CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-247

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-247 **Date of Submission: September 27**, 2005

Generic Name	Flunisolide HFA
Brand Name:	**Aerospan**
Formulations:	Inhalation Aerosol
Route of Administration:	Oral
Indication:	Asthma
Type of Submission:	Response to Approvable Letter/Labeling
Sponsor (s):	Forest Laboratories, Inc. Jersey City, NJ
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.

Background:

This a response to approvable letter dated July 26, 2005 for switching from CFC to HFA product. From the clinical pharmacology perspective this is mainly a labeling revision. The NDA was originally reviewed by the Office of Clinical Pharmacology and Biopharmaceutics on April 26, 2001. No new clinical pharmacology related information was submitted since.

Labeling Comments:

Based on the original review of the clinical pharmacology information and the discussion for the members of the review team and the sponsor, the following are the main comments to the clinical pharmacology sections of the label:

Mechanism of Action: Flunisolide hemihydrate has demonstrated marked anti-inflammatory in classical test systems. It is a corticosteroid that is several hundred times more potent than cortisol in animal anti-inflammatory assays, and several hundred times more potent than dexamethasone in anti-inflammatory effect as determined by the McKenzie skin blanching test. The clinical significance of these findings is unknown.

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_____ Trade Secret / Confidential (b4)

___X___ Draft Labeling (b4)

___X___ Draft Labeling (b5)

_____ Deliberative Process (b5)

Reviewer's Note:

As stated above, the above comments are made after discussion with other team review team members and the medical officer. It should be noted that other minor comments or changes may be made to the final label after discussion with the sponsor and at the time of approval.

RECOMMENDATION:

Please ensure the above labeling comments are incorporated into the label. Other minor comments and editorial changes may be made to the final labeling as necessary.

Reviewer

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Clinical Pharmacology and Biopharmaceutics 2

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Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader----------

cc: HFD-570, HFD-870 (Al Habet, Fadiran, and Malinowski), Drug file (Biopharm File, Central Document Room).

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/s/

Sayed Al-Habet
1/24/2006 11:52:18 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
1/24/2006 12:08:59 PM
BIOPHARMACEUTICS
I concur

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-247
Type of submission:	Answers to comments sent in approvable letter
Proprietary Drug Name:	Flunisolide HFA Inhaler System
Generic Name:	Flunisolide Hemihydrate
Indication:	Treatment of Asthma.
Dosage Form:	Solution.
Strength:	—— per puff
Route of Administration:	Oral Inhalation
Inhalation device:	Bespak® HFA Inhalation System (MDI)
Applicant:	Forest Laboratories, Inc.
Clinical Division:	DPADP (HFD-570)
Submission Dates:	December 7, 2001
Reviewer:	Sandra Suarez-Sharp, Ph.D.

BACKGROUND

Flunisolide HFA Inhaler System has been developed by Forest Laboratories, Inc. as a non-CFC alternative to Aerobid® (flunisolide) Inhaler System. Flunisolide HFA Inhaler System is a metered-dose aerosol system (MDI).

Flunisolide HFA Inhaler System is indicated for the maintenance treatment of asthma as a prophylactic therapy in adult and pediatric patients four years of age and older. The proposed starting dose in adults and adolescents is 2 inhalations twice daily —— total daily dose). In children (ages 4 to 11) the recommended starting dose is 1 —— inhalations twice daily (—— µg total daily dose).

In support of this application, the sponsor submitted on April 27, 2000 the results of clinical safety and efficacy studies as well as the results of five pharmacokinetic studies. The PK studies were conducted to assess dose-proportionality following inhalation of flunisolide HFA, to determine the *in vivo* lung deposition following inhalation of flunisolide HFA with and without spacer using pharmacoscintigraphy, and to compare the safety (measured as hydrocortisone suppression) and pharmacokinetics of flunisolide HFA and Aerobid® CFC.

From these studies, the lung deposition studies supported the inclusion of the Bespak® spacer since this item increased the central/peripheral deposition and decreased the oropharynx deposition. In addition, this preliminary study gave the sponsor an idea of the dose regimen for the HFA Inhaler System by roughly comparing the deposition following inhalation from this device and the one obtained from the already approved Aerobid® CFC inhaler System. However, because the clinical relevance of scintigraphy is unknown, the sponsor was discouraged to reflect any lung deposition information in the label.

The sponsor showed dose proportionality after single dose, but not after multiple dosing (dose-adjusted $AUC0_{\rightarrow last}$ for one puff is significantly smaller than those obtained

after two and four puffs). These conclusions were based on P values, therefore the following comment was sent to the sponsor regarding this issue on dose proportionality:

COMMENTS TO SPONSOR

- Please submit 90% confidence intervals for the point estimates (ratio of geometric means) for dose adjusted AUC and Cmax for studies ANC-PK1-98-06-000 and ANC-PK2-97-03-000. This information is needed if the sponsor wants to claim in the label dose proportionality of the drug using this inhalation system.

PRESENT SUBMISSION

On December 7, 2001 the sponsor submitted a response of the deficiencies shown in the approvable letter sent by the Agency on May 7, 2001. The response to the above CPB question is as follows:

The newly calculated 90% confidence intervals for Cmax and AUC contain point 1 (100% in ratio) in all cases when a p-value of greater than 0.05 was reported. Both statistical approaches (90% confidence intervals and p-values) are in agreement with each other. Therefore, the same conclusions may be drawn based upon the previously reported p-values and the newly calculated 90% confidence intervals for the assessment of dose proportionality of Cmax and AUC in the dose range of 85 to 340 mcg of Flunisolide after single and multiple doses.

Thus, the following statement, which is made on pages 2 and 3 of the draft package insert with respect to dose proportionality, is supported by the newly calculated 90% confidence intervals as well as the previously reported p-values:

"Over the dose range of 85 mcg to 340 mcg of Flunisolide HFA Inhaler System, values for Cmax increase proportionately with dose after single as well as multiple dose administration."

REVIEWER'S REMARKS

This reviewer has checked the 90% confidence intervals calculated by the sponsor and agrees with the statement that over the dose range of 85 mcg to 340 mcg of Flunisolide HFA Inhaler System, values for Cmax increase proportionately with dose after single as well as multiple dose administration. However, this statement does not hold true for the AUC since the majority of 90% confidence intervals do not contain point 1 (100% in ratio). Despite of this, the above statement that claims dose proportionality based on Cmax is true and will be accepted in the label as such.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed answers to comments sent by sponsor on December 7, 2001 for NDA 21-247. The claim in the label in terms of dose proportionality is acceptable.

Reviewer

_____

Sandra Suarez-Sharp, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Emmanuel Fadiran, Ph.D., Team leader _____

cc

NDA 21-247/N-000:	Division File
HFD-870:	Malinowski, Hunt
HFD-570:	Fadiran, Starke, Jafari, Suarez-Sharp
CDR:	Barbara Murphy

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/s/

Sandra Suarez
6/3/02 02:34:21 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
6/5/02 03:10:55 PM
BIOPHARMACEUTICS
I concur

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-247
Proprietary Drug Name:	Flunisolide HFA Inhaler System
Generic Name:	Flunisolide Hemihydrate
Indication:	Treatment of Asthma.
Dosage Form:	Solution.
Strength:	— µg per puff
Route of Administration:	Oral Inhalation
Inhalation device:	Bespak® HFA Inhalation System (MDI)
Dosage and administration:	**Adults (age 12 and older):** The recommended starting dose is — total daily dose). The maximum daily dose should not exceed — inhalations twice daily (680 µg total daily dose). **Children (age 4 to 11):** The recommended starting dose is 1 — inhalations twice daily — µg total daily dose). Higher doses in children have not been studied.
Applicant:	Forest Laboratories, Inc.
Clinical Division:	DPADP (HFD-570)
Submission Dates:	April 27, 2000; December 26, 2000
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader (acting):	Young-Moon Choi, Ph. D.

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Table 1. Performance of HFA MDI FLU with and without spacer and CFC MDI FLU with and without spacer

	HFA MDI N=12	HFA MDI with aerospacer N=12	CFC MDI N=4	CFC MDI with aerochamber N=4
Dose in whole lung (%)	22.6±10.4	40.4±5.5	17±10.4	23.4±11
Dose in the central lung region (%)	6.6±3.7	11.6±2.4	5.1±3.3	6.1±2.9
Dose in the intermediate lung region (%)	8.3±3.9	15.2±2.1	5.9±3.8	8.5±3.9
Dose in the peripheral lung region (%)	7.7±3.5	13.6±3.3	6±3.5	8.8±4.5
Peripheral/central zone deposition ratio	1.3±0.4	1.2±0.4	1.4±0.4	1.4±0.4
Dose in the oropharynx (%)*	59.8±7.1	14.9±5.6	66.3±4.3	12.3±10
Dose remaining on the device (%)	14.2±4.5	40.7±5.4	16.4±7.2	63.7±2

*Includes activity in the esophagus, stomach an on the exhalation filter mouthpiece. Values represent mean ± SD.

Table 2. Mean (±SD) flunisolide and 6β-OH flunisolide pharmacokinetic parameters of one, two or four puffs (85 μg per puff) of flunisolide HFA for 4.5 days.

	FLUNISOLIDE				
PK Parameter	**1 Puff Flunisolide HFA Treatment A**	**2 Puffs Flunisolide HFA Treatment B**	**4 Puffs Flunisolide HFA Treatment C**	**p-value A vs. C**	**p-value B vs. C**
Cmax (ng/mL)					
Observed	0.43 ± 0.18	1.03 ± 0.39	2.06 ± 0.74		
Dose-adjusted	1.72 ± 0.70	2.06 ± 0.79		0.08	0.85
$AUC_{0\to last}$ (ng*hr/mL)					
Observed	0.37 ± 0.17	1.22 ± 0.61	2.52 ± 1.05		
Dose-adjusted	1.46 ± 0.69	2.44 ± 1.23		0.0002*	0.48
$AUC_{0\to\infty}$ (ng*hr/mL)					
Observed	0.59 ± 0.20	1.54 ± 0.59	2.90 ± 1.06		
Dose-adjusted	2.35 ± 0.78	3.09 ± 1.18		0.03*	0.54
		β-OH FLUNISOLIDE			
Cmax (ng/mL)					
Observed		0.37 ± 0.14	0.71 ± 0.23		
Dose-adjusted		0.75 ± 0.28			0.7811
$AUC_{0\to last}$ (ng*hr/mL)					
Observed		1.48 ± 0.66	3.43 ± 1.31		
Dose-adjusted		2.96 ± 1.32			0.2150

* significant difference ($p<0.05$)

The sponsor showed similar systemic bioavailability of flunisolide (evaluated in terms of Cmax and $AUC_{0\to12h}$) and similar hydrocortisone plasma and urine

concentrations after the administration of flunisolide with either the Flunisolide HFA Inhaler System (4 puffs, μg/puff) or with Aerobid® CFC System (4 puffs, 250 μg/puff) (Table 3 and 4).

The statistical test (t-test) used by the sponsor to show no statistically significant difference between treatments does not meet the requirements of the test. The assumption of equal correlation between any 2 observations across periods made by the sponsor appears not to be true as indicated by the Durbin-Watson D test. In addition, because the studies used to address this point were designed either as a single dose study or conducted using a parallel design in which the sample size was rather small, this reviewer is of the opinion that the results obtained from the clinical trials submitted be used to decide about similarity of these formulations in terms of safety.

Table 3. Mean (±SD) flunisolide and 6β-OH flunisolide pharmacokinetic parameters following single inhalation of four puffs of Aerobid CFC (250 μg/puff) and flunisolide HFA with Bespak spacer (85 μg/puff)

PK Parameter	Flunisolide CFC Treatment A	FLUNISOLIDE Flu HFA with Bespak spacer Treatment B	p-value A vs. B
Cmax (ng/mL)	2.53 ± 1.19	3.25 ± 2.66	0.22
$AUC_{0\to last}$ (ng*hr/mL)	4.41 ± 1.59	4.99 ± 4.2	0.57
$AUC_{0\to\infty}$ (ng*hr/mL)	5.12 ± 1.0	5.82 ± 4.27	0.94
Tmax (hr)	0.18 ± 0.16	0.09 ± 0.03	0.02*
T1/2 (hr)	1.56 ± 0.31	1.43 ± 0.23	0.19
A_{ex} (μg)	1.7 ± 0.89	1.98 ± 2.29	0.69
		6β-OH FLUNISOLIDE	
Cmax (ng/mL)	0.75 ± 0.16	0.28 ± 0.17	0.0001*
$AUC_{0\to last}$ (ng*hr/mL)	3.03 ± 0.77	1.12 ± 0.98	0.0001*
$AUC_{0\to\infty}$ (ng*hr/mL)	3.75 ± 0.83	2.3 ± 1.06	0.0016*
Tmax (hr)	1.23 ± 0.52	1.15± 0.53	0.43
A_{ex} (μg)**	50.50 ± 16.89	19.69 ± 13.82	0.0001*

* significant difference (p<0 05). **A_{ex} amount of hydrocortisone excreted in urine in 12 hr.

Table 4. Mean (±SD) hydrocortisone pharmacokinetic parameters following single inhalation of four puffs of Aerobid CFC (250 μg/puff) and flunisolide HFA with Bespak spacer (85 μg/puff)

PK Parameter	Flunisolide CFC Treatment A	HYDROCORTISONE Flu HFA with Bespak spacer Treatment B	p-value A vs. B
Cmax (ng/mL)	178.7 ± 38.3	177.01 ± 33.19	0.85
$AUC_{0\to 12h}$ (ng*hr/mL)	826.7 ± 259.8	770.27 ± 184.6	0.62
Tmax (hr)	1.14 ± 3.6	1.17 ± 2.55	0.96
A_{ex} (μg)**	14.32 ± 3.68	13.9± 7.2	0.84

**A_{ex} amount of hydrocortisone excreted in urine in 12 hr.

based on the superiority of Flunisolide HFA Inhaler System compared to the placebo treatment.

- Comparability of Flunisolide HFA Inhaler System and Aerobid (CFC flunisolide) would not be an approvability issue. Comparability would be taken into account for labeling of Flunisolide HFA Inhaler System.

Pharmacokinetic Studies

ANC-PK1-97-02-000: A two-way, crossover, single dose study in healthy, young male volunteers to compare the *in vivo* deposition and pharmacokinetic properties of flunisolide when delivered from the HFA formulation with and without a spacer.

ANC-PK1-98-06-000: A three-way crossover, single and multiple dose study in healthy young male and female volunteers to demonstrate dose-proportionality at three dose levels of flunisolide when administered via the Flunisolide HFA Inhaler System.

ANC-PK2-97-03-000: A parallel, single and multiple dose study in healthy, young male and female volunteers to assess the tolerability, safety and dose proportionality of the Flunisolide HFA Inhaler System.

ANC-PK1-97-04-000: A three-way crossover, single dose study in healthy young male volunteers to evaluate delivery devices of flunisolide HFA with and without spacer.

ANC-PK1-96-01-000: A four-way, crossover, single dose study in healthy, young male volunteers to compare the safety and pharmacokinetics of flunisolide HFA and Aerobid® CFC.

During drug development the sponsor used two different devices to conduct the pharmacokinetic studies (see Table below). Three of these studies (ANC-PK1-97-02-000, ANC-PK2-97-03-000 and ANC-PK1-97-04-000) were conducted using a different valve and actuator than that used in some clinical studies and PK study ANC-PK1-98-06-000. Study ANC-PK1-96-01-000 utilized HFA formulations delivered via the [redacted] spacer. The usage of the [redacted] spacer was discontinued due to low bioavailability of flunisolide after inhalation with this spacer.

Table 1. Flunisolide HFA formulation/devices used during HFA Inhaler System development

Forest drug product lot number	PK Study number	Valve	Spacer	Remarks
41778	ANC-PK1-96-01-000	Original valve	[redacted]	Not reviewed due to significance differences in formulation/device and low lung deposition/ low bioavailability.
P01170	ANC-PK1-98-06-000	Original valve	Bespak	To-be-marketed device/formulation used in clinical trials.
P00851	ANC-PK1-97-02-000 ANC-PK2-97-03-000 ANC-PK1-97-04-000	[redacted]	Bespak; [redacted]	Comparative in-vitro performance with the to-be-marketed formulation is needed.

2.1 INTRODUCTION

2.1.1 PHARMACOKINETICS

The pharmacokinetics of flunisolide presented below is a compilation of some data from previous studies conducted with flunisolide and the findings reported in this NDA.

Absorption: Flunisolide hemihydrate is rapidly absorbed when given as an oral inhalation. Mean values for the time to maximum concentration, Tmax, of flunisolide range from 0.09 to 0.17 hr after a single 340 μg dose of Flunisolide HFA Inhaler System. The corresponding mean values for the maximum concentration, Cmax, of flunisolide vary from 1.9 to 3.3 ng/mL. The oral bioavailability of flunisolide has been reported in the past as being less than 7%.

Distribution: Flunisolide is extensively distributed in the body, with mean values for apparent volume of distribution ranging from 170 to 350 L after a single 340 μg dose of Flunisolide HFA Inhaler System. The overall lung deposition of flunisolide (% of administered dose) is 40% after a single 340 μg dose of Flunisolide HFA Inhaler System.

Metabolism: Previous studies have shown that the flunisolide that is swallowed is converted rapidly and extensively to 6β-OH flunisolide to water-soluble conjugates during the first pass through the liver. The inhaled flunisolide absorbed through the bronchial tree is converted to the same metabolites. The conversion of flunisolide hemihydrate to 6β-OH flunisolide, which is the only circulating metabolite detected in man, is thought to occur via the cytochrome P450 enzyme system, particularly the enzyme CYP3A4. In this submission, maximum levels of 6β-OH flunisolide were 0.66 ng /ml after a single 340 μg dose of Flunisolide HFA Inhaler System, and 0.71 ng/ml after multiple doses of Flunisolide HFA Inhaler System.

Excretion: Previous studies have shown that the urinary excretion of flunisolide is low. Less than 1% of the administered dose of flunisolide is recovered in urine after inhalation. In this submission, the half-life values for 6β-OH flunisolide range from 3.1 to 5.1 hr after administration of Flunisolide HFA Inhaler System in the dose range of 170 μg to 340 μg.

Disposition and Elimination: Twice daily administration of flunisolide hemihydrate for up to 14 days did not result in appreciable accumulation of flunisolide. Flunisolide is rapidly cleared from the body, independent of route of administration or dose administered. After administration of 340 μg of Flunisolide HFA Inhaler System the elimination half-life ranges from 1.3 to 1.7 hr. Flunisolide is not detectable in plasma twelve hours post-dose. The mean oral clearance values, not adjusted for bioavailability, range from 83 to 167 L/hr after a single 340 μg dose of Flunisolide HFA Inhaler System.

Special Populations: There were no gender differences in the pharmacokinetic of flunisolide after single and multiple dose administration of the Flunisolide HFA Inhaler System. Formal pharmacokinetic studies using flunisolide were not carried out in any

other special populations.

Pharmacokinetic/Pharmacodynamic Correlation. No studies have been conducted.

2.1.2 CHEMISTRY OVERVIEW

Chemical name: Flunisolide hemihydrate, the active component of Flunisolide HFA Inhaler System, is an anti-inflammatory steroid having the chemical name 6α-Fluoro-11β, 16α, 17, 21 -tetrahydroxylpregna-1, 4-diene-3, 20-alione cyclic-16, 17-acetal with acetone, hemihydrate.

Structural formula:

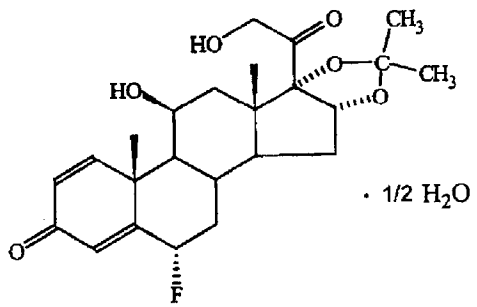

Figure 1. Structural formula of Flunisolide Hemihydrate.

Molecular formula: $C_{24}H_{31}0_6F.1/2H_20$

Molecular weight: 443.51

Solubility: It is soluble in acetone, [redacted] and practically insoluble in water.

