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APPLICATION NUMBER:

21-247

MEDICAL REVIEW

CLINICAL REVIEW

Application Type	NDA
Submission Number/Code	21-247
Letter Date	26 July 2005
Stamp Date	27 July 2005
PDUFA Goal Date	27 January 2006
Reviewer Name	Peter Starke, M.D.
Review Completion Date	January 27, 2006
Established Name	flunisolide HFA, 80 mcg
Trade Name	Aerospan™ Inhalation Aerosol
Therapeutic Class	Orally Inhaled Corticosteroid
Applicant	Forest Laboratories, Inc.
Priority Designation	S
Studied Indication/Population	Maintenance treatment of asthma in patients — years
Formulation Used	HFA Metered Dose Inhaler

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-247	**TRADE NAME:**	**Aerospan ™ (flunisolide HFA, 80** mcg) Inhalation Aerosol
APPLICANT:	Forest Laboratories, Inc.	**USAN NAME:**	Flunisolide HFA, 80 mcg inhalation aerosol
MEDICAL OFFICER:	Peter Starke, MD	**CATEGORY:**	Corticosteroid
PDUFA DATE:	27 January 2006	**ROUTE:**	Orally inhaled

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	Submission	Comments
27 July 2005		Complete response to July 24, 2003 Approvable letter
27 September 2005		Labeling
4 November 2005		Marked-up labeling
22 November 2005		Annotated package insert

RELATED APPLICATIONS

Document Date	Application Type	Comments
27 April 2000		Original NDA submission for Aerospan Inhalation Aerosol

REVIEW SUMMARY:

This is a fifth cycle review of Aerospan™ (flunisolide HFA, 80 mcg) Inhalation Aerosol, encompassing a review of the complete response to an Approvable letter dated April 20, 2004. The development program was a 505(b)(1) switch program from a CFC formulation (Aerobid) to an HFA formulation, as Forest has right of reference to all preclinical data. The application was considered Approvable from a clinical perspective in previous review cycles for ≥6 years, but not in children age 4-5 years. In previous cycles, labeling was not completely addressed. Therefore, in this cycle, the entire clinical program was reviewed as part of reviewing the proposed labeling, and labeling was addressed by all review teams. This review addresses all labeling issues.

Although the clinical program was quite limited, the clinical recommendation has not changed. The following **indication is supported: "maintenance treatment of asthma** as prophylactic therapy in adult and pediatric patients 6 years of age and older. Aerospan Inhalation Aerosol is also indicated for asthma patients requiring oral corticosteroid therapy, where adding Aerospan Inhalation Aerosol may reduce or eliminate the need for oral **corticosteroids."**

Clinical dose ranging was not performed. Clinical dosing was based on matching PK from the approved flunisolide CFC product to the proposed flunisolide HFA product. The applicant performed two pivotal efficacy and safety studies and two long-term safety studies, one each in children 4-11 years and adults/adolescents ≥12 years of age. The pivotal studies were somewhat unorthodox in style. Although the clinical program was **limited, the applicant's recommended starting and maximum doses within each age range are generally** supported.

A request for a waiver for pediatric studies below 6 years of age should be denied (i.e. deferred) for ages 6 months through 5 years, but granted for below 6 months. Note that, because of the need to time inhalation with actuation and the use of a built-in spacer (not holding chamber), this particular Aerospan Inhalation Aerosol drug product may not be appropriate for use in certain pediatric age ranges.

Two Phase 4 commitments are recommended.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: X **APPROVAL** ___ **APPROVABLE** ___ **NOT APPROVABLE**

Table of Contents

Table of Tables

Table of Figures

Referential Notation: References to source material are provided in this review. Within text, the references are bracketed [ ] and follow a standard format: the volume number; the section within the volume; the page number(s) where the source material is located; and the date [if applicable]; for example, [v 1.2, sec 5.3.5.1, p 499]. References to electronic material show the file name and letter date. References to hard copy material outside the submission (e.g., FDA reviews, correspondence, meeting minutes) are descriptive; for example, [Dr. MO's Review, Date].

CLINICAL TEAM LEADER MEMORANDUM / REVIEW

Date:	January 27, 2006
To:	NDA 21-247
From:	Peter Starke, MD Medical Team Leader Division of Pulmonary and Allergy Drug Products, HFD-570
Product:	Aerospan™ (flunisolide HFA, 80 mcg) Inhalation Aerosol
Applicant:	Forest Laboratories, Inc.

Administrative and Introduction

This is a fifth cycle review of an application for Aerospan™ (flunisolide HFA, 80 mcg) Inhalation Aerosol [previously called Flunisolide HFA Inhaler System and Aerospan HFA; hereafter referred to in this review interchangeably as Aerospan, HFA flunisolide, or flunisolide HFA], submitted by Forest Laboratories, Inc. The original application for Aerospan was submitted on April 27, 2000, with the first Approvable action taken on May 7, 2001. A complete response was submitted on December 10, 2001, with a second Approvable action taken on June 11, 2002. A complete response was submitted on February 5, 2003, with a third Approvable action taken on July 20, 2003. A complete response was submitted on October 20, 2003, with a fourth Approvable action taken on April 20, 2004. This review encompasses the complete response to the April, 2004, Approvable letter. The complete response was submitted on July 27, 2005, and the PDUFA date is January 27, 2006.

The development program for Aerospan Inhalation Aerosol was a 505(b)(1) switch program from the CFC formulation (Aerobid®) to an HFA formulation, as the company has rights of reference to all preclinical data found in the Aerobid NDA (NDA 18-340). As confirmation, Forest submitted letter to NDA 21-247 on January 26, 2006, verifying the licensing agreement between Syntex and Forest that includes rights of reference to NDA 18-340.

Aerospan is intended as an HFA replacement for Aerobid® and Aerobid-M® [menthol flavored] (flunisolide) Inhaler System (NDA 18-340, approved August 17, 1984) [hereafter collectively referred to in this review as Aerobid], which utilizes CFC as the propellant. Both products are pressurized metered dose inhaler devices (pMDI or MDI). Aerospan includes an integrated spacer device, whereas Aerobid does not.

Aerobid is approved for "the maintenance treatment of asthma as prophylactic therapy," and to reduce or eliminate the need for systemic corticosteroids in asthmatics, in children and adults age 6 and older. With the original application Forest Laboratories proposed the same indications for Aerospan, with the exception that the applicant asked for approval in children and adults age four and older. However, it was judged that the pivotal study in children did not support extension into 4-5 year olds. The current proposed indication reads: "Aerospan Inhalation Aerosol is indicated for the maintenance

treatment of asthma as prophylactic therapy in adult and pediatric patients six years of age and older. Aerospan Inhalation Aerosol 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."

This review was performed primarily to assess the basis of and to provide recommendations for labeling and labeling negotiations, which were carried out during this review cycle. In the first and all subsequent review cycles, the Clinical Team recommended an Approval action. A clinical labeling review was written by Dr. D. Birenbaum in the first cycle, but no action was taken with regard to labeling negotiations during that or subsequent cycles, since Approvable actions were taken in each cycle due to CMC deficiencies. As a result, the labeling presented with each subsequent complete response did not benefit from that initial review. To resolve this, all supports for the labeling were fully evaluated during this cycle, and are the main thrust for this review. The reader should be aware that this review encompasses and summarizes multiple phases of the review cycle; therefore, each section served a different purpose during the cycle, including: historical information from previous reviews; my own analyses, labeling review, and recommendations; a summary of the labeling revisions undertaken during this review cycle; and Phase 4 recommendations and letter comments. Each section is identified accordingly.

The remaining CMC issues to be addressed in this cycle were the DMFs for the container closure system. This submission contains a complete response to the CMC issues, along with a clinical safety update.

This submission comprises 19 volumes, all in paper. The first volume includes the CMC complete response and labeling, while the remaining 18 volumes comprise the safety update. Labeling is submitted electronically in PDF and Word formats. During this cycle, annotated labeling was requested and submitted on November 22, 2005.

Two consultations were performed during this review cycle. The Division of Medication Errors and Technical Support (DMETS) provided consultation on the proposed Trade name and labeling. The Division of Surveillance, Research, and Communication Support (DSRCS) also provided a review of the Patient Instructions for Use. All consult advice was considered, and most adopted. Please see the consults for details.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

Drug substance

The drug substance, flunisolide hemihydrate, was manufactured previously. The site of manufacture is now closed, and the site withdrawn. Thus, there is no drug substance manufacturing site to inspect prior to approval.

Drug Product

Whereas Aerobid is a suspension in CFC, Aerospan is a 0.24% w/w solution of flunisolide hemihydrate in [redacted] w/w dehydrated ethanol and 1,1,1,2-Tetrafluoroethane (HFA 134a). This new formulation contains 80 mcg flunisolide hemihydrate (equivalent to 78 mcg flunisolide) per puff (from the mouthpiece), whereas the suspension CFC formulation (Aerobid) contains 250 mcg flunisolide per puff. The drug product delivers

139 µg of flunisolide hemihydrate per actuation from the valve and 80 µg of flunisolide hemihydrate from the spacer (using a flow rate of 30 L/min for 4 sec), corresponding to 78 µg of flunisolide from the spacer. Originally, the applicant proposed use of 85 mcg to represent the dose of flunisolide hemihydrate delivered from the mouthpiece, and the study reports for the clinical trials bear this representation. However, in previous review cycles there was concern with medication dose content uniformity (DCU), which is lower than 85 mcg and closer to 80 mcg. For this **reason, the Division and Forest's came to** agreement that the dose delivered from the mouthpiece would be expressed in the labeling as 80 mcg of flunisolide hemihydrate per actuation (equivalent to 78 mcg flunisolide).

The device delivery system for the HFA formulation is new. It is a metered dose inhaler with a 50 µL metering valve and a spacer built into the actuator. It will be manufactured in 120-actuation and 60-actuation sizes using an identical container, valve, and actuator/spacer. At this point in time, a dose counter has not been integrated into the device. The proposed expiry period is 24 months.

This new drug/device combination in the Aerospan drug product is said to facilitate greater drug delivery to the lung. According to Forest, the device delivers —— erosol particles with a mass medial aerodynamic diameter (MMAD) of — µm compared to µm for Aerobid. In addition, abo — of the HFA formulation delivers particle sizes less than —— i.e. upper limit of respirable size) versus abo — of the CFC formulation. Forest claims that at the same respirable dose, th —— particle size and built-in spacer in the Aerospan product reduce the systemic exposure to flunisolide **compared to that of Aerobid. Dr. Roger's** reviews have noted that **the "amount of drug** delivered at the mouthpiece and the fine particle mass are directly dependent on the flow rate. For example, the dose delivered per actuation at 20 L/min is — % of the label claim, while at 40 L/min, it is —— of label claim. Similarly, the fine particle mass (≤ 4.0 µm aerodynamic diameter) is —— per actuation at 20 L/min and —— at 40 **L/min."**

CMC Review Issues

Please refer to the multiple reviews performed by Dr. Brian Rogers for complete CMC information.

In previous review cycles, there was concern that the DCU rises at the end of the canister life. This finding is consistent across all batches, and is seen by dose measurement but not by cascade impaction. The rise is not explained by leakage of propellant from the canister.

Previously, methodology to minimize oxidation of the drug substance was addressed, methodology for measurement of leachables and extractables were identified, and several gasket leachable specifications were set.

As of this review cycle, the only remaining CMC issues pertained to several DMFs for the container closure system. Please refer **to Dr. Roger's review for details.**

Of note, I could find no information in any of the reviews regarding device durability or life-of-the-device testing in the clinical studies. In addition to information on reliability in the hands of the patient, such testing also helps to confirm the correct instructions for

use and instructions for cleaning. Lack of life-of-the-device testing was noted by Dr. Rogers during the first review cycle, and in the first approvable letter (May 7, 2001) the Division requested submission of the results of a patient in-use study. Forest responded in subsequent submissions, and Dr. Rogers reviewed these responses in his reviews #2 and #3. This appears to have been an in-vitro study rather than evaluations of the device in patient hands performed as part of the Phase 2 and 3 studies. Information in vitro on dose content uniformity at the beginning and end of canister use was submitted and reviewed. On this basis, Dr. Rogers felt that the labeling statement that the actuator/spacer need not be cleaned is acceptable. However, lack of a patient in-use study and information from the Phase 2 and 3 studies regarding device durability is problematic, and needs to be addressed as a Phase 4 commitment (see comments at the end of this section).

For this drug product, the ex-actuator dose is — mcg, whereas the labeled emitted dose of flunisolide (i.e. ex-spacer) is 80 mcg. So, with each actuation of the device about — mcg of flunisolide is deposited within the spacer. Primarily, the deposition is likely due to larger particles landing on the walls of the spacer, allowing smaller particles to be emitted from the spacer. However, other processes may be at work. The label makes it clear that the actual emitted dose is both rate and time dependent. The labeled emitted dose is based on a flow rate of 30 L/min, a flow rate similar to that found in adults. Higher flow rates result in an emitted dose higher than labeled, and lower flow rates result in lower doses. After actuation, a delay in inspiration of just one second results in an emitted dose of 25% or less of the labeled 80 mcg dose. It is not clear whether this is due to evaporation of the ethanol, loss from the back or from the mouthpiece opening (if the lips are not firmly placed over the mouthpiece), or other factors. Regardless, the need for careful coordination between actuation and inhalation is quite clear from the data submitted. This may be handled by clear instructions for use in the DOSING AND ADMINISTRATION and Patient Instructions for Use sections of the Product Insert (PI), as well as in the Patient Leaflet (PPI). The instructions address timing of inhalation with respect to timing of actuation, as well as a statement that external spacers should not be used with this device. The need to coordinate timing of actuation and inhalation so carefully may also be a reason why this drug product should not be used in younger children, since the dose the child receives will be impossible to gauge and may be not be adequate.

The excess drug deposited in the spacer has other implications with regard to the cleaning instructions in the labeling. There remains a concern that some of this material may be deposited in the valve orifice, potentially clogging the orifice. In this regard, information regarding DCU over the life of the device is helpful, showing that with normal use this eventuality is unlikely. Note that flunisolide is soluble in ethanol but is quite insoluble in water, so rinsing with running water would not be expected to have any positive effect on amount of residue or clogging. The Agency has previously asked Forest to make changes to the device to make it difficult to separate the actuator and spacer, so cleaning inside the spacer is now difficult or impossible. Nevertheless, consideration should be given to advising weekly inspection of the orifice for clogging of the opening (may be inspected by sliding the purple actuator back within the gray spacer unit). This advice is not current present in the labeling. A patient use study should help to resolve this issue (see below).

Deposition of drug within the spacer presents other issues. Over the course of the life of the device up to 4.2 mg of drug may be deposited in the actuator/spacer. A small but unaddressed concern is that the spacer and actuator can be forcibly separated, patients could access this accumulated material and could inadvertently ingest it. However, given the difficulty with separating the two units and the insolubility of the drug substance in water, this appears to be an unlikely event.

While canisters will not be supplied without the actuator/spacer, reuse could still be an issue. The fact that this drug product contains a spacer poses concerns that patient may be tempted to re-use the actuator/spacer with canisters from other inhalational drug products. This is addressed in the labeling.

With regard to ———, the Division has had several interactions with Forest, including a teleconference on December 18, 2001 and the AE letter dated April 20, 2004, in which the Division requested Forest to provide the status and timeline for the introduction of ———

Since Forest has not performed a patient in use study or (as far as I am aware) evaluations of device reliability in the hands patients in the clinical trials, I recommend that this be requested as a Phase 4 commitment. Ideally, in all Phase 2 and 3 studies utilizing the to-be-marketed formulation, patients are asked to report devices they perceive to be broken or malfunctioning. Any device so reported is then returned and evaluated to identify the problem. Device use and performance is also evaluated through directed questions defined in the protocol. In this way, information is generated regarding the types and frequencies of device malfunction based on data from a large number of devices, and an analysis of the cause may lead to potential improvements to the device itself. In addition, a small number (e.g. 100) of devices that are **apparently functioning normally in patients'** hands should be collected near the end of the life of the device and evaluated by in vitro performance testing. These evaluations were apparently not addressed in the development program for Aerospan Inhalation Aerosol, and must be addressed in the postmarketing period as a Phase 4 commitment.

Pharmacology and Toxicology

There were no pharmacology or toxicology issues to be addressed except for labeling, which was addressed by Dr. Sancilio in this cycle.

During the third review cycle, the presence of a ——— in the drug product was addressed by submission of a negative SHE cell assay. During the fourth review cycle, leachables from the gasket were evaluated and acceptance criteria set.

Clinical Pharmacology and Biopharmaceutics

There were no pharmacology or toxicology issues to be addressed except for labeling, which was addressed by Dr. Al Habet in this cycle. Information presented below come **from Dr. Mann's Team Leader Memorandum of** April 18, 2001 and the OCPB reviews of Dr. Sandra Suarez-Sharp of April 26, 2001 and June 3, 2002.

The dosing for Aerospan, with its integrated spacer, is at approximately 1/3 that for the Aerobid without a spacer device. Doses chosen for the adult patients were based on pharmacokinetic (PK) information that compared the systemic exposure of the proposed Aerospan (flunisolide HFA) Inhalation Aerosol drug product to the marketed Aerobid (flunisolide CFC) Inhalation Aerosol drug product in adults. No formal pharmacokinetic studies were performed using the Aerospan in children. Therefore, dose selection in children relies completely on the results of the two pediatric clinical studies.

Reviewer's Note: The overall strategy for the switch program appears to have been based on the assumption that matching up systemic exposure of test (flunisolide HFA) to the reference (flunisolide CFC) is sufficient for dose-finding. Basing the clinical dose on systemic exposure (AUC) is not a conventional approach, as systemic exposure for an inhaled drug that is locally active may not predict efficacy. However, it may have important implications for safety, since matching the clinical exposure of various dosages of the two drug products allows for safety information from the old drug product to be ported to the new. Please see the labeling for efficacy and safety sections of this review for details.

There were 5 studies designed to assess the pharmacokinetics of flunisolide HFA (Table 1). 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 flunisolide HFA and Aerobid® CFC. **Dr. Suarez-Sharp's** review noted that **"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. However, because the clinical relevance of scintigraphy is unknown, the sponsor should be discouraged to reflect any **lung deposition information in the label."**

Based on AUC values, dose proportionality was shown in a single-dose study (ANC-PK-97-04), but not in a multiple-dose study (ANC-PK-97-03). It was noted that the dose adjusted AUC for a single puff of flunisolide HFA was significantly lower than that obtained after two or four puffs. The applicant argued that over the dose range of 80-320 mcg, the values for Cmax increase proportionally with dose after single- as well as multiple-dose administration. Dr. Suarez-Sharp felt that this argument was acceptable, and the label claim of dose proportionality was therefore acceptable. However, the lack of AUC dose proportionality raised some concern in children, in whom a single puff is recommended. While inability to demonstrate dose proportionality was not felt to be an approvability issue (as this finding is not entirely uncommon with the inhaled corticosteroids), the efficacy of a single puff of HFA flunisolide in children came to depend entirely upon the clinical data.

The proposed labeling includes results from HPA axis evaluations in the two 12-week, placebo- and active-controlled clinical trials and the two open-label, active-controlled, long-term safety studies. This is acceptable, although the proposed text needed extensive

editing to present the data clearly. Please see the Clinical and Labeling sections of this review for details of the studies and assessments.

The proposed labeling includes results from HPA axis evaluations from two PK/PD studies (ANC-PK-97-04 and ANC-PK-97-03). In these studies, the cortisol assessments were made either after a single dose (ANC-PK-97-04) or after single and multiple doses (13.5 days) (ANC-PK-97-03). Dr. **Sandra Suarez-Sharp's original** review concluded that hydrocortisone data from these studies should not be placed in the label. Her reasoning was that both evaluated a limited number of subjects and the larger study used a parallel design. Nevertheless, I believe it is important to include a brief description of these data to clarify how the applicant approached dose-finding for the new product. A paragraph was crafted to convey this information in the Pharmacodynamic subsection.

The following summary of the ADME, special population, and PK/PD correlation **information for flunisolide comes from Dr. Suarez-Sharp's review** [*Note that it retains the — cg description of the Aerospan drug product*]:

Table 1. Summary of PK studies submitted to original application

Study	Design	Remarks
ANC-PK-98-06	SD and MD 3-way crossover dose proportionality study in 21 healthy males and females. Treatments arms: Aerospan 80, 160, 320 mcg.	To-be-marketed device and formulation used in clinical trials
ANC-PK-97-02	SD 2-way crossover in healthy young males to compare deposition and PK with and without a spacer	Used a different valve and actuator (gasket, actuator) than that used in some clinical studies
ANC-PK-97-03	SD and MD parallel group safety, tolerability, and dose proportionality study in 31 healthy males and females. Treatments arms: Flunisolide HFA 160 and 320 mcg, and Aerobid 1000 mcg administered BID for 13.5 days.	
ANC-PK-97-04	SD 3-way crossover study in 11 healthy young males to evaluate delivery devices with and without a spacer. Treatments arms: Flunisolide HFA 4 puffs with (320 mcg) and without (? mcg) a spacer, Aerobid 4 puffs (1000 mcg).	
ANC-PK-96-01	SD 4-way crossover study in healthy young males to compare the safety and PK of HFA and CFC	Used spacer, which was discontinued due to low bioavailability of flunisolide after inhalation

Source: OCPB review, Dr. Sandra Suarez-Sharp, April 26, 2001

Clinical and Statistical

The clinical development program for Aerospan was reviewed in the first review cycle, but is summarized here. The program included four pivotal clinical trials (shown in Table 2): two 12-week efficacy and safety studies (ANC-MD-01 and ANC-MD-03) and two 1-year safety studies (ANC-MD-02 and ANC-MD-04), one each in adults/adolescents, and one each in children. The results of the 12-week studies were submitted with the original application (April 27, 2000), whereas the safety data from the long-term studies were submitted in the 120-day Safety Update to the original application (August 15, 2000) along with results of a fifth study (single-dose crossover study, ANC-MD-05). Study ANC-MD-05, also submitted with the original application and shown in Table 2, was a four-way crossover study to evaluate the taste characteristics of three different systems for the delivery of flunisolide HFA. It was not considered pivotal, and did not yield any important safety information. Summaries of both efficacy and safety from the four studies are provided in the respective Efficacy and Safety sections below.

The safety update provided with this submission includes safety data from 12 studies, as shown in Table 3. Of these studies, two were placebo-controlled (ANC-MD-07 and ANC-MD-09). The applicant provided safety analyses of the combined placebo-controlled studies, the non-placebo controlled studies, and PK studies. Review of these

safety analyses will be found in the Safety Update section below. However, the Adverse Events section of the label primarily represents the results of the two placebo-controlled pivotal studies.

