CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20549 AND 20770

Trade Name: FLOVENT ROTADISK

Generic Name: FLUTICASONE PROPIONATE

Sponsor: GLAXO WELLCOME

Approval Date: NOVEMBER 7, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20549 AND 20770

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter			X	
Approvable Letter	X			
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20549 AND 20770

APPROVAL LETTER

NOV 7 1997

NDA 20-549
NDA 20-770

Glaxo Wellcome
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Kathleen A. Prodan
Director, Regulatory Affairs

Dear Ms. Prodan:

Please refer to your new drug applications dated December 29, 1994, and September 26, 1996, received December 29, 1994, and September 27, 1996, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flovent Rotadisk, 50 mcg, 100 mcg, and 250 mcg (fluticasone propionate inhalation powder).

We acknowledge receipt of your submissions to NDA 20-549 dated February 7, April 11, 14, and 20, May 2, 19, and 31, July 13, September 13, October 16 and 26, and December 8, 1995, February 20, April 30, and November 4, 1996, and January 24, February 10, 20, 25, and 27, March 4, 5, 28, and 31, April 1 and 17, May 7, June 6, September 4, October 6, 13, 24, 27, 28, 29, and 31, and November 3, 5, and 6, 1997. The user fee goal date for this application is November 8, 1997.

We also acknowledge receipt of your submissions to NDA 20-770 dated December 2, 9, and 16, 1996, and January 2, 17, 22, and 24, February 12 and 27, March 4, 5, 28, and 31, April 17 and 21, August 28, September 4, October 13 and 31, and November 3, 5, and 6, 1997. The user fee goal date for this application is April 14, 1998.

NDA 20-549 provides for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. NDA 20-770 provides for the maintenance treatment of asthma as prophylactic therapy in patients 4 to 11 years of age.

We have completed the review of these applications including the draft labeling submitted on November 6, 1997, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and

effective for use as recommended in the enclosed marked-up draft labeling and with the revisions listed below. Accordingly, the applications are approved effective on the date of this letter. The revisions are as follows:

1. The phrase "in a Dry Place" should be added to the storage conditions on the tube labeling.

2. The term "(to deliver XX mcg)" where XX = 44, 88, or 220 mcg, should be removed from all labels and labeling.

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-549." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

We remind you of your agreements and Phase 4 commitments specified in your submission dated November 6, 1997. The Phase 4 commitments, along with the agreed upon completion dates, are listed below.

Redacted 1

page(s) of trade

secret and/or

confidential

commercial

information

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to NDA 20-549. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data, and final reports to this NDA as correspondence or as supplements, as indicated above. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to NDA 20-549, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising
and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. To comply with these regulations, all 3-day and 15-day alert reports, periodic adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 20-549 for this drug product, not to NDA 20-770. In the future, no submissions should be made to NDA 20-770.

If you have any questions, please contact Ms. Sandy Barnes, Project Manager, at (301) 827-1075.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDAs 20-549, 20-770
HFD-570/Div. Files (2)
HFD-570/CSO/S.Barnes
HFD-570/Meyer
HFD-570/Purucker
HFD-570/Koble
HFD-570/Sancilio
HFD-570/Gebert
HFD-570Conner
HFD-002/ORM (with labeling)
HFD-102/Office Director
HFD-101/L.Carter
HFD-820/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs
HFI-20/Press Office (with labeling)
HFD-021/ACS (with labeling)

Drafted by: S. Barnes/November 6, 1997/
Initialed by: C. Schumaker 11/7/97
L. Sancilio 11/7/97
C. Sun 11/7/97
D. Conner 11/7/97
R. Meyer 11/7/97
M. Purucker 11/7/97
A. Schroeder for G. Poochikian 11/7/97
J. Gebert 11/7/97
J. Jenkins 11/7/97
final:

APPROVAL (AP) NDA 20-549 [with Phase 4 Commitments]
APPROVAL (AP) NDA 20-770

DDR- Change NDA 20-770 to Type 6 NDA.

11/7/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20549 AND 20770

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-770

GlaxoWellcome
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Attention: Kathleen A. Prodan
Director, Regulatory Affairs

Dear Ms. Prodan:

Please refer to your new drug application dated September 26, 1997, received September 27, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flovent (fluticasone propionate) Rotadisk via Diskhaler, 50 mcg, 100 mcg and 250 mcg.

We acknowledge receipt of your submissions dated December 2, 9, and 16, 1996, and January 2, 17, 22, and 24, February 12 and 27, March 4, 5, 28, and 31, April 17 and 21, August 28, and September 4, 1997. The user fee goal date for this application is September 27, 1997.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following issues.

1. This application cannot be approved until NDA 20-549 Flovent Rotadisk via Diskhaler is approved since the Manufacturing and Controls section of this application consists of a reference to NDA 20-549.

2. Please submit revised draft labeling based on the preliminary revisions in the enclosed marked-up draft labeling and the following revisions.

We may have additional labeling comments following our review of the CMC data submitted to NDA 20-549 and the requested draft labeling incorporating the above comments.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product.

All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Ms. Sandy Barnes, Project Manager, at (301) 827-1075.

Sincerely yours,

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20549 AND 20770

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	**NDA 20-770**	**APPLICATION TYPE:**	**NDA**
SPONSOR:	**Glaxo-Wellcome, Inc.**	**PRODUCT/PROPRIETARY NAME:**	**Flovent Rotadisk Inhalation Powder 50/100 µg/actuation**
		USAN / Established Name:	**Fluticasone propionate**
CATEGORY OF DRUG:	**Corticosteroid**	**ROUTE OF ADMINISTRATION:**	**Oral Inhalation**
MEDICAL REVIEWER:	**Mary E. Purucker, M.D., Ph.D.**	**REVIEW DATE:**	**22 September 1997 Amended: 2 October 1997**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
26 September 1996	27 September 1996	Full NDA application	Submitted in 97 volumes.
09 December 1996	10 December 1996	Amendment	Clinical laboratory data from pivotal trial FLD220, inadvertently left out by the sponsor in the original submission.
22 January 1997	23 January 1997	Supplement	120 day safety update.
31 January 1997	N/A	FAX	Request by medical and statistical reviewers for subset analysis of growth rate characteristics of pubertal patients in clinical trial FLD220.

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
29 December 1994	NDA 20-549	Flovent Rotadisk Inhalation Powder (adult application)
	NDA 20-548	Flovent Inhalation Aerosol
	NDA 20-121	Flonase Nasal Spray

Overview of Application/Review: This is an application is for a dry powder formulation of fluticasone propionate contained in a foil wrapped "blister" which is punctured and then inhaled by means of a reusable device called a Rotadisk. The sponsor proposes Flovent Rotadisk Inhalation Powder in doses of 50 or 100 µg twice daily for use in the maintenance treatment of asthma as prophylactic therapy in children age 4 through 11 years. NDA 20-549 for Flovent Rotadisk Inhalation Powder in doses of 100 to 1000 µg twice daily is presently under review in this division for the same indication in adults and adolescents. The two applications share CMC and preclinical sections, and the final approval of this NDA is contingent upon the approval of the NDA for the adult product.

NDA 20-770 is comprised of two pivotal trials, FLIT85 and FLD220, and nine other completed supportive trials which included a total of 1173 children age 4 through 11 years. FLIT85 was a 12-week non-U.S. study for efficacy conducted with 263 patients. FLD220 was a one-year U.S. safety study conducted with 325 children which had as its primary objective to study the effects of fluticasone propionate on growth. Both of these two pivotal trials were placebo-controlled.

Pivotal study FLIT85 was successful in demonstrating the efficacy of Flovent Rotadisk Inhalation Powder at doses of 50 or 100 µg BID for the proposed indication in children, when compared to placebo. However, pivotal study FLD220 was able to demonstrate a small but statistically significant negative impact on growth rate in the children who received 100 µg BID compared to placebo which amounted to 0.66 cm/year. Children receiving 50 µg BID also had a numerical decrement in growth rate, although this did not reach statistical significance.

In conclusion, the sponsor was successful in demonstrating the efficacy of Flovent Rotadisk Inhalation Powder at 50 or 100 µg BID in the maintenance treatment of asthma in children between the ages of 4 and 11, inclusive. The small but statistically significant impact of this product on growth in these children must be included in the package labeling by the sponsor. This product has been given an "approvable" rating, again contingent upon the approval of the adult product by this division.

Outstanding Issues: Final approval of this application is contingent upon approval of NDA 20-549, Flovent Rotadisk Inhalation Powder for adults and adolescents 12 years of age and older.

Recommended Regulatory Action:	N drive location:
New Clinical Studies: _____ Clinical Hold	_____ Study May Proceed
NDAs:	
Efficacy / Label Supp.: __X__ Approvable	_____ Not Approvable
Signed: Medical Reviewer: [signature]	Date: 23 October 1997
Medical Team Leader: [signature]	Date: 10/23/97

AMENDED 10/3/97

MEDICAL OFFICER REVIEW

1.0 GENERAL INFORMATION

NDA #:	**20-770**
PRODUCT:	**Flovent Rotadisk Inhalation Powder 50/100 µg dispensed via Diskhaler Device.**
DRUG SUBSTANCE:	**Fluticasone Propionate**
DESCRIPTION:	**Finely Micronized (diameter <5 µM) dry powder fluticasone propionate**
CATEGORY:	**Inhaled Corticosteroid**
INDICATIONS:	**Maintenance Treatment of Asthma as Prophylaxis**
TARGET AGE:	**Children age 4-11 years**
DOSAGE:	**50 or 100 µg BID (Delivered dose will be 44 µg or 88 µg per actuation).**
SPONSOR:	**Glaxo-Wellcome, Inc.**
REVIEWER:	**Mary E. Purucker, MD-PhD**

DATES:

Submission date:	26 September 1996
CDER stamp date:	27 September 1996
Filing date:	25 November 1996
Reviewed:	Amended 2 October 1997

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submissions Type:	Comments:
26 Sept. 96	27 Sept. 96	NDA 20-770	97 Volumes
09 Dec. 96	10 Dec. 96	Amendment	FLD-220 Laboratory Data
22 Jan. 97	23 Jan. 97	Supplement	120 day safety update
31 Jan. 97	N/A	FAX	Request by medical and statistical reviewers for subset analysis of growth rate characteristics of pubertal patients in FLD-220

2.0 TABLE OF CONTENTS

Glossary of abbreviations used: CMC - Chemistry, Manufacturing, and Controls; NDA - New Drug Application; IND - Investigational New Drug; CDER - Center for Drug Evaluation and Research; BID - Twice daily dosing; FP - fluticasone propionate; MDI - metered dose inhaler; DPI - dry powder inhaler; MDPI - multidose powder inhaler; BLQ - below the limit of quantification, refers to assay for levels of drug; HPA - hypothalamic-pituitary-adrenal axis; BDP - beclomethasone dipropionate; PFTs - pulmonary function tests; FEV_1 - forced expiratory volume in one second; FVC - forced vital capacity; FEF_{25-75} - mid-expiratory flow rate between 25% and 75% of an FVC; AE or ADR - adverse event occurring in the context of drug exposure, i.e. adverse drug reaction; QOL - quality of life; ANOVA - analysis of variance; SE - standard error of the mean; PSC - posterior subcapsular cataract; IOP - intraocular pressure; ECG - electrocardiogram; LOQ - level of quantitation; prn - as needed; ITT - intent-to-treat population; BUD - budesonide; ICS - inhaled corticosteroid; URI/URTI - upper respiratory tract infection; ISE - Integrated Summary of Efficacy; ISS - Integrated Summary of Safety; ICH - International Conference on Harmonization.

3.0 MATERIAL REVIEWED

1. Medical officer's copy of NDA 20-770 submitted to CDER on 27 September 1996 in 97 volumes, including volumes 1.1, 1.6-1.81, and selected case report forms in volumes 1.82-1.97.
2. Volume 1.25A, a continuation of line listings of laboratory values from clinical trial FLD-220, which was inadvertently omitted from the original submission. It was requested from the sponsor on 6 December 1996 and received at CDER on 10 December 1996.
3. The 120 day safety update, submitted in two volumes on 23 January 1997.
4. Copy of the review by the Clinical Pharmacology and Biopharmaceutics Division of this agency of the sponsor's protocol FLTA1001 and *in vitro* study GDM/96/024 submitted 24 January 1997.
5. Copy of the review by the Clinical Pharmacology and Biopharmaceutics Division of this agency of the sponsor's protocol FLTB1003, submitted 4 March 1997.

4.0 BACKGROUND

4.1 General Overview

Flovent® Rotadisk Inhalation Powder is a micronized dry powder preparation of the synthetic corticosteroid fluticasone propionate. Each Rotadisk consists of a circular

The sponsor seeks pediatric approval for only the two dosage strengths, designated as Flovent Rotadisk 50 µg Inhalation Powder and Flovent Rotadisk 100 µg Inhalation Powder, for use in patients age 4 - 11 years.

A separate New Drug Application (NDA 20-549) providing for maintenance treatment of asthma in adult and adolescent patients 12 years of age and older with proposed doses of 100 µg to 1000 µg twice daily was previously submitted to the Agency on 29 December 1994. In this application, approval was sought for three dosage strengths, 50 µg, 100 µg, and 250 µg. It was deemed "not approvable" for CMC reasons (chemistry, manufacturing, and control) on 28 December 1995. Rather than await resolution of these problems and submit a Pediatric Efficacy Supplement under this prior NDA, the sponsor has elected to submit NDA 20-770 separately to the Agency for review under its own time clock. The two NDAs share CMC and preclinical sections.

4.2 Related INDs and NDAs

- NDA 20-549 Flovent (fluticasone propionate) Rotadisk Inhalation Powder
- NDA 20-548 Flovent (fluticasone propionate) Inhalation Aerosol
- NDA 20-121 Flonase (fluticasone propionate) Nasal Spray
-

4.3 Prior Marketing

In markets outside of the United States, approval has been obtained for fluticasone propionate (Flixotide™) Rotadisk inhalation powder in children 4 to 11 years of age in 27 countries, starting in early 1993 (see list below). According to the sponsor, there have been no withdrawals of fluticasone propionate Rotadisk inhalation powder, metered-dose inhaler, or Diskus inhalation powder from marketing for any reason related to safety or effectiveness.

TABLE OF COUNTRIES WHERE FLOVENT ROTADISK POWDER HAS BEEN APPROVED FOR PEDIATRIC USAGE

Country	Approval Date
Argentina	7/19/94
Australia	11/25/93
Belgium	12/2/93
Canada	7/31/95
Chile	5/94
Croatia	6/27/94
Cyprus	4/94
Denmark	4/21/93
France	11/2/93
Germany	11/30/94
Greece	7/15/94
Holland	1/25/94
Hungary	Approved
Iceland	7/1/94
Ireland	11/16/93
Israel	Approved
Italy	4/27/94
Luxembourg	3/23/94
New Zealand	Approved
Norway	2/7/94
Portugal	Approved
Slovenia	11/23/94
South Africa	11/12/93 (for children>6 yrs)
Spain	Approved
Switzerland	8/26/93
Thailand	Approved
United Kingdom	2/25/93

Reviewer's Comment: Although approval has been granted in the above countries, in some cases, the product has yet to be marketed.

5.0 CHEMISTRY, MANUFACTURING, AND CONTROLS SECTION

5.1 **Drug Substance**: Cross-referenced to pending NDA 20-549 for Flovent (fluticasone propionate) Rotadisk Inhalation Powder.

5.2 **Drug Product**: Cross-referenced to pending NDA 20-549 for Flovent (fluticasone propionate) Rotadisk Inhalation Powder.

6.0 PRECLINICAL PHARMACOLOGY AND TOXICOLOGY

Fluticasone propionate is a synthetic glucocorticoid with high topical activity and low oral bioavailability due to poor absorption and extensive first pass metabolism. The pharmacokinetic data obtained from rat and dog models indicate rapid and extensive metabolic clearance. Distribution studies have shown that a very small percentage of intratracheally or orally administered compound reaches the systemic circulation, and this material is rapidly eliminated in the bile and excreted in the feces. Fluticasone has a high affinity for the glucocorticoid receptor. The toxicity observed in animal studies appears to be typical of corticosteroid excess. There has been no detectable mutagenic or tumorigenic activity.

Studies related to the pharmacology and toxicology of the drug substance fluticasone propionate have been submitted to and reviewed by this agency in support of applications for the approved drug products Flovent® (Fluticasone Propionate Inhalation Aerosol, NDA 20-548) and Flonase® (Fluticasone Propionate Nasal Spray, NDA 20-121). Additional studies were submitted with the application for NDA for Flovent® Rotadisk Inhalation Powder (NDA 20-549), which is currently under review in this division. All three of these products contain or propose labeling which indicate they are for use by adults and adolescents 12 years and above. In contrast, the presently submitted NDA 20-770 for Flovent Rotadisk Inhalation Powder is proposed for children age 4 through 11 years. In support of this indication, the sponsor has therefore submitted a summary of three studies conducted in juvenile animals.

Two studies were performed using juvenile rats. Animals were dosed daily using the subcutaneous route to increase bioavailability relative to the inhaled route. Doses ranged from 0.4 to 10 µg/kg/day administered from day 3 of life until day 44. Animals receiving the higher doses of fluticasone manifested the standard effects associated with drugs of the glucocorticoid class. No effect on growth or indices of sexual maturation were seen at the lower doses. However, some animals dosed at the higher levels of 5 or 10 µg/kg/day did show a reduction in the rate of weight gain. There was no reported effect on sexual maturation.

A 52 week study was performed using 24 juvenile beagle dogs, 12 males and 12 females, age 9-10 weeks using fluticasone propionate administered twice daily by inhalation. Doses started at 1500 µg BID for the first 8 weeks, then were reduced to 750 µg BID for the remainder of the study. Delivered doses were calculated to be as high as 140 µg/kg/day for the first week to as low as approximately 25 µg/kg/day by the end of the study, based upon decreased actuated dosage and increased animal weights associated with maturation. Maximum plasma concentrations of fluticasone drawn 20 minutes after dosing were measured as 1470 pg/mL at the highest dosage early in the study and between <250 to 1180 pg/mL by 52 weeks. According to the sponsor, the persistence of

high average serum fluticasone levels in spite of dosage reduction may reflect saturation of absorption at the higher dosage level. The AUC was not reported.

The results of this study confirm the typical clinical and laboratory changes associated with prolonged administration of a potent glucocorticoid. With regard to specific developmental effects, the animals were "stunted" in overall growth and showed a reduction in long bone length. A decrease in the expected length of the trachea was also reported.

The sponsor acknowledges a developmental effect of fluticasone on beagle dogs when administered chronically in this dose range. However, the sponsor argues that the lowest administered dose found to produce this effect, 25 μg/kg/day, was greater than five times the highest expected dose delivered to an average 4 year old pediatric patient weighing 15 kg and receiving the maximum recommended daily dose of 200 μg. This is assuming 30% delivery to the lung. In support of this conclusion, the sponsor presents data from pediatric patients receiving 100 μg BID of fluticasone (see "Clinical Pharmacology", next section) showing plasma fluticasone concentrations in the range of 28.1 to 154 pg/mL, which compares to <250 to 1180 pg/mL in beagle dogs manifesting adverse side effects.

In conclusion, repeated administration of supratherapeutic doses of fluticasone propionate produces the typical pharmacological effects associated with glucocorticoid excess. There were no reported unexpected toxic, mutagenic, or tumorigenic effects. Developmental effects were observed in juvenile dogs receiving approximately five times the highest dosage recommended for children. A "no effect" dose was not determined in that study. Juvenile rat studies were conducted using the *subcutaneous route,* were not correlated with serum fluticasone levels, and are therefore difficult to interpret. Hence, inhaled fluticasone administered to children within the proposed dosage range could possibly have developmental effects in some individuals, although these effects would most probably be associated with a much higher dose. Because there is potential morbidity associated with the underlying disease process, asthma, any such risk may be justifiable on the basis of the possible clinical benefit.

7.0 CLINICAL PHARMACOLOGY

After intravenous administration, the pharmacokinetics of fluticasone propionate (FP) are proportional to dose after single doses of 250, 500, and 1000 μg. FP is extensively distributed within the body (Vss 4.2 L/kg), rapidly cleared (1,093 mL/min), and has a terminal elimination $T_{½}$ of 7.8 hours, although the concentration of FP at that final time point is so low as to be close to the detectable limit for the assay. Clearance is almost entirely by metabolism to the inactive 17β-carboxylic acid derivative via the CYP3A4 isozyme of cytochrome P450.

Oral bioavailability of FP is very low, probably due to presystemic metabolism by CYP3A4 in gut and liver, and is on the order of 1%. In theory, therefore, an inhibitor of CYP3A4 might increase the systemic bioavailability of FP, leading to greater systemic toxicity related to the predictable pharmacologic properties of this class of drugs. To date, no such interaction has been reported in the adverse event databases. Within this

submission, the sponsor includes data relevant to FP interactions with theophylline, the macrolide antibiotics erythromycin and clarithromycin, terfenadine, and salmeterol. At the request of the biopharmacology reviewer, the sponsor has also included formal studies of normal volunteers co-administered ketoconazole and FP, as well as the macrolide antibiotic erythromycin co-administered with FP. These studies are discussed in detail under **10.7 Drug-Drug Interactions.**

When given via the oral inhalation route, absorption occurs primarily through the target organ, the lung, and has been measured in the range of 10-30% of the nominal dose for both the MDI or DPI in adults. This means nearly complete absorption of the fraction of the nominal dose deposited in the lung. In children, the sponsor reports that no data specific to FP are available. However, studies conducted using inhaled budesonide, presumably with the same device, also indicated an absolute bioavailability of 30%. When FP is administered as a single inhaled dose in the range between 500-2000 μg, measured plasma levels appear to increase in a linear fashion. Peak plasma concentrations measured in adults ranged from 100 to 1000 pg/mL after 1000 μg delivered by inhalation, either by the MDI or the Diskhaler.

Multiple dose pharmacokinetics of FP have been studied both in adults by sparse sampling (Study FLD230, NDA 20-549) and in children (FLD220, this submission). In each of these studies, a subset of patients had plasma FP levels measured at various time points during the study. In the case of FLD220, which was a one year growth study with FP delivered via Diskhaler, the asthmatic children had plasma FP levels drawn both 20 and 40 minutes after the morning dose during visit 10 (week 24) or visit 17 (week 52). These levels were taken as an estimate of the maximum plasma concentration of FP. The sponsor provides a table, which is reproduced below, comparing the C_{max} measured during this pediatric study in comparison to the values obtained from those adult patients studied in FLD230. Although the total number of patients sampled is small, and there is significant variability in the range of FP C_{max} reported for both adults and pediatric patients, allowing for differences in weight and body composition, it appears that the absolute bioavailability of inhaled FP is comparable between adults and children.

MAXIMUM PLASMA CONCENTRATIONS OF FP IN CHILDREN AND ADULTS

Dosing regimen	PEDIATRIC FP 50 μg BID	PEDIATRIC FP 100 μg BID	ADULTS FP 100 μg BID	ADULTS FP 100 μg BID
Sampling	24 or 52 weeks	24 or 52 weeks	1 week	4 weeks
# of pts	16	13	8	6
Age, median (Range)	8 (4-11)	8 (6-10)	31 (23-56)	31 (23-56)
C_{max} pg/mL, median (Range)	BLQ (BLQ-117)	58.7 (28.1-154)	39.5 (BLQ-73.1)	BLQ (BLQ-109)

Detectable effects on hypothalamic-pituitary-adrenal (HPA) function could be

seen at inhaled doses of 1000 µg daily and above in adults, and at oral doses of 10 mg daily and above. This would correlate with a plasma level between 100 and 1000 pg/mL according to the data above, supplied by the sponsor. Effects on the HPA axis by FP in children were also studied by the sponsor in trial FLD220. This topic is reviewed below in section 8.1.

7.1 Dosing Level and Interval for Clinical Trials

According to the sponsor, doses selected for the two pivotal Diskhaler pediatric trials, 50 µg and 100 µg BID, were based upon the rationale that FP would be efficacious at half the dose of beclomethasone dipropionate (BDP, as in Beclovent® or Vanceril®, for example) which is normally prescribed, a supposition for which there is some *in vitro* and clinical support. The dosing interval, every 12 hours for the initial adult studies, had been based on widespread clinical practice with BDP at the time and the practicalities and convenience of such a regimen. Early U.S. trials seemed to support the 12-hour duration of action, and because the pharmacokinetics appeared similar between adults and children, the BID dosing interval was retained for pediatric studies. A twice daily dosing regimen is now approved in adults for Flovent MDI.

8.0 CLINICAL STUDIES

Included in this NDA submission are data from all Rotadisk and MDI studies completed as of 1 March 1996 which included patients in the 4 to 11 year age category. Included among these trials are nine completed, controlled clinical studies and two uncontrolled studies evaluating a total of 1173 patients age 4 through 11 who received FP or placebo via Diskhaler. Two of these trials, FLD220 and FLT85, are submitted as pivotal by the sponsor and are discussed in detail below. The other nine trials are considered supportive and are analyzed together in section 8.3.

8.1 Study FLD220

"A randomized, double-blind, parallel-group, comparative trial assessing the longterm safety of inhaled fluticasone propionate Rotadisks via Diskhaler, 50 µg BID and 100 µg BID versus placebo in patients aged 4 to 11 years with mild to moderate chronic asthma."

8.1.1 Objectives/Rationale

The stated objectives of this study were to compare the long-term (52 weeks) safety of inhaled FP dry powder 50 µg BID, FP 100 µg BID, and placebo delivered via Diskhaler in pediatric patients with mild to moderate chronic asthma. The primary safety parameter was change in rate of linear growth over one year. Other safety variables included monthly growth as measured by stadiometer, assessment of HPA axis function, ophthalmologic assessment including intraocular pressure (IOP) and evaluation for cataracts, routine laboratory studies, physical exam including vital signs, oropharyngeal exam, 12-lead ECGs, adverse events, and FP plasma levels in a subset of patients. As indicators of asthma stability, measurements of FEV_1, FVC, and FEF_{25-75} as well

as pulmonary auscultation were performed.

8.1.2 Design

This was a randomized, double-blind, parallel-group, placebo controlled, multicenter study. The study was structured to include a 2-week "lead-in" period during which time patients received placebo BID via Diskhaler in addition to their already prescribed asthma therapy. Patients already taking inhaled corticosteroids were permitted to continue using them throughout the lead-in period. The purpose of the lead-in was to establish a baseline for asthma stability, teach and assess proficiency with the Diskhaler, and determine study eligibility and compliance. Eligible patients then entered the 52-week treatment phase. Each patient was randomly assigned to one of three treatment groups: FP 50 μg BID, FP 100 μg BID, or placebo BID, at Visit 2. Evaluations occurred weekly for the first two weeks, than again at week 4, then every 4 weeks until the end of the study. Patients were permitted to use previously prescribed asthma medications (with the exception of other inhaled corticosteroids), including β-agonists, cromolyn sodium, and theophylline. Baseline growth velocity was established using the Visit 1 height measurement and one height measurement taken 6-18 months prior to Visit 1 using the study-specific stadiometer. Patients were stratified according to their use/non-use of inhaled corticosteroids prior to study enrollment. Recruited patients needed to be between the ages of 4 and 11 years, inclusive, for boys, and 4 through 9 years for girls, and be prepubertal according to the Tanner sexual maturity rating scale (see section 8.1.4). Patients were withdrawn from further participation in the study if any one of the following situations occurred:

1. Onset of menses for female pateints
2. Requirement for intranasal or inhaled corticosteroids, other than a burst of 7 days or less
3. Requirement for more than 2 bursts of oral corticosteroids, having a duration of >7 days.
4. Unstable asthma such that, in the opinion of the investigator, the patient should not continue.
5. Use of other excluded medications, such as known growth suppressors.

8.1.3 Setting

The trial was conducted at 19 investigational centers in the United States. Patients were treated in outpatient clinics between 20 April 1993 and 13 January 1995. The following is a table of the investigators, their location, number of patients recruited, and their classification by treatment assignment. The asterisks indicate investigators suggested for audit to the Division of Scientific Integrity (DSI).

LIST OF INVESTIGATORS PARTICIPATING IN FLD220 AND PATIENT DISTRIBUTION

INVESTIGATOR	LOCATION	PLACEBO	FP 50 BID	FP 100 BID	TOTALS
Edwin A. Bronsky	Salt Lake City, UT	8	8	9	25
Robert J. Dockhorn	Lenexa, KS	3	4	5	12
Linda B. Ford	Papillion, NE	6	7	7	20
Stanley P. Galant	Orange, CA	6	8	7	21
Peter Konig	Columbia, MO	4	4	4	12
Craig F. LaForce	Raleigh,, NC	7	8	5	20
Michael Lawrence*	Taunton, MA	8	8	7	23
Robert F. Lemanske	Madison, WI	5	3	4	12
Louis M. Mendelson	West Hartford, CT	7	6	8	21
Robert A. Nathan	Colorado Springs, CO	7	8	7	22
Nancy K. Ostrom	San Diego, CA	2	3	1	6
David S. Pearlman	Aurora, CO	7	7	8	22
Robert H. Schwartz	Rochester, NY	3	2	3	8
Dale Schrum	Jacksonville, FL	7	7	7	21
M. Ross Thomas	Omaha NE	6	8	6	20
David G. Tinkelman	Atlanta GA	6	6	6	18
Mark L. Vandewalker*	Rolla, MO	8	10	8	26
Larry W. Williams	Durham, NC	1	0	0	1
Richard A. Wyatt	Minneapolis, MN	5	4	6	15
TOTALS:		106	111	108	325

8.1.4 Summary of Study Protocol

8.1.4.1 Study Population

Inclusion Criteria

- Male or premenarchal female.
- Age: Males 4-11 years, inclusive. Not to reach their 12th birthday before Visit 2. At least 50% of male patients at each site must be between 4 and 9 years. Females 4-9 years, inclusive. Not ot reach their 10th birthday before Visit 2.
- Diagnosed with asthma by American Thoracic Society criteria: (Am Rev Resp Dis 1987; 136:225-44).
- Duration of asthma of at least 3 months prior to Visit 1. Intermittent or seasonal asthmatics were excluded.
- Patients were to have moderate, chronic asthma defined as a predicted $FEV_1 \geq 60\%$ at Visit 1 (Polgar and Promadhat, *Pulmonary function testing in children: techniques and standards*: WB Saunders, 1971).

- Patients taking inhaled corticosteroids must have been using them for at least 3 months prior to Visit 1. The maximal permitted dose at Visit 1 was: BDP 8 puffs/day, triamcinolone 8 puffs/day, flunisolide 4 puffs/day.
- Patients must have had stable asthma symptoms as per the discretion of the investigator.
- Patients must have been able to demonstrate the effective use of the Diskhaler.
- At Visit 1, the patient's measured height must have been between the 5th and 95th percentile for age and the patient's growth velocity must have been between the 10th and the 97th percentile using the Serono growth charts (charts have been reproduced by sponsor in volume 7, pp. 92-95). Growth velocity was to be determined by using the Visit 1 height and another height measurement obtained 6-18 months before Visit 1 using the study-specific stadiometer.

Exclusion Criteria

- History of life-threatening asthma.
- Tanner sexual maturity rating >1 in any category.
- History of any concomitant disease which, in the opinion of the investigator, could adversely affect the patient or outcome of the study. This included but was not limited to cardiac dysrhythmias or failure, hypertension, coronary artery disease, malignancy, growth abnormalities, significant congenital anomalies, diabetes mellitus, Cushing's or Addison's disease, chronic bronchitis or emphysema, immunologic compromise, active peptic ulcer disease, dyspnea not due to asthma, tuberculosis, skeletal disorders, hematologic, hepatic, neurologic, or renal disease.
- Substance abuse or alcohol abuse.
- Mental illness or retardation.
- Allergy to sympathomimetic drugs, or intranasal, inhaled, or systemic corticosteroids.
- Clinically significant laboratory abnormalities, as determined by the investigator.
- Clinically significant abnormal 12-lead ECG.
- History or presence of glaucoma or posterior subcapsular cataracts.
- Use of tobacco products of any form.

Concurrent Medication Usage

- Concurrent use of any other prescription or over-the-counter medication which could adversely influence asthma or promote/suppress growth was not allowed. This included β-blockers, digitalis, phenothiazines, polycyclic antidepressants, ketoconazole, CNS stimulants such as Ritalin, and hormone treatments.
- Oral, intranasal, ophthalmologic, or parenteral corticosteroid therapy during the month prior to Visit 1 was prohibited. Topical dermatologic cream or ointments of 1% or less were permitted.
- Any patient previously receding daily or alternate day oral corticosteroid treatment for longer than 2 months total within the preceding 2 years was

excluded.

- If the patient was not managed on inhaled corticosteroids at the time of study, they were excluded if they had used inhaled corticosteroids for greater than a total of 2 months during the preceding 2 years. Patients managed on inhaled corticosteroids at the time of initial assessment could continue to use them during the 2-week placebo lead-in period.
- Patients having used any investigational medication within the 90 days prior to Visit 1 were excluded.

8.1.4.2 Randomization and Blinding

At Visit 1, each patient who met the inclusion criteria was assigned a unique 5-digit subject number in accordance with his/her chronological order of presentation to the investigator. At Visit 2, patients were required to continue to fulfill the aforementioned inclusion/exclusion criteria in order to be entered into the double-blind treatment period. In addition, adequate compliance, as defined by proper Diskhaler technique and the use of at least 70% of the prescribed study drug during the lead-in period (by blister count) was required for continuation.

Patients who met the continuation criteria at Visit 2 were stratified according to their use/non-use of inhaled corticosteroids at study entry. Treatments were randomly assigned each patient in accordance with a code provided by the sponsor. The investigators, study personnel, patients, parents/guardians, and study monitors were blinded to the study treatment identity. In addition, during the two week lead-in period preceding Visit 2, neither patients nor their parents/guardians were aware that the study treatment was placebo.