2.1.3 FORMULATION AND INHALATION DEVICE

Flunisolide HFA Inhaler System is delivered in a metered-dose aerosol system containing a 0.24% w/w solution of flunisolide hemihydrate in [redacted] thanol and 1,1,1,2-Tetrafluoroethane (HFA 134a) for oral use only. Each activation delivers approximately 85 μg of flunisolide hemihydrate (equivalent to 83 μg of flunisolide) to the patient. One canister of Flunisolide HFA Inhaler System is designed to deliver 120 metered inhalations.

Flunisolide HFA is a solution formulation that does not contain chlorofluorocarbons (CFCs). The solution formulation in conjunction with a built-in spacer delivers an [redacted] size. The average particle size of flunisolide hemihydrate in the new formulation is [redacted] microns) than the CFC flunisolide hemihydrate suspension formulation ([redacted] s).

2.1.4 INDICATION (as per proposed label)

Flunisolide HFA Inhaler System is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients four years of age and older. Flunisolide HFA Inhaler System is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of those patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

2.1.5 DOSAGE AND ADMINISTRATION (as per propose label)

Adults (age 12 and older): The recommended starting dose is 2 inhalations twice daily (340 μg total daily dose). The maximum daily dose should not exceed 4 inhalations twice daily (680 μg total daily dose).

Children (age 4 to 11): The recommended starting dose is 1 — inhalations twice daily —or 340 μg total daily dose). Higher doses in children have not been studied.

Note: In all patients it is desirable to titrate to the lowest effective dose once asthma stability is achieved. The recommended total daily dose of Flunisolide HFA Inhaler System is one-third that of Flunisolide CFC Inhaler System.

3. SAFETY AND EFFICACY

Dr. Birenbamum (medical reviewer) has included in her review the following statements about the safety and efficacy findings in this NDA:

1. The results from the short-term study conducted in adults and adolescents support the efficacy and safety of 170 μg BID and 340 μg BID doses of HFA flunisolide. The long-term study demonstrated a 1 year HFA flunisolide safety profile consistent with this class of medication, without a clear signal for loss of efficacy, for mild to moderate asthma in adults and adolescent patients ≥12 years of age.
2. The short-term study conducted in children 6-11 years provides some evidence of efficacy and supports safety for 85μg bid HFA and 170μg bid doses of HFA flunisolide for the treatment of mild-moderate asthma, it provides no clear evidence of efficacy, but supports safety, in patients age 4-5 years of age. Although efficacy was demonstrated in the primary endpoint in children 6-11 years of age, it was not adequately assessed in 4-5 year old. Efficacy was not well supported by secondary efficacy parameters in 4-11 year old patients for either HFA or CFC formulations. The results from the long-term study in children does not allow for adequate assessment of 2 specific safety concerns associated with inhaled glucocorticoids in children: HPA axis effects and growth. However, this flawed trial did demonstrate a 1- year HFA flunisolide safety profile otherwise consistent with this class of medication. The trial did not demonstrate a clear signal for loss of efficacy in 6-11 year old mild asthma patients, however, the higher rate of asthma exacerbations in the 4-5 year old patients, especially during the first 8 weeks of the study, requires further evaluation. For more details about safety and efficacy findings please refer to Dr. Debra Birenbaum's review.

The present review has been focused in the following issues.

4. QUESTION BASED REVIEW

Q1. What is the effect of the Bespak spacer on the systemic exposure and lung deposition of flunisolide (FLU)? How does the flunisolide lung deposition following administration of Flu using the HFA System compare to that obtained using the CFC Inhaler System?

The sponsor conducted a pharmacoscintigraphic Study of ^{99m}Tc Labeled Flunisolide (Study ANC-PK1-97-02-000) to compare the in vivo deposition and pharmacokinetic properties of flunisolide after single dose administration of the flunisolide HFA formulation, delivered with or without the Bespak spacer.

Bespak spacer increased the overall lung deposition of flunisolide (22.6% of the total dose in the whole lung without a spacer versus 40.4% with the Bespak spacer, Table 2, Figure 1). Furthermore, Bespak spacer increased the deposition of FLU in the peripheral lung region and reduced the deposition in the oropharynx (Figure 2).

Another objective of study ANC-PK1-97-02-000 was to compare the total and regional lung deposition of flunisolide following administration of HFA flunisolide formulation with or without a spacer device to that after administration of CFC flunisolide formulation with or without a spacer device. Table 2 shows the mean values for the performance of HFA MDI Flu with and without spacer and CFC MDI Flu with and without spacer. Likewise, Figures 1 and 2 show the individual values. It seems that the HFA Inhaler System is able to increase the dose of FLU delivered to the whole lung by increasing mainly the peripheral and central lung deposition compared to that after the administration of FLU CFC. However, due to the rather small sample size (n=4) used in the CFC arm a comparison between this arm and the HFA arm (n=12) may not be statistically valid. Therefore, the sponsor will be discouraged to reflect in the label a comparison between the HFA and the CFC formulation in terms of lung deposition.

Table 2. Performance of HFA MDI FLU with and without spacer and CFC MDI FLU with and without spacer

	HFA MDI N=12	**HFA MDI with aerospacer N=12**	**CFC MDI N=4**	**CFC MDI with aerochamber N=4**
Dose in whole lung (%)	22.6±10.4	40.4±5.5	17±10.4	23.4±11
Dose in the central lung region (%)	6.6±3.7	11.6±2.4	5.1±3.3	6.1±2.9
Dose in the intermediate lung region (%)	8.3±3.9	15.2±2.1	5.9±3.8	8.5±3.9
Dose in the peripheral lung region (%)	7.7±3.5	13.6±3.3	6±3.5	8.8±4.5
Peripheral/central zone deposition ratio	1.3±0.4	1.2±0.4	1.4±0.4	1.4±0.4
Dose in the oropharynx (%)*	59.8±7.1	14.9±5.6	66.3±4.3	12.3±10
Dose remaining on the device (%)	14.2±4.5	40.7±5.4	16.4±7.2	63.7±2

*Includes activity in the esophagus, stomach an on the exhalation filter mouthpiece. Values represent mean ± SD.

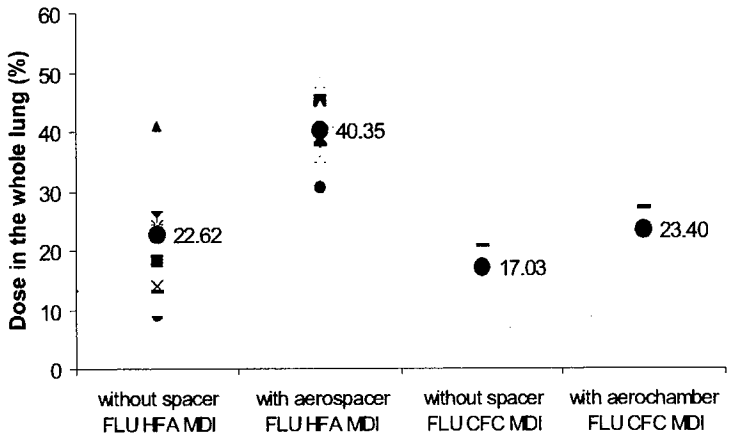

Figure 1. Percentage of dose in the whole lung following single inhalation of Flu-HFA with and without spacer and single inhalation of Flu CFC with and without spacer. Data levels represent the mean of the values.

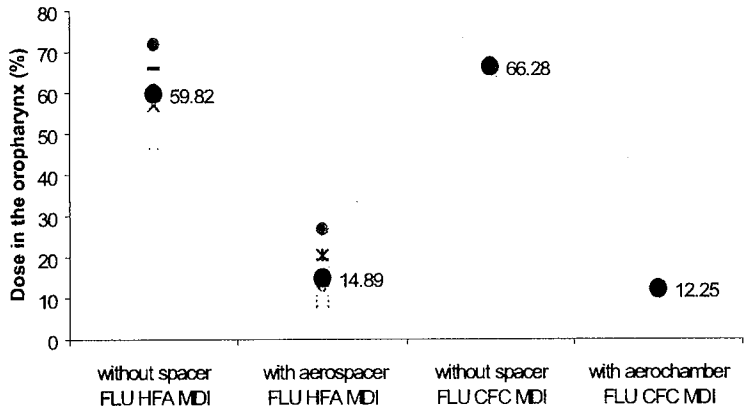

Figure 2. Percentage of dose in the oropharynx following single inhalation of Flu HFA with and without spacer and single inhalation of Flu CFC with and without spacer. Data levels represent the mean of the values.

CONCLUSION

Overall, it appears that the use of Bespak spacer offers the advantage of increased delivery of flunisolide to the lung and decreased oropharyngeal deposition of flunisolide over the CFC inhaler System. However, because this data was obtained using scintigraphy, the use of this information should be limited as an exploratory tool and not as a regulatory tool until the clinical significance of scintigraphy is well characterized.

Q2. What is the dose-systemic exposure relationship of flunisolide following inhalation using the HFA Inhaler System?

The sponsor conducted 2 different studies with the purpose of showing dose proportionality: Study ANC-PK1-98-06-000 and study ANC-PK2-97-03-000.

Study ANC-PK1-98-06-000 was a three-way, cross-over study in healthy volunteers to evaluate the dose proportionality of three dose levels of the Flunisolide HFA Inhaler System, incorporating the Bespak spacer, after single and multiple doses. After single dose administration of 1, 2 and 4 puffs (85μg/puff) of the flunisolide HFA formulation dose proportionality for flunisolide was apparently observed across the various doses for the pharmacokinetic parameters C_{max}, $AUC_{0\rightarrow last}$, and $AUC_{0\rightarrow inf}$. However, after multiple dosing no dose proportionality was observed for $AUC_{0\rightarrow last}$.

Table 3 shows that the dose-adjusted $AUC_{0\rightarrow last}$ for one puff is significantly smaller than those obtained after two and four puffs. This discrepancy may not be clinically relevant for adult patients since the dose recommended is two inhalations twice daily. However, because in children the recommended starting dose is 1—— inhalations twice daily, the clinical relevance of this lack of proportionality should be contrasted with the results from the clinical trials in this population.

Table 3. Mean (±SD) flunisolide and 6β-OH flunisolide pharmacokinetic parameters of one, two or four puffs (85 μg per puff) of flunisolide HFA for 4.5 days.

PK Parameter	1 Puff Flunisolide HFA Treatment A	2 Puffs Flunisolide HFA Treatment B	4 Puffs Flunisolide HFA Treatment C	p-value A vs. C	p-value B vs. C
FLUNISOLIDE					
Cmax (ng/mL)					
Observed	0.43 ± 0.18	1.03 ± 0.39	2.06 ± 0.74		
Dose-adjusted	1.72 ± 0.70	2.06 ± 0.79		0.08	0.85
$AUC_{0\rightarrow last}$ (ng*hr/mL)					
Observed	0.37 ± 0.17	1.22 ± 0.61	2.52 ± 1.05		
Dose-adjusted	1.46 ± 0.69	2.44 ± 1.23		0.0002*	0.48
$AUC_{0\rightarrow\infty}$ (ng*hr/mL)					
Observed	0.59 ± 0.20	1.54 ± 0.59	2.90 ± 1.06		
Dose-adjusted	2.35 ± 0.78	3.09 ± 1.18		0.03*	0.54
β-OH FLUNISOLIDE					
Cmax (ng/mL)					
Observed		0.37 ± 0.14	0.71 ± 0.23		
Dose-adjusted		0.75 ± 0.28			0.7811
$AUC_{0\rightarrow last}$ (ng*hr/mL)					
Observed		1.48 ± 0.66	3.43 ± 1.31		
Dose-adjusted		2.96 ± 1.32			0.2150

* significant difference ($p<0.05$)

Study ANC-PK2-97-03-000 was conducted to evaluate dose proportionality of two dose levels (2 and 4 puffs of 85μg/puff) of the flunisolide HFA formulation after

single and multiple doses in a parallel design. According to the sponsor, dose proportionality could be shown for flunisolide after single and multiple dosing based on the p values calculated using one-way ANOVA model (see Table 4). However, in this parallel design the sponsor included a rather small sample size in each arm, which somehow questions the validity of the study. Ninety percent (90%) confidence intervals (for C_{max} and AUC) calculated using the Fieller's theorem applied by this reviewer to the ratio of the means between HFA 2 puffs and HFA 4 puffs resulted in values which are out of the 80 to 125 goal post indicating the high variability on the data (see Table 5).

On the other hand, due to the low number of samples with quantifiable 6β-OH flunisolide concentrations after Treatment B (2 puffs), dose proportionality for this analyte could not be evaluated.

Table 4. Mean (±SD) flunisolide pharmacokinetic parameters following single and multiple inhalation (14 days) of two or four puffs (85 μg per puff) of flunisolide HFA

PK Parameter	2 Puffs Flunisolide HFA Treatment B N=12	4 Puffs Flunisolide HFA Treatment C N=12	p-value B vs. C
FLUNISOLIDE (single dose)			
Cmax (ng/mL)			
Observed	1.06 ± 0.42	2.51 ± 1.19	
Dose-adjusted	2.12 ± 0.84		0.46
$AUC_{0\to last}$ (ng*hr/mL)			
Observed	1.14 ± 0.40	2.78 ± 1.19	
Dose-adjusted	2.28 ± 0.80		0.34
$AUC_{0\to\infty}$ (ng*hr/mL)			
Observed	1.43 ± 0.38	3.14 ± 1.26	
Dose-adjusted	2.86 ± 0.76		0.72
Tmax (hr)	0.10 ± 0.04	0.10 ± 0.03	
FLUNISOLIDE (multiple dose)			
Cmax (ng/mL)			
Observed	1.48 ± 0.55	3.40 ± 1.21	
Dose-adjusted	2.99 ± 1.05		0.43
$AUC_{0\to last}$ (ng*hr/mL)			
Observed	2.06 ± 1.09	4.65 ± 1.49	
Dose-adjusted	4.11± 2.07		0.30
Tmax (hr)	0.13 ± 0.08	0.11 ± 0.04	

Table 5. Results of the Statistical Comparison (Fieller's Theorem) for flunisolide following single and multiple dose of 2 and 4 puff of Flunisolide HFA.

Pharmacokinetic Parameters	HFA 2 puffs vs. HFA 4 puffs	
	Point estimate	90% CI
	single dose	
Cmax (ng/mL)	0.84	0.58-1.2
AUCo→∞ (ng*hr/mL)	0.91	0.66-1.24
	multiple dose	
Cmax (ng/mL)	0.87	0.68-1.12
$AUC_{0\rightarrow last}$ (ng*hr/mL)	0.88	0.66-1.18

CONCLUSION

It seems that there is dose-proportionality between 2 and 4 puffs of flunisolide delivered by the flunisolide HFA Inhaler System after single and multiple dosing, but not between 1 and 2 and 1 and 4 puffs after multiple dosing. Therefore, the above information could not be used to make definitive conclusions about the existence of dose-proportionality since the information provided is inconsistent and relevant statistical information is missing.

Q3. How do the FLU systemic exposure and cortisol levels following administration of FLU using the HFA Inhaler System compare to those obtained using the CFC Inhaler System? Does the HFA with Bespak spacer compare to the actuator device/formulation?

Comparative FLU systemic exposure and hydrocortisone levels were evaluated in two different studies: study ANC-PK1-97-04-000 and study ANC-PK2-97-03-000. Study ANC-PK1-97-04-000 served also as a bridging study between the to-be-marketed formulation and formulation/devices used during development.

Study ANC-PK1-97-04-000 was conducted as a randomized, three-way crossover study in healthy volunteers to evaluate the ability of delivery devices of flunisolide with Bespak spacer, actuator and the already approved CFC formulation. Similar systemic bioavailability of flunisolide values (as evaluated by Cmax and $AUC_{0\rightarrow 12h}$) were observed after the administration of flunisolide with the Flunisolide HFA Inhaler System (340 μg) and with Aerobid® CFC (1000 μg) (Table 6, Figure 3).

The effects on endogenous hydrocortisone synthesis (measured as 12hr urine cortisol and 12hr plasma levels) were similar after single doses of Aerobid® CFC and the Flunisolide HFA Inhaler System, both formulations delivered as 4 puffs of 250 μg/puff and 85 μg/puff, respectively, suggesting again, similar FLU bioavailability (Table 7, Figure 4). However, the statistical test (t-test) used by the sponsor to show no statistically significant difference between treatments does not meet the requirements of the test. The assumption of equal correlation between any 2 observations across periods made by the sponsor appears not to be true as indicated by the Durbin-Watson D test.

Table 6. Mean (±SD) flunisolide and 6β-OH flunisolide pharmacokinetic parameters following single inhalation of four puffs of Aerobid CFC (250 μg/puff), flunisolide HFA with Bespak spacer (85 μg/puff) and Flu HFA with ——— actuator

PK Parameter	Flunisolide CFC Treatment A	Flu HFA with Bespak spacer Treatment B	Flu HFA Mark 6A Treatment C	p-value A vs. B	p-value C vs. A
		FLUNISOLIDE			
Cmax (ng/mL)	2.53 ± 1.19	3.25 ± 2.66	2.02 ± 1.03	0.22	0.12
$AUC_{0\to last}$ (ng*hr/mL)	4.41 ± 1.59	4.99 ± 4.2	3.46 ± 1.60	0.57	0.04*
$AUC_{0\to\infty}$ (ng*hr/mL)	5.12 ± 1.0	5.82 ± 4.27	4.15 ± 1.35	0.94	0.12
Tmax (hr)	0.18 ± 0.16	0.09 ± 0.03	0.17 ± 0.16	0.02*	0.65
T1/2 (hr)	1.56 ± 0.31	1.43 ± 0.23	1.93 ± 0.36	0.19	0.0008*
A_{ex} (μg)	1.7 ± 0.89	1.98 ± 2.29	1.29 ± 0.85	0.69	0.58
		6β-OH FLUNISOLIDE			
Cmax (ng/mL)	0.75 ± 0.16	0.28 ± 0.17	0.36 ± 0.08	0.0001*	0.0001*
$AUC_{0\to last}$ (ng*hr/mL)	3.03 ± 0.77	1.12 ± 0.98	1.38 ± 0.29	0.0001*	0.01*
$AUC_{0\to\infty}$ (ng*hr/mL)	3.75 ± 0.83	2.3 ± 1.06	2.18 ± 0.26	0.0016*	0.0003*
Tmax (hr)	1.23 ± 0.52	1.15± 0.53	1.27 ± 0.61	0.43	0.92
A_{ex} (μg)	50.50 ± 16.89	19.69 ± 13.82	24.21 ± 8.21	0.0001*	0.0003*

significant difference (p<0 05)

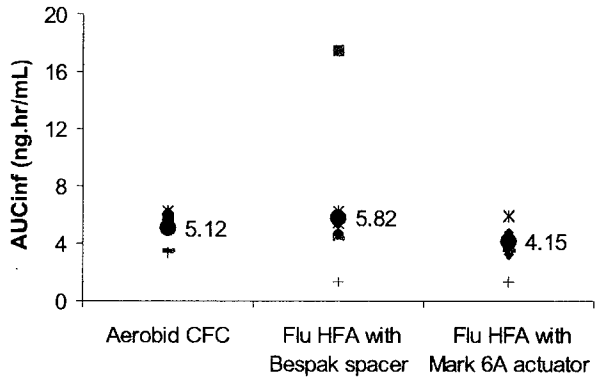

Figure 3. Individual flunisolide $AUC_{0\to\infty}$ values following single inhalation of four puffs of Aerobid CFC (250 μg/puff), flunisolide HFA with Bespak spacer (85 μg/puff) and Flu HFA with ——— actuator.

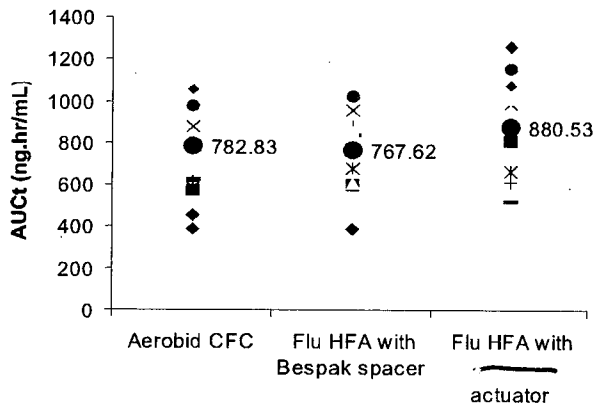

Figure 4. Individual hydrocortisone $AUC_{0\rightarrow12hr}$ values following single inhalation of four puffs of Aerobid CFC (250 µg/puff), flunisolide HFA with Bespak spacer (85 µg/puff) and Flu HFA with actuator.

