of the validation is detailed below:

Validated range	— pg/mL
Precision (%CV)	Intra-assay <5.3%
	Inter-assay <3.3%
Precision at —	Intra-assay 5.3%
	Inter-assay 1.0%
Accuracy (%bias)	< ± 7.7%
Recovery	72%

3. **Study SFCB1002 conducted to investigate the effects of salmeterol and fluticasone propionate vs. fluticasone propionate alone could not be considered as a true drug-drug interaction study. Therefore, we recommend that drug-drug interaction study conducted in the future be a study with co-administration of separate salmeterol and fluticasone propionate preparations (not a combination preparation).**

We agree that Study SFCB1002 cannot be considered a true drug-drug interaction study because observed differences could be attributed to biopharmaceutical factors. The report was included in the Flovent Diskus NDA under supporting data that was not directly relevant to the FP Diskus NDA (volume 10, page 46). Subsequently, two Diskus studies were completed as part of the salmeterol/fluticasone propionate combination Diskus program. These studies compared fluticasone propionate given alone to fluticasone propionate and salmeterol given from separate inhalers. Study SFCB1005 (Report No. GM/1997/00200/00) was a single dose study in healthy subjects and Study SFCB3019 (Report No. GM1998/00018/00) was a multiple dose study in asthma patients. There was no evidence of a significant interaction in either study. The reports are presented and discussed in the Human Pharmacokinetics and Bioavailability section of NDA 21-077 for Advair Diskus (volumes 40 through 43).

individual in the FP group had a very high concentration of terfenadine, however, the individual with the second highest concentration was in the placebo group. These types of individual comparisons are not valid across groups in a parallel study.

Furthermore, the results of the terfenadine comparisons in FLTA2001 are of limited value. These were done post-hoc and on a small subset (n=17) of the patients. They are, however, consistent with the results of FLD-230, a much larger study (n=308) conducted with the Diskhaler formulation, in which there was no increase in terfenadine concentrations among patients on FP when compared to those patients on Placebo. The results of this analysis were also reported in the Flovent Diskus NDA 20-833 (volume 16, page 142).

2. **A radioimmunoassay (RIA) method (Report No. 2685-119) was utilized for plasma fluticasone propionate determination. The standard curves were prepared between — ng/mL with CV% ranged from 4.1% to 21.2% (at — g/mL) and % accuracy of 96.6% to 106.4% (at — ng/mL). Quality control data also showed that between — ng/mL, the CV ranged from 5.0% to 11.0% (at — g/mL) and % accuracy ranged from 96.5% to 99.1%. The limit of quantitation (LOQ) was reported to be — g/mL. Since CV% was reported to be 21.2% at — ng/mL, the LOQ should be set higher, e.g. — ng/mL for future fluticasone propionate determinations.**

A RIA method for the analysis of fluticasone propionate has been validated at — — with a limit of quantitation of — (Report 2685-100). This validated method was used to analyze samples from study FLTA-2001 and the performance of all assay runs confirmed using quality control samples (QC's). The back-fit standard data provided an indication of the ability of the data reduction program to fit a standard curve to the analytical standard data and while not specifically used for assay acceptance, are an indicator of inter-assay precision for the standard curve. However, since the QC values of all analytical runs met the acceptance criteria, it is considered that the data obtained from these runs are valid.

Future fluticasone propionate determinations from new studies will no longer be carried out by radioimmunoassay. All samples are now being analyzed by a fully validated and LC-MS-MS method. This method employs

The method is specific and sensitive

NDA 20-833: fluticasone propionate 50, 100, and 250 μg
(Flovent Diskus Dry Powder Inhaler)

ATTACHMENT 2

APPEARS THIS WAY
ON ORIGINAL

Sponsor's Revised Package Insert (PK section Only)
(June 08, 1999 version)

Pharmacokinetics: ***Absorption:*** The activity of FLOVENT DISKUS is due to the parent drug, fluticasone propionate. 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 adult volunteers averaged about 18%.

Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma (n = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone propionate inhalation powder using the DISKUS. The mean fluticasone propionate plasma concentration was 110 pg/mL.

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. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism: The total clearance of fluticasone propionate is high (average, 1093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 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.

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.

Gender: Full pharmacokinetic profiles were obtained from 9 female and 16 male patients given 500 mcg twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

Pediatrics: In a clinical study conducted in patients 4 to 11 years of age with mild to moderate asthma, fluticasone propionate concentrations were obtained in 61 patients at 20 and 40 minutes after dosing with 50 and 100 mcg twice daily of fluticasone propionate inhalation powder using the DISKUS. Plasma concentrations were low and ranged from undetectable (about 80% of the plasma samples) to 88 pg/mL. Mean fluticasone propionate plasma concentrations at the 2 dose levels were 5 and 8 pg/mL, respectively.

Special Populations: Formal pharmacokinetic studies using fluticasone propionate were not carried out in any special population.

Drug-Drug Interactions: 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, — no effect on urinary excretion of cortisol. Since fluticasone propionate is a substrate of cytochrome P450 3A4, caution should be exercised when cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole) are coadministered with fluticasone propionate as this could result in increased plasma concentrations of fluticasone propionate.

MAR 23 1999

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-833
Fluticasone propionate
inhalation powder 50, 100, and 250 µg

SUBMISSION DATE:
03/30/98

BRAND NAME: Flovent Diskus

SPONSOR: GlaxoWellcome

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: A New Product With A New Device Code: 3S

TITLE: "Review of Human Pharmacokinetic and Bioavailability (PK/Bio) Studies"

BACKGROUND:

Fluticasone propionate (FP) is a synthetic, trifluorinated corticosteroid developed by GlaxoWellcome. Fluticasone reportedly possesses potent anti-inflammatory activity with negligible oral bioavailability. In the US, two FP drug products are currently available for oral inhalation for the treatment of asthma in adults and children 12 years and older, i.e., Flovent Inhalation Aerosol (NDA 20-548) and a dry powder inhaler (DPI), Flovent Rotadisk (NDA 20-549). The human pharmacokinetics and bioavailability (PK/Bio) information provided in the above 2 NDAs was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II) and the NDAs were approved by the Agency on 03/27/96 and 11/07/97, respectively. NDA 20-770 was approved later for the use of Flovent Rotadisk in pediatric patients 4 to 11 years old. Flovent Rotadisk has 3 strengths (50, 100, or 250 µg of — FP blended with lactose to a total weight of 25 mg). It consists of 4 double-foil blisters and is used with a device, Diskhaler (also known as Flovent Diskhaler).

SYNOPSIS:

On 03/30/98, the sponsor submitted NDA 20-833 and is seeking approval for a second FP DPI, Flovent Diskus. It is for the same indication as Flovent Diskhaler in adults and children 4 years and older. Diskus is a specially designed plastic device containing a double-foil strip with blisters of 50, 100, or 250 µg of — FP — with lactose to a total weight of 12.5 mg only. Diskus inhaler could provide up to one month's supply of medication (60 blisters per device). The proposed dosing regimens are shown below which are the same as those for the currently approved Flovent Diskhaler with an additional recommendation for QD dosing. Please see the package insert (PI) for details.

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adults and Adolescents		
Bronchodilators alone*	100 µg BID	500 µg BID
Inhaled Corticosteroids*	100-250 µg BID	500 µg BID
Oral Corticosteroids	— BID	1000 µg BID
Children 4 to 11 years old		
Bronchodilators alone	50 µg BID	100 µg BID
Inhaled Corticosteroids	50 µg BID	100 µg BID

Submitted under NDA 20-833, there were 6 human PK/Bio study reports which have not been reviewed previously by OCPB. Three are pivotal and the other 3 are supportive. Two pivotal PK studies are parts of the clinical trials which tested Flovent Diskus, **1)** in adult patients employing 500 µg BID as compared to Flovent Diskhaler 500 µg BID and placebo (No. **FLTA2001**) and **2)** in pediatric patients employing 50 and 100 µg BID as compared to Flovent Diskhaler 50 and 100 µg BID and placebo (No. **FLTA2006**). The third pivotal one is a single-dose, drug-drug interaction study comparing Flovent Diskus 500 µg with salmeterol/FP (250/500) and placebo in 12 healthy adults (No. **SFCB1002**).

Three supportive PK studies are for **1)** comparison of Flovent MDI 500 µg BID with Flovent MDI 1000 µg QD given in the AM or PM and with placebo in 12 healthy male volunteers (No. FLTB1001) in order to test the effects of dosing regimen on the PK and PD of FP, **2)** the absolute bioavailability (F_{abs}) of multiple doses of FP dry powder (0.1, 1, and 10 mg) in hard gelatin capsules compared to an intravenous (IV) dose and placebo in 21 male healthy volunteers (No. 94-027), and **3)** the F_{abs} of FP 4 mg Nebules compared to an IV dose and placebo in 12 male healthy volunteers (No. 94-042). The above pivotal PK/Bio studies are reviewed and the supportive studies are briefly reviewed as well.

The sponsor provided basic PK information (including Diskus) on FP obtained previously and it is summarized below:

1. The IV doses of FP 250-1000 µg were tested in humans. The plasma levels of fluticasone post dosing could be described by a 3-exponential decay with a mean terminal half-life of 7.8 hr. The mean plasma clearance (CL) value was calculated to be 1,093 ml/min. Renal CL is negligible (unchanged drug represented <0.02% of an IV dose). The mean volume of distribution at steady state (Vd_{ss}) was estimated to be 4.2 L/kg with a mean plasma protein binding of around 91%.

2. The oral F_{abs} is <1%, primarily due to incomplete absorption and extensive first-pass elimination in the liver and gut. FP is rapidly metabolized almost entirely

by the cytochrome P-450, CYP3A4 isozyme to an inactive major metabolite, 17β-carboxylic acid derivative (GR36264X). Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites (including conjugates). The major route of disposition is the biliary secretion of metabolites and parent drug in the feces. The metabolite has about 2000 times less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro*. Therefore, the pharmacologic activity is primarily due to the parent drug.

3. The mean F_{abs} for Flovent MDI was calculated to be about 30% and those for Flovent Diskhaler and Diskus were 13.5% and 18.0%, respectively. The PK of FP after BID administration of MDI (500 to 2000 µg total daily) has been studied and the main site of absorption of FP into the systemic circulation is the lungs. Post BID dosing of MDI, the steady state is achieved within two weeks, with an accumulation ratio of approximately 1.5.

4. In a clinical trial using Flovent Diskhaler, full PK profiles were obtained from a small group of patients (13 females and 24 males) receiving FP 100 and 500 µg BID for analysis of possible gender differences. No overall differences in PK between gender were found.

5. The influence of erythromycin (oral 330 mg TID), a substrate and an inhibitor of CYP3A4, was studied for D-D interaction with 500 µg BID using Flovent MDI in 8 (M+F) healthy volunteers. The results show no increase in systemic exposure of FP. Furthermore, the effect of ketoconazole (200 mg/day) on the PK of single doses of FP 1000 µg via MDI was studied in 8 (M+F) healthy volunteers. The results showed that ketoconazole had significant effects on the PK of FP. The above findings are already included in the PI. *In vitro* D-D interaction was investigated between FP and terfenadine. The results indicated that at the terfenadine plasma level of 4.72 ng/ml and FP level of 0.3 ng/ml (achieved with clinical dosing), significant PK interaction is unlikely.

The PK and pharmacodynamic (PD) relationship of plasma FP (AUC_{0-24}) and plasma cortisol suppression (% decrease from baseline AUC_{0-24}) was also presented using previous single-dose PK data available (IV, oral, and inhaled) in healthy subjects. The above PK/PD relationship reportedly could be described by a sigmoid E_{max} model with an AUC_{0-24} value of 3.2 ng-hr/ml for FP to cause a 50% decrease in cortisol AUC_{0-24}. For cortisol production (release rate), the EC_{50} for plasma FP level was reported to be 0.134 ng/ml. Similar results were obtained from another study in asthmatic patients, the AUC of FP to produce a 50% decrease in cortisol production was estimated to be 3.0 ng-hr/ml which is similar to that obtained in healthy subjects. Finally, it was further concluded that the relationship between plasma FP levels and plasma cortisol suppression is direct, route independent and similar in both healthy subjects and asthmatic patients.

For this NDA, the sponsor employed the three strengths of the to-be-marketed formulation in the pivotal clinical and PK/Bio studies. For the device, there were 4 minor mechanical changes/refinements during the clinical development. *In vitro* tests were performed to assure consistency of dose delivery and the data were reviewed by the chemist. It is concluded that the changes may be less of a concern. Finally, OCPB reviewed previously the analytical methods used for determining plasma FP levels (RIA and LC-MS) and terfenadine levels (LC-MS) in the original NDA. This NDA used the same assay methods. However, the assay methodologies and their validation reports for plasma cortisol and urinary free cortisol levels were either incomplete or not clearly stated in this NDA as to whether or not the same assay method(s) was/were used as those reviewed previously in the original NDA.

Studies Submitted In The Current NDA:

Study No. **FLTA2001**

This is a randomized, placebo-controlled, parallel, double-dummy double-blind clinical trial in 213 adolescent and adult (M+F) patients with asthma (12-76 years old, mean: 32.6). The PK of FP 2x 250 µg BID via the Diskus and Diskhaler for 84 days were compared. All patients had plasma levels of FP measured at 0, 20, and 40 min from Days, 1, 7, 28, and 84 post morning dosing. Complete 12-hr plasma profiles of FP were obtained from 41 patients (a subset of 3 clinical sites) at pre-dose, 20 min, 40 min, and 1, 2, 3, 4, 5, 6, 8, 10, and 12 hr post dosing and for cortisol as well on Days 1, 7, and 28 for calculating PK and PD data/parameters. Patients co-administered with terfenadine in this clinical trial (7 in placebo group, 4 in Diskus group, and 6 in Diskhaler group) were also analyzed for D-D interaction.