8.1.4.3 Dosing

At Visit 1, all patients received placebo Rotadisks for the 2-week pre-treatment lead-in period. They were instructed to inhale one blister twice daily at 8:00 AM and 8:00 PM. Diskhaler technique was evaluated as described above.

8.1.4.4 Treatment Arms

At Visit 2 eligible patients were randomly assigned to one of three treatment groups for the 52-week double-blind treatment period:

- Placebo BID
- FP 50 μg BID
- FP 100 μg BID

In addition, all patients received a supply of albuterol (Ventolin ®) syrup and albuterol inhalation aerosol for relief of acute asthma symptoms, as needed. Patients were permitted to use previously prescribed anti-asthma medications such as theophylline, cromolyn sodium, or β-agonists throughout the study. Other inhaled corticosteroids were discontinued following the lead-in period.

8.1.4.5 Assessments

Please see appended *Flowchart of Study Procedures* for details concerning safety and efficacy assessments at each study visit (reproduced from Volume 7, Appendix 1, pp. 92-93). There were a total of 17 clinic visits occurring over a time span of approximately 1 year. Following a 2-week lead-in period, visits occurred at weekly intervals for the first three visits, then at two weeks, then at 4 week intervals until the end of the study. Patients who dropped out of the study for any reason had a final study assessment performed as soon as possible, which consisted of all procedures scheduled for Visit 17 (normally occurring at week 52).

Assessment of patient compliance was measured by blister counts of returned study drug at each drug dispensing visit and was defined as use of at least 70% of the prescribed study drug during any given time period. As stated above, patients who failed to fulfill this criteria of compliance, or who failed to master correct Diskhaler technique, during the 2 week run-in period were withdrawn from the study. Blister counts were conducted at all study visits which required study medication to be returned (Visits 2 and Visits 5-17).

Efficacy Assessments:

Efficacy assessment was not a stated primary objective of this study. However, pulmonary function tests (PFTs) were performed at all visits as a measure of disease stability. In addition, a post-hoc analysis of withdrawals for lack of efficacy using the Kaplan-Meier method was performed (see *Statistical Analysis* section). PFTs included FEV_1, FVC, and the FEF_{25-75}. Tests were conducted in triplicate and the set with the highest FEV_1 was recorded on the case report form. The protocol specified ATS recommendations concerning instrument calibration, performance of testing, and test interpretation (Am Rev Respir Dis 1987; 136: 1285-98). PFTs were optional for patients 4 and 5 years of age.

In addition to PFTs, other efficacy assessments included pulmonary auscultation, performed at each visit, and a "Physician Global Assessment". The latter was performed at Visits 2, 7, 10, 13, and 17 and included the following 4-point scale evaluation of a given patient's asthma control:

- 0=Ineffective
- 1=Satisfactory
- 2=Effective
- 3=Very Effective

Safety Evaluations:

Safety was assessed using the following procedures:

1. Growth: Change in rate of linear growth was the primary endpoint of this study. Growth measurements included height, weight, and bone age radiographs of the left hand and wrist. Standing heights were

measured at Visits 1, 2, and 5-17 using a Harpenden wall-mounted stadiometer, calibrated prior to each measurement. Measurement were taken with the patient barefoot and using the same procedure at each visit. At Visits 1, 2, and 5-17, patient weights were taken without shoes or socks, using the same scale at each visit. Radiographs of the left hand and wrist were taken by local radiologists at Visits 2, 10, 17 and sent to the Fels Institute (Yellow Springs, Ohio) for bone age assessment (Roche et al; "Assessing the skeletal maturity of the hand-wrist: Fels Method" ; Illinois: Charles C. Thomas, 1988).

Reviewer's Comment: In the original protocol, it is never explicitly stated that change in linear growth rate would be the sole primary endpoint. Multiple endpoints were given, all related to safety (all are listed below). However, the sponsor did prospectively perform the necessary power analysis to determine the total number of patients needed to complete the study in order for a predetermined alteration in growth to be detected. Since the primary endpoint is safety, and safety is presumably defined by the absence of an adverse event, change in growth rate, impact on the HPA axis, etc., a Bonferroni correction for multiple endpoints makes no sense and, in fact, would be far less conservative than no correction. In other words, by declaring multiple safety endpoints, the sponsor is certainly at a disadvantage with respect to "winning" in this trial.

2. Ophthalmologic Examination: Examinations were performed by ophthalmologists at Visits 1, 5, 10, and 17. The examination included a slit-lamp evaluation for posterior subcapsular cataracts and an assessment of intraocular pressure for glaucoma. The presence of these abnormalities at screening Visit 1 would lead to patient exclusion. Their detection during the double-blind treatment period would result in early termination.
3. Adverse Events: Adverse events (AEs or ADRs) and concomitant medication use were assessed at each visit and recorded in the Case Report Form according to the date and time of occurrence, type, severity, causality, action taken, outcome, and seriousness. Causality was assessed by the investigator as *unrelated, unlikely, possibly, probably or almost certainly related* to the study drug. Adverse events reported at the final study visit were followed by the investigator until resolution or stabilization occurred. Serious ADRs were to be reported within 48 hours to the sponsor, deaths or other life-threatening events within 24 hours.
4. Clinical Laboratory Testing: (see attachment) Clinical laboratory tests, including hematology, serum electrolytes, liver enzymes, renal function, Type I procollagen, and morning plasma cortisol, were conducted at Visits 1, 7, 10, and 17. Twelve hour urine specimens for creatinine, free cortisol, and 17-hydroxycorticosteroid were collected at baseline, Visit 10, and Visit 17. All specimens were to be collected while patients were in a fasted state. The abnormalities detected during screening or during study participation were assessed. At the discretion of the investigator, the

subject could then be terminated, continued, or have repeat testing.

5. FP Plasma Levels: FP plasma levels were measured once during the study on a subset of patients, a total of 44. Sampling occurred at Visit 7, 10, or 17, with levels drawn 20 and 40 minutes after inhaling the study drug.
6. HPA Axis Function: HPA axis function was assessed by measurement of fasting morning plasma cortisol and 12-hour urinary free cortisol and 17-hydroxycorticosteroid excretion. Urinary volume and creatinine concentrations were also obtained to allow excretion rates to be determined. Blood samples for cortisol determinations were obtained at Visits 2, 10, and 17. Patients began collecting specimens with the second void after the evening meal.
7. Physical Examinations/Vital Signs: Physical examinations were conducted at Visits 1, 7, 10, 13, and 17. In addition to routine parameters and vital signs, which were recorded immediately prior to PFT testing, special attention was paid to pulmonary auscultation and to Sexual Maturity Rating (SMR) based on SMR Tanner Staging (see attachment). Patients with an SMR rating >1 at screening were excluded from the study. Patients who developed a rating greater than 1 during the study were allowed to continue. However, to fulfill the study objectives of assessing growth in only prepubescent patients, data from pubescent patients were not included in the prepubertal analyses.
8. Oropharyngeal Examination: Examination of the mouth and pharynx for evidence of fungal infection was performed at each study visit. If evidence of oral infection was found, cultures were taken and appropriate therapy instituted. Patients with culture-positive infection were allowed to continue in the study while on anti-infective treatment at the investigator's discretion.
9. 12-lead ECG: Twelve lead electrocardiograms were recorded at Visits 1, 10, 17 and/or Early Termination. During the screening period an abnormal, clinically significant disqualifying ECG was defined as a tracing consistent with myocardial ischemia, left or right ventricular hypertrophy, intraventricular conduction abnormalities such as a bundle branch block, or rhythm disturbances. In the event of a new or worsening ECG during the double blind phase of the study, the tracing would be repeated and the patient followed at the discretion of the investigator. As with other ADRs, a judgment concerning the relationship between the abnormality and the drug would be made by the investigator.
10. Pharmacoeconomic Survey: Questionnaires containing Quality of Life (QOL) self-assessments, including general QOL, asthma-specific QOL, and productivity were completed by the patient and/or parent/guardian at Visits 2, 10, and 17 after ADR assessment and prior to performance of other study procedures.

8.1.4.6 Concurrent Medications:

This topic was discussed under 8.1.4.1 *Study Population.*

8.1.4.7 Patient Compliance:

This topic was discussed under 8.1.4.5 *Assessments,* second paragraph.

8.1.4.8 Patient Withdrawal from the Study:

Patients who dropped out of the study for any reason had a final study assessment as soon as possible. Early Termination procedures (all procedures scheduled for Visit 17, see attachment) were completed and recorded in the case report form. Clinically significant ADRs, ECG abnormalities, laboratory studies, or physical examination findings were to be followed or treated until satisfactorily resolved. Patients who were discontinued due to failure to satisfy the continuation criteria (see 8.1.4.2) or due to asthma exacerbation requiring hospitalization or treatment with asthma medication excluded by the protocol were considered complete and evaluable. Alternative asthma treatment was prescribed as judged appropriate by the investigator, and the patient was followed as necessary by the investigator or primary physician.

8.1.4.9 Endpoints:

Safety was the primary endpoint, and was defined by all of the following measurements (described in detail under 8.1.2.5)**:**

- Growth: monthly height measurement and bone age films of left hand and wrist
- Ophthalmologic examinations
- Clinical adverse events and concomitant medications
- Clinical laboratory testing
- FP plasma levels
- HPA axis function
- Physical examination with sexual maturity rating
- Oropharyngeal examinations
- 12-lead ECGs
- Vital signs

8.1.4.10 Statistical Analysis:

Background/Population: The primary safety endpoint of this trial was change in rate of linear growth velocity over one year. The sponsor utilized *Tinkelman et al, Pediatrics 92, 1, 64-77 (1993)* as a reference to estimate mean and standard deviation for height velocity, gender differences, pubertal influences, and dropout rate among asthmatic children ages 6-11 receiving inhaled BDP in one arm of a randomized clinical trial. Based on these data, study completion by a minimum of 90 patients per treatment group was estimated to provide at least 80% power to

detect a difference in height velocity of 1.0 cm/yr (±2.7 cm/yr) between any two treatment groups using a two-sided t-test with a significance level of 0.05. The proposed sample sizes also provided at least 80% power in detecting a difference of 16% between any two treatment groups in the proportion of patients reporting an adverse event.

The Intent-to-Treat population was defined as all patients randomly assigned to treatment who received at least one dose of blinded study drug. Analyses using the Intent-to-Treat population were based on all available data for these patients. All analyses were performed for the Intent-to-Treat population. Subpopulation analyses for the primary safety endpoint were performed for prepubescent completers, steroid-dependent, and steroid-naive prepubescent completers, and male vs female prepubescent completers.

Reviewer Comment: Based on the Tinkelman et al reference cited above, it was thought that the subpopulation of pubescent completers, especially males, would potentially be of particular interest, since it was this subpopulation who showed the most marked impact of daily inhaled BDP on growth parameters. This was discussed with the statistical reviewer, who requested such data from the sponsor. The total number of subjects fulfilling these criteria was so small, however, as to make subgroup analysis not statistically meaningful.

Comparisons between treatment groups for age, height, and weight were based on ANOVA, controlling for investigator. Comparisons between treatment groups for sex, ethnic origin, and screening pulmonary auscultation were based on the Cochran-Mantel-Haenszel test, controlling for investigator. Predicted normal values for PFTs were based on equations from *Polgar and Promadhat, WB Saunders, Philadelphia (1971)* for patients age 4-11 and screening visit assessments were tested using ANOVA.

Safety Analyses: Significance testing was performed on mean and mean change from baseline in height, skeletal age, and growth velocity. Investigator effects, treatment-by-investigator interactions, and age were included in the model and a significance level of 0.10 was used to evaluate the treatment-by-investigator interaction. In each case, testing was performed on data from all investigators, combined, controlling for investigator effect. ANOVA was used to compare unadjusted values at baseline, and change-from-baseline values at all other times, including endpoint. Endpoint was defined as the final evaluable measurement for the patient, whether completers or dropouts. Investigators with ≤1 patient in each one of the treatment arms at any visit during the study treatment were combined into one investigational group for all analyses.

Other safety assessments were performed on the intent-to-treat population and pairwise analyses were performed between treatment groups using Fisher's exact test. These assessments were based on clinical adverse events, laboratory tests, physical examinations, oropharyngeal examinations, ophthalmologic examinations, VS, and 12-lead ECGs. Any abnormal test both pretreatment and

at the end of treatment were individually tabulated. Measures of HPA axis function were handled slightly differently. Creatinine-corrected 12-hour urinary cortisol and 17-hydroxycorticosteroid were analyzed using ANOVA. Patients were also stratified by low or normal unstimulated AM cortisol, urinary free cortisol, and 17-hydroxycorticosteroid.

Efficacy Analyses: Although this was not an efficacy trial, spirometry, survival, and the physician-rated global assessment of effectiveness were analyzed.

Kaplan-Meier estimates of the probability of patients remaining in the study were calculated, and the Kaplan-Meier probabilities over time were plotted. Overall and pairwise treatment comparisons were based on the Log-Rank test of the Kaplan-Meier estimates of survival.

Physician-rated global assessment was summarized by treatment and visit. The Cochran-Mantel-Haenszel test controlling for investigator was used to compare all treatments simultaneously. The last evaluable assessment was also summarized and tested.

Statistically significant differences in spirometry between and among treatment groups were evaluated using a model which accounted for investigator and treatment-by-investigator interactions. In each case, testing was performed on data from all investigators combined. ANOVA was used to compare unadjusted values at baseline, and change-from-baseline values at all other times. Investigators without ≥1 patents per treatment arms at any visit during the study treatment were combined into one investigational group for all analyses. Hypothesis tests for selected summary intervals were included, as was the endpoint, which was defined as the final evaluable measurement for the patient whether they completed the study or withdrew.

8.1.5 Results

8.1.5.1 Study population characteristics:

A total of 344 patients at 19 investigational sites met inclusion criteria and were entered into the single-blind placebo lead-in period. A total of 19 patients failed to meet continuation criteria, hence 325 eligible patients were randomized to receive one of the three study treatments. Of these eligible patients, 263 (81%) completed the study, including 76/106 (72%) placebo, 98/111 (88%) FP50 BID, and 89/108 (82%) FP100 BID. The most common reason for discontinuation was lack of efficacy, which was the case for 28 of the 62 withdrawals (19% of the placebo group; 4% of each of the FP groups). Adverse events constituted 6/62 cases or 9.6%.

Patients were stratified by recent inhaled corticosteroid treatment prior to randomization. Other demographic characteristics are displayed in the table which follows.

DEMOGRAPHIC CHARACTERISTICS AT ENTRY FOR STUDY FLD220

	Placebo	FP50 BID	FP100 BID	Total
Number	106	111	108	325
Gender				
Female %	25%	26%	24%	25%
Male %	75%	74%	76%	75%
Ethnicity				
Caucasian	84%	98%	97%	87%
Non-Cauc.	16%	2%	3%	13%
Age (range) yr.	8.5 (4.2-12)	8.5 (4.5-11.9)	8.2 (4.0-11.9)	8.4 (4.0-12.0)
Hgt (range) cm.	130.5 (98.2-162.3)	130.4 (104.0-153.0)	128.9 (101.2-165.0)	129/9 (98.2-165.0)
Wgt (range) lb.	66.2 (30.0-128.5)	66.1 (34.0-133.0)	64.8 (30.0-170.9)	65.7 (30.0-170.9)
Prior Inhaled Corticosteroids	46%	50%	55%	53%
% Predicted FEV_1 Prebronchodilator	89%	86%	88%	-

Reviewer's Comment: Patient groups appeared to be reasonably well-balanced at study entry, with the possible exception of a slightly younger population in the FP 100 BID group, which may have impacted on the pubertal status and hence growth rate calculations and data point inclusion in the final analysis. Significantly more placebo patients did withdraw during this study, as would be expected.

8.1.5.2 Efficacy Analysis

Evaluation of efficacy was not an objective of this study. However, pulmonary function testing, physician global assessment, and Kaplan-Meier estimates of survival were presented.

Spirometric measurements were performed at each visit throughout the study. Mean change from baseline in FEV_1 showed statistically significant improvement in each of the FP groups compared to placebo at Weeks 1, 4, 8, 24, 32, 52, and treatment endpoint. The absolute change in FEV_1 increased throughout the study and was maximum by study endpoint, probably reflecting the participating childrens' growth, although rate of improvement appeared to plateau between 24 and 32 weeks. Baseline mean FEV_1 was comparable between the three groups: 1.65 L/sec for placebo, 1.63 L/sec for FP50, and 1.57 L/sec for FP100. Mean change from baseline in FEV_1 at study endpoint was 0.13 L/sec for placebo, 0.22 L/sec for FP50, and 0.28 L/sec for FP100. Although the difference between each of the FP groups and placebo was significant, there was no difference between the two dose levels of FP. This was true at all timepoints measured.

Physician Global Assessment was rated on a four-point scale (see section *8.1.4.5*). At the end of treatment, 80% of FP100 patients and 77% of FP50 patients had their treatment rated as effective or very effective, compared to 45% of placebo patients.

The probability of remaining in the study for the entire year without withdrawing due to lack of efficacy was 95% for FP50 and FP100 patients, compared to 80% for placebo patients.

Reviewer's Comment: This includes withdrawal only for lack of efficacy. All-cause withdrawal will be discussed in the next section.

8.1.5.3 Safety Analysis

The safety analysis included all patients who received at least one dose of the study medication (intent-to-treat), including 106 placebo, 111 FP50, and 108 FP100 for a total of 325 patients. The mean duration of exposure was 307 days for placebo patients compared to 345 and 334 for the FP50 and FP100 treatment groups, respectively. All analyses were performed on the intent-to-treat population, as well as selected subgroups as appropriate, such as study completers, prepubertal patients (who were identified prospectively), or "steroid dependent" subjects.

Reviewer's Comment: In the case of a clinical trial in which the primary endpoint is safety, in particular, linear growth rate, it is reasonable to examine both the study completers as well as the intent-to-treat population. Clearly, if inhaled fluticasone has an impact on growth velocity, a patient who drops out early may not have had sufficient duration of exposure for a growth effect to occur. If growth velocity is then calculated from this abbreviated exposure and carried forward in the analysis, a true dose-related effect may be diluted.

In addition, using a level of statistical significance of $p \leq 0.05$ in a two-sided test, while generally regarded as the gold standard in efficacy trials, may not be appropriate for a safety trial, depending upon what level of certainty that an undesirable drug effect is occurring is acceptable. Some sources suggest a more conservative $p \leq 0.10$.

8.1.5.3.1 Growth

Height was measured at each clinic visit and growth velocity calculated from baseline height. Change in growth velocity was calculated for the 28 week (6 month) and 52 week (12 month) time points and compared to prior growth velocity calculated from baseline height and one prior pre-study value. Change in yearly growth rate was reported for the intent-to-treat population as well as various subsets including study completers, prepubescent patients, by gender, and by prior inhaled corticosteroid usage.

Results from the intent-to-treat population are displayed in the table below. Baseline mean heights were not statistically different across treatment groups for this population. Mean change from baseline in height as well as mean growth velocity fell within the normal range by Serono growth chart. However, both values were reduced in the two FP treatment groups in comparison to placebo. This difference achieved statistical significance for the placebo vs. FP100 comparison for both change in height ($p=0.034$) and mean growth velocity ($p=0.031$), although not in

change in growth velocity (p=0.084).

INTENT-TO-TREAT (N=325): GROWTH

	Placebo (N=106)	FP50 BID (N=111)	FP100 BID (N=108)
Mean Height in cm (SE) Baseline Week 52	130.6 (1.23) 138.3 (1.52)*	130.6 (1.13) 137.0 (1.19)**	129.0 (1.18) 133.8 (1.30)***
Δ Height in cm (SE) at week 52	6.39 (0.18)	6.11 (0.15)	5.73 (0.13)[1]
Mean Growth Velocity in cm/yr (SE) at week 52	6.32 (0.17)	6.07 (0.15)	5.66 (0.12)[2]
Δ Growth Velocity in cm/yr (SE) at week 52	0.13 (0.17)	-0.09 (0.18)	-0.44 (0.14)[3]

* N=76 at week 52
** N=98 at week 52
***N=89 at week 52

[1]p=0.034 vs placebo
[2]p=0.031 vs placebo
[3]p=0.084 vs placebo

Results from the protocol-defined subgroup of prepubertal patients are displayed in the table below. Again, baseline heights were not statistically different across treatment groups and mean change in height and growth velocity again fell within the normal range. However, change in height and mean growth velocity were again reduced in the FP groups relative to placebo. This numerical difference was again most pronounced in the placebo vs. FP100 comparison, although the p values did not achieve statistical significance: p=0.112 for change in height and p=0.108 for mean growth velocity.

PREPUBESCENT PATIENTS (N=268):GROWTH

	Placebo (N=87)	FP50 (N=85)	FP100 (N=96)
Height in cm (SE) Baseline Week 52	127.5 (1.19) 133.8 (1.46)*	128.3 (1.27) 134.5 (1.31)**	127.2 (1.15) 132.0 (1.22)***
Δ Height in cm (SE) at week 52	6.15 (0.17)	5.94 (0.16)	5.73 (0.13)[1]
Mean Growth Velocity in cm/yr (SE) at week 52	6.10 (0.17)	5.91 (0.16)	5.67 (0.13)[2]
Δ Growth Velocity in cm/yr (SE) at week 52	-0.11 (0.15)	-0.40 (0.20)	-0.46 (0.15)[3]

* N=57 at week 52
** N=74 at week 52
***N=79 at week 52

[1]p=0.112 vs placebo
[2]p=0.108 vs placebo
[3]p=0.223 vs placebo

The sponsor has also performed a similar analysis on the subset of prepubescent patients who completed the study (Tables 44-47, Volume 7, pp 150-153). Although minor differences in growth rates were evident

during the first half of the study, final overall growth rates were unchanged from those values given in the table above.

The sponsor argues that the small but consistent numerical difference in growth rate among the FP patients compared to placebo may have been the result of a disproportionate attrition of younger, slower growing patients from the placebo group. In support of this argument, the sponsor cites change in the chronological age of each of the three treatment groups over the 52 week study. While the mean ages of the placebo and FP50 groups were found to increase by 1.03 and 1.02 years, respectively, the mean age of the FP100 group increased by 0.89 years. The sponsor then commissioned a post-hoc analysis of 47 matched prepubescent patients from each treatment group who completed the entire study. These patients were matched for age, gender, use/non-use of inhaled corticosteroids, and skeletal age. The results of this analysis are displayed in the table below. Although none of the differences were statistically significant, there is again a numerical difference between the rate of growth of placebo compared to each of the FP groups, again in the direction suggesting decreased rate of growth among the FP treatment arms.

AGE-MATCHED PATIENTS (N=141):GROWTH

	Placebo (N=47)	FP50 N=47)	FP100 (N=47)
Mean age (year)	7.90	7.96	7.90
Height in cm (SE) Baseline Week 52	not given	not given	not given
Δ Height in cm (SE) at week 52	6.07 (0.17)	5.84 (0.14)	5.66 (0.16)[1]
Mean Growth Velocity in cm/yr (SE) at week 52	6.01 (0.17)	5.81 (0.14)	5.60 (0.16)[2]
Δ Growth Velocity in cm/yr (SE) at week 52	-0.20 (0.16)	-0.62 (0.19)[3]	-0.53 (0.20)[4]

[1]p=0.121 vs placebo
[2]p=0.116 vs placebo
[3]p=0.114 vs placebo
[4]p=0.284 vs placebo

In conclusion, fluticasone propionate administered via diskhaler does appear to be associated with a small but numerically consistent decrement in yearly growth rate when given in the doses studied over one year to children between the ages of 4 and 11. This effect is below the predefined "clinically significant" decrement of 1.0 cm/year and achieves a statistically significant $p<0.05$ only in FP100 treatment group in

comparison to placebo in the intent-to-treat population, but the trend is apparent in all subgroups analyzed.

8.1.5.3.2 Bone age

Reviewer's Comment: The sponsor has referenced a book describing the technique whereby bone age was determined (Roche et al: "Assessing the Skeletal Maturity of the Hand-Wrist: FELS Method"; Charles C. Thomas; Springfield, Ill; 1988). This reviewer has examined a copy of this book, in order to understand the process by which bone age was estimated. Bone age determination predicated upon metaphyseal lengthening would have different implications than a determination based upon progress of epiphyseal closure, and would bear a different relationship to linear growth rate. The process described in this text uses a composite of findings from a standard radiograph of child's wrist, where the extremity is precisely positioned at a predetermined distance from the film and from the x-ray source. Age estimation was based upon 677 children studied from birth until adulthood, between the years 1929 and 1975. Bone age as determined by a given radiograph is a composite of 94 possible computer entries based upon multiple factors, including first appearance of ossification centers in carpal bones, metaphyseal lengthening, size of the epiphyseal zone, etc. The complexity of this process is therefore not unlike the many factors which determine linear growth rate.

In many respects, trends in bone age among treatment groups paralleled the findings in the growth rate study. The table below shows baseline values for each of the three treatment groups in the intent-to-treat population as well as overall changes at the end of the one year study. Although there were no statistically significant differences in bone age at baseline, at one year mean change from baseline in skeletal age was significantly different from placebo for both FP groups and, in fact, significantly less for the FP100 group compared to the FP50 group. Mean skeletal age increased from baseline by 1.51 years in the placebo group compared to 1.17 years in the FP50 and 0.81 years in the FP100 groups ($p=0.026$ overall). The sponsor argues that this result may be explained by a disproportionate increase in chronological age among the placebo patients compared to the FP groups due to a dropout of more of the younger patients in the placebo group. However, chronological age increased by only 1.03 years among placebo patients compared to 1.02 years in the FP50 group and 0.89 years in the FP100 group. Changes in age ratios among the three groups due to dropouts therefore cannot be the sole explanation.

INTENT-TO-TREAT: SKELETAL AGE

	Placebo	FP50 BID	FP100 BID	Total
Patients Studied				
Baseline	**106**	**110**	**108**	**324**
52 weeks	**76**	**97**	**89**	**262**
Mean Skeletal Age in yrs (SE)				
Baseline	**8.64 (0.22)**	**8.49 (0.20)**	**8.24 (0.22)**	**-**
52 weeks	**10.15 (0.26)**	**9.66 (0.22)**	**9.05 (0.23)[1]**	**-[2]**
Mean ΔSkeletal Age from Baseline in yrs	**1.18 (0.06)**	**1.19 (0.05)**	**0.95 (0.05)[3]**	**-[4]**
Mean ΔChronological Age in yrs	**1.03**	**1.02**	**0.89**	**-**

[1]p=0.005 vs placebo
[2]p=0.015 overall
[3]p=0.008 vs placebo
[4]p=0.006 overall

The sponsor has performed a similar analysis for the prepubescent patient subset, which appears in the table below. Again, there were no statistically significant differences in age across treatment groups at baseline. Numerical differences suggesting slower skeletal age advancement in the FP groups compared to placebo persisted, however. These differences achieved statistical significance only among the FP100 patients vs placebo at one year (p=0.048).

PREPUBESCENT PATIENTS: SKELETAL AGE

	Placebo	FP50 BID	FP100 BID	Total
Patients Studied				
Baseline	**87**	**84**	**96**	**267**
52 weeks	**57**	**77**	**79**	**213**
Mean Skeletal Age in yrs (SE)				
Baseline	**8.06 (0.20)**	**7.94 (0.20)**	**7.88 ((0.21)**	**-**
52 weeks	**9.34 (0.25)**	**9.03 (0.22)**	**8.70 (0.22)[1]**	**-**
Mean ΔSkeletal Age from Baseline in yrs	**1.13 (0.06)**	**1.13 (0.06)**	**0.95 (0.50)[2]**	**-[3]**

[1]p=0.073
[2]p=0.048
[3]p=0.146

In conclusion, fluticasone propionate given by inhalation over one year at the doses administered in this study is associated with slower skeletal age advancement in children age 4-11 years when compared to placebo. The clinical significance of this finding is presently obscure, but

is consistent with the results of the growth study described above. It raises the possibility, however, that any growth effects of FP are due to a slowed bone growth and maturation and therefore any effect on ultimate adult height is even less certain.

8.1.5.3.3 Ophthalmological Examinations

Lenticular opacity and intraocular pressure were primary concerns of these examinations, as posterior subcapsular cataracts and increased intraocular pressure (IOP) or glaucoma are potential corticosteroid side effects.

One patient randomized to the FP100 group developed a posterior subcapsular cataract (PSC) in the left eye at Week 24, and was dropped from the study. The patient had been receiving inhaled BDP for approximately 2 years before entering the study. The PSC was likely related to inhaled corticosteroids, although it is unclear whether FP was the sole agent responsible.

Glaucoma developed in one patient in the FP100 groups at Week 24, and the patient was withdrawn from the study. Although elevated IOP was documented at baseline in this patient, and family history was notable for glaucoma, the patient was none-the-less enrolled as a study participant. A second patient randomized to the FP50 group developed elevated IOP, but this was not classified as glaucoma. The child was not terminated from the study.

In conclusion, fluticasone propionate administered by inhalation in the doses studied had no consistent impact on the new occurrence of PSC or glaucoma in children, although it is potentially etiologic for these AE's in a small number of susceptible patients. Databases should be monitored for these events once population exposure becomes broader.

8.1.5.3.4 Laboratory Data

Type I procollagen (in μg/L) was measured at baseline, 24 weeks, and at the end of the study. Levels in the placebo group, which were slightly higher than in either of the two FP groups at baseline, were at essentially the same level at the end of the study. Levels in the two FP groups were increased by less than 10% relative to baseline at the end of the study, not statistically significant. The clinical importance of an elevation in this index of bone turnover in young, growing children remains unclear.

Other routine clinical laboratory studies were conducted at screening, 12 weeks, 24 weeks, and at the end of treatment or at early termination. No significant unexpected laboratory abnormalities occurred, with the exception of a moderate elevation in the hepatic transaminases AST and ALT in a single patient receiving FP100, who was subsequently

dropped from the study. Enzymes declined over 7 weeks of follow up. Eosinophilia, as might be expected with asthma, was also observed among several patients in all three study groups. More of the FP patients experienced a decline in total eosinophil count than in the placebo group. There was no reported occurrence of clinically significant hyperglycemia or hypertriglyceridemia among the FP or placebo patients.

8.1.5.3.5 Adverse Events

Adverse event tabulation was performed on the intent-to-treat population, comprised of 325 patients who had received at least one dose of study medication. Of these patients, 305 (94%) reported one or more adverse events during the year-long study. This unusually high proportion of patients complaining of adverse events may be attributable to lengthy duration of this study. There were no deaths. Two events met the regulatory definition of serious, one being a febrile seizure (FP50) and the other respiratory arrest (placebo). There were 6 subjects withdrawn due to adverse events, including 4 in the FP100 group and 3 in the placebo group. Of the 4 patients receiving active medication, one was withdrawn by the parent due to unusual weight gain. This subject was an 11 year old male who was 146.5 cm and 99.5 lb at the start of the study. At early termination slightly over 5 months later, he weighed 113 lb but had grown only 1.6 cm. He remained prepubertal by Tanner staging, and no mention was made of cushingoid features, acneiform rash, or other evidence of hypercortisolism on physical exam. Final serum glucose was within the normal range. Two of the other FP100 patients were withdrawn due to an abnormal ophthalmological exam, development of glaucoma or posterior subcapsular cataract (see 8.1.5.3.3). The fourth patient had developed unexplained abnormal transaminases (see 8.1.5.3.4).

The sponsor has tabulated all adverse events by body system, gender, and the investigator's impression of its relationship to study drug. In spite of the increased relative dropout rate of placebo patients compared to FP patients, making total average number of exposure days greater for the FP groups, the overall adverse event rates were very similar: 95% for placebo, 95% for FP50, and 92% for FP100. As would be expected in this age group, the most frequent adverse events were diseases of the respiratory and ENT systems. ENT events appeared comparable overall across treatment groups, although the relative frequency of individual disorders such as otitis media or allergic rhinitis showed some minor variations. Respiratory adverse events were slightly more common among placebo patients (75% compared to 66% of FP50 and 68% of FP100).

There were other minor differences between the three treatment groups for less common adverse events. For example, under "Miscellaneous Infections", there were an increased number of events

overall in the FP groups relative to placebo. As shown below, this is true in particular of chicken pox, viral infections, and oral candidiasis in the FP groups compared to placebo. Again, the overall frequency of these events were low and of unclear clinical significance:

TABLE OF MISCELLANEOUS ADVERSE EVENTS

	Placebo	FP50	FP100
Patients with Events	101 (95%)	105 (95%)	99 (92%)
Miscellaneous Infection	6 (6%)	17 (15%)	13 (12%)
Chicken Pox	2 (2%)	6 (5%)	4 (4%)
Viral Infection	3 (3%)	6 (5%)	2 (2%)
Oropharyngeal Candidiasis	1 (<1%)	3 (3%)	1 (<1%)

8.1.5.4.6 HPA Axis Effect

HPA axis function was assessed periodically during the study via AM plasma cortisol and 12-hour urine collections for urinary free cortisol and 17-hydroxycorticosteroid excretion. These data were expressed as percentage of patients who were found to have abnormally low values for each of these tests at *any point* post-randomization. Individual abnormal values of AM plasma cortisol were also reported, in addition to the mean±SE for each group at baseline, week 12, week 24, and week 52. Urinary excretion of free cortisol and 17-hydroxycorticosteroid were provided as the mean±SE for each treatment arm at baseline, week 24, and week 52, both as excretion rate and normalized to creatinine.

