CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-833

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

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

APPLICATION #:	**NDA 20-833**	**APPLICATION TYPE:**	**Safety Update**
SPONSOR:	**Glaxo Wellcome Research Pk., N.C.**	**PRODUCT/PROPRIETARY NAME:**	**Flovent Diskus 50, 100, 250 μg**
INDICATION:	**Maintenance treatment of asthma; Ages ≥ 4 years**	**USAN / Established Name:**	**Fluticasone propionate (FP; as dry powder formulation)**
CATEGORY OF DRUG:	**Corticosteroid**	**ROUTE OF ADMINISTRATION:**	**Orally inhaled**
MEDICAL REVIEWER:	**M.Purucker, MD, PhD**	**REVIEW DATE:**	**29 Sept. 2000**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	Document ID #:	Submission type/Comments:
30 March 2000	N 000 AZ	Complete response
13 April 2000	N 000 SU	Amendment covering 2 Nov. 1998 to 31 Dec. 1999
7 September 2000	N 000 BL	Revised labeling

RELATED APPLICATIONS

Document Date:	Document ID #:	Comments:
30 March 1998	NDA 20-833 000	Original NDA submission

Overview of Application/Review: This is a review of the 2nd resubmission of NDA 20-833 for Flovent Diskus. From a clinical standpoint, the key issue that has delayed final approval has been the inability to demonstrate the safety and efficacy of once daily dosing for either adult or pediatric patients. In the current resubmission, the sponsor has agreed to withdraw the indication(s).

Review of the safety update lead to the recommendation that _____ be added to the list of adverse events observed during the post-marketing period.

Labeling changes were recommended in the following sections/subsections: CLINICAL PHARMACOLOGY, CLINICAL PHARMACOLOGY/Pharmacodynamics subsection, Clinical Trials, Clinical Trials/ Pediatric Experience, ADVERSE EVENTS, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED.

Outstanding Issues: From the clinical standpoint, the product is recommended for approval if the labeling changes identified in this review are implemented.

Recommended Regulatory Action: | **N drive location:**

NDAs:

Efficacy / Label Supp.: ___X___ **Approvable** _____ **Not Approvable**

Signed: Medical Reviewer: /S/ **Date:** 29 September 2000

Division Director: ___ **Date:** 9/29/2000

Cataracts will also be added to. — avoid

151

1. ABBREVIATIONS:

CSS	Churg Strauss Syndrome
DPI	Dry powder inhaled
FP	Fluticasone Propionate
MDI	Metered dose inhaler
NDA	New Drug Application
PSC	Posterior subcapsular cataract
SAE	Serious Adverse Event
SRS	Spontaneous (adverse event) reporting system

2. DOCUMENTS REVIEWED:
   - Complete response to approvable letter (30 March 2000)
   - Updated product labeling (7 Sept. 2000)
   - Safety update (13 April 2000)

3. BACKGROUND

The NDA for Flovent Diskus was reviewed and found to be approvable on 30 March 1999. Deficiencies in the clinical program for the "once daily indication" for adults and children were identified in the approvable letter. The Division considered the sponsor's complete response of 8 June 1999 to be insufficient to support the safety and efficacy of the once daily indication, and in this most recent complete response, the sponsor has chosen to withdraw it. There was no other pending clinical issue to be addressed in this response.

The labeling submitted by the sponsor has been revised to reflect changes made in the new product labeling for Advair (NDA 21-077), approved 24 August 2000, to include both the package insert and the patient package insert.

4. SAFETY UPDATE

The submission is comprised of a single volume and covers the 14-month period from 2 November 1998 until the end of 1999. Included are safety data for ongoing or completed clinical trials for all orally inhaled formulations of FP, all indications. These totaled 66, of which only four were ongoing studies of Flovent Diskus. This section is followed by a compilation of SAEs, deaths, and pregnancies for all formulations of orally inhaled FP marketed worldwide, reported directly to the sponsor or received through other worldwide spontaneous reporting systems (SRS). Finally, the sponsor includes a limited review of the medical literature searched primarily for clinical pharmacology references to FP.