An RIA method (Report No. 2685-119) was used for plasma FP determination. The standard curves were prepared between [redacted] ng/ml with CV% ranged from 4.1% to 21.2% (at [redacted] ng/ml) and % accuracy of 96.6% to 106.4% (at [redacted] ng/ml). Quality control data also showed that between [redacted] ng/ml, the CV% ranged from 5.0% to 11.0% (at [redacted] ng/ml) and % accuracy ranged from 96.5% to 99.1%. The limit of quantitation (LOQ) was reported to be [redacted] ng/ml. Since CV% was reported to be 21.2% at [redacted] ng/ml, the LOQ should be set higher, e.g. [redacted] ng/ml.

For the analysis of plasma cortisol levels at [redacted], it was reported in the Internal Project No. 3888 that the [redacted] and reagents were used. However, no such report was found in the NDA. For terfenadine, the LC-MS (Report No. 53041/BXS) method that was used and reviewed previously was employed for plasma terfenadine determination. The summary information on the assay performance, however, was not provided.

Results and Conclusion:

No statistically significant differences in PK between Diskus and Diskhaler were found as shown in Table 1:

Table 1. Mean PK parameters of FP in Adult Patients

PK Parameters[a]	DISKUS (6M+5F)	DISKHALER (10M+4F)
C_{max} Range (ng/ml)		
C_{max} Median (ng/ml)	0.104	0.130
Mean (± SD)[b] C_{max} (ng/ml)	0.110 ± 0.060	0.130 ± 0.051
Geom. L.S. Mean[c] C_{max} (ng/ml)	0.092	0.120
(95% CI)	(0.064, 0.133)	(0.086, 0.166)
Geom. L.S. Mean[c] T_{max} (hr)	0.50	0.67
(95% CI)	(0.33, 2.00)	(0.33, 10.00)
Geom. L.S. Mean[c] $AUC_{0\text{-last}}$ (ng-hr/ml)	0.474	0.412
(95% CI)	(0.298, 0.756)	(0.272, 0.622)

[a]. Data obtained from Day 28 (Visit 6).
[b]. Arithmetic mean ± standard deviation (SD).
[c]. Geometric least square mean with 95% confidence interval in parenthesis.

Steady state was achieved by Day 7 and the accumulation ratio at Day 28 was calculated to be about 1.7 which is close to that reported previously (1.5). No overall differences in the mean (± SD) fluticasone plasma levels obtained from 16 male patients (0.111 ± 0.051 ng/ml) and 9 female patients (0.137 ± 0.065 ng/ml) were found. For plasma cortisol levels, the mean $AUC_{0\text{-}12}$ values were 99.2, 107.4 and 128.3 μg-hr/dl for placebo (n=13), Diskus (n=13), and Diskhaler (n=15), respectively (p=0.057). Due to measurement without pre-treatment baseline, the % changes from baseline could not be calculated for pairwise comparison.

Terfenadine (oral 60 mg QD or BID) was also administered to some patients in this PK subset. Four patients (out of 7) enrolled in the placebo group, 2 (out of 4) in the Diskus group, and all 6 in Diskhaler group had measurable terfenadine plasma levels. For the analysis of D-D interaction between FP and terfenadine, the populations of the above two device groups (2 plus 6) were pooled, since there were no differences in FP PK between Diskus and Diskhaler.

For terfenadine arithmetic mean C_{max} and $AUC_{0\text{-last}}$, the overall ratios of FP group/placebo group were calculated by this reviewer. The ratios were 1.40 and 2.09, respectively indicating much greater systemic exposure of terfenadine when co-

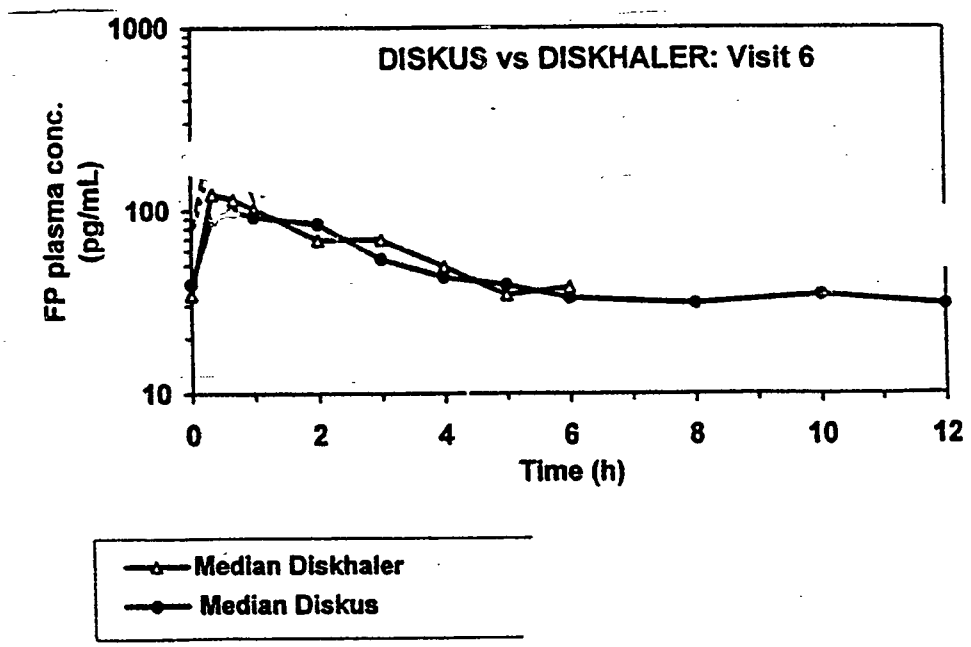
administered with FP. For FP arithmetic mean C_{max} and $AUC_{0\text{-last}}$, the overall ratios for with terfenadine group (n=9) vs. without terfenadine group (n=16) were also calculated and found to be 0.79 and 0.93, respectively.

The above calculations were different from those reported by the sponsor, i.e., for terfenadine mean C_{max} and $AUC_{0\text{-last}}$, the point estimates of the overall ratio of FP group/placebo group were reported to be 0.55 and 0.49 indicating no greater systemic exposure of terfenadine when co-administered with FP. The above discrepancies most likely were due to a switch of both the reported mean C_{max} and $AUC_{0\text{-last}}$ between the placebo and treatment groups (page 30 vs. pages 70 and 75, volume 1.19). However, similar point estimates were reported for FP mean C_{max} and $AUC_{0\text{-last}}$ with terfenadine group vs. without terfenadine group, 0.83 and 0.84 ($p>0.05$).

The median 0-12 hr plasma profiles of fluticasone after Diskus and Diskhaler at Visit 6 (Day 28) were shown below in Figure 1:

Figure 1:

Comparative median plasma fluticasone propionate concentrations over 12 hours after dosing with the Diskhaler versus the Diskus at Visit 6 (day 28)



Reviewer's Comments:

For terfenadine mean C_{max} and $AUC_{0\text{-last}}$ values, the overall ratios of FP group/placebo group recalculated by this reviewer were 1.40 and 2.09, respectively. The recalculated ratios indicate that co-administration of FP and terfenadine led to increase in parent terfenadine plasma levels. The above ratios were opposite to the point estimates of the

overall ratios of FP group/placebo group reported by the sponsor, 0.55 and 0.49. The above discrepancies most likely were due to a switch of both the reported mean C_{max} and $AUC_{0\text{-last}}$ values between the placebo and treatment groups (page 30 vs. pages 70 and 75, volume 1.19) by the sponsor. Although it is less of a co. .ern since terfenadine has been withdrawn from the market, the above discrepancies (in ratios) need to be addressed by the sponsor.

Study No. **FLTA2006**

This is a randomized, placebo-controlled, parallel, double-dummy double-blind clinical trial in pediatric (M+F) patients with asthma (4-11 years old, mean: 8.4). The PK of FP 50 and 100 µg BID via the Diskus and Diskhaler for 84 days were compared. Plasma FP levels were measured at 20 and 40 min in a subgroup of patients on Day 84 (Visit 10 at 12th week) post morning dosing. Urine was also collected for a 24-hr period twice during the study, at baseline and prior to or on the Visit 10.

An RIA method (Report No. 2685-138) was used for plasma FP determination. The standard curves were prepared between — ng/ml with CV% ranged from 2.9% to 15.2% (at — ng/ml) and % accuracy ranged from 94.9% to 106%. Quality control data also showed that between — ng/ml, the CV% ranged from 9.8% to 17.0% (at — ng/ml) and % accuracy ranged from 89.9% to 96.3% (at — ng/ml). For the analysis of plasma and urinary cortisol levels at ——— no assay method and validation report were provided in the human PK/Bio section.

The mean plasma C_{max} values of FP obtained from the current clinical trial No. FLTA 2006 in 4-11 year-old asthmatic patients are summarized below:

Table 2. Mean PK parameters of FP in Pediatric Patients

Flovent Device	Diskus		Diskhaler	
Dosing Regimen	50 µg BID	100 µg BID	50 µg BID	100 µg BID
No. of Subjects[a]	31 (18M+13F)	30 (24M+6F)	37 (20M+17F)	26 (17M+9F)
C_{max} Range (ng/ml)				
Median C_{max} (ng/ml)	BQL	BQL	BQL	0.034
Arithmetic Mean[b] C_{max} (ng/ml)	0.005 (0.017)	0.008[c] (0.016)	0.013 (0.022)	0.030[c] (0.029)
% of Samples Being BQL[d]	87%	80%	70%	42%
Urinary Cortisol[e,f] (mg/24 hr)	8.7 (n=61)	8.4 (n=57)	8.4 (n=63)	7.7 (n=47)
% Change[f,g] from baseline	+9.6% (n=60)	+0.9% (n=55)	-11.9% (n=57)	-22.1% (n=45)

[a]. No. of subjects who had evaluable PK data.

[b]. Mean ± SD.
[c]. Statistically significant (p=0.001)
[d]. Below the quantitation limit (BQL: 0.025 ng/ml)
[e]. Geometric LS mean (placebo: 7.8 mg/24 hr; n=35)
[f]. Obtained from all available patients after treatment for 84 days.
[g]. Mean % change in urinary cortisol excretion (placebo: -12.8%; n=33).

Pediatric patients in the Diskus 100 µg BID group had a mean C_{max} value significantly lower than that in the Diskhaler 100 µg BID group (p=0.001), but no significant difference was noted in the two lower-dose groups (p=0.069). The dose proportionality in the mean C_{max} values between the 50 and 100 µg BID treatments could not be demonstrated for Diskus (p=0.389), but it was for Diskhaler (p=0.015). No significant differences were also found in % change of 24-hr urinary cortisol excretion when compared to placebo group (p>0.05).

Reviewer's Comments:

The above comparisons with statistical analyses done by the sponsor (either p>0.05 or p<0.05) are complicated due to the fact that the majority of the plasma samples were BQL. Nevertheless, the pediatric patients in the Diskus treatment groups seemingly had consistently greater % of FP plasma C_{max} levels being BQL.

Study No. **SFCB1002**

This is a randomized, placebo-controlled, double-blind, single-dose, 3x3 cross-over study in 12 healthy male subjects. A washout period of >6 days was used. The PK of FP with/without salmeterol plus placebo (using Diskus device) were compared. Five inhalations of FP 100 µg (total 500 µg, Batch No. not provided), 5 inhalations of salmeterol/FP (50/100 µg), and 5 inhalations of matched placebo were employed. Complete plasma FP and cortisol levels and urinary cortisol levels were obtained.

Parameter	Treatment	Geom. LS Mean	Point Estimate[a]	p-value
C_{max} (ng/ml)	Sal/FP FP	146 105	1.39	**<0.001***
$AUC_{0\text{-last}}$ (ng-hr/ml)	Sal/FP FP	889 1146	0.78	0.12
T_{max} (hr)	Sal/FP FP	0.21[b] 2.00[b]	1.50	**0.001***

[a]. Ratio of Sal/FP vs. FP alone.
[b]. Median values.

It appears that combination Sal/FP had a more rapid absorption which resulted in higher mean C_{max} and shorter mean T_{max} values. For PD, the % changes (post- vs. pre-treatment) in the 24-hr and 12-hr urinary cortisol excretion for the placebo group were -2.1% and 6.3%, respectively. By the same token, the % changes for Sal/FP and FP groups were -4.4% and –6.7%, respectively (not significant; p=0.164), however, it was significant for comparison in 12-hr urinary cortisol excretion, 2.0% vs. –2.6%, respectively (p=0.041). It is noted that the median T_{max} obtained from the treatment group of FP alone was seemingly much longer than that in study No. FLTA 2001, 0.50 hr. The reasons for the above differences are not known.

Reviewer's Comments:

The above findings for the effects of plasma FP levels on 12-hr urinary cortisol excretion are seemingly consistent with the fact that the majority of adverse events were reported in Sal/FP group.