The sponsor reported no significant difference between treatment groups in the frequency of occurrence of low AM plasma cortisol values post-randomization. In addition, there was no significant difference between mean cortisols in each of the three groups at baseline or at any of the subsequent times during which AM cortisol was sampled.

Reviewer's Comment: Although this information provides some reassurance, AM serum cortisol is a relatively insensitive marker of HPA axis effects.

Rates of excretion of cortisol and 17-hydroxycorticosteroid were reported per 12-hour urine collection. Both the raw data expressed as "µg excreted" as well as the values corrected for creatinine were analyzed. There were no significant differences between groups in rates of 12-hour urinary 17-hydroxycorticosteroid excretion at baseline, week 24, or week 52 when adjusted for creatinine (Vol. 9, p. 408), although unadjusted rate of excretion was significantly lower for the FP100 group compared to placebo at week 52 (p=0.036; Vol. 9, p. 406). As pointed out by the sponsor, this likely reflects the lower baseline rate of excretion. In the case of cortisol, the unadjusted 12-hour urine cortisol excretion rate was significantly less for the FP100 group at week 52 compared to placebo

(p=0.039), although this difference is no longer apparent when these values are adjusted for creatinine (p=0.412; Vol. 9, p. 409).

Reviewer's Comment: Both of these analyses were performed across the three groups at baseline, midway through the study, and at study endpoint. What seems most curious about the sponsor's analysis of these parameters is the failure to compare the difference in excretion ratios at baseline and at week 52 within a single group. A decrement in the rate of urinary cortisol or 17-hydroxycorticosteroid excretion at week 52 compared to baseline in a single group of patients who have been newly exposed to chronic inhaled corticosteroid therapy may be indicative of an HPA axis effect. Using the data supplied by the sponsor, this analysis may be performed for the 12-hour urinary cortisol excretion rate and cortisol/creatinine ration (see table below). Notice that the cortisol excretion ratio has not changed for the placebo group, whereas it has fallen by approximately 15% for the FP50 group and over 40% for the FP100 group.

The 6 month data point for the FP50 group has not been included in this analysis because the number seems "driven" by a single abnormal value, which has been included in the sponsor's calculation of mean and SE of urinary cortisol and 17-hydroxycorticosteroid: Brodsky subject number 2605 had values which were greater than two orders of magnitude higher than the next recorded reading and probably should not have been included in the analysis (Volume 9, page 420).

INDICES OF HPA AXIS EFFECTS: CHANGE FROM BASELINE

	Placebo	FP50	FP100	Total
Number of Patients				
Baseline	106	111	108	325
Week 52	75	97	89	261
12-hr urinary cortisol excretion in µg (SE)				
Baseline	60.33 (7.52)	56.07 (4.46)	61.14 (12.1)	-
Week 52	52.50 (3.75)	50.61 (5.53)	41.99 (2.61)	-
12-hr urinary ratio of cortisol/creatinine				
Baseline	0.23 (0.03)	0.20 (0.01)	0.29 (0.07)	-
Week 52	0.23 (0.05)	0.17 (0.02)	0.17 (0.01)	-
% Δ 12-hr urinary cortisol excretion				
µg %	113.0 %	18.10%	131.3%	-
ratio %	0	115.0%	141.4%	-

In conclusion, although there appears to be no impact of inhaled fluticasone propionate on AM cortisol when given to children at the doses described, this is a relatively insensitive index of HPA axis function. Urinary cortisol excretion, while not indicating significant differences across treatment groups, did show a substantial decrement compared to baseline in the FP100 group but not in placebo. The FP50 group showed an intermediate effect. Hence, inhaled fluticasone propionate does have a

measurable impact on at least one index of HPA axis function. No tests designed specifically to test adrenal reserve, such as ACTH stimulation, were performed in this study. The clinical significance of these findings remain unclear, and no clinical signs of adrenal suppression were noted in the trial.

8.1.5.3.7 FP Plasma Levels

Fluticasone propionate plasma levels were measured in a subset of patients in each of the three groups at 20 and 40 minutes after dosing at one study visit in order to obtain a general measure of C_{max}. In all, 15 placebo, 16 FP50, and 13 FP100 subjects were studied at each time point. FP was measured via RIA and could be detected down to 25 pg/ml in patient's serum. Of the 16 FP50 patients studied, only 3 had levels detectable at both time points, compared to 12/13 FP100 patients. On the other hand, the serum concentrations when detectable were not strictly dose proportional, since the mean plasma levels of FP were very close between the FP50 and FP100 groups, although the standard errors were very high. There appeared to be no age or gender effect on plasma FP levels.

8.1.5.3.8 Physical Examination including Vital Signs

The frequency of occurrence of new physical examination abnormalities compared to baseline was not significantly different across groups. Similarly, pre-treatment and endpoint mean vital signs were similar among the groups. No instances of new onset hypertension were reported among participants during the course of the trial. Adverse events or findings of special interest, such as opthalmologic or oropharyngeal changes, are discussed separately in this review (8.1.5.3.3 and the following section, respectively). The sponsor does not report or analyze changes in weight or body mass index in this section.

8.1.5.3.9 Oropharyngeal Candidiasis

Eight occurrences of candidiasis were diagnosed in five patients, including three on FP50, and one each on FP100 and placebo. One additional occurrence of candida-like lesions of the oropharynx was reported in a patient on FP100. All patients were successfully treated and none were dropped from the study. One patient had the FP50 temporarily withdrawn during one episode, but was restarted later.

In conclusion, as with all other inhaled corticosteroids, fluticasone propionate inhalation powder is capable of causing oropharyngeal fungal infections. The frequency or severity of these infections does not appear to be unusual compared with other inhaled corticosteroids, at least as assessed by the limited data available through this study.

8.1.5.3.10 Electrocardiogram (ECG)

Twelve-lead ECGs were taken at baseline, week 24, and at the final study visit. Five patients had post-baseline abnormalities, all were asymptomatic. Abnormalities were not consistent across patients nor did they appear to have any relationship to the study drug.

8.1.6 Conclusions

8.1.6.1 Efficacy Conclusions

The primary purpose for study FLD-220 was not efficacy, however, supportive data were collected during this year-long trial for safety purposes. Spirometry, Kaplan-Meier survival analysis, and Physician Global Assessment data are convincing that fluticasone propionate dry powder via diskhaler at 50 or 100 μg BID does have sustained efficacy in the pediatric patient population studied.

8.1.6.2 Safety Conclusions

Chronic treatment of children with mild to moderate asthma with Flovent Diskhaler at doses of FP 50 or 100 μg BID is well-tolerated for periods of up to one year. Nevertheless, data submitted in support of this application indicate three areas of safety concerns which should be considered in the final product labeling.

First, there appears to be a small but consistent, dose-dependent effect of FP on linear growth. While this decrement in growth rate achieves statistical significance only in the FP100 group of the intent-to-treat population relative to placebo, the trend can be detected in all subgroups analyzed, whether pubescent subjects are eliminated or not. Even when post-hoc analysis of a subgroup of age-matched patients is performed, this trend can still be noted.

Second, a decline from baseline in creatinine-corrected overnight urinary cortisol excretion was seen in FP patients at the end of the study compared to placebo. Although data points are few, this effect may be dose-related. No measures of stimulated cortisol production as an indicator of adrenal reserve were performed, hence the finding of diminished overnight cortisol is of unclear clinical significance.

Third, two adverse ophthalmologic events occurred during this study, both probably related to study drug, although in one case this is disputed by the sponsor. Although rare, the occurrence of one episode each of posterior subcapsular cataract and increased IOP/glaucoma during this clinical trial deserves consideration in product labeling.

8.2 Study FLIT85

"A multi-center, randomized, double-blind placebo-controlled study to compare the

efficacy and safety of fluticasone propionate (FP) dry powder, 200 μg daily, and FP dry powder, 100 μg daily, via a Diskhaler inhaler to placebo dry powder via a Diskhaler inhaler in children with asthma."

8.2.1 Objectives/Rationale

The objectives of this study were to investigate the efficacy and safety of FP dry powder dosed at 50 μg BID or 100 μg BID, by comparison with placebo dry powder, all administered via a Diskhaler inhaler, in children aged 4-11 years. The primary efficacy assessments were AM and PM PEFR recorded in diary cards and withdrawals from the study due to lack of efficacy of study treatment. Secondary efficacy assessments included spirometry as measured in clinic (PEFR, FEV_1, FVC, and $FEF_{25-75\%}$), asthma symptom scores, use of "rescue" albuterol, and night-time awakenings due to asthma which required "rescue" albuterol use. The primary safety assessment was incidence of adverse events recorded during the study period. Secondary assessments were change in routine clinical laboratory tests, urinalysis, and physical examination including vital signs, oropharyngeal examination, and pulmonary auscultation.

8.2.2 Design

This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group study. The study consisted of a 2 week run-in period and a 12-week treatment period, after which there was a 2 week follow-up period.

During the 2 week single blind run-in period, all patients received placebo Rotadisks via a Diskhaler and were permitted to use albuterol on a prn basis only.

Each patient was required to fulfill the following criteria during the screening period in order to be randomized to study treatment:

- Demonstrated a PEFR of ≤75% predicted normal either at Visit 1 or in the 3 months preceding Visit 1.

  OR

  Have a PEFR between 75% and 90% predicted normal and have fulfilled <u>two</u> of the following:

  1. Asthma symptom scores of at least 1 (see below) on 4 or more occasions during the last 10 days of the run-in period.
  2. Wakening during the night or in the early morning due to asthma on 1 or more occasions during the last 10 days of the run-in period.
  3. Usage of >4 doses of albuterol on 4 of the last 10 days of the run-in period.
  4. At least 15% reversibility of airways function as measured by FEV_1 or PEFR in response to β-agonist therapy at Prestudy Visit or Visit 1.

- Demonstrated adequate compliance defined as ability to use the Diskhaler inhaler and mini-Wright peak flow meter correctly and either they or their parents were able to complete the diary cards satisfactorily and were able

to record PEFR.

- Use albuterol on a prn basis only.

Patients who satisfactorily completed the screening period were randomly assigned to the double-blind treatment for a period of 12 weeks. Patients were instructed to use the albuterol rescue, dosed as 200 μg DPI via Diskhaler, only as needed. Other anti-asthma therapy could be continued as long as it was not on the excluded medication list and provided that the dose, route, and frequency remained constant. Anticholinergic agents, long acting β_2-agonists, combination inhalers, and other short acting bronchodilators were prohibited, with the exception of the albuterol "rescue" medication supplied as part of the study.

Patients were to be withdrawn from the study for lack of efficacy if they experienced any of the following :

1. "Rescue" albuterol use >8 doses on >2 days in any 7 day period.
2. In any 7 day period, >2 nighttime awakenings requiring "rescue" albuterol.
3. PEFR readings below the 15% stability limit on >3 days out of any 7 day period.
4. FEV_1 at any study visit which was below the 15% stability limit and remained low at repeat testing within 12 hours.
5. FEV_1 at any study visit below the 15% stability limit and, in the opinion of the investigator, the patient's asthma had deteriorated significantly.

Reviewer's Comment: These situations defined above are also referred to as "Continuation Criteria" by the sponsor.

8.2.3 Setting

The study was conducted at 29 study sites in 9 countries in outpatient clinic settings between 15 April 1993 and 13 September 1994. The following table is a listing of the investigators, their locations, and the distribution of patients by treatment assignment:

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LIST OF INVESTIGATORS PARTICIPATING IN FLIT85 AND PATIENT DISTRIBUTION, INTENT-TO-TREAT POPULATION

INVESTIGATOR	LOCATION	PLACEBO	FP 50 BID	FP 100 BID	TOTAL
	Finland	3 (3%)	2 (2%)	2 (2%)	7 (3%)
Dr. Erkka Valovirta	Turku	3	2	2	7
Dr. Ilkka Anttolainen[1]	Lahti	-	-	-	-
	France	23 (25%)	25 (29%)	24 (28%)	72 (27%)
Dr. Isabelle Pin	Grenoble	1	2	2	5
Dr. F-Xavier Lebas	Le Mans	2	2	3	7
Dr. Aziz Reman	Alencon	4	4	4	12
Dr. Brigitte Perrin	Montpelier	2	0	2	4
Dr. Claude LeLoet	Rouen	2	2	2	6
Dr. Pierre Scheinmann	Paris	2	2	1	5
Dr. Etienne Bidat	Paris	2	3	2	7
Dr. Jacques Robert	Decines	1	2	0	3
Dr. Jean Levy	Sain Ouen	1	2	2	5
Dr. Martine Grosclaude	Saint Peray	4	4	4	12
Dr. Daniel Murciano	Gennevilliers	2	2	2	6
Prof C. Y. Yeung	Hong Kong	2 (2%)	1 (1%)	2 (2%)	5 (2%)
	Israel	22 (24%)	21 (25%)	22 (26%)	65 (25%)
Dr. Y. Katz	Zrifin	10	10	10	30
Dr. C. Geller-Bernstein	Rechovot	6	5	6	17
Dr. A. Goldberg	Kfar Saba	6	6	6	18
	Italy	9 (10%)	7 (8%)	7 (8%)	23 (9%)
Prof. F. M. De Benedictis	Perugia	2	1	1	4
Dr. G. De Candussio	Torino	2	2	1	5
Prof. A. Boner	Verona	2	2	2	6
Prof. G. Rossi	Genova-Quarto	3	2	3	8
	Portugal	11 (12%)	12 (14%)	11 (13%)	34 (13%)
Prof. Dr. Mario Queiros	Porto	7	8	7	22
Dr. Rosado Pinto	Lisboa	4	4	4	12
Porf. Lee Bee Wah	Singapore	4 (4%)	4 (5%)	4 (5%)	12 (5%)
	Spain	14 (15%)	11 (13%)	12 (14%)	37 (14%)
Dr. N. Cobos	Barcelona	5	4	4	13
Dr. G. Garcia-Hernandez	Madrid	8	7	8	23
Dr. J. Sierra	Barcelona	1	0	0	1
	UAE	4 (4%)	2 (2%)	2 (2%)	8 (3%)
Dr. Abdulla Al-Khayat	Dubai	1	2	1	4
Dr. A. Abdul Razzaq	Alain	3	0	1	4
TOTAL		92	85	86	263

[1]Four patients entered the run-in period, but were not randomized

8.2.4 Summary of Study Protocol

8.2.4.1 Study Population

Inclusion Criteria:

- Boys or girls aged 4-11 years, inclusive.
- Diagnosed with asthma, which included recurrent episodes of bronchoconstriction or cough.
- No hospital admissions for asthma in the 3 months preceding the Pre-Study Visit.
- No viral illness in the 4 weeks prior to the Pre-study Visit.

- No use of inhaled corticosteroids in the 3 months prior to the Pre-study Visit.
- No change in their regular respiratory medication during the 4 weeks prior to the Pre-study Visit.
- Have demonstrated adequate use of the Diskhaler inhaler and mini-Wright peak flow meter during the two week run-in period.
- Have demonstrated compliance with diary card recording of asthma symptoms during the two week run-in period.
- Have used albuterol distributed during the run-in period on a prn basis only.
- Have a PEFR of ≤90% predicted normal at Visit 1.
- Have a PEFR of ≤75% predicted normal at some time during the 3 months preceding Visit 1, or during Visit 1 itself.
- If the patient had a PEFR of between 75-90% predicted normal, they could be enrolled if they also fulfilled at least 2 of the following criteria:
  - i. Asthma symptom scores of at least 1 on 4 or more occasions during the last 10 days of the run-in period (see below)
  - ii. Wakening during the night or in the early morning due to asthma on 1 or more occasions during the last 10 days of the run-in period.
  - iii. Usage of >4 does of albuterol on 45 or more days out of the last 10 days of the run-in period.
  - iv. At least 15% reversibility of airways function as measured by FEV_1 or PEFR in response to β_2-agonist therapy at Pre-study Visit or Visit 1.

Exclusion Criteria:

- Use of oral or parenteral corticosteroids in the 1 month prior to the Pre-study Visit, during the run-in period, or having received them continuously for 2 months or longer at any time.
- Systemic infection within the 4 weeks preceding the Pre-study Visit which, in the opinion of the investigator, could possibly affect their baseline lung function or symptom scores.
- Any symptoms, including nocturnal symptoms and PEFR variability, which unduly bothered them or concerned the physician during the run-in period.
- Asthma symptoms present only during the pollen season.
- Any serious, unstable, concurrent disease.
- Known or suspected hypersensitivity to or recognized side effect of, corticosteroids, which was unacceptable to the patient.
- Dyspnea not due to asthma.
- Concurrent use of oral decongestant or antihistamines, with the exceptions of chlorpheniramine or dexchlorpheniramine.
- Use of another investigational drug within the preceding 1 month.

Acceptable Concurrent Medication Usage:

- Patients could continue with other asthma therapy, such as theophylline, cromolyn sodium, or immunotherapy, provided that the route, dose, and frequency remained

constant throughout the study. These medications could not include other β_2-agonists, anticholinergics, or combination inhalers, with the exception of the "rescue" albuterol dispensed as part of the study.

- Patients were permitted to use intranasal corticosteroids, with the exception of those containing fluticasone propionate as the active ingredient, if needed during the study.
- Antifungal lozenges were permitted for treatment of oropharyngeal candidiasis.
- Oral decongestant or antihistamines were permitted, with the exceptions of chlorpheniramine or dexchlorpheniramine.

Reviewer's Comment: It has been debated in the allergy literature whether intranasal corticosteroids or systemic anti-allergy medications such as antihistamines could impact on asthma control, either through direct action on pulmonary tree or indirectly through control of one of the "triggers" of asthma. As long as these medications remained stable during the study, there should have been no problem.

8.2.4.2 Randomization and Blinding

Patients were assigned to one of the three treatment groups by random code supplied by the sponsor. To ensure that the required number of younger patients were recruited, patients >6 years were allocated treatment numbers from the top of the list while children ≤6 years received numbers from the bottom of this same list. Investigators who studied 6-12 patients were to recruit 3 patients ≤6 years while those who studied >12 patients were to recruit 25% of their patients ≤6 years.

The study was double-blinded. Treatment identity for each patient was kept in a sealed envelope which was available in the event of an emergency. Code breaks were to be accounted for at the end of the study, although the code break envelopes were apparently lost for a total of 12 patients. By verbal report to the sponsor from the investigators involved, none of these envelopes was opened.

8.2.4.3 Dosing

Study medication for the treatment period of the study were packed in four-weekly treatment packs. Patients were given a treatment pack containing a Diskhaler inhaler and 18 Rotadisks, each disk containing 4 blisters of one dose each, at Clinic Visit 1. They were instructed to inhale one blister twice daily, once in the morning and once in the evening, and to perform any efficacy measurements prior to dosing. Patients were given packages of 18 Rotadisks at subsequent clinic visits, 4 and 5, but continued to use the same Diskhaler inhalation device throughout the study.

8.2.4.4 Treatment Arms

During the 2-week run-in period, patients received single blinded placebo via Diskhaler inhaler. Eligible participants were then randomized to receive one of three treatments for the 12-week study:

Placebo BID
FP 50 μg BID
FP 100 μg BID

Following completion of the 12-week study, there occurred a 2-week follow-up period during which patients could be prescribed whatever medications were appropriate for asthma symptom control, in an open-label manner.

8.2.4.5 Assessments

Please see the appended *Figure 1, Protocol FLIT85,* which is a flowchart of study procedures, for details concerning safety and efficacy assessments at each study visit (reproduced from Volume 35, p.66). There were a total of 8 clinic visits occurring over a time span of 16 weeks. Following the Pre-Study Visit, there was a 2 week lead-in period, during which time patients received placebo via Diskhaler. Eligible patients were then randomized at Visit 1, and were seen at weekly intervals for the first 4 weeks of the study. There was next an assessment at 8 weeks (Visit 5), followed by the final scheduled visit of the randomized phase of the trial at 12 weeks (Visit 6). A Follow up Visit was to occur 2 weeks following completion of the trial. In the case of patients who withdrew, or were withdrawn, from the study for any reason, assessments which were normally scheduled for Visit 6 were performed as soon as possible if the situation permitted.

Assessment of patient compliance was performed at each clinic visit. The sponsor has defined *Compliance* as the ability to complete the diary card satisfactorily, to withhold asthma medications appropriately before each clinic visit, and to use the prescribed study drug for at least 70% of the time (by blister count). A question in the Clinical Record Form and information in the diary card were used to establish correct use of study medication.

Efficacy Assessments:

The primary efficacy endpoints were:

1. Morning and evening peak expiratory flow rate (PEFR)

PEFR was to be measured in the morning upon arising and in the evening just before retiring, prior to any study medication administration, using an age-appropriate hand-held mini-Wright peak flow meter. The best of three efforts was to be recorded. If inhaled "rescue" albuterol was used within 4 hours, this was to be documented on the diary card.

Reviewer's Comment: Presumably the sponsor was collecting these data to exclude that particular measurement of PEFR which was obtained within the 4 hour window. If this measurement were included, and there was indeed a positive therapeutic impact of FP on asthma control, this effect would be diluted to the disadvantage of the study drug.

2. Withdrawal due to lack of efficacy of treatment

Patients were to be discontinued if they met any of the predetermined criteria (See section 8.2.2).

Reviewer's Comment: It was never stated by the sponsor whether a Bonferroni correction was to be made for multiple endpoints, either in the originally submitted protocol or in the statistical section available to this reviewer in this submission. That is, what if the sponsor had "won" on only one or two of the three possible endpoints? Because no adjustment for multiple endpoints was planned, presumably the sponsor intended to "win" on all 3 endpoints.

The secondary efficacy endpoints were:

1. Spirometry performed in the clinic
   For all children 6 and older, and for selected patients younger than 6, PEFR, FEV_1, FVC, and FEF_{25-75} were to be performed at each clinic visit. The best of three efforts were to be recorded. Again, if inhaled "rescue" albuterol was used within 4 hours, this was to be recorded.
2. Diary card data
   - Night-time awakenings: The number of times patients awoke with asthma symptoms requiring the use of rescue albuterol.
   - Total Albuterol use: The total number of doses of rescue medication used on a daily basis.
   - Daytime asthma symptom scores:
     0. Very well, no asthma, unrestricted activity
     1. Mild symptoms or wheezing or short of breath on exercise, otherwise asthma not troublesome.
     2. Asthma troublesome but able to carry out most daily activities.
     3. Asthma bad, unable to carry out daily activities as normal, such as attend school.
   - Exercise asthma symptoms scores:
     0. Walk, run and able to play games with no problems.
     1. Walking no problem, but slightly wheezy and breathless when running and playing.
     2. Slightly breathless and wheezy when walking, very breathless and wheezy when running, playing.
     3. Very breathless, tight-chested and wheezy when walking. Unable to run or to play games.

Reviewer's Comment: It would have been useful to know whether diary entries were made before or after PEFR determinations, since this could have influenced the patient's subjective sense of well-being.

Safety Assessments:

1. Adverse Events: Recorded at each clinic visit, including the date of onset, frequency, severity, outcome, causality, action taken, and whether the event met the regulatory definition of "serious".
2. Laboratory Evaluations: Clinical laboratory tests (Hematology;

Biochemistry including electrolytes, glucose, renal function, and liver function tests; and Urinalysis) were performed at Visit 1 and Visit 6, or early termination of treatment. Laboratory tests were reviewed for clinically significant "out-of-range" values, and if warranted the test was repeated and the patient followed up.

3. Physical examination: Including vital signs, pulmonary auscultation, and oropharyngeal examination. These were performed at the Pre-Study Visit and at Visit 6 or at premature termination.

8.2.4.6 Concurrent Medications:

This topic was discussed under 8.2.4.1 *Study Population.*

8.2.4.7 Patient Compliance:

This topic was discussed under 8.2.4.5 *Assessments.*

8.2.4.8 Patient Withdrawal from the Study:

Patient withdrawal due to lack of efficacy was discussed under 8.2.2 *Design.* Reasons for withdrawal were recorded on the Clinical Record Form. When a patient discontinued the study, assessments ordinarily made on Visit 6, including clinical evaluation, spirometry, physical examination, clinical laboratory, and adverse events, were completed in a timely manner, if possible.

8.2.4.9 Endpoints:

The primary and secondary endpoints of this trial were efficacy endpoints, and were discussed in detail under 8.2.4.5 *Assessments.*

8.2.4.10 Statistical Analysis:

Sample Size Based upon a desired power of 90% to detect a difference between treatment groups of 15 L/min in PEFR, 372 patients were to be studied, 124 per treatment group. This assumed a standard deviation of 36 L/min and a two-sided significance level of 0.05.

Reviewer's Comment: Because of problems in recruiting suitable children, only 263 patients could be randomized. The standard deviation of 36 L/min was based upon two studies conducted by the sponsor, FLIP20 and FLIP 39, which are discussed in section 8.3. How the "clinically significant" difference of 15 L/min was chosen was not discussed.

Populations The Total Population was defined as all patients who completed the Pre-Study Visit. The Intent-to-Treat Population was defined as all patients randomized except those for whom evidence existed that study medication was not taken. The Efficacy Population consisted of the Intent-to-Treat Population minus those patients not fulfilling the continuation criteria (see 8.2.2 above), noncompliant patients (8.2.4.5), patients who took a disallowed medication (8.2.4.1), or who were recruited

in spite of failing to meet the inclusion criteria (8.2.4.1). Data from the excluded population was either totally or partially excluded, depending upon the violation and when it occurred. The primary population for performing the efficacy analysis apart from survival was the Intent-to-Treat.

Reviewer's Comment: According to the sponsor, the decision to exclude data was made without knowledge of the patient's treatment group.

Efficacy Variables

Primary Efficacy Variables: Mean AM and PM PEFR were calculated for baseline, Treatment Weeks 1 through 12, Week 13+, and the "last evaluable week" based upon the average of the available patient diary data for that week. A pairwise comparison of change from baseline PEFR was next made between treatments for FP100 vs placebo, FP50 vs placebo, and FP100 vs FP50. Tests for the effects of gender, country, age, and baseline PEFR were also performed using the F-test from the ANCOVA model.

The probability of patients remaining in the study over time were compared between treatment groups using the Log-rank test on Kaplan-Meir estimates of survival. Calculations were based upon patients who *should* remain as opposed to who *actually* remained based upon failure to meet continuation criteria (8.2.2).

Secondary Efficacy Variables: For each of Weeks 1 through 13+ and Endpoint, mean change from baseline in daily asthma symptom score was compared between treatments using the van-Elteren test stratifying for country. Daily asthma symptom score for exercise, number of night-time awakenings, and total symptomatic albuterol use were analyzed in the same way.

For each clinic spirometry values, PEFR, FEV_1, FVC, and $FEF_{25-75\%}$, baseline was defined as the value obtained at clinic Visit 1, and change from baseline was reported for each week the patient remained in the study.

Safety

Treatments were compared with respect to all adverse events (AEs) in each body system. The sponsor also included breakdown by frequency, whether the AE was considered to be drug-related, AE severity, withdrawals due to AEs, AEs by gender, and ethnicity.

Physical examinations including vital signs and laboratory analyses were also tabulated.

8.2.5 Results

8.2.5.1 Study population characteristics:

A total of 368 patients were screened for this study. Of these, 263 patients who were distributed among 28 centers successfully completed the run-in period, were randomly assigned to treatment, and received at least one dose of study medication. The treatment assignment and general demographics of these 263 patients are presented in the table below. Notice that unlike Study FLD-220, participants were not stratified by inhaled corticosteroid use at study entry, although prior medication use was listed by the sponsor. The groups were comparable with regard to baseline spirometry.

Reviewer's Comment: A surprisingly large number of patients were withdrawn prior to randomization, 104 or 28%, compared to 19/344 or <6% in Study FLD-220, reviewed in 8.1. The reasons given by the sponsor were failure to meet entry criteria (59 or 57%) or occurrence of an adverse event (17 or 16%). Because these dropouts occurred before randomization, and the most common adverse event leading to discontinuation was asthma exacerbation, this could have fortified the study population with stable subjects, conceivably less likely to show a dose response.

Unlike Study FLD-220, the sponsor did not stratify patients for prior inhaled corticosteroid use. It was the intention of the sponsor to enroll only patients who were "steroid naive," that is, having asthma treated with only prn β-agonists prior to entering the study. This was due to concern about giving "corticosteroid-dependent" patients a placebo. As may be expected in this population, a significant number of patients had received pulses of inhaled, systemic, or intranasal corticosteroids in the recent past (see Table DL 6 in Volume 44, p.28), although patients who had used these products within the antecedent month or had more than 60 days of inhaled corticosteroid use during the 2 years prior to study entry were excluded.

With the exception of intranasal corticosteroids, patients were not allowed to continue corticosteroids into the study period. Although controversial, the continuation of intranasal corticosteroids could have influenced the results of this trial by controlling one potential asthma trigger, allergic rhinitis. Use of intranasal steroids and anti-histamines was continued without regard to treatment group, and probably would not have influenced the results of this trial.

DEMOGRAPHIC CHARACTERISTICS AT ENTRY FOR STUDY FLIT-85

	Placebo	FP50 BID	FP100 BID	Total
Number	92	85	86	263
Gender				
Male %	56 (61%)	50 (59%)	60 (70%)	166 (63%)
Female %	36 (39%)	35 (41%)	26 (30%)	97 (37%)
Ethnicity				
Caucasian %	78 (85%)	76 (89%)	70 (81%)	224 (85%)
non-Caucasian %	14 (15%)	9 (11%)	16 (19%)	39 (15%)
Age (range) yr.	8 (4-11)	8 (4-12)	8 (4-12)	8 (4-12)
Height (range) in.	50 (42-62)	51 (41-65)	50 (39-62)	51 (39-65)
Weight (range) lb.	62 (35-112)	64 (31-165)	63 (30-130)	63 (30-165)

Of the 263 patients who started the randomized segment of the trial, there were 214 completers and 49 dropouts, 33 (36%) among the placebo group, 11 (13%) among the patients receiving FP50, and 5 (6%) among the FP100 group. The most common reason for withdrawal was the occurrence of an adverse event, which accounted for 25/49 or 50% of withdrawals overall, and lack of efficacy, accounting for another 15/49 or 31%. In the case of patients randomized to the fluticasone arms, they were more likely to drop out due to an adverse event. In contrast, the placebo patients were equally likely to drop out due to lack of efficacy as to an adverse event.

The sponsor has divided the study participants into two groups for analysis: all patients enrolled who received at least one dose of study drug, or the Intent-to-Treat Population, and the "Efficacy" Population, defined by the sponsor as all those patients in the Intent-to-treat Population "who closely adhered to the requirements of the protocol." Separate analyses were performed on both populations.

8.2.5.2 Compliance

Compliance was defined as >70% usage of the study medication by blister count and review of diary card entry. The sponsor reported that 87-95% of patients were compliant at any given visit, and that the rates were similar across groups.

8.2.5.3 Efficacy Analysis

For all primary and secondary endpoints, the efficacy analysis was performed on both the Intent-to-treat (ITT) as well as the efficacy populations, although for survival analysis only the efficacy population was used. There were 263 patients in the ITT population, 169 of whom were included in the efficacy population and 94 of whom were completely excluded. A summary of patient disposition and reason for exclusion appear below:

	Treatment Group		
	Placebo	FP50	FP100
Intent-to-Treat Population	92	85	86
Number (%) excluded	35 (38%)	32 (38%)	27 (31%)
Reason for exclusion:			
Randomization error	2	2	1
Did not meet spirometry inclusion criteria	24	24	20
Disallowed medication	9	6	6
Efficacy Population	57	53	59

8.2.5.3.1 Primary and Secondary Endpoint Results-- Intent-to-Treat Population

The primary efficacy variables were morning and evening PEFR, expressed as change from baseline compared to endpoint. These results, in addition to selected secondary endpoints, are presented in the table below. The p-values are given both for active treatment compared to placebo and for FP50 vs FP100, although there was no significant difference with regard to any of the efficacy endpoints between the two doses of fluticasone. Withdrawal due to lack of efficacy of treatment was analyzed only for the efficacy population.

PRIMARY AND SECONDARY ENDPOINT ANALYSIS: INTENT-TO-TREAT

Variable	Treatment	N	Baseline Mean ±SE	Change from Baseline Mean±SE	p-values: FP50 vs placebo FP100 vs placebo FP50 vs FP100
1° Variables					
Mean AM PEFR (L/min)	Placebo	92	207 ± 7	17 ± 5	
	FP50	85	199 ± 7	50 ± 5	<0.001
	FP100	86	194 ± 7	57 ± 4	<0.001
					0.451
Mean PM PEFR (L/min)	Placebo	92	219 ± 7	11 ± 5	
	FP50	85	210 ± 7	44 ± 4	<0.001
	FP100	86	205 ± 7	53 ± 4	<0.001
					0.154
2° Variables					
Daily Asthma Symptom Score (Scale 0-3)	Placebo	90/88*	0.63 ± 0.06	-0.01 ± 0.08	
	FP50	85/83*	0.66 ± 0.06	-0.43 ± 0.08	<0.001
	FP100	86/84*	0.63 ± 0.06	-0.44 ± 0.06	<0.001
					0.698
Exercise Asthma Symptom Score (Scale 0-3)	Placebo	84/76*	0.69 ± 0.07	-0.03 ± 0.10	
	FP50	75/71*	0.74 ± 0.07	-0.55 ± 0.07	<0.001
	FP100	79/72*	0.69 ± 0.08	-0.43 ± 0.08	0.004
					0.146
Mean Number Night-time Awakenings	Placebo	90/89*	0.21 ± 0.04	-0.01 ± 0.06	
	FP50	85/83*	0.22 ± 0.03	-0.14 ± 0.05	0.006
	FP100	84/79*	0.29 ± 0.05	-0.24 ± 0.05	0.001
					0.573
Mean Daily "Rescue" Albuterol Use (Doses/day)	Placebo	83/77*	1.08 ± 0.12	0.26 ± 0.35	
	FP50	80/75*	1.20 ± 0.12	-0.70 ± 0.16	0.001
	FP100	83/74*	1.42 ± 0.15	-1.02 ± 0.16	<0.001
					0.330
Clinic PEFR (L/min)	Placebo	90/88*	192 ± 6	39 ± 5	
	FP50	83/83*	197 ± 7	50 ± 5	0.082
	FP100	85/84*	189 ± 7	63 ± 5	<0.001
					0.113
Clinic FEV_1 (Liters)	Placebo	80/76*	1.33 ± 0.04	0.07 ± 0.04	
	FP50	70/69*	1.42 ± 0.05	0.17 ± 0.03	0.007
	FP100	74/70*	1.36 ± 0.05	0.25 ± 0.03	<0.001
					0.143
Clinic FVC (Liters)	Placebo	79/75*	1.67 ± 0.06	0.05 ± 0.04	
	FP50	70/69*	1.74 ± 0.07	0.16 ± 0.04	0.043
	FP100	74/71*	1.73 ± 0.20	0.20 ±0.04	0.002
					0.322
Clinic FEF_{25-75} (Liters)	Placebo	79/75*	1.40 ± 0.07	-0.03 ± 0.07	
	FP50	69/68*	1.48 ± 0.07	0.26 ± 0.08	<0.001
	FP100	74/70*	1.40 ± 0.07	0.34 ± 0.06	<0.001
					0.655

*Indicates number of patients at baseline/number of patients at endpoint.