Table 7. Mean (±SD) hydrocortisone pharmacokinetic parameters following single inhalation of four puffs of Aerobid CFC (250 µg/puff), flunisolide HFA with Bespak spacer (85 µg/puff) and Flu HFA with actuator

	HYDROCORTISONE				
PK Parameter	**Flunisolide CFC Treatment A**	**Flu HFA with Bespak spacer Treatment B**	**Flu HFA Treatment C**	**p-value A vs. B**	**p-value B vs. C**
Cmax (ng/mL)	178.7 ± 38.3	177.01 ± 33.19	172.13 ± 32.8	0.85	0.56
$AUC_{0\rightarrow12h}$ (ng*hr/mL)	826.7 ± 259.8	770.27 ± 184.6	880.6 ± 236.4	0.62	0.41
Tmax (hr)	1.14 ± 3.6	1.17 ± 2.55	0.54 ± 1.16	0.96	0.27
A_{ex} (µg)**	14.32 ± 3.68	13.9± 7.2	16.92 ± 6.6	0.84	0.44

**A_{ex} amount of hydrocortisone excreted in urine in 12 hr.

One objective of study ANC-PK1-97-03-000 was to compare the degree of cortisol suppression between the CFC formulation and the HFA formulation. According to the sponsor, no statistically significant differences in hydrocortisone pharmacokinetic parameters were found when comparing the Aerobid CFC (1000 µg) treatment with the flunisolide HFA 340 µg treatment either after single or multiple dose. However, ninety percent (90%) confidence intervals for the point estimates of the hydrocortisone C_{max} and AUC ratio for treatment A (CFC) vs treatment C (HFA 4 puffs) (Table 8) were out of 80-125 goal post. One can argue that the results on hydrocortisone levels are in favor of the HFA formulation since higher hydrocortisone levels mean less effect on the HPA axis and therefore, fewer side effects. However, because this study was conducted using a parallel design in which the number of samples was rather small, this reviewer is of the opinion to rely on the safety results obtained from the clinical trials. The sponsor will be discouraged to display hydrocortisone plasma concentrations in the label since the concentrations of these two compounds were determined using an inappropriate stock solution.

Table 8. Results of the Statistical Comparison (Fieller's Theorem) for hydrocortisone PK parameters following multiple administration of all the treatments.

Pharmacokinetic Parameter	CFC vs. HFA	
	Point estimate	90% CI
Cmax (ng/mL)	1.17	0.75-1.9
$AUC_{0\rightarrow12h}$ (ng*hr/mL)	1.43	0.74-3.48

CONCLUSION

It seems that the systemic bioavailability of flunisolide (as evaluated by C_{max} and $AUC_{0\rightarrow12h}$) and safety profiles were similar after the administration of flunisolide with either the Flunisolide HFA Inhaler System (340 μg) and with Aerobid® CFC (1000 μg). In addition, no statistical significant differences ($p > 0.05$) in hydrocortisone levels were observed between treatments. The statistical test (t-test) used by the sponsor to show no statistically significant difference between treatments does not meet the requirements of the test. The assumption of equal correlation between any 2 observations across periods made by the sponsor appears not to be true as indicated by the Durbin-Watson D test. In addition, because the studies used to address this point were designed either as a single dose study or conducted using a parallel design (study ANC-PK1-97-03-000) in which the sample size was rather small, this reviewer is of the opinion that the results obtained from the clinical trials submitted be used to decide about similarity of these formulations in terms of safety.

Q4. Is the dosage regimen proposed in children for Flu HFA Inhaler System supported by pharmacokinetic information?

The sponsor did not submit any PK information for the pediatric use of this formulation. Therefore, the appropriateness of the proposed regimen in children will be evaluated based on the results of the safety and efficacy trials conducted in this population. It may be necessary that the sponsor be requested to evaluate the steady state flunisolide plasma levels and 24hr urine cortisol in children as a phase four commitment.

5. GENERAL COMMENTS

- Because the clinical relevance of scintigraphy is unknown, the sponsor should be discouraged to reflect any quantitative (percentages) lung deposition information in the label. The use of Scintigraphy should be limited as an exploratory tool and not as a regulatory tool until its clinical significance is well characterized.
- Due to the rather small sample size used in the CFC arm in study ANC-PK1-97-02-000, a comparison between this arm and the HFA arm in terms of lung deposition may not be statistically valid. Therefore, the sponsor will be discouraged to reflect in the label a comparison between the HFA and CFC formulations in terms of lung deposition.
- The sponsor was requested to submit a comparison of the in-vitro performance (particle size distribution, spray pattern, plume geometry) of the formulations used

with the ———————— and the to-be-marketed formulation as a support of the bridging study.

- The sponsor was requested to provide 90% confidence intervals applied to normalized $AUC_{0\rightarrow\infty}$ and Cmax geometric mean ratio (considering the higher dose as a reference) if claims in the label are to be made in terms of dose proportionality across the doses of FLU HFA used.
- The sponsor will be discouraged to display hydrocortisone plasma concentrations in the label since the concentrations of these two compounds were determined using an inappropriate stock solution.
- Study ANCPK1-97-04-000 resulted in no differences in FLU systemic exposure and hydrocortisone levels following inhalation of the CFC formulation (1000 μg) or the HFA formulation (340 μg). The statistical test (t-test) used by the sponsor to show no statistically significant difference between treatments does not meet the requirements of the test. The assumption of equal correlation between any 2 observations across periods made by the sponsor appears not to be true as indicated by the Durbin-Watson D test. In addition, because the studies used to address this point were designed either as a single dose study or conducted using a parallel design in which the sample size was rather small, this reviewer is of the opinion that the results obtained from the clinical trials submitted be used to decide about similarity of these formulations in terms of safety.
- The attached label does not reflect the final comments of the reviewers since further revision of this label is needed by the FDA.

6. COMMENTS TO SPONSOR

The following comments should be conveyed to the sponsor:

1. Please submit 90% confidence intervals for the point estimates (ratio of geometric means) for dose adjusted AUC and Cmax for studies ANC-PK1-98-06-000 and ANC-PK2-97-03-000. This information is needed if the sponsor wants to claim in the label dose proportionality of the drug using this inhalation system.
2. Please include outliers in the calculation of the standard curve and quality control accuracy and precision (inter- and intra-day) for flunisolide, its metabolite, and hydrocortisone for all the in study- and pre-study validation data submitted.
3. Please submit in vitro performance, such as particle size distribution, plume geometry and spray pattern of the following lots and the to-be-marketed formulation, if different: P00851 (Forest drug product lot number), CT-97-017 (3M drug product lot number).
4. It is recommended that the sponsor develop a more sensitive assay for determining plasma concentrations of flunisolide for future studies, since after the administration of one puff many points were below the limit of quantitation.

7. RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-247 submitted on April 27, 2000. The overall Human Pharmacokinetic Section is acceptable to OCPB. The sponsor needs to submit 90% confidence intervals (ratio of geometric means) of the dose

adjusted AUC and Cmax obtained from studies ANC-PK1-98-06-000 and ANC-PK2-97-03-000 if a claim in the label is made in terms of dose proportionality of the drug using this inhalation system.

In addition, the pharmacokinetic/statistical data presented are insufficient to draw a definitive conclusion regarding the existence of similar extent of systemic exposure of flunisolide delivered by the HFA Inhaler System or by the CFC Inhaler System. Because the studies used to address similar systemic exposure between Aerobid® CFC (1000 μg) and flunisolide HFA Inhaler System were designed either as a single dose study or conducted using a parallel design in which the sample size was rather small, this reviewer is of the opinion that the results obtained from the clinical trials submitted be used to evaluate the HFA versus CFC safety performance. Please forward the above comments (page 19) to the sponsor.

Reviewer

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Sandra Suarez-Sharp, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Young-Moon Choi, Ph.D., Acting Team leader _____

cc

NDA 21-247/N-000:	Division File
HFD-870:	Malinowski, Hunt
HFD-570:	Choi, Birenbaum, Barnes, Suarez-Sharp
CDR:	Barbara Murphy

"Pharmacoscintigraphic Study of ^{99m}Tc Labeled Flunisolide Following Inhalation From HFA Pressurized Metered Dose Inhalers"

Study ANC-PK1-97-02-000
Volumes: 22-23

OBJECTIVE

To compare the *in vivo* deposition and pharmacokinetic properties of flunisolide after single dose administration of the flunisolide HFA formulation, delivered with or without the Bespak spacer.

SUBJECTS

Fourteen (14) male subjects were entered into the study and twelve (12) subjects completed part I of the study. The average age of the subjects who completed the study was 32 ± 8 years (range: 22 - 43 years). Four subjects, who had completed part I of the study, also received Treatments C and D.

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a randomized, two-way crossover study in healthy, young male volunteers. Subjects received the following treatments in randomized order (doses are given as approximate values ex-mouthpiece):

Part I:

Treatment A: Single dose of four (4) puffs of 129 μg/puff of the Flunisolide HFA formulation without a spacer.

Treatment B: Single dose of four (4) puffs of 85 μg/puff of the Flunisolide HFA Inhaler System.

Four subjects, having completed Treatments A and B, received the following treatments in sequential order:

Part II:

Treatment C: Single dose of four (4) puffs of 250 μg/puff of Aerobid® CFC without a spacer.

Treatment D: Single dose of four (4) puffs of 100 μg/puff of Aerobid® CFC delivered with aerochamber®.

There was a 7-day washout between treatments in Part I and between Part I and Part II. There was a 2-day washout period between treatments in Part II.

FORMULATION

The following formulations and batch numbers where used in this study.

Table 1. Flunisolide formulation used in this study

Study Drug/Strength	Batch Number
Aerobid® CFC	96744, 960502
Aerochamber	60302, 60402
Flunisolide HFA (3M Pharmaceuticals, Inc.)	P00851
Bespak spacer (Bespak Inc.)	0958

PARTICLE SIZING

As the most important factor governing lung deposition of an inhaled aerosol is its particle size distribution (PSD), this parameter was measured *in vitro* before proceeding with the clinical study for the following quantities:

- Flunisolide from an MDI to which the radiolabel has not been added (designated 'Unlabelled' drug);
- Flunisolide from an MDI to which the radiolabel has been added (designated 'Labelled' drug);
- The ^{99m}Tc radiolabel.

In vitro tests to determine the size distribution of both drug and radiolabel in different particle size fractions were carried out using a High Precision Multi-Stage Liquid Impinger (HPMLI). The HPMLI comprised a sample [redacted] Measurements of PSD were made using the HPMLI operated at a flow rate of [redacted]

PHARMACOKINETIC MEASUREMENTS

Blood sampling

Blood samples were taken at 0.0 hr (pre-dose) and 5, 10, 20 and 30 min and 1, 2, 4, 6, 8 and 12 hr after administration of active drug. Plasma was analyzed for flunisolide and 6β-OH flunisolide.

Analytical Method

Flunisolide and 6β-OH flunisolide concentrations in human plasma were determined by LC/MS.

Sample Preparation and Bioassay

The analysis of flunisolide and 6β-OH flunisolide was a solid phase procedure using [redacted] of human plasma. [redacted] was the internal standard. The extract was

Scintigraphic imaging

Immediately following administration of the radiolabelled aerosol, scintigraphic images were recorded using a ——— as described below:

- Posterior view of the chest;
- Anterior view of the chest;
- Right lateral view of the oropharynx;
- Anterior and posterior abdominal views if necessary, ie. if activity had spread through the intestine, beyond the field of view in either of the chest images;
- Image to record any activity on items external to the body, as follows: MDI actuator and spacer (where applicable); Exhalation filter

DATA ANALYSIS

Pharmacokinetic Data Analysis

The major pharmacokinetic parameters such as Cmax, $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$ and T_{max} were derived using non-compartmental techniques.

Scintigraphic Data Analysis

The data from the study were analyzed in line with Pharmaceutical Profiles Standard Operating Procedure for 'Quality Control of Gamma Camera Data Analysis' using a custom written region of interest program. Numerical data were downloaded automatically from the ——— computer into a customized spreadsheet.

The counts in each named area were expressed as a percentage of the metered dose which was determined from the sum of the total body counts in addition to those deposited on the MDI actuator, the spacer where applicable and on the exhalation filter. The data were analyzed to obtain the following parameters:

- Percentage of the dose in the whole lung;
- Percentage of the dose in the central lung region;
- Percentage of the dose in the intermediate lung region;
- Percentage of the dose in the peripheral lung region;
- Peripheral zone/central zone deposition ratio (lung penetration index);
- Percentage of the dose deposited in the oropharynx (including activity in the esophagus, stomach and on the mouthpiece of the exhalation filter where appropriate);
- Percentage of the dose retained on the actuator and spacer (where appropriate);
- Percentage of the dose in exhaled air.

Statistical Analysis

The pharmacokinetic parameters Cmax, $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, T_{max}, T1/2, CI/F and Vdss/F following each treatment were compared by Student's paired t-test ——— . Only pharmacokinetic parameters for the two different HFA treatments were compared statistically. The Wilcoxon matched-pairs signed ranks test was used to determine whether differences between the deposition patterns for the HFA MDI with and without the Aerospacer were significant.

SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

RESULTS

Particle Sizing

The PSDs of 'unlabelled' drug, 'labelled' drug and radiolabel were comparable for the HFA MDI; mean fine particle fractions (FPFs) were [redacted] respectively. In addition, the fine particle dose (FPD) for the 'labelled' drug was similar to that of the 'unlabelled' drug ([redacted], respectively) (individual data not shown in here). According to the sponsor, the results demonstrate that the labelling process had not adversely affected the formulation and that the radiolabel would act as a valid marker for the drug.

Lung Deposition

The use of a spacer device in combination with the HFA formulation increased the overall lung deposition of flunisolide (22.6% of the total dose in the whole lung without a spacer versus 40.4% with the Bespak spacer, Table 2, Figure 1). Also, it seems that drug penetrated the lungs more deeply when administered with a spacer. The drug deposition into the peripheral lung regions after the administration of the HFA formulation with the Bespak spacer (13.6%) was higher compared to the HFA formulation without a spacer (7.7%). In addition, oropharyngeal deposition was reduced when using a spacing device (HFA formulation: 59.8% without spacer, 14.9% with the Bespak spacer, Figure 2).

The use of a spacer device in combination with the Aerobid® CFC increased the lung deposition of flunisolide (17.0% of the total dose in the whole lung with Aerobid® CFC alone versus 23.4% with Aerobid® CFC plus Aerochamber) (Table 2) but to a lesser extent when compared to the HFA treatments.

Reviewer's Remarks

The comparison between the CFC and HFA Inhaler Systems may not be appropriate in this case due to the small number of subjects used in the evaluation of lung deposition for the CFC formulation.

Table 2. Performance of HFA MDI Flu with and without spacer and CFC MDI Flu with and without spacer

	HFA MDI	HFA MDI with aerospacer	CFC MDI	CFC MDI with aerochamber
Dose in whole lung (%)	22.6±10.4	40.4±5.5	17±10.4	23.4±11
Dose in the central lung region (%)	6.6±3.7	11.6±2.4	5.1±3.3	6.1±2.9
Dose in the intermediate lung region (%)	8.3±3.9	15.2±2.1	5.9±3.8	8.5±3.9
Dose in the peripheral lung region (%)	7.7±3.5	13.6±3.3	6±3.5	8.8±4.5
Peripheral/central zone deposition ratio	1.3±0.4	1.2±0.4	1.4±0.4	1.4±0.4
Dose in the oropharynx (%)*	59.8±7.1	14.9±5.6	66.3±4.3	12.3±10
Dose remaining on the device (%)	14.2±4.5	40.7±5.4	16.4±7.2	63.7±2

* Includes activity in the esophagus, stomach an on the exhalation filter mouthpiece. Values represent mean and ± SD.

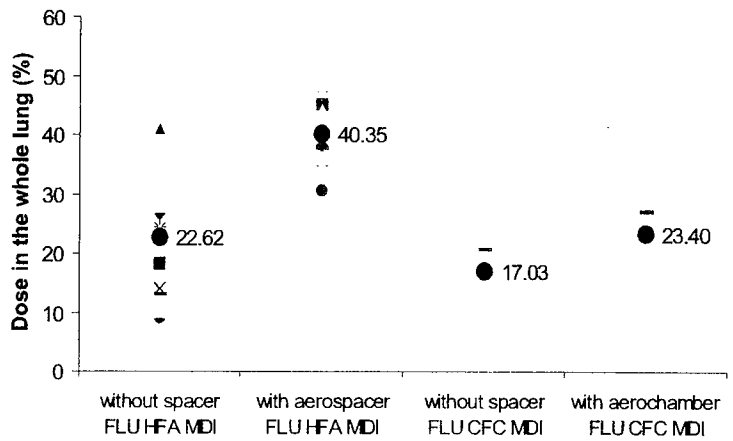

Figure 1. Percentage of dose in the whole lung following single inhalation of Flu HFA with and without spacer and single inhalation of Flu CFC with and without spacer. Data levels represent the mean of the values.

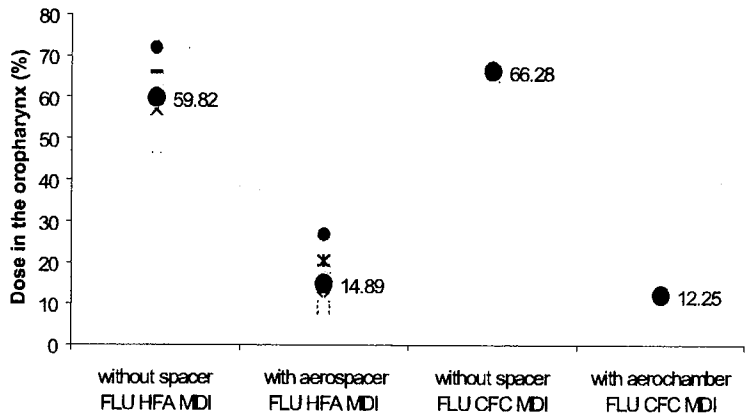

Figure 2. Percentage of dose in the oropharynx following single inhalation of Flu HFA with and without spacer and single inhalation of Flu CFC with and without spacer. Data levels represent the mean of the values.

In-study Validation of Bioanalytical method

Table 3. Assay performance (in-study validation) for flunisolide and 6β-OH flunisolide

	Flunisolide	6β-OH Flunisolide
Accuracy		
Inter-day Presicion		
Intra-day Presicion		

Pharmacokinetic Results

The 12-hr sample for Subject 12 after the administration of 4 puffs of the HFA formulation with the Bespak spacer showed high concentrations for both flunisolide and 6β-OH flunisolide. These values were not included in the pharmacokinetic analysis. Three earlier time points in the same subject (4 hr, 6 hr and 8 hr) had concentrations below the limit of quantitation. Also, for all other subjects the 12-hr blood sample had concentrations below the limit of quantitation.

Figures 3 shows the average flunisolide plasma concentrations after single administration of puffs of flu HFA with and without spacer. Figures 4 and 5 show the individual flunisolide Cmax and $AUC_{0\rightarrow t}$ following single inhalation of both treatments, respectively. The mean pharmacokinetic parameters for flunisolide and 6β-OH-

flunisolide after administration of both treatments are presented in Tables 4.

Pharmacokinetic parameters for flunisolide were generally similar after the administration of the HFA flunisolide formulation delivered with or without a spacer. Significant differences were noted for CI/F and T1/2 values (Table 4). According to the sponsor, the differences in the half-lives of elimination and in clearance may be attributed to the comparatively low number of time points above the limit of quantitation in the elimination phase. This might have resulted in difficulty in accurately estimating the T1/2 value.

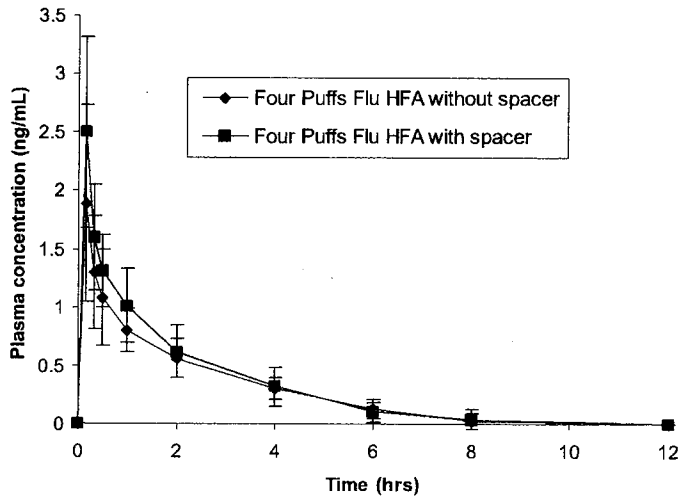

Figure 3. Mean flunisolide plasma concentration-time profiles following single inhalation of four puffs of flunisolide HFA with and without spacer. Bars represent ±SD.