There were two deaths reported from clinical studies, neither were likely attributable to FP. One patient with independent risk factors for DVT died following an acute pulmonary embolism. The other death occurred during the run-in phase of a clinical trial. There were 49 patients who experienced at least one SAE during clinical studies, 34 of whom were receiving FP. Seven (7) of this total were receiving FP DPI (Diskus or Diskhaler). The most frequently reported SAEs were lower respiratory tract infections or complaints. Eight patients were diagnosed with pneumonia requiring hospitalization during clinical trials. Five of these patients were age < 24 months (range 9 to 23 mos.; total daily dose: 125 –1000 μg) and had been enrolled in a single trial of FP via the

Babyhaler® device.

There were six deaths reported to the sponsor from worldwide spontaneous reporting systems. Four of these deaths occurred in elderly individuals (age 64 – 86 yrs) who were receiving both FP and salmeterol. It is unclear whether the medication was in the form of a combination product, such as Advair, or as separate inhalers. All four of these individuals were coded as succumbing to "cardiac" deaths by the reporting system(s). Causality related to FP is therefore heavily confounded by age, the prevalence of cardiac morbidity and mortality in this age group, and the co-administration of a long-acting β-agonist known to have cardiac effects. There were two other deaths, an adolescent boy and an elderly man, each due to infectious complications. The 13-year old boy, who was a CS-dependent asthmatic, died of pneumonia, pneumococcal sepsis, and acute adrenal insufficiency. The 93 year old man, who was receiving low to moderate doses of inhaled FP, died of fungal pneumonia and ventilatory failure.

There were 135 spontaneous reports of SAEs in the sponsor's database. Events of interest include 10 cases of pediatric adrenal insufficiency with or without growth suppression reported. Ages ranged from 4 to 16 years (median 6 years, mean 8.2 years) and total daily dose of FP ranged from 440 μg to 1500 μg. There was one case of TB reactiviation reported in an elderly man. There were 10 cases of eosinophilic syndromes, of which 7 were labeled as CSS. With regard to bone adverse events, there were three cases of avascular necrosis (hip, ankle) reported and one of fracture (vertebral) associated with osteoporotic changes. There were eight patients who reported cataract, one verified as PSC in a 45 year old woman receiving 880 µg/day of FP MDI and one reported in a 4 year old girl. There were 11 cases of pneumonia, not counting CSS and/or the two deaths reported above. There was a single occurrence of thrombocytopenia reported in a 2 year old child.

There were 3 pregnancies reported in the clinical studies among patients using FP and 26 reported from the post-marketing database. Of this total of 29, three ended in fetal demise, three were associated with SAEs (2) or congenital anomaly (1) in the newborns, and the remaining 23 either had a normal outcome or no further information is available.

Based upon this information, the ADVERSE EVENTS section reflecting the postmarketing experience should be updated to include and cataracts.

5. LABELING COMMENTS

(Note: The numbering referred to in these comments follow according to the "strike-out" version of the label.)

- In the CLINICAL PHARMACOLOGY section, under "Mechanism of Action," the final paragraph numbered 62 to 66 should be deleted.

- In the CLINICAL PHARMACOLOGY section, Pharmacodynamics subsection, 3rd paragraph, lines 141 to 148 should be revised to be consistent with the labeling for

- In the CLINICAL PHARMACOLOGY section, **Pharmacodynamics** subsection, 4th paragraph, lines 151 to 152 should be revised to accurately reflect the data. In particular, the labeling should refer to

- In the **Clinical Trials** subsection, pp. 5 – 8, for each clinical trial displayed in Figures 1 – 4, within the text, include the baseline value of FEV_1 for each placebo arm and Flovent Diskus arm.

- In the **Clinical Trials** subsection, pp. 8 – 9, delete lines 215 – 221. This information, , is confusing and unscientific.

- In the **Clinical Trials** subsection, p. 9, under **Pediatric Experience**, lines 222 – 231, include information to clarify that this trial, FLTA2006, was a device comparison study and therefore of the otal enrollees actually received Flovent Diskhaler rather the Flovent Diskus.

- In the **Clinical Trials** subsection, p. 9, under **Pediatric Experience**, lines 237 – 238, the final sentence should be changed to read as follows:

- In the ADVERSE EVENTS section, lines 556-557 should read: "Adverse events, whether or not considered drug related by the investigators, ..."