When measured by two of the three primary endpoints, fluticasone

propionate administered via Diskhaler demonstrated clear efficacy in the children studied in this trial. As can be seen by the table above, these findings are corroborated by nearly all of the secondary endpoints, with the exception of the clinic FP50 PEFR compared to placebo. Both of the doses chosen by the sponsor showed efficacy compared to placebo, however, there was no significant difference between the two doses in any of the primary or secondary endpoints studied. For each of the primary and most of the secondary endpoints, there did appear to be a trend toward better asthma control in the FP100 group compared to FP50. An assessment of the evaluable population showed similar results.

Reviewer's Comment: The lack of a dose-response may in part be due to underpowering of the study, perhaps as a consequence of the recruitment difficulties.

8.2.5.3.2 Patient drop-out due to lack of efficacy

The third primary endpoint was probability of remaining in the study over time (survival). A total of 49 patients were withdrawn after randomization, 33 in the placebo group (36% of all placebo patients), 11 in FP50 (13%), and 4 (5%) in FP100. Of the 33 dropouts in the placebo group, 27 were for asthma exacerbation (adverse event) or for lack of efficacy. This result corroborates the results found using each of the other two primary endpoints, that is, fluticasone propionate via Diskhaler administered at a dose of 50 or 100 μg BID is efficacious in controlling symptoms of asthma in the children studied.

Statistical analysis of survival was performed for the efficacy population only. Overall, the number of patients meeting the withdrawal criteria were 36 (63%) for placebo, 22 (42%) for FP50, and 17 (29%) for FP100. The p-values for the log-rank test on Kaplan-Meir estimates of survival again showed significant survival advantage for each of the FP groups compared to placebo, although there was no difference between the two dose levels. Again, similar to the other endpoints discussed, there did appear to be a trend toward greater efficacy in the higher compared to the lower dose of FP.

8.2.5.4 Safety Analysis

The safety analysis included all patients who received any study medication, the intent-to-treat population. This was comprised of 263 patients, 93 placebo, 85 FP50, and 87 FP100. The sponsor reports that two patients were counted twice in the analysis because they inadvertently received more than one treatment pack of medication during the course of the study.

8.2.5.4.1 Adverse Event Frequency

A total of 49 patients withdrew prematurely from the study, 33 in placebo, 11 in FP50, and 5 in FP100. Because of the significantly greater dropout rate in the placebo population, the extent of exposure in terms of patient-days was greater in the FP groups compared to placebo. When expressed as mean days of exposure, this was 66 days for placebo compared to 81 and 83 days for FP50 and

FP100, respectively; therefore, based on duration of exposure alone, a totally random adverse event (AE) would be more likely to occur in the FP exposed groups compared to placebo. Hence, it is reassuring that the overall frequency of AEs appears to be comparable between the groups.

The table below displays a compilation of all reported adverse events by body system. The body system classification is elaborated to include events of greater interest *or* if the difference in frequency of the event was >2% between placebo and active treatment. Notice that the most frequently recorded AE is asthma (exacerbation), which is significantly greater among the placebo patients compared to the FP50 or FP100 groups. There was no statistical difference in asthma occurrence between the two FP groups, however.

NUMBER AND PERCENTAGE OF PATIENTS WITH AN ADVERSE EVENT

Adverse Event	Placebo		FP50		FP100	
Number of Patients	n=93	%	n=85	%	n=87	%
Number of patients with at least one event	59	63%	55	65%	53	61%
General	5	5%	3	4%	3	3%
Allergic Rxn	0		0		1	
Headache	4		2		2	
Respiratory/ENT[1]	50/19	54/20%	34/18	40/21%	35/28	40/32%
Asthma	40		11		16	
Cough	8		5		4	
Rhinitis	6		5		16	
Pharyngitis	4		2		4	
Tonsillitis	3		6		6	
Dysphonia	0		0		3	
Ocular[2]	3	3%	3	4%	5	6%
Gastrointestinal/Oral[3]	8/0	8%	8/1	9/1%	3/5	3/6%
Hematologic	0	0	0	0	1	1%
Muskuloskeletal	1	1%	0	0	0	0
Neurologic	1	1%	4	5%	1	1%
Dermatologic	2	2%	1	1%	5	6%
Urogenital	0	0	1	1%	0	0
Miscellaneous Infections/Fever[4]	1/9	1/10%	1/8	1/9%	2/6	2/7%
Fever	9	10%	8	9%	6	7%
Oropharyngeal Candidiasis	1	1%	1	1%	2	2%
Miscellaneous	2	2%	2	2%	1	1%

[1] Respiratory and ENT were combined from Table 9, Volume 35, however, the "Number" and " %" of persons experiencing an AE could not be pooled because an unidentified number of patients experienced more than one event.

[2] No reports of elevated IOP, glaucoma, or PSC.

[3] GI and Dental/Oral AEs were also combined from Table 9, Volume 35. Again, the "Number" and "%" of persons experiencing an adverse event could not be pooled since some patients experienced more than one event.

[4] Pooled, see above.

Notice also that there is an increased incidence of "rhinitis" among the FP100 patients compared to the other two groups. This was not further explained in the submission, although "rhinitis" as a reason for study withdrawal accounted for only one study dropout, as compared to 21 for "asthma." In addition, there was a surprisingly low overall incidence of oropharyngeal candidiasis, which was not significantly different between the three groups. Oropharyngeal candidiasis was also not listed as a reason for study withdrawal. Finally, ocular events were rare, and there were no reported cases of elevated intraocular pressure, glaucoma, or cataracts, although these findings were not specifically sought.

8.2.5.4.2 Serious Adverse Events

There were no deaths reported at any time during the study. There were a total of six adverse events which met the regulatory definition of "serious." Two of these events, both "asthma," occurred during the run-in period and both resulted in study withdrawal. Two other events listed as "asthma" occurred during the study period among the placebo patients, each patient required hospitalization and each did recover. One of the two continued in the study and the other was withdrawn. There were two serious events which occurred among patients receiving fluticasone. One patient in the FP100 group was mistakenly prescribed an excessive amount of theophylline because of an asthma exacerbation. The 6th patient was in the FP50 group and reportedly developed right lower lobe pneumonia during the final week of the study. It is likely that the only two serious adverse events directly attributable to study medication were "asthma exacerbations" occurring in the two placebo patients.

8.2.5.4.3 Laboratory Examinations

There did not appear to be any laboratory abnormalities directly attributable to study medication. There was no increased incidence of hyperglycemia or hyperlipidemia among the FP participants. In addition, no patient was withdrawn because of laboratory abnormalities. This study did not specifically follow HPA axis effects.

8.2.5.4.4 Vital Signs/Physical Exams

There did not appear to be any change in vital signs (VS) or physical exam directly attributable to study medication, except possibly the four episodes of oropharyngeal candidiasis recorded among study participants. No patient was discontinued because of changes in VS or physical examination. The FP groups did not appear to have an increased incidence of hypertension.

8.2.6 Conclusions

8.2.6.1 Efficacy Conclusions

Study FLIT85 provides convincing evidence that fluticasone propionate *Rotadisks* administered via *Diskhaler* at 50 or 100 μg BID is efficacious in controlling symptoms of asthma in pediatric patients age 4-11 years. Each of the three primary efficacy parameters, AM and PM PEFR and study survival, favored the fluticasone arms. Although a dose-response could not be demonstrated, a trend seemed to favor the FP100 arm. It should be kept in mind that the age and size of the participants in this trial varied widely, hence the dose which was most appropriate for a 120 lb., 11 year old boy may not apply to a 35 lb., 4 year old girl. Because the trial did not have adequate power to detect a dose response, if there is indeed a dose-response, it is unlikely that a subgroup analysis based on participant age or weight would be helpful in this regard. For this reason, it is necessary to recommend that the lowest possible dose which controls symptoms should be prescribed.

The primary endpoints were corroborated by nearly all of the secondary endpoints, although again a statistical dose-response was not demonstrated for any of these parameters.

8.2.6.2 Safety Conclusions

Fluticasone propionate was well-tolerated by children in this study based upon its overall adverse effect profile and dropout rate. Surprisingly, there did not appear to be an increased incidence of oropharyngeal candidiasis reported among active treatment patients. There was an unexplained increased incidence of rhinitis, however, which nevertheless did not lead to study withdrawal. It should be noted that this trial was not designed to look for impact on the HPA axis or upon growth parameters. For this reason, no conclusions can be drawn from FLIT85 with regard to these endpoints.

8.3 Nonpivotal Studies

Data from 30 clinical trials have been included with this application. The sponsor has included a table, *Table 2.2 Table, of Studies, Controlled Clinical Trials,* contained in Volume 1, p. 129, which lists 14 trials that have been submitted by the sponsor specifically to support the use of fluticasone propionate at doses of 50 μg BID and 100 μg BID as maintenance treatment of asthma in pediatric patients aged 4-11 years. Two of these studies, FLD220 and FLIT85, are pivotal for safety and efficacy and have already been reviewed in sections 8.1 and 8.2, respectively. The twelve additional studies, several conducted using the Diskus or MDPI device rather than the Diskhaler, have been summarized in the table below. Five of these studies are ongoing (asterisks*) and will not be further discussed. The other seven are reviewed individually below in this section.

There are 16 studies which were not included in the table below (or in *Table 2.2*).

These trials were conducted for indications other than the maintenance treatment of asthma in children, were uncontrolled, are incomplete, or utilized a preparation of fluticasone propionate other than dry powder (i.e. MDI aerosol or nebules). Their review will be comprised solely of a compilation of any serious or noteworthy adverse events.

SUPPORTIVE CONTROLLED CLINICAL TRIALS FLUTICASONE PROPIONATE INHALATION POWDER

Protocol Number	Study Design	Treatment	Number per Arm	Duration (Days)	Age Range in years (Mean)
(Placebo Controlled)					
FLIP20	Parallel	Placebo BID	130	28	6-14
		FP 50 µg BID	128		(9)
FLIS02	Crossover	Placebo + FP 200 µg + BUD 200 µg	24	15**	6-12
		Placebo + FP 400 µg + BUD 400µg	24		(9)
(Dose Comparison)					
FLIP39	Parallel	FP 50 µg BID	97	84	6-17
		FP 100 µg BID	99		(10)
(Active Control)					
FLIP58	Parallel	FP 200 µg BID	119	56	4-13
		BUD 200 µg BID	110		(8.2)
FLIP51	Crossover	FP 100 µg BID	19	15	7-14
		BDP 200 µg BID	19		(11)
		BDP 400 µg BID	19		
*FLTB3013	*	*	*	*	*
*FLTB3015	*	*	*	*	*
(Device Comparison)					
FMDT01	Parallel	FP 50 µg BID (Diskhaler)	133	28	4-12 (8)
		FP 50 µg BID (MDPI Diskus)	134		
FMDT02	Parallel	FP 100 µg BID (Diskhaler)	167	28	4-74 (27)
		FP 100 µg BID (MDPI Diskus)	164		
*FLTA2006	*	*			
(MDPI Studies)					
*FLTA2007	*	*	*	*	*
*FLTA2008	*	*	*	*	*

Study is incomplete and not discussed in detail.

***Three 15 day dosing periods, each period followed by a 15 day washout; lead-in was 7 days, follow up was 14 days.*

8.3.1 FLIP20

This was a 4-week, randomized, double-blind, placebo controlled study to assess the safety and efficacy of a single dose of FP, 50 μg BID administered via Diskhaler, in a population of children age 6-12 years with moderate to moderately severe chronic asthma. FLIP20 was an international study conducted at 32 sites in 12 different countries. The study commenced in April, 1993 and was able to recruit 274 children fitting the inclusion criteria who were not receiving inhaled corticosteroids. Of the patients recruited, 258 received study medication, 250 completed the study, and 236 closely adhered to the protocol ("Efficacy population").

The primary efficacy endpoints were change in diary AM and PM PEFR from the baseline established during the lead-in period compared to placebo. Secondary endpoints included exercise and night-time symptom scores, clinic spirometry, and "rescue" albuterol. This study was able to demonstrate statistical significance in both of the primary endpoints, AM and PM PEFR, although the numerical changes were very small. For example, PM PEFR increased from 269 L/min to 297 in the FP group compared to 278 L/min to 281 in the placebo group, for a difference of 25 L/min. This was following an "adjustment" in the final PEFR which increased the FP PEFR from 292 to 297 and decreased the placebo PEFR from 284 to 281. Had the unadjusted values been used, the difference would have been less, only 17 L/min. When a similar analysis was applied to the AM PEFR data, the difference between the two groups was again numerically small, but statistically significant in favor of treatment. Although these changes in spirometry were numerically small, this finding is not unexpected given the rather brief duration of the study. Recall that in pivotal study FLD220, maximal improvement in mean FEV_1 was not achieved for several months.

With regard to secondary endpoints, the sponsor did demonstrate significant improvement in FP treated patients compared to placebo in number of symptom-free days, "rescue-free" days, days with no exercise-related symptoms, and clinic visit FEV_1, but not in the number of symptom-free nights. Survival in study was not an endpoint, however, there were only a total of 8 withdrawals, 5 in the placebo group and 3 in FP.

With regard to safety, both treatments were well-tolerated with few serious adverse events, and none occurring in the FP group during treatment. There were a total of 32 adverse events (AEs) reported in 28/128 (22%) patients in the FP group and 54 AEs reported in 42/130 (32%) in the placebo group, not significantly different. The most commonly reported AEs were upper respiratory tract infections (7 in FP and 8 in placebo) and asthma exacerbation (4 in FP and 7 in placebo). HPA axis function was assessed with mean plasma cortisol in a subgroup of 112 patients. This did not show any distinctly abnormal trend, although one patient receiving FP did have a decline from 5.9 mg/L to 1.9 mg/L. One 11 year old female patient reported a "weight gain" of 4.2 kg during treatment with FP. The child subsequently lost this weight following

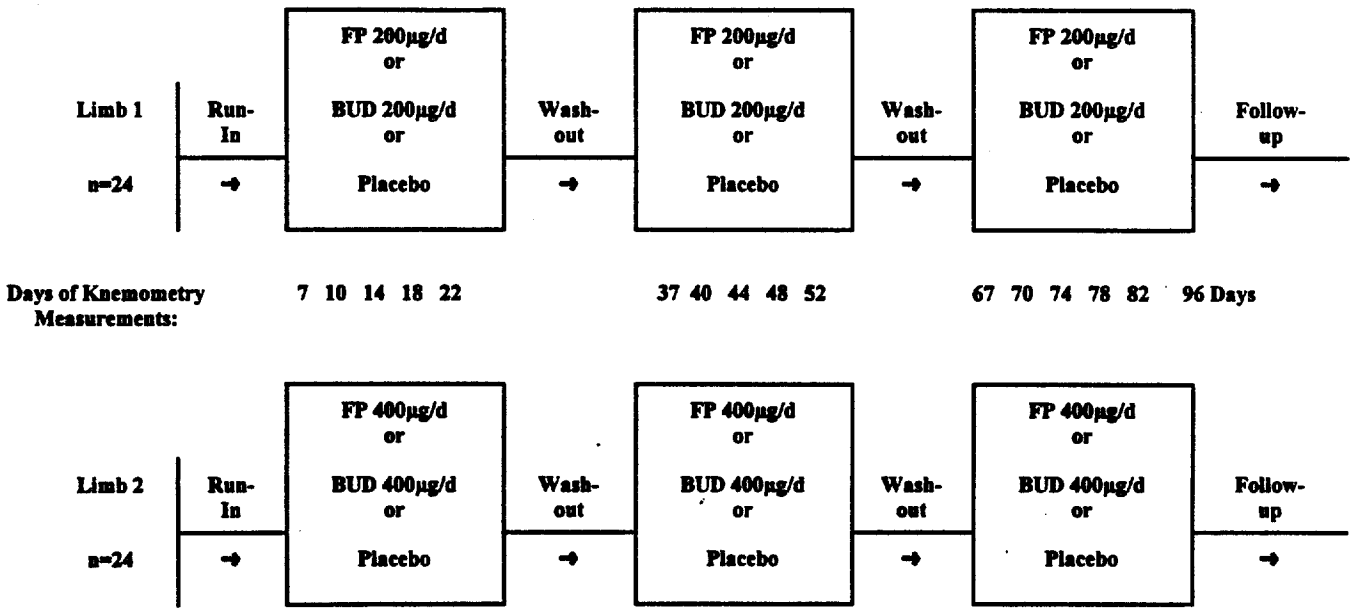
discontinuation of therapy. This event was thought likely by the investigator to be related to drug treatment. Oral candidiasis and hoarseness did not emerge as significant problems.

In conclusion, FP administered at a dose of 50 μg BID to children age 6-12 years with moderately severe chronic asthma for 4 weeks was well tolerated but showed marginal clinical, although statistically significant, efficacy in the primary endpoints. Efficacy was corroborated by most of the secondary endpoints.

8.3.2 FLIS02

This was a randomized, placebo controlled, double-dummy, cross-over study conducted at a single center to determine the impact of inhaled budesonide administered via Turbohaler (100 μg BID and 200 μg BID) and FP (100 μg BID and 200 μg BID) on longitudinal growth in pre-pubertal children age 6-12 years with mild asthma. The study recruited a total of 48 patients, 47 of whom completed the entire 96 day trial. Participants were included only if their asthma could be controlled on prn β-agonists, and the patients had not received inhaled or systemic corticosteroids in the 2 months preceding the trial. A diagram of the trial design appears below:

FLIS02 STUDY DESIGN



Each treatment period lasted for 15 days, followed by a 15 day washout period. Knemometry was performed at baseline and at each clinic visit during the active 15 day treatment periods. Laboratory assessments, including urinary free cortisol, were performed at baseline and at the end of each treatment period. Clinic spirometry and AM/PM PEFR were also recorded, as was "rescue"

albuterol use, and night-time, daily, and exercise symptom scores.

The primary endpoint was mean growth rate, measured over each treatment period using knemometry of the lower leg and expressed as mm/week(wk). In *Limb 1*, mean growth rates were 0.35 mm/wk in placebo, 0.38 during FP 200 µg/day, and 0.26 during BUD 200 µg/day. There was no significant difference between treatment groups. In *Limb 2*, on the other hand, mean growth rates were 0.52 mm/wk for placebo, 0.37 during FP 400 µg/day, and 0.30 during BUD 400 µg/day. The growth rate during BUD 400 µg/day was significantly lower than that during placebo (-0.21 mm/wk, p=0.012) but there were no significant differences between FP 400 µg/day and placebo (-0.15 mm/wk, p=0.088).

Reviewer's Comment: It should be noted that based on a prior study, the sponsor had estimated lower leg growth velocity to be 0.20 mm/week and designed the study to have an 89% chance of detecting a 0.21 mm/week difference between treatments. The standard deviation turned out to be higher than expected, 0.3 mm/week, and therefore with only 24 patients per limb, the study only had 60% power to detect the clinical difference of 0.21 mm/week. It is therefore possible that a true treatment effect existed in the other active treatments as well (i.e. FP 200 µg/d, FP 400 µg/d, BUD 200 µg/d), but the study was not adequately powered to detect this effect.

Each of these interpretations requires the reviewer to accept the sponsor's premise: that is, that linear growth can be measured accurately over a short term interval of only 15 days and that variations in growth over such short cycles are clinically meaningful or predictive. In addition, substituting lower leg knemometry for longterm growth has not yet achieved widespread acceptance. For these reasons, the "growth" results found in this study are provocative but cannot be regarded as conclusive.

This was not a study designed to assess efficacy, and the population of mild asthmatics chosen were not sufficiently symptomatic at baseline for a difference in PEFR, spirometry, or symptom scores to be detected for any of the treatments chosen, compared to placebo.

With regard to safety, all treatments were well-tolerated with no serious adverse events (AEs) and an approximately equal incidence of AEs among all treatment groups. The most common AEs were upper respiratory infection (URI), sore throat, and vomiting, none clearly related to treatment. Among the expected AEs, there were no reported occurrences of oropharyngeal candidiasis or hoarseness. As in the prior study reviewed, there was one child, a six year old female, who had a significant weight gain of 2.3 kg over 12 weeks occur during the active phase of this study.

With regard to HPA axis, 24 hour urinary free cortisol excretion (UFC), corrected for creatinine, was significantly lower compared to placebo following both FP 100 µg BID and FP 200 µg BID as well as BUD 200 µg BID, but not after BUD 100 µg BID. The sponsor reported no concurrent evidence of hypo- or hyper-cortisolism in any of the patients studied.

In conclusion, inhaled budesonide when given via turbuhaler at 400 μg/day to children age 5-12 with mild asthma is associated with a statistically significant decrement in short-term linear growth rate when measure via knemometry. This effect was not seen at doses of budesonide of 200 μg/day or at doses of fluticasone propionate given via Diskhaler of 200 or 400 μg/day, although the study was underpowered and therefore could have missed an effectwhich the sponsor designated as important. HPA axis effects measured by urinary free cortisol showed abnormally low excretion associated with both doses of fluticasone and for the higher dose of budesonide, which was asymptomatic. Each treatment was well-tolerated with regard to adverse events. There was no improvement in any efficacy parameters in this population of mild asthmatics.

8.3.3 FLIP39

This was a randomized, double-blind, 12 week, parallel group study comparing two doses of fluticasone propionate, 50 or 100 μg BID, given to children age 6-16 years with moderate to severe asthma. This trial included neither a placebo arm nor an active control arm. It was conducted between May, 1989 and February, 1990 at 23 centers located in 7 countries in Europe and the Middle East.

Reviewer's Comment: A clinical trial which includes neither a placebo arm nor active control arm can provide no conclusive information with regard to efficacy unless a significant difference between the doses is found. This review will therefore be descriptive and brief.

The study recruited a total of 273 children who required daily inhaled corticosteroids (ICS). Following a two week lead-in period during which time BDP 100 μg BID was substituted for their usual ICS, 196 of these children were randomized to receive treatment, 97 to receive FP 50 μg BID and 99 to receive FP 100 μg BID via Diskhaler. After completion of the 12 week study period, the patients were seen again at a 2 week follow-up visit. With the exception of ICS, the patients could use their usual asthma medication during the study, as well as prn albuterol which was supplied by the sponsor. The primary endpoint of this trial was given as AM and PM PEFR. Secondary endpoints included daily asthma symptom scores recorded in a diary, use of "rescue" β-agonist, subjective assessments of efficacy, and clinic spirometry. Safety was assessed via adverse event recordings, physical examination, and clinical laboratory studies including AM plasma cortisol.

With regard to efficacy, AM PEFR went from 301 L/min during the run-in to 320 L/min at the end of 12 weeks for the FP 50 μg BID compared to 297 L/min to 317 L/min for FP 100 μg BID. The change was not significant between dose levels of FP or compared to baseline. Similar results were seen for PM PEFR. Secondary endpoints showed a trend toward better control at the *lower dose* of FP

midway through the study, but this was not sustained to the 12 week point.

With regard to safety, the number and severity of AEs was not significantly different between the two groups. There were no deaths. The most common AEs were asthma exacerbation, URI, and viral infection, which were evenly distributed between the two groups. A total of 5 events which occurred during the randomized part of the trial met the regulatory definition of serious, primarily asthma exacerbations requiring hospitalization, and not significantly different between the two doses. HPA axis assessment revealed asymptomatic decreases in random AM cortisol in 6 patients receiving FP 50 μg BID and in 7 receiving FP 100 μg BID which were for the most part reversible with discontinuation of treatment.

In conclusion, Study FLIP39 demonstrates that children age 6-17 with moderate to severe asthma who are managed chronically on ICS can be switched from BDP 100 μg BID to fluticasone propionate via Diskhaler at 50 or 100 μg BID with no significant change in measured AM or PM PEFR. There was no significant difference between the two doses in any measure of asthma control or in the overall incidence of adverse events. However, because of study design, the clinical meaning of these results is debatable.

8.3.4 FLIP58

This was a randomized, double-blind, double-dummy, 8 week, parallel-group study to compare FP 200 μg BID to BUD 200 μg BID in a population of asthmatic children age 1-13 years whose management already required daily inhaled corticosteroids (ICS).

Reviewer's Comment: Again, the sponsor has conducted a study with no placebo arm. In addition, there was no "washout period" during the lead-in phase of the study prior to randomization, where patients could be taken off of their ICS and tested for asthma stability. Therefore, no definitive conclusions concerning safety or efficacy can be made from this trial, unless a significant difference is found between active treatments.

A total of 285 patients were enrolled in this study, 229 of whom completed that lead-in phase and were randomized to receive study medication, 119 in the FP arm and 110 in the BUD arm. Each patient received both a Diskhaler (FP) and a Turbuhaler (BUD), only one of which contained active medication. The primary endpoint was based upon daily AM and PM PEFR recorded in the diary distributed to each patient. Secondary endpoints included spirometry measured in clinic, numerical scores of asthma control at rest and during exercise, nighttime sleep disturbance, and "rescue" albuterol use.

The sponsor reported a statistically greater improvement in AM PEFR in the FP compared to the BUD group at 8 weeks, a difference which was not seen in the PM PEFR parameter. There was no difference between the two groups on any of the secondary endpoints.

Reviewer's Comment: The absolute difference between the two groups the sponsor is referring to

is extremely small, 256 L/min during lead-in to 274 L/min for FP (Δ18 L/min) compared to 261 L/min during lead-in to 270 L/min for BUD (Δ11 L/min). The fact that none of the secondary endpoints showed a significant difference, and that this change compared to lead-in is not significant, argues against it having any clinical meaning. In addition, the absolute magnitude of the change is comparable to the change seen in the placebo arm of a study of similar duration, FLIP20.

Both treatments were well tolerated, with an equivalent number of adverse events occurring in each group. The most common adverse events were also identical to those reported previously. There were no deaths and no serious adverse events directly attributable to treatment. HPA axis effects were measured by AM cortisol, which were not statistically different between treatment arms at the end of the study.

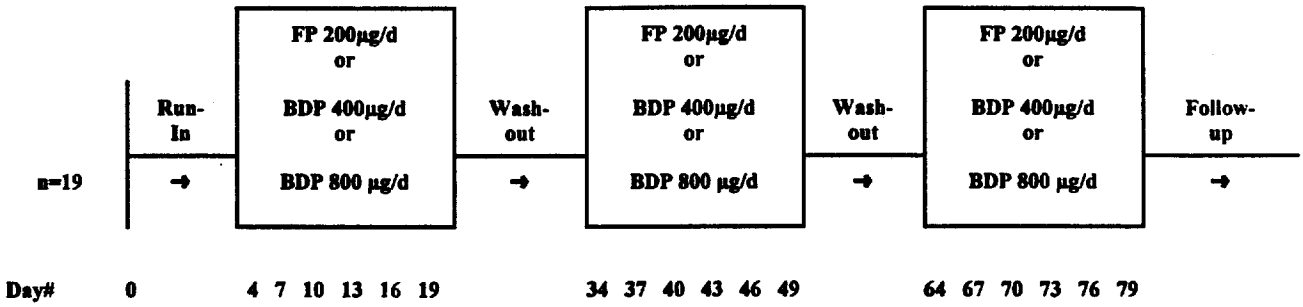
Reviewer's Comment: Again, this is a very insensitive measure of HPA axis function, and because these patients were not steroid-naive, and there was no placebo group, it is difficult to know what to make of this information.

In conclusion, this trial demonstrated that asthmatic children managed on daily inhaled corticosteroids could be safely switched to either budesonide at 200 µg BID or fluticasone propionate via Diskhaler at the same dose with no significant change in indices of asthma control and no difference in safety profile between the two arms.

8.3.5 FLIP51

This was a randomized, double-blind, three-way, three-period crossover study to investigate longitudinal growth, using knemometry, in children with mild asthma during treatment with BDP 400 µg BID, BDP 200 µg BID, and FP 100 µg BID. A total of 19 prepubertal children between the ages of 7 and 14 who were not presently managed on ICS were recruited at a single center in Denmark. Following a 4-day lead-in period during which time they received placebo inhaler, these patients were randomized to receive study medication in one of three sequences (see diagram below). Knemometry was performed at approximately 3 day intervals during dosing. Each treatment period was separated by a 15 day washout.

STUDY PLAN FOR FLIP51



The primary endpoint was longitudinal growth measured over 15 days by knemometry during each treatment. Secondary endpoints were calcium and bone metabolism and HPA axis effects. Patients also recorded daily asthma scores, AM and PM PEFR, and "rescue" albuterol use in a diary. Spirometry, clinical laboratory studies, and physical examinations including height and weight were also assessed after each treatment period.

There was no significant difference between the three groups with regard to growth rate as measured by knemometry, although there was a "trend" toward slower growth among the high dose BDP group. Similarly, there was no significant difference between the three groups as measured by any index of asthma control. Adverse events were rare and similar between the groups. More patients in the high dose BDP group had post-treatment plasma cortisols which were below the lower limits of normal (5 in BDP 800, 3 in BDP 400, 1 in FP 200). The children were asymptomatic, however, and repeat values drawn later had normalized.

In conclusion, this was a very limited study involving few patients and including no placebo group. The data did suggest, however, that BDP dosed at 400 µg BID, which is twice the recommended daily dosage for children, may increase the possibility of decreased growth rate or asymptomatic decrease in serum cortisol.

8.3.6 FMDT01

This was a randomized, double-blind, double-dummy, parallel-group, 4 week study which was conducted to determine the clinical equivalence between FP 50 µg BID delivered via multidose powder inhaler (MDPI) and the Diskhaler in children aged 4-11 years. No PK data were reported. There was no placebo arm. Sixty-nine percent of study participants were receiving inhaled corticosteroids (ICS) at baseline, which were discontinued with no "wash-out" period prior to study medication administration.

A total of 362 patients entered the lead-in, 267 of whom were randomized to treatment, 133 in the Diskhaler arm and 164 in the Diskus arm. The primary

endpoint was a comparison of the AM PEFR between the two groups. Patient preference and the usual safety assessments were also made.

Mean AM PEFR recorded for the intent-to-treat population during lead-in was 230 L/min for the MDPI group compared to 222 for the Diskhaler patients. At the end of 4 weeks, this had improved slightly to 248 L/min (▲18) for the MDPI and to 244 (▲22) for the Diskhaler, not significantly different between the two devices.

Reviewer's Comment: Since there is no placebo arm, it is difficult to know how to interpret this change from baseline. Again, the absolute magnitude of the change is similar to that seen in the placebo arm of a trial of the same duration, FLIP20.

There were no significant differences between the two devices in any of the other safety or efficacy endpoints measured. No unexpected or excessive number of adverse events associated with fluticasone propionate dry powder 50 µg BID delivered by either of these devices occurred.

In conclusion, this study suggests that children age 4-11 who have asthma and who are managed on daily ICS may be switched to DPI FP at a dosage of 50 µg BID, delivered by Diskhaler or by MDPI, with no significant difference between the two devices in safety or in indices of asthma control, at least in the short term.

8.3.7 FMDT02

This was a randomized, double-blind, double-dummy, parallel group, 4 week study which was conducted to determine the clinical equivalence between FP 100 µg BID delivered via an MDPI compared to a Diskhaler in adult and pediatric patients with asthma. The design, conduct, and goals of this trial were identical to the preceding study, except that the population was expanded to include adolescents and adults in addition to children.

A total of 463 patients entered the lead-in, 331 of whom received treatment (Intent-to-treat population). The intent-to-treat group included 115 children age 4-11 years, 61 in the MDPI group and 54 in the Diskhaler group, of whom 35 or 30% were age 7 or younger. At baseline, 73% were being managed on inhaled corticosteroids, which were not "washed out" during the lead-in.

This was primarily a device comparison trial conducted to discern patient preference, although again certain safety and efficacy endpoints were reported. Mean AM PEFR recorded for the subgroup of children age 4-11 years was 249 L/min for the MDPI group compared to 250 for the Diskhaler patients. At the end of 4 weeks, this measurement had improved slightly to 266 L/min (▲17) for the MDPI and to 269 (▲19) for the Diskhaler, not significantly different between the two devices. There were no significant differences between the two devices in any of the other safety or efficacy endpoints measured.

Reviewer's Comment: Again, with no placebo arm, this information is difficult to interpret, and the magnitude of the change approaches that seen with placebo in comparable trials.