Table 4. Mean (±SD) flunisolide pharmacokinetic parameters following single inhalation of four puffs of flunisolide HFA with and without Bespak spacer

PK Parameter	4 Puffs Flu HFA without spacer	4 Puffs Flu HFA with spacer	p-value
FLUNISOLIDE			
Cmax (ng/mL)	1.89 ± 0.84	2.5 ±0.82	0.088
$AUC_{0\rightarrow last}$ (ng*hr/mL)	3.05 ± 0.65	3.52 ±1.3	0.285
$AUC_{0\rightarrow\infty}$ (ng*hr/mL)	3.58 ± 0.71	3.95 ±1.32	0.409
Tmax (hr)	0.18 ±0.05	0.17 ±0	0.328
T1/2 (hr)	2.24 ±0.63	1.69 ±0.39	0.019*
CL/F (L/hr)	99 ±25	149 ±69	0.035*
Vdss (L)	318 ±110	350 ±126	0.5
β-OH FLUNISOLIDE			
Cmax (ng/mL)	0.29 ±0.08	0.21 ±0.07	0.01*
$AUC_{0\rightarrow last}$ (ng*hr/mL)	1.09 ±0.31	0.61 ±0.31	0.001*
Tmax (hr)	1.67 ±0.89	1 ±0.19	0.049*

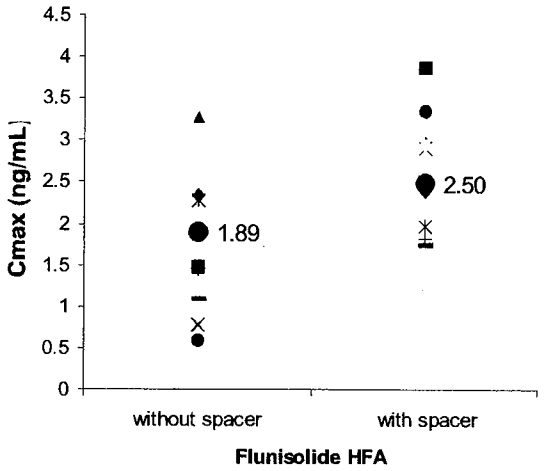

Figure 4. Individual flunisolide Cmax values following single inhalation of four puffs (85 μg per puff/with spacer, 129 μg per puff/without spacer) of flunisolide HFA.

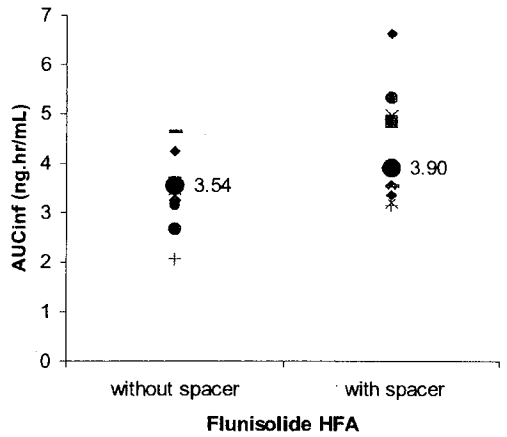

Figure 5. Individual flunisolide $AUC_{0\to\infty}$ values following single inhalation of four puffs (85 μg per puff/with spacer, 129 μg per puff/without spacer) of flunisolide HFA.

Overall, significant differences were noted for all calculated 6β-OH flunisolide PK values. It appears that after the administration of flunisolide without a spacer systemic levels of 6β-OH flunisolide formed were higher. The sponsor believes that this may be, in part, due to the greater oral deposition of flunisolide when delivered without a spacer.

SAFETY RESULTS

There were no serious adverse events reported or observed. No subject discontinued participation due to adverse events. A total of eight (8) adverse events were reported during this study. Six (6) of these adverse events were mild in severity and two (2) of these adverse events were moderate in severity.

Although abnormal laboratory values were observed in a total of three (3) subjects that met the criteria for clinical significance, none of these values were considered to be clinically important. Subject 001 had an elevated cholesterol after study completion, subject 002 had an elevated glucose before study treatment, and subject 008 had a decreased potassium following study treatment. No clinically important individual events or trends were noted in vital signs.

All of the pre- and post-dose ECGs were normal. All of the pre- and post-dose pulmonary function tests were normal. The mean FEV1 value (% of predicted value) at screening were 103.2 ± 7.5. At the end of the study the mean FEV1 value was 102.6 ± 7.1.

DISCUSSION

The objective of this study was to measure the total and regional lung deposition of flunisolide following administration of a an HFA flunisolide formulation with or without a spacer device or administration of a CFC flunisolide formulation with or without a spacer device. Due to the rather small sample size used in the CFC arm a comparison between this arm the HFA in terms of lung deposition may not be statistically valid. Therefore, this reviewer disregarded the study in which CFC is compared to HFA.

Based on the pharmacokinetic results systemic flunisolide delivery was similar following the administration of HFA flunisolide (4 puffs of 85 μ/puff) with the Bespak spacer compared to the administration of HFA flunisolide (4 puffs of 129 μg/puff) without a spacer.

The lung deposition of flunisolide was increased significantly when the HFA formulation was administered with the Bespak spacer compared to the administration of the HFA formulation without a spacer. In addition, oropharyngeal deposition of flunisolide was reduced with the use of a spacer device.

Although scintigraphy is a novel and promising tool for use in the development of inhaled drug products, the clinical relevance of results obtained using this methodology is currently unknown. The interpretation of the data should be done cautiously keeping in mind the following issues: (1) labeled drug may differ aerodynamically from unlabeled drug; (2) the label may leach off the drug; (3) the label may be attenuated due to body tissue; (4) the biospace relevant for clinical efficacy is seldom known and (5) there are few, if any, well documented linkages of pulmonary deposition to clinical outcomes. Therefore, scintigraphy should be limited to use as an exploratory and not a regulatory tool until its clinical meaning is well characterized.

CONCLUSION

Overall, it appears that the use of a spacer device offers the advantage of increased delivery of flunisolide to the lung and decreased oropharyngeal deposition of flunisolide. However, because this data was obtained using scintigraphy, the use of this information

should be limited as an exploratory and not as a regulatory tool until the clinical meaning of scintigraphy is well characterized.

COMMENTS

- Because the clinical relevance of scintigraphy is unknown, the sponsor should be discouraged to reflect a quantitative lung deposition information in the label. The use of Scintigraphy should be limited as an exploratory tool and not as a regulatory tool until its clinical meaning is well characterized.
- Due to the rather small sample size used in the CFC arm a comparison between this arm and the HFA arm in terms of lung deposition may not be valid. Therefore, this reviewer disregarded the study in which CFC is compared to HFA. The sponsor will be discouraged to reflect in the label a comparison between the HFA and the CFC formulation in terms of lung deposition.

"A Three-Way, Multiple Dose, Dose Proportionality Study of Aerobid® HFA Aerohaler in Healthy Volunteers"

Study ANC-PK1-98-06-000
Volumes: 36-44

OBJECTIVE

To evaluate the dose proportionality of three dose levels of the Flunisolide HFA Inhaler System, incorporating the Bespak spacer, after single and multiple doses.

SUBJECTS

Twenty-one (21) subjects (12 males and 9 females) were entered and all subjects completed the study. The average age of the subjects was 31±8 years (range: 19 - 51 years).

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a randomized, three-way crossover study in healthy volunteers. Subjects received the following treatments (doses are given as approximate values ex-mouthpiece):

Treatment A: One (1) puff of 85 μg/puff of the Flunisolide HFA Inhaler System BID, for 4 1/2 days.
Treatment B: Two (2) puffs of 85 μg/puff of the Flunisolide HFA Inhaler, BID for 4 1/2 days.
Treatment C: Four (4) puffs of 85 μg/puff of the Flunisolide HFA Inhaler, BID for 4 1/2 days.

FORMULATION

The following formulations and batch numbers where used in this study.

Table 1. Flunisolide formulation used in this study

Study Drug/Strength	Batch Number	Manufacture Date
Flunisolide HFA Inhaler System (3M Pharmaceuticals, Inc.)	971258	11/97
Bespak spacer (Bespak Inc)	2955	

PHARMACOKINETIC MEASUREMENTS

Blood sampling

Blood samples were taken at 0.0 hr (pre-dose) and 5, 10, 20 and 30 min and 1, 2, 4, 6, 8 and 12 hr after administration of active treatments on Day 1 (single dose) and Day 5 (multiple doses). Plasma was analyzed for flunisolide and 6β-OH flunisolide concentrations.

Analytical Method

Flunisolide and 6β-OH flunisolide concentrations in human plasma were determined by LC/MS.

Sample Preparation and Bioassay

The analysis of flunisolide and 6β-OH flunisolide was a solid phase procedure using — L of human plasma. ——— was the internal standard. The extract was

SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

DATA ANALYSIS

Pharmacokinetic Data Analysis

The major pharmacokinetic parameters such as Cmax, $AUC_{0\to t}$, $AUC_{0\to\infty}$ and T_{max} were derived using non-compartmental techniques. Dose proportionality was evaluated by adjusting the flunisolide PK parameters Cmax, $AUC_{0\to t}$ and $AUC_{0\to\infty}$ to the highest dose (4 puffs).

Statistical Analysis

An analysis of variance (ANOVA) model ——— was performed on the pharmacokinetic parameters using the GLM procedures. The ANOVA model included the variables sequence, subject (nested in sequence), period, and treatment. Comparisons between treatment C and treatment A as well as between treatment B and treatment C were carried out by the contrasts. Gender effects were analyzed by pooling the dose-adjusted data from all treatments and performing an analysis of variance (ANOVA) on the pharmacokinetic parameters using the GLM procedures of SAS.

Reviewer's Remarks

Study ANC-PK1-98-06-000 is a dose proportionally study using the to-be-marketed formulation. Ninety percent (90%) confidence intervals of the Cmax and AUC geometric means after single and multiple administration may be required if the sponsor wants to claim dose-proportionality of flunisolide using this device/formulation.

RESULTS

Analytical Method

Pre-Study Validation

Recovery:

[redacted]

Limit of Quantitation

Flunisolide and 6β-OH Flunisolide: The limit of quantitation for either analyte was 0.1 ng/mL.

Stability

QC samples at three concentrations underwent three (3) freeze-thaw cycles. The concentrations found after repeated freeze/thaw cycles were within ±20% of the theoretical values for all analytes. The two analytes in the final extract showed bench-top stability (%CV ranged from 1.90 to 4.83%) up to three (3) days. The two analytes showed stability in frozen plasma at - 30°C for at least seven (7) months. QC samples were within ±20% of theoretical values during the entire storage period.

Table 2. Pre-study validation information for flunisolide and 6β-OH flunisolide

	Flunisolide	**6β-OH flunisolide**
Linearity	Satisfactory: Standard curve range from [redacted]	Satisfactory: Standard curve range from [redacted]
Accuracy	Satisfactory: [redacted]	Satisfactory: [redacted]
Inter-day Presicion	Satisfactory: [redacted]	Satisfactory: [redacted]
Intra-day Presicion	Satisfactory: [redacted]	Satisfactory: [redacted]
Specificity	Satisfactory: Chromatograms submitted	Satisfactory: chromatograms submitted

In Study validation

Table 3. Assay performance (in-study validation) for flunisolide and 6β-OH flunisolide

	Flunisolide	6β-OH flunisolide
Accuracy	Satisfactory:	Satisfactory:
Inter-day Presicion	Satisfactory:	Satisfactory:
Intra-day Presicion	Satisfactory:	Satisfactory:

Pharmacokinetic Results

In the case of one subject (Subject 015) all but two flunisolide and two 6β-OH flunisolide plasma concentrations during all three-treatment periods were below the limit of quantitation. Therefore, data from this subject were not included in the calculation of average concentration values and no pharmacokinetic parameters were derived for this subject.

Figures 1 and 2 show the average flunisolide plasma concentrations following administration of all treatments (1, 2 and 4 puffs) on Day 1 (single dose) and on Day 5 (multiple doses), respectively. Figures 3 and 4 show the individual flunisolide Cmax and $AUC_{0\to\infty}$ following single inhalation of the three treatments, respectively. Figures 5 and 6 show the individual flunisolide Cmax and $AUC_{0\to\infty}$ following multiple inhalation after the three treatments, respectively. The mean pharmacokinetic parameters for flunisolide and 6β-OH flunisolide after single and multiple administration of the three treatments are presented in Table 4 and 5, respectively.

There was no accumulation of flunisolide in plasma after multiple dosing since all pre-dose flunisolide concentrations on Day 4 were below the limit of quantitation (data not shown). Quantifiable concentrations of 6β-OH flunisolide after administration of multiple doses of 1 puff of the flunisolide HFA formulation were too few to derive pharmacokinetic parameters. There was some accumulation of 6β-OH flunisolide after multiple doses of 2 and 4 puffs of the flunisolide HFA formulation.

Dose proportionality across doses following single and multiple administration was investigated by adjusting the parameters Cmax, $AUC_{0\to t}$ and $AUC_{0\to\infty}$ for flunisolide to the highest dose (4 puffs of the flunisolide HFA formulation). Following single administration, no statistically significant differences were observed for these parameters after dose-adjustment (Table 4).

After multiple dosing, no statistically significant differences were noted for flunisolide C_{max} across the three treatments. There were no AUC differences when comparing 2 puffs of the flunisolide HFA formulation with 4 puffs of the flunisolide HFA formulation. Significant differences were observed for $AUC_{0\to t}$ and $AUC_{0\to\infty}$ for

flunisolide when comparing 1 puff with 4 puffs of the flunisolide HFA formulation.

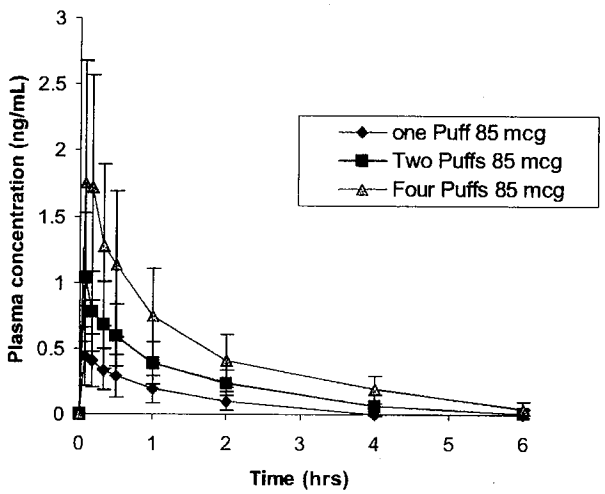

Figure 1. Mean flunisolide serum concentration-time profiles following single inhalation of one, two or four puffs (85 μg per puff) of flunisolide HFA. Bars represent ±SD.

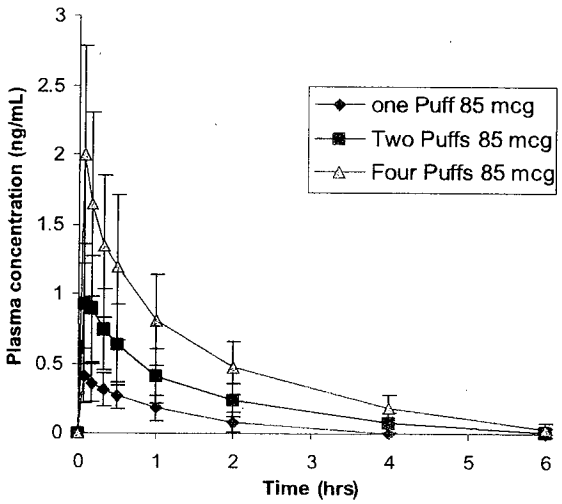

Figure 2. Mean flunisolide serum concentration-time profiles following inhalation of one, two or four puffs (85 μg per puff) of flunisolide HFA for 41/2 days. Bars represent ±SD.

In addition, significant differences were observed for T1/2 when comparing 1 with 4 puffs of the flunisolide HFA formulation. According to the sponsor, this effect on T1/2 and AUC may in part be due to the fact that after administration of 1 puff of the flunisolide HFA formulation the number of quantifiable concentrations of flunisolide in the elimination phase was limited.

Table 4. Mean (±SD) flunisolide and β-OH flunisolide pharmacokinetic parameters following single inhalation of one, two or four puffs (85 μg per puff) of flunisolide HFA.

PK Parameter	1 Puff Flunisolide HFA Treatment A	2 Puffs Flunisolide HFA Treatment B	4 Puffs Flunisolide HFA Treatment C	p-value A vs. C	p-value B vs. C
		FLUNISOLIDE			
Cmax (ng/mL)					
Observed	0.52 ± 0.16	1.06 ± 0.47	1.92 ± 0.92		
Dose-adjusted	2.08 ± 0.65	2.12 ± 0.94		0.39	0.51
$AUC_{0\to last}$ (ng*hr/mL)					
Observed	0.47 ± 0.18	1.16 ± 0.57	2.43 ± 1.19		
Dose-adjusted	1.90 ± 073	2.32 ± 1.15		0.25	0.63
$AUC_{0\to\infty}$ (ng*hr/mL)					
Observed	0.75 ± 0.15	1.48 ± 0.58	2.73 ± 1.21		
Dose-adjusted	2.99 ± 0.62	2.97 ± 1.15		0.34	0.44
Tmax (hr)	0.12 ± 0.06	0.12 ± 0.10	0.13 ± 0.06	0.49	0.47
T1/2 (hr)	1.07 ± 0.33	1.23 ± 0.43	1.31 ± 0.42	0.10	0.49
CL/F (L/hr)	119 ± 29	135 ± 59	167 ± 137	0.17	032
Vdss/F (L)	179 ± 44	216 ± 66	288 ± 159	0.01*	0.03*
		6β-OH FLUNISOLIDE			
Cmax (ng/mL)					
Observed		0.37 ± 0.14	0.66 ± 0.25		
Dose-adjusted		0.74 ± 0.29			0.5064
$AUC_{0\to last}$ (ng*hr/mL)					
Observed		1.50 ± 0.56	2.85 ± 1.13		
Dose-adjusted		3.01 ± 1.12			0.7933
$AUC_{0\to\infty}$ (ng*hr/mL)					
Observed		2.10 ± 0.41	3.61 ± 1.02		
Dose-adjusted		4.20 ± 0.81			0.0399*
Tmax (hr)		1.46 ± 0.62	1.39 ± 0.86		0.7933
T1/2 (hr)		2.79 ± 0.91	3.15 ± 1.13		0.3082

* significant difference (p<0 05)

Table 5. Mean (±SD) flunisolide and 6β-OH flunisolide pharmacokinetic parameters following inhalation of one, two or four puffs (85 μg per puff) of flunisolide HFA for 41/2 days.

PK Parameter	1 Puff Flunisolide HFA Treatment A	2 Puffs Flunisolide HFA Treatment B	4 Puffs Flunisolide HFA Treatment C	p-value A vs. C	p-value B vs. C
FLUNISOLIDE					
Cmax (ng/mL)					
Observed	0.43 ± 0.18	1.03 ± 0.39	2.06 ± 0.74		
Dose-adjusted	1.72 ± 0.70	2.06 ± 0.79		0.08	0.85
$AUC_{0\to last}$ (ng*hr/mL)					
Observed	0.37 ± 0.17	1.22 ± 0.61	2.52 ± 1.05		
Dose-adjusted	1.46 ± 0.69	2.44 ± 1.23		0.0002*	0.48
$AUC_{0\to\infty}$ (ng*hr/mL)					
Observed	0.59 ± 0.20	1.54 ± 0.59	2.90 ± 1.06		
Dose-adjusted	2.35 ± 0.78	3.09 ± 1.18		0.03*	0.54
Tmax (hr)	0.13 ± 0.08	0.12 ± 0.06	0.11 ± 0.04	0.29	0.38
T1/2 (hr)	0.95 ± 0.35	1.22 ± 0.39	1.34 ± 0.31	0.0001*	0.13
CL/F (L/hr)	164 ± 65	130 ± 58	137 ± 69	0.08	0.60
Vdss/F (L)	221 ± 69	230.2± 113	254.2± 103	0.23	0.30
β-OH FLUNISOLIDE					
Cmax (ng/mL)					
Observed		0.37 ± 0.14	0.71 ± 0.23		
Dose-adjusted		0.75 ± 0.28			0.7811
$AUC_{0\to last}$ (ng*hr/mL)					
Observed		1.48 ± 0.66	3.43 ± 1.31		
Dose-adjusted		2.96 ± 1.32			0.2150
Tmax (hr)		1.54 ± 0.82	1.38 ± 0.53		0.4783
T1/2 (hr)		3.09 + 1.03	3.13 ± 0.64		0.5913

* significant difference (p<0 05)

Table 6 shows the results of the statistical comparison of pharmacokinetic parameters of flunisolide on Day 1 and Day 5. Significant differences were noted for the parameters Cmax, $AUC_{0\to t}$, $AUC_{0\to\infty}$ and Vdss/F for flunisolide after 1 puff of the flunisolide HFA formulation. After administration of 2 puffs and 4 puffs of the flunisolide HFA formulation no statistical differences were noted for any of the pharmacokinetic parameters.