Table 2. Summary of studies submitted to the clinical section of the original application

Study	Population	Design	Duration	Treated (Tot/Flun)	Mean Age ± SD	Sex M/F
ANC-MC-01	Adult & adol mild-mod asthma	R, DB, PC, AC, MC, 2-wk AC run-in	12 weeks	669/288	36.0 ± 14.5	306/363
ANC-MC-02	Adult & adol mild-mod asthma	R, OL, AC, MC, flexible-dose, 1-wk AC run-in	52 weeks	215/162	33.1 ± 13.8	101/114
ANC-MC-03	Peds mild-mod asthma	R, DB, PC, AC, MC, 2-wk AC run-in	12 weeks	583/231	8.5 ± 2.0	380/203
ANC-MC-04	Peds mild-mod asthma	R, OL, AC, MC, flexible-dose, 1-wk AC run-in	52 weeks	235/152	8.3 ± 2.1	145/90
ANC-MC-05	Adult stable asthma	R, OL, PC, 4-way crossover (taste characteristics)	1 dose	52/52	36.2	22/30

Source: V2, p10

Table 3. Summary of studies with safety data in this re-submission

Study	Population	Design	Duration	Treated (Tot/Flun)	Mean Age ± SD	Sex M/F
ANC-MD-07	Peds mild asthma	R, DB, PC, MC, 1-wk run-in	52 weeks	242/119	6.5 ± 1.6	145/97
ANC-MD-08	Adult & ped mild-mod asthma	OL, MC, flexible dose, 1-wk run-in	52 weeks	31/31	19.0 ± 15.5	112/19
ANC-MD-09	Adult & adol mild-mod asthma	R, DB, PC, MC, 1-wk run-in	12 weeks	366/243	40.4 ± 14.2	143/223
ANC-MD-10	Adult asthma	R, DB, SC, 2-wk crossover	6 weeks	30/28	43.5 ± 9.8	6/24
ANC-MD-14	Adult mild-mod asthma	OL, SC	6 weeks	12/12	32.8 ± 6.6	6/6
ANC-MD-16	Adult mild-mod asthma	OL, MC, 2-wk run-in	8 weeks	47/47	38.6 ± 12.1	16/31
ANC-MD-17	Adult & adol mild-mod asthma	R, DB, AC, MC, 2-wk run-in	16 weeks	167/82	36.2 ± 13.7	57/110
ANC-MD-21	Adult & ped mild-mod asthma	OL, MC	5 weeks	134/134	32.5 ± 16.1	49/85
ANC-MD-22	Adult & adol mild-mod asthma	R, DB, AC, MC, 2-wk run-in	8 weeks	124//64	36.8 ± 15.0	44/80
22008	Adult asthma	R, SB, SD, AC	1 dose	52/26	44.1 ± 13.6	14/38
PPL-553	Adult mild asthma	OL, SC, 2-way crossover	1 dose	14/14	38 ± 9	10/4
PPL-663	Normal volunteers	OL, SC, 2-way crossover	1 dose	14/14	37.4 ± 13.2	7/7

Source: V2, p12

Efficacy

Support for approval of Aerospan comes from two pivotal placebo-controlled 12-week studies conducted in 1252 adult and pediatric mild-to-moderate asthma patients and two open label 52-week safety studies conducted in 450 adult and pediatric mild-to-moderate asthma patients, one of each in adults and adolescents and one of each in children.

The reader should be aware of the unusual design of this clinical development program, which entailed a switch from the CFC to the HFA formulation. The applicant started with finding HFA doses that matched to the flunisolide CFC drug product in systemic exposure. Then the clinical studies were performed using both the HFA and CFC drug products to support and confirm these doses.

Both efficacy studies assessed an identical primary endpoint of change from baseline in percent predicted FEV_1 after 12 weeks of treatment, as well as similar secondary endpoints and safety parameters. The studies employed an unusual study design of randomization following a two week open-label run-in period in which all patients received 500 mcg flunisolide CFC inhalation aerosol (Aerobid) BID to assure clinical stability. Patients were then followed to see if they maintained, improved, or lost stability. In these studies, Aerospan demonstrated consistent, statistically significant separation from placebo in the primary endpoint in adults and adolescents and in children 6-11 years. Except for the 80 mcg dose in adults, there was almost no separation of doses seen in either the adult or the pediatric study. Presumably this is because of the withdrawal from stability design, but also possibly because this is not always seen in ICS asthma studies. Efficacy was supported by trends in several secondary endpoints in adults and adolescents, but was not supported by these endpoints in children. Although the pediatric trial included 4-5 year old patients, efficacy was in this age group was assessed by secondary endpoints, and the results were judged to not be supportive of efficacy.

Reviewer's Note: The issues mentioned above are discussed in the sections related to implications for labeling, whereas the sections below regarding the conduct, results, review, and conclusions of each of the studies recount the information extracted from Dr. D. Birenbaum's Medical Officer review, Dr. M. Mann's Team Leader/Deputy Director review, and Dr. J. Gebert's Statistical reviews of the original application. While wording from the reviews is not specifically presented in quotation marks, much of the material comes directly from these reviews. The doses used in the clinical trials were originally represented as 85 mcg per actuation, but are more appropriately represented as 80 mcg. Since the original reviews used the 85 mcg representation, and since the information in this section summarizes those reviews, this section retains the applicant's original representation of 85 mcg per actuation. Note also that the original reviews refer to the drug product as HFA flunisolide rather than flunisolide HFA or Aerospan; this representation is kept when quoting from the source material.

Study ANC-MD-01

This was a 12-week, 33-center, double-blind, double dummy, parallel arm dose ranging, active- and placebo-controlled trial conducted in 669 asthmatics 12-78 years of age. All patients were nonsmoking asthmatics with an FEV_1 of 45-90% of predicted after a washout period, exhibited a 12% increase in FEV_1 after 180mcg of albuterol, and were using orally inhaled corticosteroids at a stable dose for a minimum of 30 days prior to screening.

Treatment arms included:

Product	Dosage	Administration	Dosing Group
HFA Flunisolide 85 mcg* (Aerospan)	85 mcg* BID	one puff BID	low dose HFA
	170 mcg* BID	two puffs BID	medium dose HFA
	340 mcg* BID	four puffs BID	high dose HFA
CFC Flunisolide 250 mcg (Aerobid)	250 mcg BID	one puff BID	low dose CFC
	500 mcg BID	two puffs BID	medium dose CFC
	1000 mcg BID	four puffs BID	high dose CFC
Placebo		BID	
* The dose per actuation is more correctly represented to be 80 mcg. For clarity, the information presented in this section retains the **applicant's original representation of 85 mcg** per actuation.			

Following a two week open-label run-in period in which all patients received 500 mcg flunisolide CFC BID (and albuterol as needed) to assure clinical stability, patients were randomized to treatment, and followed to see if they maintained, improved, or lost stability. Sample size was chosen to show comparability of the averaged HFA doses (170 mcg BID and 340 mcg BID) with the averaged CFC doses (500 mcg BID and 1000 mcg BID), with combined doses to have 180 patients for each formulation. The primary endpoint was the change from baseline in percent predicted FEV_1 after 12 weeks treatment. Baseline was defined as the study visit immediately following the two-week open label treatment period. The primary analysis was an ANCOVA analysis of the endpoint percent-predicted FEV_1 with baseline value as covariate and treatment effect in the model (no center factor or treatment by center interaction included). There was no discussion of multiple comparison issues in the protocol or study report, but the study **report mentioned the use of Tukey's method to analyze for dose response (using both** dose and log dose in a covariate model.) The primary efficacy variable was analyzed using this methodology.

At 12 selected sites, HPA axis was assessed by 24-hour creatinine-corrected urine free cortisol, cosyntropin (Cortrosyn) stimulation test (i.e. plasma cortisol levels), and markers of bone metabolism (urinary deoxypyridinoline and serum osteocalcin). To be considered normal, the cosyntropin stimulation response required a plasma cortisol increment of at least 7 mcg/100mL above control and an absolute plasma cortisol value ≥18 mcg/100mL within 60 minutes after administration.

Demographics, previous history, and baseline efficacy variables of treatment groups were comparable. There were 88 patients 12-17 years of age. Most patients had mild-moderate asthma, with mean percent predicted FEV1 72.4 at screening. As might be expected, there were more discontinuations (32.7%) from the placebo group than other treatment groups (11.5-22.4%).

The applicant's results were confirmed by the FDA statistical reviewer. Table 4 and Table 5 show the treatment means and p-values compared to placebo for the primary efficacy variable. Both the medium (170 mcg BID) and high dose (340 mcg BID) HFA arms were superior to placebo for the primary endpoint (p=0.012 and p=0.003,

respectively). After a rise in percent predicted FEV_1 during the run-in period for all treatment groups, percent predicted FEV_1 declined over the course of treatment for the placebo group whereas percent predicted FEV_1 was maintained for the 170 mcg and 340 mcg BID HFA treatment groups, as shown in Figure 1. Placebo patients deteriorated 4.3% from baseline after 12 weeks of treatment while the 170 mcg BID arm deteriorated by only 0.2% and the 340 mcg BID arm improved by 0.3%. While the effect size (difference between treatment and placebo for primary endpoint) was less than the 5% difference used to power the trial (4.06% and 4.58% differences, for medium and high doses, respectively), actual FEV_1 differences (161cc and 186cc for medium and high doses, respectively) reflected a reasonable measure of clinical benefit. In the PI, the applicant is seeking to show the results of the study graphically, but uses percent change from screening FEV_1 rather than the primary variable and endpoints. This is not appropriate.

Secondary efficacy parameters, including AM (peak flow rate) PEFR, AM and PM asthma symptom scores, as needed albuterol use, and nocturnal awakenings, 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 and showed a trend for dose ordering among the three HFA arms.

The flunisolide CFC arms were included for the purpose of including comparisons of interest, and not to show non-inferiority. As expected, both the medium and high dose CFC doses demonstrated efficacy versus placebo based on the primary endpoint. **Comparing HFA to CFC "dose for dose":** the low dose HFA arm performed somewhat better than the low dose CFC arm, while medium and high doses of each formulation were fairly comparable with a suggestion that the CFC 1000 mcg dose may be more effective than the HFA 340 mcg dose.

There were no safety signals of concern. **AE tables are shown in Dr. Birenbaum's** review, but not shown here. The trial included an assessment of urinary cortisol levels and also evaluated the incidence of non-responders to a Cortrosyn 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.

The conclusion from the primary and secondary reviews was that this study supports the approval of Aerospan for the maintenance control of asthma in adults and adolescents age 12 and older. Both 170 mcg BID and 340 mcg BID dosages showed efficacy, with a subtle evidence of added benefit for 340 mcg BID over 170 mcg BID for both primary and secondary efficacy endpoints and no evidence of increased risk. The recommendation was for starting doses of 170 mcg BID (2 puffs BID), with instructions that doses up to 340 mcg BID (4 puffs BID) could also be used.

Table 4. ANC-MD-01, Treatment means (Standard Deviations) for % predicted FEV_1

Product	Dosage	N	Baseline	12 Weeks (LOCF)	Change
HFA	85 mcg BID	73	81.8 (14.3)	79.1 (15.3)	-2.6 (11.3)
	170 mcg BID	100	79.2 (15.2)	79.2 (18.4)	0.0 (12.0)
	340 mcg BID	113	80.6 (14.7)	81.0 (16.1)	0.4 (9.8)
CFC	250 mcg BID	75	81.1 (16.4)	75.2 (20.1)	-5.9 (14.9)
	500 mcg BID	103	79.7 (15.5)	79.6 (18.1)	-0.1 (11.1)
	1000 mcg BID	98	79.5 (17.6)	81.3 (18.8)	1.7 (10.8)
Placebo		101	83.6 (12.0)	79.1 (16.4)	-4.5 (12.2)

Source: FDA review: Dr. James Gebert, March 2, 2001

Table 5. ANC-MD-01, Least squares means (LSM) and P-values* from ANCOVA for % predicted FEV_1

Product	Dosage	LSM Placebo	LSM Treatment	Difference	p-value
HFA	85 mcg BID	-4.369	-2.816	1.553	0.389
	170 mcg BID	-4.247	-0.190	4.057	0.012
	340 mcg BID	-4.247	0.332	4.579	0.003
CFC	250 mcg BID				
	500 mcg BID	-4.251	-0.221	4.029	0.012
	1000 mcg BID	-4.251	1.536	5.786	0.000

* Pairwise for placebo and HFA 85 mcg, within HFA + placebo for HFA comparisons or CFC + placebo for CFC comparisons. P-values are not corrected for multiple comparisons.

Source: FDA review: Dr. James Gebert, March 2, 2001

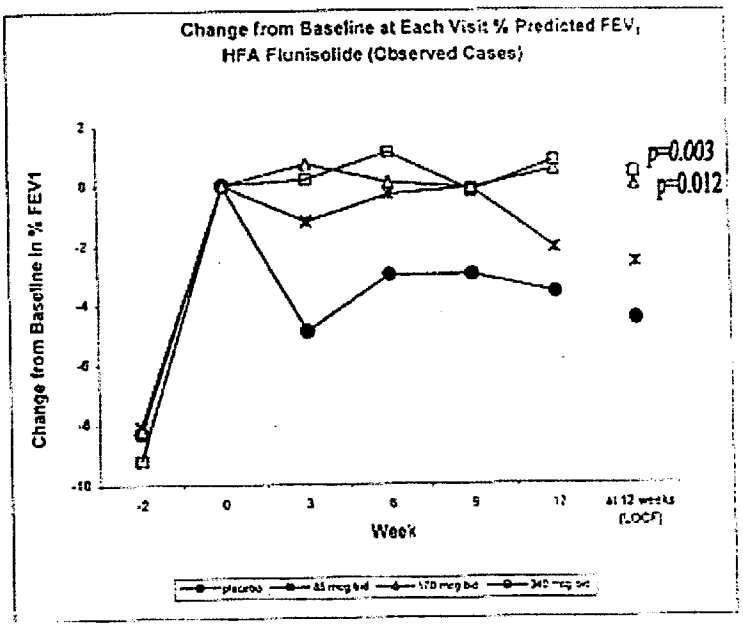

Figure 1. ANC-MD-01, Change from baseline in percent predicted FEV_1 at each study visit

Source: FDA review: Dr. D. Birenbaum, April 16, 2001, p26

Study ANC-MD-03

Study ANC-MD-03 was a 12-week, 51-center, double-blind, double dummy, parallel arm dose ranging, active and placebo control trial conducted in 583 mild-moderate asthma patients age 4-11 years, including 61 patients 4-5 years of age. The design was similar to that of Study ANC-MD-01, including evaluation of HPA axis at 12 study sites. Patients had to have a history of orally inhaled corticosteroid, nedocromil, or cromolyn use at stable doses, or asthma symptoms requiring the use of a short acting beta-agonist ≥3 times a week, for a minimum of 30 days prior to enrollment. Following the 2-week open-label run-in phase (flunisolide CFC 500 mcg BID), patients were randomized to the following treatment arms:

Product	Dosage	Administration	Dosing Group
HFA Flunisolide 85 mcg[1] (Aerospan)	85 mcg[1] BID	one puff BID	low dose HFA
	170 mcg[1] BID	two puffs BID	high dose HFA
CFC Flunisolide 250 mcg (Aerobid)	250 mcg BID	one puff BID[2]	low dose CFC
	500 mcg BID	two puffs BID[2]	high dose CFC
Placebo		BID	

[1] The dose per actuation is more correctly represented to be 80 mcg. For clarity, the information presented in this section retains the **applicant's original representation of 85 mcg** per actuation.

[2] A spacer was used with the CFC drug product in patients 4-5 years of age

Patients were followed to see if they maintained, improved, or lost stability with a primary endpoint of the change from baseline in % predicted FEV_1. Efficacy in patients

4-5 years of age was assessed by in-clinic peak flow rates (PEFR), as well as by recorded diary parameters like asthma symptom scores. 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. The protocol did not stratify patients based on prior use of either inhaled or systemic corticosteroid.

A total of 583 patients were randomized and 571 patients were included in the ITT efficacy analysis (12 patients were randomized but had no efficacy data, 4 placebo, 4 HFA, 3 CFC). Of the ITT population, 61 were age 4-5 (evaluated by PEFR), while 510 patients were age 6-11 (evaluated by % predicted FEV_1). More males than females were randomized (65.2% versus 34.8%, respectively). The majority of patients were white (69.5%), and the mean age was 8.5 ± 2.0 years. CFC and HFA treatment groups had similar numbers and percentages (ranging from 9 patients and 7.9% to 13 patients and 10.6% per treatment group) of 4-5 year old patients, however, the placebo group had the highest number and percentage (18 patients, 15.5%). The treatment groups were comparable at baseline in demographic and baseline efficacy variables. Most patients had mild asthma, with mean percent predicted FEV_1 81.2% at screening. Prior inhaled corticosteroid use was 51% in the placebo group, 57% in both HFA groups, and 51% and 59% in the low and high dose CFC groups, respectively. Prior use of oral or parenteral corticosteroid was low but not similar across treatment arms (1.7% and lowest in the placebo group, 8.1% and highest in the 250 mcg CFC group). Balance across treatment arms for this history of prior exposure is important in assessing the effects of the study treatment on the HPA axis. Treatment groups experienced a mean 6.2% improvement in % predicted FEV_1 during the run-in phase.

Results for the primary efficacy endpoint in children age 6-11 are presented in Table 6 and Table 7. As in study ANC-MD-01, after a rise in percent predicted FEV_1 during the run-in period for all treatment groups, percent predicted FEV_1 declined over the course of treatment for the placebo group whereas percent predicted FEV_1 was maintained for the active treatment groups, as shown in Figure 2. Significant differences from placebo were seen for HFA 85 mcg BID and HFA 170 mcg BID for the primary efficacy analysis as well as for the CFC doses. The results were surprising in that the lower HFA dose had the better result, whereas the CFC dose arms showed the anticipated dose ordering effect. As in the adult and adolescent trial, effect size was less than the 5% difference used to power the trial. Although there was no stated methodology for handling multiple comparisons, the FDA statistician considered **that "both doses of the HFA formulation** were significantly different from placebo using pairwise tests and for suspected comparability of the 170 mcg dose with the approved CFC dose for children (making this comparison the primary comparison of interest) both HFA doses should be considered **significant for the primary efficacy variable."**

The study did not support the efficacy of Aerospan in children 4-5 years of age. PEFR showed favorable trends for both HFA treatment arms compared to placebo, but there were no statistically significant differences between the HFA treatment and placebo for endpoint in-clinic PEFRs or diary variables in 4-11 year olds or in the 6- 11 year old subset, with no apparent added benefit for the HFA 170 mcg BID arm over HFA 85 mcg BID. Dr Mann noted various possibilities for these results, including the relatively small sample size of 4-5 year patients, the variability in this endpoint, and the possibility that

younger patients may find the inhaler more difficult to use reliably. In the end, the decision was made that the evidence did not support use in the 4-5 year old population.

The comparison of HFA to CFC treatment groups for the primary variable in 6-11 year old patients is of interest. There were no significant differences between HFA 170 mcg BID and CFC 500 mcg BID groups for the primary efficacy parameter or any of the secondary efficacy parameters in these patients. Unlike in the HFA treatment groups, in the CFC treatment groups a dose response trend was noted (Table 7).

There were no serious safety signals of concern. AE tables are shown in Dr. **Birenbaum's review, but not shown here.** 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 Cortrosyn 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 mcg BID arm, 1 in the CFC 250 mcg arm, and 1 in the CFC 500 mcg BID arm. While oral moniliasis did not reach an incidence of >3% and is therefore not reflected in the [PI] AE table, the incidence was between 1-3% and is reflected in the AE listings following the AE table.

The conclusion from the reviews was that this study supports the approval of Aerospan for the maintenance control of asthma in children age 6 through 11, but not in patients age 4-5 years. There was no clear treatment difference between any of the four active treatments. Both HFA dosages (85 mcg and 170 mcg BID) were effective in maintaining control of asthma in children age 6 through 11, but there was no added benefit for the 170 mcg BID dose over the 85 mcg BID dose for either primary or secondary efficacy endpoints. Importantly, there was also no evidence of increased risk for the higher dose. The recommendation was for starting doses of 85 mcg BID (1 puff BID), with instructions that 170 mcg BID (2 puffs BID) could also be used. The reviews concluded that the data from this study do not support the efficacy of Aerospan for children age 4-5 years. An additional study, perhaps using PEFR as an endpoint and including a larger sample size, was recommended to validate efficacy in this population.

Table 6. ANC-MD-03, Treatment means (Standard Deviations) for % predicted FEV_1

Product	Dosage	N	Baseline	12 Weeks (LOCF)	Change
HFA	85 mcg BID	103	88.6 (12.45)	89.8 (17.52)	1.2 (12.03)
	170 mcg BID	103	87.7 (13.87)	87.9 (18.02)	0.2 (12.18)
CFC	250 mcg BID	110	88.2 (15.94)	88.7 (16.80)	0.5 (13.68)
	500 mcg BID	103	87.5 (14.61)	90.2 (13.34)	2.6 (9.59)
Placebo		95	85.0 (14.31)	81.6 (17.57)	-3.4 (13.41)

Source: FDA review: Dr. James Gebert, March 2, 2001

Table 7. ANC-MD-03, Least squares means (LSM) and P-values* from ANCOVA for % predicted FEV_1

Product	Dosage	LSM Placebo	LSM Treatment	Difference	p-value
HFA	85 mcg BID	-3.55	1.32	4.87	0.008
	170 mcg BID	-3.53	0.35	3.88	0.034
CFC	250 mcg BID	-3.83	0.84	4.67	0.012
	500 mcg BID	-3.70	2.94	6.64	0.0001
* Within HFA + placebo for HFA comparisons or CFC + placebo for CFC comparisons. P-values are not corrected for multiple comparisons					

Source: FDA review: Dr. James Gebert, March 2, 2001

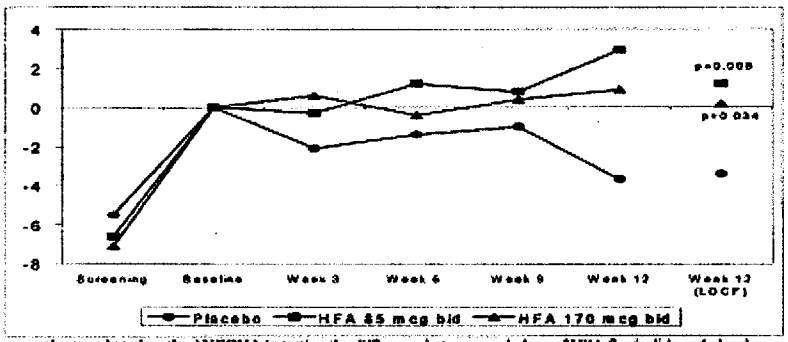

Figure 2. ANC-MD-03, Change from baseline in percent predicted FEV_1 at each study visit

Source: FDA review: Dr. D. Birenbaum, April 16, 2001, p49

Data Quality, Integrity, and Financial Disclosure

DSI audits were carried out during the initial application review cycle. At that time, an inspection of Study ANC-MD-03 (the pediatric study) Site 26 (Dr. Leonard Caputo) questioned the data integrity for this site. The agency notified the applicant and requested a reanalysis of the data from Study ANC-MD-03, deleting patients from this site. The applicant responded in a submission dated February 14, 2001.

The site enrolled a total of 22 patients, of which 20 were randomized and 17 were included in the intent-to-treat (ITT) population in the original analyses. Fourteen patients were in the 6- to 11-year-old group. The **applicant's reanalysis is presented in** Table 8. FDA review concluded that these results were similar to the original analysis and lead to the same conclusion that for the primary efficacy analysis that both doses of Aerospan were significantly different from placebo. Other efficacy variables did not show significance for the pediatric population.