There were no adverse events which were unexpected, given the population studied and the pharmacologic class of this drug. In addition, the overall number and distribution of adverse events gave no indication that children were disproportionately affected.

In conclusion, this study suggests that adult or pediatric patients with asthma who are controlled with daily ICS may be switched to FP 100 μg BID, delivered by Diskhaler or by MDPI, without a significant difference between the two devices in indices of safety or of asthma control.

9.0 INTEGRATED SUMMARY OF EFFICACY

9.1 Identification of Adequate and Well-Controlled Studies

The sponsor has identified a total of 7 studies to be included in the Integrated Summary of Efficacy (ISE). These include the two pivotal trials FLD220 and FLIT85, the placebo-controlled, single dose, 4-week trial FLIP20, the dose comparison trial without a placebo FLIP39, the active control trial using budesonide but no placebo FLIP58, and the two device comparison trials FMDT01 and FMDT02, neither of which was placebo-controlled (see table at the beginning of 8.3). This section will discuss only the three trials whose design included a placebo arm, FLD220, FLIT85, and FLIP20. The remainder will be reported under "9.1 Uncontrolled Studies".

The salient design features and main efficacy endpoints of the Intent-to-treat population from the three trials included in the ISE appear in the table below.

PULMONARY FUNCTION TEST RESULTS: MEAN CHANGE FROM BASELINE

Trial	Arms	Duration (days)	N (Intent-to-Treat)	AM PEFR (ΔBaseline) L/min	FEV_1 (ΔBaseline) L
FLIP85		90	261		
	Placebo		92	17	0.07
	FP 50 μg BID		84	50	0.17
	FP 100 μg BID		85	57	0.25
FLD220		365	325		
	Placebo		106	-	0.09
	FP 50 μg BID		111	-	0.20
	FP 100 μg BID		108	-	0.25
FLIP20		28	251		
	Placebo		125	11	0.05
	FP 50 μg BID		126	27	0.15

A total of 835 patients were studied in these three controlled clinical trials, 514 of whom received the active drug. Duration of treatment ranged from 4 weeks to one year, with 388 of these patients studied for 12 weeks or longer. Patients recruited into the two longer studies were all between the ages of 4 and 11, although the 4 week study age limits were 6 through 12 years, inclusive. The spirometry tabulated above reflects end-of-treatment values. All three of these trials involved a "washout" period in which a baseline asthma stability for each patient off of inhaled corticosteroids, if they were being administered, was established.

The mean change from baseline in PEFR was available for only two of these studies, and ranged from 27 L/min for FP dosed at 50 μg BID for 4 weeks to 57 L/min for FP dosed at 100 μg BID for 12 weeks, both significantly different from placebo. Although not a primary endpoint, all three trials showed clinic FEV_1 to be consistently significantly greater in patients receiving FP compared to placebo. These two spirometric measurements of efficacy were corroborated by nearly all of the secondary endpoints, including "rescue" albuterol use and asthma symptom scores. Survival in study, which was the third primary efficacy variable for the pivotal trial FLIT85, showed significant advantage in favor of the FP-treated patients both in this trial and in FLD220, although not in the relatively brief 4-week FLIP20.

In conclusion, fluticasone propionate 50 or 100 μg BID delivered via Diskhaler showed convincing efficacy in children age 4-11 with moderate asthma on all primary and nearly all secondary endpoints in controlled clinical trials.

9.2 Uncontrolled Studies

There were six additional uncontrolled trials, the active controlled studies FLIS02, FLIP58, and FLIP51, the dose comparison study FLIP39, and the device comparison studies FMDT01 and FMDT02. Overall, the data generated in these trials adds little to the conclusions drawn from the controlled clinical studies, except to suggest that fluticasone propionate Diskhaler in the doses studied had efficacy roughly comparable to the inhaled corticosteroids budesonide and beclomethasone dipropionate, although no strict μg perμg comparisons can be made.

9.3 Analysis of Dose-Response

In general, it has been difficult to find a consistent dose-response relationship on standard clinical endpoints for any of the inhaled corticosteroids presently in use in the treatment of asthma. Fluticasone propionate Diskhaler is no exception. Although a trend favoring FP 100 μg BID over FP 50 μg BID was observed, this failed to reach statistical significance in any of the studies submitted. There are probably no reasons unique to this drug product or to these particular clinical trials, although it is possible that the 12 week pivotal study FLIT85 was underpowered due to recruitment difficulties and could possibly have detected a statistical difference had the anticipated 372 patients actually been recruited. In the absence of these data, it is scientifically correct to recommend that dosing in children always be initiated at the lowest dose, 50 μg BID, unless convincing

clinical evidence suggests otherwise. Whether a higher starting dose is justified based on these dose-response trends needs to be assessed taking into account the risk:benefit considerations.

9.4 Onset of Effect

Daily measurements of PEFR and other efficacy parameters were recorded during week 1 of the pivotal 12-week trial FLIT85. For both doses, FP 50 μg BID or FP 100 μg BID, statistically significant improvement in PEFR was seen by 48 hours although numerical improvement was noted within 24 hours. Symptom scores and "rescue" albuterol use registered improvement by 72 hours. Clinic FEV_1 had improved by day 7, but improvement in the number of nighttime awakenings did not occur until beyond the first week of therapy. The curve of PEFR vs. time was the most steep during week 1 and then appeared to plateau, although numerical improvement continued out to 4 weeks.

9.5 Efficacy in Subpopulations

Study FLD220 stratified patients for prior inhaled corticosteroid usage during the process of randomization. Study FLIT85 excluded these patients. If a subgroup analysis is performed for patients receiving inhaled corticosteroids in FLD220, there is no significant difference in efficacy as measured by FEV_1 between the two groups who received FP compared to placebo. Surprisingly, there is actually a numerical trend toward greater efficacy in the steroid-naive patients, even though the ICS group had had a "washout" period during which time baseline stability was assessed. It is possible that this washout period, then, was not of sufficient duration. The sponsor also performed subgroup analysis by gender and by racial background. There was no difference in efficacy between male and female children. No difference was found when analyzed by ethnicity, although the studies was comprised overwhelmingly of Caucasian children (>80%).

9.6 Long-term Effectiveness, Tolerance, and Withdrawal

The sponsor presents two studies in support of the long-term efficacy of FP via Diskhaler in children, FLD220 and FLIP20E, neither of which had efficacy as a primary endpoint. FLD220 was designed to measure the impact of FP on growth over one year, although spirometry was measured during clinic visits as a safety parameter. FLIP20E was an open-label extension of the 4 week efficacy study FLIP20. As an unblinded, non-placebo controlled study, it cannot be used to definitively support effectiveness.

In spite of the lack of data to specifically support long-term efficacy, there is conversely no evidence to indicate that control of asthma deteriorates over time. During the 12-week efficacy study FLIT85, PEFR continued to show a nonsignificant numerical improvement over time, even after an apparent "plateau" of stability had been achieved. As mentioned above, children participating in FLD220 were followed for FEV_1. Like PEFR in FLIT85, this remained stable following attainment of a plateau of stability.

No data were presented by the sponsor specifically to address the issue of withdrawal. Spirometry was not performed during the follow up visit for FLD220.

However, there was no increased incidence of adverse events at this visit which would be suggestive of any clinically significant withdrawal effect during the follow up period.

10.0 Integrated Summary of Safety (ISS)

Safety data from 1614 pediatric exposures to inhaled fluticasone propionate have been included in the ISS submitted by the sponsor in support of FP Diskhaler. Of these exposures to the inhaled drug substance, 1399 are from the DPI, 1173 of these via Diskhaler, and 215 are from the MDI. Only DPI trials have been included in tables providing exposure, demographics, and distribution information. The "Adverse Events" section will include non-DPI trials, where the data is available. However, only FP Diskhaler data will be used to construct the table of the most frequently reported adverse events. Data from the MDI or DPI non-Diskhaler trials will be reported separately.

This NDA is unusual in that it supports solely the *pediatric* indication for this dry powder inhaled corticosteroid, which is not yet approved for adults. For this reason, one of the two pivotal trials had as its primary endpoint change in axial growth rate over one year, a safety parameter not pertinent to the adult patient population. This ISS will therefore include separate sections to discuss those safety issues which are relevant to the pediatric patient population, including growth, HPA axis effects, and ophthalmological findings. HPA axis effects will presented as a distinct subsection under "Laboratory Results," and ophthalmological findings will be a subsection under "Physical Examinations." Growth effects cannot be easily placed under "Physical Examinations" or "Adverse Events", because it was a primary endpoint of a pivotal study. For this reason, it will be contained within its own section, and will be in addition to the usual sections of adverse events and clinical laboratory evaluations.

10.1 Demographics of Exposed Population

The overall demographic characteristics for the 1399 pediatric exposures to FP in the DPI studies appears in the table below. As a whole, the patients were quite similar across dosage groups, that is >90% Caucasian, two-thirds male, and slightly over 8 years in mean age (range 4-11 years). If the dimensions of an "average" child in this study population could be given, this child would be 4½ feet tall (131 cm) and weigh 66 lbs. (range 98-175 cm tall, 30-171 lb.). There does appear to be a reasonably good representation of all age groups within this distribution, since fully 25% of the participants recruited into the pivotal trial FLIT85 were reported to be younger than age 7 years, and 13% of the children studied in the pivotal safety trial FLD220 were age 4-6 years, inclusive. The sponsor reports in the ISS that there were 122 patients participating in the FP DPI trials were age 4-5 years, although the precise distribution by studies was not presented in summary tabular form. This very young group of children would therefore constitute 8.7% of the total exposed pediatric population. Ethnic subgroups are very small, the study population was overwhelmingly Caucasian. It is therefore difficult to make determinations of relative safety with regard to ethnicity, although there is no historical reason to believe this would differ across ethnic lines. With regard to gender, prior to puberty, approximately twice as many boys as girls are diagnosed with asthma,

thereafter the sex incidence is equal (R.E. Behrman et al; *Textbook of Pediatrics*; 14th edition; W.B. Saunders; 1992). The composition of the study therefore reflects the epidemiology of the disease in children.

In conclusion, the demographics of the patient population are sufficiently representative with regard to gender and age to support a conclusion with regard to safety.

DEMOGRAPHICS OF CHILDREN EXPOSED TO FP DPI

	Placebo	FP 50 BID Diskhaler	FP 100 BID Diskhaler	All other FP DPI
N (%)	352	541	346	512
Gender				
Female	121 (34%)	176 (33%)	113 (33%)	184 (36%)
Male	231 (66%)	365 (67%)	233 (67%)	328 (64%)
Age (years)				
Mean	8.2	8.1	8.1	-
Range	4-11	4-11	4-11	4-11
Ethnicity				
Black	14 (4%)	12 (2%)	8 (2%)	3 (<1%)
Non-Cauc., Non-Black	29 (8%)	36 (7%)	28 (8%)	29 (6%)
Caucasian	309 (88%)	493 (91%)	310 (90%)	480 (93%)
Height (cm)				
Mean	132.0	130.8	130.8	131.0-133.2
Range	98.2-175.3	103.9-167.6	99.1-165.0	99.1-162.6
Weight (lbs)				
Mean	66.8	65.3	65.1	64.3-65.1
Range	30.0-134.0	30.9-165.4	29.8-170.9	30.0-133.0

10.2 Extent of Exposure, Patient Disposition, and Survival

Duration of exposure to study medication is presented in the table below. Although most exposures to FP DPI (Diskhaler in addition to MDPI) were for 12 weeks (84 days) or less, 354 children received treatment for at least 6 months (using 196 days as a breakpoint), and 168 of these children were treated for one year or longer. These numbers exceed the minimum duration of exposure consistent with ICH guidelines for a new molecular entity (300 patients for 6 months, 100 for 1 year).

If only the Diskhaler is considered, the median exposure time for FP 100 BID was 90 days, compared to 33 days for FP 50 BID and placebo. The shorter duration of exposure for placebo reflects in part the higher dropout rate, primarily for lack of efficacy. The short duration of the FP 50 BID group was not due to dropouts, only 7% compared to 19% for placebo, but rather to the inclusion of a single large clinical trial of only 4 weeks duration, FLIP20. This trial included 258 patients evenly distributed between placebo and FP 50 BID arms, and included no patients receiving FP 100 BID.

In conclusion, there is adequate exposure of the proposed patient population to both doses of fluticasone propionate dry powder delivered via Diskhaler to provide a satisfactory assessment of safety, both from a scientific and a regulatory perspective.

DISPOSITION, EXPOSURE, AND STUDY COMPLETION: FP DPI

	Placebo	FP 50 BID Diskhaler	FP100 BID Diskhaler	Other FP DPI
N	352	541	346	512
<28 days	48 (22%)	99 (18%)	56 (16%)	126
29-84 days	138 (39%)	225 (41%)	72 (21%)	246
85-196 days	50 (14%)	98 (18%)	113 (33%)	9
197-364 days	41 (12%)	49 (9%)	43 (12%)	94
≥365 days	45 (13%)	69 (13%)	62(18%)	37
Treatment days				
mean	121	118	158	-
median	33	33	90	-
Completed study	285 (81%)	505 (93%)	313 (90%)	494 (96%)
Discontinued study	67 (19%)	36 (7%)	33 (10%)	18 (4%)
adverse event	20 (6%)	8 (1%)	9 (3%)	-
lack of effect	33 (9%)	9 (2%)	5 (1%)	-
other	14 (4%)	19 (4%)	19 (5%)	-

10.3 Growth Effects

There were three studies which specifically addressed growth as an endpoint, FLIS02, FLIP51, and FLD220. FLIS02 and FLIP51 used knemometry of the lower leg to measure growth rates over 15 day dosing intervals. FLD220 used stadiometry to measure linear growth over a one year period.

Relative to placebo, a small, but statistically significant, decrement in growth rate was reported in FLIS02 among patients receiving the comparator product, budesonide (BUD), at doses of 400 μg/day. This effect was not seen in the FP group relative to placebo, primarily because the placebo period used for this FP comparison had a slower rate relative to the placebo group for BUD, not because of a difference in growth rate between the two active treatments. FLIP51 identified a nonsignificant trend toward decreased growth rate among the comparator product beclomethsone dipropionate (BDP) compared to the FP group, however, this study did not include a placebo control and therefore cannot be definitively interpreted. It should be remembered when drawing conclusions from these two trials that very few patients were studied, that the duration of observation was short, and that a surrogate endpoint for long-term growth, knemometry, was used to provide the information. These data are therefore of limited utility in determining the impact of FP via Diskhaler on rate of growth in children.

FLD220 was a 12-month study of 325 asthmatic children treated with FP 50 or 100 μg BID or placebo. Growth was evaluated at baseline and at monthly intervals using stadiometry measurements (see table below). Growth rate was corroborated using bone age x-rays and was assessed at baseline, 6 months, and 12 months.

There was a small but statistically significant decrement in the rate of growth in the intent-to-treat population among the patients receiving FP 100 μg BID relative to children receiving placebo. A decrement in growth rate was also seen among the

children who received the lower dose of FP 50 μg BID, although it did not achieve statistical significance. This same trend was evident whether the subpopulation examined was limited to only prepubescent patients, as was specified in the protocol, or an "age matched" subgroup which had been chosen for a post-hoc analysis. In the latter two cases, the decrement again did not reach the level of statitistical significance.

The "normal" growth rate for children in the age range of 4-11 years (4-9 for girls) is approximately 6 cm/year, although there is individual variation. It should be noted that the growth rates reported for both doses of FP, as well as for placebo, were within the normal range. The Serono Growth Charts provided by the sponsor (Volume 7, pp. 95-98) predict that children in this age range are mostly on a downward-sloping "plateau" in rate of change of growth, although the curve is relatively flat for both sexes around age 8, approximately the mean age for children entered into this study. The growth effect noted above persisted in a dose-related manner in spite of a post-hoc adjustment for age performed by the sponsor.

GROWTH IN CM OVER ONE YEAR: FLD220

	Intent-to-Treat (N=325)	Prepubescent (N=268)	Age-matched (N=141)
Placebo	6.39	6.15	6.07
FP 50 μg BID	6.11	5.94	5.84
FP 100 μg BID	5.66*	5.73	5.66

* p=0.034 vs placebo

As stated above, the changes in linear growth rate observed in these children were paralleled by similar changes in skeletal age. There was a statistically significant difference in skeletal age between placebo and FP 100 μg BID which was not entirely explained by differences in chronological age. This difference persisted even when corrected for prepubertal patients only (see table below). The technique for establishing bone age radiographically is complex but well-validated (see discussion in section 8.1.5.3.2), and therefore provides a useful substantiation of the stadiometry data.

MEAN CHANGE IN SKELETAL AGE RELATIVE TO CHRONOLOGICAL AGE AT 52 WKS: FLD220

	Intent-to-Treat ΔBone age	Prepubescent ΔBone age	ΔChronological Age
Placebo	1.18 yrs	1.13 yrs	1.03 yrs
FP50	1.19 yrs	1.13 yrs	1.02 yrs
FP100	0.95 yrs*	0.95 yrs**	0.89 yrs

* p=0.008 vs placebo
** p=0.048 vs placebo

In conclusion, it is reasonable to conclude that the decelerating growth rates observed in this study which involved both linear growth as well as skeletal age were a

consequence of study medication, fluticasone propionate via Diskhaler, rather than alterations in demographics such as chronological age or solely as a consequence of the disease process, asthma. Although the differential dropout of unstable asthma patients in the placebo arm may have biased the results somewhat against FP, even the age-matched case control analysis suggested a growth effect. The difference in linear growth between placebo and FP 100 μg BID was small, <1 cm over one year (0.66 cm), although statistically significant. The mean overall growth rates for each group did remain within the normal range, which is approximately 6 cm per year.

The sponsor has also cited a report from the literature in which 6 severely asthmatic children between the ages of 4 and 10 years were treated with high doses of FP via Diskhaler, ≥1000 μg/day. These children attended an asthma clinic in the UK and had been switched to FP for purposes of better asthma control. All 6 of these children had been managed on ≥800 μg/day of BDP or BUD, and were then switched to FP at 1000-2250 μg/day. Growth retardation was noted in each of these children, who were secondarily screened for biochemical evidence of adrenal insufficiency (see 10.5.1 below). There was no evidence of increase or change in the use of oral corticosteroids during the period of time when FP was used. One 7 year old boy was switched from BUD at 2000 μg/day to FP via Diskhaler at 1500 μg/day. He was noted to have decreased growth velocity over the subsequent year. His growth rate had returned to normal 9 months after his dose of FP was reduced to 500 μg/day. (*Todd et al; "Growth and adrenal suppression in asthmatic children treated with high dose of fluticasone propionate"; Lancet 348:27, 1996).*

Certainly this report should not be given the same consideration as a controlled clinical trial, but treated more as 6 adverse events from the literature. The doses of fluticasone reported were vastly in excess of the doses proposed by the sponsor, and the apparent impact on growth was reversible with reduction in total daily dosage in the one case where it was examined. This report supports the assertion that FP does have a dose-related impact on linear growth rate, and should therefore, like all corticosteroids, be used in the lowest possible dosage which controls the disease. This report could be used to argue that FP may have a more powerful growth suppressive effect than alternative inhaled corticosteroids. However, in the two clinical trials where this was examined, FLIS02 and FLIP51, FP in doses equivalent to BDP or BUD did not appear to produce a greater impact on growth as measured by knemometry. Although unconventional technology was used to measure growth, and both studies were brief in duration, the data generated are still more interpretable than case reports or adverse event reports.

10.4 Adverse Events

Below is a tabulation of any adverse event which occurred at a frequency exceeding 5% in any of the three treatment groups. Dysphonia and oropharyngeal candidiasis, which occurred at a frequency <5%, are also included since they are expected adverse events associated with long-term inhaled corticosteroid use. Adverse events recorded during administration of other dosage schedules of FP Diskhaler have all been pooled in the final column. Adverse events which occurred in an active treatment group

at an overall frequency ≥2% above the placebo rate have been highlighted. Note that tonsillitis is included in this list, because its incidence differed between placebo and FP 100 μg BID active treatment by ≥2%. Adverse events are grouped by organ system in the order of frequency of occurrence.

TABLE OF ADVERSE EVENTS, FP DISKHALER

Adverse Event (N)	Any FP Disk. (1173)	Placebo (352)	FP 50 μg BID (541)	FP 100 μg BID (346)	Other FP Disk. (286)
Any event (%)	724 (62)	227 (64)	330 (61)	235 (68)	159 (56)
Respiratory	504 (43)	175 (50)	216 (40)	173 (50)	115 (40)
upper resp. infection	191 (16)	72 (20)	88 (16)	79(23)	24 (16)
asthma	171 (15)	52 (15)	68 (13)	41 (12)	62 (22)
cough	153 (13)	54 (15)	51 (9)	62 (18)	40 (14)
influenza	50 (4)	17 (5)	26 (5)	17 (5)	7 (2.4)
wheezing	54 (5)	4 (<1)	21 (4)	19 (5)	14 (5)
bronchitis	30 (3)	14 (4)	11 (2)	16 (5)	3 (1)
dyspnea	37 (3)	1 (<1)	8 (1)	13 (4)	16 (6)
Ear, Nose, and Throat	362 (31)	113 (31)	158 (29)	137 (40)	67 (25)
rhinitis	110 (9)	32 (9)	41 (8)	43 (12)	26 (10)
pharyngitis	128 (11)	37 (11)	62 (11)	54 (16)	12 (4)
sinusitis	69 (6)	42 (12)	31 (6)	36 (10)	2 (1)
otitis media	56 (5)	25 (7)	27 (5)	19 (5)	10 (3)
nasal congestion	57 (5)	17 (5)	29 (5)	22 (6)	6 (2)
nasal discharge	40 (3)	11 (3)	16 (3)	16 (5)	8 (3)
tonsillitis	12 (1)	3(1)	6 (1)	6 (2)	0 (0)
dysphonia	13 (1)	0 (0)	6 (1)	3 (1)	4 (1)
Miscellaneous	164 (14)	42 (12)	75 (14)	56 (16)	33 (10)
fever	119 (10)	33 (9)	54 (10)	42 (12)	23 (8)
Neurological	101 (9)	37 (11)	48 (9)	38 (11)	15 (5)
headache	75 (6)	30 (9)	35 (6)	33 (10)	7 (2)
Gastrointestinal	129 (11)	44 (13)	59 (11)	46 (13)	24 (8)
nausea and vomiting	66 (6)	19 (5)	23 (4)	25 (7)	8 (3)
oropharyngeal candidiasis	8 (1)	0 (0)	3 (<1)	2 (<1)	3 (1)
Ophthalmological	55 (5)	9 (3)	19 (4)	15 (4)	21 (7)
conjunctivitis	38 (3)	8 (2)	10 (2)	9 (3)	17 (6)

The increased incidence of dyspnea and wheezing among the treated population relative to placebo is notable, although reports of these problems are not unexpected in the patient population studied, and these events did not lead to study withdrawal. There were also increased reports of rhinitis, tonsillitis, and URI among the FP 100 μg BID relative to placebo, although averaged over all exposure groups, there was no difference. Two expected side effects of long-term inhaled corticosteroids, oropharyngeal candidiasis and dysphonia, were only present among the active treatment groups, although at a relatively low frequency.

Reviewer's Comment: It should be noted that this table represents a composite of 14 clinical trials of differing design and duration, from 15 days to one year, and that not all of these trials were placebo controlled. The numbers reported therefore do not represent a true incidence, and comparability of absolute numbers is also open to some question. The sponsor has used this reasoning to exclude the one year trial FLD220 from the table constructed for labeling purposes (see below, under "11.0 Label Review")

10.4.1 Deaths, Serious Adverse Events, and Withdrawals

There were no deaths recorded in the pediatric DPI trials submitted in support of this NDA. The sponsor reports that 16 deaths have occurred in pediatric patients participating in other clinical trials of FP. Fifteen of these events occurred during one study, FLIL99, which is an ongoing study of premature infants conducted in the UK, where FP MDI is given in high doses for prevention of broncho-pulmonary dysplasia of prematurity. Of the 15 deaths, 11 had received placebo and 4 had received FP MDI. If anything, these data are suggestive of efficacy, not of a safety concern. There was one additional death reported, which occurred two months following the completion of study FLIT40, which was a non-US study comparing BDP via MDI to FP MDI. The child had been randomized to the BDP rather than FP MDI arm, and died approximately 2 months after the completion of the trial as the result of an asthma exacerbation.

The 120 day safety update submitted 23 January 1997 added an additional 3 deaths to this list, all of which occurred in the aforementioned study FLIL99. All three were in the placebo group.

The patients withdrawn from treatment with FP Diskhaler due to an adverse event are tabulated below. Overall, few patients withdrew from study treatment due to an adverse event, only a total of 41. The highest rate of withdrawal due to an adverse event occurred in the placebo group, 20 (6% of the placebo group). The most frequently reported adverse events that caused withdrawal were asthma exacerbation, wheezing, and URI, which together accounted for 29 withdrawals. Each of the 11 other reasons were recorded only once, and are tabulated below. There were 5 patients who withdrew for reasons which may have been related to the systemic or local effects of the corticosteroid.

These included oropharyngeal candidiasis, development of a cataract, increase in intraocular pressure ("glaucoma"), dysphonia, and weight gain.

WITHDRAWALS DUE TO ADVERSE EVENTS IN COMPLETED DPI TRIALS

	Placebo	FP 50 µg BID	FP 100 µg BID	Other FP DPI
Number of Exposures	352	541	346	286
Withdrawals due to AE N (%)	20 (6%)	7 (1%)	10 (3%)	4 (2%)
Asthma	14	4	4	2
URI	2	0	1	-
Wheezing	1	1	0	-
Cough	1	0	0	-
Rhinitis	0	0	1	-
Chicken Pox	1	-	-	-
Allergic Reaction	-	1	-	-
"Pneumopathy"	-	1	-	-
Weight Gain	-	-	1	-
Cataract	-	-	1	-
Glaucoma	-	-	1	-
Oral Candidiasis	-	1	1	-
Hepatitis	1	-	-	-
Tonsillitis	-	-	-	1
Dysphonia	-	-	-	1

The overall numbers of patients who experienced serious adverse events in completed DPI Diskhaler trials was very small, and is given in the table below by treatment group. Most of the serious AEs were respiratory in nature and not unexpected among this patient population. There did not appear to be any serious events attributable to the local or the systemic effects of corticosteroids.

SERIOUS ADVERSE EVENTS OCCURRING IN COMPLETED DPI TRIALS

	Placebo	FP 50 µg BID	FP 100 µg BID	Other FP DPI
Number of Exposures	352	541	346	286
Number with Serious AE	5 (1%)	7 (1%)	3 (!%)	7 (2%)
asthma	3	2	2	2
pneumonia	1	0	0	1
wheezing	0	2	0	0
fever	0	0	0	2
appendicitis	0	1	1	1
abdominal pain	0	0	0	1

Among the ongoing DPI trials, an 8 year old boy with a prior history of depression apparently developed psychotic symptoms and attempted suicided by jumping out of a 2nd story window. There were no other serious adverse events

occurring which could be produced as a manifestation of systemic corticosteroids. The child recovered with appropriate medication.

10.4.2 Adverse Events: Literature and Post-marketing Surveillance

The sponsor has compiled a list of pediatric adverse events from the literature published between May, 1994 and July, 1996. Events occurring prior to May, 1994 were included in NDA 20-549, FP Diskhaler for patients age 12 and older. This event compilation includes no surprises. There were 6 reports of growth retardation associated with adrenal suppression, discussed in more detail in the "Growth" and "Laboratory" sections of this review. Additionally, there were 3 reports of unintentional, asymptomatic, chronic overdoses of FP in children age 5 months to 4 years. There were 2 reports of Cushing's syndrome developing in children who were receiving FP at 500 μg BID, which is 5 times the proposed label's dose. There was one report each of acute psychotic reaction, hypothermia, and anorexia associated with FP via Diskhaler at doses of 100 μg BID or greater. In each of these cases, except for the chronic overdoses, the events reported could be attributable to systemic effects of corticosteroids.

There were two reports of worsening of symptoms associated with inadequate delivery of FP. It is not entirely clear from the material provided whether this was device failure or incorrect device usage. One event resolved with systemic corticosteroids, asthma remained "difficult to control" in the second case.

10.5 Laboratory Analysis

10.5.1 HPA Axis Abnormalities HPA Axis Abnormalities

The sponsor has submitted data from the 11 clinical trials in which some measure of HPA axis function was performed. Only three of these studies, FLD220, FLIP20, and FLIS02, incorporated placebo arms or ICS-free periods, where baseline measurements could be established, and are therefore interpretable. Two types of HPA axis measurements were used, the relatively insensitive and nonspecific plasma cortisol level, and the much more sensitive, but perhaps less clinically predictive, urinary cortisol excretion rate.

FLD220 was a one year parallel group study of 325 asthmatic children who were randomized to receive one of two doses of FP, 50 or 100 μg BID, or placebo. Approximately half of the children were receiving ICS at screening, which was "washed out" during the two week lead-in period. Urinary cortisols were measured after this washout. AM cortisols were measured at screening, and would therefore be expected to reflect antecedent medication. No significant differences were found between treatment groups, or compared to baseline, with regard to AM cortisol. However, 12-hour urinary cortisol excretion corrected for creatinine did show a dose related decrement compared to baseline, although there was no statistical difference across groups.

FLIP 20 was a 12-week parallel group study of 268 asthmatic children, who were not receiving ICS at baseline, who were randomized to receive either placebo or FP 50 μg BID. The subgroup of 112 patients who were selected for plasma cortisol determinations showed no significant difference between values measured at baseline compared to study endpoint.

FLIS02 was a 3-period, 3-way crossover trial with 15 day treatment periods, each separated by 15 days for ICS "washout" to occur. There were two arms, FP 100 μg BID or BUD 100 μg BID or placebo or FP 200 μg BID or BUD 200 μg BID or placebo. 24-hour urinary free cortisol was measured following each 15 day period. Compared to placebo, each of two doses of FP as well as the higher dose of BUD resulted in significantly lowered excretion of cortisol corrected for creatinine.

As noted above, the remainder of the trials submitted had no placebo group, and often patients were managed on ICS, or even systemic steroids, at baseline. These trials are of limited utility. For the most part, random serum cortisols remained within the normal range, although there were scattered reports of apparently asymptomatic low cortisol levels, indicating that FP, like other inhaled corticosteroids, may lead to adrenal suppression in the susceptible individual. In support of this statement, a review of the literature disclosed 6 case reports from a single article the literature (above citation, section 10.3). Six children with severe asthma who were switched to FP via Diskhaler at doses between 1000 and 2250 μg/day were reported to have developed biochemical evidence of adrenal suppression, which in one case was reversible with a decrease in dosage. These children were picked up because of growth suppression, no mention was made of any symptoms of adrenal insufficiency.

In conclusion, at least two of three placebo controlled clinical trials in which some measure of HPA axis was assessed showed a measurable effect of inhaled FP via Diskhaler on adrenal function in a dose-related manner. No tests of adrenal reserve were submitted, and the clinical significance of these findings remains uncertain. These patients all remained asymptomatic. This small but measurable effect in no way approaches the magnitude of that historically observed for systemic corticosteroids like prednisone. Very high doses of FP, in excess of 1000 μg/day, are associated with clinical adrenal suppression. These observations again support the argument that FP via Diskhaler should be used in the lowest dose which controls symptoms in the pediatric population.

10.5.2 Indices of Bone Growth and Turnover

Several biochemical tests believed to be indicative of bone growth or remodeling were assessed during clinical trials of FP Diskhaler. In particular, procollagen Type 1 C-terminal peptide and serum osteocalcin were measured as markers of bone formation and serum type-1 carboxyterminal telopeptide and urinary hydroxyproline excretion were measured as markers of bone resorption. The levels of these bone metabolism markers were highly variable throughout the

studies where they were measured, and showed no consistent pattern of change. Pathological fracture or osteopenia was not listed as an adverse event.

10.5.3 Clinical Laboratory Studies

With the exception of the changes in measures of HPA axis function discussed above, there were no clinically significant changes in laboratory studies directly attributable to drug treatment in the trials submitted as part of this NDA.

10.6 Physical Examination/Vital Signs

10.6.1 Ophthalmological Effects

Ophthalmological effects were specifically sought for the DPI FP only in study FLD220. The sponsor also references study FLI220, in which 102 children were exposed to the MDI formulation of FP at doses of 25 μg BID and 50 μg BID. All other reports under "Ophthalmological" in the Adverse Event Table below represent spontaneous reports from trial participants.

In FLD220, ophthalmologic examinations, including intraocular pressure (IOP) and slit lamp for posterior subcapsular cataracts (PSC), were performed by at baseline and at Weeks 4, 24, and 52. A total of two patients, one in the FP 50 μg BID and another in the FP 100 μg BID group, had elevations in IOP while under treatment. A single patient in the 100 μg BID group was reported to have developed "trace" PSC in one eye after 24 weeks of treatment, after coming into the trial on previou inhaled BDP. These three events are included in the AE table below.

In FLI220, ophthalmologic examinations were performed at a baseline and at 12 weeks. In screens for elevated IOP or PSC, none were detected during treatment.

In conclusion, there appears to be a small (<1%) but measurable incidence of corticosteroid-associated ocular abnormalities in children dosed chronically with FP DPI via Diskhaler.

10.6.2 Routine Physical Examinations

No significant abnormalities attributable to drug treatment emerged during the clinical trials submitted as part of this NDA. Surprisingly, even the frequency of oropharyngeal candidiasis was not significantly increased in active treatment compared to control.

10.6.3 Vital Signs

No clinically significant changes in vital signs directly attributable to drug treatment emerged during the trials submitted as part of the NDA.