A gender analysis was performed for the pharmacokinetic parameters of flunisolide and 6β-OH flunisolide on Day 5. Table 7 displays the average values for flunisolide and its metabolite by gender and corresponding p-values. There were no gender differences for major pharmacokinetics parameters (Cmax, $AUC_{0\to t}$; $AUC_{0\to\infty}$) of flunisolide and 6β-OH flunisolide Day 5. The observed gender differences in Tmax for 6β-OH flunisolide may be considered chance occurrence.

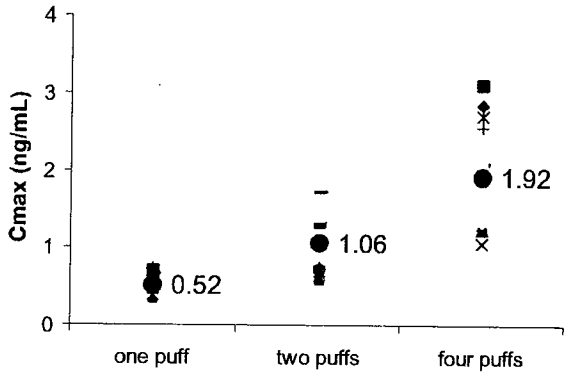

Figure 3. Individual flunisolide Cmax values following single inhalation of one, two or four puffs (85 μg per puff) of flunisolide HFA (not dose-adjusted).

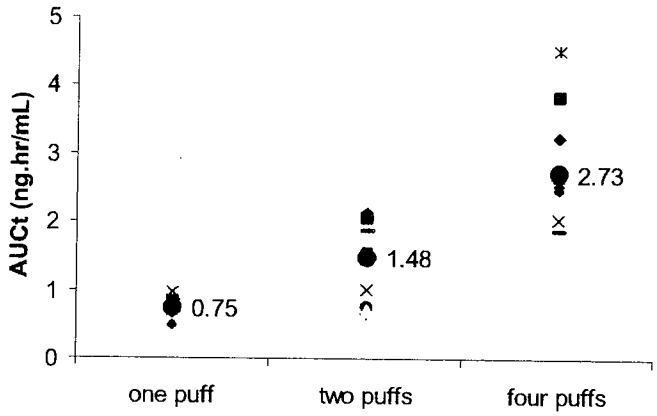

Figure 4. Individual flunisolide $AUC_{0\rightarrow\infty}$ values following single inhalation of one, two or four puffs (85 μg per puff) of flunisolide HFA (not dose-adjusted).

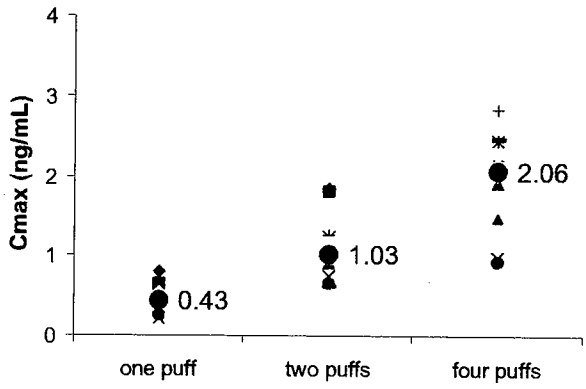

Figure 5. Individual flunisolide Cmax values following multiple inhalation of one, two or four puffs (85 µg per puff) of flunisolide HFA for 41/2 days (not dose-adjusted).

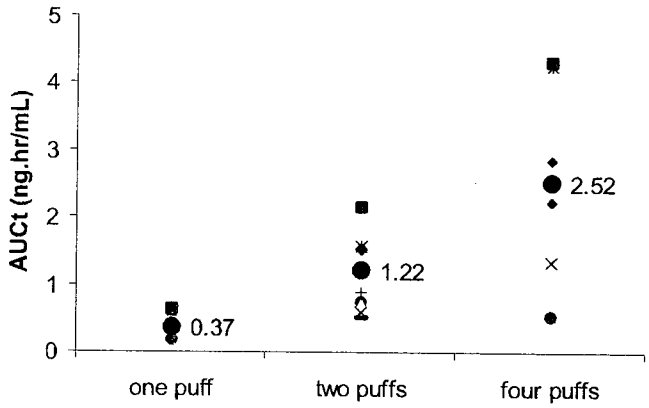

Figure 6. Individual flunisolide $AUC_{0\rightarrow t}$ values following multiple inhalation of one, two or four puffs (85 µg per puff) of flunisolide HFA for 41/2 days (not dose-adjusted).

Table 6. Results of the Statistical Comparison of Pharmacokinetic Parameters of Flunisolide on Day 1 and Day 5.

Pharmacokinetic Parameter	1 Puff Flunisolide HFA	2 Puffs Flunisolide HFA	4 Puffs Flunisolide HFA
Cmax (ng/mL)	0.01*	0.94	0.33
$AUC_{0\rightarrow last}$ (ng*hr/mL)	0.04*	0.79	0.57
AUCo→∞ (ng-hr/mL)	0.04*	0.31	0.41
T1/2 (hr)	0.32	0.71	0.19
Tmax (hr)	0.42	0.89	0.78
CL/F (L/hr)	0.05	0.38	0.38
Vdss/F (L)	0.01 *	0.99	0.31

* significant difference (p<0 05)

Table 7. Results of the Gender Analysis for Pharmacokinetic Parameters of flunisolide and 6β-OH flunisolide on Day 5.

PK Parameter	Male (n=12)	Female (n=8)	P value
	FLUNISOLIDE		
Cmax (ng/mL)	1.81 ± 0.71	2.38 ± 0.93	0.13
$AUC_{0\rightarrow last}$ (ng*hr/mL)	2.07 ± 0.93	2.46 ± 1.21	0.25
$AUC_{0\rightarrow\infty}$ (ng*hr/mL)	2.84 ± 0.85	2.95 ± 1.27	0.90
Tmax (hr)	0.13 ± 0.09	0.10 ± 0.04	0.28
T1/2 (hr)	1.29 ± 0.42	1.11 ± 0.36	0.30
Cl/F (L/hr)	133.22 ± 48.15	154.69 ± 130.85	0.55
Vdss/F (L)	234.97 ± 83.30	226.54 ± 147.87	0.95
	β-OH FLUNISOLIDE		
Cmax (ng/mL)	0.76 ± 0.24	0.69 ± 0.28	0.70
$AUC_{0\rightarrow last}$ (ng*hr/mL)	3.61 ± 1.02	2.58 ± 1.50	0.07
Tmax (hr)	1.67 ± 0.70	1.15 ± 0.55	0.01*
T1/2 (hr)	3.31 ± 0.84	2.74 ± 0.68	0.14

* significant difference (p<0 05)

Safety Results

There were no serious adverse events reported or observed. No subject discontinued participation due to adverse events. Seventeen (17) subjects reported a total of fifty-three (53) adverse events during this study. Thirty-seven (37) of these adverse events were mild, fourteen (14) were moderate and two (2) severe.

Although abnormal laboratory values were observed in a total of eight (8) subjects that met the criteria for clinical significance, none of these values were considered to be clinically important. No clinically important individual events or trends were noted in vital signs. All of the pre- and post-dose ECGs were normal.

DISCUSSION

A comment should be made regarding the concentration measurements of 6β-OH flunisolide obtained in this study. Average 6β-OH flunisolide concentrations in study ANC-PK1-98-06-000 were found to be approximately three times as high as after the same doses of flunisolide in the other three PK studies which were analyzed using a different stock solution of 6β-OH flunisolide. However, as noted in the other PK studies, within-study comparisons of 6β-OH flunisolide concentrations are still accurate since the same 6β-OH flunisolide stock solution was used within a study.

The purpose of this study was to evaluate the dose proportionality of three (3) dose levels of the flunisolide HFA formulation, delivered with the Bespak spacer, following single and multiple doses. After single dose administration of 1, 2 and 4 puffs of the flunisolide HFA formulation dose proportionality for flunisolide was observed across the various doses for the pharmacokinetic parameters Cmax, $AUC_{0\rightarrow last}$, and $AUC_{0\rightarrow inf}$. However, after multiple dosing no dose proportionality was observed for $AUC_{0\rightarrow last}$. Table 4 shows that the dose-adjusted $AUC_{0\rightarrow last}$ for one puff is significantly smaller than those obtained after two and four puffs. This discrepancy may not be clinically relevant for adult patients since the dose recommended is two inhalations twice daily. However, because in children the recommended starting dose is 1 — inhalations twice daily, the clinical relevance of this lack of proportionality should be contrasted with the results from the clinical trials in this population.

This reviewer believes that if the sponsor wants to claim the existence of dose proportionality for flunisolide, it will be necessary that the sponsor submits 90% confidence intervals of the ratio of the geometric means for Cmax and AUC.

CONCLUSION

It seems that there is dose-proportionality between 2 and 4 puffs of flunisolide delivered by the flunisolide HFA Inhaler System after single and multiple dosing, but not between 1 and 2 and 1 and 4 puffs after multiple dosing. Therefore, the above information could not be used to make definitive conclusions about the existence of dose-proportionality since the information provided is inconsistent and relevant statistical information is missing.

There were no gender differences for major pharmacokinetics parameters (Cmax, $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$) of flunisolide and 6β-OH flunisolide following multiple dosing of Flunisolide Inhaler System.

COMMENTS

- The sponsor will be requested to use a more sensitive assay for determining plasma concentrations of flunisolide, since after the administration of one puffs many points were below the limit of quantitation.

- The sponsor was requested to provide 90% confidence intervals for the ratio of the normalized $AUC_{0\rightarrow\infty}$ and Cmax geometric means (considering the higher dose as a reference) if claims in the label are to be made in terms of dose proportionality for flunisolide.

"A Parallel, Multiple Dose Study to Assess the Safety and Dose Proportionality of Flunisolide Following Inhalation from HFA pMDI in Healthy Volunteers."

Study ANC-PK2-97-03-000
Volumes: 24-30

OBJECTIVE

To assess the safety, tolerability and dose proportionality following inhalation of the flunisolide HFA formulation after single and multiple doses.

SUBJECTS

Thirty-three (33) subjects were entered into the study and thirty-one (31) subjects (10 males and 21 females) completed the study. The average age of the subjects was 30 ± 2 years (range: 18 - 51 years).

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a parallel, multiple dose study in healthy, young male and female volunteers. Subjects received the following treatments (doses are given as approximate values ex-mouthpiece):

Treatment A: Four (4) puffs of 250 μg/puff of Aerobid® BID, for 13.5 days
Treatment B: Two (2) puffs of 85 μg/puff of the Flunisolide HFA Inhaler, BID for 13.5 days.
Treatment C: Four (4) puffs of 85 μg/puff of the Flunisolide HFA Inhaler, BID for 13.5 days.

FORMULATION

The following formulations and batch numbers where used in this study.

Table 1. Flunisolide formulation used in this study

Study Drug/Strength	Batch Number	Manufacture Date	Expiration Date
Aerobid® CFC	960888		2/99
Flunisolide HFA Inhaler System (3M Pharmaceuticals, Inc.)	CT-97-017	4/97	
Bespak spacer (Bespak Inc.)	2955		

PHARMACOKINETIC MEASUREMENTS

Blood sampling

Blood samples were taken at 0.0 hr (pre-dose) and 5, 10, 20 and 30 min and 1, 2, 4, 6, 8 and 12 hr after administration of active treatments on Day 1 (single dose) and Day 14 (multiple doses). Plasma was analyzed for flunisolide, 6β-OH flunisolide and hydrocortisone concentrations.

Analytical Method

Flunisolide, 6β-OH flunisolide and hydrocortisone concentrations in human plasma were determined by LC/MS.

Sample Preparation and Bioassay

The analysis of flunisolide, 6β-OH flunisolide or hydrocortisone was a solid phase extraction procedure using [illegible] L of human plasma. Because [illegible] is an [illegible]

DATA ANALYSIS

Pharmacokinetic Analysis

The major pharmacokinetic parameters such as Cmax, $AUC_{0\to t}$, $AUC_{0\to\infty}$ and Tmax were derived after single and multiple dose administration. Dose proportionality was evaluated by adjusting the flunisolide dose proportional parameters Cmax, $AUC_{0\to t}$ and $AUC_{0\to\infty}$ to the highest dose (4 puffs).

Statistical Analysis

The one-way analysis of variance (ANOVA) model with effect of treatment was used to analyze the pharmacokinetic parameters Cmax, $AUC_{0\to t}$, $AUC_{0\to\infty}$, Tmax, CL/F and Vdss/F. The HFA 340 μg BID group was compared to the Aerobid® CFC 1000 μg BID group via a two-sample t-test and the mean square error from the ANOVA model was used as the error term in the t-test. All statistical tests were conducted at a two-sided 0.05 level.

Reviewer's Remarks

Study ANC-PK2-97-03-000 is a dose proportionally study for Flu HFA and a comparative study between the CFC formulation and HFA formulation of flunisolide. Because this study was conducted as a parallel design, this reviewer consulted the statistics departments (Dr. David Hoberman) to obtain advice about the validity of the statistical test used to analyze the data in this study. Dr. Hoberman recommended to use the Fieller's Theorem to be applied to the ratio of the means for Cmax and AUC for treatments A vs. C and B vs. C.

SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

RESULTS

Analytical Method Pre-Study Validation

Recovery:

Hydrocortisone: Recoveries were tested at two plasma concentrations. The values of % recovery were

Limit of Quantitation

Hydrocortisone: The limit of quantitation for either analyte was 5.0 ng/mL

Stability

QC samples at three concentrations underwent three (3) freeze-thaw cycles. The concentrations found after repeated freeze/thaw cycles were within ± 20% of the theoretical values for all analytes. The two analytes in the final extract showed bench-top stability (%CV ranged from 1.90 to 4.83%) up to three (3) days. The two analytes showed stability in frozen plasma at - 30°C for at least seven (7) months. QC samples were within ± 20% of theoretical values during the entire storage period.

Table 2. Assay performance (pre-study validation) for hydrocortisone

	Hydrocortisone
Linearity	Satisfactory:
Accuracy	Satisfactory:
Inter-day Presicion	Satisfactory:
Intra-day Presicion	Satisfactory:
Specificity	Satisfactory: Chromatograms submitted

In-study validation

Table 3. Assay performance (in-study validation) for flunisolide and 6β-OH flunisolide

	Flunisolide	**6β-OH flunisolide**	**Hydrocortisone**
Accuracy	Not reported	Not reported	Not reported
Inter-day Presicion	Satisfactory:	Satisfactory:	Satisfactory:
Intra-day Presicion	Satisfactory:	Satisfactory:	Satisfactory:

Pharmacokinetic Results

Figures 1 and 2 show the average flunisolide plasma concentrations of all treatments (2 and 4 puffs of flu HFA and 4 puffs of flu CFC) following single and multiple dosing, respectively. Figures 3 and 4 show the average hydrocortisone plasma concentrations after single and multiple (Day 14) administration of all treatments. Figures 5 and 6 show the individual flunisolide Cmax and $AUC_{0\rightarrow t}$ following multiple inhalation for all three treatments, respectively. Figures 7 and 8 show the individual hydrocortisone Cmax and $AUC_{0\rightarrow 12h}$ following multiple inhalation of all treatments, respectively.

The mean pharmacokinetic parameters for flunisolide after single and multiple administration of the three treatments are presented in Table 4. The mean pharmacokinetic parameters for 6β-OH flunisolide and hydrocortisone after single and multiple administration of the three treatments are presented in Table 5 and 6, respectively. Table 7 shows the results of the statistical comparison of the pharmacokinetic parameters of flunisolide and hydrocortisone using the Fieller's Theorem for all of the treatments.

Flunisolide Pharmacokinetics

Significant differences were observed for flunisolide $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow inf}$ on Day 1 (single dose) (Table 4) when comparing 4 puffs of 250 μg/puff of the Aerobid® CFC with 4 puffs of 85 μg/puff of the HFA flunisolide formulation delivered via the Bespak Spacer. Mean values were higher after administration of the Aerobid® CFC formulation than after the administration of the HFA formulation.

On Day 14 significant differences were observed only for flunisolide Tmax (higher values after administration of the Aerobid® CFC formulation than after the administration of the HFA formulation). The sponsor believes that this could be attributed in part to the oropharyngeal deposition of a higher amount of flunisolide after administration of Aerobid® CFC than after the HFA formulation. However, this reviewer believes that this may be due to a higher amount of flu HFA (in solution) readily available to be absorbed into the systemic circulation than that after administration of Flu CFC (in suspension).

Dose proportionality across the two HFA doses was investigated by adjusting the parameters Cmax, $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow inf}$ for flunisolide, on Day 1 and Cmax and $AUC_{0\rightarrow t}$ on Day 14 to the highest dose (4 puffs of flunisolide HFA). Dose proportionality was observed for all pharmacokinetic parameters for the HFA flunisolide treatments on Days 1 and 14.

A statistical comparison of the flunisolide pharmacokinetic parameters on Day 1 versus Day 14 (Table 7) revealed differences for T1/2 and Tmax after Treatment A, for Cmax after Treatment B, and for the comparison of $AUC_{0\rightarrow t}$ on Day 14 versus $AUC_{0\rightarrow inf}$ on Day 1.

Ninety percent (90%) confidence intervals of the point estimates of the flunisolide Cmax and AUC ratio for treatment A (CFC) vs. treatment C (HFA 4 puffs) and treatment B (HFA 2 puffs) vs. treatment C (HFA 4 puffs) (Table 7) were out of 80-125 goal post established for bioequivalence.

6β-OH Flunisolide Pharmacokinetics

After administration of 2 puffs of 85 μg/puff of the HFA flunisolide formulation delivered via the Bespak Spacer (Treatment B), no pharmacokinetic parameters were derived for 6β-OH flunisolide. The sponsor stated that this was due to the low number of samples with quantifiable levels of 6β-OH flunisolide in the elimination phase. On Days 1 and 14 (Table 5) significant differences in the exposure to 6β-OH flunisolide, based on Cmax and $AUC_{0\rightarrow t}$ were detected between the Aerobid CFC and the flunisolide HFA treatment. The sponsor stated that this could be attributed in part to the lower oropharyngeal deposition of flunisolide after administration of the flunisolide HFA formulation with the Bespak spacer.

A statistical comparison of the pharmacokinetic parameters on Day 1 versus Day 14 after Treatments A and C revealed differences for Tmax after Treatment A.

Hydrocortisone Pharmacokinetics

No statistically significant differences for hydrocortisone pharmacokinetic parameters were found when comparing the Aerobid CFC treatment with the flunisolide HFA 340 μg treatment either after single or multiple dose (Table 6). However, ninety percent (90%) confidence intervals of the point estimates of the hydrocortisone Cmax and AUC ratio for treatment A (CFC) vs. treatment C (HFA 4 puffs) and treatment B (HFA 2 puffs) vs. treatment C (HFA 4 puffs) (Table 7) were out of 80-125 goal post established for bioequivalence.