Study No. **FLTB1001**

This is a randomized, placebo-controlled, parallel, double-blind, 4x4 crossover study in 12 healthy male subjects (22-44 years old; mean 29) and 11 subjects completed the study. A washout period of >7 days was used. Single doses of 1000 µg (4 x 250 µg/per actuation) were given by MDI (CFC 11/12 with 1% lecithin) to test the effects of different dosing regimen on the HPA axis, i.e., placebo, 1000 µg FP QD in the morning, 1000 µg FP QD in the evening, and 500 µg FP BID.

Twenty-four hr plasma FP levels (pre-dose, 0.75 and 4 hr plus 12, 12.25, 12.5, 12.75, 13, 14, 16, 18, 20, and 22 hr) were obtained. Twenty-four plasma cortisol levels (0, 1, 2, 4, 6, 8, 10, 13, 14, 16, 18, 20, and 22 hr) and 24-hr urinary cortisol excretion on Days –1 and 1 and 12-hr data (0. 1, 2, 4, 6, 8, 10, and 12 hr) on Day 2 were obtained.

Plasma FP levels were determined by an LC-MS method (Report No. WBP/95/051). The standard curves were prepared between — ng/ml with CV% ranged from 3.9% to 11.7% (at — ng/ml) and % accuracy ranged from 95.8% to 108.8% (at — ng/ml). Quality control data also showed that between — ng/ml, the CV% ranged from 7.0% to 14.6% (at — ng/ml) and % accuracy ranged from 98.2% to 110.9% (at — ng/ml).

For the analysis of plasma and urinary cortisol levels, an RIA procedure using a ^{125}I tracer was employed and the validation was performed at the ——— (Report No. RD 347/21072). The standard curves were prepared between — µg/dl with CV% ranged from 2.5% to 5.3% and % accuracy ranged form 87% to 112%. Quality control data also showed that between — µg/dl,

the CV% ranged from 7.7% to 15.7% (at — µg/dl) and % accuracy ranged from 86.8% to 97.3%.

The above data are consistent with those obtained in the validation report. Inter- and intra-assay precision were all <10%. The LOQ is reported to be — , and the sensitivity is — . Crossreactivity study results showed that prednisolone gave the highest value of 76%, 11-deoxycortisol the second highest, 11.4%, and prednisone the third, 2.3%. The rest of the compounds tested showed <1% crossreactivity.

Due to limited samples (0.75 and 4 hr post morning dose), the PK of AM dosing could not be formally assessed nor the influence of AM vs. PM dosing on FP PK. Only the mean $C_{0.75\text{-hr}}$ and $C_{4.0\text{-hr}}$ were compared. For AM dosing, they were 0.240 and 0.206 ng/ml which were slightly higher than PM dosing, 0.213 and 0.109 ng/ml. For BID dosing, they were 0.147 and 0.126 ng/ml (AM) and 0.163 and 0.089 ng/ml (PM), respectively.

The sponsor concluded that when compared to pre-treatment, the 0-24 hr urinary cortisol excretion was shown to decrease by 56%*, 53%, 45% and 23% (geometric mean of the change) following 1000 µg QD given AM or PM, 500 µg BID, and placebo, respectively. The significant difference ($p<0.05$) compared to placebo group is expressed in bold with an asterisk shown in the **Column 2** of Table 3 below. By the same token, the 9:00 AM plasma cortisol level decreased by 24%, 50%* 43%* and 6% (**Column 3**) and the 24-hr plasma cortisol AUC values decreased by 54%*, 44%*, 51%* and 11% (**Column 4**).

Table 4. Comparisons Among Treatments

Treatment Contrast	p-value 0-24 hr Urinary Cortisol Excretion	Plasma AM Cortisol Level	Plasma Cortisol $AUC_{0\text{-}24}$
FP AM vs. PLB	**0.032***	0.392	**<0.001***
FP PM vs. PLB	0.064	**0.002***	**<0.001***
FP BID vs. PLB	0.225	**0.002***	**<0.001***
FP AM vs. FP PM	0.790	**0.019***	0.195
FP AM vs. FP BID	0.289	**0.031***	0.570
FP PM vs. FP BID	0.432	0.686	0.442

*. Statistically significant ($p<0.05$).

Furthermore, for 9:00 AM plasma cortisol level decrease, **1)** the FP AM vs. FP PM dosing ($p=0.019$) and **2)** FP AM vs. FP BID dosing ($p=0.031$) also showed significant differences. Nevertheless, all three dosing regimens had significant effects on the plasma cortisol $AUC_{0\text{-}24}$ ($p<0.001$).

Reviewer's Comments:

The above PK study employed the currently marketed Flovent MDI (with — lecithin). However, there is no PK study to link the currently marketed Flovent MDI (with — lecithin) and the to-be-marketed Flovent Diskus. Thus, the clinical relevance of these study results to Diskus is not known.

Study Nos. **C94-027 and C94-042**

In Study No. C94-027, the F_{abs} of multiple doses of FP dry powder (0.1, 1, and 10 mg) in hard gelatin capsules compared to an intravenous (IV) dose and placebo was investigated in 21 male healthy volunteers. The results showed that the F_{abs} value could only be obtained form the highest FP oral dose (10 mg BID), 1.28% (by RIA method) and 0.91% (by LS-MS method). A statistically significant decrease in urinary cortisol excretion for the oral 10 mg BID dosing was seen.

In Study No. C94-042, the F_{abs} of FP 4 mg Nebules compared to an IV dose and placebo was also investigated in 12 male healthy volunteers (No. 94-042). The results showed that the F_{abs} value for the 4000 µg Nebules was calculated to be 8% and the decreases in 24-hr urinary cortisol excretion were -47% and -41% by nebulization and IV, respectively.

Specific Comments to the Reviewing Medical Officer:

1. Study No. **FLTA2001** showed no significant differences in systemic exposure (FP PK) [and plasma cortisol AUC_{0-12} data (FP PD) as well] for 500 µg BID given via Flovent Diskhaler and Diskus to adults patients. No additional PK study was conducted to support the highest recommended dosing of 1000 µg BID for adult patients taking oral corticosteroids as previous therapy.

2. For pediatric patients who participated in the PK study No. **FLTA 2006**, > 80% of plasma samples obtained from both 50 and 100 µg BID dose groups were below quantitation limit (— ng/ml). Therefore, the above pediatric PK study provided very limited information on the systemic exposure of FP using Flovent Diskus.

   Pediatric patients in the Diskus 100 µg BID group had a mean C_{max} value significantly lower than that in the Diskhaler 100 µg BID group, but no significant difference was noted in the two lower-dose groups. Although the % changes in 24-hr urinary cortisol excretion were not significantly different from placebo group for both Diskus and Diskhaler groups, the lower changes found in Diskus groups as compared to Diskhaler groups were seemingly consistent with

the PK findings, a trend towards less cortisol suppression in the Diskus group. It is not known as to whether or not the greater % of plasma FP levels being BQL (and thus less or lack of suppression in 24-hr urinary cortisol levels) in Diskus group is due to the stability of the Diskus drug product or a reflection of performance of the Diskus device.

3. For QD vs. BID dosing regimens, a PK study conducted using MDI (No. **FLTB1001**) could not provide **1)** good comparison for AM vs. PM or QD vs. BID dosing using MDI due to only 2 blood samples collected in AM dosing and **2)** good assessment of QD dosing regimen for Flovent Diskus due to missing PK link between Flovent MDI and Diskus.

RECOMMENDATION:

GlaxoWellcome's NDA 20-833 (Flovent Diskus 50, 100, and 250 µg fluticasone propionate) that was submitted on 03/30/98 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB is of the opinion that the human PK/Bio section of this NDA is acceptable from an OCPB's perspective. The following Comment Nos. 4, 5, and 6 and Labeling Comment, as appropriate, need to be conveyed to the sponsor.

GENERAL COMMENTS: (Nos. 4, 5, and 6 need to be sent to the sponsor)

1. The sponsor is seeking approval for three strengths of Flovent Diskus, i.e., 50, 100, and 250 µg. Although the above three strengths had been tested in the clinical trials, ideally,

2. Two separate assay methods (RIA and LC-MS) were used for determining plasma FP levels in several PK studies. The two methods were compared in one supportive study No. C94-027, and the results showed comparable PK data.

3. The assay methodologies and their validation reports for plasma cortisol and urinary free cortisol levels were either incomplete or not clearly stated in the NDA as to whether the same assay method(s) was/were used as those used in the previous NDA. Therefore, it is recommended that the complete assay methodology information and the validation report be provided in the future NDA submissions.

4. For terfenadine mean C_{max} and $AUC_{0\text{-last}}$ values (in a drug–drug interaction analysis in Study No. **FLTA2001**), the point estimates of the overall ratio of FP group/placebo group were reported to be 0.55 and 0.49 (page 30, volume 1.19)

indicating no greater systemic exposure of terfenadine when co-administered with FP. However, based on the raw data reported on pages 70 and 74, volume 1.19, the overall ratios of FP group/placebo group for terfenadine mean C_{max} and $AUC_{0\text{-last}}$ values recalculated by this reviewer were 1.40 and 2.09, respectively. The recalculated ratios indicate that co-administration of FP and terfenadine led to increase in parent terfenadine plasma levels. Although it is less of a concern since terfenadine has been withdrawn from the market, it is recommended that the above discrepancies (in ratios) be addressed.

5. An RIA method (Report No. 2685-119) was used for plasma fluticasone propionate (FP) determination. The standard curves were prepared between — , ng/ml with CV% ranged from 4.1% to 21.2% (at — ng/ml) and % accuracy of 96.6% to 106.4% (at — ng/ml). Quality control data also showed that between — ng/ml, the CV% ranged from 5.0% to 11.0% (at — ng/ml) and % accuracy ranged from 96.5% to 99.1%. The limit of quantitation (LOQ) was reported to be — ng/ml. Since CV% was reported to be 21.2% at — ng/ml, the LOQ should be set higher, e.g., — ng/ml for future FP determination.

6. The PK study No. SFCB1002 was conducted to investigate the effects of Salmeterol/FP vs. FP alone. The above study could not be considered as a true drug-drug interaction study. Therefore, it is recommended that if a drug-drug interaction study is to be conducted in the future, a well designed PK study with co-administration of separate salmeterol and FP preparations (not a combination preparation) be conducted.

LABELING COMMENT: (Needs to be sent to the sponsor)

The following labeling comment is from the Office of Clinical Pharmacology and Biopharmaceutics. It is recommended that the following labeling be incorporated in the package insert.

1

1 Draft Labeling Page(s) Withheld

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CPB Briefing on 03/19/99: Drs. M.L. Chen, R. S. Uppoor, Y.M. Choi, S. Kim, and S. Al-fayoumi

03/23/99

/S/

03/14/99

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

RD initialed by Ramana. Uppoor, Ph.D. RU 03/15/99

FT initialed by Ramana. Uppoor, Ph.D. /S/ 03/23/99

cc: NDA 20-833, HFD-570 (Purucker, Cobbs), HFD-870 (M.L. Chen, R. Uppoor, T.M. Chen), CDR (B. Murphy).

NDA 20-833: fluticasone propionate 50, 100, and 250 μg
(Flovent Diskus Dry Powder Inhaler)

ATTACHMENT 1

Sponsor's Proposed Package Insert (3/98 Version)

17 Draft Labeling Page(s) Withheld

ATTACHMENT 2

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Individual Study Reports

The hardcopies of the above individual study reports have been retained in HFD-570 document room and can be obtained upon request

Study No. FLTA2001

[redacted]

TITLE

A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PARALLEL-GROUP, COMPARATIVE TRIAL OF INHALED FLUTICASONE PROPIONATE ROTADISKS® VIA DISKHALER® 500MCG BID, MULTI-DOSE POWDER 500MCG BID, AND PLACEBO IN ADOLESCENT AND ADULT PATIENTS WITH MILD TO MODERATE ASTHMA
Pharmacokinetic Analysis of Fluticasone Propionate Plasma Concentrations and Pharmacodynamic Analysis of Cortisol Plasma Concentrations

OBJECTIVES

The objectives of the clinical study were to compare the efficacy and safety of fluticasone propionate (FP) 500mcg BID via Multi-Dose Powder Inhaler (Diskus), FP 500mcg BID Rotadisks via Diskhaler (Diskhaler) and placebo BID in adolescent and adult patients with mild to moderate asthma.

The primary objective of the pharmacokinetic analysis was:
- to compare the pharmacokinetics of FP following administration from the Diskhaler and the Diskus.

The secondary objectives of the pharmacokinetic analysis were:
- to assess the gender effect on the pharmacokinetics of FP
- to assess the influence of concomitant administration of terfenadine (T) on the pharmacokinetics of FP
- to compare the pharmacodynamic effect on plasma cortisol following administration of FP from placebo, the Diskhaler and the Diskus
- to evaluate the accumulation of FP upon repeat dosing in patients.

DESIGN

The study was a randomized, double-blind, double-dummy, parallel-group, placebo-controlled, multicenter trial in patients with a diagnosis of asthma. Patients were treated on an outpatient basis and attended the clinic at the initial screening visit (14 ± 3 days before Treatment Day 0) and at double-blind Treatment Weeks 0, 1, 2, 3, 4, 6, 8, 10, and 12. The study population was stratified according to whether or not patients were receiving inhaled corticosteroids before study entry.

SUBJECTS

A full 12h sampling profile was performed in the pharmacokinetic (PK) population, which consisted of 15 patients in the Diskhaler group (6 female, 9 male), 13 patients in the Diskus group (6 female, 7 male) and 13 patients in the placebo group (4 female, 9 male). A limited 0, 20 and 40min sampling was performed in the Intent-To-Treat (ITT) population, which consisted of 78 patients in the Diskhaler group (35 female, 43 male), 64 patients in the Diskus group (28 female, 36 male) and 70 patients in the placebo group (32 female, 38 male).