10.7 Drug-Drug and Drug-Disease Interactions

Oral bioavailability of FP is very low, probably due to presystemic metabolism by CYP3A4 in gut and liver. In theory, therefore, an inhibitor of CYP3A4 might increase the systemic bioavailability of FP, leading to greater systemic toxicity related to the predictable pharmacologic properties of this class of drugs. Within the submission, the sponsor includes data relevant to FP interactions with theophylline, terfenadine, salmeterol, and the macrolide antibiotics erythromycin and clarithromycin. At the request of the biopharmacology reviewer, the sponsor has submitted three additional studies to ascertain the potential interaction between FP and ketoconazole (FLTB1003), FP and terfenadine (GDM/96/025), and FP and erythromycin (FLTA1001).

FLTB1003 was a randomized, double-blind, placebo-controlled, two-way cross-over study in healthy male (n=4) and female (n-4) volunteers. These eight participants were dosed with 1000 μg FP via inhalation or placebo with and without co-administered ketoconazole, 200 mg by mouth. The pharmacokinetic and pharmacodynamic studies which followed demonstrated that FP plasma concentrations were approximately 3.3 times higher when FP was administered with ketoconazole. In addition, repeated dosing with ketoconzole lead to a statistically significant effect of FP on 24 hour plasma cortisol ($AUC_{24,cort}$), plasma cortisol being less in the ketoconazole treated group compared to placebo. Based on the data from this study, the increase in plasma concentrations of fluticasone propionate when co-administered with ketoconazole can be expected to increase the likelihood of HPA axis suppression on therapeutic doses of inhaled FP.

FLTA1001 was a randomized, double-blind, two-way cross-over study in healthy male (n=3) and female (n=5) volunteers. These eight participants received 500 μg BID of FP via MDI or matching placebo with or without co-administered erythromycin base, 333 mg TID by mouth. The pharmacokinetic profile of FP was followed out to 12 hours and pharmacodynamic behavior of plasma cortisol was followed for 24 hours. No statistically significant effects on FP systemic exposure were seen with coadministration of erythromycin. In addition, there was no significant effect on plasma cortisol concentrations or urinary cortisol excretion. Based on the results of this study, there seems unlikely to be a clinically significant interaction between the CYP3A4 inhibitor erythromycin and FP.

Corroborating this study is the sponsor's reveiw of the adverse event profiles of those patients who were co-administered FP and either one of the two macrolide antibiotics erythromycin or clarithromycin during the controlled clinical trials of FP DPI. Although fewer than 30 patients received FP or either one of these two drugs concomitantly, these patients had no greater incidence of adverse events than those who received FP alone.

Study GDM/96/024 was an *in vitro* investigation into potential FP-terfenadine cytochrome P450-3A4 interactions in human liver microsomes. The metabolism of FP to its major metabolite GR36264 was examined in the presence or absence of varying concentrations of terfenadine (ketoconazole was the positive control). Although terfenadine exhibited competititve inhibition of FP metabolism with increasing dose, the K_i for this interaction was nearly 100-fold more than the C_{max} of terfenadine following an oral dose of 60 to 120 mg. Similarly, FP exhibited competitive inhibition of the

metabolism of terfenadine to hydroxyterfenadine with a mean K_i which was nearly 1000-fold higher than the C_{max} of FP following a 1 mg inhaled dose. Based on these results, the sponsor concluded that a clinically significant interaction between these two agents was unlikely, certainly under normal dosing conditions. As pointed out by the biopharmacology reviewer, however, the sponsor did not test the potential of any of the metabolites of the parent compounds to inhibit the other agent, and these metabolites could have lower K_i's, which approach the therapeutic serum levels of the parent compounds. However, this scenario is extremely unlikely *in vivo*. In conclusion, there is no scientific evidence to suggest that a clinically significant interaction between FP and terfenadine may exist.

The sponsor corroborated the *in vitro* study by evaluating the adverse event profile of patients enrolled in the FP DPI controlled clinical trials who took FP and terfenadine concomitantly. Although very few patients met these criteria, they reported no unusual adverse events, such as cardiac symptoms or signs of hypercortisolism, suggestive of a clinically significant interaction.

With regard to theophylline, this drug is processed by CYP1A2, and it's serum levels are therefore unlikely to be increased by co-administration of FP, or vice versa. No formal pharmacokinetics studies were performed. The sponsor examined the adverse event profile of children enrolled in the two pivotal trials, FLD220 and FLIT85, who were concomitantly treated with FP and theophylline. The overall occurrence rate of AEs was similar between theophylline/placebo and theophylline FP. The rate of "headache" as a specific AE was higher in the FP/theophylline groups (38%) compared to the placebo/theophylline group (18%). Serum theophylline levels were not performed.

With regard to the potential drug interaction between FP and salmeterol, both drugs are metabolized by CYP3A4 but neither is known to be an inhibiter. Formal pharmacokinetics studies were not conducted, and the adverse event profile in the controlled clinical trial and adverse event databases did not indicate any significant interaction clearly attributable to co-administration of these two drugs.

In conclusion, there is a documented pharmacokinetic and pharmacodynamic interaction between FP the CYP3A4 inhibiter ketoconazole leading to increased serum levels of FP and decreased serum cortisol AUC. The product labeling should reflect this potentially clinically significant interaction. This is in contrast to another CYP3A4 inhibitor, the macrolide antibiotic erythromycin, which does not demonstrate such an interaction. Terfenadine, which is metabolized by 3A4 but does not significantly inhibit it, is unlikely to have a clinically significant interaction with FP, based on the *in vitro* studies submitted by the sponsor.

With regard to drug-disease interactions, the incidence and severity of chicken pox was examined using the clinical trials database. Compared to placebo, children who received FP had no increased risk of acquiring chicken pox, and there was no case which resulted in a serious adverse event.

10.8 Long-term Adverse Effects

The safety profile of FP Diskhaler was evaluated by tabulating adverse events

occurring after 120 days of treatment. There was an increased incidence of dysphonia, pharyngitis, and oropharyngeal candidiasis which emerged among the FP patients compared to placebo. There were no significant new or unexpected adverse events with long-term use.

10.9 Overall Safety Conclusions

Safety data from 11 FP DPI pediatric studies and supportive safety data from 3 FP MDI pediatric studies show that Flovent Rotadisk Inhalation Powder via Diskhaler administered at dosages of 50 μg BID and 100 μg BID is well tolerated in children 4-11 years old. For the most part, the safety profile for these pediatric patients was similar to that observed in the adult/adolescent population, and tended to be what was expected of an asthmatic population. There did emerge one issue which is unique to this pediatric patient population, growth, and a second issue, a potential interaction with the drug ketoconazole, which is also metabolized by the CYP3A4 system, which should be reflected in the product labeling.

As noted earlier in this review, in the discussion of clinical trial FLD220, there was a statistically significant but clinically small decrement in growth rate among children treated with FP 100 μg BID compared to placebo in the intent-to-treat population. A non-significant trend was also evident among the children treated with the lower dose, FP 50 μg BID. These results were corroborated by bone age studies. The magnitude of this decrement is small, under 1 cm/year at the higher dose, and its overall longterm significance on adult stature may be counterbalanced by an improvement in asthma control and hence overall quality of life in the FP-treated children. The decision to use FP must be individualized, and the lowest possible dose which can control the disease ought to be used.

With regard to drug interactions, because FP is metabolized by CYP3A4, it is clear that the CYP3A4 inhibiter ketoconzole can raise serum FP levels and secondarily lead to depressed 24-hour serum cortisol AUC. Because the impact of FP on growth in children appears to be dose-related, and evidence of systemic hypercortisolism does appear at higher than the recommended does of this agent, HPA axis suppression or other indices of systemic hypercortisolism could emerge at doses of FP that are within the labeled range. In addition, there are rare patients who appear to be unusually sensitive to the systemic effects of inhaled corticosteroids. Co-administration of FP with ketoconazole could worsen the problem. Unfortunately, there does not appear to be any way to prospectively identify these individuals.

In conclusion, FP via Diskhaler in the dose proposed by the sponsor appears to be safe, with an adverse event profile which is monitorable and which can be incorporated into product labeling.

11.0 STUDY AUDIT

Two investigators participating in clinical trial FLD220 were selected for audit, Dr. Mark Vandewalker (Rolla, Missouri) and Dr. Michael Lawrence (Taunton, Massachusettes), based primarily upon total numbers of patients studied. Although the

field inspectors found some minor departures from FDA regulations and/or accepted clinical investigaitional practice, no serious violations were uncovered which might jeopardize conclusions concerning the safety or efficacy of Flovent Rotadisk inhalation powder administered via Diskhaler.

12.0 LABEL REVIEW

12.1 General Comments about the Sponsor's Proposed Package Insert

The sponsor has submitted draft labeling for Flovent Rotadisk inhalation powder, pediatric indication, and has presented it in two separate columns. The left-hand column contains labeling for the indication of maintenance treatment of asthma as prophylactic therapy in adults and adolescents 12 years of age and older. This labeling incorporates information from the approved product Flovent Inhalation Aerosol (NDA 20-548) as well as Flovent Rotadisk inhalation powder (NDA 20-549, under review in this division). The right-hand column contains the proposed additions and revisions to incorporate a pediatric claim, and includes information from the two pivotal trials, FLD220 and FLIT85, discussed in this document. The pediatric revisions have been incorporated to generate a single package insert, which is reviewed below.

The review of this proposed package insert has been divided into two sections. First is the "General Comments" section, containing the rationale for the proposed revisions. This is followed by a "strike-out" review, containing the specific, recommended changes.

General Comments:

- Under the **Pharmacodynamics** subheading of the **CLINICAL PHARMACOLOGY** section, it is stated that overnight urinary excretion of cortisol and 17-hydroxy-corticosteroid was not significantly different across treatment groups when 325 children were dosed with placebo or 50 or 100 μg fluticasone propionate twice daily for one year. We suggest that some additional information be provided regarding the total number of patients in each treatment arm who were found to have abnormal results. Comparing the mean excretion rates of these two corticosteroids across treatment arms could dilute a true impact of the medication in a small number of patients, and this information is potentially of value to clinicians in determining risk:benefit, or in increasing vigilance for possible corticosteroid-related adverse events. The suggested wording has been inserted in the text of the package insert which follows this section. Although not required, HPA axis data from the clinical trial FLIS02 could also be included in this section, since a significant difference in 24-hour urinary cortisol excretion was found between the placebo group and the groups administered fluticasone propionate at 100 or 200 μg BID, or budesonide at 200 μg BID, and FP 100 μg BID is within the labeled range of the product for children.

- Also within the **CLINICAL PHARMACOLOGY** section, under the **Special Populations** subheading, reference is made to the pharmacokinetic study conducted as a part of the pediatric trial FLD220. The subset of children studied were found to have a

higher mean and peak fluticasone propionate level when compared to adults when both are dosed at 100 μg BID, and this should be reflected in the labeling.

- Under the **Clinical Trials** subheading of the **CLINICAL PHARMACOLOGY** section, spirometry results from FLD220 have been used to construct a figure showing improvement in lung function (FEV_1) over one year. The primary objective of FLD220 was safety, and in particular the change in rate of linear growth over one year, not efficacy, which was a secondary endpoint. If the sponsor wishes to include a figure showing change in FEV_1 over time in children, the results of a trial such as FLIT85, which had improvement in lung function as a primary endpoint, should be used. Alternatively, if the sponsor chooses to use results from study FLD220 to support an efficacy claim, the figure should display *Survival in Study* versus *Time,* since this was a primary endpoint, although reported for reasons of safety rather than efficacy.

- Under the **General** subheading of the **PRECAUTIONS** section, the sponsor should incorporate information concerning the pharmacokinetic and pharmacodynamic interaction between ketoconazole and fluticasone propionate. In a clinical trial of 8 normal volunteers, co-administration of these two drugs lead to a sustained increase in FP levels in the blood, and a concomitant decrease in plasma cortisol levels. Alternatively, this interaction could be described separately under a "drug-drug interactions" section, which the insert presently lacks. Also in the "drug-drug interactions" section, we suggest that a sentence describing clinical study FLTA1001, which showed a *lack* of a pharmacokinetic interaction between FP and the CYP3A4 inhibitor erythromycin, be included.

- Also under the **General** subheading of the **PRECAUTIONS** section, after the fifth paragraph starting with "A reduction of growth velocity in children...", the sponsor has inserted a sentence claiming a lack of effect on growth of inhaled FP given at 50 or 100 μg twice daily over one year, referring to the results of clinical trial FLD220. This assertion is inaccurate. The sponsor should include a statement acknowleding that growth effects do occur, and to quantitate them, that is, that the observed decrement in growth rate was 0.66 cm/year at doses of fluticasone propionate of 100 μg BID administered over a one year period. It is also reasonable to point out that although a negative impact on growth was observed, the growth rates of the children who were receiving FP were nevertheless within the normal range for their age. The sponsor may also wish to include a discussion of corroborative findings such as delayed skeletal age advancement, as measured radiographically. It should also be stated that the long-term impact of these findings on adult stature remains unknown, that the risk-benefit must be determined for each individual patient, and that the lowest possible dose which controls the disease should be utilized.

- Under the **Pediatric Use** section, the sponsor proposes to insert the phrase "Although doses of 50 and 100 μg FP inhalation powder twice daily were without significant effect

on growth in children aged 4 to 11 years..." This statement is inaccurate and should be excluded, based on the information from clinical trial FLD220.

- Under the **ADVERSE REACTIONS** section, a table displaying the overall adverse experiences with >3% incidence in controlled clinical trials was amended by the sponsor to incorporate events experienced by pediatric patients age 4 years and older. The following adverse events also occurred at an incidence exceeding 3% among pediatric patients age 4-11 and should therefore be included, but not necessarily in tabular form. It would be acceptable to include them as text under the **ADVERSE EVENTS** heading, noting that these particular events were found to occur more frequently in the pediatric population.

ADVERSE EVENT	Placebo n=352	Flovent 50 µg BID n=541	Flovent 100 µg BID n=346
cough	15%	9%	18%
dyspnea	<1%	1%	4%
nausea and vomiting	5%	4%	7%

- Also under **ADVERSE EVENTS,** the section describing systemic glucocorticoid effects reported in controlled clinical trials should be modified to reflect the occurrence of one episode each of abnormal weight gain, posterior subcapsular cataract, and glaucoma in study FLD220. Each of these events lead to study withdrawal by the affected patient.

- Under the **DOSAGE AND ADMINISTRATION** section, the recommended starting dose for children age 4 to 11 years who are presently managed on inhaled corticosteroids now reads 50-100 µg twice daily. Because of dose dependent side effects, we believe this should read "50 µg twice daily."

Cc:
HFD-570 (NDA 20-770, NDA 20-548, NDA 20-549, Division File)
HFD-570/Purucker/Clin
HFD-570/Meyer/Clin
HFD-570/Barnes/CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20549 AND 20770

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA #: 20-770 MAY 31 1997

Applicant: Glaxo Wellcome

Name of Drug: Flovent (Fluticasone Propionate) Rotadisk Inhalation Powder

Indication: Asthma

Documents Reviewed: Volumes 1.1, 1.7, 1.35 dated September 26, 1996 and amendments with data diskettes dated December 2,1996; January 2, 1997; and January 17, 1997; a fax dated January 31, 1997;and an amendment dated February 12,1997.

This review pertains to two studies of fluticasone propionate in children 4-11 years of age.

The medical officer for this submission is Mary Purucker, M.D. (HFD-570), with whom the review was discussed.

I. Background

This reviewer requested more data from the sponsor to aid in his statistical review. The sponsor provided the data diskette containing height velocity data from study FLD-220 and diary data from study FLIT-85 in their December 2, 1996 submission.

This reviewer could not duplicate some of the analyses of FLIT-85 from the data diskette provided on December 2, 1996. The sponsor discovered that the data diskette provided on December 2, 1996 was incorrect. They provided a new diskette in their January 17, 1996 submission. The sponsor explained the error as a coding problem. This reviewer could still not generate the p-values for PEFR data from the data diskettes provided. There were numerous telephone conversations with the sponsor that were needed to resolve these problems.

This reviewer also requested two additional analyses from the sponsor. One was to provide growth data from pubescent patients in FLD-220. This information was provided in a fax from the sponsor on January 31, 1997. The other was an analysis of Week 1-12 diary data from FLIT-85. These later analyses were requested because the protocol stated that these analyses were to be provided whereas the sponsor only provided analyses by week. Significance of the Week 1-12 analyses would confirm that the sponsor did not provide the weekly analyses because the overall analyses failed to demonstrate significance. The Week 1-12

analyses was provided in the February 12, 1997 submission.

II. Study FLD-220

A. Study Description and Method of Analysis

This was a randomized, double-blind, parallel group study with a 52 week treatment period comparing fluticasone propionate (FP) 50 mcg BID, FP 100mcg BID and placebo in children 4 to 11 years of age having asthma. It was mainly a safety study to assess how chronic treatment with fluticasone would affect the children.

The study entered males 4 to 11 and females aged 4 to 9 years. The primary efficacy variable, as stated in the protocol, was height velocity. The sponsor calculated that a sample size of 120 patients per treatment group would provide 80% power of detecting a 1.00 cm/year difference in height velocity, assuming a standard deviation of 2.7 cm/year and a completion rate of 75%. In the study that generated the above estimates, males 6-11 years old had a height velocity of about 1.9 cm/year, whereas females 6-11 years old had a height velocity of 0.2 cm/year. [The height velocity estimates for females seems incorrect. This estimate was found, however, in both the sponsor's study report and study protocol.] The sponsor did not state what the ratio of males to females was expected to be in the present study. The sponsor also did not state how non-completers were being factored into these computations. [One would be led to assume that they were being excluded.]

On-treatment clinic visits were at weeks 1, 2 and 4 and every 4 weeks afterwards to week 52.

The sponsor proposed to analyze height and rate of growth at each visit.

The sponsor, also, analyzed FEV_1, survival in the study without dropping out for lack of efficacy and physician global assessments. The physician made assessments of the patient treatment at baseline and weeks 12, 24, 36 and 52 using a 4-point scale (0=ineffective, 1=satisfactory, 2=effective, 3=very effective.)

The sponsor did not state explicitly in the protocol what methods of analysis would be used. The protocol stated that estimates would be adjusted for baseline differences. [There was no indication that baselines were adjusted for in any of the sponsor's analyses. The sponsor did, however, analyze changes from baseline.]

The sponsor analyzed changes from baseline in height, FEV_1, and growth velocity with an analysis of variance with factors

treatment, investigator and treatment-by-investigator interaction. The sponsor used SAS Proc Lifetest for the survival (in the study) analysis. Global assessments were analyzed by a Cochran-Mantel-Haenszel test using investigators as strata and Scores=modridit. The sponsor reported the general association p-value. [This reviewer will report the more appropriate p-value (row means equal) in this review.]

B. Results

Three hundred twenty-five patients (106 placebo, 111 FP 50mcg BID and 108 FP 100mcg BID) were randomized into the study. There were 268 prepubescent children and 57 children who reached puberty during the study. There were 244 males and 81 females in the study. Fifty-three percent were corticosteroid-naive and 47% were classified as corticosteroid-dependent.

The treatment groups were comparable in demographic variables although numerically the FP 100mcg BID group was slightly smaller on average by 1.5 cm and younger by 4 months.

Thirty (28%) of the placebo patients withdrew from the study compared to 13 (12%) of FP 50mcg BID patients and 19 (18%) of FP 100mcg BID patients. Patients withdrawing for lack of efficacy were 20 (19%) on placebo and 4(4%) in each of the two FP groups. Both FP treatments were significantly different from placebo with respect to survival in the study (not dropping out with respect to lack of efficacy) using the logrank test ($P<0.001$).

Sponsor's Table 24 presents the mean changes from baseline for FEV_1 at the clinic visits and at endpoint. Both FP treatments were significantly different from placebo at endpoint and at about half of the clinic visits.

Sponsor's Table 27 presents the physician's assessments at baseline, Weeks 12, 24, 36 and 52, and at endpoint. FP 100mcg BID showed significant better physician assessments than placebo at all on-treatment assessment times (Weeks 12, 24, 36, and 52). FP 50mcg BID showed significantly better assessments than placebo only at Weeks 24 and 52.

Sponsor's Table 30 presents the mean changes from baseline for height at the clinic visits. After week 24, a dose response linear trend was seen in the treatment means. At week 52, the FP 100mcg BID group showed significantly less growth than the placebo group. This effect on height is also apparent in the analysis of growth velocity at Week 52 (Sponsor's Table 32).

If the pre-pubescent completers are separated into two groups depending whether they are steroid dependent or steroid naive, the dose response ordering in changes from baseline in height is

not so clear cut (Sponsor's Tables 48 and 49). Among the steroid naive completers, FP 50mcg and FP 100mcg groups showed comparably less growth than placebo. Among the steroid dependent pre-pubescent completers, growth of all three groups were comparable, with greater growth in the FP 50mcg group than in the other two groups.

Sponsor's Table 36A shows the mean growth velocities for the pubescent patients. Although the sample size is small, numerically the growth velocity of the FP 100mcg BID group is the lowest.

C. Reviewer's Comments

Although this was mainly a safety study, both doses of FP showed more efficacy than placebo in FEV_1, survival in the study and physician assessments. Although the sponsor did not specify a primary analysis for these variables, or specify how the multiple comparison issue would be handled, the results presented demonstrate efficacy.

The sponsor's sample size discussions seem to indicate that males and females might be expected to have greatly different growth velocities. Such was not the case in this study.

The results for height showed that FP affected growth, especially in pubescent patients and pre-pubescent steroid naive completers. An effect on steroid dependent pre-pubescent completers was not seen. Their growth may have already been affected by previous steroid usage.

III. Study FLIT-85

A. Study Description and Method of Analysis

This was a multi-center, randomized, double-blind, placebo controlled study with a two week run-in period and a twelve week treatment period.

Patients recorded their peak flows on rising and on retiring in a diary. They also recorded daily scores for the level of symptoms during the day, during the night, and during exercise according to the following assessments:

i) How was your asthma today?
   0 - Very Well, no asthma, unrestricted activity
   1 - Mild asthma symptoms or wheezing or short of breath e.g. on exercise/hurrying- otherwise asthma not troubling
   2 - Asthma troublesome but able to carry out most daily activities

/

3 - Asthma bad, unable to carry out daily activities as normal e.g. unable to go to school.

ii) How much could you do today? (Scored at night)
0 - Walk, run and able to play games with no problems
1 - Walking no problem, but felt slightly wheezy and breathless when running and playing.
2 - Slightly breathless and wheezy when running, playing
3 - Very breathless, tight-chested and wheezy when walking. Unable to run and play games.

iii) Number of night time awakenings

iv) Patients recorded the number of ventodisks/rotocaps that they needed to use on a daily basis.

Diary data including PEFRs were analyzed by averaging over a week of assessments. If a patient took beta agonist medication within 4 hours of assessment, that day was not included in the weekly average. [This is consistent with what was done in the Flovent MDI studies in adults.]

Baseline for the diary data was the average of the 10 days before treatment.

The response variables AM PEFR and PM PEFR were analyzed as changes from baseline by an analysis of covariance with factors treatments, countries, treatment-by-country interaction, age and baseline value. [This reviewer found out that he could get similar results as the sponsor by entering age using the CEIL function of SAS. This function uses the smallest integer larger than or equal to the age of the patient. Age was still handled as a numerical covariate as opposed to being a classification variable.]

Other diary card variables were analyzed as changes from baseline using a van-Elteren test stratifying for country.

Rather than providing the number of puffs of albuterol used or the number of awakenings, some patients wrote "Y/YES" or "N/NO". The sponsor changed these to 1 for "Y/YES" and 0 for "N/NO". This solution is reasonable. [The sponsor had used codes 8 and 9 for these cases. That was the coding error in the data set originally sent to this reviewer. Analyses on the data set coded in that way would give inaccurate results.]

Endpoint analysis corresponds to the last week of diary data. This may be different than the last weekly value.

B. Results

There were 264 patients randomized into the study. One patient who was randomized did not receive treatment. The intent-to-treat population was, therefore, 263 patients (92 on placebo, 85 on FP 50 mcg BID and 86 on FP 100mcg BID). There were 29 study sites in 9 countries. Finland, Hong Kong, Singapore and United Arab Emirates were pooled because of small sample size.

There were 33 patients (36%) who withdrew on placebo compared to 11 (13%) and 5 (6%) on FP 50 mcg BID and FP 100mcg BID, respectively. Of these 15 (13 on placebo and 2 on FP 50 mcg BID) were for treatment failure.

The probability of remaining in the study over time (survival) according to pre-specified withdrawal criteria for lack of efficacy indicated that both FP groups were significantly different from placebo using a logrank test ($p<0.01$). Overall the number of patients in the efficacy population meeting the pre-defined withdrawal criteria who should have been withdrawn were 36(63%), 22(42%), and 17(29%) for placebo, FP 50mcg BID and FP 100mcg BID, respectively. [The sponsor did not do this analysis on the intent-to-treat population but used the protocol correct population, called the efficacy population.] The investigators did not follow the criteria for withdrawal appropriately as can be seen from the fact that there were only 15 treatment failure withdrawals.

The treatment groups were comparable at baseline in demographic variables and baseline efficacy variables.

Table 1 contains the treatment means and p-values comparing treatments from the endpoint analysis of the intent-to-treat population. Both Flovent treatments were effective in all 5 diary variables at the endpoint analyses.

C. Reviewer's Comments

The protocol specified the periods of analysis for the diary PEFR data would be Weeks 1-4, Weeks 5-8, Weeks 9-12, and Weeks 1-12. The study report analyzed weekly periods and endpoint. This reviewer requested that the sponsor provide the analyses of weeks 1-12 to verify that the sponsor had not chosen the endpoint analysis because the Weeks 1-12 analyses had failed to demonstrate efficacy. These analyses were provided in the sponsor's February 12, 1997 submission. Both doses of FP were significantly different from placebo for AM and PM PEFR in the Weeks 1-12 analyses.

The analysis of AM and PM PEFR is as specified in the protocol. The analysis of the other diary card variables was specified to

be a Wilcoxon Rank Sum test. The Van-Elteren test used is a blocked Wilcoxon test that stratifies by countries. This is sufficiently close to the protocol to be considered appropriate.

The reviewer was able to duplicate the sponsor's analyses after much communication with the sponsor. Since in preliminary analyses this reviewer did not obtain the sponsor's p-values, the reviewer worried that the data were inaccurate. When the issues of which investigators were in which countries, which countries were pooled, how age came into the model were settled, the reviewer was able to duplicate the sponsor's results.

IV. Overall Comments

Both studies demonstrate that both doses of Flovent are effective in pediatric patients. Both doses of Flovent were significantly different from placebo in survival in the study, endpoint FEV_1, and physician's assessment of overall condition in study FLD-220. Both doses of Flovent were significantly different from placebo in survival in the study and all endpoint diary variables in FLIT-85.

Study FLD-220 is suggestive that Flovent has an effect on growth with more effect for the FP 100mcg dose. The mean growth velocity of the FP 100 BID group was significantly less than the placebo group from baseline to Week 52. The relevance of this effect must be left to clinical judgement.

James R. Gebert, Ph.D.
Mathematical Statistician HFD-715

Concur: Dr. Wilson 5/7/97

Dr. Nevius 5/31/97

This review contains 7 pages of text and 8 pages of tables.

cc:
Orig NDA 20-770
HFD-570
HFD-570/Dr. Purucker
HFD-570/Ms. Barnes
HFD-715/Div. File
HFD-715/Dr. Gebert
HFD-715/Dr. Wilson

Table 24

MEAN CHANGE FROM BASELINE IN FEV1 (LITERS) PRIOR TO A.M. DOSE
Number of Subjects, Mean (Standard Error) of Change From Baseline
Investigator: All

	Placebo		FP50 BID		FP100 BID		Overall-[1]	Placebo vs FP50	Placebo vs FP100	FP50 vs FP100
Number of subjects	96		100		97					
Baseline[2]	96	1.65(0.04)	100	1.63(0.04)	97	1.57(0.04)	0.568	0.998	0.348	0.347
WEEK 1	95	0.01(0.02)	98	0.09(0.02)	96	0.11(0.02)	0.010	0.016	0.004	0.666
WEEK 2	96	0.00(0.02)	98	0.06(0.02)	97	0.09(0.02)	0.066	0.070	0.029	0.651
WEEK 4	95	0.03(0.02)	98	0.11(0.02)	96	0.11(0.02)	0.018	0.007	0.030	0.743
WEEK 8	94	0.04(0.02)	98	0.13(0.02)	94	0.14(0.02)	0.011	0.007	0.011	0.815
WEEK 12	90	0.01(0.02)	98	0.08(0.02)	94	0.11(0.02)	0.055	0.053	0.028	0.810
WEEK 16	85	0.00(0.03)	98	0.13(0.02)	94	0.15(0.02)	0.148	0.057	0.221	0.497
WEEK 20	85	0.07(0.03)	97	0.15(0.02)	94	0.17(0.02)	0.123	0.095	0.091	0.901
WEEK 24	82	0.05(0.03)	95	0.14(0.02)	90	0.14(0.02)	0.024	0.011	0.029	0.801
WEEK 28	79	0.10(0.03)	94	0.17(0.03)	86	0.19(0.02)	0.297	0.241	0.134	0.743
WEEK 32	72	0.10(0.03)	94	0.17(0.02)	83	0.23(0.02)	0.009	0.028	0.003	0.314
WEEK 36	73	0.15(0.02)	92	0.19(0.03)	83	0.22(0.03)	0.315	0.236	0.121	0.710
WEEK 40	72	0.19(0.03)	92	0.25(0.03)	81	0.24(0.03)	0.293*	0.124*	0.293*	0.640
WEEK 44	72	0.18(0.03)	92	0.22(0.02)	80	0.23(0.03)	0.209	0.097*	0.147	0.968
WEEK 48	70	0.16(0.02)	92	0.22(0.02)	80	0.25(0.03)	0.076	0.093	0.025	0.497
WEEK 52	70	0.13(0.03)	90	0.22(0.02)	80	0.28(0.03)	0.003	0.035	0.001	0.114
Endpoint[3]	96	0.09(0.03)	98	0.20(0.02)	97	0.25(0.03)	<.001	0.004	<.001	0.361

[1] P-values compare mean change in FEV1 and are based on the analysis of variance F-test.
[2] At baseline, comparisons are made using the actual values.
[3] Endpoint analysis is performed on the last spirometry date.
* Indicates a significant (p <= 0.05) investigator effect exists.
^ Indicates a significant (p <= 0.10) treatment-by-investigator interaction exists.

Table 27

PHYSICIAN GLOBAL ASSESSMENT
Number (%) of Subjects
Investigator: All

	Placebo	FP50 BID	FP100 BID	TOTAL	p-value [1]
Number of Subjects	106	111	108	325	
Baseline					0.578
Ineffective	6 (6%)	9 (8%)	4 (4%)	19 (6%)	
Satisfactory	59 (56%)	70 (63%)	65 (60%)	194 (60%)	
Effective	22 (21%)	20 (18%)	19 (18%)	61 (19%)	
Very effective	19 (18%)	12 (11%)	20 (19%)	51 (16%)	
Week 12					0.414
Ineffective	5 (5%)	4 (4%)	2 (2%)	11 (4%)	
Satisfactory	30 (31%)	23 (21%)	24 (23%)	77 (25%)	
Effective	40 (41%)	53 (49%)	43 (41%)	136 (44%)	
Very effective	22 (23%)	28 (26%)	35 (34%)	85 (28%)	
Week 24					<0.001
Ineffective	8 (9%)	4 (4%)	0	12 (4%)	
Satisfactory	31 (36%)	16 (16%)	17 (17%)	64 (22%)	
Effective	26 (30%)	51 (50%)	43 (44%)	120 (42%)	
Very effective	22 (25%)	32 (31%)	38 (39%)	92 (32%)	
Week 36					0.049
Ineffective	4 (5%)	4 (4%)	0	8 (3%)	
Satisfactory	24 (30%)	15 (15%)	16 (18%)	55 (20%)	
Effective	28 (35%)	47 (47%)	35 (38%)	110 (41%)	
Very effective	23 (29%)	34 (34%)	40 (44%)	97 (36%)	
Week 52					<0.001
Ineffective	5 (7%)	4 (4%)	0	9 (3%)	
Satisfactory	28 (37%)	14 (14%)	11 (12%)	53 (20%)	
Effective	21 (28%)	39 (40%)	25 (28%)	85 (32%)	
Very effective	22 (29%)	41 (42%)	53 (60%)	116 (44%)	
Endpoint[2]					<0.001
Ineffective	26 (25%)	8 (7%)	4 (4%)	38 (12%)	
Satisfactory	32 (30%)	17 (15%)	18 (17%)	67 (21%)	
Effective	24 (23%)	41 (37%)	28 (26%)	93 (29%)	
Very effective	23 (22%)	44 (40%)	58 (54%)	125 (39%)	

[1] P-values are based on the Cochran-Mantel-Haenszel test, controlling for investigator.
[2] Endpoint value is the last collected assessment.