- In the ADVERSE EVENTS section, under the "Observed During Clinical Practice" section, include

- In the DOSAGE AND ADMINISTRATION section, the lines 632-633 beginning with "NOTE" should be bolded and moved to line 621 directly above the table.

- In the DOSAGE AND ADMINISTRATION section, the lines 650-653 indicating should be deleted.

- In the HOW SUPPLIED section, on line 679, the word "every" should be changed to "all" and the word "blister" should be the plural "blisters."

CC: *Division File/NDA 20-833/HFD-570*
Purucker/MO/HFD-570
Barnes/PM/HFD-570

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	NDA #20-833	APPLICATION TYPE:	Amendment to NDA
SPONSOR:	GlaxoWellcome	PRODUCT/PROPRIETARY NAME:	Flovent Diskus
INDICATION:	Asthma	USAN / Established Name:	Fluticasone propionate
CATEGORY OF DRUG:	Corticosteroid	ROUTE OF ADMINISTRATION:	Orally inhaled
MEDICAL REVIEWER:	Mary Purucker, MD, PhD	REVIEW DATE:	03 Dec.1999

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	PDUFA Date:	Submission Type:	Comments:
7 June 1999	8 December 1999	Response to "approvable" letter	Reanalysis of data in original NDA; No new studies

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
30 March 1998	Original NDA	5 indications requested: adult asthma (BID), pediatric asthma (BID), oral corticosteroid-sparing, [redacted]

Overview of Application/Review: The NDA for Flovent Discus was reviewed and found to be approvable on 30 March 1999. Deficiencies in the clinical program for the "once daily indication" were identified in the approvable letter, and the sponsor's response to these deficiencies is the subject of this submission.

Outstanding Issues: The NDA remains approvable, but only if the QD indication is withdrawn .

Recommended Regulatory Action: N drive location:

NDAs:

Efficacy / Label Supp.: X Approvable _____ Not Approvable

Signed: Medical Reviewer: /S/ Date: 3 Dec. 1999

Division Director: _____ Date: 12/7/99

6 Page(s) Withheld

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	NDA 20-833	APPLICATION TYPE:	Full NDA
SPONSOR:	GlaxoWellcome	PRODUCT/PROPRIETARY NAME:	Flovent Diskus
		USAN / Established Name:	Fluticasone propionate
CATEGORY OF DRUG:	Corticosteroid	ROUTE OF ADMINISTRATION:	Inhaled
MEDICAL REVIEWER:	Mary Purucker, MD, PhD	REVIEW DATE:	3/31/1999

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	*CDER Stamp Date:*	*Submission Type:*	*Comments:*
30 March 1998	31 March 1998	Full NDA	Flovent Diskus in 311 volumes
23 July 1998	24 July 1998	NDA amendment	120 day safety update
12 October 1998	13 October 1998	NDA amendment	Reanalysis of three RCCT excluding data contributed by Dr. [redacted] (FLTA2001, FLTA2005, FLTA2006)

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
30 September 1997	NDA 20-549, 20-770	Flovent Rotadisk via Diskhaler
	NDA 20-548	Flovent MDI: 44, 110, 220 µg/actuation
6 December 1993	IND 44-090	IND for Flovent MDPI

Overview of Application/Review: Flovent Diskus is a multi-dose powder inhaler (MDPI) containing 60 blisters of dry powder fluticasone propionate (FP) in a lactose blend. It is similar in formulation to the approved Flovent Rotadisk dispensed via the Diskhaler, except that the increased number of doses per unit was designed to increase dosing convenience for patients, compared to the 4 dose per Rotadisk Diskhaler and each Rotadisk blister has a fill weight of 25 g lactose compared to 12.5 g lactose for the Diskus. The application is comprised of 9 pivotal safety and efficacy studies covering all three blister strengths of Flovent Diskus, 50, 100, and 250 mcg/blister, and a range of indications. This application provides sound data to support the safety and efficacy of FP Diskus dosed twice daily for the maintenance treatment of asthma in adults and adolescents (at 100, 250, and 500 mcg BID) and children (at 50 and 100 mcg BID). It also supports the safety and efficacy of FP Diskus 500 or 1000 mcg BID administered as an oral corticosteroid-sparing agent. This application fails to support once daily administration of FP Diskus at any dose studied, for any age group studied, for reasons of marginal efficacy and due to chemistry issues.