Table 8. Study ANC-MD-03, Treatment Means (Standard Deviations) for Percent-Predicted FEV_1 for Patients Aged 6-11 Years with Site 26 patients deleted

	N	Baseline	12 Weeks (LOCF)	Change
Placebo	93	84.9 (14.36)	81.7 (17.62)	-3.3 (13.52)
HFA 85 mcg BID	100	88.8 (12.40)	90.0 (17.44)	1.2 (12.15)
HFA 170 mcg BID	100	87.6 (14.03)	88.0 (18.14)	0.4 (12.18)
CFC 250 mcg BID	107	88.2 (16.11)	88.6 (16.97)	0.5 (13.74)
CFC 500 mcg BID	99	87.6 (14.76)	90.3 (13.53)	2.7 (9.62)

Source: FDA Review, Dr James Gebert, March 5, 2001

Table 9. Study ANC-MD-03, Treatment Effects and P-values from ANCOVA (Pairwise) for Percent -Predicted FEV_1 for Patients Aged 6-11 Years

Treatment	Treatment Effect [a]	P-Value
HFA 85 mcg BID	4.82	0.010
HFA 170 mcg BID	3.99	0.032
CFC 250 mcg BID	4.56	0.015
CFC 500 mcg BID	6.57	<0.001
a Least squares mean of treatment – least squares mean of Placebo		

Source: FDA Review, Dr James Gebert, March 5, 2001

Labeling Implications for Efficacy: INDICATION, CLINICAL STUDIES, and DOSING AND ADMINISTRATION sections

The original clinical reviews (both primary and secondary) noted that the clinical trial data from the adult and adolescent pivotal study provided fairly robust evidence about the range of effective and safe doses in a population of non-smoking, relatively healthy, mild-to-moderate asthma patients (FEV1 of 45%-90% predicted), who had been previously maintained on orally inhaled corticosteroids but none of whom were on systemic corticosteroids. The reviewers felt that the proposed Indication was supported. Therefore, the INDICATION section requires no major changes, just minor editing.

The reviews went on to state that numerical dose ordering was observed, although dose response did not reach statistical significance; at the same time, systemic and local adverse events did not increase as dose increased. Although it was numerically better than placebo, the low dose (80 mcg BID) did not reach statistical significance. Therefore, this single study in adult and adolescents 12 years of age and older was felt to provide the basis for support of the applicant's proposed starting dose of 160 mcg BID (2 inhalations twice daily) in this age range, with a maximum dose of 320 mcg BID (4 inhalations twice daily).

Nevertheless, the original reviews expressed that there are limitations to the clinical data and what it brings to the labeling. The adult/adolescent study did not assess efficacy or safety of doses higher than 320 mcg BID. The reviewers were concerned that higher doses might be necessary to control asthma in more severe populations or in populations being weaned from systemic corticosteroids. Dosing information these populations was not generated in this development program. As a result they considered that this

information must be extrapolated from the Aerobid labeling, knowing roughly equipotent doses based on systemic exposure (PK data) and the efficacy data in the clinical study, while still maintaining the maximum daily dose of 320 mcg BID, as studied. The DOSING AND ADMINISTRATION section includes a dose conversion chart, along with a statement regarding the maximum recommended dose for each age group (Table 10). I do not agree with use of such a table. Please see the discussion below for my reasoning.

Table 10. Table for conversion of CFC or equivalent inhaled corticosteroid product to HFA dosing

	DOSE (mcg BID)	
Flunisolide CFC	500	1000
Flunisolide HFA	160	320

While I do have some concern with dosing above the approved doses, I do not share the same reasoning [as the original reviewers] as my basis of concern. I am concerned that physicians and patients, having become accustomed to prescribed doses up to 1000 mcg BID of the CFC product, may be tempted to use doses higher than 320 mcg BID thinking that the systemic exposure (and therefore safety) may be less. This may be fueled by the observation that the highest dose CFC group (1000 mcg BID) fared slightly better than the highest dose HFA group (320 mcg BID) [this was also true for the highest doses studied in the pediatric study], providing a suspicion that clinically the highest doses of the HFA may not be equipotent to the previous CFC drug product. However, given the safety profile of the two drug products at this point in time, I believe this is adequately handled in the labeling.

There is less confidence about pediatric dosing. The results of the pediatric study suggested that 6-11 year old mild-to-moderate asthma patients treated with 80 mcg BID was efficacious. Interestingly, no dose response was demonstrated between the 80 mcg and 160 mcg BID doses. In fact, reverse dose ordering was seen, despite the fact that in the PK studies in adults the dose adjusted AUC for a single puff was significantly lower than that obtained after two or four puffs. This makes it appear that numerically the highest dose CFC (500 BID) was superior to the highest dose HFA (160 BID). This makes it hard to interpret the results of the study. One possibility raised in the medical reviews was that the 80 mcg dose is at the plateau of the dose response curve for efficacy in this age range. I believe that the results are just what they are, perhaps a bit quirky, and one should be careful to avoid over-interpretation. Regardless, it was helpful that there was no dose ordering of adverse events. As a result, it comes down to this single study in children 6-11 years of age, quirks and all, to provide the basis for support of the **applicant's proposed starting dose** of 80 mcg BID (1 inhalation twice daily) in this age range, with a maximum dose of 160 mcg BID (2 inhalations twice daily). The original reviewers accepted the results to support the proposed dosing, as do I.

Just as for the adult study, there are limitations to the clinical data and what it brings to the labeling. Perhaps more than for the adult study, patients with more severe asthma were not enrolled and patients were not required to have been on ICS previously, requiring extrapolation of information from the Aerospan labeling to more severe patients. In addition, the highest adult dose of 320 mcg BID was not assessed, limiting

the maximum dose in patients 6-11 years of age to 160 mcg BID. Finally, Aerospan was only partially assessed in patients 4-5 years of age. Although efficacy was not demonstrated, no special safety concerns were noted either. On this basis, it is reasonable to mention this population in the setting of the clinical trials, but to limit the indication to patients 6 year s of age and older.

However, I have more fundamental issues with both of the studies. As noted earlier in this review, the design of this CFC-to-HFA switch development program was unusual and perhaps unorthodox. Dose-finding was based on systemic PK that matched exposure to HFA doses to the marketed flunisolide CFC drug product, Aerobid. Then the two clinical studies were performed using both the HFA and CFC drug products to confirm these doses and provide some general comparative data. This approach may be helpful from a safety perspective, but may not be ideal from an efficacy perspective, as systemic exposure related to safety more than it relates to local efficacy within the lung. In addition, both efficacy studies employed an unusual study design of withdrawal from stability. Following a two week open-label run-in period in which all patients received 500 mcg flunisolide CFC inhalation aerosol BID to assure clinical stability, patients were then randomized and followed to see if they maintained, improved, or lost stability. The primary endpoint was change from baseline in percent predicted FEV_1 after 12 weeks of treatment.

Such study designs maximize patient stability prior to randomization, and the resultant separation from placebo in primary and secondary endpoints is generally as a result of deterioration of the placebo treatment group. Therefore, such study designs are most suited to making a statement regarding clinical stability after a switch from a different ICS to Aerospan, but do not specifically define a dose for starting a patient on an ICS (i.e. providing a dose sufficient to stabilize a patient on ICS for the first time). As such, the designs are totally silent regarding onset of effect, as they are really looking at offset of effect. In addition, this program was limited to evaluations in a relatively narrow population and lacks data in different asthma populations, as is generally expected in a clinical development program. As a result, one gains a sense of the overall efficacy of a range of doses, but cannot make definitive statements regarding dosing.

Unfortunately, these issues were not addressed in the original clinical reviews, and a decision regarding Approvability has already been made. Presumably this decision was made based on the pharmacologic experience with this drug, with the expectation that the clinical trials would provide some evidence of the pharmaceutics of the new formulation. This reviewer did not attempt to go back to pre-NDA discussions that may have been held between the Agency and the applicant in the 1990s to identify the bases for these studies. That said, it is appropriate to remove the comparative dosing table, and to replace much of the comparative wording with more generic information re a range of doses, and titration to the lowest effective dose. In addition, information regarding onset of action should be modified and made more generic. The applicant also wished to include efficacy results from the two long-term, non-placebo-controlled safety studies within the CLINICAL TRIALS section, stating that Aerospan maintained efficacy clinically over the year of treatment. It is not appropriate to include uncontrolled results from a safety study in the efficacy section, so these statements were removed. Finally, statements should be inserted regarding the relative lack of data in certain populations,

e.g. patients who are maintained on oral corticosteroids, in the DOSING AND ADMINISTRATION section.

Safety

The safety database for this NDA comes from three sources, two of which were presented in the original application, and one of which is submitted with the latest complete response. The original application presented safety from the two 1-year safety studies and from the two pivotal 12-week efficacy and safety studies discussed above. As in the Efficacy section above, the information presented below regarding the conduct, results, review, and conclusions of each of the studies **are extracted from Drs. Birenbaum's and Mann's MO and TL reviews of the original application.**

The new information is from a safety update presented with this complete response. Since several of the studies presented in the safety update include safety information from long-term or placebo-controlled studies, selected studies were reviewed and are discussed in the subsection below.

Of note, while the 12-week placebo-controlled study (ANC-MD-01) in adolescents and adults enrolled patients up to 78 years of age, the open-label safety study (ANC-MD-02) only enrolled patients up to 62 years of age. In study ANC-MD-01, the number of geriatric patients was about 1%, so the number of geriatric patients evaluated in this application is too small to provide an adequate safety assessment in this age range.

Safety from Pivotal Efficacy Studies (ANC-MD-01 and ANC-MD-03)

In the two pivotal placebo-controlled trials, 519 adult and pediatric patients 4-78 years of age were exposed to Aerospan 80 mcg BID, 160 mcg BID, and 320 mcg BID for a mean duration of 76.7, 78.2, and 80.5 days, respectively (pediatric patients 4-11 years of age were not exposed to the 320 mcg BID dose). Safety information from each study is presented within the Efficacy section above, where the trials are discussed in full.

As part of my review, I matched the treatment-emergent AEs tables listed in previous reviews with those listed in the currently proposed PI (Table 11). The there were no discrepancies. While the Safety Update submitted with this complete response contained safety information from two placebo-controlled studies, these studies have yet to be reviewed. Therefore, the only placebo-controlled studies appropriate to inform the AE table in the label are the two pivotal placebo-controlled safety and efficacy studies.

Table 11. Proposed AE table for PI: Adverse Events reported in controlled trials (ANC-MD-01 and ANC-MD-03) with an incidence of >3% in any Aerospan group and more common than in the placebo group, % of patients

ADVERSE EVENT	PLACEBO (n = 220)	Aerospan (TWICE DAILY)		
		80 MCG (n = 189)	160 MCG (n = 217)	320 MCG (n = 113)
BODY AS A WHOLE				
Headache	12.7	9.0	13.8	8.8
Fever	5.0	6.9	3.7	0.9
Allergic Reaction	2.3	4.2	4.6	4.4
Pain	3.6	2.6	4.6	1.8
Accidental Injury	2.3	3.7	3.7	3.5

ADVERSE EVENT	PLACEBO (n = 220)	Aerospan (TWICE DAILY)		
		80 MCG (n = 189)	160 MCG (n = 217)	320 MCG (n = 113)
Infection, Bacterial	0.9	3.7	0.9	0.9
Back Pain	2.3	0.5	3.2	1.8
DIGESTIVE SYSTEM				
Vomiting	4.1	4.2	4.6	0.0
Dyspepsia	1.4	2.1	3.2	3.5
RESPIRATORY SYSTEM				
Pharyngitis	13.2	17.5	16.6	16.8
Rhinitis	10.0	9.0	15.7	3.5
Cough Increased	7.7	8.5	5.5	1.8
Sinusitis	5.5	7.4	4.1	8.8
Epistaxis	0.9	3.2	0.9	0.0
SKIN AND APPENDAGES				
Rash	3.2	2.6	3.7	1.8
UROGENITAL SYSTEM				
Urinary Tract Infection	0.5	1.1	0.9	3.5

Sources: FDA review: Dr. D. Birenbaum, April 16, 2001, p118; Proposed PI for Aerospan 7/26/2005.

Long-term Safety Studies

The two 52-week safety studies were not placebo-controlled. Both were open-label, active-controlled safety studies, in which 314 adult and pediatric patients received Aerospan. Of the 162 randomized adult and adolescent patients who were exposed to Aerospan for a mean duration of 279 +/- 127 days, 100 completed the study. Of the 152 randomized pediatric patients who received Aerospan for a mean duration of 295 +/- 120 days, 106 completed the study.

Reviewer's Note: Information presented below regarding safety from the two pivotal studies comes from Dr. Mann's Deputy Director/Team Leader secondary review of the original application, dated April 24, 2001. For convenience and clarity, it is reproduced here in full. For this reason, section retains the applicant's original representation of 85 mcg per actuation.

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 mcg total daily dose for beclomethasone and 680 mcg 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."

[*Reviewer's Note: The study included measurement of 24-hour urinary free cortisol and effects of Cortrosyn stimulation at baseline (week 2) and at weeks 26 and 52 in a subset of patients at 15 selected sites.*] "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. Cortrosyn stimulation tests were also performed in a subset of patients and showed similar results across treatment groups for mean values, with slightly more non-responders 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 follow-up was not very good, with one third of flunisolide and one quarter of beclomethasone 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 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 Cortrosyn 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 follow-up was not very good, with one third of flunisolide and cromolyn patients discontinuing prematurely versus about one fifth of beclomethasone 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."**

In addition, Dr. Birenbaum's review noted that, although growth was evaluated in this study, the design was not adequate to allow for meaningful interpretation of the results. There were also concerns about the evaluations of HPA axis in this study, and it was felt that the methodology did not allow a clear assessment of long-term effects on HPA axis. Randomization was accomplished without stratification based on prior history of steroid exposure, and HPA axis was assessed by cosyntropin stimulation in a subset of patients and not evaluated by timed urinary or blood cortisol levels. In general, cosyntropin stimulation is more appropriate for assessment of HPA axis dysfunction, whereas timed urinary or blood cortisol levels are felt to be more sensitive to minor alterations in HPA axis function.

Safety Update

Reviewer's Note: The Safety Update retained the applicant's original representation of 85 mcg per actuation. Because several tables from the applicant's submission are shown, this section retains the 85 mcg per actuation representation.

The safety update provided with this submission included safety data from 12 studies in 1233 subjects, of whom 814 were treated with at least one dose of Aerospan. Two of these studies were placebo-controlled (ANC-MD-07 and ANC-MD-09) and therefore potentially could inform the labeling for this drug product. However, it is important to note that the study reports for these two placebo-controlled studies were not submitted to the original NDA; as a consequence the full study reports have not been previously reviewed. While the applicant states that ANC-MD-07 was previously submitted to the NDA, this occurred with the previous complete response, and the applicant was informed at that time to wait until the application is approved prior to submitting a new supplement to the NDA with previously unreviewed studies. For this reason, at this point in time this

safety information is of limited value. For example, it would be inappropriate to place safety information from these studies into the AE table in the Adverse Events section, although AE information from these studies could be placed in the 'Adverse Events from other Sources' sub-section of the Adverse Events section. Hence, the only material submitted and reviewed here is the summary data submitted as part of the Safety Update in this complete response.

That said, safety data from these two studies as well as the non-placebo controlled studies are presented in several sections below. The applicant provided safety analyses of the four combined placebo-controlled studies, the non-placebo controlled studies, and PK studies. The applicant's safety analysis compared the two adult and the two pediatric placebo controlled studies. Since the two new studies were not reviewed in depth, this analysis is considered reasonable only for assessing if there were any new safety trends, and the new material was reviewed with that frame of reference. Safety information from the uncontrolled studies was reviewed in a cursory fashion for trends only.

Overall, my review revealed no new safety trends, with one exception: similar numbers and percents of patients discontinued due to a treatment emergent adverse event (TEAE) for the AE of asthma exacerbation in the placebo and in the 340 mcg QD arms in study ANC-MD-09, whereas the number and percent of TEAEs in the 170 mcg BID arm were numerically less (Table 12). While no evaluation of efficacy of this dose was undertaken here, the implication may be that the 340 mcg QD dose may not provide pharmacodynamic effects to the site of action in the lungs similar to the same nominal daily dose but divided into a BID dosing. This is not surprising, as similar findings have been noted with other orally inhaled corticosteroids that are meant to be dose in a BID fashion, but are dosed in a daily fashion instead.

A total of 19 patients in the 12 studies reported serious adverse events (SAEs) during the treatment phase, of whom 9 received placebo, 8 Aerospan, and 2 fluticasone MDI. Review showed no trends in SAEs. SAEs and TEAEs in the placebo-controlled studies are discussed below.

Table 12. TEAEs resulting in discontinuation from placebo-controlled studies ANC-MD-07 and ANC-MD-09

Panel 13. TEAEs That Resulted in Discontinuation from Placebo-Controlled Studies ANC-MD-07 and ANC-MD-09

	ANC-MD-07		ANC-MD-09		
	Placebo (N=123)	HFA flunisolide (N=119)	*Placebo (N=123)*	*HFA flunisolide*	
				340 mcg QD (N=121)	*170 mcg BID (N=122)*
	Number (%) of Patients in Safety Population				
Total Discontinued*	8 (6.5)	4 (3.4)	20 (16.3)	17 (14.0)	10 (8.2)
Preferred Term					
Asthma	6 (4.9)	0	14 (11.4)	15 (12.4)	6 (4.9)
Infection	0	0	1 (0.8)	2 (1.7)	1 (0.8)
Bronchitis	0	0	3 (2.4)	1 (0.8)	0
Sinusitis	1 (0.8)	0	2 (1.6)	1 (0.8)	0
Rhinitis	0	0	0	1 (0.8)	0
Fever	0	0	0	1 (0.8)	0
Nausea	0	1 (0.8)	0	1 (0.8)	0
Dyspnea	0	0	1 (0.8)	0	0
Dyspepsia	0	0	1 (0.8)	0	0
Stomach ulcer hemorrhage	0	0	1 (0.8)	0	0
Alopecia	0	0	0	0	1 (0.8)
Rash	0	0	0	0	1 (0.8)
Otitis media	0	0	1 (0.8)	0	0
Taste perversion	0	2 (1.7)	0	0	1 (0.8)
Cough increased	1 (0.8)	0	0	0	0
Ear disorder	1 (0.8)	0	0	0	0
Asthenia	0	1 (0.8)	0	0	0
Infection viral	1 (0.8)	0	0	0	0
Gastrointestinal disorder	0	1 (0.8)	0	0	0
Personality disorder	0	1 (0.8)	0	0	0
Insomnia	0	1 (0.8)	0	0	0
Dizziness	0	1 (0.8)	0	0	0

* An individual patient might be counted in more than one preferred term
Data source: Study report ANC-MD-07, Table 6.6; Study report ANC-MD-09, Table 5.4. (Appendix I)

Source: NDA 21-247, Submission of 7/27/05, V1, p26

Study ANC-MD-07

Study ANC-MD-07 was a 52-week multicenter, randomized, double-blind placebo-controlled growth study evaluating 170 mcg (2 puffs of 85 mcg) BID (n=119) or placebo BID (n=123) in 4-10 year old children with mild asthma. The applicant compared the safety data from this study with the 12-week, placebo-controlled, pivotal pediatric efficacy and safety study, ANC-MD-03. The studies being of different lengths, the extent of exposure was different, so comparisons are difficult. Demographic profiling showed that the patients in study ANC-MD-07, having been limited to a maximum inclusion age of 9.5 years (mean 6.5, SD 1.6 years), were younger on average than their counterparts in study ANC-MD-03 (mean 8.5, SD 2.0 years).

Review of the summary information for this study showed no safety trends. There were 7 SAEs reported, 6 in the placebo (4 asthma, 1 viral illness, 1 anaphylactic reaction), and 1 (hostility) in the Aerospan group. TEAE incidence by body system and treatment group are presented in Table 13, and TEAEs reported in ≥3% of patients treated with Aerospan are presented in Table 14 and Table 15. A total of 12 patients discontinued due to a TEAE, 8 (6.5%) in the placebo, and 4 (3.4%) in HFA flunisolide group. The two trends of note were not new or unexpected: 6 cases (4.9%) of asthma causing discontinuation in the placebo-treated patients vs 0 cases in Aerospan-treated patients, and 2 cases (1.7%) of taste perversion causing discontinuation in the Aerospan-treated patients vs 0 cases in placebo-treated patients.

Table 13. ANC-MD-03 and ANC-MD-07, TEAE incidence by body system and treatment group in children age 4-11 years

Panel 16. TEAE Incidence by Body System and Treatment Group in the Placebo-Controlled Pediatric Studies (Studies ANC-MD-03 and ANC-MD-07)

	ANC-MD-03			*ANC-MD-07*	
	Placebo (N=116)	HFA flunisolide (N=231)	CFC flunisolide (N=236)	Placebo (N=123)	HFA flunisolide (N=119)
	Number (%) of Patients				
At least one TEAE	*78 (67.2)*	*162 (70.1)*	*165 (69.9)*	*107 (87.0)*	*96 (80.7)*
Body as Whole	45 (38.8)	84 (36.4)	85 (36.0)	91 (74.0)	68 (57.1)
Cardiovascular System	1 (0.9)	1 (0.4)	1 (0.4)	2 (1.6)	0
Digestive System	10 (8.6)	36 (15.6)	30 (12.7)	26 (21.1)	27 (22.7)
Hemic and Lymphatic System	0	5 (2.2)	2 (0.8)	4 (3.3)	5 (4.2)
Metabolic and Nutritional Disorders	0	2 (0.9)	3 (1.3)	1 (0.8)	1 (0.8)
Musculoskeletal System	0	2 (0.9)	1 (0.4)	1 (0.8)	1 (0.8)
Nervous System	0	6 (2.6)	6 (2.5)	5 (4.1)	6 (5.0)
Respiratory System	52 (44.8)	103 (44.6)	110 (46.6)	79 (64.2)	67 (56.3)
Skin and Appendages	7 (6.0)	12 (5.2)	17 (7.2)	24 (19.5)	17 (14.3)
Special Senses	14 (12.1)	23 (10.0)	16 (6.8)	39 (31.7)	36 (30.3)
Urogenital System	0	2 (0.9)	6 (2.5)	7 (5.7)	4 (3.4)

Data Source: Study Report ANC-MD-03, Table 5.1.CS; Study Report ANC-MD-07, Table 6.2. (Appendix I)

Source: NDA 21-247, Submission of 7/27/05, V1, p35

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Table 14. ANC-MD-03 and ANC-MD-07, TEAEs reported in ≥3% of patients treated with Aerospan in children age 4-11 years, Part 1

Panel 18. TEAEs Reported in ≥3% of Patients Treated with HFA flunisolide in the Pediatric Placebo-Controlled Studies ANC-MD-03 and ANC-MD-07					
	ANC-MD-03			*ANC-MD-07*	
	Placebo (N=116)	*HFA flunisolide (N=231)*	*CFC flunisolide (N=236)*	*Placebo (N=123)*	*HFA flunisolide (N=119)*
	Number (%) of Patients			Number (%) of Patients	
At least one TEAE	*78 (67.2)*	*162 (70.1)*	*165 (69.9)*	*107 (87.0)*	*96 (80.7)*
Preferred Term					
Viral infection	15 (12.9)	15 (6.5)	23 (9.7)	61 (49.6)	45 (37.8)
Pharyngitis	19 (16.4)	44 (19.0)	39 (16.5)	35 (28.5)	27 (22.7)
Fever	10 (8.6)	19 (8.2)	19 (8.1)	24 (19.5)	27 (22.7)
Rhinitis	17 (14.7)	37 (16.0)	34 (14.4)	18 (14.6)	26 (21.8)
Cough increased	9 (7.8)	23 (10.0)	30 (12.7)	27 (22.0)	22 (18.5)
Sinusitis	7 (6.0)	19 (8.2)	10 (4.2)	22 (17.9)	16 (13.4)
Otitis media	9 (7.8)	10 (4.3)	11 (4.7)	16 (13.0)	16 (13.4)
Gastroenteritis	2 (1.7)	3 (1.3)	2 (0.8)	9 (7.3)	12 (10.1)
Headache	11 (9.5)	30 (13.0)	35 (14.8)	17 (13.8)	10 (8.4)
Asthma	17 (14.7)	23 (10.0)	26 (11.0)	10 (8.1)	2 (1.7)
Vomiting	6 (5.2)	15 (6.5)	10 (4.2)	12 (9.8)	10 (8.4)
Accidental injury	1 (0.9)	7 (3.0)	11 (4.7)	13 (10.6)	10 (8.4)
Ear disorder	1 (0.9)	1 (0.4)	0	9 (7.3)	9 (7.6)
Flu syndrome	4 (3.4)	4 (1.7)	8 (3.4)	15 (12.2)	8 (6.7)
Conjunctivitis	1 (0.9)	4 (1.7)	1 (0.4)	10 (8.1)	7 (5.9)
Bronchitis	2 (1.7)	4 (1.7)	4 (1.7)	10 (8.1)	6 (5.0)
Taste perversion	1 (0.9)	3 (1.3)	0	2 (1.6)	6 (5.0)
Rash	4 (3.4)	9 (3.9)	13 (5.5)	9 (7.3)	5 (4.2)
Abdominal pain	4 (3.4)	9 (3.9)	10 (4.2)	7 (5.7)	4 (3.4)
Voice alteration	0	0	3 (1.3)	0	4 (3.4)

Source: NDA 21-247, Submission of 7/27/05, V1, p39

Table 15. ANC-MD-03 and ANC-MD-07, TEAEs reported in ≥3% of patients treated with Aerospan in children age 4-11 years, Part 2

Panel 18. TEAEs Reported in ≥3% of Patients Treated with HFA flunisolide in the Pediatric Placebo-Controlled Studies ANC-MD-03 and ANC-MD-07

	ANC-MD-03			*ANC-MD-07*	
	Placebo (N=116)	*HFA flunisolide (N=231)*	*CFC flunisolide (N=236)*	*Placebo (N=123)*	*HFA flunisolide (N=119)*
Pain	1 (0.9)	8 (3.5)	8 (3.4)	4 (3.3)	3 (2.5)
Nausea	1 (0.9)	8 (3.5)	6 (2.5)	2 (1.6)	3 (2.5)
Diarrhea	1 (0.9)	7 (3.0)	6 (2.5)	4 (3.3)	3 (2.5)
Epistaxis	2 (1.7)	6 (2.6)	1 (0.4)	4 (3.3)	3 (2.5)
Laryngitis	0	4 (1.7)	0	6 (4.9)	3 (2.5)
Urticaria	1 (0.9)	2 (0.9)	1 (0.4)	7 (5.7)	3 (2.5)
Lymphadenopathy	0	1 (0.4)	1 (0.4)	4 (3.3)	3 (2.5)
Eczema	0	1 (0.4)	2 (0.8)	5 (4.1)	3 (2.5)
Ear pain	2 (1.7)	5 (2.2)	8 (3.4)	4 (3.3)	2 (1.7)
Infection bacterial	2 (1.7)	8 (3.5)	6 (2.5)	1 (0.8)	0

Data source: Study Report ANC-MD-03, Table 5.1.CS; Study Report ANC-MD-07, Table 6.2. (Appendix I)

Source: NDA 21-247, Submission of 7/27/05, V1, p40

Study ANC-MD-09

Study ANC-MD-09 was a 12-week multicenter, randomized, double-blind placebo-controlled study evaluating 340 mcg (4 puffs of 85 mcg) QD in the evening, 170 mcg (2 puffs of 85 mcg) BID, or placebo in adults and adolescents with asthma. Since the dose, duration, and population match to study ANC-MD-01, the applicant compared the safety data from these two studies. Demographic profiles and extent of exposure were similar.