Table 30

MEAN HEIGHT (cm.)
Number of Subjects, Mean (Standard Error)
Investigator: All

	Placebo	FP50 BID	FP100 BID	Overall-[1]	Placebo vs FP50	Placebo vs FP100	FP50 vs FP100
Number of subjects	106	111	108				
BASELINE	106 130.6(1.23)	111 130.6(1.13)	108 129.0(1.18)	0.387	0.802	0.287	0.188
WEEK 4	104 130.9(1.23)	108 130.9(1.15)	106 129.2(1.20)	0.377	0.798	0.278	0.186
WEEK 8	101 131.2(1.27)	108 131.3(1.15)	104 129.7(1.22)	0.477	0.681	0.422	0.226
WEEK 12	97 131.8(1.29)	108 132.1(1.14)	104 130.4(1.22)	0.438	0.691	0.385	0.204
WEEK 16	95 132.2(1.31)	108 132.3(1.15)	104 130.6(1.21)	0.405	0.769	0.324	0.193
WEEK 20	93 132.6(1.32)	106 132.5(1.15)	103 131.1(1.22)	0.473	0.848	0.345	0.244
WEEK 24	87 133.9(1.37)	103 133.5(1.16)	98 131.2(1.26)	0.193	0.959	0.121	0.109
WEEK 28	85 134.3(1.40)	103 133.8(1.15)	94 131.5(1.26)	0.156	0.920	0.095	0.087
WEEK 32	79 135.1(1.48)	101 134.5(1.17)	92 131.7(1.28)	0.094	0.939	0.064	0.051
WEEK 36	79 135.9(1.46)	100 135.1(1.17)	91 132.0(1.28)	0.075	0.922	0.051	0.041
WEEK 40	79 136.3(1.48)	99 135.5(1.18)	89 132.5(1.29)	0.122	0.914	0.076	0.067
WEEK 44	79 136.8(1.47)	99 136.0(1.17)	89 132.8(1.30)	0.106	0.921	0.068	0.057
WEEK 48	76 137.4(1.52)	99 136.4(1.18)	89 133.2(1.30)	0.094	0.849	0.057	0.056
WEEK 52	76 138.3(1.52)	98 137.0(1.19)	89 133.8(1.30)	0.081	0.727	0.042	0.060

[1] P-values compare mean HEIGHT and are based on the analysis of variance F-test.
* Indicates a significant (p <= 0.05) investigator effect exists.
^ Indicates a significant (p <= 0.10) treatment-by-investigator interaction exists.

AH30341 BIO$STAT_FLD:[FLD220.TABLES]HEIGHT_MEAN.SAS;1 SMBv:(01,05) 08DEC95:08:14

Table 32

MEAN GROWTH VELOCITY (cm./year)
Number of Subjects, Mean (Standard Error)
Investigator: All

	Placebo	FP50 BID	FP100 BID	Overall-[1]	Placebo vs FP50	Placebo vs FP100	FP50 vs FP100
Screening[2]	106 6.11(0.10)	111 6.15(0.10)	108 6.15(0.09)	0.882*	0.854*	0.605	0.758*
Baseline to Week 28	85 5.97(0.17)	103 5.76(0.17)	94 5.62(0.15)	0.520	0.689	0.227	0.452
Week 28 to Week 52	76 6.70(0.26)	98 6.35(0.21)	89 5.68(0.18)	0.099*	0.363	0.031	0.175*
Baseline to Week 52	76 6.32(0.17)	98 6.07(0.15)	89 5.66(0.12)	0.095	0.465	0.031	0.123

[1] P-values compare mean GROWTH VELOCITY and are based on the analysis of variance F-test.
[2] The screening growth velocity has been calculated based on the height at visit one and the height taken 6-18 months before visit one
* Indicates a significant (p <= 0.05) investigator effect exists.
· Indicates a significant (p <= 0.10) treatment-by-investigator interaction exists.

Table 48

MEAN CHANGE FROM BASELINE IN HEIGHT (cm.)[1]
Number of Subjects, Mean (Standard Error) of Change From Baseline
Investigator: All

	Placebo	FP50 BID	FP100 BID
Number of subjects	33	41	44
WEEK 4	33 0.40(0.08)	41 0.29(0.07)	44 0.38(0.07)
WEEK 8	33 0.77(0.08)	41 0.60(0.09)	44 0.89(0.09)
WEEK 12	33 1.59(0.08)	41 1.48(0.08)	44 1.61(0.09)
WEEK 16	33 1.83(0.11)	41 1.62(0.10)	44 1.83(0.09)
WEEK 20	33 2.14(0.10)	41 2.02(0.10)	44 2.10(0.10)
WEEK 24	33 2.99(0.14)	41 2.79(0.10)	44 2.81(0.10)
WEEK 28	33 3.28(0.14)	41 3.08(0.11)	44 3.15(0.10)
WEEK 32	32 3.88(0.15)	41 3.65(0.12)	44 3.51(0.11)
WEEK 36	33 4.35(0.18)	41 3.97(0.13)	44 4.01(0.13)
WEEK 40	33 4.66(0.18)	41 4.33(0.14)	44 4.33(0.14)
WEEK 44	33 5.19(0.20)	41 4.78(0.15)	44 4.73(0.15)
WEEK 48	33 5.55(0.19)	41 5.23(0.17)	44 5.19(0.14)
WEEK 52	33 6.41(0.24)	41 5.82(0.17)	44 5.86(0.14)

[1] Subjects with height measurement at baseline and at Week 52 and SMR scores of one.

Table 49

MEAN CHANGE FROM BASELINE IN HEIGHT (cm.)[1]
Number of Subjects, Mean (Standard Error) of Change From Baseline
Investigator: All

	Placebo	FP50 BID	FP100 BID
Number of subjects	24	33	35
WEEK 4	24 0.31(0.06)	33 0.33(0.05)	35 0.36(0.08)
WEEK 8	24 0.68(0.11)	33 0.74(0.09)	35 0.71(0.10)
WEEK 12	24 1.40(0.13)	33 1.52(0.12)	35 1.36(0.11)
WEEK 16	24 1.55(0.15)	33 1.79(0.12)	35 1.56(0.11)
WEEK 20	24 1.97(0.16)	33 2.28(0.13)	35 2.05(0.12)
WEEK 24	24 2.70(0.15)	33 2.74(0.18)	35 2.68(0.13)
WEEK 28	24 3.02(0.19)	33 3.15(0.21)	35 3.04(0.15)
WEEK 32	24 3.34(0.20)	33 3.64(0.21)	35 3.39(0.17)
WEEK 36	24 3.88(0.23)	33 4.08(0.20)	35 3.76(0.19)
WEEK 40	24 4.26(0.22)	33 4.51(0.24)	35 4.55(0.35)
WEEK 44	24 4.73(0.23)	33 5.04(0.24)	35 4.66(0.20)
WEEK 48	23 5.15(0.24)	33 5.33(0.27)	35 4.97(0.21)
WEEK 52	24 5.80(0.23)	33 6.09(0.29)	35 5.58(0.23)

[1] Subjects with height measurement at baseline and at Week 52 and SMR scores of one.

Table 36A

MEAN GROWTH VELOCITY (cm./year)[1]
Number of Subjects, Mean (Standard Error)
Investigator: All

	Placebo	FP50 BID	FP100 BID
Screening[2]	19 6.14(0.16)	26 5.62(0.16)	12 6.01(0.22)
Baseline to Week 26	19 6.58(0.43)	26 6.04(0.34)	11 5.70(0.33)
Week 26 to Week 52	19 7.48(0.66)	24 6.99(0.51)	10 5.68(0.92)
Baseline to Week 52	19 6.99(0.45)	24 6.56(0.33)	10 5.61(0.46)

[1] Subjects with SMR > 1.
[2] The screening growth velocity has been calculated based on the height at visit one and the height taken 6-18 months before visit one

Table 1

Mean changes from baseline for diary variables. Endpoint analysis of intent-to-treat Population Study FLIT-85

				P-Values	
	Placebo (N=91)	FP 50 BID (N=85)	FP 100 BID (N=86)	FP 50 Vs P	FP 100 Vs P
A.M. PEFR	17	50	57	<0.001	<0.001
P.M. PEFR	11	44	53	<0.001	<0.001
Daily Asthma Score	-0.01	-0.43	-0.44	<0.001	<0.001
Daily Asthma Score for exercise	-0.03	-0.55	-0.43	<0.001	0.004
Beta Agonist usage	0.15	-0.70	-1.02	0.001	<0.001
Number of Nighttime awakenings	0.04	-0.14	-0.24	0.006	0.001

N for AM and PM PEFR. The Ns for other analyses were smaller because some patients did not include these assessments on their diary cards.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20549 AND 20770

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Boiles

JUN 25 1997

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20,770

FLOVENT® (FLUTICASONE PROPIONATE) INHALATION
ROTADISK® VIA DISKHALER®

GLAXO INC.
FIVE MOORE DRIVE
RESEARCH TRIANGLE PARK, NC 27709

SUBMISSION DATE:
26 SEPTEMBER 1996

REVIEWER:
DALE P. CONNER, PHARM.D.

TYPE OF SUBMISSION: NDA

Background

Fluticasone propionate (S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate) is an anti-inflammatory corticosteroid, approved as a metered-dose inhaler for the treatment of asthma (NDA 20-548) and as a nasal spray for the treatment of symptoms of allergic rhinitis (NDA 20-121). The molecular weight is 500.6. It is nearly insoluble in water, slightly soluble in methanol and 95% ethanol, and freely soluble in DMSO and dimethylformamide. The Rotadisk® via Diskhaler® dry powder formulation of fluticasone propionate is currently under review for the maintenance treatment of asthma in adults (NDA 20-549) and adolescents (NDA 20-770).

The recommended starting dose for fluticasone propionate from the MDI is 84 μg twice daily, for those patients who are on beta-agonists alone or controlled on the equivalent of 336 μg of beclomethasone dipropionate. For those patients not controlled on the equivalent of 336 μg or greater of beclomethasone propionate the starting dose is 210 μg twice daily. For patients taking oral corticosteroids, a starting dose of 840 μg twice daily is recommended. No dosage adjustment is recommended for geriatric patients. Oral bioavailability of the corticosteroid fluticasone propionate is very low, probably due to presystemic metabolism by CYP3A4 in the gut and liver.

This NDA was submitted to extend the recommended age range for the fluticasone propionate dry powder inhaler to the pediatric population (ages 4 to 11 years). Normally this would be a supplemental submission but the original NDA (20-549) has not yet been approved. The sponsor elected to submit this document as a separate NDA.

Summary

This NDA contains one new pharmacokinetic study in the pediatric age group. This study was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study in patients aged 4 to 11 years with chronic, non-seasonal, mild to moderate, stable asthma. Two doses of fluticasone propionate (50 μg and 100 μg BID) and a placebo were studied. A subset of patients (n=16 low dose and n=13 high dose) had measurements for plasma fluticasone propionate performed at 20 and 40 minutes

after dosing at one study visit. Most of the plasma concentrations from the 50 µg dose group were below the level of quantitation (BLQ) of the assay. The mean of the maximum plasma concentrations from the 100 µg treatment group was 58.7 pg/mL. This was slightly higher than the maximum plasma concentrations from 100 µg of fluticasone propionate given to adult patients in Study FLD 230. This difference, based on a cross-study comparison of small numbers of patients, is probably not clinically significant.

Recommendation

This NDA is approvable from a Clinical Pharmacology perspective.

Dale P. Conner 6/25/97

Dale P. Conner, Pharm.D.
Team Leader
Div. of Pharmaceutical Evaluation II

Mei-Ling Chen, Ph.D. 6/25/97
Division Director

cc:
HFD-570 (NDA 20,770, Division File, Barnes, Meyer)
HFD-870 (MChen, Conner)
HFD-850 (Lesko)
HFD-340 (Viswanthan)
CDR (Barbara Murphy)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

APPENDIX

TITLE: A randomized, double-blind, parallel-group, comparative trial assessing the long term safety of inhaled fluticasone propionate Rotadisks® Via Diskhaler® 50mcg BID and 100mcg BID versus placebo in patients aged 4 to 11 years with mild to moderate chronic asthma (FLD-220)

OBJECTIVES

To compare the long term safety and pharmacoeconomic outcomes of fluticasone propionate (FP) 50mcg BID, 100mcg BID and placebo BID.

STUDY DESIGN

This was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study in male (n=244) and female (n=81) patients aged 4 to 11 years with chronic, non-seasonal, mild to moderate, stable asthma. A subset of patients (n=16 low dose and n=13 high dose) had measurements for plasma fluticasone propionate performed at 20 and 40 minutes after dosing at one study visit. Following a two week placebo (in addition to their normal asthma medications) lead-in period, patients were randomly assigned to one of three treatments for a 52 week treatment period. Treatments were:

Treatment A: Fluticasone propionate 50mcg BID from the Rotadisk® via Diskus® dry powder inhaler
Treatment B: Fluticasone propionate 100mcg BID from the Rotadisk® via Diskus® dry powder inhaler
Treatment C: Placebo BID from the Rotadisk® via Diskus®

PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

The sampling scheme and low plasma concentrations resulting from normal doses of fluticasone propionate do not allow calculation of pharmacokinetic parameters.

RESULTS

Plasma concentrations were very low at the 50 µg BID dose. Eight of 16 patients had plasma concentrations below the level of quantitation (BLQ) of the assay (25 µg/mL) at both timepoints sampled. At 100 µg BID, most patients had plasma concentrations above the lower limit of the assay.

Table 1. Median (range) maximum plasma concentrations of fluticasone propionate in pediatric patients

	50 µg BID	100 µg BID	Adult 100 µg BID*
n	16	13	8
Age (y)	8 (4-11)	8 (6-10)	31 (23-56)
C_{max} (pg/mL)	BLQ (BLQ-117)	58.7 (28.1-154)	39.5 (BLQ-73.1)

* *Study FLD-230 after 1 week*

COMMENTS

The sampling strategy of this study does not give an accurate estimate of C_{max}. At best, the plasma concentrations at these timepoints can be compared across studies with adult data. The maximum (measured) concentrations in children appear slightly higher than those in adults. This difference is probably not clinically significant.

MAR 3 1 1997

Clinical Pharmacology & Biopharmaceutics Review

NDAs 20-549, 20-770, 20-548

Flovent™ (fluticasone propionate)

Glaxo Wellcome
Five More Drive
P.O. Box 13398
Research Triangle Park, NC 27709

SUBMISSION DATE:
4 March 1997

REVIEWER:
Dale P. Conner, Pharm.D.

TYPE OF SUBMISSION: Response to FDA Request/Comment

This submission contains a study report on the potential drug interaction of fluticasone propionate with ketoconazole, which inhibits cytochrome P450 3A4 (CYP3A4), the isoenzyme shown to be responsible for the elimination of fluticasone propionate.

TITLE: A study to assess the effects of ketoconazole on the pharmacokinetics and systemic pharmacodynamics of inhaled fluticasone propionate in healthy volunteers. (Protocol No. FLTB1003)

BACKGROUND

The Rotadisk® via Diskhaler® dry powder formulation of fluticasone propionate is currently under review for the maintenance treatment of asthma in adults (NDA 20-549) and adolescents (NDA 20-770). A CFC based MDI of FLOVENT™ (NDA 20-548) was recently approved.

Oral bioavailability of the corticosteroid fluticasone propionate is very low, probably due to presystemic metabolism by CYP3A4 in the gut and liver. In theory, an inhibitor of CYP3A4 might increase the systemic bioavailability of fluticasone propionate leading to greater systemic toxicity such as HPA axis suppression. This study was requested of the sponsor to determine whether this drug interaction actually occurs.

OBJECTIVES

1. To evaluate whether the concomitant administration of ketoconazole affects the pharmacokinetics of fluticasone propionate
2. To evaluate whether the concomitant administration of ketoconazole affects the systemic pharmacodynamics of fluticasone propionate.

STUDY DESIGN

This was a randomized, double-blind, placebo-controlled, two-way, cross-over, single-center study in healthy male (n=4 completed) and female (n=4 completed) volunteers. Each treatment period consisted of 12.5 days with a washout period of at least 2 weeks. Treatments were:

Treatment A: Two doses of MDI 1000 µg inhaled fluticasone propionate, 250 µg per actuation

Treatment B: Two doses of inhaled MDI matching placebo (4 actuations)

Subjects received these treatments on Days 2 and 11 at 0900 hours. All subjects received ketoconazole (Nizoral®) 200 mg (at 0700) on Days 6-11 in both periods.

Blood samples for plasma fluticasone propionate were collected at 0 (pre-dose), 5, 15, 30, 45 min, and 1, 2, 4, 6, 8, 10, 12, 16, 24, 28, 34 and 48 hours after the morning dose on days 2 and 11 of each period. Blood samples for plasma cortisol determinations were collected at 0, 2, 4, 6, 8, 10, 12, 16, 20 and 24 hours on Day 1 and after the morning fluticasone propionate dose on Days 2 and 11 of each treatment period. Twenty-four hour urinary cortisol excretion was determined for each treatment.

PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

The sponsor calculated the following pharmacokinetics parameters: AUC_{last}, AUC_{∞}, $\%AUC_{ex}$, AUC_{12}, C_{max}, C_{12}, t_{max}, λ_z, and $t_{1/2}$.

The following pharmacodynamic parameters were calculated for plasma cortisol: $AUC_{24,cort}$, $C_{ave,cort}$, $C_{max,cort}$, $t_{max,cort}$, $C_{min,cort}$ and $t_{min,cort}$.

RESULTS

Only a partial pharmacokinetic analysis could be performed due to problems with sample identification for those plasma samples collected for fluticasone propionate analysis. Samples collected for cortisol analysis were used after the cortisol assay had been performed, where possible, to assay for fluticasone propionate. Following the fluticasone propionate treatment, only the samples of 6 subjects could be assayed. The following table shows the main pharmacokinetic data which could be calculated from this limited pharmacokinetic analysis.

Table 1. Median pharmacokinetic parameters of fluticasone propionate with (Day 11) and without (Day 2) co-administration of ketoconazole.

	Day 2			Day 11				
	N	Median	(range)	N	Median	(range)	N	Median ratio Day 11/Day 2
$AUC_{2\text{-}last}$ (ng.h/mL)	5	1.56		5	2.78		4	2.3
$AUC_{2\text{-}\infty}$ (ng.h/mL)	5	2.27		4	4.32		4	2.5
$t_{1/2}$ (h)	5	5.1		4	7.1		3	1.3

Figure 1. Mean fluticasone propionate (FP) plasma concentrations with and without co-administration of ketoconazole (K).

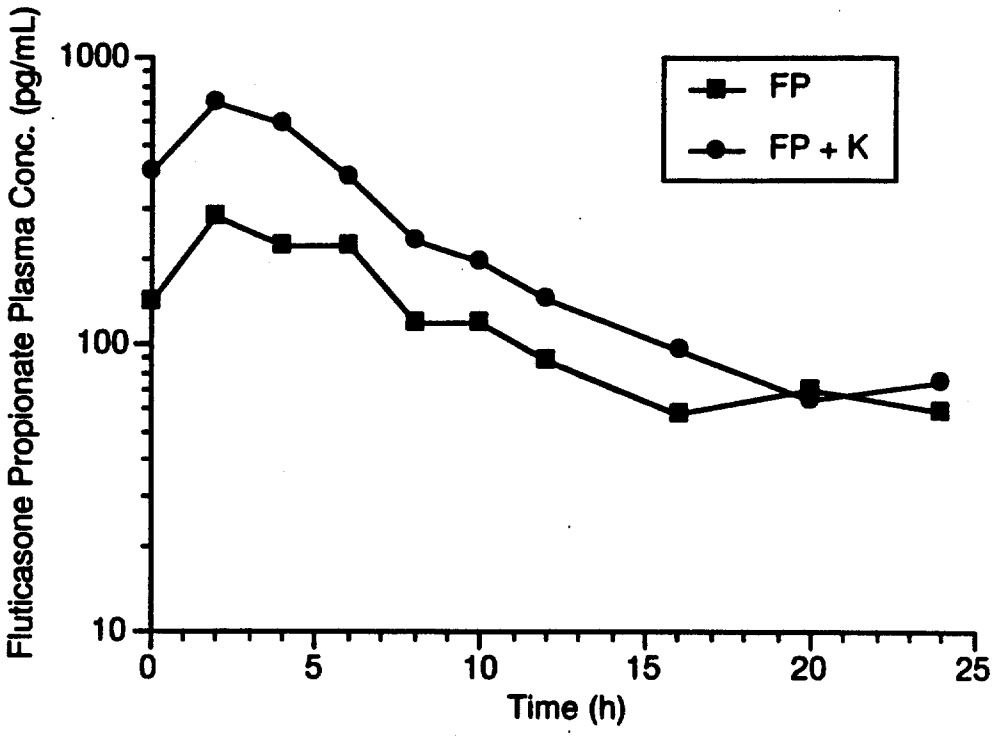
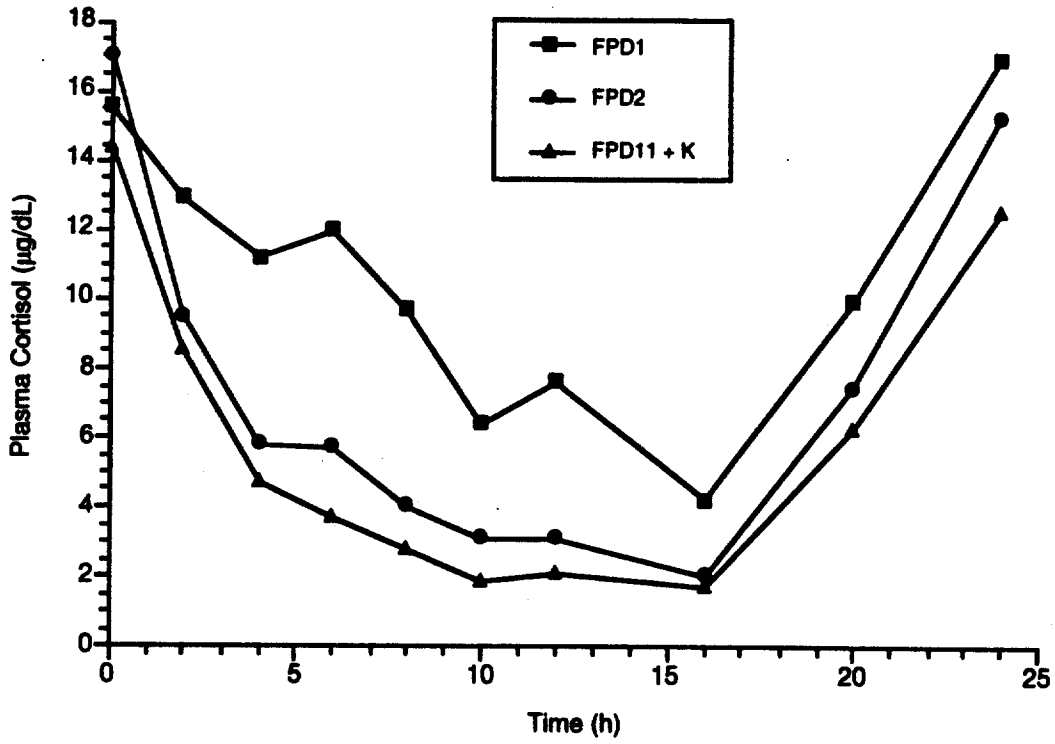


Table 2. Effect of ketoconazole on plasma and urinary (UC) cortisol after placebo (P) and fluticasone propionate (FP)

		Day 1 (pre-treatment)		*Day 2 (no ketoconazole)*		*Day 11 (ketoconazole)*	
Parameter	**Trt**	**N**	**LS Mean (95% CI)**	**N**	**LS Mean (95% CI)**	**N**	**LS Mean (95% CI)**
$AUC_{24,cort}$	P	8	176 (104, 435)	8	205 (166, 251)	8	248 (202, 305)
(µg.h/dL)	FP	8	212 (103, 368)	8	121 (98, 148)	8	81 (66, 99)
24h UC (µg)	P	8	58.6 (31.5, 78.6)	8	53.8 (40.4, 71.6)	8	37.5 (28.1, 49.9)
	FP	8	49.3 (22.2, 89.2)	8	29.6 (22.2, 39.4)	8	13.5 (10.2, 18.0)
			Median (range)		**Median (range)**		**Median (range)**
$C_{min,cort}$	P	8	1.9	8	1.7	8	3.6
	FP	8	3.9	8	0.6	8	BQL
$C_{max,cort}$	P	8	12.9	8	15.8	8	16.7
	FP	8	17.0	8	15.1	8	13.6

Figure 2. Mean plasma cortisol concentrations for the fluticasone propionate (FP) treated group at pre-treatment (FPD1), FP treatment with no ketoconazole (FPD2) and FP treatment with ketoconazole (FPD11 + K)



The sponsor concluded that the limited pharmacokinetic data showed that fluticasone propionate plasma concentrations were approximately 2.5 times higher when fluticasone propionate was administered with ketoconazole. In addition there was a statistically significant effect of repeated dosing with ketoconazole on the effect of fluticasone propionate on 24 h plasma cortisol ($AUC_{24,cort}$) but not on 24 h urinary cortisol excretion.

COMMENTS

This study has been reviewed by the Office of Clinical Pharmacology. The findings from the ketoconazole study should be included in the next labeling revision for the approved product and in proposed labeling for other fluticasone propionate inhalation products under review.

1. Based on the results of this study this reviewer concludes that there is a pharmacokinetic interaction between fluticasone propionate and the CYP3A4 inhibitor ketoconazole. The sponsor's estimate of a 2.5 times increase in plasma concentrations when fluticasone propionate is administered with ketoconazole is based on median data. A more appropriate estimate based on arithmetic mean data yields a factor of a 3.3 increase.
2. Based on the data from this study the increase in plasma concentrations of fluticasone propionate when co-administered with ketoconazole and, theoretically, other inhibitors of CYP3A4 can be expected to increase the likelihood of HPA axis suppression on therapeutic doses of inhaled fluticasone propionate.

Dale P. Conner 3/25/97

Dale P. Conner, Pharm.D.
Team Leader
Div. of Pharmaceutical Evaluation II

Mei-Ling Chen 3/31/97

Mei-Ling Chen, Ph.D., Division Director

cc:
HFD-570 (NDA 20,770, NDA 20,548, NDA 20,549, Division File, Barnes, Meyer, Otulana)
HFD-870 (MChen, Conner)
HFD-850 (Lesko)
HFD-340 (Viswanthan)
CDR (Barbara Murphy)

JUN 5 1997

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
NDA 20-770, Review No. 1

NDA: 20-770

Serial Number: 1

Date of Submission: 9/26/96

Information to be Conveyed to Sponsor: Yes (X), No ( )

Reviewer: Lawrence F. Sancilio, Ph.D.

Date Review Completed: 6/2/97

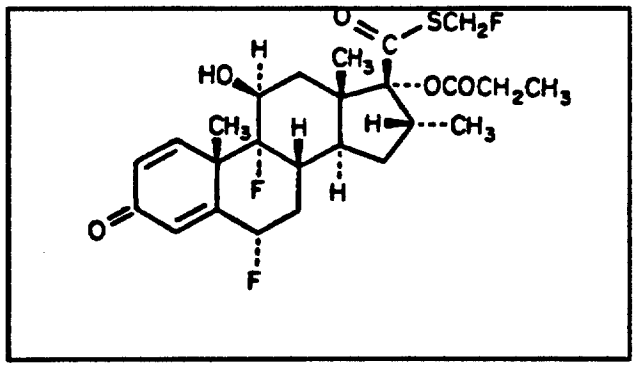
Sponsor: Glaxo Inc.
5 Moore Drive
Research Triangle Park, NC 27709

Drug Name: Fluticasone propionate

Chemical Name: S-fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α- methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate

CAS No. 80474-14-2

Structure:



Molecular Weight and Formula: 500.6 ($C_{25}H_{21}F_3O_5S$)

Related INDs, NDAs:

Class: Glucocorticoid

Indication: Maintenance treatment for bronchial asthma in children 4-11 yrs old.

Clinical Formulations:, Micronized fluticasone propionate, 50-100 mcg/dose

Route of Administration and Dose: Inhalation aerosol; 50-100μg twice daily.

Previous Review(s), Date(s), and Reviewer(s):

NDA 20-121, Nasal Spray, A. Mukherjee, 3/29/93,
NDA 20-121, Nasal Spray, B. Hayes, 5/3/94
NDA 20-549, Rotodisk Inhalation, L.F. Sancilio, 12/13/95

Preclinical Studies Submitted and Reviewed in this NDA

Fluticasone propionate has been approved for use as a nasal spray, a metered dose inhaler and an inhalation powder. Its pharmacology and toxicology has been reviewed which is amended to this review. A 1-year inhalation study in juvenile dogs was submitted in this NDA. This was undertaken to determine whether the steroid administered by inhalation would affect the maturation of the respiratory tract since this NDA is for the use of inhaled fluticasone propionate in young patients 4 to 11 years of age. No other preclinical studies are warranted for the approval of this NDA.

Toxicology

Multi-Dose

52-Week Inhalation Study in Juvenile Dogs, No. WPT/95/096, Vol. 1.2, p 9.

GLP signed statement: Yes.

Site the study was conducted:

Study Dates: 2/16/94- 1/31/96

Study Report Date: 2/16/96

Method

Animals: Nine-10 week old M and F (2.3-5.3 kg) Beagle dogs, (12 M and 12 F/ group)

Housing: 4/ kennel from 0 to week 5; thereafter 2 of the same sex and dose group were housed in each kennel.

Compounds: Fluticasone propionate (Batch No. U93/057A), GR106642X, HFA Propellant, (Batch No. U93/262A 510)

Formulation: Aerosol in a MDI containing fluticasone propionate and the propellant, GR106642X or the propellant alone. Administration was by inhalation via an oropharyngeal tube. The total dose delivered was 74 (65-82) mg for each metered dose. Each metered dose contained 50 μg of fluticasone propionate. Mass median aerodynamic diameter (MMAD)$\pm$ geometric standard deviation: 2.1$\pm$ 1.7μm; 99% of the MMAD was$<$ 7 μm.

Dose: Group 1,Control (Sham)
Group 2, Propellant, Weeks 1-8, 30 metered doses/day; Weeks 9-52, 15 metered doses/day
Group 3, Fluticasone propionate, Week 1, M, 126 and F, 140 μg/kg/day;
Week 8, M, 82 and F, 91 μg/kg/day;
Weeks 8-52,M, 25 and F, 26 μg/kg/day
Due to adverse effects, the dose was reduced at week 8 and thereafter. The initial dose was selected from a 4-week toxicity study in juvenile dogs whereby an inhalation dose of 508 μg/dog was tolerated.

The following parameters were determined.

Clinical Observations: Daily.

Body Weight: Prior to start of study and weekly thereafter.

Food Consumption: Weekly; results are expressed as mean daily food consumed per dog.

Ophthalmoscopy: Prior to start of study and during weeks 4, 12, 25 and 51.

Electrocardiography: Prior to start of study and during weeks 4, 12, 25 and 51.

Chest Girth Measurement: Prior to start of study and during weeks 4, 12, 25 and 51.

Abdominal Girth Measurement: Prior to start of study and during weeks 9 (1 M and 1 F in Groups 2 and 3), 12, 25 and 51.

Long Bone Measurements: Prior to start of study and during weeks 8, 12, 24, 36 and 48 of dosing and at necropsy.

Radiography of Neck: Under anesthesia lateral radiographs were taken prior to start of study and during week 52.

Physical Appearance: Photographs (full side and lateral side view) were taken during weeks 9, 12, 25 and 51 of 1 M and 1 F in Groups 2 and 3 during weeks 9, 12, 25 and 51.

Hematology, Urine Analysis, Clinical Chemistry: Prior to start of study and during weeks 8, 13, 26 and 52.

Plasma Cortisol Levels: Immediately before and 1.5 h after stimulation with Synacthen (250 μg i.v./dog.) Prior to start of study and during weeks 8, 13, 26 and 52.
Plasma Levels of fluticasone propionate:

Groups 1 and 2: Day 1, 20 min and 24 h after dosing.
Weeks 4, 8, 13, 26 and 52, before dosing, and 20 min after dosing (weeks 4 and 8) on each occasion.

Group 3: Day 1, before dosing then 5, 10, 20, and 40 min, and 2, 4 and 24 h after the first dose.
Weeks 4, 8 and 13: before dosing, and 20 min after dosing (weeks 4 and 8) on each occasion.
Weeks 26 and 52: before dosing then 2, 5, 10, 20, and 40 min, and 2, 4 h after dosing on each occasion.

Necropsy

Organs weighed were: adrenals, brain, heart, kidneys, liver, ovaries, spleen, testes with epididymides, thymus, prostate and thyroids with parathyroids. The whole lungs were weighed, the right lobe was weighed wet and dried (48 h at 80°C).

Tracheas were measured in the following manner: 1. Total length (distance from the cricoid cartilage to the bifurcation; 2. The number of rings from the cricoid cartilage to the bifurcation; 3. The horizontal and vertical external diameters of the 2nd, 10th, 20th and 30th rings; 4. The width of the 2nd, 10th, 20th and 30th rings.

Tissues examined histologically were: adrenals, brain, heart, kidneys, liver, spleen, thymus, larynx, tracheal bronchial lymph nodes and trachea with bifurcation. For lungs, the apical (left), cardiac (left), intermediate and both diaphragmatic lobes including the bronchus/bronchioles and peripheral lung sections.

Results

Mortality: Group 1: None.
Group 2: 1 F (week 31), sacrificed for humane reasons.
Group 3: 1 M (week 7), cause of death unknown.
Group 3: 1 F (week 8), operated for hernia and did not improve, killed for humane reasons.
Group 3: 1 F (week 9), enlarged hernia, sacrificed for humane reasons.
Group 3: 1 F (week 31), difficult hernia, sacrificed for humane reasons.

Clinical Observations: These are summarized in the following table.

Observations at 52 Weeks	Incidence		
	Group 1(Sham)	Group 2 (Vehicle)	Group 3 (Test)
Hernia			
Umbilical	0/24	1/23	13/24[a]
Eye Discharge	0/24	0/23	7/20
Abdominal Distension			
Slight to Marked	0/24	0/23	12/20
Hair Loss/Thinning			
Ears	2/24	0/23	20/20
Legs/Feet	1/24	1/23	16/20
Chest	0/24	0/23	5/20
Back	1/24	0/23	16/20

[a]Include 4 animals that were sacrificed during the 52 weeks.