Outstanding Issues: Once the CMC issues are addressed and satisfactory labeling is accomplished (to remove the QD indication and to better reflect the database), this application should be approvable.

Recommended Regulatory Action:

NDAs: X Approvable Not Approvable

Signed: Medical Reviewer: [signature] Date: 31 March 99

Medical Team Leader: [signature] Date: 3/31/99

1 TABLE OF CONTENTS

2 INTRODUCTION

Inhaled fluticasone propionate (FP) for the treatment of asthma first received marketing approval in Europe in 1993, and is presently available in over 40 countries throughout the world both as a dry powder formulation (DPI) in addition to an inhalation aerosol. The latter presentation of this product, Flovent® Metered Dose Inhaler (MDI), was approved in the U.S. on 27 March 1996 in three dosage strengths, 44, 110, and 220 µg/actuation, for the maintenance treatment of asthma as prophylactic therapy for adults and adolescents age 12 years and older. An oral corticosteroid-sparing indication was also approved for Flovent MDI at starting doses of 880 µg BID.

The Flovent® MDI is a pressurized canister containing the drug substance FP in combination with a CFC propellant, which acts as a carrier to facilitate delivery of the drug to the lower airways. Because of the international phase-out of CFC's for environmental reasons, the sponsor has chosen to develop dry powder formulations of this drug dispensed via different delivery devices. U.S. regulatory approval was granted to the FP Rotadisk® Inhalation Powder via Diskhaler® in November of 1997, also for three dosage strengths, 50, 100, and 250 µg/actuation. The Diskhaler® was also approved for maintenance treatment of asthma, but carried a wider pediatric indication, that is, approval down to age 4 years rather than 12 years, as with the MDI. Although the sponsor did not submit a controlled clinical trial to support an oral corticosteroid (CS)-sparing indication, dose proportionality-PK studies between the MDI and the Diskhaler® suggested that the two products would be therapeutically similar, and the Diskhaler® was given the oral CS-sparing indication, as well.

One potential problem with the FP Rotadisk® Inhalation Powder dispensed via Diskhaler® is its limited supply of medication per disk, only four doses (or blisters) per Rotadisk,® which is adequate for two days, at most. The current NDA 20-833 for Flovent Diskus® represents an attempt by the sponsor to make powder delivery of FP more convenient for patients. Flovent Diskus® is a multi-dose powder inhaler (MDPI) containing 60 blisters of drug per device. At a BID dosing schedule, each device would have the capability to provide medication for up to one month. While an MDPI may not entirely replace an MDI due to patient preference, it is believed its usage could be substantial, because of the broader proposed indications for this product compared to the MDI (pediatric, once daily).

3 APPROACH TO REVIEW

This reviewer's approach has been to divide the clinical trials data section into three broad categories of review in order to parallel the sponsor's proposed indications for this product. The first section covers the oral corticosteroid-sparing indication and is comprised of the pivotal trials FLTA2002 and FLTA2002*LTE, the open-label, long-term extension of the former trial. The second section covers both pediatric indications, conventional BID dosing plus

once daily dosing, and includes clinical trials FLTA2006, FLTA2007, and FLTA2008. The third section covers both adult and adolescent indications, conventional BID dosing plus once daily dosing, and includes clinical trials FLTA2001, FLTA2003, FLTA2004, FLTA2005, and FLTA2016. The latter trial has been summarized very briefly in this document because

— negate any possibility of approval of once daily dosing for this product at the present time.

4 CLINICAL TRIALS SECTION

4.1 Clinical Trial(s) conducted to support the oral corticosteroid-sparing indication:

4.1.1 FLTA2002

"A randomized, double-blind, placebo-controlled trial of fluticasone propionate 500 mcg BID or 1000 mcg BID via the Multi-Dose Powder Inhaler, or placebo with optional open-label fluticasone propionate 1000 mcg BID via Multi-Dose Powder Inhaler in subjects with chronic oral steroid-dependent asthma"