Review of the summary information for this study provided with this application showed one new safety trend, discussed below. There were 3 SAEs reported, 3 in placebo-treated patients (1 asthma, 1 stomach ulcer/hemorrhage, 1 chest pain), and 3 in HFA flunisolide - treated patients (1 asthma, 1 ketosis, 1 abdominal pain/rectal hemorrhage). TEAE incidence by body system and treatment group are presented in Table 16, and TEAEs reported in ≥3% of patients treated with HFA flunisolide are presented in Table 17.

Table 16. ANC-MD-01 and ANC-MD-09, TEAE incidence by body system and treatment group in adults and adolescents

Panel 15 . TEAE Incidence by Body System and Treatment Group in the Placebo-Controlled Adult and Adolescent Studies (Studies ANC-MD-01 and ANC-MD-09)					
	ANC-MD-01			*ANC-MD-09*	
	Placebo (N=104)	HFA flunisolide (N=288)	CFC flunisolide (N=277)	Placebo (N=123)	HFA flunisolide (N=243)
	Number (%) of Patients				
At least one TEAE	*65 (62.5)*	*170 (59.0)*	*162 (58.5)*	*78 (63.4)*	*148 (60.9)*
Body as Whole	36 (34.6)	94 (32.6)	98 (35.4)	30 (24.4)	68 (28.0)
Cardiovascular System	1 (1.0)	10 (3.5)	3 (1.1)	5 (4.1)	3 (1.2)
Digestive System	14 (13.5)	29 (10.1)	25 (9.0)	19 (15.4)	24 (9.9)
Endocrine System	0	1 (0.3)	0	0	1 (0.4)
Hemic and Lymphatic System	1 (1.0)	0	0	0	3 (1.2)
Metabolic and Nutritional Disorders	3 (2.9)	6 (2.1)	9 (3.2)	6 (4.9)	4 (1.6)
Musculoskeletal System	2 (1.9)	8 (2.8)	5 (1.8)	6 (4.9)	10 (4.1)
Nervous System	4 (3.8)	13 (4.5)	14 (5.1)	4 (3.3)	7 (2.9)
Respiratory System	38 (36.5)	86 (29.9)	86 (31.0)	43 (35.0)	80 (32.9)
Skin and Appendages	5 (4.8)	13 (4.5)	16 (5.8)	5 (4.1)	10 (4.1)
Special Senses	4 (3.8)	14 (4.9)	8 (2.9)	3 (2.4)	20 (8.2)
Urogenital System	2 (1.9)	15 (5.2)	7 (2.5)	2 (1.6)	4 (1.6)
Data Source: Study Report ANC-MD-01, Table 5.1; Study Report ANC-MD-09, Table 5.1. (Appendix I)					

Source: NDA 21-247, Submission of 7/27/05, V1, p34

Table 17. ANC-MD-01 and ANC-MD-09, TEAEs reported in ≥3% of patients treated with Aerospan in adults and adolescents

Panel 17. TEAEs Reported in ≥3% of Patients Treated with HFA flunisolide in the Placebo-Controlled Studies ANC-MD-01 and ANC-MD-09

	ANC-MD-01			*ANC-MD-09*	
	Placebo (N=104)	*HFA flunisolide (N=288)*	*CFC flunisolide (N=277)*	*Placebo (N=123)*	*HFA flunisolide (N=243)*
	Number (%) of Patients			Number (%) of Patients	
At least one TEAE	65 (62.5)	170 (59.0)	162 (58.5)	78 (63.4)	148 (60.9)
Preferred Term					
Asthma	21 (20.2)	16 (5.6)	25 (9.0)	15 (12.2)	30 (12.3)
Rhinitis	5 (4.8)	18 (6.3)	16 (5.8)	7 (5.7)	26 (10.7)
Infection	0	3 (1.0)	5 (1.8)	11 (8.9)	25 (10.3)
Pharyngitis	10 (9.6)	44 (15.3)	37 (13.4)	14 (11.4)	18 (7.4)
Sinusitis	5 (4.8)	14 (4.9)	15 (5.4)	6 (4.9)	13 (5.3)
Accidental injury	4 (3.8)	12 (4.2)	12 (4.3)	6 (4.9)	13 (5.3)
Headache	17 (16.3)	27 (9.4)	34 (12.3)	9 (7.3)	12 (4.9)
Taste perversion	0	5 (1.7)	4 (1.4)	2 (1.6)	12 (4.9)
Bronchitis	0	5 (1.7)	0	6 (4.9)	8 (3.3)
Cough increased	8 (7.7)	7 (2.4)	10 (3.6)	7 (5.7)	7 (2.9)
Rash	3 (2.9)	6 (2.1)	11 (4.0)	3 (2.4)	6 (2.5)
Back pain	4 (3.8)	9 (3.1)	12 (4.3)	1 (0.8)	5 (2.1)
Pain	7 (6.7)	9 (3.1)	19 (6.9)	3 (2.4)	4 (1.6)
Viral infection	3 (2.9)	15 (5.2)	17 (6.1)	0	3 (1.2)
Allergic reaction	4 (3.8)	23 (8.0)	21 (7.6)	1 (0.8)	1 (0.4)
Dyspepsia	3 (2.9)	9 (3.1)	9 (3.2)	3 (2.4)	1 (0.4)

Data source: Study Report ANC-MD-01, Table 5.1.2; Study Report ANC-MD-09, Table 5.1. (Appendix I)

Source: NDA 21-247, Submission of 7/27/05, V1, p26

Non-Placebo-Controlled Studies

Of the 10 non-placebo-controlled studies, only two appeared to be of sufficient duration to yield much safety information, ANC-MD-08 and ANC-MD-17. Study ANC-MD-08 was a 52-week open label study. Drawbacks were that a flexible dose of HFA flunisolide was used, and the study population was quite small, 31 patients in total. Study ANC-MD-17 was a double-blind, randomized active-controlled study of 16 weeks duration in adult and adolescent asthmatics. Patients were randomized to either HFA 170 mcg (2

puffs of 85 mcg) BID or fluticasone 220mcg (2 puffs) BID. Because of the limitations of the safety data, the applicant's summary of safety was reviewed for any safety trends, but only the safety reports from the two placebo-controlled studies were reviewed in depth. My review showed no safety trends.

Special populations

Single and multiple dose pharmacokinetic studies with flunisolide HFA showed no specific gender differences; no formal pharmacokinetic studies were performed in other special populations. Among flunisolide HFA exposed patients across all four clinical trials, 53.8% were male and 46.2% were female. In the combined adult pivotal and 52 week studies, 79% were Caucasian, 13.2% were Black, 5.5% were Hispanic and 2.3 % were other. Gender and racial differences were not prospectively studied in the clinical trials, however, post-hoc assessments of the trial data uncovered no specific gender or racial differences for either safety or effectiveness.

Very few elderly patients received flunisolide HFA treatment in the single adult pivotal trial (1.0% >65 years of age) and none in the 52-week open-label trial.

Instead, more appropriate geriatric wording will be substituted, based on the Geriatric Labeling Guidance.

In the clinical studies with Aerospan, patients with renal and hepatic impairment were excluded from enrollment, so no specific information is available regarding these patients.

Also excluded from the clinical trials were pregnant patients. This drug is classified in Pregnancy Category C. As with other corticosteroids, flunisolide hemihydrate has been shown to be teratogenic and fetotoxic in rabbits and rats at doses of 40-200 mcg/kg/day.

Aerospan, with its integrated Bespak spacer, may not be an appropriate drug / delivery device for younger children and infants. While the sponsor included patients down to 4 years of age in one of the pivotal trials, efficacy in the 4-5 year age range was evaluated only by secondary measures. While there were no safety signals in this age range, there was no evidence of efficacy either; the label should reflect this information.

In the Precautions: Pediatric Use sub-section, the applicant proposes to include information from growth in the pediatric safety study and from a growth study with Aerospan. Growth information in the NDA submission was considered not interpretable, and the growth study has yet to be reviewed. Therefore, this information will be deleted from the labeling.

In the Agency NDA acknowledgement letter dated June 23, 2000, Forest Laboratories was asked to submit a pediatric drug development plan. In my review, I was not able to ascertain that this had been submitted. A request for a waiver was received with this submission. The Division has not changed it's view that a pediatric drug development plan for flunisolide for children and infants down to 6 months of age is needed. Therefore, the request for a waiver should be denied for ages 6 months through 5 years, but granted for below 6 months. Forest should be granted a deferral for the 6 month through 5 year age range.

Overall Assessment of the Safety Database and Applicability to Labeling

In general, the safety database for this NDA is relatively small, and relies in part on previous safety findings with the CFC formulation. Limitations of the safety database are as follows: The studies did not enroll patients with more severe asthma, cigarette smokers, patients who were taking systemic (oral) corticosteroids, patients with significant medical conditions, or pregnant/lactating women. The studies did not rigorously assess growth or HPA axis effects in children, or assess potential for cataracts, increased intraocular pressure, glaucoma, or decreased bone density in adults. Flunisolide is metabolized by the cytochrome p-450 metabolism; yet, drug-drug interaction was not assessed in the HFA switch program. Limitations with regard to special populations are discussed in the Special Populations section below.

Nevertheless, this approach is not unreasonable from a safety perspective, given the premise for the switch program of matching systemic exposure of the HFA to the CFC drug products. Such a design does allow consideration of accumulated safety data from the previous flunisolide CFC drug product. Such safety data is referred to in both the Clinical Pharmacology as well as the Adverse Reactions sections of the labeling, and is generally reasonable.

Bearing the limitations in mind, there were no unusual or unexpected safety findings in this program; i.e. most findings were expected based on the drug class, formulation, and route of administration. In general, it appears that the therapeutic margin of safety for HFA formulation is comparable to the CFC formulation. Therefore, class labeling for other orally inhaled corticosteroids is sufficient to deal with the labeling of safety issues.

However, the class labeling for orally inhaled corticosteroid drug products has changed somewhat since the NDA was submitted. Therefore, to complete the labeling, labeling was reviewed from more recently approved products, including Qvar®, Flovent® HFA, and Asmanex® Twisthaler. In particular, since patients on oral or systemic corticosteroids were not studied, with regard to instructions for medical providers about how to switch from systemic corticosteroids to inhaled corticosteroid aerosols the labeling relies upon the labeling from the previous CFC formulation as well as a table to allow switching from the CFC to comparable doses of HFA drug product. That said, a **brief summary from Dr. Birenbaum's review** of the safety findings follows.

Incidence of serious adverse events (SAEs) was low across all four studies. Among patients treated in the 12-week double-blind studies, 14/1252 experienced an SAE, with the highest percentage in the placebo group (1.8%) as compared to the pooled flunisolide group (1%). The most commonly reported SAE was asthma. Among patients treated in the two 52-week uncontrolled studies, 11/314 patients SAEs in the Aerospan group. Eight of these 11 patients were in the pediatric trial and 6 of these pediatric patients had exacerbations of asthma.

The most commonly reported side effects (>10% of all patients) in the two placebo controlled studies were pharyngitis, rhinitis and headache. Side effects that are known class effects of systemic corticosteroid drugs (adrenal insufficiency following systemic steroid withdrawal, HPA axis suppression, and growth suppression in children) were not observed. Local side effects such as pharyngitis, voice alteration, oral moniliasis, taste perversion and dyspepsia were more frequent in patients who received Aerospan.

Appropriately, the Adverse Reactions section relies almost entirely upon the two placebo-controlled studies, and as noted in a section above, the AE table appears to include all relevant AEs from those studies. There is a sub-section of Adverse Events from Other Sources, which includes the two open-label 52-week studies and additional AEs carried over from the CFC label.

In my review of the labeling there were two specific labeling issues pertaining to safety, only one of which was addressed adequately in the original reviews. The first (and adequately addressed) is the issue of including pediatric growth data from the long-term open label safety study. The applicant is seeking to add information from all four studies to the Clinical Trials and Precautions: Pediatric Use subsections. The reviews stated that monitoring for growth was not rigorously performed in the pediatric studies, and I agree. Monitoring of this type requires a degree of rigor that was not present in this development program. The applicant has performed a stand-alone growth study, but this has not yet been reviewed. The recommendation was that growth information not appear in the labeling, and I concur.

The second issue is that of inclusion of HPA axis evaluations from the two placebo-controlled and two open label studies. In addition to porting data from the CFC product, the applicant is seeking to add information from all four studies to the Pharmacodynamics subsection. The original reviews discuss the fact that monitoring for growth and HPA axis effects was not rigorously performed in the pediatric studies, but fail to make a recommendation regarding inclusion of the HPA information. The evaluation for HPA axis suppression by cosyntropin stimulation and/or urinary cortisols in the four studies did not reveal any significant findings. My sense was that the information is important to include in the labeling; the information should be extensively edited to more clearly and precisely present the results.

Porting of HPA axis data from the original CFC drug product does not appear reasonable, particularly in light of having data from the clinical trials with the HFA formulation. As far as I was able to determine, no dedicated HPA axis study was performed with either formulation. If it had been, this recommendation might have been different. However, the description of the CFC studies is generally poor, with no data on how they were conducted and no specific HPA axis results. In one case, a study included 6 healthy volunteers. Therefore, the relevance of such information with a different formulation is considered questionable. Data from small PK studies that did not use the to-be-marketed HFA device are also not of sufficient quantity or quality to include in the label.

That said, I do believe it is important to convey the applicant's unconventional methodology for dose-finding by linking PK and PD from the CFC and HFA formulations in two studies. This information should appear in the Pharmacodynamics subsection, as discussed in the Clinical Pharmacology and Biopharmaceutics section of this review.

Trade Name

During this review cycle, it was determined that the proprietary and established names should be Aerospan™ (flunisolide HFA, 80 mcg) Inhalation Aerosol. With this complete response submission (i.e. this review cycle), the applicant had proposed "Aerospan

HFA™ (flunisolide inhalation aerosol)". During this and previous review cycles, trade name consults were performed by the Division of Medication Errors and Technical Support (DMETS); acceptance of the trade name Aerospan was recommended on each occasion. In this cycle, DMETS had no objections to the trade name provided that only one of the following trade names is approved: Aerospan (NDA 21-247) ——— ——— and that the application be approved within 90 days of signature of the consult, dated November 14, 2005.

Summary and Recommendations

From a clinical perspective, this application was considered Approvable in the first review cycle. Although my review of the development program in this cycle reveals gaps in the program, the clinical recommendation has not changed. Bearing in mind the limitations of the overall program, a brief summary of what is supported in the labeling follows. For specific details of what the studies support with regard to labeling, please refer to the sections of this review entitled Labeling Implications for Efficacy: INDICATION, CLINICAL STUDIES, and DOSING AND ADMINISTRATION sections and Overall Assessment of the Safety Database and Applicability to Labeling, which may be found at the end of the Efficacy and Safety sections of this review, respectively.

The proposed indication is: "maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients 6 years of age and older." Previously the decision was made that approval is not supported in children age 4-5. In the first review cycle, we stated that for 4-5 year old patients a study that demonstrates efficacy over placebo would be required. The application also supports the following secondary indication: "Aerospan Inhalation Aerosol is also indicated for asthma patients requiring oral corticosteroid therapy, where adding Aerospan Inhalation Aerosol may reduce or eliminate the need for oral corticosteroids." This is acceptable based on previous labeling for the Aerobid (flunisolide CFC) drug product, similar systemic exposure (AUC and/or Cmax), and approximately equipotent clinical data.

The applicant's proposed dosages for each of these age ranges is appropriate. The recommended starting in adults and adolescents age 12 and older is 160 mcg twice daily (2 puffs BID), not to exceed 320 mcg twice daily. The recommended starting dose in children age 6 through 11 is 80 mcg twice daily (1 puff BID), not to exceed 160 mcg twice daily. However, the proposed table to convert patients from the CFC to the HFA drug product in the DOSING AND ADMINISTRATION section is not acceptable. The proposed labeling in this section requires modification to make it more generic to a range of doses that are clinically applicable to the individual patient. Since patients maintained on oral corticosteroids were not studied during the development program, the labeling should state as such and derive recommendations that are general to all patients being weaned from oral corticosteroids.

A request for a waiver for pediatric studies below 6 years of age was received with this submission. The Division has not changed it's view that a pediatric drug development plan for flunisolide for children and infants down to 6 months of age is needed. Therefore, the request for a waiver should be denied for ages 6 months through 5 years, but granted for below 6 months. Forest should be granted a deferral for the 6 month

through 5 year age range. Regarding future pediatric studies with this drug product, it should be kept in mind that because of the need to time inhalation with actuation and the use of a built-in spacer (not a holding chamber) this particular Aerospan Inhalation Aerosol drug product may not be appropriate for use in certain pediatric age ranges.

Near the end of the review cycle, the need was identified for Forest to commit to two postmarketing Phase 4 commitments, as discussed in this review and in the sections below.

Summary of Labeling Revisions

In this review cycle, labeling was addressed by all review teams. Labeling modifications were made based on the above review and recommendations. Carton and container labeling was addressed, although the PI and PPI were the focus of intense review and revision by the clinical team. The many interchanges between the Division and Forest during the course of the review cycle are not discussed or shown here. The following is a brief summary of the major changes to the labeling made by the Division and agreed to by the applicant during this review cycle.

- It was determined that the proprietary and established names should be AEROSPAN (flunisolide HFA, 80 mcg) Inhalation Aerosol. This is similar to the designation used for Qvar. The entire label was edited to follow this approach.
- The DESCRIPTION and HOW SUPPLIED sections were extensively edited. Appropriate wording was adopted from the Qvar®, Flovent® HFA, and Asmanex® Twisthaler labels.
- The Pharmacodynamics subsection was rewritten to more clearly present the HPA axis data from the four clinical studies. HPA axis data from the previous CFC formulation was removed. This section now represents more clearly how the clinical doses were decided upon as part of the Aerospan development program.
- The Clinical Trials subsection was extensively edited to reflect the nature of the two pivotal trials.
    - The original figures shown in the proposed labeling reflected change from screening in percent predicted FEV_1. This was not the primary efficacy measure. The figures were replaced with figures that show the primary endpoint of change from **baseline** in percent predicted FEV_1. Results are represented with time on the X axis, and percent predicted FEV_1 on the Y axis. The placebo treatment group is shown, but not the CFC treatment groups. The legend includes the N for each dosage. P-values are included. In Figure 1, the to-be-approved doses of Aerospan (160 and 320 mcg, but not the 80 mcg) and placebo are represented. Figure 2 follows a similar approach.
    - Growth data was removed (see comments below).
    - The applicant ensured that the presentation of the pediatric study, including the figure, reflects the number of patients without site 26. Updated numbers were included in this section.
- The WARNINGS and PRECAUTIONS sections were updated to match current labeling recommendations for inhalational corticosteroid drug products. Appropriate wording was adopted from the Qvar®, Flovent® HFA, and Asmanex® Twisthaler labels.

  - In the Clinical Trials and the PRECAUTIONS: Pediatric Use sub-sections, the applicant proposed to include information from growth in the pediatric safety study and from a since-completed growth study with Aerospan. Growth data from the original NDA clinical trials was considered not interpretable. Results of the stand-alone growth study were included in the fourth cycle submission, but not reviewed. Descriptions of these studies were removed from the labeling. The study report for the growth study should be (re)submitted as a supplement post-approval. In this section, the numbers of patients studied reflect the numbers exposed to Aerospan Inhalation Aerosol.
  - The PRECAUTIONS: Geriatric Use subsection was updated with the latest recommended geriatric wording, based on the Geriatric Labeling Guidance. In this section, the numbers of patients studied reflect the numbers exposed to Aerospan Inhalation Aerosol.
- The ADVERSE REACTIONS section was extensively edited. The primary AE table was verified from the original NDA review. Updated numbers were included in this section.
- The DOSAGE AND ADMINISTRATION section was revised and extensively edited. Since the time to onset of symptom relief was not studied in the clinical trials with the HFA formulation, more generic wording of 2-4 weeks onset was substituted. The proposed table to convert patients from the CFC to the HFA drug product was removed since the proposed dosing schema was not evaluated and equivalence was not evaluated between the proposed doses of the HFA drug product and approved doses of the CFC drug product. Labeling was modified to make it more generic to a range of doses that are clinically applicable to the individual patient. Since patients maintained on oral corticosteroids were not studied during the HFA development program, the labeling was changed to include recommendations that are general to all patients being weaned from oral corticosteroids, and are not specific to Aerospan alone.
- The Patient Instruction sheet (PPI) was extensively edited to present information at the level of understanding of the patient, not the physician. Since risk information should be presented separately from patient instructions for use, the PPI was separated into two sections, **a 'Patient Information' section and an 'Instructions for Use' section. The Division requested Forest** to replace some of the figures with updated figures. Because this instruction sheet is new, because Aerospan includes a built-in spacer, and because use of Aerospan Inhalation Aerosol requires precise timing of inhalation with actuation, I recommend that a label comprehension study be performed as a Phase 4 commitment to evaluate how effective the patient Instructions for Use in providing these instructions to patients. Part of this commitment should be to simplify the instructions as much as possible.