TREATMENTS

The study treatments were: Placebo BID, Diskhaler 500mcg BID and Diskus 500mcg BID. The double-blind treatment started 14 ± 3 days after the initial screening visit and lasted 12 weeks. The patient were instructed to inhale at approximately 8 A.M. and 8 P.M.

MEASUREMENTS

Pharmacokinetics and Pharmacodynamics

In the PK population, blood samples were drawn for the analysis of FP, cortisol and T on Visit 2 (1^{st} dose), Visit 3 (day 7 ± 2 days), and Visit 6 (day 28 ± 2 days) over 12 hours after dosing. Blood was drawn prior to dosing (0h) then 20min (0.333h), 40min (0.667h), 1h, 2h, 3h, 4h, 5h, 6h, 8h, 10h and 12h after dosing. In the ITT population, blood samples were drawn for analysis of FP prior to dosing (0min) and 20 and 40min after dosing on Visit 2 (1^{st} dose) and Visit 6 (day 28 ± 2 days), and prior to dosing (0min) on Visit 10 (day 84 ± 3 days).

RESULTS

Pharmacokinetics

Influence of gender. The gender effect did not approach statistical significance in any parameter at any time point post treatment. As there were no gender effect, data from both genders were combined in the subsequent analyses.

Parameter	Visit	p-value
C_{max} [1]	V6	0.183
C_{max} [2]	V6	0.298
AUC_{last} [1]	V6	0.270
AUC_{tau} [1]	V6	0.278

[1] Full 12 hour plasma concentration profile
[2] Limited 0, 20, and 40 minute sampling

Comparison of the two devices

Parameter	Visit [1]	DISKHALER Geom. LS Mean	DISKHALER 95% CI [2]	DISKUS Geom. LS Mean	DISKUS 95% CI [2]	Ratio DISKUS/ DISKHALER Point Estimate	Ratio DISKUS/ DISKHALER 90% CI [3]
C_{max} [4] (pg/mL)	V2	64.8	44.8, 93.6	59.3	42.2, 83.2	0.92	0.60, 1.39
	V3	127.7	93.2, 175.1	114.7	79.4, 165.8	0.90	0.60, 1.35
	V6	119.5	86.2, 165.6	92.1	63.7, 133.2	0.77	0.51, 1.16
C_{max} [5] (pg/mL)	V2	60.9	52.7, 70.4	61.3	52.4, 71.8	1.01	0.84, 1.21
	V6	106.6	92.2, 123.2	97.1	82.4, 114.5	0.91	0.76, 1.10
AUC_{last} [4] (pg.h/mL)	V2	162.4	101.9, 258.7	139.7	91.0, 214.4	0.86	0.51, 1.46
	V3	431.7	289.8, 643.2	506.4	317.9, 806.7	1.17	0.70, 1.96
	V6	411.6	272.4, 621.9	474.3	297.8, 755.6	1.15	0.69, 1.94
AUC_{tau} [4] (pg.h/mL)	V2	263.8	164.6, 422.9	374.9	221.2, 635.3	1.42	0.79, 2.56
	V3	664.2	467.3, 944.1	608.9	419.3, 884.2	0.92	0.60, 1.40
	V6	674.4	452.6, 1005	574.0	395.3, 833.4	0.85	0.54, 1.34

Parameter	Visit [1]	DISKHALER Median	DISKHALER Range	DISKUS Median	DISKUS Range	Difference DISKUS - DISKHALER Point Estimate	Difference DISKUS - DISKHALER 90% CI
t_{max} [4] (h)	V2	1.00	[	0.67	[ ]	-0.08	-0.33, 0.00
	V3	0.67		0.67		0.00	0.00, 0.17
	V6	0.67		0.50		0.00	-0.17, 0.00
C_{tau} [4] (pg/mL)	V2	BQL		BQL		0.00	0.00, 0.00
	V3	BQL		44.4		0.00	0.00, 20.30
	V6	BQL		30.4		2.55	0.00, 16.35
C_0 [5] (pg/mL)	V2	BQL		BQL		0.00	0.00, 0.00
	V6	32.4	[ ]	40.0	[ ]	0.00	-7.45, 0.00
	V10	38.3		39.8		0.00	-2.40, 3.30

[1] Visits 2, 3, 6, and 10 correspond to 1st dose, day 7 (±2 days), day 28 (±2 days), and day 84 (±3 days), respectively
[2] CI (confidence interval) calculated using unpooled estimates of error
[3] CI (confidence interval) calculated using pooled estimates of error
[4] Full 12 hour plasma concentration profile
[5] Limited 0, 20, and 40 minute sampling
BQL Below the Limit of Quantification. For C_{max}, AUC_{last}, and AUC_{tau}, the summary statistics and statistical analysis used estimated BQL values based on half of the LLOQ. For C_{tau} and C_0, BQL values were set = 0.

The Diskus presented a similar systemic exposure compared to the Diskhaler. AUC_{last} values were slightly higher for the Diskus compared with the Diskhaler, however this difference was not statistically significant.

Influence of concomitant administration of terfenadine. As there was no device influence and no device-by-visit interaction the data from the three visits and two devices were combined in the analysis of T influence. There was no statistically significant influence of T on FP pharmacokinetic parameters. This was confirmed by a ratio T/ No T close to one for C_{max}, AUC_{last} and AUC_{tau}, and by a difference T - No T of zero for t_{max}, C_{tau} and C_0.

		Ratio T / No T	
Parameter		Point Estimate	90% CI [1]
C_{max} [2]	(pg/mL)	0.83	0.63, 1.10
C_{max} [3]	(pg/mL)	1.04	0.94, 1.16
AUC_{last} [2]	(pg.h/mL)	0.84	0.57, 1.23
AUC_{tau} [2]	(pg.h/mL)	1.07	0.74, 1.54

		Difference T - No T	
Parameter		Point Estimate	90% CI
t_{max} [2]	(h)	0.00	0.00, 0.17
C_{tau} [2]	(pg/mL)	0.00	0.00, 0.00
C_0 [3]	(pg/mL)	0.00	0.00, 0.00

[1] CI (confidence interval) was calculated using pooled estimates of error
[2] Full 12h plasma concentration profile
[3] Limited 0, 20, and 40min sampling
For C_{max}, AUC_{last}, and AUC_{tau}, the statistical analysis used estimated BQL values based on half of the LLOQ.
For C_{tau} and C_0, BQL values were set = 0.

Assessment of steady-state. As there was no device influence the data from the two devices were combined. Steady-state was achieved by Visit 3 (day 7).

Parameter	Slope from Visit 3 to Visit 6 °		Ratio Visit 6 / Visit 3	
	Point Estimate	90% CI	Point Estimate	90% CI [1]
C_{max} [2]	0.15	-0.04, 0.35	0.88	0.66, 1.16
AUC_{last} [2]	0.07	-0.21, 0.34	0.95	0.66, 1.36
AUC_{tau} [2]	0.06	-0.06, 0.19	0.97	0.71, 1.32

Parameter		Difference Visit 6 - Visit 3	
		Point Estimate	90% CI
t_{max} [2]	(h)	0.00	-0.17, 0.00
C_{tau} [2]	(pg/mL)	0.00	-6.00, 0.00

° Unit for slope = change / day

[1] CI (confidence interval) calculated using pooled estimates of error

[2] Full 12h plasma concentration profile

For C_{max}, AUC_{last}, and AUC_{tau}, the statistical analysis used estimated BQL values based on half of the LLOQ. For C_{tau}, BQL values were set = 0.

Accumulation ratio. As there was no device influence, the data from the two devices were combined. Accumulation was approximately 1.7 fold, considering C_{max} (the accumulation ratio calculated using AUC_{tau} could not be used as a reliable parameter as AUC_{tau} could be determined for only a very limited number of patients on Visit 2).

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Parameter	Ratio Visit 6 / Visit 2	
	Point Estimate	90% CI [3]
C_{max} [1]	1.70	1.27, 2.27
C_{max} [2]	1.67	1.47, 1.90
AUC_{tau} [1]	2.01	1.39, 2.90

[1] Full 12h plasma concentration profile
[2] Limited 0, 20, and 40min sampling
[3] CI (confidence interval) calculated using pooled estimates of error
For C_{max} and AUC_{tau}, the statistical analysis used estimated BQL values based on half of the LLOQ

Pharmacodynamics

There was no statistically significant differences in $AUC_{tau,cort}$ among the three treatments. At Visit 6, the geometric mean of plasma cortisol $AUC_{tau,cort}$ was 99.2 mcg.h/dL (95% CI: 76.0 to 129.6), 128.3 mcg.h/dL (95% CI: 100.5 to 163.7) and 107.4 mcg.h/dL (95% CI: 83.2 to 138.5) for placebo, Diskhaler and Diskus respectively. The individual $AUC_{tau,cort}$ values observed after treatment with the Diskhaler and the Diskus were within the inter-individual variability observed after placebo treatment. The gender effect did not approach statistical significance in $AUC_{tau,cort}$:

Parameter	Visit	p-value
$AUC_{tau,cort}$ [1]	V6	0.197

[1] Full 12 hour plasma concentration profile

CONCLUSIONS

There was no statistically significant difference in systemic exposure to FP following a 500mcg BID inhaled administration via the Diskhaler or the Diskus. The pharmacodynamic results were in very close agreement: the 12h plasma cortisol concentrations were not different between placebo, the Diskhaler and the Diskus. There was no gender effect on the pharmacokinetics and the pharmacodynamics of FP. Concomitant administration of oral T had no influence on the pharmacokinetics of FP. Steady-state was achieved on day 7 of treatment. The mean accumulation of FP upon repeat dosing was estimated to be approximately 1.7 fold.

TABLE 2

Demographic data and terfenadine regimen of the populations used for the pharmacokinetic analysis: (a) Patients with a 12h fluticasone propionate plasma concentration profile.

	Placebo	Diskhaler FP 500mcg BID	Diskus FP 500mcg BID
Number of Subjects	13	15	13
Gender			
Female	4 (31%)	6 (40%)	6 (46%)
Male	9 (69%)	9 (60%)	7 (54%)
Ethnic Origin			
Black	1 (8%)	0	0
Caucasian	11 (85%)	14 (93%)	10 (77%)
Other	1 (8%)	1 (7%)	3 (23%)
Age Group			
11-17 years	5 (38%)	2 (13%)	2 (15%)
18-64 years	8 (62%)	13 (87%)	11 (85%)
65 years or over	0	0	0
Age, years			
n	13	15	13
Median	23.0	29.0	28.0
Minimum	13	13	15
Maximum	61	46	58
Mean	29.2	28.3	30.8
sd	16.4	9.4	12.7
CV	56.3	33.0	41.1
Height, inches			
n	13	15	13
Median	66.0	69.0	67.0
Minimum	60	62	58
Maximum	73	74	75
Mean	66.2	68.0	67.2
sd	3.7	3.8	4.9
CV	5.5	5.5	7.3
Weight, pounds			
n	13	15	13
Median	157.0	176.0	190.0
Minimum	110	102	108
Maximum	250	250	220
Mean	158.2	176.7	163.5
sd	44.6	42.3	41.6
CV	28.2	24.0	25.4
Terfenadine Use (Seldane orally)			
NO	7 (54%)	8 (53%)	6 (46%)
YES	6 (46%)	7 (47%)	7 (54%)

Figure 5

Comparative median plasma fluticasone propionate concentrations over 12 hours after dosing with the Diskhaler versus the Diskus at Visit 6 (day 28)