Body Weight: Group 1 vs Group 2:Week 8, no effect.
Group 3 vs Group 2: Week 8, M, -19%, F, -17%
Week 52, M, -16%, F, -12%

Food Consumption: Based on cumulative effect: Group 3 vs Group 2: Weeks 1- 8, no effect
Group 3 vs Group 2: Weeks 9-52, M, -3.2%
F, -6.7%

Ophthalmoscopy: Epiphora (abnormal outflow of tears down the check): Group 1, 0/24, Group 2, 0/23, Group 3, 10/20.

Electrocardiography: No effect.

Girth Measurement: The results are summarized in the following table.

Area	% Change From Group 2 (Vehicle)	
	Group 1 (Sham)	Group 3
Abdominal		
Week 25	M, +2.5 F, +5.7	M, +6.7 F, +15.9
Week 51	M, +8.4 F, +11.0	M, +2.3 F, +12.4

Changes in the chest girth was not remarkable.

Long Bone Measurements:

Time of Measurement	% Change From Group 2 (Vehicle)	
	Group 1 (Sham)	Group 3
Week 8	M, -3.0 F, -1.0	M, -12.1 F, -14.4
Week 53	M, -2.4 F, 0	M, -10.4 F, -13.6

Radiography of Neck: No data given.

Photographs: Week 9: Majority of animals in Group 3 showed: 1. a stunted physical appearance of short tail and snout with pot belly abdomen, and 2. protruding/enlarged eyes.

Hematology and Clinical Chemistry changes are listed in the following table.

Parameter	% Change From Group 2 (Vehicle) by Group 3			
	Week 8		Week 52	
	M	F	M	F
White Blood Count	13[a]	41	25[a]	3 [a]
Neutrophils	36	88	33	12 [a]
Lymphocytes	-41	-61	18[a]	-14 [a]
Eosinophils	-100	-100	- 84	-77
Monocytes	212	200	35[a]	133 [a]
Partial Thromboplastin Time	27	16	19	11 [a]
Fibrinogen	28	33	42	38
Alkaline Phosphatase	34	27	16[a]	40
LDH	31[a]	46	32	20
αHBDH (α-hyrdoxybutyrate dehydrogenase)	50[a]	75	5[a]	16 [a]
Serum Phosphorous	-13	-27	14	10
Cholesterol	23	27	37	43
Triglycerides	31[a]	41	12[a]	17 [a]

[a] P > 0.05

Cortisol Levels in Response to Synacthen (% Decrease):
Week 8: M, Prior to administration of Synacthen: > 69%
1.5 h after administration of Synacthen: > 96%
F, Prior to administration of Synacthen: > 85%
1.5 h after administration of Synacthen: > 97%

Week 52: M, Prior to administration of Synacthen: > 82%

1.5 h after administration of Synacthen: > 97%

F, Prior to administration of Synacthen: > 87%
1.5 h after administration of Synacthen: > 98%

Urine Analysis: Weeks 8 and 52: Increase in pH in M and F.

Plasma Levels

Fluticasone propionate was assayed in plasma using a radio immune assay. The Limit of Quantification was 0.05 and 0.25 ng/ml for weeks 1 and 8 and 52, respectively. Since there was no difference in the plasma levels in the M and F dogs, the results were pooled. During the study, the plasma levels of fluticasone propionate prior to its administration were low, ranging from <0.05-0.11 ng/ml at weeks 1 and 8 and <0.25-0.27 ng/ml at week 52. The 20 and 40 min mean plasma levels are shown in the following table.

Day	Mean Plasma Level ng/ml, N=8	
	20 min	40 min
7	0.99	1.14
56	0.98	ND
182	< 0.72	0.79
364	0.78	0.78

ND, Not determined

Necropsy

Organ Weight: The results are summarized in the following table.

Organ Weight	% Change From Group 2 (Vehicle)			
	Absolute		Relative	
	M	F	M	F
Liver	+15	+37	+27	+38
Adrenals	-56	-62	ND	ND
Thyroids	No Change	+22	ND	ND
Lungs (whole)	-30	-36	ND	-26
Left Lobe (wet)	-39	-34	ND	ND
Left Lobe (dry)	-41	-37	ND	ND
Gonads	-26	No Change	ND	ND

ND, Not Determined

Tracheal Measurements: Change From Group 2 (Vehicle) by treated (Group 3) group.

No. of Tracheal Rings: M and F, no change.

Length: M, -11.6%, F, -12.3%

The results of the tracheal ring dimensions are shown in the following table.

Ring Location	% Decrease From Group 2 (Vehicle), $p<0.05$	
	Males	Females
C2		
Horizontal External Diameter	14.1	14.6
Vertical External Diameter	14.4	16.8
Width (height)	12.5	13.1
C10		
Horizontal External Diameter	25.1	23.2
Vertical External Diameter	21.1	18.4
Width (height)	12.5	8.3
C20		
Horizontal External Diameter	28.5	26.8
Vertical External Diameter	19.3	22.9
Width (height)	10.1	18.4
C30		
Horizontal External Diameter	30.0	27.4
Vertical External Diameter	24.4	25.3
Width (height)	22.9	23.5

Macroscopic Pathology: The results are summarized in the following table. Data from the Sham-treated animals were not presented since none of the findings in the treated animals were seen in the sham-treated animals.

Organ/Finding	Incidence			
	Males		Females	
	Control (Vehicle)	Treated	Control (Vehicle)	Treated
	N= 11	11	12	9
External Appearance				
Hair Thinning/Loss	0	5	0	3
Ventral abdomen, comedones	0	8	0	5
Pot-Bellied	0	6	0	8
Skin, thin and/or flaky	0	7	0	5
Inguinal hernia	0	3	0	2
Skeletal Muscle				
Abdominal wall, thin	0	6	0	3
Body Cavities				
Abdomen and thorax, Abundant adipose tissue	0	6	0	8
Lungs				
Soft pale patchy non-collapsible areas/foci	0	4	0	2
Trachea				
Mucosal Surface, mucoid Material adhering to surface	0	6	0	1
Slight distortion in orientation of rings (misshaapen trachea)	0	2	0	1
Liver				
Texture, friable	0	6	0	6
Rounded Edges	0	2	0	6
Adrenal Gland				
Thinning of cortex	0	10	0	8
Thymus				
Not visible	0	8	0	7

Histopathology:

In the 4 (1 M and 3 F) animals that died or killed for humane reasons, pathologic changes seen that were related to treatment were marked thymus involution (2/3 F), sparse germinal centers in the tracheobronchial lymph nodes (1/1 M, 1/3 F), reduced cellularity of the white pulp of the spleen (1/1, M, 3/3, F), minimal swelling/cytoplasmic rarefaction of centrolobular hepatocytes (2/3 F) and atrophy of the zonae fasiculata and reticularis of the adrenals (1/1 M, 2/3 F). The respiratory tract showed decreased basophilia of bronchial cartilages (1/1 M, 2/3 F), alveolar septal mineralization (3/3 F), pneumonia (1/1 M, 3/3 F), hypertrophy of bronchial epithelium with decreased prominence of goblet cells, dilated bronchial glands (1/1 M, 3/3 F) and inflammatory exudate in the trachea and larynx (2/3 F). The hernia seen in the 3 F dogs was due to an apparent exacerbation of a preexisting condition resulting from the asthenia of the abdominal muscle caused by fluticasone propionate.

The results seen in animals at termination are summarized in the following table. Data from the Sham treated animals were not presented since none of the findings were seen in this group.

APPEARS THIS WAY
ON ORIGINAL

Organ/Finding	Incidence			
	Males		Females	
	Control (Vehicle)	Treated	Control (Vehicle)	Treated
	N= 11	11	12	9
Larynx				
Inflammatory Exudate	0	6	0	1
Carina				
Focal mineralization of tracheal cartilages	2	7	1	0[a]
Trachea				
Area of luminal distortion and dilation	0	1	0	1
Lungs				
Decreased width and decreased basophilia of bronchial cartilages	0	10	0	9
Focal mineralization of bronchial cartilages	0	6	0	6
Mineralization of bronchial walls	0	2	0	6
Hypertrophy of bronchial/bronchiolar epithelium	0	9	0	5
Decreased prominence of goblet cells in bronchial/bronchiolar mucosa	0	6	0	3
Dilated bronchial glands	0	8	0	7

[a] carina from 1 animal was lost

Organ/Finding	Incidence			
	Males		Females	
	Control (Vehicle)	Treated	Control (Vehicle)	Treated
	N= 11	11	12	9
Mucus and inflammatory cells in bronchi/bronchioles	2	5[a]	1	3[a]
Tracheobronchial lymph node				
Sparse germinal centers	3	6[a]	1	5
Liver				
Generalized swelling/cytoplasmic rarefaction of hepatocytes	0	6	0	4
Swelling/cytoplasmic rarefaction of centrilobular hepatocytes	0	4	0	5
Adrenals				
Atrophy of zonae fasiculata and reticularis	0	11	0	9
Spleen				
Generalized reduced cellularity Of white pulp	0	10	0	3[a]
Thymus				
Involution				
Total	6	8	5	7[a]
Marked	0	6	0	6
Pneumonia	0	3[a]	0	2[a]

[a] $P > 0.05$

Summary and Conclusion

A 1 year inhalation study was conducted in juvenile dogs with fluticasone propionate. This study was undertaken to determine whether fluticasone propionate causes unexpected developmental changes in the respiratory tract of young animals which can be extrapolated to children for which fluticasone propionate will be used.

In M and F juvenile beagle dogs, initial doses of 126/140 μg/kg (0.49 mg, total dose) were administered by inhalation. This dose was selected from the results of 52-week and 4-week studies in dogs. A dose of 501 μg/dog was well tolerated in the 4- week study. In this study, after 8 weeks, the dose was reduced to 25/26 μg/kg (0.25 mg, total dose) because of toxicity. The median MMAD was 2.1μm indicating that deposition occurred in the tracheobronchial region.

At the end of 8 weeks, 1 M and 1 F in the treated group died. The cause of death in the M was unknown; the F that was operated for a hernia as an indirect result of fluticasone propionate administration was killed for humane reasons. The other animals showed marked weight loss, abdominal distension and eye discharge as a result of the steroid effect.

At the end of 52 weeks weight loss was still evident; clinical toxic signs were umbilical hernias, abdominal distension, excessive eye tearing and hair loss and thinning. The animals showed a stunted appearance. Food consumption was slightly decreased from week 8 to 52.

The increased incidence of umbilical hernias and pot-bellied abdomens was probably due to a preexisting condition that was exacerbated by the thinning of the abdominal wall as a consequence of the glucocorticoid effect by fluticasone propionate. Increased abdominal girth was quite evident at week 25 and not at week 51. Changes were not seen with the chest girth. Long bone lengths were decreased at week 8 and continued to be less than the control (vehicle) group by week 53. These effects were also related to the steroid effect.

Changes in the white blood count were more prevalent at 8 weeks than at 51 weeks. Neutrophils and monocytes were increased and lymphocytes were decreased. At week 52, only the eosinophil count was still markedly decreased in the M and F. Consistent changes in clinical chemistry parameters were increased fibrinogen and cholesterol levels. Urinary pH was elevated.

Adrenal suppression was quite evident indicating a full steroid effect. At week 8 and thereafter, cortisol levels were markedly low prior to and after administration of the adrenal cortex stimulant, Synacthen. This was further reflected by changes in the adrenal glands. There was a decrease in adrenal weight; macroscopically, the cortex showed thinning.

Microscopically, there was atrophy of the zonae fasiculata and reticularis. These changes are characteristic of exogenous corticosteroid administration.

The plasma levels at 20 min following inhalation at week 8 was approximately 25% higher than that seen at 20 and 40 min on week 52. Since the dose at week 8 was > 3 times that at week 52, the change in the pharmacokinetics may be attributed to the toxic effects of fluticasone propionate.

At necropsy, there were an increase in the absolute and relative weights of the liver, and decreased absolute and relative lung weight. Changes in the liver were attributed to generalized swelling/cytoplasmic rarefaction of hepatocytes and centrilobular hepatocytes. There was a decrease in absolute wet weight and a decrease in absolute dry weight of the right cardiac lobe of the lung. The respective decrease and increase in absolute wet and dry weights as the sponsor indicated were the result of decreased secretions and increased alveolar thickness that are characteristic of glucocorticoids.

Emphasis was placed on the effect of fluticasone propionate on the development respiratory tract, in particular, the trachea. The number of tracheal rings was not affected. There was a decrease in the width, vertical and horizontal external diameters of tracheal rings C2, C10, C20 and C30. The highest change was seen at ring C30. Macroscopically, the tracheas of 3/20 dogs showed a slight distortion in orientation of rings; histologically, 2/3 (1 M and 1 F) of these animals showed an area of luminal distortion and dilation. Inflammatory exudate was present in the larynx and focal mineralization or mineralization occurred in the carina, bronchial cartilages and bronchial wall. The lungs showed decreased width and decreased basophilia of the bronchial cartilages, hypertrophy of the bronchial/bronchiolar epithelium, decreased prominence of goblet cells, the presence of mucus and inflammatory cells in the bronchi/bronchioles, dilated bronchial glands, sparse germinal centers in the tracheobronchial lymph nodes, reduced cellularity of the white pulp of the spleen and thymus involution. Some of these effects were related to the immunosuppression produced by fluticasone propionate. The pneumonia in some animals was also attributed to immunosuppression.

SUMMARY and EVALUATION

This NDA is for fluticasone propionate to be administered by inhalation as a dry powder for the prophylactic treatment of asthma in children 4-11 years old. The maximum human daily inhalation dose is 100 μg twice a day. The formulation consists of fluticasone propionate and lactose, a commonly used excipient for dry powder inhalers. The Pharmacology and Toxicology of fluticasone propionate have been studied in depth. Attached is the review of the pharmacologic and toxicologic studies submitted in NDA 20-549 for dry powder fluticasone propionate for use in adolescents and adults 12 years of age and older.

In this NDA a 1 year inhalation study was conducted in juvenile beagle dogs 9-10 week old. Focus was on the respiratory tract to determine whether unusual changes occurred in the respiratory tract. The following tables compares the findings in the 1 year study in juvenile and adult dogs. In the adult study, the dogs received from metered dose inhalers (50 μg/ burst) 4, 10 and 30 bursts in divided doses daily. This was equal to 7.8, 16.8 and 50 μg/ kg in M and 7.3, 19.1 and 51.5 μg/ kg in F; in the juvenile dogs only 1 dose level was tested. They received from metered dose inhalers (50 μg/ burst) 30 bursts in divided doses 4 hr apart daily. Initially, the dose was 126-140 μg/kg which after 8 weeks due to toxicity, the dose was decreased to 25-26 μg/kg (15 bursts). Comparison was made with the 50-51.5 μg/kg dose in adult dogs and the one dose level in juvenile dogs. Data for the adult dogs were taken from the review of Dr. Mukhergee (NDA 20-121, 3/29/93).

Although both groups received 30 bursts from the fluticasone inhaler, the dose in the juvenile dogs was higher than that in the adult dogs (weeks 1 and 9, 126/140 and 82/91 μg/kg vs 50/51.5 μg/ kg) prior to being lowered after week 8. However, the plasma levels were apparently comparable (plasma levels were determined 20 and 40 and 30 min following inhalation in the juvenile and adult dogs, respectively) throughout the study. Despite decreasing the daily inhalation dose in the juvenile dogs from 126-140 μg/kg to 25/26 μg/kg on week 8 due to toxicity, the plasma levels were similar throughout the study. There were no obvious reasons other than possible alteration in bioavailability to account for the similarity in plasma levels especially during the first 8 weeks whereby the inhalation dose in the juvenile dogs was approximately 3 times the dose in the adult dogs. Toxicity was not a factor since it was not evident in the juvenile animals until after week 4.

Although both groups showed signs of hypercorticosteroidism, the juvenile animals showed increased systemic toxicity thereby indicating greater sensitivity than the adult dogs, i.e., abdominal hernias, eye discharge and reduced cellularity of white pulp in the spleen. Some of the juvenile animals were moribund and were killed on a humane basis. This maybe due to different pharmacokinetics because after week 8, the inhalation dose of fluticasone propionate given to the juvenile dogs was half that administered to the adult animals (25-26 μg/kg vs 50-51.5 μg/kg) and yet showed similar plasma levels. Respiratory tract toxicity was quite evident in the juvenile dogs; none of the pathological changes observed in the juvenile dogs were seen in the adult dogs animals. This may be a local effect since the dose in the juvenile dogs was 124-140 and 82/91 μg/kg during the first 8 weeks in contrast to 50-51.5 μg/kg throughout the study in the adult animals. Although the daily dose was reduced to 25-26 μg/kg after 8 weeks in the juvenile dogs, it cannot be determined whether the respiratory changes were initiated or already induced during the first 8 weeks of dosing.

Observation/Parameter	Present, + Absent, 0 Adult Beagle Dog 50-51.5 μg/kg	 Juvenile Beagle Dog 26-140 ↓ to 25-26 μg/kg
Mortality/Moribund Condition	None	C, 1/24, T, 4/24
Body Weight	M, -30%, F, +11%	M, -16%, F, -12
Abdominal Hernia	0	+
Abdominal Distension	+	+
Eye Discharge	0	+
Hair Loss/Thinning	+	+
Long Bones, ↓ in Length	Not Determined	+
Eosinophilia	0	+
Fibrinogen Levels, ↑	0	+
Cholesterol Levels, ↑	+	+
Creatinine and Urea Levels, ↓	+	0
Thymus Atrophy	+	+
Liver Weight, ↑	+	+
Rarefication of Centrilobular Hepatocytes	+	+
Adrenals, Cortical hypoplasia	+	+
↓ Adrenal response to stimulation	+	+
Spleen, reduced cellularity of white pulp	0	+
Plasma level, ng/ml		
Day 1	0.92[c]	
Day 7		0.99[a] 1.14[b]
Day 32	1.07	
Day 56		0.98[a]
Day 182/185	0.88[c]	<0.72[a] 0.79[b]
Day 361/364	0.78[c]	0.78[a] 0.78[b]

[a] Determined 20 min after dosing
[b] Determined 40 min after dosing
[c] Determined 30 min after dosing

Respiratory Tract Changes	Present, + Absent, 0 Adult Beagle Dog 50-51.5 μg/kg	 Juvenile Beagle Dog 126-140 ↓-25-26 μg/kg
Trachea, ↓ in Diameter of tracheal rings C2, C10, C20, C30	0	+
↓ Tracheal Length	0	+
Disorientation of rings/ Is this considered misshapen trachea (?)	0	+(3/23)
Area of luminal distortion and dilation	0	+
Larynx, Inflammatory Exudate	0	+
Carina, Focal mineralization of tracheal cartilages	0	+
Lungs, Decreased width and decreased basophilia of bronchial cartilages	0	+
Bronchi, Focal mineralization of bronchial cartilages	0	+
Mineralization of bronchial walls	0	+
Hypertrophy of bronchial/bronchiolar epithelium	0	+
Decreased prominence of goblet cells in bronchial/bronchiolar mucosa	0	+
Dilated bronchial glands	0	+
Mucus and inflammatory cells in bronchi/bronchioles	0	+
Tracheobronchial lymph node, Sparse germinal centres	0	+

Fourteen day pharmacokinetics study was conducted with inhaled fluticasone propionate in pediatric patients at the maximum daily dose of 200 μg/day. The plasma levels ranged from 28.1- 154 pg/ml. The following table show that the plasma levels in juvenile dogs during this 1 year study were 5-41 x the plasma levels observed with the maximum daily inhalation dose in pediatric patients. Since the only dose level tested in the 1 year juvenile dog study showed toxicity, it was not possible to determine an adequate safety margin based on comparative plasma levels.

Day	20 or 40 min Mean Plasma Level in Juvenile Dogs pg/ml, N=8	Plasma Levels in Juvenile Dogs Relative to Human Plasma Levels, 28.1-154 pg/ml, in Pediatric Patients (N=13)
7	1140	7-41
56	980	6-35
182	790	5-28
364	780	5-28

Points Discussed with Medical Officer

Information was related to the Medical Officer, Dr. M. Purucker, that fluticasone propionate in juvenile dogs at a toxic inhalation dose produced a low but not significance incidence (3/20) of disorientation of tracheal rings. This reviewer's recommendation is that the changes in the structure of the trachea in juvenile dogs by inhaled fluticasone propionate do not pose a potential clinical adverse effect.

Labeling Review

The following changes in the label regarding preclinical data are recommended. The maximum recommended daily inhalation dose in children, 4-11 years old, is 200 μg and 2000 μg in Adults, > 11 years. Deletions are highlighted with a ~~strikeout~~ and additions are highlighted in RED. The respective body weights of the children and adults were 16 kg and 50 kg. Relationship of the preclinical dose to the maximum human dose based on mcg/m^2 were calculated using km factors of 6 for rats, 3 for mice, 12 for rabbits, 37 for adults and 25 for children to determine the respective mcg/m^2.

1 page

PURGED

Draft Labeling

RECOMMENDATIONS

This NDA is for fluticasone propionate to be administered by inhalation as a dry powder for the treatment of asthma. It is similar to NDA 20-549 except that fluticasone propionate will be administered to patients 4-11 years. From a preclinical standpoint, this NDA is approvable.

The proposed changes in the label for the preclinical areas are recommended.

Lawrence F. Sancilio 6/2/97

Lawrence F. Sancilio, Ph.D.
Pharmacologist/Toxicologist

June 5, 1997

cc. /Division File, NDA 20-770
/RMeyer, HFD-570
/C.S.O., HFD-570
/LFSancilio, HFD-570
/JSun, HFD-570
Attachments: NDA 20-121, A. Mukherjee, 3/29/93
NDA 20-549, L.F. Sancilio, 12/13/95

Approved by J. Sun, Ph.D.

n:\NDA\20770\pharm\96-09-26.rev

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20549 AND 20770

ADMINISTRATIVE DOCUMENTS

AMENDMENT TO ITEM 13
Patent Information for
FLOVENT® ROTADISK® FOR INHALATION
NDA 20-549
NDA 20-770*

The following submission of patent term expiration information is made subsequent to the decisions rendered by the United States District Court, Eastern District of Virginia (*Merck & Co. v. Kessler*, 903 F. Supp. 964, 38 U.S.P.Q.2d (BNA) 1727, 1995) and the United States Court of Appeals for the Federal Circuit (*Merck & Co. v. Kessler*, 80 F.3d 1543, 38 U.S.P.Q.2d (BNA) 1347, 1996).

4,335,121

By action of the Uruguay Round Agreements Act, Public Law 103-465, signed by the President on 8 December, 1994, the expiration date of United States Patent, 4,335,121, is 13 February, 2001.

The undersigned attests the above-listed patent was in force 8 June, 1995 without the benefit of any patent extension derived under 35 USC § 156.

Beyond the 13 February, 2001 date, Applicant has obtained a 1004-day extension under the Hatch-Waxman Amendments (35 USC § 156) bringing the expiration date of United States Patent, 4,335,121, to **14 November, 2003.** This is less than the 14-year cap of the Hatch-Waxman Amendments.

Additionally, the following patents also claim the drug or method of using the drug that is the subject of the above-identified NDA:

4,627,432

i) United States Patent 4,627,432 having an expiration date of **9 December, 2003.**

ii) Drug Product (administration system).

iii) Owned by Glaxo Group Limited, London, England.

4,778,054

i) United States Patent 4,778,054 having an expiration date of **18 October, 2005.**

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* NDA 20-770 is currently being submitted to support the use of Flovent Rotadisk for Inhalation for the maintenance treatment of asthma as prophylactic therapy in adults and children

ii) Drug Product (administration system).

iii) Owned by Glaxo Group Limited, London, England.

4,811,731

i) United States Patent 4,811,731 having an expiration date of **29 July, 2006**

ii) Drug Product (administration system)

iii) Owned by Glaxo Group Limited, London, England.

Des. 299,066

i) United States Patent Des. 299,066 having an expiration date of **20 December, 2002.**

ii) Drug Product (administration system).

iii) Owned by Glaxo Group Limited, London, England.

The Agent for Glaxo Group Limited is: David J. Levy, Patent Counsel, Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, North Carolina 27709; 919/483-2723, facsimile 919/483-7988.

The undersigned further attests that the above-listed patents cover the formulation, composition, or method of use of FLOVENT® ROTADISK® FOR INHALATION. This product is the subject of this application for which approval is being sought.

Date: 09/25/96

Charles E. Dadswell
Attorney for Applicant
Registered Patent Attorney
Registration No. 35,851

EXCLUSIVITY SUMMARY for NDA # 20-770 SUPPL #

Trade Name Flovent Rotadisk, 50 mcg, 100 mcg and 250 mcg
Generic Name fluticasone propionate inhalation powder
Applicant Name Glaxo Wellcome HFD- 570

Approval Date November 7, 1997

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /_X_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X_/

   If yes, what type? (SE1, SE2, etc.)

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_X_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-548 Flovent inhalation aerosol NDA# 19-958 Cutivate Cream

NDA # 20-121 Flonase Nasal Spray NDA # 19-957 Cutivate Ointment

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /_X_/ NO /___/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X_/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # FLIT 85

Investigation #2, Study # FLD-220

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #
NDA # _____ Study #

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1, Study # FLD 220

Investigation # 2, Study # FLIT 85

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /_X_/ ! NO /___/ Explain:

Investigation #2

IND # _____ YES /_X_/ ! NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____
_____ ! _____
_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____
_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Sandy Barnes
Title: Project Manager

11/17/97
Date

John K. Jenkins, M.D., F.C.C.P.
Division Director

11/19/97
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

II. Marketing Exclusivity

NDA 20-770

Flovent™ (fluticasone propionate) Rotadisk Inhalation Powder

Request for Marketing Exclusivity

Pursuant to Section 505(c)(3)(D)(iv) and 505(j)(4)(D)(iv) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.108(b)(4), Glaxo Wellcome Inc. requests three years of exclusivity from the date of approval of Flovent™ (fluticasone propionate) Rotadisk Inhalation Powder (50, 100, and 250mcg rotadisks) for the maintenance treatment of asthma as prophylactic therapy in children 4 to 11 years of age.

We hereby certify as to the following:

Section 7, Item VI.H. of this application contains a list of published studies or publicly available reports of clinical investigations known to Glaxo Wellcome through a literature search that are relevant to the use of Flovent Rotadisk Inhalation Powder the maintenance treatment of asthma as prophylactic therapy in children 4 to 11 years of age. This search consists of literature published since submission of the original NDA for Flovent Rotadisk Inhalation Powder (NDA 20-549; December 29, 1994) and covers the time period from May 1994 to July 1996. Glaxo Wellcome has thoroughly searched the literature and to the best of our knowledge, the list is complete and accurate and, in our opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of Flovent Rotadisk Inhalation Powder for such use.

Thus, Glaxo Wellcome Inc. is entitled to exclusivity as this application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and sponsored by Glaxo Wellcome Inc. The following investigations are "essential to the approval of the application" in that there are no other data available that could support FDA approval of the application.

UCR/95/024 A Randomized, Double-Blind, Parallel-Group Comparative Trial Assessing the Long Term Safety of Inhaled Fluticasone Propionate Rotadisk® via Diskhaler® 50mcg BID and 100mcg BID versus Placebo in Patients Aged 4 to 11 Years with Mild to Moderate Chronic Asthma (FLD-220).

GRP/95/012 A Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Compare the Efficacy and Safety of Fluticasone Propionate Dry Powder 200mcg Daily via a Diskhaler Inhaler and Fluticasone Propionate 100mcg Daily via a Diskhaler Inhaler in Comparison with Placebo Dry Powder via a Diskhaler Inhaler in Children with Asthma (FLIT85).

The clinical investigations are defined as "new" as they have not been relied on by the FDA to demonstrate substantial evidence of effectiveness of previously approved drug products for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by FDA to demonstrate the effectiveness or safety in a new patient population of a previously approved drug application.

US Study FLD-220 was "conducted or sponsored by Glaxo Wellcome" in that Glaxo Wellcome Inc. was the sponsor of the investigational new drug application (IND) under which the investigation essential to the approval of the application was conducted. Non-US study FLIT-85, also sponsored by Glaxo Wellcome Inc., was conducted with the approval of ethics committees and where regulatory approval was required, was obtained from the relevant health authority. Informed consent was obtained for all patients and the study was performed in accordance with the Declaration of Helsinki and in subsequent amendments.

Kathleen A. Prodan

Kathleen A. Prodan
Director, Regulatory Affairs

III. DEBARMENT CERTIFICATION

In accordance with the certification provision of the Generic Drug Enforcement Act of 1992 as outlined in correspondence dated July 29, 1992, from Daniel L. Michels, Office of Compliance, Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

Clinical Team Leader Review Memorandum

Memorandum to:	NDA 20-770 file
Product:	Flovent Rotadisk for Diskhaler
Memo date:	9-19-97
Memo from:	Robert J. Meyer, MD Medical Team Leader, DPDP

This memorandum is to document the secondary review conclusions on the NDA for the pediatric indication for the Flovent Rotadisk products, application number 20-770. The secondary review was carried out concurrently with Dr. Purucker's primary review of 20-770. Additionally, Dr. Meyer was the medical reviewer for 20-549, the original application for the Flovent Rotadisk products. This NDA, clinically approvable, is still under review due to CMC concerns. Finally, Dr. Meyer co-reviewed study FLD-220, the pediatric growth/safety trial, as a part of his review of the pediatric efficacy supplement for Flonase, the nasal formulation of fluticasone propionate.

Overview:

Fluticasone propionate was approved for marketing in the inhalation aerosol formulation in March 1996. The approved population is adults and children ages 12 and above. The Flovent Rotadisk NDA was filed concomitantly with the MDI, but has yet to receive approval, mostly for CMC reasons (with remaining labeling issues). This application is under review currently with a due date for the current cycle in November 1997. In order to get the pediatric indication as soon as possible, the sponsor submitted the pediatric efficacy data for the dry powder formulation of Flovent as a separate NDA - 20-770. This NDA, then, is for the use of Flovent Rotadisk via Diskhaler in children ages 4 - 11 years of age. Once approval of 20-549 and 20-770 are gained, the administrative plans are to recombine these two NDAs.

Efficacy:

The efficacy data for this NDA in part presume the clinical approvability of NDA 20-549. For the specific pediatric indication, there are two primary studies which offer assurance of efficacy, FLD-220 and FLIT-85. though FLD-220 was not primarily designed as an efficacy trial, it offers clear evidence of efficacy on nearly all pre-specified efficacy endpoints, including study participation or "survival," spirometry, symptoms, and self-measured PEFRs. FLIT-85 was a non-US efficacy trial that also examined doses of 50 and 100 µg daily in mild to moderate asthmatics and, again, provides convincing evidence of efficacy. Neither study strongly suggests any dose response for efficacy (as usual for inhaled corticosteroids) and neither examined titration issues. Finally, there are no data addressing the use of Flovent Rotadisk as an oral corticosteroid sparing agent in the pediatric population.

Safety:

The safety data in this NDA were reasonably extensive, including the long term safety trial with the 50 and 100 µg BID doses in a one year growth / HPA axis study.

Though both doses were well tolerated (and effective) over the year's duration, this study shows a clear, dose-dependent trend towards growth suppression with the Flovent Rotadisk that becomes statistically significant on several measures for the 100 µg BID dosing, though the actual effect is relatively small (less than 0.75 cm/year). There is also some evidence of adrenal axis effects from the urinary cortisol measures, which again trend towards a dose-dependent decrease from baseline. All told, the systemic safety findings are useful and important for labeling, but do not preclude approval. The few additional local safety findings pertinent to this population can be summarized in a brief narrative in the AE section of the label.

Overall Conclusions:

I am in agreement with Dr. Purucker's assessment that this application is approvable from the clinical standpoint. There clearly needs to be statements in the *Precautions* section of the label relating the growth and HPA findings of this study. I also feel that, since there was no dose response found for efficacy but there was for safety, the 50 µg BID dose should be the usual recommended starting dose and doses of 100 µg BID should only be used for difficult asthma and titration downward should be attempted when control of asthma is gained.

Recommendation:

I recommend approval of this product, once all CMC issues and labeling issues are resolved. Since the CMC is still outstanding and this action will be "approvable," our labeling comments included in the letter will still be fairly general. I also recommend that the sponsor be asked to update the Flovent MDI labeling to reflect the pediatric growth data, even though approval for the MDI below the age of 12 has not been sought, since we know that the MDI has comparable to perhaps higher bioavailability and since adolescents are still growing.

Robert J. Meyer, MD
Medical Team Leader
Division of Pulmonary Drug Products
9/26/97

CC: Purucker/Medical Officer/HFD-570
Meyer/Medical Team Leader/HFD-570
Barnes/project manager/HFD-570
Division File/HFD-570
NDA #20-770

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: 3 October 1997

FROM: Mary E. Purucker, M.D., Ph.D., Medical Reviewer

SUBJECT: Amendment to NDA 20-770, Flovent Rotadisk Inhalation Powder, Pediatric Application; Sponsor: GlaxoWellcome.

TO: Original NDA, Division File, HFD-570

The clinical review of NDA 20-770 has been amended. With regard to pivotal study FLD220, the difference in yearly growth rate between children who received placebo and children treated with 100 μg BID of fluticasone propionate in the intent-to-treat population should read 0.66 cm/year, not 0.73 cm/year. The review has been amended on the following pages to reflect this change:

- On the second page, third paragraph of the cover sheet, under the section entitled "Overview of Application/Review."
- On pages 67 and 78 of the review itself.
- On pages 11 and 13 of the label review.

This change has been communicated to the sponsor, with whom it will be discussed in detail during a telecon scheduled for 6 October 1997.

APPEARS THIS WAY