Request for Phase 4 Commitments

At the end of the review cycle, the need for two Phase 4 commitments was identified. The following comments were faxed to the applicant on January 26, 2005.

> We have completed our review of your NDA and have the following concerns regarding the device durability and labeling.

1. Ideally, in all Phase 2 and 3 studies utilizing the to-be-marketed formulation, patients are asked to report devices they perceive to be broken or malfunctioning. Any device so reported is then returned and evaluated to identify the problem. Device use and performance is also evaluated through directed questions defined in the protocols. In this way, information is generated regarding the types and frequencies of device malfunction based on data from a large number of devices, and an analysis of the cause may lead to potential improvements to the device itself. In addition, a small number (e.g. 100) of devices that are apparently **functioning normally in patients' hands** should be collected near the end of the life of the device and evaluated by in vitro performance testing. These evaluations were apparently not addressed in the development program for Aerospan Inhalation Aerosol, and must be addressed as a post marketing study commitment. The dose counter reliability study to which you have agreed would not adequately address the issue of device durability. However, collection of this type of information could be incorporated into clinical or marketing studies, if any further clinical studies are planned.
2. Aerospan Inhalation Aerosol is a complex device, including a built-in spacer that makes the device unique and increases the complexity of use. In addition, the instruction that the patient should inhale within one second of actuation is quite specific, and may not be easy for the patient to comprehend. While you have developed a specific tear-off Patient Instructions for Use to instruct patients in the proper use of the device, the instructions are quite complex and are untested in the hands of the patient. In order to evaluate the utility of the labeling, perform a label comprehension study to ensure that patients are able to read and use the device in the manner specified in the labeling. A label comprehension study should test, for example, whether the written instructions provide sufficiently clear instructions that patients can open, inspect, use, and close the device appropriately. It should also test whether the written instructions provide sufficiently clear instructions that patients can appropriately learn to time the inhalation to actuation. Such a study may identify any problems with the device handling and use, and inform modification of the Patient Instructions for Use.

In order to address these issues listed above submit post marketing study commitments as listed below.

1. A study to comprehensively address device durability and reliability.

   Protocol Submission: XXX (propose date)

   Study Start: XXX (date)

   Final Report Submission: Propose a date with a two-year time frame.
2. A labeling comprehension study to ensure that patients are able to read and use the device in the manner specified in the labeling.

   Protocol Submission: XXX (date)

   Study Start: XXX (date)

   Final Report Submission: Propose a date with a two-year time frame.

Comments for Approval Letter

I suggest that the following comments accompany the approval letter.

1. We remind you to submit the results of a growth study to the NDA.

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/s/

Peter Starke
1/27/2006 09:19:45 AM
MEDICAL OFFICER

Badrul Chowdhury
1/27/2006 09:41:16 AM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-247	**TRADE NAME:**	Aerospan™
APPLICANT:	Forest Laboratories, Inc.	**USAN NAME:**	Flunisolide HFA inhalation aerosol
MEDICAL OFFICER:	Katherine Szema, MD		
TEAM LEADER:	Peter Starke, MD	**CATEGORY:**	Corticosteroid
DUE DATE:	April 2, 2004	**ROUTE:**	Inhaled

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
October 20, 2003			Complete response to July 30, 2003 Approvable letter

RELATED APPLICATIONS

Document Date	Application Type	Comments
April 27, 2000		Original NDA submission for Flunisolide HFA inhalation aerosol

REVIEW SUMMARY:

This application is a fourth cycle complete response to an Approvable action for Aerospan™ (Flunisolide Hemihydrate, HFA Inhalation Aerosol) [previously called Flunisolide HFA Inhaler System, and later Aerospan™ (Flunisolide HFA) Inhalation Aerosol by the Applicant]. The original application was submitted on April 27, 2000, and the first Approvable action was taken on May 7, 2001. A complete response to that action was submitted on December 10, 2001, with subsequent second Approvable action taken on June 10, 2002. The most recent Approvable action was taken on July 30, 2003. In all previous cycles, the deficiencies were chemistry related; this submission addressed chemistry (and pharmacology/toxicology) issues only, with no clinical issues.

There are several major CMC issues, briefly summarized here. There may be a problem with the gasket composition. The analytical methods for extracting and analyzing leachables are not clearly identified. An extractables/leachables correlation has not been adequately defined. Some of the leachables have not been analyzed individually.

There are several major Pharm/Tox issues, briefly summarized here. These issues are new issues, being raised as leachables from the gasket have been identified by the Applicant and reported to the NDA. According to the pharmacology/toxicology reviewer, Larry Sancilio, Ph.D., there are [redacted] compounds that are of concern. [redacted] of these compounds have structural alerts far above the established cutoff of [redacted] y. Most of their values approach [redacted] /. [redacted] compounds do not have structural alerts; however, their values are close to [redacted] ay. Because of previously unidentified leachables, further genotoxicity assessments must be performed.

During both this and the previous cycle, trade name ODS consults were performed (Consult #01-0050-02, 01-0050-3). Acceptance of the trade name Aerospan was recommended on each occasion. Both consults included other labeling recommendations, of which only the CMC recommendations were addressed. Note that the Applicant proposes Aerospan™ (Flunisolide HFA) Inhalation Aerosol, whereas the trade name consult recommended the name Aerospan™ (Flunisolide Hemihydrate, HFA Inhalation Aerosol). It is recommended that the latter terminology be used. Of note for future review cycles, the labeling recommendations in both consults were not addressed in this cycle.

During the first review cycle, a clinical labeling review was written by Dr. D. Birenbaum. During this cycle clinical aspects of labeling were not addressed.

OUTSTANDING ISSUES:

Clinical aspects of labeling including relevant sections of the ODS trade name consults will need to be re-reviewed prior to labeling negotiations during the next cycle.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS	APPROVAL	X	APPROVABLE	NOT APPROVABLE

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/s/

Katherine Szema
4/1/04 01:19:40 PM
MEDICAL OFFICER
M.O. #4 review

Peter Starke
4/1/04 01:22:10 PM
MEDICAL OFFICER
I concur. (This is review cycle #4.)

Appears This Way
On Original

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-247	**TRADE NAME:**	Aerospan™
APPLICANT:	Forest Laboratories, Inc.	**USAN NAME:**	Flunisolide HFA inhalation aerosol
MEDICAL OFFICER:	Peter Starke, MD		
TEAM LEADER:	Eugene Sullivan, MD	**CATEGORY:**	Corticosteroid
DUE DATE:	24 July 2003	**ROUTE:**	Inhaled

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
5 February 2003			Complete response to June 11, 2002 Approvable letter
21 February 2003			Proposed canister and carton labeling

RELATED APPLICATIONS

Document Date	Application Type	Comments
27 April 2000		Original NDA submission for Flunisolide HFA inhalation aerosol

REVIEW SUMMARY:

This application is a third cycle complete response to an Approvable letter dated June 11, 2002, for Aerospan™ (Flunisolide HFA inhalation aerosol) [previously called Flunisolide HFA Inhaler System by the sponsor]. The original application was submitted on April 27, 2000, and the first Approvable action was taken on May 7, 2001. A complete response to that action was submitted on December 10, 2001, with subsequent second Approvable action taken on June 11, 2002. In both previous cycles, the deficiencies were chemistry related, and this submission addressed chemistry issues only, with no clinical issues.

There are several major CMC issues, briefly summarized here. There is concern with medication dose delivery, which rises at the end of the canister life. This finding is consistent across all batches, and is seen by dose measurement but not by cascade impaction. The rise is not explained by leakage of propellant from the canister. During this review cycle, the presence of a [redacted] in the drug product was addressed by submission of a negative SHE cell assay. However, the need to find methodology to minimize oxidation of the drug substance has not been addressed. Methodology for measurement of extractables is not finalized, and any new extractables may need to be qualified.

During this cycle, a trade name ODS consult resulted in acceptance of the trade name Aerospan. The consult did include other labeling recommendations, all of which were addressed by the CMC reviewer except for Dosage and Administration recommendations. During previous cycles, a clinical labeling review was written by Dr. D. Birenbaum. Therefore, during this cycle clinical aspects of labeling were not addressed, except that the label was scanned and compared to other inhaled corticosteroid labels to ensure that all relevant sections were present. While some labeling issues were identified, no sections were missing from the proposed package insert.

OUTSTANDING ISSUES:

Clinical aspects of labeling including relevant sections of the ODS trade name consult will need to be re-reviewed prior to labeling negotiations during the next cycle.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS	____	**APPROVAL**	X	**APPROVABLE**	____	**NOT APPROVABLE**
OTHER ACTION:							

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/s/

Peter Starke
7/24/03 04:23:23 PM
MEDICAL OFFICER

Eugene Sullivan
7/24/03 04:55:27 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division Of Pulmonary Drug Products (HFD-570)

APPLICATION #:	21-247	**APPLICATION TYPE:**	New Drug Application
SPONSOR:	Forest Laboratories, Inc.	**PROPRIETARY NAME:**	Flunisolide HFA Inhaler System
CATEGORY:	glucocorticoid	**USAN NAME:**	Flunisolide hemihydrate
		ROUTE:	Oral inhalation
MEDICAL OFFICER:	Debra Birenbaum, M.D.	**REVIEW DATE:**	April 16, 2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
April 27, 2000	April 27, 2000	New drug application	Submission does not contain the Final Study Reports from 2 long-term safety studies
May 31, 2000	June 1, 2000	NDA 21-247 N000BZ; IR Response	Revised Table of Contents
May 31, 2000	June 5, 2000	NDA 21-247 NC IR Response	Revised Table of Contents
June 16, 2000	June 20, 2000	NDA 21-247 BS; IR Response	Clarification for electronically submitted SAS data set contents
August 28, 2000	August 30, 2000	NDA 21-247 SU	120 day safety update including Final study Reports of 2 long-term safety studies
September 27, 2000	October 4, 2000	BM IR Response	TEAE Table for ANC-MD-01
April 05, 2000		IND 51, 456	Statistical review and analysis-SAS data sets and documentation
October 25, 2000	October 27, 2000	IND 51, 456; N-108	Annual Report for period 8/31/99-8/30/00
February 14, 2001	February 15, 2001	BM IR response	Re-analysis of efficacy excluding Site 26

RELATED APPLICATIONS

Application Type	Comments
NDA 18-340	Approved Aug 17, 1984: Aerobid Inhaler System (pMDI) containing flunisolide hemihydrate suspended in CFC propellant
NDA 20-409	Nasarel Nasal Spray
NDA 18-148	Nasalide Nasal Spray

REVIEW SUMMARY: Two adequate and well controlled Phase three studies evaluating the efficacy and safety of HFA flunisolide for the maintenance treatment of asthma as prophylactic therapy in 1252 adult and pediatric mild-moderate asthmatic patients were submitted in the NDA, as well as results from 5 pharmacokinetic studies in adults. Two 52-week, open label, active controlled studies in 450 adult and pediatric mild-moderate asthma patients evaluating safety were submitted with the 120-day Safety Report. Clinical data support the effective use of HFA flunisolide in the maintenance treatment asthma at the doses studied in adults and children ≥6 years of age, with a safety profile consistent with this drug class. Re-analysis of the primary efficacy endpoint in children 6-11, after exclusion of one pediatric site (20 randomized patients) following DSI audit, continued to support efficacy in the pediatric population. Although children 4-5 years of age were included in the pediatric trial, further studies are needed to support efficacy in this age group. Major revisions to the proposed label will need to be negotiated prior to final drug approval.

OUTSTANDING ISSUES: Unresolved CMC concerns.

RECOMMENDED REGULATORY ACTION FROM A CLINICAL PERSPECTIVE

NDA ___X___ **APPROVABLE** _____ **NOT APPROVABLE**

Reviewer: _____ **Date:** _____

Team Leader: _____ **Date:** _____

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. RECOMMENDATIONS

A. Recommendations on Approvability

Asthma is an inflammatory disorder of the airways that is a common chronic disease of major public health importance in both adult and pediatric patients. Flunisolide HFA Inhaler System is an anti-inflammatory corticosteroid drug, administered by a pressurized metered dose inhaler with an integrated spacer device, and a propellant that is no known to deplete the ozone layer of the Earth's atmosphere.

In a single adequate and well controlled trial in adults and adolescents, and a single adequate and well controlled pediatric trial, Flunisolide HFA demonstrated consistent, statistically significant benefit in the primary endpoint, change from baseline in percent predicted FEV_1 after 12 weeks of treatment, for maintenance prophylactic therapy of mild-moderate asthma patients six years of age and older. Significant efficacy of this drug was also supported by several secondary endpoints in adults and adolescents, but was not supported by these endpoints in children. Although the pediatric trial included 4-5 year old patients, efficacy was not demonstrated in this age group. The study did not require 4-5 year old patients to have primary endpoint assessments and this drug failed to demonstrate efficacy in secondary endpoints.

Adverse events associated with Flunisolide HFA Inhaler System compared with placebo were consistent with the currently marketed Flunisolide CFC formulation (containing chlorofluorocarbon which may potentially deplete atmospheric ozone), as well as other drugs in the corticosteroid class.

Common side effects (>10% of adult and/or pediatric patients) seen with HFA flunisolide in placebo controlled 12- week trials included pharyngitis, rhinitis, and headache, and were similarly seen in open-label one-year studies that compared HFA flunisolide to other inhaled aerosol asthma controller medications. As with other inhaled corticosteroids, class-label warnings about transfer of patients from systemic corticosteroid to inhaled corticosteroid association with adrenal insufficiency and death, as well as unmasking of allergic conditions are necessary. Further, warnings about potential for immune suppression, bronchospasm following aerosol inhalation, and that this drug is not indicated for relief of acute bronchospasm, are required. Precautions about the potential for orally inhaled corticosteroids to cause reduction in growth velocity, HPA-axis dysfunction, cataracts, increased intraocular pressure and glaucoma are also necessary.

From a clinical perspective after weighing benefits and risks of administering this drug, Flunisolide HFA Inhaler System is approvable in adults and children $\geq$ 6 years of age for the maintenance treatment of chronic asthma as prophylactic therapy. By extrapolation, as a reformulation of marketed CFC flunisolide, Flunisolide HFA Inhaler System is also approvable for patients requiring oral corticosteroid therapy for asthma, where adding Flunisolide HFA may reduce or eliminate the requirement for oral corticosteroids over time.

B. Recommendations on Phase 4 Studies and Risk Management

Potential adverse effects of chronic inhaled HFA flunisolide on growth and the HPA axis in children were not rigorously assessed in the pediatric studies submitted with this NDA. Typically, this would be required as a phase 4 commitment. Assessment of growth has been shown to be a more sensitive measure of potential systemic effect of inhaled corticosteroid than our current measures of HPA axis function. An ongoing well-designed, [redacted] may obviate need for further HPA axis assessments as a Phase 4 study, unless results of this ongoing study present new concerns. However, a Phase 4 commitment that investigates chronic use of inhaled HFA flunisolide on bone density in adolescents and adults is recommended, since there is growing post-marketing evidence suggesting that inhaled corticosteroid use may be associated with decreased bone mineral density. Current class labeling for other inhaled corticosteroids does not include this potential toxicity.

II. SUMMARY OF CLINICAL FINDINGS

A. Brief Overview of Clinical Program

Flunisolide HFA Inhaler System is an anti-inflammatory glucocorticoid administered by a pressurized metered dose inhaler via oral inhalation. The clinical drug development is supported by two pivotal trials conducted in 1252 adult and pediatric mild-moderate asthma patients and two 52-week safety studies conducted in 450 adult and adult and pediatric mild-moderate asthma patients.

Study ANC-MD-01, the pivotal adult and adolescent Phase 3 trial, and Study ANC-MD-03, the pivotal pediatric Phase 3 trial, assessed an identical primary endpoint, similar secondary endpoints, and safety parameters to support this drug's indication for the maintenance treatment of asthma as prophylactic therapy. Study ANC-MD-02, a 52 week open-label, active controlled trial in adults and adolescents, and Study ANC-MD-04, a 52 week open-label, active controlled trial in children assessed general safety as well as specific safety issues associated with chronic inhaled corticosteroid use in those specific patient populations.

Overall number of patients exposed to Flunisolide HFA Inhaler System was 833 across all four studies.

B. Efficacy

Two trials served as the basis for evaluating effectiveness of this drug and are summarized below.

Study ANC-MD-01 was a multicenter, double-blind, double dummy, parallel arm dose ranging, active and placebo control trial conducted in 669 asthma patients age 12 and older, which assessed effectiveness of the drug after 12 weeks of twice daily therapy. Most patients had mild-moderate asthma, with mean percent predicted FEV_1 72.4 at screening. All patients were

previously exposed to inhaled steroids. Following a two week run-in period in which all patients received 1000 mcg Flunisolide CFC, patients were randomized to receive Flunisolide CFC 250 mcg, 500 mcg, 1000 mcg twice daily, Flunisolide HFA 85 mcg, 170 mcg, 340 mcg twice daily, or placebo for twelve weeks.

The primary endpoint, change from baseline in percent predicted FEV_1 after 12 weeks treatment, is a proven reliable surrogate measure of clinical benefit for the asthma patient. This study demonstrated statistically significant superiority of medium (170 mg BID) and high (340 mcg BID) doses of HFA flunisolide over placebo for the primary endpoint ($p=0.12$ and $p=0.003$ for medium and high doses, respectively). The effect size was less than the 5% difference used to power the trial (4.05% and 4.58% differences, for medium and high doses, respectively), however this study also assessed actual FEV_1 differences. These actual FEV_1 differences (161 cc and 186 cc for medium and high doses, respectively) reflected a reasonable measure of clinical benefit.

Statistically significant superiority was demonstrated also demonstrated in several secondary endpoints, including asthma symptom scores, as needed albuterol use, daytime peak flow rate, and nocturnal awakenings.

Flunisolide CFC also demonstrated statistical superiority of medium and high doses over placebo, for the primary efficacy endpoint and several secondary endpoints. Trial design was not adequate to demonstrate comparability of the low, medium and high doses of HFA flunisolide with CFC flunisolide, however, no statistically significant differences were observed.

Effectiveness of this drug was also demonstrated by data showing that asthma was reported four times more frequently in the placebo group as in the HFA flunisolide groups, and significantly fewer patient dropouts from the study due to exacerbation of asthma or insufficient therapeutic effect, in those patients treated with HFA flunisolide as compared with patients treated with placebo.

Study ANC-MD-03 was a multicenter, double-blind, double dummy, parallel arm dose ranging, active and placebo control trial conducted in 583 mild-moderate asthma patients age 4-11, including 61 patients 4-5 years of age, which assessed effectiveness of the drug after 12 weeks of twice daily therapy. Patients 4-5 years of age were not required to have primary endpoints assessments of FEV_1 because most young children this age are unable to perform spirometry. Drug effectiveness in this young population was assessed by secondary endpoints, including in-clinic peak flow rates (PEFR) and recorded diary parameters like asthma symptom scores.

Most patients (age 6-11 years) had mild asthma, with mean percent predicted FEV_1 81.2% at screening. Not all patients were previously exposed to inhaled steroids. Following a two-week run-in period in which all patients received 500 mcg Flunisolide CFC, patients were randomized to receive Flunisolide CFC 250 mcg or 500 mcg twice daily, Flunisolide HFA 85 mcg or 170 mcg, twice daily, or placebo for twelve weeks.

This study demonstrated statistically significant superiority of the low (85 mg BID) and medium (170 mcg BID) doses of HFA flunisolide over placebo for the primary endpoint ($p=0.008$ and

patients who received HFA flunisolide. In addition, local side effects such as pharyngitis, voice alteration, oral moniliasis, taste perversion and dyspepsia were observed more frequently in patients who received HFA flunisolide.

Patients with chronic asthma, a common respiratory pulmonary condition, are likely to require chronic maintenance therapy for multiple years, if not decades, and marketing exposure for this drug may be high. Much of this assessment for safety is based on known corticosteroid class effects, and how this drug compared to the currently marketed formulation of Flunisolide CFC, approved 17 years ago, as well as how it compared to placebo. The therapeutic margin of safety for HFA flunisolide appears comparable to Flunisolide CFC.

However, these trials can only be predictive of safety. Widespread use in the population, over an extended period of time, is necessary to clarify any potential for toxicity. These studies did not enroll patients with more severe asthma, cigarette smokers, patients who were taking systemic corticosteroids, patients with significant medical conditions, or pregnant/lactating women, further limiting assessments of safety in real-world use. These studies did not rigorously assess growth or HPA axis effects in children, or assess potential for cataracts, increased intraoccular pressure, glaucoma, or decreased bone density in adults. Drug-drug interaction was not assessed in a drug that has cytochrome p-450 metabolism. Although systemic drug exposure is lower via the inhaled route, use of this drug with other inhaled drugs has not been studied and may be important with chronic exposure.

Risk associated with this drug class is reasonably manageable. Class labeling and black box labeling for known potential toxicities to include instructions for monitoring and recommendations for action, as well as instructions for medical providers about how to switch from systemic corticosteroids to inhaled corticosteroid aerosols, and instructions to titrate the inhaled drug to the lowest effective dose has been used to manage risk for other inhaled glucocorticoids. A clearly written patient package insert that reinforces directions for proper use, and lists common and serious side effects that can be associated with this drug class, has also been used to manage risk with other drugs in this class.

D. Dosing

Doses chosen for the adult patients were based on pharmacokinetic (PK) information that compared Flunisolide HFA to marketed Flunisolide CFC. The Flunisolide HFA Inhaler System, with its integrated spacer, is dosed at 1/3 the marketed Flunisolide CFC formulation used without a spacer device. PK information was apparently extrapolated to children, although no formal pharmacokinetic studies in children were performed using HFA flunisolide.

Clinical trial data from the adult and adolescent pivotal trial provided fairly robust evidence about the range of effective and safe doses in non-smoking, relatively healthy, mild-moderate asthma patients. The recommended starting dose of HFA flunisolide for adult and adolescents 12 years of age and older is 170 mcg BID (2 inhalations twice daily). The dose should not exceed 340 mcg BID (4 inhalations twice daily).

In the adult and adolescent trial, numerical dose ordering for efficacy was observed, although dose response did not reach statistical significance; generally, systemic and local adverse events did not increase as dose of HFA flunisolide increased. However, this trial did not assess safety of doses of HFA flunisolide higher than 340 mcg BID, which might be necessary to control asthma in more severe populations. The low dose (85 mcg BID) of HFA flunisolide did not reach a statistically significant level of effectiveness in adults and adolescents with mild-moderate asthma, although it was numerically better than placebo.

There is less confidence about the least effective pediatric dose. Data suggested that 6-11 year old mild asthma patients treated with 85 mcg BID HFA flunisolide were in the dose response curve plateau for efficacy. No dose response for efficacy was demonstrated in the pediatric trial, nor was dose ordering of adverse events. On the other hand, patients with more severe asthma were not enrolled.