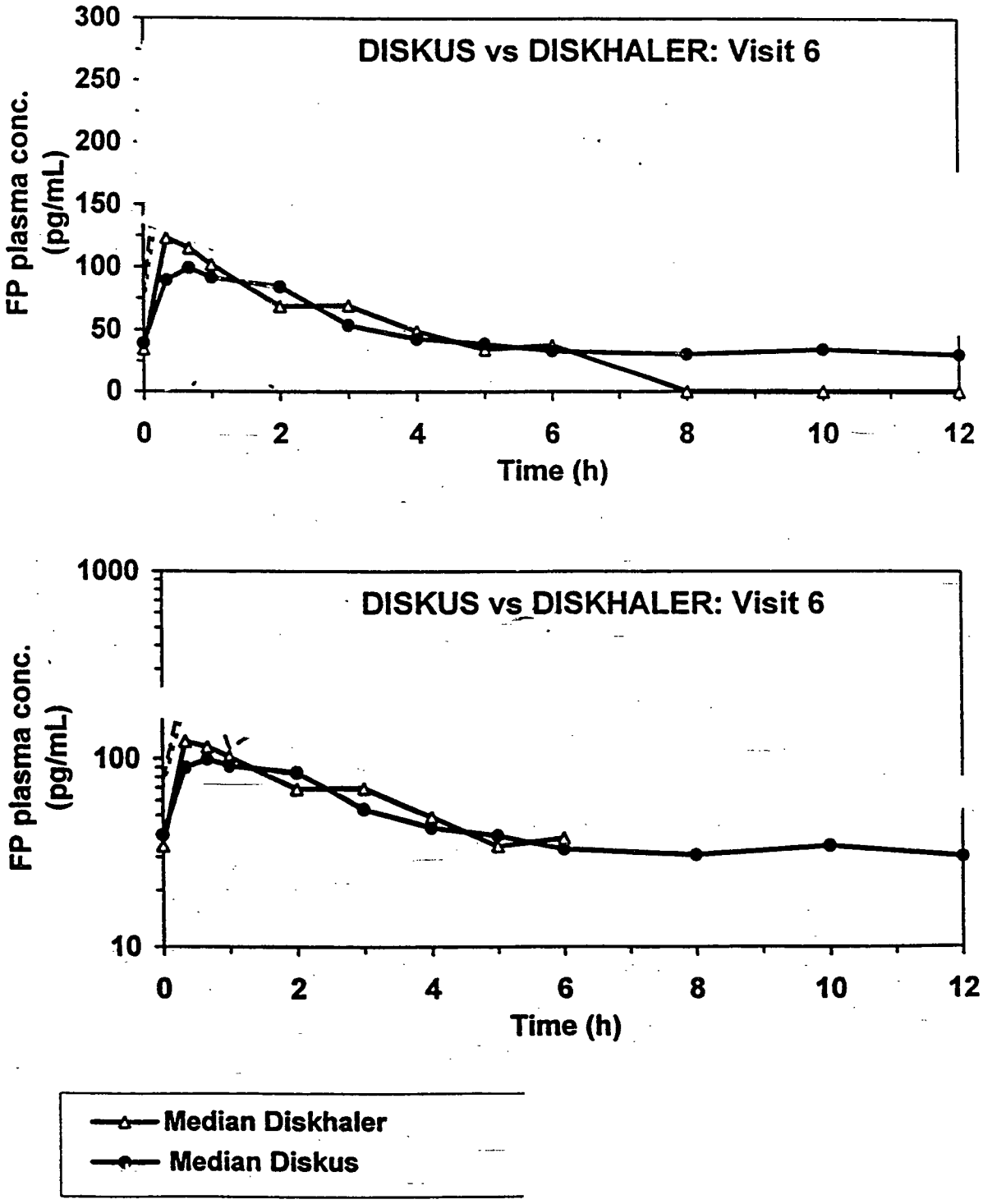

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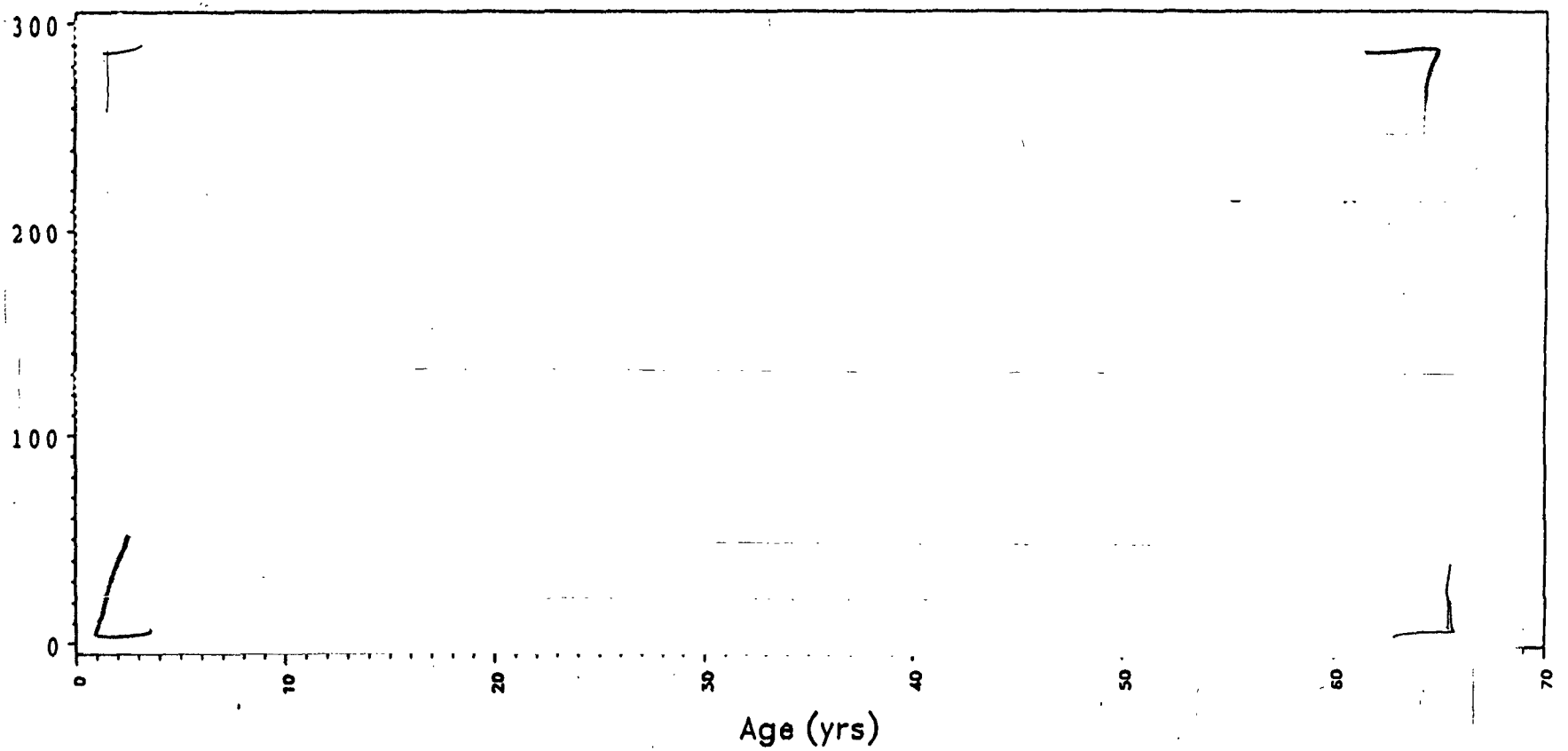
Figure 29
Influence of gender and age on the maximum observed plasma fluticasone propionate concentration (Cmax) over 0, 20 and 40 min after dosing with the Diskhaler and the Diskus on Visit 6 (day 28)



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Study No. FLTA2006

[redacted]

TITLE

A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PARALLEL GROUP TRIAL ASSESSING THE EFFICACY AND SAFETY OF FLUTICASONE PROPIONATE 50 OR 100MCG BID VIA THE MULTI-DOSE POWDER INHALER, FLUTICASONE PROPIONATE 50 OR 100MCG BID VIA THE DISKHALER® AND PLACEBO IN SUBJECTS AGED 4 TO 11 YEARS WITH CHRONIC ASTHMA.
Pharmacokinetic Analysis of Fluticasone Propionate Plasma Concentrations and Pharmacodynamic Analysis of Urinary Cortisol Excretion

OBJECTIVES

The objectives of the clinical study were to compare the efficacy and safety of fluticasone propionate (FP) 50 and 100mcg BID via Multi-Dose Powder Inhaler (Diskus), FP 50 and 100mcg BID Rotadisks via Diskhaler (DH) and placebo BID in asthmatic pediatric subjects aged 4 to 11 years.

The primary objective of the present analysis was:
- to compare the pharmacokinetics of FP in terms of maximum plasma concentrations (C_{max}) following administration from the Diskus and the Diskhaler.

The secondary objectives of the analysis were:
- to assess the gender effect on the pharmacokinetics of FP
- to compare the pharmacodynamic effect on 24-hour urinary cortisol excretion (UC) following administration of placebo and FP from the Diskus and the Diskhaler.

DESIGN

The study was a stratified, randomized, double-blind, double-dummy, parallel-group, placebo-controlled, multicenter trial in asthmatic pediatric subjects aged 4-11 years with a diagnosis of asthma. Subjects were randomly assigned to one of the following five double-blind treatments for 12 weeks: FP 50mcg via Diskus (Diskus 50 BID), FP 100mcg BID via Diskus (Diskus 100 BID), FP 50mcg via Diskhaler (DH 50 BID), FP 100mcg BID via Diskhaler (DH 100 BID), or inhaled placebo BID (placebo). Subjects were treated on an outpatient basis and attended the clinic at the initial screening visit (14 ± 2 days before Treatment Day 0) and at Treatment Weeks 0, 1, 2, 3, 4, 6, 8, 10, and 12. The study population was prospectively stratified according to whether subjects were taking inhaled corticosteroids or cromolyn (ICT), or bronchodilator therapy alone (BDT), prior to study entry.

SUBJECTS

A total of 437 subjects completed the screening period and met the randomization criteria at Visit 2 and were randomly assigned to placebo (N=86), Diskus 50 BID (N=90), Diskus 100 BID (N=87), DH 50 BID (N=91) and DH 100 BID (N=83). Of the subjects enrolled, 319 completed the study: 39 in the placebo group, 69 in the Diskus 50 BID group, 71 in the Diskus 100 BID group, 77 in the DH 50 BID group and 63 in the DH 100 BID group.

A limited 20 minute and 40 minute blood sampling was performed to measure FP in plasma in a subgroup of subjects. Evaluable data could be obtained in 124 subjects: 31 subjects in the Diskus 50 BID group (13 F, 18 M), 30 subjects in the Diskus 100 BID group (6 F, 24 M), 37 in the DH 50 BID group (20 F, 17 M), and 26 subjects in the DH 100 BID group (9 F, 17 M).

Urine was collected during any 24-hour period between Visits 1 and 2, and between Visits 9 and 10 (or at discontinuation). Evaluable data could be obtained in 250 subjects: 33 subjects in the placebo group (13 F, 20 M), 60 subjects in the Diskus 50 BID group (28 F, 32 M), 55 subjects in the Diskus 100 BID group (19 F, 36 M), 57 in the DH 50 BID group (25 F, 32 M), and 45 subjects in the DH 100 BID group (18 F, 27 M).

TREATMENTS

The study treatments were:
- Inhaled placebo BID (placebo)
- Diskus 50mcg BID (Diskus 50 BID)
- Diskus 100mcg BID (Diskus 100 BID)
- Diskhaler 50mcg BID (DH 50 BID)
- Diskhaler 100mcg BID (DH 100 BID).

The double-blind treatment started 14 ± 2 days after the initial screening visit and lasted 12 weeks.

MEASUREMENTS

Pharmacokinetics and Pharmacodynamics

In the subgroup of subjects, blood samples were drawn for the analysis of FP in plasma on Visit 10 (day 84 ± 2 days) or the discontinuation visit at 20 minutes and 40 minutes after the morning dose. In a larger group of subjects, urine was collected over 24 hours to measure cortisol between Visits 1 and 2 (baseline) and between Visits 9 and 10 (or at discontinuation).

RESULTS

Pharmacokinetics

Influence of gender. The gender effect did not approach statistical significance in C_{max} values (p=0.208).

Comparison of the two devices. Plasma concentrations were low in these asthmatic children.

- At 50mcg BID, no difference between the two devices was observed for C_{max} (p=0.069). The percentage of C_{max} values below the quantification limit (BQL) was larger for the Diskus (87%) than for the Diskhaler (70%).
- At 100mcg BID the Diskus provided lower C_{max} levels than the Diskhaler (p=0.001). The percentage of BQL C_{max} values was larger for the Diskus (80%) than for the Diskhaler (42%).

Influence of dose. An influence of dose on C_{max} could be detected only with the Diskhaler.

- With the Diskhaler, the difference in doses reached statistical significance (p=0.015). The percentage of BQL C_{max} values was 70% and 42% for the DH 50 BID and DH 100 BID groups, respectively.
- With the Diskus no difference between doses could be shown (p=0.389). There was a similarly large number of BQL values at the two doses (87% and 80% for the Diskus 50 BID and Diskus 100 BID groups, respectively).

The following tables summarize the C_{max} results and pairwise treatment comparisons.

	Diskus		Diskhaler	
	50mcg BID	100mcg BID	50mcg BID	100mcg BID
N	31	30	37	26
Cmax (pg/mL)				
Median	BQL	BQL	BQL	34.3
Range				
Mean	5.4	7.8	13.4	30.3
SD	17.3	16.4	21.7	29.0
% of BQL values	87%	80%	70%	42%

BQL= Below Quantification Limit
N=number of subjects

Treatments Comparisons for C_{max}

Treatment Comparison	Estimate (pg/mL)	90% CI (pg/mL)	p-value
DH 50 BID - DH 100 BID	-.20	-32.80, 0.00	0.015
Diskus 100 BID - DH 100 BID	-21.45	-37.70, 0.00	0.001
Diskus 50 BID - DH 50 BID	0.00	0.00, 0.00	0.069
Diskus 50 BID - Diskus 100 BID	0.00	0.00, 0.00	0.389

Due to the large number of C_{max} values reported as BQL, the distribution of the data is highly skewed with a large number of ties at zero. This may affect the validity of the Wilcoxon rank sum test. Consequently, a supportive analysis was performed using Fisher's exact test. For this analysis, the C_{max} for each subject was classified as either BQL or quantifiable. The results of this analysis were consistent with the Wilcoxon rank sum analysis.

Pharmacodynamics

There were no statistically significant differences in 24-hour urinary cortisol (UC) among the five treatments. Compared with placebo, there was no effect of any FP treatment on UC. Although the difference was not statistically significant, there was with the Diskus a slight increase in UC (mcg/24h) when compared with both placebo and Diskhaler, which is of no safety concern. This was also apparent when the results were expressed as % change from pre-treatment baseline. As a marker of overall systemic exposure to FP, UC results showed that the two devices were similar.

The following tables summarize the UC results following the 12 weeks of study treatment and pairwise treatment comparisons.