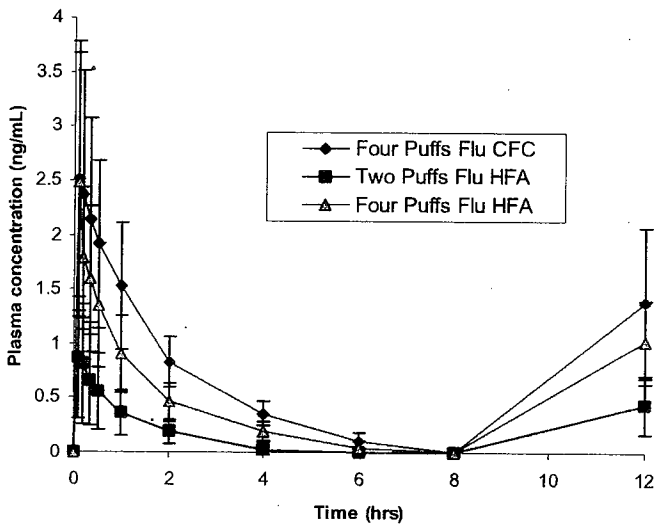

Figure 1. Mean flunisolide plasma concentration-time profiles following single inhalation of four puffs (250 μg per puff) of Aerobid® CFC and two or four puffs (85 μg per puff) of flunisolide HFA. Bars represent ±SD.

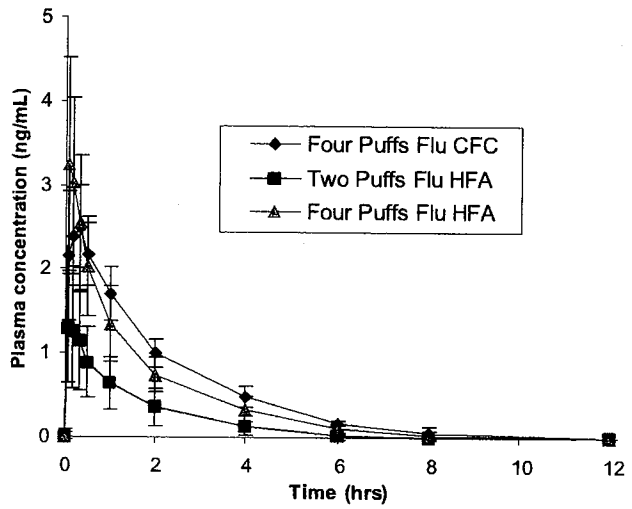

Figure 2. Mean flunisolide plasma concentration-time profiles following multiple inhalation of four puffs (250 μg per puff) of Aerobid® CFC and two or four puffs (85 μg per puff) of flunisolide HFA. Bars represent ±SD.

Table 4. Mean (±SD) flunisolide pharmacokinetic parameters following single and multiple inhalation of two or four puffs (85 μg per puff) of flunisolide HFA or four puffs (250 μg per puff) of Aerobid CFC

PK Parameter	4 Puffs Flunisolide CFC Treatment A N=8	2 Puffs Flunisolide HFA Treatment B N=12	4 Puffs Flunisolide HFA Treatment C N=12	p-value A vs. C	p-value B vs. C
FLUNISOLIDE (single dose)					
Cmax (ng/mL)					
Observed	2.62 ± 1.19	1.06 ± 0.42	2.51 ± 1.19	0.78	
Dose-adjusted		2.12 ± 0.84			0.46
$AUC_{0\to last}$ (ng*hr/mL)					
Observed	4.65 ± 1.61	1.14 ± 0.40	2.78 ± 1.19	0.01*	
Dose-adjusted		2.28 ± 0.80			0.34
$AUC_{0\to\infty}$ (ng*hr/mL)					
Observed	5.0 ± 1.61	1.43 ± 0.38	3.14 ± 1.26	0.01*	
Dose-adjusted		2.86 ± 0.76			0.72
Tmax (hr)	0.12 ± 0.09	0.10 ± 0.04	0.10 ± 0.03	0.29	
FLUNISOLIDE (multiple dose)					
Cmax (ng/mL)					
Observed	2.56 ± 0.56	1.48 ± 0.55	3.40 ± 1.21	0.14	
Dose-adjusted		2.99 ± 1.05			0.43
$AUC_{0\to last}$ (ng*hr/mL)					
Observed	5.68 ± 1.02	2.06 ± 1.09	4.65 ± 1.49	0.21	
Dose-adjusted		4.11± 2.07			0.30
Tmax (hr)	0.30 ± 0.13	0.13 ± 0.08	0.11 ± 0.04	0.0001*	

Table 5. Mean (±SD) βOH-flunisolide pharmacokinetic parameters following single and multiple inhalation of two or four puffs (85 μg per puff) of flunisolide HFA or four puffs (250 μg per puff) of Aerobid CFC

PK Parameter	4 Puffs Flunisolide CFC Treatment A (N=8)	4 Puffs Flunisolide HFA Treatment C (N=12)	p-value A vs. C
βOH-FLUNISOLIDE (single dose)			
Cmax (ng/mL)	0.86 ± 0.2	0.22 ± 0.05	0.0001*
$AUC_{0\to last}$ (ng*hr/mL)	3.14 ± 0.72	0.67 ± 0.38	0.0001*
$AUC_{0\to\infty}$ (ng*hr/mL)	3.68 ± 0.69	nc	nc
Tmax (hr)	1 ± 0.0.46	1.23 ± 0.68	0.49
βOH-FLUNISOLIDE (multiple dose)			
Cmax (ng/mL)	0.87 ± 0.25	0.29 ± 0.08	0.0001*
$AUC_{0\to last}$ (ng*hr/mL)	3.77 ± 1.04	1.07 ± 0.38	0.0001*
Tmax (hr)	1.5 ± 0.53	1.24 ± 0.71	0.38

Table 6. Mean (±SD) hydrocortisone pharmacokinetic parameters following single and multiple inhalation of two or four puffs (85 μg per puff) of flunisolide HFA and four puffs (250 μg per puff) of Aerobid CFC

PK Parameter	4 Puffs Flunisolide CFC Treatment A (N=8)	2 Puffs Flunisolide HFA Treatment B (N=11)	4 Puffs Flunisolide HFA Treatment C (N=12)	p-value A vs. C
HYDROCORTISONE (single dose)				
Cmax (ng/mL)	204.5 ± 59.4	271.6 ± 175.4	210 ± 106.66	0.96
$AUC_{0\to t}$ (ng*hr/mL)	605.7 ± 277.5	1194 ± 1022	787.5 ± 607.7	0.4
Tmax (hr)	0.13 ± 0.35	0.06 ± 0.15	0.10 ± 0.29	0.82
HYDROCORTISONE (multiple dose)				
Cmax (ng/mL)	167.1 ± 24.5	254.4 ± 152.2	196 ± 77.2	0.56
$AUC_{0\to t}$ (ng*hr/mL)	538 ± 106.2	1058 ± 718	773.5 ± 568.8	0.33
Tmax (hr)	0.03 ± 0.06	0.03 ± 0.10	0.07 ± 0.17	0.5

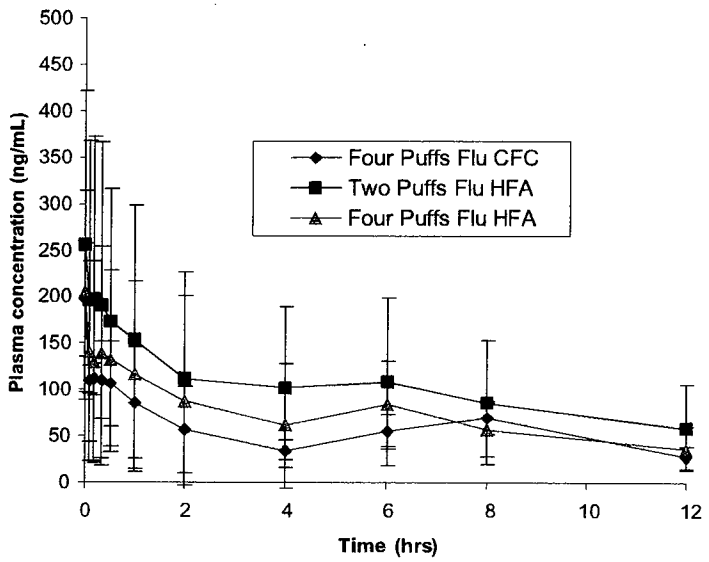

Figure 3. Mean hydrocortisone plasma concentration-time profiles following single inhalation of four puffs (250 μg per puff) of Aerobid® CFC and two or four puffs (85 μg per puff) of flunisolide HFA. Bars represent ±SD.

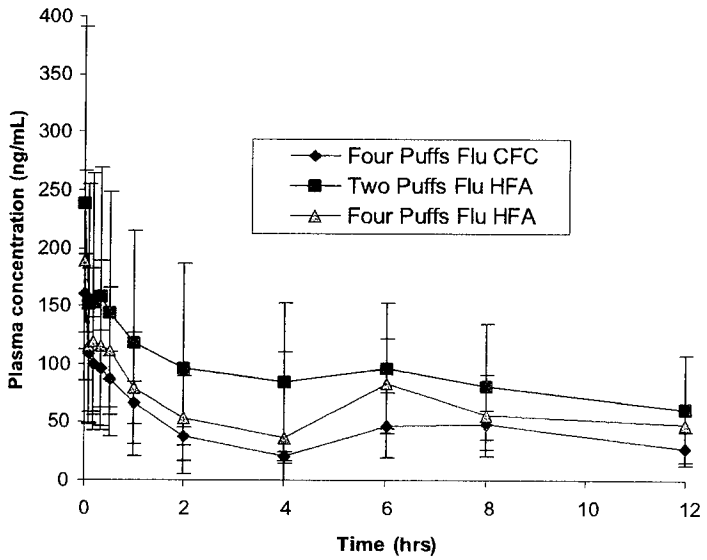

Figure 4. Mean hydrocortisone plasma concentration-time profiles following multiple inhalation of four puffs (250 μg per puff) of Aerobid® CFC and two or four puffs (85 μg per puff) of flunisolide HFA. Bars represent ±SD.

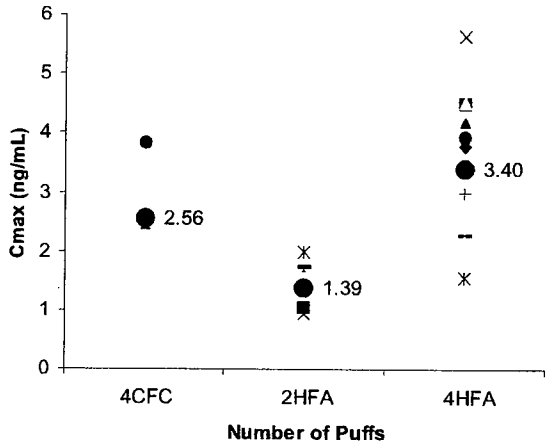

Figure 5. Individual flunisolide Cmax values following multiple inhalation of four puffs (250 μg per puff) of Aerobid® CFC and two or four puffs (85 μg per puff) of flunisolide HFA.

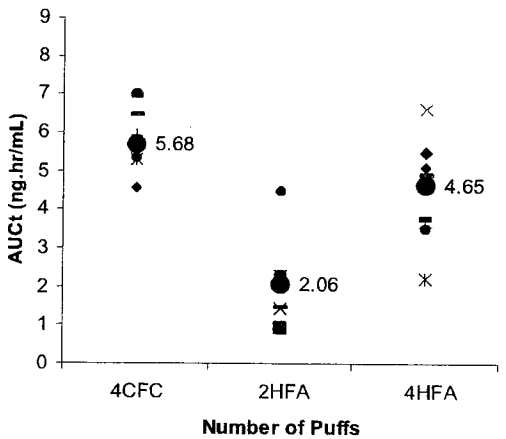

Figure 6. Individual flunisolide $AUC_{0\rightarrow t}$ following multiple inhalation of four puffs (250 μg per puff) of Aerobid® CFC and two or four puffs (85 μg per puff) of flunisolide HFA.

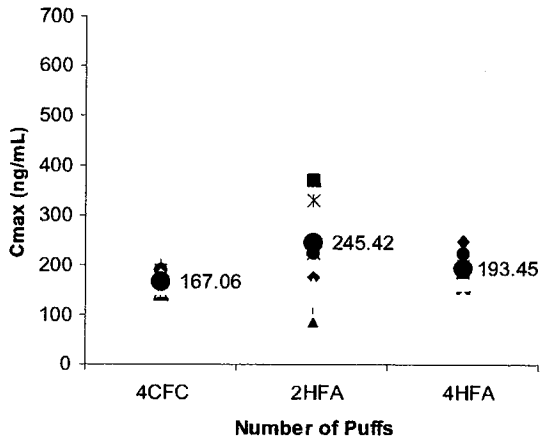

Figure 7. Individual hydrocortisone C_{max} values following multiple inhalation of four puffs (250 μg per puff) of Aerobid® CFC and two or four puffs (85 μg per puff) of flunisolide HFA.

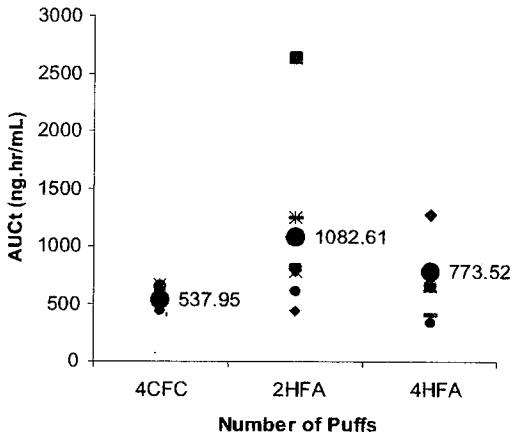

Figure 8. Individual hydrocortisone $AUC_{0\rightarrow t}$ values following multiple inhalation of four puffs (250 μg per puff) of Aerobid® CFC and two or four puffs (85 μg per puff) of flunisolide HFA.

Table 7. Results of the statistical comparison (Fieller's Theorem) for flunisolide and hydrocortisone following single and multiple dose for all the treatments.

Pharmacokinetic Parameter	A vs C		B vs C	
	Point estimate	90% CI	Point estimate	90% CI
		Flunisolide single dose		
Cmax (ng/mL)	0.95	0.69-1.32	0.84	0.58-1.2
$AUCo \rightarrow \infty$ (ng*hr/mL)	0.63	0.48-0.79	0.91	0.66-1.24
		Flunisolide multiple dose		
Cmax (ng/mL)	1.34	1.02-1.76	0.87	0.68-1.12
$AUC_{0 \rightarrow last}$ (ng*hr/mL)	0.82	0.63-1.04	0.88	0.66-1.18
		Hydrocortisone multiple dose		
Cmax (ng/mL)	1.17	0.75-1.9	1.3	0.91-1.92
$AUC_{0 \rightarrow 12h}$ (ng*hr/mL)	1.43	0.74-3.48	1.36	0.85-2.38

A=4 Puffs Flunisolide CFC; B=2 Puffs Flunisolide HFA; C=4 Puffs Flunisolide HFA. PK parameters used for 2 puffs were dose-normalized to the highest dose.

Safety Results

There were no serious adverse events reported in this study. No subject discontinued participation due to adverse events. A total of thirty-three (33) adverse events were reported by sixteen (16) subjects during this study. Nineteen (19) adverse events were mild in severity and fourteen (14) adverse events were moderate in severity. Fourteen (14) adverse events were reported during treatment with 4 puffs of 250 μg/puff of Aerobid® CFC. These included headache (3), nausea (3), confusion (2), coughing (2) delirium (1), dizziness (1) myalgia (1) and tinnitus (1). Twelve (12) adverse events were reported during treatment with 2 puffs of 85 μg/puff of the flunisolide HFA formulation delivered via the Bespak spacer. These included headache (7), heart disorder (1), herpes simplex (1), nausea (1), pharyngitis (1), somnolence (1). Seven (7) adverse events were experienced during treatment with 4 puffs of 85 μg/puff of the flunisolide HFA formulation delivered via the Bespak spacer. These included headache (5), coughing (1) and somnolence (1)

Although abnormal laboratory values were observed in a total often (10) subjects that met the criteria for clinical significance, none of these values were considered to be clinically important. All of these values were either elevated cholesterol or triglyceride levels at screening or at the end of study examination. No clinically important individual events or trends were noted in vital signs. All of the pre- and post-dose ECGs were normal.

All of the pre- and post-dose pulmonary function tests were normal. The mean FEV1 value at screening were 97.3 ± 14.0, 95.8 ± 10.6 and 97.4 ± 80 for Treatments A, B and C, respectively. At the end of the study the mean FEV1 values were 94.1 ± 15.6, 96.1 ± 9.3 and 97.3 ± 8.0.

DISCUSSION

One objective of this study was to evaluate dose proportionality of two (2) dose levels of the flunisolide HFA formulation after single and multiple doses in a parallel design. According to the sponsor, dose proportionality could be shown for flunisolide on Day 1 and 14 based on the p values calculated by the sponsor using one-way ANOVA model. However, 90% confidence intervals for the ratio of dose-normalized Cmax and AUC means between HFA 2 puffs and HFA 4 puffs resulted in values which are out of the 80 to 125 goal post indicating the high variability on the data. In this parallel design the sponsor included a rather small (inappropriate) sample size in each arm, which somehow questions the validity of the study. In study ANC-PK1-98-06-000 the sponsor conducted a three-way cross over study to show dose proportionality between 3 dose levels following single and multiple administration of flu using the HFA Inhaler System. Because a cross-over design is more appropriate than a parallel design and considering the inappropriate application of a parallel design in this study, this reviewer is of the opinion to disregard this study as to support dose-proportionality following inhalation of flu using the HFA Inhaler System. On the other hand, due to the low number of samples with quantifiable 6β-OH flunisolide concentrations after Treatment B, dose proportionality for this analyte could not be evaluated.

Another objective of this study was to compare the degree of hydrocortisone suppression between the CFC formulation and the HFA formulation. According to the sponsor, no statistically significant differences for hydrocortisone pharmacokinetic parameters were found when comparing the Aerobid CFC treatment with the flunisolide HFA 340 μg treatment either after single or multiple dose (Table 6). However, ninety percent (90%) confidence intervals of the point estimates of the hydrocortisone Cmax and AUC ratio for treatment A (CFC) vs treatment C (HFA 4 puffs) (Table 7) were out of 80-125 goal post. One can argue that the results on hydrocortisone levels are in favor of the HFA formulation since higher hydrocortisone levels mean less effect on the HPA axis and therefore, fewer side effects. However, because this study was conducted using a parallel design in which the number of sample was rather small, this sponsor is of the opinion to rely again on the safety results obtained from the clinical trials.

CONCLUSION

Dose proportionality could be shown by the sponsor for flunisolide after single and multiple dosing based on the p values calculated using one-way ANOVA model (see Table 4). Likewise, the sponsor showed similar systemic exposure following multiple administration of Flu CFC and Flu HFA. However, in this parallel design the sponsor included a rather small sample size in each arm, which somehow questions the validity of the study. Ninety percent (90%) confidence intervals (for C_{max} and AUC) calculated using the Fieller's theorem applied by this reviewer to the ratio of the means between HFA 2 puffs and HFA 4 puffs resulted in values which are out of the 80 to 125 goal post indicating the high variability on the data (see Table 5).

This study should be disregard in terms of showing dose-proportionality and one should rely on the results of the three-way cross over study (ANC-PK1-98-06-000) conducted by the sponsor to assess the existence of dose-proportionally of three dose levels of Flu administered using the HFA Inhaler System.

Since the statistical analysis as well as the sample size used by the sponsor in this parallel design are inadequate, this reviewer recommends that the results from the safety studies obtained from the clinical trials be used to evaluate the HFA versus the CFC safety performance.

COMMENTS

- The sponsor was requested to provide 90% confidence intervals for the ratio of the dose-normalized $AUC_{0\rightarrow\infty}$ and Cmax geometric means if claims in the label are to be made in terms of dose proportionally after inhalation of flunisolide using the HFA Inhaler System.
- Although 12 hours plasma hydrocortisone level may be acceptable, 24 hr plasma hydrocortisone levels are more recommended for assessing the degree of cortisol suppression.
- The sponsor will be discouraged to display hydrocortisone plasma concentrations in the label since the concentrations of these two compounds were determined using an inappropriate stock solution.