Based on the results for the single pivotal pediatric trial in mild-moderate asthma patients, the starting dose in children 6-11 years of age should be 85 mcg BID (1 inhalation twice daily). The dose should not exceed 170 mcg BID (2 inhalations twice daily).

The highest adult dose was not assessed in pediatric patients, therefore no conclusions about safety of the 340 mcg HFA flunisolide dose can be made for children 6-11 years of age.
This drug was also assessed in patients as young as 4 years of age. Although efficacy was not demonstrated at either the 85 mcg BID or 170 mcg BID doses, no special safety concerns were noted in the small numbers of HFA flunisolide exposed 4-5 year old mild asthma patients.

E. Special populations

No specific gender differences were observed after single and multiple dose administration of HFA flunisolide in pharmacokinetic studies. No formal pharmacokinetic studies were carried out in any other special populations. Among HFA flunisolide exposed patients across all four clinical trials, 53.8% were male and 46.2% were female. In the combined adult pivotal and 52 week studies, 79% were Caucasian, 13.2% were Black, 5.5% were Hispanic and 2.3 % were other. Gender and racial differences were not prospectively studied in the clinical trials, however, post-hoc assessments of the trial data uncovered no specific gender or racial differences for either safety or effectiveness.

Very few elderly patients received HFA flunisolide treatment in the single adult pivotal trial and the 52-week open-label trial ((1.0% > 65 years of age), and patients with renal and hepatic impairment were excluded from enrollment. Pregnant patients were also excluded for the study. This drug is classified in Pregnancy Category C. As with other corticosteroids, flunisolide hemihydrate has been shown to be teratogenic and fetotoxic in rabbits and rats at doses of 40-200 mcg/kg/day.

A pediatric drug development plan for HFA flunisolide in children and infants as young as 6 months of age is recommended, since CFC-containing inhaled corticosteroid alternatives are being phased out. However, the Flunisolide HFA Inhaler System, with its integrated Bespak spacer, may not be an appropriate drug delivery device in younger children and infants. Forest Laboratories was asked to submit their pediatric drug development plan on June 23, 2000, in a letter from the Agency acknowledging receipt of the NDA. Their plan or a request for a waiver has not been received.

CLINICAL REVIEW

1.0 INTRODUCTION AND BACKGROUND

Aerobid and Aerobid-M (menthol flavored) are approved and marketed pressurized metered dose inhalers (pMDI) indicated for the maintenance treatment of asthma as prophylactic therapy. They are also indicated for asthma patients who require systemic corticosteroid administration, where adding Aerobid may reduce or eliminate the need for systemic corticosteroids. Aerobid is administered by oral inhalation and contains the glucocorticoid flunisolide hemihydrate suspended in chlorofluorocarbons (CFCs). Chlorine released from CFCs is believed to enter into a catalytic cycle that results in destruction of stratospheric ozone, thus depriving the earth of its major barrier against harmful UV-B radiation.

HFA-134a, a hydrofluoroalkane that contains no chorine and is without known potential to destroy the ozone layer, was developed as an alternative propellant to CFC. The biological safety of HFA-134a has been generally accepted as a safe propellant substitute, however, use of this new propellant required substantial changes in the pMDI design, materials used in the metering chamber and valve, the manufacturing and filling process, and the formulation of flunisolide hemihydrate. In contrast to the existing CFC flunisolide formulation suspension, HFA flunisolide is a 0.24% solution of HFA in [redacted] alcohol, which delivers aerosol particles with a mass median aerodynamic diameter (MMAD) of about [redacted], compared with the CFC flunisolide formulation that has an MMAD of about [redacted]m. Particle size differences between the two formulations affected the respirable fraction. Approximately [redacted] of the HFA flunisolide dose has a particle size less than [redacted], the upper limit of the respirable dose, whereas HFA flunisolide has a respirable fraction of approximately [redacted].

The Applicant developed an HFA flunisolide pMDI device, Flunisolide HFA Inhaler System (flunisolide hemihydrate) with an integrated spacer designed to reduce to reduce oropharyngeal deposition, to potentially deliver a larger proportion of the drug to the lungs and less to the oropharynx. A reduction in the dose required for treatment efficacy has potential advantages of reducing potential local and/or systemic side effects.

This NDA was submitted April 27, 2000, and contained the results of five pharmacologic studies conducted in adults and two pivotal Phase 3 clinical studies. The clinical studies assessed the efficacy and safety of HFA Flunisolide Inhaler System in children and adults fours years of age and older, for the maintenance treatment of asthma as prophylactic therapy. Two active controlled additional studies assessing safety in adults and children fours of age and older with 52-weeks of open-label use were submitted with the 120-day Safety Report.

1.1 PROPOSED INDICATION

Flunisolide HFA Inhaler System was developed for the maintenance treatment of asthma as prophylactic therapy in children, adolescents and adults 4 years of age and older. The Applicant also seeks indication of Flunisolide HFA Inhaler System for patients requiring oral corticosteroid therapy for asthma, where adding Flunisolide HFA may reduce or eliminate their requirement for oral corticosteroids over time.

1.2 CHEMISTRY

USAN: flunisolide hemihydrate. It has a molecular weight of 443.51 and the following molecular formula: $C_{24}H_{31})_6F\cdot 1/2\ H_2O$

USP chemical name: pregna-1, 4-diene-3, 20-dione, 6-fluoro-11, 21 hydroxy-16, 17-((1-methylethylidene) bis (oxy)) -, hemihydrate, (6α 11β, 16α)

Drug Product: Flunisolide hemihydrate, USP (0.24% weight); dehydrated alcohol (10.0% weight); 1,1,1,2-tetrafluoroethane (propellant HFA-134a; 89.76% weight).

Trade Name: not yet established

The active pharmaceutical ingredient, flunisolide hemihydrate, micronized, is supplied by [redacted] The drug product is manufactured by 3M Pharmaceuticals at their [redacted]

Dosage Form: The to-be-marketed formulation for flunisolide hemihydrate is a pressurized metered dose inhaler system with a built-in actuator/spacer assembly. The spacer functions to reduce deposition of larger particles in the oropharyngeal region. The MMAD is about [redacted] Amount of drug delivered ex-valve is about 139 mcg/actuation. The amount of drug delivered ex-spacer is about 85 mcg/actuation. There are about 120 doses in Flunisolide HFA Inhaler System.

There are several identified manufacturing problems at 3M Pharmaceuticals ———. See the Chemist Review (Brian Rogers, PhD) for a complete discussion of these deficiencies.

Dose: Proposed starting dose is ——— years of age and older. The dose is not to exceed ———.

Proposed starting dose is ——— years of age. The dose is not to exceed ———

1.3 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

Five pharmacokinetic studies were conducted to assess dose-proportionality following inhalation of HFA flunisolide, to determine *in vivo* lung deposition following inhalation of HFA flunisolide both with and without a spacer (via pharmacoscintigraphy), and to compare hydrocortisone suppression and pharmacokinetics of HFA flunisolide with CFC flunisolide. All studies were conducted in adults. There were no pharmacologic studies performed in children.

The results of the lung deposition studies supported use of the Bespak spacer. This integrated device increased the central and peripheral drug deposition in the lung and decreased oropharyngeal deposition.

Dose proportionality was shown after a single dose but not after multiple dosing. Dose adjusted $AUC_{0\text{-last}}$ for one puff is significantly smaller than that obtained after two or four puffs. Potential clinical relevance of this discrepancy for adults is not a concern, since the starting dose in adults is — puffs. This finding was a potential concern in children, where children may receive only one puff BID. Absence of PK data in children resulted in complete reliance on the clinical data from the single pivotal pediatric trial, and results of the 52-week pediatric safety study.

Similar systemic flunisolide bioavailability (C_{max} and $AUC_{0\text{-}12h}$) and similar hydrocortisone plasma and urine concentrations were observed after the administration of flunisolide with either 4 puffs HFA flunisolide (340 mcg total dose) or with 4 puffs CFC flunisolide (2000 mcg total dose). However, the validity of these results was questioned by the Clinical Biopharmacology Reviewer, Sandra Suarez-Sharp, PhD. (see Dr Suarez-Sharp's review for details of her concerns).

Absorption: Flunisolide hemihydrate was rapidly absorbed when given as an oral inhalation. Mean T_{max} after a single dose of 340 mcg HFA flunisolide ranged from 0.09-0.17 hour. Corresponding mean C_{max} ranged from 1.9-3.3 ng/mL. Oral bioavailability was reported as <7%.

Distribution: Flunisolide is extensively distributed in the body. Mean volume of distribution following a single HFA flunisolide dose is 170-350 L. Overall lung deposition of HFA Flunisolide after a single dose using the Bespak integrated spacer is 40%.

Metabolism: Prior studies showed that swallowed flunisolide is rapidly and extensively converted into 6-OH flunisolide and to water-soluble conjugates during first pass through the liver. Inhaled flunisolide is converted to the same metabolites. Conversion to 6-OH flunisolide, which is the only detected circulating metabolite in humans, is thought to occur via the cytochrome P450 enzyme system, particularly CYP3A4. Maximum plasma levels of 6-OH flunisolide were o.66 ng/mL after a single dose of 340 mcg HFA flunisolide and 0.71 ng/mL after multiple doses.

Excretion: Prior studies showed that there is <1% urinary excretion of flunisolide after inhalation. The half-life of 6-OH flunisolide ranged from 3.1-5.1 hours after 170 mcg-340 mcg HFA flunisolide doses.

Disposition and Elimination: BID administration of HFA flunisolide for up to 14 days did not result in an appreciable accumulation of flunisolide. Elimination half-life ranged from 1.3-1.7 hours following administration of 340 mcg HFA flunisolide. Flunisolide was not detectable in the plasma 12 hours post-dose and mean oral clearance, not adjusted for bioavailability ranged from 83-167 L/hr after a single 340mcg HFA flunisolide dose.

1.4 FOREIGN MARKETING HISTORY

There is no foreign marketing approval for Flunisolide HFA Inhaler System, nor has any been sought. Two flunisolide-containing products are marketed outside the US. One is an inhalation product indicated for the treatment of asthma, launched between the second half of 1986 and the end of 1987. It is manufactured by [redacted] and is supplied to [redacted]

An inhaled nasal product for rhinitis containing flunisolide is marketed both in the US and abroad. As of 1992, [redacted] supplied drug substance for this product to Australia, Belgium, Canada, France, Germany, Israel, Italy, Japan, Poland, Portugal, Sweden, Switzerland, Turkey, the United Kingdom, and Yugoslavia. Additionally, the finished product was sent to the Bahamas, Barbados, Bermuda, Cyprus, Denmark, Finland, Hong Kong, Iceland, Jamaica, Kenya, Liberia, Luxembourg, Malaysia, Mexico, the Netherlands, Norway, Oman, Pakistan, Poland, Portugal, and Singapore.

The Applicant reports that no product containing flunisolide was ever withdrawn from marketing due to safety or effectiveness.

1.5 APPROACH TO REVIEW

The Medical Officer clinical review commenced with an overall appraisal of the NDA as reported in the Medical Officer filing review dated June 13, 2000. Pivotal study data in support of the proposed indication and dose were then assessed for efficacy and safety, and comprised the core of this review, with particular attention to proposed label claims. Supporting safety studies submitted with the 120-day Safety Report also received detailed review. The Applicant's Final Study Reports and Appendicies provided the bulk of material reviewed, however, where indicated, electronic patient Case Report Forms and SAS transport data sets submitted in lieu of Case Report Form tabulations were also examined.

Many of the Applicant's tables submitted in the Final Study Reports were scanned into this review and these are acknowledged. Some of the Applicant's graphs were also scanned into this review and these are also acknowledged. A few tables were constructed from other tabulations, and/or created by working jointly with the statistician, James Gebert, PhD., who provided collaborative assistance throughout the review of this application.

After review of all clinical trials, compilation of an Integrated Summary of Safety (ISS) was undertaken. The ISS provided by the Applicant, including the summaries provided from the Applicant's literature search, and a review conducted by Joyce Weaver, Pharm.D, Division of Drug Risk Evaluation I, for reported post-marketing adverse events and an additional literature search, were the principle materials used. Individual patient line listings and CRFs were checked where indicated.

A detailed Integrated Summary of Effectiveness (ISE) was not included in the Medical Officer Review (MOR), however, because this MO did not believe that such integration would be meaningful. The two pivotal trials providing the basis for efficacy were performed in very different patient populations in which the efficacy assessment parameter, FEV_1, was difficult to integrate across adult and pediatric populations. However, the Applicant's ISE Report was reviewed in detail and a very brief Medical Officer ISE for the primary efficacy parameter, secondary efficacy parameters, treatment effect size, dose response, and efficacy response by age, race, and gender is included in this MOR. The approach to these summaries was to address specific issues that resulted from review of the individual studies.

After data auditing by DSI uncovered data integrity concerns for one pediatric center, efficacy data were then re-assessed for the pediatric pivotal trial, in consultation with Dr. James Gebert.

This review concluded with labeling review and comments for clinical sections. Final conclusions were made after weighing benefits of this drug against potential toxicities.

1.6 SUMMARY TABLE OF CLINICAL TRIALS

PROTOCOL NUMBER, COUNTRY	STUDY DATES	STUDY DESIGN	TREATMMENT, DOSES	NUMBER RECEIVING EACH TREATMENT	TREATMENT DURATION	AGE RANGE (MEAN)	NUMBER MALE / FEMALE DOSED
ANC-MD-01 USA; 33 centers	1/6/98 – 12/18/98	multicenter, randomized, double-blind, placebo and active controlled, Phase 3 study in adult and adolescent patients >/= 12 years with mild-moderate asthma 1^0 endpoint: change % predicted FEV_1 from baseline after 12 weeks	Run-in: CFC flunisolide 500 mcg bid and prn albuterol DB randomized: HFA flunisolide: 85, 170, 340 mcg bid CFC flunisolide: 250, 500 1000 mcg bid Placebo bid	HFA flunisolide: 85 mcg bid: 75 170 mcg bid: 100 340 mcg bid: 113 CFC flunisolide: 250 mcg bid: 76 500 mcg bid: 103 1000 mcg bid: 98 Placebo: 104	12 weeks	12-78 years (33 years)	306/363
ANC-MD-03 USA; 51 centers	8/3/98 – 7/17/99	multicenter, randomized, double-blind, placebo and active controlled, Phase 3 study in pediatric patients 4-11 years with mild-moderate asthma 1^0 endpoint: change % predicted FEV_1 from baseline after 12 weeks	Run-in: CFC flunisolide 500 mcg bid and prn albuterol DB randomized: HFA flunisolide: 85 and 170 mcg bid CFC flunisolide: 250 and 500 mcg bid Placebo bid	HFA flunisolide: 85 mcg bid: 114 170 mcg bid: 117 CFC flunisolide: 250 mcg bid: 123 500 mcg bid: 113 Placebo: 116	12 weeks	4-11 years (8.5) (years)	380/203
ANC-MD-02 USA; 24 centers	6/25/98-10/12/99	Multicenter, randomized, flexible dose, Open-label, active controlled, parallel group, Phase 3 safety trial in adults and adolescents with mild-moderate asthma Endpoints included HPA axis assessments, routine clinical labs, ECGs, VS, PE, spirometry	Run-in: previous dose of inhaled anti-inflammatory medication and prn albuterol Open-label randomized: HFA flunisolide flexible doses: 85-340 mcg bid Beclomethasone flexible total daily doses 252-672 mcg	HFA flunisolide: 162 Beclomethasone: 53	52 weeks	12-62 years (33) (years)	101/114

PROTOCOL NUMBER, COUNTRY	STUDY DATES	STUDY DESIGN	TREATMMENT, DOSES	NUMBER RECEIVING EACH TREATMENT	TREATMENT DURATION	AGE RANGE (MEAN)	NUMBER MALE / FEMALE DOSED
ANC-MD-02 USA; 24 centers	7/6/98-11/30/99	Multicenter, randomized, flexible dose, Open-label, active controlled, parallel group, Phase 3 safety trial in children with mild-moderate asthma Endpoints included HPA axis assessments, growth, routine clinical labs, ECGs, VS, PE, spirometry	Run-in: previous dose of inhaled anti-inflammatory medication and prn albuterol Open-label randomized: HFA flunisolide flexible doses: 85-170 mcg bid Beclomethasone flexible total daily doses (>/= 6 years of age): 84-168 mcg bid Cromolyn flexible total daily doses (>/= 6 years of age): 1600 bid-qid	HFA flunisolide: 152 Beclomethasone: 39 Cromolyn: 44	52 weeks	4-11 years (8.3) (years)	145/90

STUDY ANC-MD-01 (vol. 1.47 et seq.)

Initiation Date: January 6, 1998
Completion Date: December 18, 1998

RÉSUMÉ

This dose ranging, active and placebo controlled efficacy and safety study, in 669 randomized adult and adolescent patients age 12-78 years included non-smoking asthmatics who had a history of orally inhaled corticosteroid use at a stable dose for a minimum of 30 days prior to screening. Patients who met inclusion and exclusion criteria entered a 2-week open label run-in phase in which they all received treatment with CFC flunisolide 500µg twice daily, and albuterol as needed. They then entered a 12-week double-blind treatment phase in which they were randomly assigned to receive one, two or four puffs twice daily of either HFA flunisolide (85 µg/puff), CFC flunisolide (250µg/puff), or placebo (HFA and/or CFC). Since the run-in phase included treatment with an active 500 µg bid CFC flunisolide dose, 500 µg bid CFC flunisolide and 170 µg bid HFA flunisolide during the double-blind treatment phase would be expected to maintain the improvement observed during the run-in phase.

The study demonstrated statistically significant superiority of medium (170µg BID) and high doses (340µg BID) of HFA flunisolide over placebo on the primary endpoint: change from baseline in percent predicted FEV_1 after 12 weeks treatment. The study also demonstrated statistically significant superiority of medium and high doses of HFA flunisolide vs. placebo in actual FEV_1, daytime PEFR, prn albuterol use, nocturnal awakenings and asthma symptom scores. Patients treated with low dose (85µg) HFA flunisolide showed numerical superiority over placebo, but this group did not demonstrate statistically significant superiority over placebo for the primary endpoint. CFC flunisolide superiority of medium and high doses over placebo was also demonstrated for the primary efficacy parameter as well as several of the secondary efficacy parameters. Dose response curves for both HFA flunisolide and CFC flunisolide indicate numerical dose ordering across low, medium and high doses and suggest dose response, however, sample size was not adequate to demonstrate dose response . Sample size was also not adequate to demonstrate comparability of the low, medium and high doses of HFA flunisolide compared with CFC flunisolide low medium and high doses, however, no statistically significant differences were observed in this study.

With respect to safety, HFA flunisolide was better or similar to placebo and to CFC flunisolide. The incidence of abnormal safety test results in chemistry, hematology, urinalysis, vital signs, ECGs and physical exams were low and similar among all groups. Urinary cortisol excretion and plasma cortisol values pre and post cortrosyn stimulation were similar across placebo, HFA and CFC flunisolide groups, as was the incidence of oral candidiasis. The most commonly reported treatment emergent adverse events (TEAEs> 10% in any group) were pharyngitis and headache, which were reported at a similar rate among treatment groups. Asthma was reported 4 times as frequently in the placebo group as in the HFA group and discontinuations secondary to an adverse event occurred more frequently in the placebo group, than in either the HFA or CFC flunisolide treatment groups.
Overall, this study supports the efficacy and safety of 170µg BID and 340µg BID doses of HFA flunisolide in the treatment of adult and adolescent patients with mild to moderate asthma.

2.1 STUDY DESCRIPTION

DESIGN: Multi-center, randomized, double-blind, placebo and active controlled, dose-ranging 12 week efficacy and safety study of HFA flunisolide at BID doses of 83, 170, and 340 µg, and CFC flunisolide at BID doses of 250, 500 and 1000µg.

POPULATION: 650 mild to moderate asthmatic adults and adolescents >/=12 years of age with a history of orally inhaled corticosteroid use at stable doses for a minimum of 30 days prior to enrollment.

MATERIALS: Aerobid Inhaler System (CFC) 250 µg/puff without Aerochamber spacer 1,2 or 4 puffs BID, Flunisolide HFA Inhaler System with built-in Bespak spacer 1,2 or 4 puffs BID, Albuterol Inhalation Aerosol (prn use), HFA placebo or CFC placebo.

OBJECTIVES: Primary - to demonstrate the efficacy and safety of medium and high doses of HFA flunisolide hemihydrate after 12 weeks of treatment in adult and adolescent asthma patients in comparison to placebo. **Secondary** - to demonstrate efficacy and safety of medium and high doses of HFA flunisolide in change from baseline in actual FEV_1, prn inhaled-agonist use, AM and PM peak expiratory flow rate (PEFR), daily, AM, PM asthma symptom scores, and nocturnal awakenings requiring albuterol use.

The following additional secondary parameters were evaluated: to compare efficacy and safety of the HFA flunisolide formulation with the CFC formulation; to evaluate low dose HFA flunisolide vs. placebo; to evaluate the dose response relationship using change from baseline and screening in both primary and secondary efficacy parameters; to evaluate time to drop-out for exacerbation of asthma; to evaluate effects of HFA flunisolide vs. placebo on percent predicted FEV_1, actual FEV_1, and mean prn albuterol use after 6 weeks treatment.

CRITERIA: Patients were expected to have an FEV_1 of 45%-90% of predicted prior to inhalation of 180μg(2 puffs) albuterol after a washout period of various defined drugs (Vol 1.47, Section 5.3.6), a 12 % increase in their FEV_1 after 2 puffs of albuterol at or within 2 months prior to screening, used an orally inhaled corticosteroid at a stable dose for a minimum of 30 days prior to Visit 1, and be a nonsmoker - defined as no smoking history within one year of Visit 1 with a total lifetime smoking history of 10 pack years. Pregnant or nursing mothers, significant pulmonary disease other than asthma, and history of an acute asthma exacerbation within 6 weeks of Visit 1, excluded patients from the study.

CONDUCT: Patients who met inclusion and exclusion criteria at Visit 1 (Week-2) were entered into a 2-week, open label run-in period during which time they were all treated with 500μg BID of CFC flunisolide and as needed albuterol. Patients recorded asthma symptoms BID, AM and PM PEFR (prior to taking their dose of CFC flunisolide), use of prn albuterol, and the number of nocturnal awakenings secondary to asthma which required use of albuterol.

At 12 selected sites, HPA axis were assessed by measuring 24-hour urine free cortisol and effects of Cortrosyn stimulation on plasma cortisol. Values for urinary free cortisol were standardized by the creatinine concentrations of the sample and expressed as the ratio of cortisol excretion per mg creatinine. A normal response for the Cortrosyn stimulation test required a plasma cortisol increment of at least 7 mcg/100mL above the control value within 60 minutes after Cortrosyn administration and an absolute plasma cortisol value ≥ 18 mcg/ 100mL within 60 minutes. Markers of bone metabolism (urinary deoxypyridinoline and serum osteocalcin) were also measured at those sites.

Single dose tolerability was assessed by lung spirometry and clinical symptoms at the time of the first dose of randomized study drug in at least half the randomized patients at 4 selected study sites.

Visit 1 assessments included, medical history, physical examination, vital signs, spirometry, clinical labs (to include mouth/throat smear and culture for fungus, hematology, chemistry, U/A) and 12-lead ECG were also assessed.