	Placebo	Diskus		Diskhaler	
		50mcg BID	100mcg BID	50mcg BID	100mcg BID
24h UC (mcg) *					
N	35	61	57	63	47
Geom. LS Mean†	7.8	8.7	8.4	8.4	7.7
(95% CI)	(6.2, 9.8)	(7.4, 10.3)	(7.0, 10.0)	(7.1, 10.0)	(6.4, 9.4)
Median	7.3	9.0	9.2	7.5	7.7
Range	—	—	—	—	—
24h UC (% Change) **					
N	33	60	55	57	45
Median	-12.8	+9.6	+0.9	-11.9	-22.1
Range	—	—	—	—	—

* Between Visits 9 and 10 (or at discontinuation). To convert to nmol, multiply by 2.76
** Change from pre-treatment baseline values
† The geometric LS mean and associated 95% CI are based only on subjects with both pre-visit 2 and pre-visit 10 assessments.

Treatment Comparisons for 24-hour Urinary Cortisol Excretion (mcg/24h) *

Treatment Comparison	Ratio Estimate	90% CI	p-value
Diskus 50 BID / Placebo	1.12	0.88, 1.41	0.447
Diskus 100 BID / Placebo	1.08	0.85, 1.37	0.614
DH 50 BID / Placebo	1.08	0.85, 1.37	0.589
DH 100 BID / Placebo	0.99	0.77, 1.27	0.954
Diskus 50 BID / DH 50 BID	1.03	0.84, 1.26	0.801
Diskus 100 BID / DH 100 BID	1.09	0.87, 1.35	0.538
Diskus 50 BID / Diskus 100 BID	1.04	0.85, 1.27	0.773
DH 50 BID / DH 100 BID	1.09	0.88, 1.36	0.512

* Between Visits 9 and 10 (or at discontinuation).

CONCLUSIONS

- In asthmatic pediatric subjects, fluticasone propionate plasma concentrations were very low following dosing with fluticasone propionate 50mcg or 100mcg BID via both the Diskus and the Diskhaler.

- Maximum fluticasone propionate plasma levels were lower with the Diskus than with the Diskhaler.

- There was no gender effect on plasma fluticasone propionate phamacokinetics.

- As a marker of overall systemic exposure to fluticasone propionate, 24-hour urinary cortisol excretion results showed that the two devices were similar. Compared with placebo, there was no effect of any fluticasone propionate treatment on 24-hour urinary cortisol excretion.

Table 2

Summary of Demographic Data for Patients Included in the Analysis of Plasma FP Cmax

	Statistic or Category	Treatment			
		50 MDPI	100 MDPI	50 DH	100 DH
Age (years)	N	31	30	37	26
	Mean	8.35	7.97	8.24	8.38
	Std.Dev.	1.924	1.974	2.241	2.192
	Median	9.00	8.00	9.00	9.00
	Minimum	5.00	4.00	4.00	4.00
	Maximum	11.00	11.00	11.00	11.00
Gender	N	31	30	37	26
	Female	13 (42%)	6 (20%)	20 (54%)	9 (35%)
	Male	18 (58%)	24 (80%)	17 (46%)	17 (65%)
Ethnic Origin	N	31	30	37	26
	Black	3 (10%)	3 (10%)	4 (11%)	4 (15%)
	Hispanic	3 (10%)	1 (3%)	1 (3%)	2 (8%)
	Oriental	0 (0%)	0 (0%)	1 (3%)	0 (0%)
	White	24 (77%)	24 (80%)	31 (84%)	20 (77%)
	Other	1 (3%)	2 (7%)	0 (0%)	0 (0%)
Height (cm)	N	31	30	37	26
	Mean	133.4	132.3	133.0	133.0
	Std.Dev.	14.03	14.39	15.71	13.38
	Median	132.1	129.5	132.1	134.6
	Minimum	111.8	109.2	99.1	106.7
	Maximum	167.6	165.1	165.1	157.5
Weight (kg)	N	31	30	37	26
	Mean	34.8	34.9	33.0	33.2
	Std.Dev.	14.84	14.29	12.09	10.93
	Median	29.9	31.5	30.4	32.4
	Minimum	18.6	20.4	16.8	15.9
	Maximum	75.7	78.0	64.4	63.5

Table 4

Summary of Demographic Data for Patients Included in the Analysis of 24 Hour Urinary Cortisol

	Statistic or Category	Treatment				
		Placebo	50 MDPI	100 MDPI	50 DH	100 DH
Age (years)	N	33	60	55	57	45
	Mean	8.42	8.50	8.35	8.44	8.09
	Std.Dev.	2.107	2.087	2.101	2.053	2.193
	Median	9.00	9.00	9.00	9.00	8.00
	Minimum	4.00	4.00	4.00	4.00	4.00
	Maximum	11.00	11.00	11.00	11.00	11.00
Gender	N	33	60	55	57	45
	Female	13 (39%)	28 (47%)	19 (35%)	25 (44%)	18 (40%)
	Male	20 (61%)	32 (53%)	36 (65%)	32 (56%)	27 (60%)
Ethnic Origin	N	33	60	55	57	45
	Black	2 (6%)	8 (13%)	7 (13%)	6 (11%)	8 (18)
	Hispanic	1 (3%)	4 (7%)	4 (7%)	5 (9%)	3 (7%)
	Oriental	1 (3%)	0 (0%)	0 (0%)	2 (4%)	0 (0%)
	White	29 (88%)	47 (78%)	43 (78%)	43 (75%)	34 (76%)
	Other	0 (0%)	1 (2%)	1 (2%)	1 (2%)	0 (0%)
Height (cm)	N	33	60	55	57	45
	Mean	135.6	134.8	133.8	134.9	131.0
	Std.Dev.	15.08	14.43	14.89	15.46	14.34
	Median	134.6	135.9	137.2	137.2	132.1
	Minimum	104.1	101.6	101.6	104.1	106.7
	Maximum	170.2	167.6	165.1	165.1	157.5
Weight (kg)	N	33	60	55	57	45
	Mean	39.2	36.0	33.8	33.4	31.9
	Std.Dev.	15.21	14.00	12.01	12.99	12.23
	Median	35.8	33.1	33.6	30.4	29.9
	Minimum	15.4	12.7	15.4	17.2	15.9
	Maximum	73.9	75.7	78.0	71.2	63.5

Study No. FLTB1001

Report No. GCP/95/041
Protocol No. FLTB1001

SUMMARY OF REPORT GCP/95/041

Part I : Pharmacodynamics.

TITLE

To compare the effects of the dosing schedule of inhaled fluticasone propionate using various tests of HPA-axis function.

OBJECTIVES

The primary objectives were:

1) To compare the effects of AM, PM and AM-PM dosing of inhaled FP on the HPA-axis.

2) To investigate the variability of agreement between the different tests of HPA-axis function.

These data are described in Part I of the report.

The secondary objectives were:

3) To further validate the PK/PD relationship with inhaled FP after PM dosing.

4) To investigate the chronopharmacodynamics of inhaled FP.

These data will be described in Part II of the report.

Note: The investigation of the chronopharmacokinetics and the comparison of AM and PM dosing on the PK/PD relationship was not possible due to the limited number of samples. Consequently, the samples were used to mainly characterise PM dosing, as there was no PK data and very limited plasma PD data available.

DESIGN AND TREATMENTS

Design:

This was a double-blind, randomised, placebo-controlled, four period, cross-over study. Each study period consisted of 2.5 study days, separated by at least 7 days.

There were four treatment periods. Blindness was achieved by supplying each subject with four identical MDIs, which contained either FP or placebo. Two inhalations were taken at 30 second intervals from two of these inhalers in the morning and from the other two inhalers in the evening.

Treatments:

FP 1000µg (4 x 250µg/actuation) CFC 11/12 metered dose inhaler (MDI) containing —lecithin was given as a single morning dose at 09.00h.

FP 1000µg (4 x 250µg/actuation) CFC 11/12 MDI containing —ecithin was given as a single night time dose at 21.00h.

FP 500µg (2 x 250µg/actuation) CFC 11/12 MDI containing —ecithin was given as a twice daily regime at 09.00h and 21.00h.

Placebo CFC 11/12 MDI containing —lecithin as 4 actuations twice daily at 09.00h and 21.00h.

Dosing was staggered around 09.00h and 21.00h for different subjects, but a 12 hour interval was maintained for each individual subject.

SETTING/STUDY DATES

The study was performed at the Glaxo Wellcome Clinical Pharmacology Unit, Northwick Park between 21st June and 8th August 1995.

First dosing day: 11th July 1995
Last dosing day: 1st August 1995

SUBJECTS

Twelve healthy male subjects (mean age 29y, range 22 to 44y; mean weight 78.7kg, range 59.4 to 99.4kg) were recruited into the study, 11 subjects completed the study. One subject withdrew from the study due to personal reasons. There were no limitation on the ethnic origin of the volunteers.

MEASUREMENTS

Pharmacodynamics: Urine for cortisol analysis was collected as 12h aliquots from 09.00h day -1 to 21.00h day 2. Blood samples (1mL) for plasma cortisol analysis (morning at 09.00h and serial 0 - 24h) were taken at 0, 1, 2, 4, 6, 8, 10, 12, 13, 14, 16, 18, 20, 22, on days -1 and day 1 and 0, 1, 2, 4, 6, 8, 10, and 12 hours on day 2.

Pharmacokinetics: Blood samples (3mL) for plasma FP concentration were taken at 0, 45', 4h, 12h, 12h 5', 12h 15', 12h 30', 12h 45', 13h, 14h, 16h, 18h, 22h, and 24h on Day 1 and 4h and 12h on Day 2.

Samples were timed relative to the first (nominal) inhalation of each treatment.

SAFETY

A screening medical was performed within three weeks of the first study day.

Laboratory safety screens (clinical chemistry, haematology, urinalysis, hepatitis B/C, and urine drugs) were performed within three weeks pre-study. Clinical chemistry, haematology and urinalysis were repeated within 4 to 10 days post-study.

The total blood volume to be taken during the study was approximately 515mL.

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

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RESULTS

Pharmacodynamics:

The results are summarised in the tables below.

i) Effects of AM, PM and AM-PM dosing of inhaled FP on the HPA-axis.

FP Dosing Regimen	Measurement of HPA-axis function	
	24h Urinary Cortisol Excretion(nmol)*	
	Pre-treatment	Post-treatment
1000µg FP 09.00h	183.2 (102.6, 727.8)	84.8 (BLQ, 251.2)
1000µg FP 21.00h	227.0 (50.6, 1141.1)	91.4 (BLQ, 537.2)
500µg FP 09.00h , 21.00h	216.0 (52.7, 489.3)	133.1 (23.8, 263.6)
Placebo	182.9 (80.1, 359.3)	155.0 (44.9, 383.2)
	09.00h Plasma Cortisol (nmol/L)*	
1000µg FP 09.00h	311.9 (259.4, 408.5)	251.2 (110.4, 298.1)
1000µg FP 21.00h	309.1 (198.7, 565.8)	179.4 (BLQ, 298.1)
500µg FP 09.00h , 21.00h	317.4 (226.3, 521.6)	201.5 (BLQ, 383.6)
Placebo	325.7 (209.8, 408.5)	276.0 (201.5, 416.8)
	0-24h Plasma Cortisol (nmol/L)*	
1000µg FP 09.00h	193.4 (132.5, 248.4)	104.9 (41.4, 143.5)
1000µg FP 21.00h	184.9 (140.8, 311.9)	129.7 (38.6, 160.1)
500µg FP 09.00h , 21.00h	190.4 (138.0, 259.4)	104.9 (44.2, 176.6)
Placebo	220.8 (124.2, 289.8)	168.4 (135.2, 242.9)

* medians (range)
BLQ: Below Level of Quantification

The 24h urinary cortisol decreased compared to pre-treatment on average(using geometric mean of the change), by 56%, 53%, 45% and 23% following 1000µg inhaled FP given as a single AM and PM dose, as a twice daily dose and following an inhaled dose of placebo, respectively.
The morning plasma cortisol decreased compared to pre-treatment on average (using change in arithmetic means), by 24%, 50%, 43% and 6% following 1000µg inhaled FP given as a single AM and PM dose, as a twice daily dose and following an inhaled dose of placebo, respectively.

The 0-24h plasma cortisol weighted mean decreased compared to pre-treatment on average (using geometric mean of the change), by 54%, 44%, 51% and 11% following 1000µg inhaled FP given as a single AM and PM dose, as a twice daily dose and following an inhaled dose of placebo, respectively.

ii) Variability of agreement between the different tests of HPA-axis function

Treatment Contrast	p - value 24h Urinary Cortisol Excretion	Plasma AM Cortisol	Plasma 24h Cortisol
FP AM/PL	0.032	0.392	<0.001
FP PM/PL	0.064	0.002	<0.001
FP AM + PM/PL	0.225	0.002	<0.001
FP AM/FP PM	0.790	0.019	0.195
FP AM/FP AM + PM	0.289	0.031	0.570
FP PM/FP AM + PM	0.432	0.686	0.442

All active study drugs resulted in effects on the HPA-axis as compared to placebo. Generally there was good agreement in sensitivity when using 24h plasma cortisol and 24h urinary cortisol excretion measurements. 24h urinary cortisol excretion and 24h plasma cortisol may be underestimated following the twice daily regimen as they were calculated from the time of the AM dose. Morning cortisol measurements were more sensitive following a single night-time inhaled FP dose and doses given as a twice daily regimen as compared to doses given in the morning.

Pharmacokinetics:

These data will be described in Part II of the report.