"An Open-Label, Three-Way Crossover, Single Dose Study to Compare the Pharmacokinetics of Flunisolide HFA with Aerobid® CFC Formulation in Healthy Young Male Volunteers"

Study ANC-PK1-97-04-000
Volumes: 34-36

OBJECTIVE

To evaluate the ability of delivery devices of flunisolide HFA, with or without spacer, to produce pharmacokinetic profiles of flunisolide comparable to those of the currently marketed Aerobid® CFC formulation.

SUBJECTS

Twelve (12) male subjects were entered into the study. Eleven (11) subjects completed the study. The average age of the subjects who completed the study was 24 ± 5 years (range: 18-35 years).

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a randomized, three-way crossover study in healthy volunteers. Subjects received the following treatments in randomized order (doses are given as approximate values ex-mouthpiece):

Treatment A: Single dose of four (4) puffs of 250 μg/puff of Aerobid® CFC.
Treatment B: Single dose of four (4) puffs of 85 μg/puff of the Flunisolide HFA Inhaler System (Bespak spacer).
Treatment C: Single dose of four (4) puffs of 129 μg/puff of the Flunisolide HFA with the Mark 6A (Maroon) actuator.

There was a 7-day washout between periods.

FORMULATION

The following formulations and batch numbers where used in this study.

Table 1. Flunisolide formulation used in this study

Study Drug/Strength	Batch Number	Expiration Date
Aerobid® CFC (treatment A)	960723	11/98
Flunisolide HFA inhaler system (3M Pharmaceuticals, Inc.) (treatment B and C)	P00851	
Bespak spacer (Bespak Inc.) (treatment B)	P00853	
[illegible] actuator (treatment C)	P00866	

PHARMACOKINETIC MEASUREMENTS

Blood and urine sampling

Blood samples were taken at 0.0 hr (pre-dose) and 5, 10, 20 and 30 min and 1, 2, 4, 6, 8 and 12 hr after administration of active drug. Urine was collected for a period of 12 hours. Plasma and urine were analyzed for flunisolide, 6β-OH flunisolide, and hydrocortisone concentrations.

Analytical Method

Flunisolide, β-OH flunisolide, and hydrocortisone concentrations in human plasma were determined by LC/MS/MS.

Plasma Preparation and Bioassay

The analysis of flunisolide, 6β-OH flunisolide or hydrocortisone was a solid phase extraction procedure using [redacted] of human plasma. Because [redacted] is an [redacted]

Urine Preparation and Bioassay

The analysis of Flunisolide, 6β-OH flunisolide, and hydrocortisone was a liquid-liquid extraction procedure using [redacted] of human urine sample. The organic extract was [redacted]

Pharmacokinetic Data Analysis

The major pharmacokinetic parameters such as Cmax, $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$ and Tmax were derived. Total amounts of flunisolide, 6β-OH flunisolide and hydrocortisone excreted into urine (Aex) were determined during 12 hr after administration of active treatment.

Statistical Analysis

An analysis of variance (ANOVA) was performed on the pharmacokinetic parameters using the GLM procedures of SAS. The ANOVA model included the variables Sequence, Subject (nested in Sequence), Period, and Treatment. Comparisons between Treatment C and Treatment A as well as between Treatment B and Treatment A were carried out by the two-sample t-test, where the residual error term from the ANOVA model was used as the error term.

Reviewer's Remarks

Study ANC-PK1-97-04-000, is a comparison between the to-be-marketed formulation (Bespak Inhaler System), a formulation used in the PK studies during product development ([redacted] acuator) and an approved product of flunisolide (CFC aerobid® Inhaler System). According to Dr. Huberman the ANOVA test used in here to show no statistically significant difference between treatments is questionable. The assumption of equal correlation between any 2 observations across periods made by the sponsor appears not to be true as indicated by the Durbin-Watson D test.

RESULTS

Plasma Bioanalytical Method

In-study Validation

Table 2. Assay performance (in-study validation) for flunisolide, 6β-OH flunisolide, and hydrocortisone

	Flunisolide	6β-OH Flunisolide	Hydrocortisone
Accuracy	Satisfactory: [redacted]	Satisfactory: [redacted]	Satisfactory: [redacted]
Inter-day Presicion	Satisfactory: [redacted]	Satisfactory: [redacted]	Satisfactory: [redacted]
Intra-day Presicion	Satisfactory: [redacted]	Satisfactory: [redacted]	Satisfactory: [redacted]

Urine Bioanalytical method

Recovery:

Flunisolide: [redacted]

6β-OH Flunisolide:

Hydrocortisone:

Limit of Quantitation

Flunisolide: [redacted]

6β-OH Flunisolide:

Hydrocortisone:

Stability

QC samples at three concentrations underwent three (3) freeze-thaw cycles. The concentrations found after repeated freeze/thaw cycles were within ± 20% of the theoretical values for all analytes.

Pre-study Validation

Table 3. Pre-study validation for flunisolide, 6β-OH flunisolide, and hydrocortisone

	Flunisolide	6β-OH Flunisolide	Hydrocortisone
Linearity	Satisfactory:	Satisfactory:	Satisfactory:
Accuracy	Satisfactory:	Satisfactory:	Satisfactory:
Inter-day Presicion	Satisfactory:	Satisfactory:	Satisfactory:
Intra-day Presicion	Satisfactory:	Satisfactory:	Satisfactory:
Specificity	Satisfactory: Chromatograms submitted	Satisfactory: chromatograms submitted	Satisfactory: chromatograms submitted

Table 4. Assay performance (in-study validation) for 6β-OH flunisolide, flunisolide and hydrocortisone

	Flunisolide	6β-OH Flunisolide	Hydrocortisone
Accuracy	Satisfactory:	Satisfactory:	Satisfactory:
Inter-day Presicion	Satisfactory:	Satisfactory:	Satisfactory:
Intra-day Presicion	Satisfactory:	Satisfactory:	Satisfactory:

SAFETY MEASUREMENTS

Safety was evaluated by monitoring of adverse events, clinical laboratory, physical examinations, and vital sign evaluations.

Pharmacokinetic Results

The mean plasma concentration-time profiles for flunisolide and hydrocortisone after administration of the three treatments are presented in Figures 1 and 2, respectively. The mean pharmacokinetic parameters for flunisolide and 6β-OH flunisolide are presented in Tables 5. Table 6 contains the mean PK parameters for hydrocortisone after the administration of the three treatments.

The individual Cmax and $AUC_{0\rightarrow inf}$ values for flunisolide following inhalation of the three treatments are presented in Figures 3 and 4, respectively. The individual $AUC_{0\rightarrow 12h}$ values for hydrocortisone following the three treatments are presented in Figure 5.

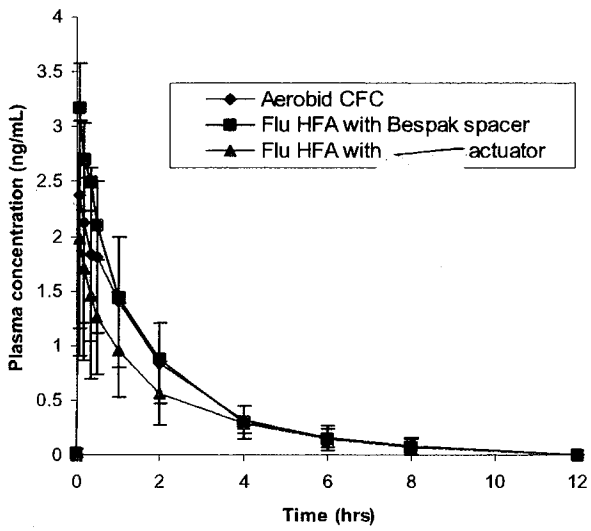

Figure 1. Mean flunisolide plasma concentration-time profiles following single inhalation of four puffs of Aerobid CFC (250 μg/puff), flunisolide HFA (85 μg/puff) and Flu HFA with actuator. Bars represent ±SD.

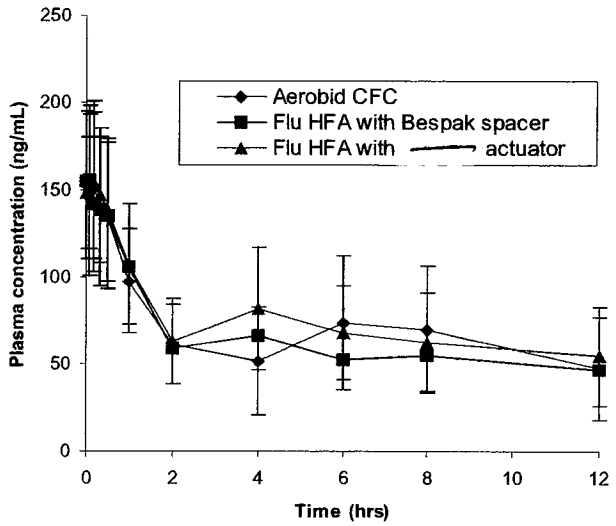

Figure 2. Mean hydrocortisone plasma concentration-time profiles following single inhalation of four puffs of Aerobid CFC (250 μg/puff), flunisolide HFA with Bespak spacer (85 μg/puff) and Flu HFA with actuator. Bars represent ±SD.

Table 5. Mean (±SD) flunisolide and 6β-OH flunisolide pharmacokinetic parameters following single inhalation of four puffs of Aerobid CFC (250 μg/puff), flunisolide HFA with Bespak spacer (85 μg/puff) and Flu HFA with actuator

PK Parameter	Flunisolide CFC Treatment A	FLUNISOLIDE Flu HFA with Bespak spacer Treatment B	Flu HFA Treatment C	p-value A vs. B	p-value C vs. A
Cmax (ng/mL)	2.53 ± 1.19	3.25 ± 2.66	2.02 ± 1.03	0.22	0.12
$AUC_{0\to last}$ (ng*hr/mL)	4.41 ± 1.59	4.99 ± 4.2	3.46 ± 1.60	0.57	0.04*
$AUC_{0\to\infty}$ (ng.hr/mL)	5.12 ± 1.0	5.82 ± 4.27	4.15 ± 1.35	0.94	0.12
Tmax (hr)	0.18 ± 0.16	0.09 ± 0.03	0.17 ± 0.16	0.02*	0.65
T1/2 (hr)	1.56 ± 0.31	1.43 ± 0.23	1.93 ± 0.36	0.19	0.0008*
A_{ex} (μg)	1.7 ± 0.89	1.98 ± 2.29	1.29 ± 0.85	0.69	0.58
		6β-OH FLUNISOLIDE			
Cmax (ng/mL)	0.75 ± 0.16	0.28 ± 0.17	0.36 ± 0.08	0.0001*	0.0001*
$AUC_{0\to last}$ (ng*hr/mL)	3.03 ± 0.77	1.12 ± 0.98	1.38 ± 0.29	0.0001*	0.01*
$AUC_{0\to\infty}$ (ng*hr/mL)	3.75 ± 0.83	2.3 ± 1.06	2.18 ± 0.26	0.0016*	0.0003*
Tmax (hr)	1.23 ± 0.52	1.15± 0.53	1.27 ± 0.61	0.43	0.92
A_{ex} (μg)**	50.50 ± 16.89	19.69 ± 13.82	24.21 ± 8.21	0.0001*	0.0003*

**A_{ex} amount of drug excreted in urine in 12 hr.

Table 6. Mean (±SD) hydrocortisone pharmacokinetic parameters following single inhalation of four puffs of Aerobid CFC (250 µg/puff), flunisolide HFA with Bespak spacer (85 µg/puff) and Flu HFA with [illegible] actuator

PK Parameter	HYDROCORTISONE Flunisolide CFC Treatment A	Flu HFA with Bespak spacer Treatment B	Flu HFA [illegible] Treatment C	p-value A vs. B	p-value B vs. C
Cmax (ng/mL)	178.7 ± 38.3	177.01 ± 33.19	172.13 ± 32.8	0.85	0.56
$AUC_{0\rightarrow12h}$ (ng*hr/mL)	826.7 ± 259.8	770.27 ± 184.6	880.6 ± 236.4	0.62	0.41
Tmax (hr)	1.14 ± 3.6	1.17 ± 2.55	0.54 ± 1.16	0.96	0.27
A_{ex} (µg)**	14.32 ± 3.68	13.9± 7.2	16.92 ± 6.6	0.84	0.44

**A_{ex} amount of hydrocortisone excreted in urine in 12 hr.

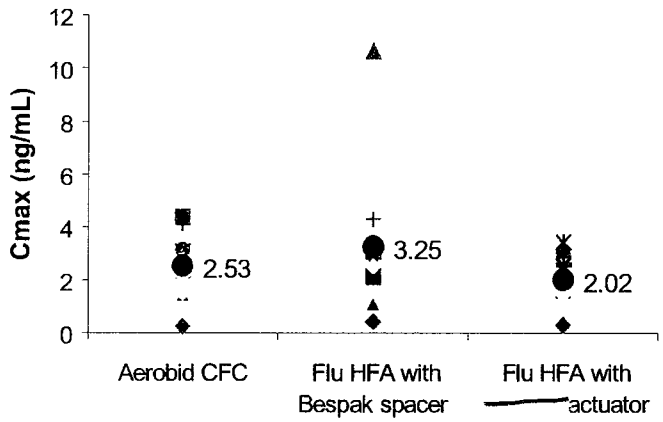

Figure 3. Individual flunisolide Cmax values following single inhalation of four puffs of Aerobid CFC (250 µg/puff), flunisolide HFA with Bespak spacer (85 µg/puff) and Flu HFA with [illegible] actuator.

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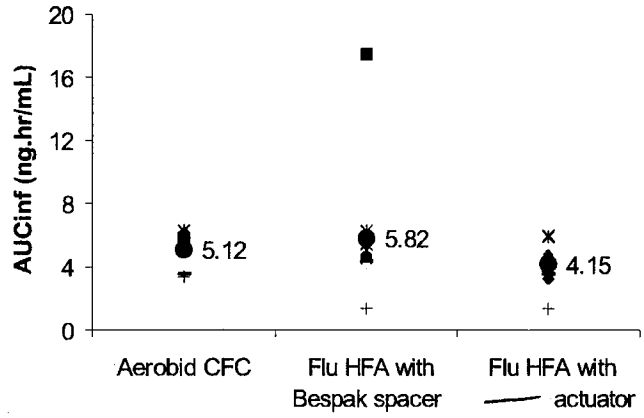

Figure 4. Individual flunisolide $AUC_{0\to\infty}$ values following single inhalation of four puffs of Aerobid CFC (250 μg/puff), flunisolide HFA with Bespak spacer (85 μg/puff) and Flu HFA with actuator.

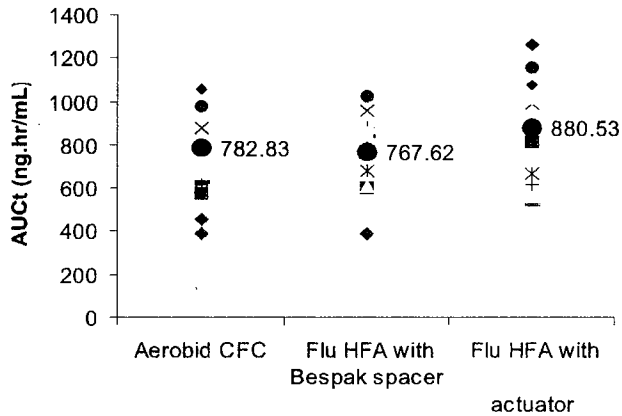

Figure 5. Individual hydrocortisone $AUC_{0\to12hr}$ values following single inhalation of four puffs of Aerobid CFC (250 μg/puff), flunisolide HFA with Bespak spacer (85 μg/puff) and Flu HFA with actuator.

SAFETY RESULTS

There were no serious adverse events reported or observed. No subject discontinued participation due to adverse events. Two subjects reported a total of eight (8) adverse events during this study. Four (4) adverse events were reported after administration of 4 puffs of 85 μg/puff of the flunisolide HFA formulation delivered via the Bespak spacer. These included dizziness (mild), nausea (mild) and rhinitis (mild). Four (4) adverse events were reported after administration of 4 puffs of 129 μg/puff of the flunisolide HFA formulation with the actuator. These included dizziness (severe), headache (severe), pharyngitis (moderate) and vomiting (moderate).

Although abnormal laboratory values were observed in a total of two (2), none of

these values were considered to be clinically important. No clinically important individual event or trends were noted in vital signs. All of the pre- and post-dose ECGs were normal. All of the pre- and post-dose pulmonary tests were normal.

DISCUSSION

Chromatographic data showed that the 6β-OH flunisolide stock solution used in this study, which was beyond the one-year expiration date, might be higher in concentration by as much as a factor of three. Consequently, 6β-OH flunisolide concentrations were underestimated. The sponsor has argued that the pharmacological activity 6β-OH flunisolide is low compared to that of flunisolide (200-fold difference) and that within-study comparisons of 6β-OH flunisolide concentrations are still accurate since the same 6β-OH flunisolide stock solution was used within a study. This reviewer agrees with this statement. However the sponsor will be discouraged to display 6β-OH flunisolide plasma concentrations in the label.

In this study, single doses of Aerobid CFC, Flunisolide HFA Inhaler System and Flunisolide HFA (with ——— actuator), delivered as 4 puffs of 250 μg/puff, 85 μg/puff and 129 μg/puff, respectively, resulted in similar $AUC_{0\to\infty}$ values for plasma flunisolide (Table 5) and similar $AUC_{0\to12h}$ values for plasma cortisol (Table 6). Urinary excretion of cortisol over 12 hours was independent of formulation, ranging from 13.9 to 16.9 μg (Table 6). This reviewer and Dr. Hoberman (statistician) believe that test to show no statistically significant difference between treatments is questionable. The assumption of equal correlation between any 2 observations across periods made by the sponsor appears not to be true as indicated by the Durbin-Watson D test. In addition, because this study was design as a single dose study, this reviewer recommends that the results obtained from the clinical trials submitted be used to decide about similarity of these formulations in terms of safety.

Exposure to 6β-OH flunisolide was significantly less after administration of flunisolide with the Flunisolide HFA Inhaler System compared to Aerobid® CFC (Table 6). The sponsor believes that it may be due to a lower amount of flunisolide deposited in the oropharyngeal region after administration with the Flunisolide HFA Inhaler System. If this is true, then more flunisolide is converted into 6β-0H flunisolide using the CFC system, which in turn becomes available systemically.

Statistically significant lower values of T_{max} were obtained following flunisolide administration with the HFA Inhaler System than those observed with the CFC System. These lower values were expected since flunisolide solution formulation from the HFA Inhaler System is more readily available than flunisolide suspension from the CFC Inhaler System.

CONCLUSION

The sponsor showed similar systemic bioavailability of flunisolide (evaluated in terms of Cmax and $AUC_{0\to12h}$) and similar hydrocortisone plasma and urine concentrations after the administration of flunisolide with either the Flunisolide HFA Inhaler System (4 puffs, 85μg/puff) or with Aerobid® CFC System (4 puffs, 250 μg/puff) (Table 3 and 4).

The statistical test (t-test) used by the sponsor to show no statistically significant difference between treatments does not meet the requirements of the test. The assumption of equal correlation between any 2 observations across periods made by the sponsor appears not to be true as indicated by the Durbin-Watson D test. In addition, because this study was designed as a single dose this reviewer is of the opinion that the results obtained from the clinical trials submitted be used to decide about similarity of these formulations in terms of safety.