Visit 2 concluded the run-in period. Patients who had a pre-bronchodilator FEV_1 90% or greater than the pre-bronchodilator value at Visit 1, daily asthma symptom scores ≥ 3 per day and ≤ 12 per day for 5 days out of 7, and mean total albuterol intake of ≤ 6 puffs/day prior to Visit 2 (Week 0, baseline), were randomized into eight treatment groups for the 12-week double-blind, double dummy phase of the trial. These patients were assigned to receive one, two or four puffs twice daily of HFA flunisolide (85 μg/puff), CFC flunisolide (250μg/puff), and/or placebo (HFA or CFC). Four canisters were dispensed and patients were instructed to always inhale from the canister labeled HFA first, followed by the CFC canister. HPA axis assessment and testing for bone metabolism were also performed at this visit.

Patients were instructed to return at three-week intervals for review of diary cards (AM and PM PEFR were to be recorded prior to taking their dose of study drug) and adverse events, concomitant medications, and spirometry for Visits 3-6. At Visit 6 (Week 12), vital signs, physical examination, clinical laboratory tests, 12-lead ECGs, and HPA axis/ markers of bone metabolism were assessed. Additionally, adverse events, concomitant medications, and diary cards were reviewed and spirometry was performed. Spirometry was performed by an assessor blinded to the number of puffs/canister of study drug taken by the patient. All patients were instructed to withhold bronchodilator for at least six hours prior to spirometry assessments at each visit and were further instructed not to take their morning dose of study medication prior to their office visits.

DATA ANALYSIS: The protocol defined primary efficacy variable was change from baseline in percent predicted FEV_1 after twelve weeks treatment. This was expressed as least squares mean difference (LSM) from baseline of each HFA flunisolide compared with placebo in percent predicted FEV_1 after 12 weeks of treatment. Both the medium and high doses of HFA flunisolide were compared to placebo using an ANCOVA model. The Fisher's Least Significant Difference test was used to adjust for multiple comparisons. The same analytic approach was used for all secondary endpoints. Tukey's method was used to evaluate the dose response relationship, in which the most extreme p-value computed from a linear model with the original dose vs. a model with a log-transformed dose was taken. Kaplan Meier curves were used to present to analyze time to dropout due to asthma exacerbation. Adverse events were tabulated. Descriptive statistics were used to analyze results of laboratory tests, vital signs, and HPA axis assessments. Missing data was imputed by the last observation carried forward (LOCF).

The Final Study Report analyzed patients based on the ITT population for efficacy (defined as all randomized patients who received at least one dose of study drug and had at least one follow-up assessment of the primary efficacy parameter after baseline (661 patients). A safety population (669 patients) was defined as all randomized patients who received at least one dose of study drug, i.e. all treated patients, for the analysis of safety. Sample size was calculated based on a 90% power to detects a 5% difference at the two-sided 0.05 significance level in the primary efficacy parameter.

It should be noted that the primary objective analyzed in the final study report changed from the primary objective stated in the final protocol. The primary objective changed from "To demonstrate whether the HFA and CFC formulations of flunisolide provide comparable efficacy, as measured by FEV1 in patients with mild to moderate asthma," to "To demonstrate the efficacy of medium and high doses of HFA flunisolide hemihydrate after 12 weeks treatment in adult and adolescent asthma patients in comparison with placebo," without protocol amendment. The applicant states that Statistical Analysis Plan (SAP) was finalized prior to unblinding of study data (Vol 1.47 p. 00128). Since this objective change and plans for the final SAP were made prior to unblinding of the data, and given the fact that the primary efficacy parameter did not change, this does not represent a significant review issue.

2.2 PATIENT DISPOSITION

863 patients were enrolled at a total of 33 investigator sites; 669 patients were randomized to receive study drug. Eight (1.2%) of the randomized patients never had a follow-up assessment of the primary efficacy variable and were not included in the analysis for efficacy. Of these, 3 were in the placebo group, 2 were in the HFA flunisolide groups, and 3 were in the CFC flunisolide groups, as shown in table 2.2A (from applicant's in-text table 3, vol. 47).

Table 2.2A Patient Disposition

	Placebo	*HFA 85 µg*	*HFA 170 µg*	*HFA 340 µg*	*CFC 250 µg*	*CFC 500 µg*	*CFC 1000 µg*	*Total*[a]
Patients Enrolled[b]								863
Not Randomized[b]								194
Patients Randomized	104	75	100	113	76	103	98	669
Did not take any study drug	0	0	0	0	0	0	0	0
Safety Population	104	75	100	113	76	103	98	669
No post-baseline efficacy data	3	2	0	0	1	0	2	8
ITT Efficacy Population	101	73	100	113	75	103	96	661
Completed Study[c] (%)	70 (67)	63 (84)	85 (85)	100 (89)	59 (78)	90 (87)	81 (83)	548 (82)

See section 6.1 for definitions of study populations.

[a] Total of all flunisolide HFA, flunisolide CFC, and placebo groups.
[b]Since patients were not yet assigned to study treatment groups, there is only a total for the number of patients enrolled and not randomized.
[c]Patients who received 12 weeks of double-blind medication; p=0.001 based on Cochran Mantel Haenszel test for no difference among dose groups.

82% (548/669) of randomized patients completed the study. The lowest percentage of patients completing the study was in the placebo group (67%) and the highest was in the HFA flunisolide 340µg group (89%). The percentage of study completers in the active groups ranged from 78%-89%. Reasons for patient discontinuation are shown in Table 2.2B (from applicant's in-text table 5, vol. 47) below.

Table 2.2B Patients Discontinued from the Study

Reason	*Placebo*	*HFA 85 µg*	*HFA 170 µg*	*HFA 340 µg*	*CFC 250 µg*	*CFC 500 µg*	*CFC 1000 µg*	*Total*[a]
Safety Population	n=104	n=75	n=100	n=113	n=76	n=103	n=98	n=669
Total discontinued from study	34 (32.7)	12 (16.0)	15 (15.0)	13 (11.5)	17 (22.4)	13 (12.6)	17 (17.3)	121 (18.1)
Adverse event/ intercurrent illness	20 (19.2)	4 (5.3)	8 (8.0)	4 (3.5)	10 (13.2)	8 (7.8)	9 (9.2)	63 (9.4)
Insufficient efficacy	5 (4.8)	3 (4.0)	2 (2.0)	1 (0.9)	1 (1.3)	2 (1.9)	4 (4.1)	18 (2.7)
Consent withdrawn	3 (2.9)	1 (1.3)	1 (1.0)	3 (2.7)	2 (2.6)	1 (1.0)	2 (2.0)	13 (1.9)
Lost to follow-up	1 (1.0)	0	1 (1.0)	3 (2.7)	0	2 (1.9)	1 (1.0)	8 (1.2)
Protocol violation	1 (1.0)	1 (1.3)	0	0	1 (1.3)	0	0	3 (0.4)
Non-compliance	2 (1.9)	1 (1.3)	0	0	0	0	0	3 (0.4)
Did not meet Randomization Criteria	0	1 (1.3)	0	0	0	0	0	1 (0.1)
Other[b]	2 (1.9)	1 (1.3)	3 (3.0)	2 (1.8)	3 (3.9)	0	1 (1.0)	12 (1.8)

[a] Total of all flunisolide HFA, flunisolide CFC, and placebo groups.
[b] Other reasons include: patient moved out of area, blind was broken due to improper packaging, patient left for vacation and returned only for visits 5 and 6, patient had conflicting schedule, visit 5 #1 inhaler did not work, and family emergency

2.3 PATIENT CHARACTERISTICS

There were no overall important differences among the treatment groups for sex, race, smoking history, and number of pack years. The mean age of the safety population was 36 years and minorities represented 18.5% of patients. The 88 patients in the 12-17 year-old subgroup were 13% of the total population, and these patients made up 8.0 - 18.4 % of the seven treatment groups. At screening, the majority of patients had moderate asthma, with mean percent predicted FEV_1 72.4% +/-12.28 (recalculated by the Knudson formula). 100% of patients in the safety population reported previous inhaled corticosteroid use. 96% of patients had previously used a short acting beta-agonist, and the pattern of anti-asthmatic medication use was not different among treatment groups.

The study population had mild asthma, with a mean percent predicted FEV_1= 72.4 at screening. Overall, there were no important differences among treated groups for length of asthma history or mean number of days with asthma symptoms per week. Further, there were no important differences in medical history abnormality, vital signs at baseline, or treatment groups at baseline for any efficacy measurement in the ITT population. Imbalance for height and weight at baseline was observed among treatment groups, however, the primary efficacy endpoint evaluates change in % predicted FEV_1, which does at least correct for height.

2.4 TREATMENT COMPLIANCE

Greater than 90% of all ITT patients were compliant with taking their inhaled study drug at all visits, and there were no apparent differences among any of the seven treatment groups. Patient compliance was determined by dividing the actual total number of puffs of inhaled steroid used and recorded in the diary cards between each visit, by the predicted total number of puffs of inhaled steroid (total number of puffs the patient should have taken between each visit). It should be noted however, that diary data alone may be an unreliable assessment of compliance.

2.5 EFFICACY REVIEW

To test the validity of pooling the two placebo groups, an analysis of covariance was performed on the placebo populations (2 and 4 puffs) for the primary efficacy variable, change from baseline in percent predicted FEV_1 after 12 weeks treatment, and showed no difference. A combined placebo group was therefore used in all analyses.

The primary objective was analyzed as change from baseline to 12 weeks of treatment in percent predicted FEV_1 using the ITT population (all those randomized patients who received at least one dose of study drug and had at least one follow-up assessment of the primary efficacy parameter). Baseline was defined as the study visit immediately following the two-week open label run-in period with 500 μg CFC flunisolide BID and an improvement in pulmonary function (8.3 % for % predicted FEV_1) was observed. The goal of the double blind treatment phase was to observe whether this improvement was maintained, exceeded, or lost. At the conclusion of the trial, the measured effect sizes of the active treatments compared to placebo were due to both improvement in pulmonary function of patients who received high active doses and the deteriorating pulmonary function of patients on placebo. Medium CFC and HFA doses maintained the improvement observed after treatment with medium CFC doses during the run-in period.

2.5.1 Primary efficacy parameter: medium and high dose HFA flunisolide

Placebo-treated patients had a mean decline of 4.5 % in % predicted FEV_1 and medium dose HFA flunisolide maintained the improvement observed in the run-in period. Percent predicted FEV_1 of patients on the high dose of HFA flunisolide was improved from baseline after 12 weeks of treatment. Statistically significant differences were shown between both HFA flunisolide dose groups and placebo (Table 2.5.1, applicant's in-text table 18, vol.47). However, it should be noted that these results show less than a 5% difference as planned in the power analysis. It is also interesting to note that after an 8.3% mean improvement in % predicted FEV_1 for all screened patients who were randomized at baseline, the placebo group declined only 4.5%.

Table 2.5.1 Comparison of HFA Flunisolide Medium and High Doses to Placebo: Percent Predicted FEV_1 After 12 Weeks Treatment (LOCF)

Appears This Way On Original

	Placebo	170 µg bid			340 µg bid			Overall[a] p-Value
	LSM[b]	LSM	Difference[c]	p-Value[d]	LSM	Difference	p-Value[d]	
Percent Predicted FEV_1	-4.247	-0.190	4.057	0.012	0.332	4.579	0.003[d]	0.007

[a] p-value is based on the ANCOVA model for overall treatment effect.
[b] LSM = least square mean for change from baseline.
[c] LSM of flunisolide dose minus LSM of placebo.
[d] p-value is based on the ANCOVA model for comparison to placebo. Fisher's LSD is applied for adjustment of multiple comparisons.

2.5.2 Secondary efficacy parameters

The overall superior treatment effects for medium and high dose HFA flunisolide groups were significant for all parameters except PM PEFR. The effects of treatment for the individual HFA Flunisolide 170 µg BID and 340µg BID dose groups were significantly superior to placebo for all parameters, except for prn albuterol use and PM PEFR (Table 2.5.2, applicant's in-text Table 20, vol. 47), and with the exception of AM PEFR, suggest dose ordering.

Table 2.5.2 Comparison of HFA Medium and High Doses to Placebo: Secondary Efficacy Parameters After 12 Weeks Treatment (LOCF)

Efficacy Parameter	*Placebo*	*170 µg HFA bid*			*340 µg HFA bid*			*Overall*
	LSM[b]	*LSM*	*Difference*[c]	*p-Value*[d]	*LSM*	*Difference*	*p-Value*	*p-Value*[a]
Actual FEV_1 (L)	-0.161	0.005	0.166	0.003	0.025	0.186	0.001	0.001
pm Albuterol Use (puffs/day)	0.734	0.286	-0.448	0.172	-0.176	-0.910	0.005	0.018
AM PEFR (L/min)	-13.91	2.442	16.354	0.010	-0.132	13.780	0.026	0.022
PM PEFR (L/min)	-9.355	1.787	11.142	0.080	2.283	11.637	0.060	0.113
Mean Daily Asthma Symptoms	0.827	-0.910	-1.737	0.001	-1.203	-2.030	0.000	0.000
AM Asthma Symptoms	0.643	-0.288	-0.931	0.001	-0.507	-1.150	0.000	0.000
PM Asthma Symptoms	0.166	-0.611	-0.777	0.005	-0.679	-0.845	0.002	0.003
Nocturnal Awakenings	0.212	0.019	-0.193	0.003	0.030	-0.182	0.004	0.003

[a] p-value is based on the ANCOVA model for the overall treatment effect.
[b] LSM = Least squares mean for change from baseline.
[c] LSM of flunisolide dose minus LSM of placebo
[d] p-value is based on the ANCOVA model for comparison to placebo. Fisher's LSD is applied for adjustment of multiple comparisons.

The overall treatment effect of medium and high dose CFC flunisolide compared to placebo treatment was statistically significantly superior for both the primary efficacy variable and several secondary efficacy parameters, including actual FEV_1, mean daily asthma symptoms, AM asthma symptoms and nocturnal awakenings. It should also be noted that the difference in actual FEV_1 versus placebo after 12 weeks treatment was 161 mL in the 170 mcg HFA flunisolide BID group, and 186 mL in the 340 mcg HFA flunisolide BID group. These actual differences demonstrate reasonable clinical benefit.

Demonstrated superiority for both the CFC and HFA medium and high dose flunisolide groups vs. placebo enabled the applicant to then make an efficacy comparison between the two dose formulations. No significant differences between the two formulations stratified by medium and high doses with respect to change from baseline in primary and secondary efficacy parameters after 12 weeks treatment were demonstrated.

Although this study did not find a significant difference, it should be noted that conclusions about comparability should be made with caution because the study was not designed nor powered as a non-inferiority trial. Comparability may be more reliably inferred from the dose response curves, with further supportive analyses using Tukey's method.

Change from baseline to endpoint for % predicted FEV_1 and actual FEV_1 for HFA and CFC flunisolide across low, medium and high doses are presented in Figures 1 and 2 (applicant's Figures1 and 2, vol. 47). Deterioration of lung function from Week 0 is demonstrated in the placebo group, with some deterioration also seen in the low dose HFA group. Medium and high dose HFA groups maintain or improve in lung function from baseline, although a consistent difference between these groups is not maintained throughout the 12 weeks of the trial.

Figure 1

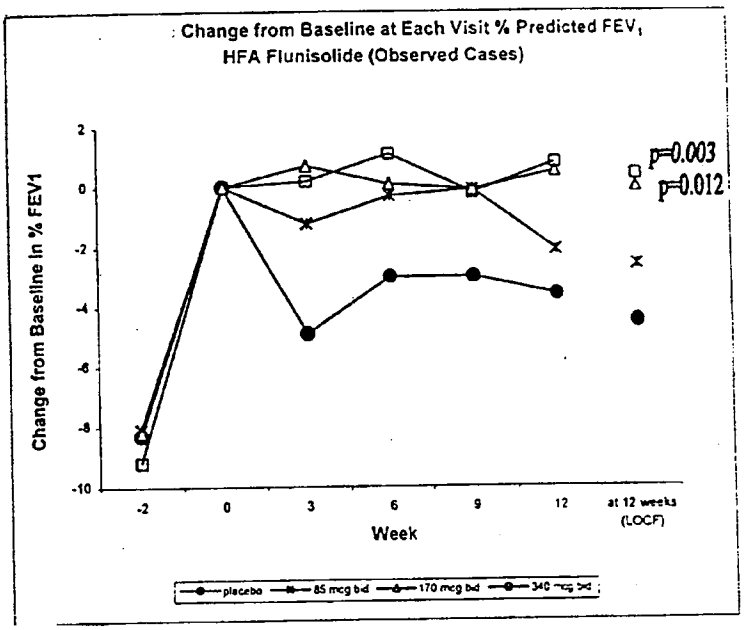
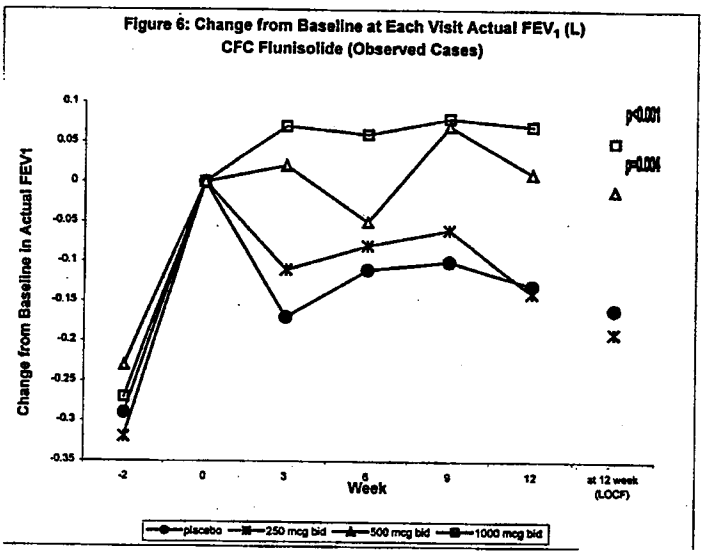


Figure 2



Numerical dose related effects are further demonstrated in the dose -response curves seen in Figures 3 and 4 (applicant's in-text figures 7 and 8, vol. 47), in which dose ordering is seen for CFC flunisolide, and to a somewhat lesser degree, HFA flunisolide formulations. This is effect is seen in both change from screening and change from baseline. On qualitative inspection, these curves may weakly signal that the high dose CFC formulation may be more effective than high dose HFA.

Figure 3

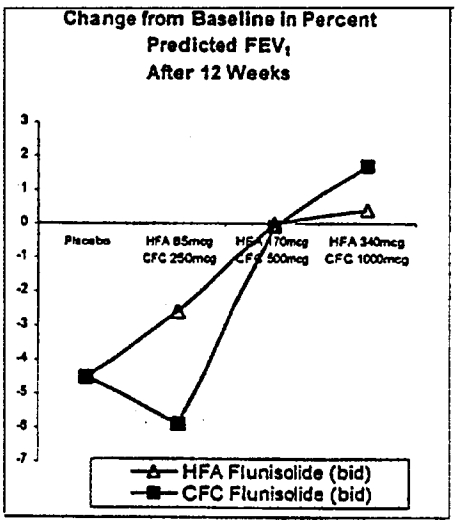
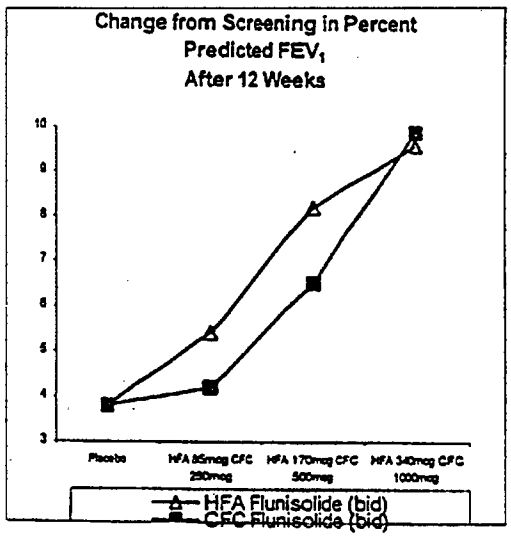


Figure 4

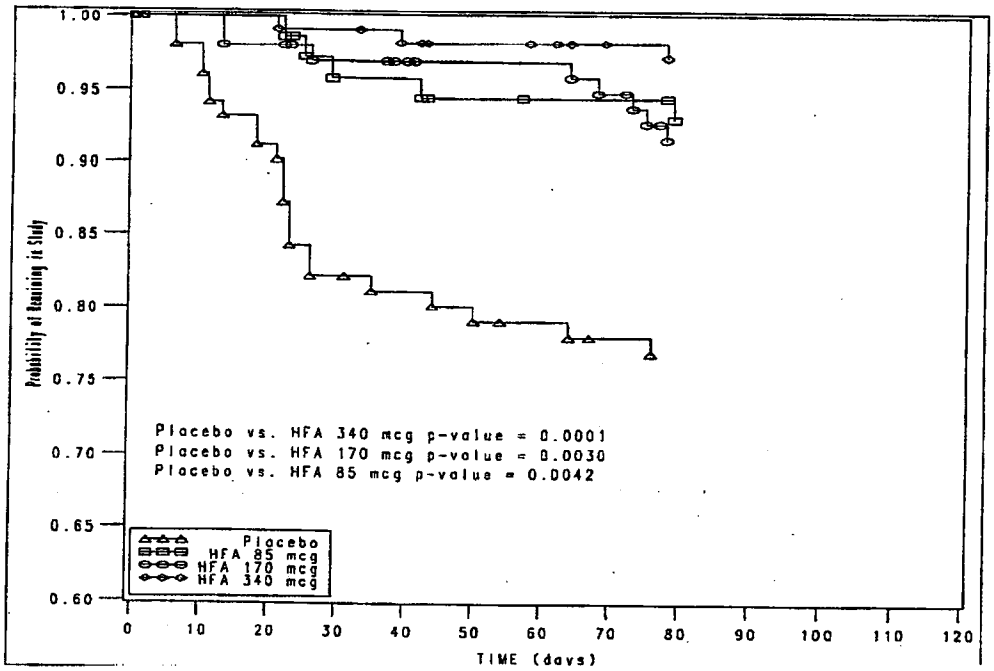


The dose response relationships for both the HFA and CFC flunisolide formulations were also evaluated using Tukey's method for the change from baseline and change from screening in the percent predicted FEV_1 after 12 weeks. Both the linear and log-linear dose models showed statistically significant slopes ($p<0.05$) when placebo was included in models for the change from baseline. When placebo was excluded from the evaluation of the change from baseline, neither model yielded a significant slope ($p>/=0.05$). The dose response curves themselves are somewhat dissimilar and cross at the high dose. However, sample size was not adequate to demonstrate dose response. Sample size was also not adequate to demonstrate comparability of the low, medium and high doses of HFA flunisolide compared with CFC flunisolide low medium and high doses, however, no statistically significant differences were observed in this study.

Time to dropout due to asthma exacerbation or insufficient therapeutic effect demonstrated a significant difference in all three HFA flunisolide dose groups (figure 5; applicant's in-text Figure 11, vol. 47).

Figure 5

TIME TO DROPOUT DUE TO EXACERBATION OF ASTHMA OR INSUFFICIENT THERAPEUTIC EFFECT.



The percent of drop-outs for asthma exacerbation or insufficient therapeutic effect from baseline to week 12 was 22.1% in the placebo group, 6.7% (p-0.0042 in comparison with placebo based on log ranks), 8.0% (p-0.0030), and 2.7 % (p-0.0001) in the low, medium and high HFA flunisolide groups, respectively.