Adverse Events and Subject Withdrawals:

The study procedures and drugs were well tolerated. There were no serious adverse events.

One subject withdrew from the study due to personal reasons.

Laboratory Safety Screening:

There were no clinically significant changes in the parameters measured at the pre- and post-study haematology, clinical chemistry and urinalysis screens.

CONCLUSIONS

There was no effect of dosing schedule of inhaled FP on 24h urinary and plasma cortisol. On 09.00h (morning) plasma cortisol, however, there was a significant effect of PM dosing and AM-PM dosing, but not of AM dosing. This confirms that the effects of corticosteroids on 09.00h (morning) plasma cortisol are dependant on the time of dosing. These results suggest that switching from a BID to a single dose regimen with the same total daily dose does not influence the effect of FP on the HPA-axis.

Both 24h urinary and 24h serial plasma cortisol have comparable sensitivity at detecting HPA-axis effects and appeared more sensitive than the early morning cortisol measurement.

SUMMARY OF REPORT GCP/95/041

Part II : Pharmacokinetics.

TITLE

To compare the effects of the dosing schedule of inhaled fluticasone propionate using various tests of HPA-axis function.

OBJECTIVES

The primary objectives were:

1) To compare the effects of AM, PM and AM-PM dosing of inhaled FP on the HPA-axis.

2) To investigate the variability of agreement between the different tests of HPA-axis function.

These data are described in Part I of the report.

The secondary objectives were:

3) To further validate the PK/PD relationship with inhaled FP after PM dosing.

4) To investigate the chronopharmacodynamics of inhaled FP.

These data are described in Part II of the report.

DESIGN AND TREATMENTS

Design:
This was a double-blind, randomised, placebo-controlled, four-period, cross-over study. Each study period consisted of 2.5 study days, separated by at least 7 days.

There were four treatment periods. Blindness was achieved by supplying each subject with four identical MDIs, which contained either FP or placebo. Two inhalations were taken at 30 second intervals from two of these inhalers in the morning and from the other two inhalers in the evening.

Treatments:

FP 1000µg (4 x 250µg/actuation) CFC 11/12 metered dose inhaler (MDI) containing — lecithin was given as a single morning dose at 09.00h and placebo at 21.00h (4 actuations) [FPAM].

FP 1000µg (4 x 250µg/actuation) CFC 11/12 MDI containing — lecithin was given as a single night time dose at 21.00hand placebo at 09.00h (4 actuations) [FPPM].

FP 500µg (2 x 250µg/actuation) CFC 11/12 MDI containing — lecithin was given as a twice daily regime at 09.00h and 21.00hand placebo at 09.00h (2 actuations) and at 21.00h (2 actuations) [FPAP].

Placebo CFC 11/12 MDI containing — lecithin as 4 actuations twice daily at 09.00h and 21.00h [P].

Dosing was staggered around 09.00h and 21.00h for different subjects, but a 12 hour interval was maintained for each individual subject.

SETTING/STUDY DATES

The study was performed at the Glaxo Wellcome Clinical Pharmacology Unit, Northwick Park between 21st June and 8th August 1995.

First dosing day: 11th July 1995
Last dosing day: 1st August 1995

SUBJECTS

Twelve healthy male subjects (mean age 29y, range 22 to 44y; mean weight 78.7kg, range 59.4 to 99.4kg) were recruited into the study, 11 subjects completed the study. One subject withdrew from the study due to personal reasons. There were no limitation on the ethnic origin of the volunteers.

MEASUREMENTS

Pharmacodynamics: Urine for cortisol analysis was collected as 12h aliquots from 09.00h on day -1 to 21.00h on day 2. Blood samples (1mL) for plasma cortisol analysis (morning at 09.00h and serial 0-24h) were taken at 0, 1, 2, 4, 6, 8, 10, 12, 13, 14, 16, 18, 20 and 22h on days -1 and day 1 and 0, 1, 2, 4, 6, 8, 10, and 12 h on day 2.

Pharmacokinetics: Blood samples (3mL) for plasma FP concentration were taken at 0 (09.00h), 45', 4h, 12h (21.00h), 12h 5', 12h 15', 12h 30', 12h 45', 13h, 14h, 16h, 18h and 22h on day 1, and 0, 4h and 12h on day 2.

Samples were timed relative to the first (nominal) inhalation of each treatment.

SAFETY

A screening medical was performed within three weeks of the first study day.

Laboratory safety screens (clinical chemistry, haematology, urinalysis, hepatitis B/C, and urine drugs) were performed within three weeks pre-study. Clinical chemistry, haematology and urinalysis were repeated within 4 to 10 days post-study.

The total blood volume to be taken during the study was approximately 515mL.

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

RESULTS

Pharmacodynamics

The results are described in Part I of the report

Pharmacokinetics

Due to the limited sampling from 09.00h to 21.00h, the pharmacokinetics of the AM dose and consequently any influence of AM vs. PM dosing could not be completely determined. Plasma profiles indicated that: (1) the dose inhaled was variable from one dosing occasion to another; and (2) there was a slight rebound in absorption of the morning dose when the evening dose was given. Two pharmacokinetic analyses were performed: (1) a non compartmental analysis of the PM profiles (FPPM, FPAP); and (2) a modelling analysis with the evaluation of the relative bioavailability between AM and PM doses. A summary of the main pharmacokinetic parameters and results of the statistical analysis is presented below.

Non Compartmental Analysis. The pharmacokinetics of the PM doses appeared to be consistent, accounting for the dose difference and the expected accumulation. Due to limited sampling between 9AM and 9PM, the pharmacokinetics of the AM dose could not be completely assessed. However, plasma concentrations at 45' and 4h appeared to be slightly higher in the morning.

Parameter (units)	FPAM N		FPPM N		FPAP N	AM	PM
C_{45min} (pg/mL) *	9	240	9	213	9	147	163
C_{4h} (pg/mL) *	7	206	8	109	7	128	89
C_{max} (pg/mL)		-	10	266	7	-	179
t_{max} (h) *		-	10	13+	7	-	13+
AUC_{∞} (ng.h/mL)		-	7	1720		-	-
AUC_{12} (ng.h/mL)		-	8	1220	5	-	1465
$t_{1/2}$ (h)	5	10	7	7	5	-	7

Geometric mean (95% CI) excepted: * median (range) - not applicable
+Times are relative to the 9am FP dose N=number of subjects

Pharmacokinetic Compartmental Modelling. The absorption, inter-compartmental distribution and elimination pharmacokinetic rate constants were similar between dosing regimens. Following the single FP AM dose, a rebound in plasma concentrations at the time of the PM placebo administration was observed. It was negligible in most subjects, and was quantifiable in only 3 out of 8 subjects (8, 13 and 55% of total predicted AUC_{∞}). Following the BID regimen, the amount available for absorption was predicted to be slightly (14% as a mean) higher in the morning compared with the evening.

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Parameter (units)	FPAM		FPPM		FPAP	
	N		N		N	
k01 (h^{-1})	9	2.16 (0.59, 7.92)	9	2.87 (0.90, 9.17)	9	2.50 (0.82, 7.68)
k12 (h^{-1})	8	3.92 (1.19, 12.88)				
k21 (h^{-1})	8	0.57 (0.29, 1.14)				
k10 (h^{-1})	9	0.74 (1.43, 3.73)	9	0.67 (1.41, 3.20)	9	0.75 (1.44, 3.87)
$t_{1/2}$ (h) †	9	7.7 (5.5, 10.7)	9	8.3 (5.5, 12.7)	9	7.5 (5.3, 10.6)
Ratio AM Dose / PM Dose		-		-	7	1.14 (0.86, 1.51)

Geometric mean (95% CI) † Terminal half-life - not applicable N=number of subjects

Pharmacokinetics-Pharmacodynamics. The pharmacodynamic parameters of cortisol were Vd (fixed to 33.7L), R_{max} (fixed at 2862 µg/h), ke (estimated to 0.63 h^{-1}; 95% CI: 0.58, 0.69), $T_{min,c}$ (estimated to 15.27h; 95% CI: 14.38, 16.25), $T_{max,c}$ (estimated to 21.11h; 95% CI: 20.95, 21.26), R_{max2} (estimated to 4986µg/h; 95% CI: 4165, 6084), Ery (the variance of the spread of the maximum release rate, estimated to 0.27 h^{-2} ; 95% CI: 0.22, 0.34).

The effect of FP on cortisol release rate was characterised by and EC_{50} of 71 pg/mL (95% CI: 34, 144), 98 pg/mL (95% CI: 48, 221) and 103 pg/mL (95% CI: 35, 264) for FPAM, FPPM and FPAP, respectively.

Simulations of $AUC_{24,cort}^{ss}$ of cortisol at steady-state allowed a full comparison of the AM-PM, AM and PM dosing vs placebo. Analysis of variance showed no statisitcally significant differences between the FP regimens. These results were in agreement with data measured following a single dose.

Simulated Plasma Cortisol $AUC_{24,cort}^{ss}$ of Cortisol (µg.h/dL) at Steady-State

N	P	FPAM	FPPM	FPAP
9	166.7 (147.7, 188.1)	76.8 (56.5, 104.3)	97.4 (69.3, 137.0)	81.4 (58.3, 113.7)

Geometric mean (95% CI) N=number of subjects

Treatment Contrast	Ratio	95% CI	p-value
FPAM / P	0.46	(0.34, 0.63)	<0.001
FPPM / P	0.58	(0.43, 0.80)	0.002
FPAP / P	0.49	(0.36, 0.67)	<0.001
FPAM / FPPM	0.79	(0.57, 1.08)	0.134
FPAM / FPAP	0.94	(0.69, 1.29)	0.704
FPPM / FPAP	1.20	(0.87, 1.64)	0.254

Adverse Events and Subject Withdrawals:

The study procedures and drugs were well tolerated. There were no serious adverse events.

One subject withdrew from the study due to personal reasons.

Laboratory Safety Screening:

There were no clinically significant changes in the parameters measured at the pre- and post-study haematology, clinical chemistry and urinalysis screens.

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CONCLUSIONS

- The was no influence of the time of dosing on absorption, distribution and elimination haracteristics of fluticasone propionate.
- E_{50} values with regards to cortisol plasma concentrations were similar regardless of the time of administration
- There was no statistically significant influence of the time of administration of fluticasone propionate on simulated steady-state plasma cortisol concentrations.
- The influence of the time of dosing on HPA axis in terms of 24 h plasma cortisol can be assessed following single doses.
- These results show that switching from a BID to a single daily dose regimen does not influence the effect of fluticasone propionate on the HPA-axis.

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10. TABLES

TABLE 1
DEMOGRAPHIC PROFILE

Subject Number	Volunteer Number	Sex	Age	Ethnic Origin	Weight (kg)
1	22024	Male	25	Caucasian/White	87
2	22130	Male	28	Caucasian/White	87.6
3	24212	Male	31	Caucasian/White	74.6
4	22401	Male	24	Caucasian/White	92.1
5	30160	Male	22	Caucasian/White	74.5
6	21679	Male	23	Asian (not Oriental)	59.4
7	21291	Male	33	Caucasian/White	83.8
8	22326	Male	27	Caucasian/White	99.4
9	30168	Male	30	Caucasian/White	70.3
10	24368	Male	30	Caucasian/White	75.2
11	22323	Male	44	Caucasian/White	70.5
12	24326	Male	26	Caucasian/White	70.3

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Study No. SFCB1002

SUMMARY OF REPORT GCP/95/040

TITLE

A study to evaluate the safety, tolerability, pharmacokinetics and systemic pharmacodynamic effects of fluticasone propionate (FP) in the salmeterol/FP Diskus™ Inhaler.

OBJECTIVES

The objectives of the study were:

1. To investigate if the salmeterol/FP Diskus™ Inhaler had acceptable safety and tolerability following single doses.

2. To investigate if the addition of salmeterol to FP in the salmeterol/FP Diskus™ Inhaler affects the systemic exposure to FP following single doses.

DESIGN

This was a randomised, double-blind, placebo-controlled, three-way cross-over study. There was a washout period of at least six days between treatments.

SETTING/STUDY DATES

The study was carried out at the
— , between 26 April and 07 June 1995.

SUBJECTS

Twelve healthy male subjects, of Caucasian origin, completed the study. They had a mean age of 30 years (range 18-47 years) and a mean weight of 72.5kg (range 63.5-85.9kg).

TREATMENTS

Treatments were given as five inhalations, at 30 second intervals, from a Diskus™ Inhaler containing salmeterol/FP (50/100µg per blister), FP (100µg per blister) or placebo:

Treatment	Dose per inhalation	No. of inhalations	Total dose
Salmeterol/fluticasone propionate	50/100µg	5	250/500µg
Fluticasone propionate	100µg	5	500µg
Placebo	0	5	0

MEASUREMENTS

Pharmacodynamics:

Urinary cortisol concentrations were determined from timed urine collections made at 0-4h, 4-8h, 8-12h and 12-24h on each dosing day and at equivalent time points the day prior to dosing, to provide a baseline. Samples were timed relative to the first (nominal) inhalation of each treatment.

Pharmacokinetics:

Blood samples (5mL) for determination of plasma FP concentrations were taken pre-dose, at 5, 10, 15 and 30 minutes and at 1, 2, 3, 4, 5, 6, 8, 12, 16, 24 hours post-dose.

Safety:

Laboratory safety screens, which included clinical chemistry, haematology and urinalysis, were performed within three weeks pre-study, 24 hours after each treatment and 7-10 days post-study. All adverse events reported during the study were recorded.