COMMENTS

- Although 12 hours plasma and urine cortisol level may be acceptable, 24 hr plasma and urine cortisol levels are more recommended to assess the degree of cortisol suppression.
- To assess the degree of systemic side effects of inhaled drugs, it is recommended to assess the extent of systemic exposure after multiple administration of the drug. Because this study was design as a single dose study, this reviewer recommends that the findings obtained in the clinical trials submitted be used to decide about similarity of these formulations in terms of safety.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-247**	**Brand Name**	**Flunisolide HFA Inhaler System**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Flunisolide**
Medical Division	**DPADP**	**Drug Class**	**Glucocorticoid**
OCPB Reviewer	**Sandra Suarez-Sharp**	**Indication(s)**	**Asthma**
OCPB Team Leader	**Young Moon Choi (acting)**	**Dosage Form**	**solution (MDI)**
		Dosing Regimen	• **1-2 puffs bid children 11 years old)** • **2 puffs bid (>12 years old)**
Date of Submission	**April 10, 2000**	**Route of Administration**	**Oral Inhalation**
Estimated Due Date of OCPB Review	**April 9, 2001**	**Sponsor**	**Forest Laboratories, Inc.**
PDUFA Due Date	**April 27, 2001**	**Priority Classification**	**Standard**
Division Due Date	**April 13, 2001**		

3 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	5	4	One study was not reviewed due to low bioavailability/ discontinuation of the device used.
multiple dose:	X	2	2	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	2	2	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X	1	1	
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan Pharmacoscintigraphy	X	1	1	
Literature References	X			
Total Number of Studies		5	4	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. See page 19 of the BP review
QBR questions (key issues to be considered)	• Question 1: In vivo lung deposition • Question 2: Dose-proportionality • Question 3: Systemic exposure of FLU CFC vs. FLU HFA • Question 4: PK in children	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-247, HFD-850 (Electronic Entry), HFD-570 (Birenbaum, Barnes), HFD-870 (Suarez-Sharp, Choi, Hunt, Malinowski)), CDR (B. Murphy)

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/s/

Sandra Suarez
4/26/01 12:26:21 PM
BIOPHARMACEUTICS

Young-Moon Choi
4/26/01 02:26:46 PM
BIOPHARMACEUTICS

Division Director's Memorandum

Date:	Monday, May 07, 2001
NDA:	21-247
Sponsor:	Forest Pharmaceuticals
Proprietary Name:	No final name accepted Flunisolide HFA inhalation aerosol
From:	Robert J. Meyer, MD, Director, Division of Pulmonary and Allergy Drug Products.

Introduction: This is the first review cycle for this reformulation effort of Aerobid, NDA 21-247 from Forest. This HFA formulation has many parallels to the recently approved QVAR, including its manufacturing (as it is produced by 3M). It is a solution product (at room temperature) whose particle size leads to differing pharmaceutical properties than the suspension it is meant to replace. Additionally, (and unlike QVAR), the product incorporates a built in tube-spacer device somewhat akin to Azmacort.

CMC: The are a large number of CMC issues, however, none of them are insurmountable. The most important are that the site of manufacture for the drug product does not have a satisfactory inspection and the drug substance source is being change (without any supportive data on the effects or lack thereof of this change). There are also numerous specifications and tests that need implementation or adjusting, and several deficient DMFs. These are detailed in Dr. Roger's review.

Pharm/Tox: Except for labeling and the issue of a structural alert in the product that may require qualification (——— flunisolide), the pharm/tox issues have been satisfactorily addressed. The findings of the bridging studies were largely predictable for this class of compound and did not identify significant issues unique to the formulation that would preclude clinical marketing to this sensitive population (asthmatics).

Biopharmaceutics: There are both pharmacokinetic and pharmacodynamic comparisons with the CFC product. This product is intended to approximate the CFC product in terms of efficacy puff-for-puff, though the nominal doses greatly differ (85 mcg for the HFA ex-spacer vs. 250 mcg ex-actuator). It appears that the efficacy results are reasonably comparable (though by no means definitively "equivalent") and the systemic exposures also look similar puff-for-puff, but certainly much less with the HFA product mcg-for-mcg.

Clinical / Stastical: See Dr. Birenbaum's review and Dr. Mann's secondary review memos for details. Basically, this product is clinically approvable, but the sponsor did not provide adequate data for 4 and 5 year olds to support the proposed indicated age range and the data suggest a 1 puff starting dose in children as being appropriate (not the ——— as the sponsor proposed). These and other labeling issues will need to be addressed in the response.

Labeling: A final acceptable name has not been arrived at (though a submission late into the review cycle proposed two names that will be reviewed by OPDRA and DPADP). Preliminary labeling comments will be sent in the action.

Conclusions: This product is clinically approvable. Once the CMC issues have been addressed, satisfactory DMFs and EERs are in place and labeling issues have been resolved, this product can be approved.

Robert J. Meyer, MD
Director,
Division of Pulmonary and Allergy Drug Products

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/s/

Robert Meyer
5/7/01 02:01:33 PM
MEDICAL OFFICER

Clinical Team Leader Review

NDA:	21,247
Product:	flunisolide HFA (85 ug/puff) Metered Dose Inhaler with built-in Bespak Spacer
Sponsor:	Forest Laboratories
Indication:	maintenance treatment of asthma
Dose:	two to four puffs BID in adults/adolescents age 12 and older one ——— puffs BID in children age 4 through 11
Date:	4/18/01
Reviewer:	Marianne Mann, Deputy Director, DPADP

Background

There are two approved metered dose inhalers containing the anti-inflammatory steroid, flunisolide: Aerobid Inhaler, Aerobid-M (menthol flavored) Inhaler. Both of these products are marketed by Forest Laboratories, and utilize CFC as a propellant. Each is approved for the maintenance treatment of asthma when given prophylactically and to reduce or eliminate the need for systemic corticosteroids in asthmatics.

Forest Laboratories, in NDA 21,247, is now proposing a flunisolide metered dose inhaler for the same indications as above which replaces CFC with HFA as the propellant. This new solution formulation contains 85 ug flunisolide per puff, whereas the suspension CFC formulation contains 250 ug flunisolide per puff. The device delivery system for the HFA formulation is new and includes a spacer that facilitates greater drug delivery to the lung. Notably, about — of the HFA flunisolide formulation delivers particle sizes less than — (i.e. of respirable size) versus about — of the CFC flunisolide formulation.

The desired indication statement for HFA flunisolide is almost identical to that of the older CFC formulation, with the exception that the sponsor now asks for approval in children and adults age four and up, while the CFC formulation has been approved in children and adults age six and up. The proposed indication for HFA flunisolide reads: "for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients four years of age and older" and "for patient requiring oral corticosteroids over time. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time."

Summary of Chemistry Review Concerns

There were multiple chemistry deficiencies noted by the chemistry reviewer, Dr. Rogers, and therefore an approval action was not possible for this NDA. These deficiencies included (but were not limited to) the following:

- The DMF for the drug substance is inadequate. Additional information is requested.

- Test methods and validation studies for acceptance of all exipients, including validation studies for the propellant methods, are necessary and will be requested.
- A number of GMP deficiencies were noted at the inspection of the manufacturing facility (3M Pharmaceuticals). A satisfactory inspection is required before the application can be approved.
- Heat stress testing was felt to possibly be inadequate and addition information validating this process was requested.
- Tighter release criteria were recommended for dose content and uniformity, as well as for ethanol content of the final drug product. The proposed impurity and water specifications for the final drug product also need to be tightened.
- The acceptance criteria for microscopic evaluation need to be more specific. Data is requested that limit the identity, size, and quantity of all particles that are not flunisolide hemihydrate.
- Complete priming studies, including data from a single actuation, are necessary to establish priming requirements for the minimum recommended dose of 1 puff BID in children.

Summary of Biopharmacolology Review Concerns

There were 4 studies designed to assess the pharmacokinetics of HFA flunisolide. Although dose proportionality was shown in a single dose study, a multiple dose study failed to demonstrate this. It was noted that the dose adjusted AUC for a single puff of HFA flunisolide was significantly lower than that obtained after two or four puffs. This raised some concern in children, in whom a single puff is recommended. Efficacy of a single puff of HFA flunisolide in children therefore depends solely on clinical data. Importantly, the inability to demonstrate dose proportionality is not felt to be an approvability issue, and this finding is not entirely uncommon with the inhaled corticosteroids.

Similar Cmax and AUC values for systemic levels of flunisolide were observed after 4 puffs of HFA flunisolide (340 mcg total dose) compared to 4 puffs of CFC flunisolide (2000 mcg total dose). However, the submitted application did not include an analysis of comparative bioavailability (using 90% confidence intervals for the ratio of geometric means for Cmax and AUC). A claim of equivalent exposures between these two formulations (at a dose of 4 puffs of each formulation) is not supported without this type of analysis. Importantly, this is again not an approvability issue.

Summary of Clinical Review Findings and Concerns

There were four clinical trials: a 12-week pivotal trial in adults/adolescents, a 12-week pivotal trial in children, a 1-year safety study in adults/adolescents, and a 1-year safety study in children.

Study ANC-MD-01: 12 week pivotal trial in adults and adolescents
This 12-week trial enrolled 863 patients age 12-78 years of age, who were randomized to one of 7 treatment arms:

- HFA flunisolide: one puff BID (85 ug BID) (low dose HFA)
- HFA flunisolide: two puffs BID (170 ug BID) (medium dose HFA)
- HFA flunisolide: four puffs BID (340 ug BID) (high dose HFA)
- CFC flunisolide: one puff BID (250 ug BID) (low dose CFC)
- CFC flunisolide: two puffs BID (500 ug BID) (medium dose CFC)
- CFC flunisolide: four puffs BID (1000 ug BID) (high dose CFC)
- Placebo

Patients were randomized to treatment after a 2-week, open label, run-in phase in which they received active treatment with CFC flunisolide at a dose of 500 ug BID to assure clinical stability. They were then randomized to a treatment arm, and followed to see if they maintained, improved, or lost stability. The primary endpoint was the change from baseline in % predicted FEV_1.

The medium and high dose HFA flunisolide arms were superior to placebo for the primary endpoint. Placebo patients deteriorated 4.3% from baseline after 12 weeks of treatment while the medium dose HFA arm deteriorated by only 0.2% and the high dose HFA arm improved by 0.3%. Secondary efficacy parameters also supported the efficacy of the medium and high HFA doses. The time to dropout due to exacerbation of asthma was longer in all three HFA arms versus placebo. The "time to dropout due to asthma" analysis also showed a trend for dose ordering among the three HFA arms, and was therefore supportive of efficacy.

The CFC flunisolide arms were not included for the purposes of showing non-inferiority, however comparisons are of interest. As expected, both the medium and high dose CFC flunisolide doses demonstrated efficacy versus placebo based on the primary endpoint. This finding supports the validity of the study results. Comparing HFA to CFC "dose for dose": the low dose HFA flunisolide arm performed somewhat better than the low dose CFC arm, while medium and high doses of each formulation were fairly comparable.

There were no safety signals of concern. The trial included an assessment of urinary cortisol levels and also evaluated the incidence of non-responders to a cotrosyn stimulation test at week 12. There was no signal of concern regarding HPA axis suppression in either the CFC or HFA arms for either of these analyses.

Conclusions
Both 170 ug BID HFA flunisolide and 340 ug BID HFA flunisolide were effective and safe in maintaining control of asthma in adolescents and adults age 12 and older. There is subtle evidence of added benefit for 340 ug BID over 170 ug BID

for both primary and secondary efficacy endpoints and no evidence of increased risk. This study supports the approval of HFA flunisolide in adults and adolescents for the maintenance control of asthma. Starting doses of 170 BID (2 puffs BID) should be recommended, with instructions that doses up to 340 ug BID (4 puffs BID) could also be used.

Study ANC-MD-03: 12 week pivotal trial in children
This trial was similar in design to the adult trial, but enrolled pediatric patients ranging from age 4 to 11 and randomized them to one of the following treatment arms for a total duration of 12 weeks, following a 2-week run-in maintenance phase:

- HFA flunisolide: one puff BID (85 ug BID) (low dose HFA)
- HFA flunisolide: two puffs BID (170 ug BID) (high dose HFA)
- CFC flunisolide: one puff BID (250 ug BID) (low dose CFC)
- CFC flunisolide: two puffs BID (500 ug BID) (high dose CFC)
- Placebo

Patients were followed to see if they maintained/improved/lost stability regarding the primary endpoint of the change from baseline in % predicted FEV_1. Of note, for patients age 4-5, the change from baseline in % predicted FEV_1 was replaced by in-clinic PEFR for the primary efficacy analysis. The study was powered to detect a 5% difference between medium dose HFA and placebo for the primary efficacy endpoint of change from baseline in % predicted FEV_1.

A total of 571 patients were included in the ITT analysis for efficacy. Of these, 61 were age 4-5 and were evaluated for PEFR, while 510 patients were age 6-11 and were evaluated for change from baseline in % predicted FEV_1.

Results for children age 6-11 for the primary efficacy endpoint follow:

Difference in the Change from Baseline FEV_1% Predicted
Flunisolide Dose Arm Minus Placebo Arm
Children Age 6-11

	Difference*	p-value
85 ug BID HFA Flunisolide	4.87	0.008
170 ug BID HFA Flunisolide	3.88	0.034
250 ug BID CFC Flunisolide	4.67	0.012
500 ug BID CFC Flunisolide	6.64	0.0001

*LSM of change from baseline in flunisolide dose arm minus that of placebo arm

As noted above, although both HFA dose arms were superior to placebo, the results were surprising in that the lower HFA dose had the better result. Both CFC dose arms were also superior to placebo, but these showed the anticipated dose ordering effect.

Results for the 4-5 year olds based on PEFR failed to show statistical significance, although favorable trends were noted for both HFA treatment arms compared to placebo. The relatively small sample size of patients enrolled in this age group and the variability in this endpoint may have resulted in lack of significance, or it is possible that younger patients find the inhaler more difficult to reliably use. There again appeared to be no significant benefit for the HFA 170 BID arm over HFA 85 BID in 4-5 year old patients.

There were no serious safety signals of concern. The most common event leading to treatment discontinuation was asthma, and this occurred in 12% of placebo subjects versus 10% of pooled HFA and 7.6% of pooled CFC groups. The next most common AE leading to treatment discontinuation was pharyngitis, occurring in 0%, 1.7% and 1.3 % of placebo, HFA, and CFC groups, respectively. There was no evidence of plasma cortisol suppression after Cotrosyn stimulation in either the HFA or CFC groups when compared to placebo. However, four cases of oral moniliasis were reported in the HFA groups versus none in the placebo arm (two occurred in the HFA 85 ug BID arm, 1 in the CFC 250 ug arm, and 1 in the CFC 500 ug BID arm.

Conclusions
These data support that both 85 ug BID HFA flunisolide and 170 mg BID HFA HFA flunisolide were effective and safe in maintaining control of asthma in children age 6 through 11. There was no added benefit for the 170 ug BID dose over the 85 ug BID dose for either primary or secondary efficacy endpoints. Importantly, there was also no evidence of increased risk for the higher dose. This study supports the approval of HFA flunisolide in children ages 6 through 11. Starting doses of 85 ug BID (1 puff BID) should be recommended, with instructions that 170 ug BID (2 puffs BID) could also be used. The available data do not support the efficacy of flunisolide at <u>any</u> dose for children age 4-5. An additional study, perhaps using PEFR as an endpoint and including a larger sample size, is recommended to validate efficacy in this younger population.

Study ANC-MD-02: 1 year safety trial in adults/adolescents
This was a 1-year, open label study performed in adults and adolescents age 12 through 62. A total of 215 randomized subjects were evaluated for safety following 52 weeks of open label treatment with either HFA flunisolide or beclomethasone. Randomization was 3:1 for flunisolide:beclomethasone, and dosing was flexible ranging up to 672 ug total daily dose for beclomethasone and 680 ug total daily dose for flunisolide. Comparisons of safety were made between flunisolide and beclomethasone. It is difficult to draw firm conclusions from these comparisons, particularly due to randomization being 3:1 in favor of flunisolide, and to the variable doses that were prescribed.

Two thirds of the patients in the flunisolide arm completed the 1-year trial versus three quarters of the beclomethasone group, suggesting that beclomethasone was better tolerated.

Patient discontinuations due to adverse events occurred twice as often in the flunisolide arm: 7.4% of flunisolide patients (n=12) versus 3.8% of beclomethasone patients (n=2), suggesting again that beclomethasone was better tolerated. The adverse events that led to discontinuation in the flunisolide arm were relatively random and varied, with the exception that 5 subjects discontinued due to taste perversion (versus none in the beclomethasone arm). Taste perversion therefore appears to be a significant adverse event unique to flunisolide.

HPA axis was evaluated in a subset of 136 subjects using 24 hour urine cortisol. Results showed no signal for concern other than a modest decrease in urinary cortisol levels in the HFA flunisolide arm at 6 weeks, which was not sustained at the end of the study. Cotrosyn stimulation tests were also performed in a subset of patients and showed similar results across treatment groups for mean values, with slightly more nonreponders in the flunisolide arm vs. beclomethasone (9.1% versus 7.4%).

Conclusions
This open label study broadly compared the tolerability of a variety of flunisolide doses versus a variety of beclomethasone doses in adult and adolescent asthmatic subjects over a one year period. Patient followup was not very good, with one third of flunisolide and one quarter of becoclomethasone patients dropping out prior to the end. The results show no major concerns regarding flunisolide, although subtle trends tended to favor beclomethasone regarding tolerability in many analyses.

Study ANC-MD-04: 1 year safety trial in children
This was a 1-year, open label study performed in children age 4 through 11. A total of 241 subjects were evaluated for safety following 52 weeks of open label treatment with either HFA flunisolide, beclomethasone, or cromolyn sodium. Of the 241 enrolled subjects, 30 were age 4-5, and all of these subjects received HFA flunisolide at a dose of 85 ug (one puff) twice a day. The remaining 201 enrolled children, age 6-11, were randomized to receive:

- HFA flunisolide (85 ug/puff) at a dose range of one to two puffs twice daily;
- beclomethasone (84 ug/puff) at a dose range of one to two puffs twice daily;
- cromolyn sodium (800 ug/puff) at a dose range of two to four puffs twice daily.

A total of 152 patients were randomized to receive varying doses of HFA flunisolide versus a total of 39 who received beclomethasone and 44 who received cromolyn. It is difficult to draw firm conclusions from comparisons across the 3 study arms, particularly due to randomization being 3:1 in favor of flunisolide, and to the variable doses of each drug that were prescribed.

Approximately two thirds of the patients in the flunisolide arm completed the 1-year trial versus more than three quarters of the beclomethasone group, and two

thirds of the cromolyn group, suggesting that beclomethasone was better tolerated.

Patient discontinuations due to adverse events occurred twice as often in the flunisolide and cromolyn arms versus the beclomethasone arm: 5.9% of flunisolide and 6.8% of cromolyn patients discontinued due to an AE versus 2.6% of beclomethasone, again suggesting that beclomethasone was better tolerated. The adverse events that led to discontinuation in the flunisolide arm were relatively random and varied, and included asthma exacerbations. Asthma was reported as an SAE in 6 flunisolide subjects, one cromolyn subject and no beclomethasone subjects. Taste perversion was not reported in this pediatric study, unlike the adult/adolescent trial, and this was somewhat surprising. Clinical thrush was reported in 4 patients (2.2%) in the HFA flunisolide arm versus no patient in either the beclomethasone or cromolyn arms.

HPA axis was evaluated in a subset of 84 subjects using a 250 ug IV cotrosyn stimulation test. All three groups responded similarly to this test. One patient in each of the corticosteroid arms shifted from a "responder" to a "non-responder" in this analysis versus no patients in the cromolyn arm.

Conclusions
This open label *study broadly compared the tolerability of a variety of flunisolide doses versus a variety of beclomethasone and cromolyn doses in pediatric patients age 4-11 over a 1-year period. Patient followup was not very good, with one third of flunisolide and cromolyn patients discontinuing prematurely versus about one fifth of becoclomethasone patients. The results show no major concerns regarding flunisolide, although subtle trends tended to favor beclomethasone in both efficacy and safety parameters evaluated. Clinical thrush occurred in 4 pediatric patients (2.2%) in this study, and should be mentioned in labeling.*

Overall Summary
Conclusions from this NDA review follow:

- Approval is supported in adults and adolescents age 12 and older. The appropriate dose of HFA flunisolide in adults and adolescents age 12 and older is 2 puffs BID (170 mcg BID). Dosing may increase up to 4 puffs BID (340 mcg BID) if needed.
- Approval is supported in children age 6-11. The appropriate dose of HFA flunisolide in children age 6 through 11 is 1 puff BID (85 mcg BID). Dosing may increase up to 2 puffs BID (170 mcg BID) if needed.
- Approval is not supported in children age 4-5. For 4-5 year old patients, a study that demonstrates efficacy over placebo would be required, and could include am PEFR as the primary outcome variable.

- Growth studies in this NDA submission were not interpretable. An ongoing growth study in children age 4 and older is underway, and results should be submitted when available.
- Resubmitted labeling should recommend dosing in children age 6 through 11 with 1 puff BID, allowing for 2 puffs BID if necessary. Resubmitted labeling should address efficacy after removing Dr. Caputo's site from the database, but it is not necessary to remove his site from the safety database.
- The NDA resubmission should include complete financial disclosure information for all clinical investigators, using forms 3454 or 3455.
- The pediatric drug development plan for children age 6 months through 5 years of age should be submitted.

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Marianne Mann, M.D., Deputy Director, DPADP

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/s/

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