Efficacy analyses performed at treatment week 6 using the ANCOVA model, and using measurements at week three for patients with missing values at week 6, demonstrated that at medium and high doses of HFA flunisolide maintained or increased the improvements achieved from the run-in period in percent predicted FEV_1, actual FEV_1, and mean daily prn albuterol use. Those patients who received placebo deteriorated in all three of the measured efficacy parameters after 6 weeks of therapy. Similar results were seen in the medium and high dose groups for CFC flunisolide compared to placebo.

Patients who were treated with low dose HFA flunisolide had numerically better responses than placebo treatment for the primary and all secondary efficacy parameters. However, low dose HFA flunisolide was not statistically superior to placebo for the primary efficacy parameter, actual FEV_1, or nocturnal awakenings.

At week 3 (Visit 3), statistically significant differences for all efficacy parameters when comparing the medium and high doses of flunisolide to placebo were demonstrated. These differences were maintained through week 12, except for PM PEFR of the medium HFA flunisolide dose compared to placebo and for prn albuterol use (Table 5; applicant's in-text Table 29, vol. 47)

Table 5 p-Values[a] for Comparison of Onset of Effect at Week 3 and 12 Weeks (LOCF)

Efficacy Parameters	*HFA Flunisolide vs. Placebo at Week 3 (Visit 3)*					*HFA Flunisolide vs. Placebo at 12 Weeks (LOCF)*				
	Overall p-Value	*170 µg*		*340 µg*		*Overall p-Value*	*170 µg*		*340 µg*	
		Difference	*p-Value*	*Difference*	*p-Value*		*Difference*	*p-Value*	*Difference*	*p-Value*
Percent Predicted FEV_1 (%)	0.000	5.357	0.000	4.973	0.000	0.007	4.057	0.012	4.579	0.003
Actual FEV_1 (L)	0.000	0.193	0.000	0.175	0.000	0.001	0.166	0.003	0.186	0.001
prn Albuterol Use (puffs/day)	0.000	-0.881	0.001	-1.076	0.000	0.018	-0.448	0.172	-0.910	0.005
AM PEFR (L/min)	0.003	16.596	0.002	12.284	0.005	0.022	16.354	0.010	13.780	0.026
PM PEFR (L/min)	0.001	14.180	0.005	16.534	0.001	0.113	11.142	0.080	11.637	0.060
Daily Symptoms	0.000	-1.663	0.000	-2.166	0.000	0.000	-1.737	0.001	-2.030	0.000
AM Symptoms	0.000	-0.855	0.000	-1.144	0.000	0.000	-0.931	0.001	-1.150	0.000
PM Symptoms	0.000	-0.798	0.001	-0.970	0.000	0.003	-0.777	0.005	-0.845	0.002
Nocturnal Awakening (per night)	0.000	-0.206	0.000	-0.165	0.002	0.003	-0.193	0.003	-0.182	0.004

[a] p-values from ANCOVA analysis for comparisons between formulations and placebo.

It should be noted that the first post-baseline visit in which FEV_1 was measured did not occur until week 3, therefore only diary data were available to evaluate onset of effect at weeks 1 and 2. At week 2, significant superiority was demonstrated for all diary efficacy parameters when comparing medium and high dose HFA flunisolide to placebo. At week one, significant benefit was demonstrated for 5/7 diary data efficacy parameters when comparing the high dose of HFA flunisolide to the placebo group. It can be concluded that onset of effect occurs within three weeks of BID dosing with HFA flunisolide.

2.6 REVIEWER'S COMMENTS ON EFFICACY

This study is an adequate and well controlled trial in which the efficacy of medium and high doses of HFA flunisolide have been demonstrated to be superior to placebo for the primary efficacy parameter, a measure of improved lung function in mild to moderate asthmatic adults and adolescents. Further, medium and high dose flunisolide also demonstrated superiority over placebo for all secondary efficacy parameters except PM PEFR. Of note, PM PEFR trended in an acceptable direction, but did not show statistical significance.

A dose response relationship was suggested, but not significantly demonstrated for both HFA and CFC formulations. Comparability analyses of HFA flunisolide and CFC flunisolide showed no significant differences using Tukey's method, however, it should be noted that the dose response curves for HFA and CFC flunisolide across low, medium and high doses are dissimilar in shape and slope, and cross at the high dose. On the other hand, the dose response at the medium doses of HFA and CFC flunisolide are superimposed. It should be further noted, that sample size was not adequate to demonstrate whether the 340 µg HFA flunisolide dose is different from the 1000 µg flunisolide dose.

The applicant claims onset of effect for the medium and high doses of HFA flunisolide within 1-2 weeks, however, the primary efficacy variable was not measured until week three. There is a suggestion of improved asthma symptomatology prior to week three, however superiority over placebo is seen only in the high dose HFA group at week one for 5/7 secondary efficacy parameters. At week two, all 7 secondary efficacy parameters for both medium and high dose groups are significantly better than placebo.

2.7 SAFETY REVIEW

2.7.1 Patient exposure

669 patients were exposed to double-blind medication during the treatment phase of the study for an average duration of 75.7 +/- 21.9 days. The mean duration of exposure to study drug was lowest in the placebo group, which may reflect early dropouts due to insufficient therapeutic effect. (Table 2.7.1, applicant's in-text table 32, vol.47)

Table 2.7.1 Treatment Duration: Safety Population

	Placebo (n=101)	*HFA 85 µg (n=73)*	*HFA 170 µg (n=100)*	*HFA 340 µg (n=113)*	*CFC 250 µg (n=75)*	*CFC 500 µg (n=103)*	*CFC 1000 µg (n=96)*	*Total (n=669)*	*p-Value*[b]
Mean	65.7	77.4	78.3	80.5	75.6	78.2	74.5	75.7	0.084
SD	30.5	20.8	18.1	13.8	22.2	18.4	23.7	21.9	
Median	84.0	84.0	84.0	84.0	84.0	84.0	84.0	84	
Range	1-97	1-101	6-106	1-98	10-106	7-92	1-91	1-106	

[a] Duration = number of days treated during the double-blind phase.
[b] p-Value based on Kruskal-Wallis test across all seven treatments.

2.7.2 Treatment Emergent Adverse Events (TEAE)

65 patients (62.5%) of patients in the placebo group, 170 (59.0%) of patients in the pooled HFA flunisolide group, and 162 (58.5%) of patients in the pooled CFC flunisolide group reported TEAEs. There did not appear to be a difference in the percent of patients reporting at least one TEAE in any treatment group. Asthma was reported by 20.2% of placebo-treated patients, which was approximately four times more frequent than asthma reported by those patients in the pooled HFA flunisolide groups (5.6%). Pooled CFC flunisolide-treated patients also reported asthma less frequently than the pooled placebo group (9.0%). Further, the incidence of asthma in the pooled placebo group was greater than twice that seen in any of the HFA dosing groups.

The most frequently reported TEAEs (>10% in any dose group) were similar across the treatment groups. Further, no dose dependant increase of reported TEAEs was seen. Allergic reaction, viral infection, and rhinitis occurred at an incidence of >=5% in one or more HFA dose groups and at a frequency twice or more than that of the placebo treatment group. (Table 2.7.2; applicant's Table FDA 926.1, amendment submission dated 9/27/00). This was similarly seen in the CFC groups, with the exception of rhinitis. Although rhinitis was seen at an increased rate over placebo, it did not occur at a frequency reaching twice the rate over placebo.

Table 2.7.2 Incidence of TEAEs (greater than 3%) in Patients Receiving HFA and CFC Flunisolide: No. (%) of Safety Patients

	Placebo	HFA Flunisolide (BID Dosing)			CFC Flunisolide (BID Dosing)		
	(N=104)	85 mcg (N=75)	170 mcg (N=109)	340 mcg (N=113)	250 mcg (N=76)	500 mcg (N=103)	1008 mcg (N=98)
COSTART Preferred Term	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
BODY AS A WHOLE							
ABDOMINAL PAIN	1 (1.0%)	1 (1.3%)	1 (1.0%)	2 (1.8%)	0 (0.0%)	2 (1.9%)	4 (4.1%)
ACCIDENTAL INJURY	4 (3.8%)	5 (6.7%)	3 (3.0%)	4 (3.5%)	4 (5.3%)	4 (3.9%)	2 (2.0%)
ALLERGIC REACTION	4 (3.8%)	8 (10.7%)	10 (10.0%)	5 (4.4%)	7 (9.2%)	6 (5.8%)	8 (8.2%)
ASTHENIA	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.6%)	0 (0.0%)	3 (3.1%)
BACK PAIN	4 (3.8%)	1 (1.3%)	6 (6.0%)	2 (1.8%)	3 (3.9%)	6 (5.8%)	3 (3.1%)
CHEST PAIN	2 (1.9%)	1 (1.3%)	2 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	3 (3.1%)
FLU SYNDROME	1 (1.0%)	1 (1.3%)	4 (4.0%)	0 (0.0%)	2 (2.6%)	0 (0.0%)	2 (2.0%)
HEADACHE	17 (16.3%)	6 (8.0%)	11 (11.0%)	10 (8.8%)	12 (15.8%)	10 (9.7%)	12 (12.2%)
INFECTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	1 (1.0%)	4 (4.1%)
PAIN	7 (6.7%)	3 (4.0%)	4 (4.0%)	2 (1.8%)	5 (6.5%)	9 (8.7%)	5 (5.1%)
VIRAL INFECTION	3 (2.9%)	4 (5.3%)	7 (7.0%)	4 (3.5%)	2 (2.6%)	9 (8.7%)	6 (6.1%)
OVERALL INCIDENCE	36 (34.6%)	23 (30.7%)	38 (38.0%)	33 (29.2%)	27 (35.5%)	36 (35.0%)	35 (35.7%)
DIGESTIVE SYSTEM							
DIARRHEA	2 (1.9%)	0 (0.0%)	1 (1.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	3 (3.1%)
DYSPEPSIA	3 (2.9%)	1 (1.3%)	4 (4.0%)	4 (3.5%)	3 (3.9%)	4 (3.9%)	2 (2.0%)
NAUSEA	2 (1.9%)	1 (1.3%)	1 (1.0%)	0 (0.0%)	2 (2.6%)	1 (1.0%)	4 (4.1%)
OVERALL INCIDENCE	14 (13.5%)	6 (8.0%)	13 (13.0%)	10 (8.8%)	9 (11.8%)	5 (4.9%)	11 (11.2%)
MUSCULOSKELETAL SYSTEM							
MYALGIA	1 (1.0%)	1 (1.3%)	3 (3.0%)	1 (0.9%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
OVERALL INCIDENCE	2 (1.9%)	2 (2.7%)	5 (5.0%)	1 (0.9%)	2 (2.6%)	0 (0.0%)	3 (3.1%)
NERVOUS SYSTEM							
DIZZINESS	1 (1.0%)	1 (1.3%)	3 (3.0%)	0 (0.0%)	2 (2.6%)	3 (2.9%)	1 (1.0%)
OVERALL INCIDENCE	4 (3.8%)	2 (2.7%)	7 (7.0%)	4 (3.5%)	2 (2.6%)	7 (6.8%)	5 (5.1%)
RESPIRATORY SYSTEM							
ASTHMA	21 (20.2%)	4 (5.3%)	8 (8.0%)	4 (3.5%)	9 (11.8%)	8 (7.8%)	8 (8.2%)
COUGH INCREASED	8 (7.7%)	4 (5.3%)	1 (1.0%)	2 (1.8%)	3 (3.9%)	3 (2.9%)	4 (4.1%)
LUNG DISORDER	1 (1.9%)	1 (1.3%)	0 (0.0%)	1 (0.9%)	3 (3.9%)	1 (1.0%)	1 (1.0%)
PHARYNGITIS	10 (9.6%)	11 (14.7%)	14 (14.0%)	19 (16.8%)	11 (14.5%)	12 (11.7%)	14 (14.3%)
RHINITIS	5 (4.8%)	4 (5.3%)	19 (19.0%)	4 (3.5%)	5 (6.6%)	4 (3.9%)	7 (7.1%)
SINUSITIS	5 (4.8%)	2 (2.7%)	2 (2.0%)	10 (8.8%)	9 (11.8%)	3 (2.9%)	3 (3.1%)
OVERALL INCIDENCE	38 (36.5%)	22 (29.3%)	32 (32.0%)	33 (28.3%)	31 (40.8%)	26 (25.2%)	29 (29.6%)

SKIN AND APPENDAGES RASH	3 (2.9%)	2 (1.3%)	3 (3.0%)	2 (1.8%)	3 (3.9%)	5 (4.9%)	3 (3.1%)
OVERALL INCIDENCE	5 (4.8%)	2 (2.7%)	3 (3.0%)	8 (7.1%)	6 (7.9%)	6 (5.8%)	4 (4.1%)
UROGENITAL SYSTEM URINARY TRACT INFECTION	1 (1.0%)	1 (1.3%)	2 (2.0%)	4 (3.5%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
OVERALL INCIDENCE	2 (1.9%)	3 (4.0%)	4 (4.0%)	8 (7.1%)	3 (3.9%)	1 (1.0%)	5 (5.1%)

2.7.3 Treatment Discontinuation due to Adverse Events

There were no significant differences for individual adverse events that led to an increased dropout rate in any of the HFA or CFC flunisolide treatment groups compared to placebo. Overall, a larger percentage of patients discontinued due to an adverse event from the pooled placebo group (19.2%) than from the pooled HFA flunisolide group (5.6%) or the pooled CFC flunisolide group (9.4%). The most common adverse event leading to dropout was coded as asthma. Of the 47 patients (7%) that discontinued for asthma, the greatest number was in the placebo group (18 patients, 17.3%). This was greater than 4 times the percentage of patient discontinuations in the HFA flunisolide group (10 patients, 3.5%), and more than 2 times the percentage of patient discontinuations in the CFC flunisolide group (19, 6.9%). With the exception of asthma, among both pooled active treatment groups, pharyngitis and lung disorder were the only other TEAEs that accounted for >1% of patients discontinuing prematurely from the study, and both of these were in the pooled CFC flunisolide group. Overall, there did not appear to be a dose-related increase in the number of patients who discontinued prematurely from the study for either active treatment groups. (Table 2.7.3; applicant's in-text Table 42, vol. 47)

Table 2.7.3 Adverse Events Leading to Discontinuation of Treatment

Adverse Event (Body System Preferred Term)	*No. (%) of Patients*		
	Placebo (n=104)	*HFA Flunisolide Pooled (n=288)*	*CFC Flunisolide Pooled (n=277)*
One or more[a]	20 (19.2)	16 (5.6)	26 (9.4)
BODY AS A WHOLE			
Allergic reaction	0	2 (0.7)	0
Asthenia	1 (1.0)	0	0
Chest pain	0	0	1 (0.4)
Chills	0	0	1 (0.4)
Headache	0	0	1 (0.4)
Viral infection	0	0	1 (0.4)
CARDIOVASCULAR			
Syncope	0	1 (0.3)	0
DIGESTIVE			
Flatulence	0	0	1 (0.4)
Intestinal obstruction	1 (1.0)	0	0
Nausea	1 (1.0)	0	0
Oral moniliasis	0	0	1 (0.4)
Vomiting	1 (1.0)	0	0
NERVOUS			
Somnolence	0	0	1 (0.4)
RESPIRATORY			
Asthma	18 (17.3)	10 (3.5)	19 (6.9)
Pharyngitis	2 (1.9)	3 (1.0)	5 (1.8)
Cough increased	1 (1.0)	0	1 (0.4)
Bronchitis	0	1 (0.3)	0
Lung disorder	0	0	3 (1.1)
Rhinitis	0	0	1 (0.4)
Sinusitis	1 (1.0)	1 (0.3)	1 (0.4)
SKIN AND APPENDAGES			
Rash	0	0	1 (0.4)
Urticaria	0	0	1 (0.4)
UROGENITAL			
Unintended pregnancy	0	0	1 (0.4)

[a] "One or more" includes any patients for whom treatment was discontinued for one or more adverse event. Patients are counted once for "One or more" and once for each adverse event.

2.7.4 Serious Adverse Events (SAEs) and Deaths

There were no deaths in this trial. Seven randomized patients experienced non-fatal SAEs:

- accidental injury (medium dose CFC flunisolide group)
- cellulitis (high dose HFA flunisolide in a male 17 year old patient with osteomyelitis of the hand/cellulitis/Herpes Zoster exacerbation with onset approximately 1 week following the last dose of study medication)
- GI disorder (resulting in appendectomy, treatment with antibiotics for infection and removal of an ovarian cyst - CFC flunisolide group)

- intestinal obstruction (in a patient with a history of small bowel obstruction-placebo group),
- non-cardiac chest pain (in a 78 year old female undergoing a non-stress test with subsequent negative cardiac catheterization)
- 2 incidents of asthma (one patient randomized to the high dose HFA flunisolide group, one patient randomized to medium dose HFA flunisolide who received treatment in an ER and then continued in the study).

Of these seven patients, 2 discontinued from the study one patient with intestinal obstruction (placebo group) and one patient hospitalized with an acute asthma exacerbation after exposure to heavy perfume and smoke (340µg HFA flunisolide group after 20 days on study drug).

It is notable that the only two serious adverse events due to asthma were in the HFA group. Further, although the investigator did not believe that the patient with osteomyelitis/cellulitis/Zoster SAE was related to study drug and the event occurred 1 week after the last dose of study medication, steroids as a class are known immune suppressants and may have contributed to his SAE. This may be addressed by corticosteroid class labeling.

2.7.5 Clinical Laboratory Evaluation

The incidence of abnormal hematology test results was low and similar among all treatment groups (</=1% in the HFA flunisolide groups, 1%-2.6% in the CFC flunisolide groups). None of the individual patient hematology findings of potentially clinically significant hematology abnormalities (defined in Vol 1.47, after-text table 5.7) were considered clinically significant.

There were no changes from baseline chemistry that were considered clinically important by the applicant. The incidence of abnormal clinical chemistry test results was low and similar among treatment groups. The most commonly reported abnormal chemistry result in the overall safety population was elevated triglycerides (7.2%). Elevated triglycerides were reported in 10.6% of placebo patients, 8.0%, 6.0 % and 7.1% of patients treated with low, medium and high dose HFA flunisolide, respectively, and 6.6%, 7.8%, and 4.1 % of patients treated with low, medium and high dose CFC flunisolide, respectively.

Mean values at baseline and the change from baseline to 12 weeks were similar between all treatment groups for urinalysis test results.

2.7.6 Vital signs

All mean values for vital signs measurement were similar among treatment groups and the mean changes from baseline to week 12 for each group were similar and small. There were no statistically significant differences in the overall comparisons. None of the potentially clinically significant vital signs values were considered to be clinically important.

2.7.7 ECGs

There were no differences between treatment groups in the number of patients with abnormal ECG values at visits 1 or 6 nor were there clinically significant changes in ECG from the screening visit (visit1).

2.7.8 Physical examination findings

There were no differences overall among the treatment groups in the appearance of new abnormalities during the physical examination, except for increases observed in the percentage of patients with pulmonary abnormalities in the placebo group (18.3%) vs. 10.7%, 12%, and 5.3 % in the low, medium and high dose flunisolide groups respectively, and 14.5%, 10.7%, and 10.2% in the low, medium and high dose CFC flunisolide, respectively. There were also differences in the Eyes, Ears, nose and throat parameter, with placebo transition from normal to abnormal @ 12.5%, low, medium and high dose HFA flunisolide @ 20.0%, 10.0%, and 10.6%, respectively, and low medium and high dose CFC flunisolide @ 10.5%, 9.7%, and 7.1%, respectively. No explanation for these differences are offered.

2.7.9 Mouth and Throat Cultures for Candida

No increases of oral candidiasis or clinical evidence of thrush was observed across treatment groups.

2.7.10 Urinary cortisol

Absolute cortisol excretion and cortisol excretion corrected for urinary creatinine showed no apparent drug effect as measured as change from baseline over 12 weeks treatment. Further, there was no clear dose response relationship observed between HFA flunisolide and urinary cortisol excretion. The percentage of abnormal urinary cortisol values after 12 weeks treatment was numerically similar across all treatment groups, including placebo as seen in Table 2.7.10, applicant's in-text table 51.

Table 2.7.10 Number (%) of Patients with Abnormal 24-Hour Urinary Cortisol values

In-text Table 51. Number (%) of Patients With Abnormal[a] 24-Hour Urinary Cortisol Values:

Time Point	*Placebo*	*HFA 85 µg*	*HFA 170 µg*	*HFA 340 µg*	*CFC 250 µg*	*CFC 500 µg*	*CFC 1000 µg*
Baseline	5 (14.7)	4 (14.3)	5 (16.1)	4 (10.8)	2 (7.7)	8 (26.7)	6 (20.0)
n	34	28	31	37	26	30	30
Week 12	5 (21.7)	3 (12.0)	4 (14.3)	8 (24.2)	4 (20.0)	2 (8.3)	3 (12.0)
n	23	25	28	33	20	24	25

[a] Abnormal values are those values outside the normal range of 10 to 65 µg/dL

Cross-reference: After-text Table 5.11.1

2.7.11 Plasma Cortisol Levels After Cortrosyn Stimulation

The plasma cortisol levels in all three HFA groups 30 and 60 minutes post cortrosyn were stimulated to the same extent as the levels in the placebo group. The change in plasma cortisol levels from pre-cortrosyn levels was also similar between groups. Table 2.7.11A (applicant's in-text table 53, vol. 47) show the percentage of patients who are non-responders to cortrosyn stimulation assessed from baseline to endpoint. It should be noted that the differences in the percentage of new non-responders at the end of the study was higher than placebo in both lower HFA groups and highest in the 1000 mcg CFC group. This may be a weak signal of active treatment effect. However, if one assesses the simple change from baseline to end of study in non-responders to cortrosyn stimulation (Table 2.7.11B), placebo patients had the highest percentage of nonresponders overall.

Table 2.7.11A Non-Responders[a] to Cortrosyn Stimulation Test Results: Percent (No.)[b] of Patients

Time Point	*Placebo*	*HFA 85 µg*	*HFA 170 µg*	*HFA 340 µg*	*CFC 250 µg*	*CFC 500 µg*	*CFC 1000 µg*
Baseline	2.9 (1/34)	14.3 (4/28)	3.2 (1/31)	13.5 (5/37)	7.7 (2/26)	10.0 (3/30)	6.5 (2/31)
End of Study	8.0 (2/25)	7.4 (2/27)	6.9 (2/29)	12.1 (4/33)	4.8 (1/21)	14.8 (4/27)	11.1 (3/27)
New non-responder at study end[c]	5.9 (2/34)	7.1 (2/28)	6.5 (2/31)	5.4 (2/37)	3.8 (1/26)	6.7 (2/30)	9.7 (3/31)

[a] Non-responder = a patient who does not have an increase in plasma cortisol ≥ 7 µg/dL or does not have an absolute value ≥ 18 µg/dL after cortrosyn injection.
[b] Percentages are based on the no. of patients tested at post-cortrosyn stimulation.
[c] Patients who were responders at baseline and changed to non-responders at week 12.

Table 2.7.11B Change from Baseline to End of Study in Non-responders to Cortrosyn Stimulation Test: Percent of Patients

Delta[a]	Placebo	HFA 85 µg	HFA 170 µg	HFA 340 µg	CFC 250 µg	CFC 500µg	CFC 1000 µg
	5.1	-6.9	3.7	-1.4	-2.9	4.8	4.6

[a] Delta is defined as percent of non-responder patients at the end of the study minus percentage of non-responder patients at baseline

2.7.12 Serum osteocalcin and urinary deoxypyridinoline

Results of metabolic bone determinations for serum osteocalcin and urinary deoxypyridinoline showed a high degree of variability and no consistent treatment effect (vol. 47, page 00197 and applicant's after text table 5.11.4,vol 47).