RESULTS

Pharmacodynamics:

Summary of Urinary Cortisol Excretion Before and After 500µg FP and 250/500µg Salmeterol/FP Administered by Diskus™ Inhaler

Parameter	Geometric mean (range)		
	Salmeterol/FP	FP	Placebo
24h urine cortisol (nmol/24h)			
Pre-treatment	129.4 (94.7 - 184.1)	121.7 (75.4 - 232.1)	117.0 (82.5 - 161.5)
Post-treatment	123.7 (81.9 - 305.9)	113.6 (80.3 - 194.4)	114.5 (72.1 - 174.5)
% Change	-4.4	-6.7	-2.1
12h urine cortisol (nmol/12h)			
Pre-treatment	70.7 (46.0 - 102.4)	62.0 (35.2 - 128.4)	64.7 (40.2 - 93.9)
Post-treatment	72.1 (45.4 - 194.5)	60.4 (40.0 - 107.0)	68.8 (47.1 - 121.2)
% Change	2.0	-2.6	6.3

Over the 0-24 hour period post-dose, urinary cortisol excretion decreased on average by 4.4% after salmeterol/FP, 6.7% after FP and 2.1% after placebo compared with pre-treatment values. There were no significant differences in urinary cortisol excretion found with any pairwise comparisons between salmeterol/FP, FP, or placebo. The ratio (95% CI) of salmeterol/FP to FP was 1.02 (0.99 to 1.05), p=0.164.

Over the 0-12 hour period post-dose, urinary cortisol excretion increased on average by 2.0% after salmeterol/FP, decreased by 2.6% after FP and increased by 6.3% after placebo compared with pre-treatment values. The only significant difference between any pairwise comparisons was between salmeterol/FP and FP. The ratio (95% CI) of salmeterol/FP to FP was 1.05 (1.00 to 1.09), p=0.041.

Pharmacokinetics:

Summary of FP Pharmacokinetic Parameters After 500µg FP and 250/500µg salmeterol/FP Administered by Diskus™ Inhaler

Parameter	Treatment	Geometric Mean	95% CI	Ratio salmeterol/FP / FP Point Estimate	90% CI	p-value
C_{max} (pg/mL)	FP	105	89 - 123	1.39	1.29 - 1.51	<0.001
	Salmeterol/FP	146	123 - 173			
AUC_{last} (pg.h/mL)	FP	1146	776 - 1694	0.78	0.56 - 1.08	0.120
	Salmeterol/FP	889	506 - 1562			

Parameter	Treatment	Median	Range	Difference salmeterol/FP - FP Point Estimate	90% CI	p-value
t_{max} (h)	FP	2.00	—	1.50	0.00 - 2.50	0.001
	Salmeterol/FP	0.21	—			

The plasma FP concentrations after the salmeterol/FP combination showed a more rapid absorption, resulting in a higher C_{max}, then decreased more rapidly, compared to FP given alone. The ratio (90% CI) for C_{max} of salmeterol/FP to FP was 1.39 (1.29 to 1.51). The terminal half-life and consequently AUC_{∞} could not be estimated, and AUC_{last} was estimated with some uncertainty as the plasma FP concentrations in the terminal phase were fluctuating and close to the limit of quantification. For AUC_{last}, the ratio (90% CI) of salmeterol/FP to FP was 0.78 (0.56 to 1.08). This was not statistically significant (p=0.120), but the 90% CI were not within the range stated for comparability (0.75 to 1.33).

Adverse Events and Subject Withdrawals:

All the study treatments were considered to be safe and well tolerated

A total of 11 adverse events were reported, seven after salmeterol/FP (n=4), two after FP alone (n=1), and two after placebo (n=2). Six subjects did not report any adverse events. All adverse events were mild, except one report of headache which was of moderate severity. The majority of adverse events were reported after salmeterol/FP treatment and were pharmacologically expected effects of high doses of β-agonists.

No subjects were withdrawn from the study.

Laboratory Safety Screening:

There were no clinically significant changes in laboratory safety parameters attributable to the study treatments.

CONCLUSIONS

All study treatments were considered to be safe and well tolerated.

The salmeterol/FP and FP treatments were considered to be comparable with respect to 24h urinary cortisol excretion, but not to plasma FP pharmacokinetics, although the 90% CI for AUC_{last} were close to the range stated for comparability. The higher C_{max} observed with salmeterol/FP was not reflected in a greater decrease in 12 hour urinary cortisol excretion.

When compared with results from previous studies, the pharmacokinetic results for AUC_{last}, C_{max}, and t_{max} obtained in this study after salmeterol/FP were those expected from previous studies of dry powder formulations of FP.

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TABLE 2a. DEMOGRAPHIC PROFILE

Subject Number	Sex	Age	Ethnic Origin	Weight (kg)
1	Male	31	Caucasian/White	70.6
2	Male	47	Caucasian/White	74.0
3	Male	27	Caucasian/White	63.6
4	Male	18	Caucasian/White	77.2
5	Male	23	Caucasian/White	65.1
6	Male	32	Caucasian/White	73.4
7	Male	33	Caucasian/White	74.0
8	Male	29	Caucasian/White	75.3
9	Male	43	Caucasian/White	63.5
10	Male	22	Caucasian/White	79.5
11	Male	31	Caucasian/White	85.9
12	Male	22	Caucasian/White	68.4

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TABLE 2b. SUMMARY OF DEMOGRAPHIC DATA

	All Subjects
Number of Subjects	12
Sex	
Male	12
Age	
Median	30
Mean	30
SD	9
Min-Max	18-47
missing	0
Weight (kg)	
Median	73.7
Mean	72.5
SD	6.7
Min-Max	63.5-85.9
missing	0
Ethnic Origin	
Caucasian/White	12

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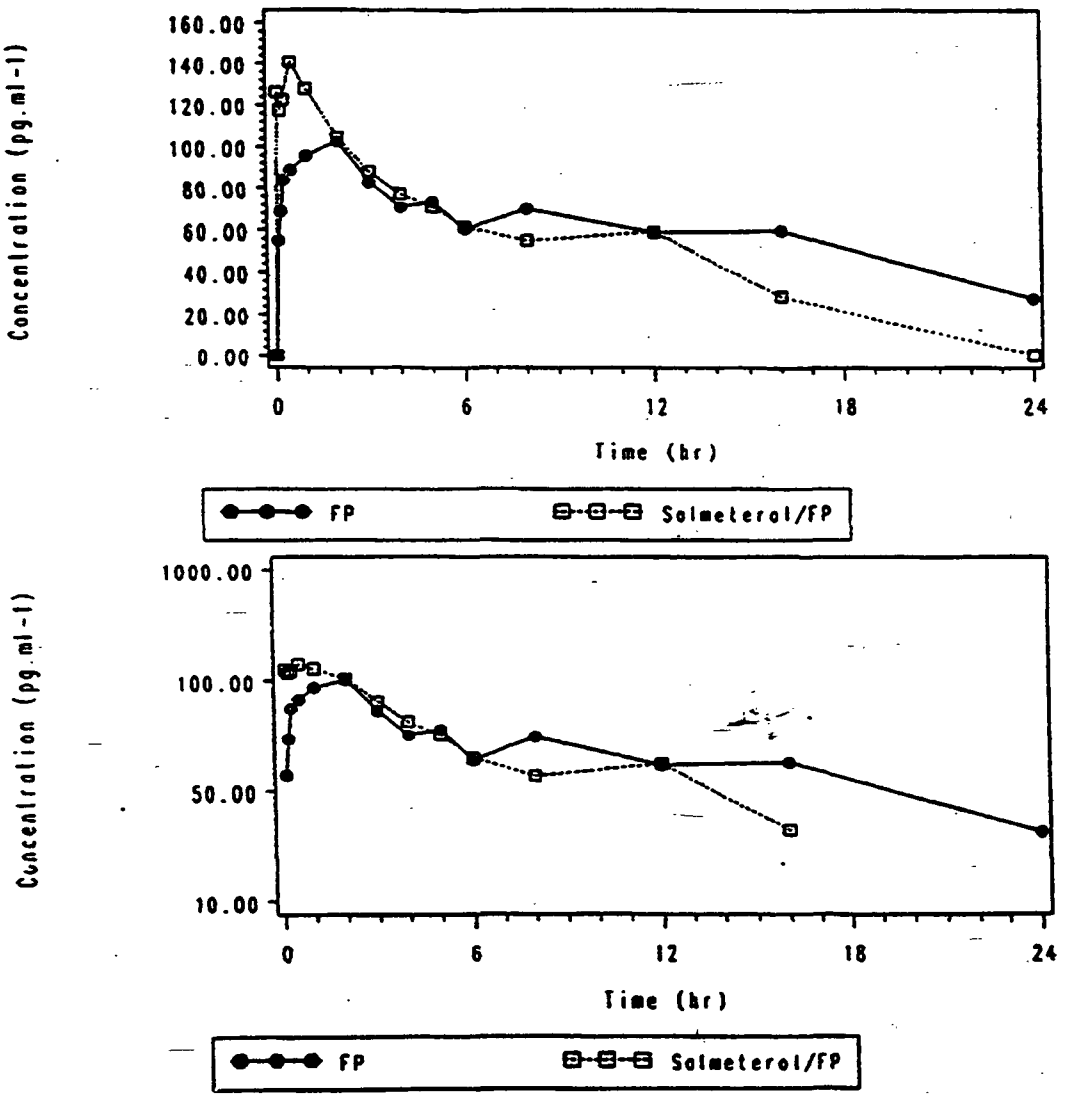
11. FIGURES

FIGURE 1. Comparative linear and semi-logarithmic plot of median plasma FP concentration-time profiles following a 500µg inhaled dose of FP and a 250/500µg inhaled dose salmeterol/FP



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Study No. C94-027(i)

Abstract

The absolute bioavailability (F) of fluticasone propionate (FP) after oral administration, and its effect on 24-hour urinary cortisol excretion (UC), were assessed in a placebo-controlled, randomised, 5-treatment, 3-period, cross-over study (incomplete block design).

Twenty-one healthy male subjects (mean age: 25 years, range: 20-32; mean weight: 72kg, range: 53-95) were recruited. The subjects received on separate occasions a single 250µg IV FP dose as a 3 minute infusion (n=21) and, double-blind, 4 days BID oral dosing with two of the following treatments: — , FP 0.1 mg (n=9), 1 mg (n=12) or 10 mg (n=11), or placebo (n=9).

All subjects had a normal response to a pre-study dexamethasone suppression test. Blood samples for plasma FP determination were taken over 24 and 12 hours following the IV and the 7th oral doses, respectively. UC was measured over 24 hours prior to the 1st and following the 7th oral doses. FP plasma concentrations were determined using a radioimmunoassay (RIA) with a — , lower limit of quantification (LOQ). After the study had been completed, part of the samples (mainly after IV and 10 mg orally) were assayed with a new LCMS assay (LOQ= —), which provides the best estimate as it is a specific and more sensitive assay.

FP was not measurable in plasma after 0.1 mg BID orally and concentrations, just above the LOQ, could be measured in only a few subjects following 1 mg BID. At 10 mg BID, F was 1.28% (median; range: , n=11) using RIA, and 0.91% (median; range: , n=10) using LCMS.

There was no effect on UC, compared to placebo, at 0.1 mg BID (LSmean ratio: 0.99; 95% CI: 0.74-1.33) and 1mg BID (LSmean ratio: 1.22; 95% CI: 0.92-1.63). A statistically significant decrease in UC was seen only at 10 mg BID (LSmean ratio: 0.59; 95% CI: 0.44-0.78; p≤ 0.001).

The study procedures and drug were well tolerated. No serious adverse events were reported. There were no clinically significant abnormalities in the laboratory safety screens.

Indexing Terms

Keywords:

Fluticasone propionate
Oral bioavailability
24h urinary cortisol excretion
Capsules
Healthy subjects
Repeated oral dosing
Intravenous

Compound Number:

CCI 18781

Study No. C94-042

Abstract

The absolute bioavailability of inhaled fluticasone propionate (FP) administered via nebulisation (high strength nebules, 2mg/2mL) and its effect on 24h urinary cortisol excretion, were assessed in a single dose, randomised, double blind, double dummy, two period cross-over study.

Twelve healthy male volunteers (mean age 29.8y, range 22 to 47y; mean weight 79.5kg, range 52 to 93.9kg) received single doses of either 4000µg inhaled FP administered via nebulisation (2 x 2mg/2mL nebules) or 250µg intravenous FP. Blood samples for FP analysis were taken pre-dose and for up to 24h post-dose. Urine for cortisol analysis was collected for 24h pre- and post-dose.

The absolute bioavailability of inhaled FP administered via nebulisation from high strength nebules was 8.0% (geometric mean, 95% CI: 6.2, 10.5%).

The 24h urinary cortisol excretion decreased, compared to pre-treatment, on average by 47% (range 90% decrease to 3% increase) after 4000µg inhaled FP administered via nebulisation and by 41% (range 64% decrease to 4% increase) after 250µg intravenous FP. The ratio of adjusted mean 24h urinary cortisol excretion between inhaled and intravenous FP was 0.99 (95% CI: 0.68, 1.44; p=0.946).

The study procedures and drugs were well tolerated. No serious adverse events were reported. There were no clinically significant abnormalities in the pre- and post-study laboratory safety screens.

Indexing Terms:

Keywords:

Fluticasone Propionate
Nebules
Absolute Bioavailability
Urinary Cortisol

Compound Number

CCI 18781