4.1.1.2 Background Information:

The oral corticosteroid (CS)[1] -sparing indication of Flovent Inhalation Aerosol (NDA 20-548) was based on data from Study FLI-210, which FLTA2002 closely resembles. FLI-210 was a 16-week, 96-subject, randomized, double-blind, placebo-controlled trial enrolling subjects requiring 5-20 mg prednisone daily (or 10-40 mg qod) who had failed previous attempts of prednisone withdrawal. Flovent MDI administered at a dose of 750 µg BID or 1000 µg BID permitted discontinuation of prednisone (the primary endpoint) in 69% of subjects receiving FP 750 BID and 88% of those receiving FP 1000 BID. In comparison, only 3% of patients assigned to placebo could be weaned off steroids by the end of the 16-week trial. FP at either dose was also superior to placebo on nearly all secondary endpoints. There also appeared to be a dose-response, that is, FP 1000 BID was numerically and in general, statistically superior to FP 750 BID on most efficacy endpoints.

FLTA2002 was a 52-week study, but was designed to include a 16-week "phase 1" segment to permit some cross study comparisons. In contrast to FLI-210, however,
FLTA2002 enrolled slightly more patients (111 vs. 96) and also recruited patients with higher daily prednisone-equivalent requirements (5 to 40 mg vs. 5 to 20 mg). Unlike the earlier study, FLTA2002 did not stratify subjects by total pre-study daily steroid dose. It also studied a wider range of FP dosage, 500 BID to 1000 BID compared to 750 BID to 1000 BID, in

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1 CS" has been freely substituted for "corticosteroid" throughout this review

spite of some *in vitro* PK data suggesting that FP via Diskhaler and Diskus are less bioavailable than via MDI (recall that systemic bioavailability may not equal delivery to the pharmacological target site in the lung). FLTA2002 included an extra 36 weeks of double blind treatment and unlike FLI-210, retained nearly all discontinued patients in a parallel open-label arm of FP 1000 BID. This strategy added primarily to the safety database, although tracking prednisone reduction, the primary endpoint, was continued for these patients, as well.

4.1.1.3 Objectives/rationale:

The stated objectives of the study were to compare the efficacy, health-related quality of life, and safety of fluticasone propionate (FP) 500 mcg BID (FP500BID), FP 1000 mcg BID (FP1000BID), and placebo BID administered via a Multi-Dose Powder Inhaler (Diskus) for 52 weeks to subjects with chronic oral corticosteroid (CS)-dependent asthma.

4.1.1.4 Setting:

FLTA2002 was conducted at 13 outpatient sites in the U.S. between 1 December 1994 and 30 August 1996. The number of patients per center ranged from 4 to 15 (4% to 15%).

4.1.1.5 Study Endpoints:

4.1.1.5.1 Efficacy Endpoints:

The primary efficacy endpoint was the percentage of subjects classified as having the following changes in oral prednisone usage compared to baseline: 100% reduction; 50-99% reduction; 1-49% reduction; no reduction; any increase. This assessment was made at each of the following time points: after the first 16 weeks of the study (phase 1), following the subsequent 36 weeks of the study (phase 2), and during open label treatment with FP1000BID for subjects withdrawn during phase 1 or 2 of the study.

Other (secondary) measurements of efficacy included:

- Mean change in maintenance dose of prednisone
- Average daily dose of prednisone
- PFT's: FEV_1, FEF_{25-75}, FVC[2]
- Diary data: PEFR, nighttime awakenings, rescue Ventolin use, symptom scores
- Survival in the study
- Health-related "Quality of Life"

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2 **For Caucasian adults 18 years and older, reference spirometric values were derived from Crapo RO et al *Am Rev Respir Dis* 1981;123:659-664; For African American adults, these values were multipled by 0.8 as recommended by ATS in *Am Rev RespirDis* 1991;144:1202-1218; For adolescent subjects between the ages of 12 and17 years, reference values were derived from G.Polgar and V.Promadhat *Pulmonary function testing in children:Techniques and Standards* 1971; Philadelphia, WB Saunders.**

- Asthma Quality of Life Questionnaire (AQLQ)[3]
- Short Form Health Survey (SF-36)[4]
- Three Item Sleep Scale (SLP)[5]
- Asthma Specific Role Physical (ASRP)[6]
- Device satisfaction questionnaire (phase 1 only)

4.1.1.5.2 Safety Endpoints:

Indices of safety included an overall assessment of asthma stability at each clinic visit, a tabulation of clinical adverse events, routine clinical laboratory tests, HPA axis assessment, PFT's, physical examination, and a 12-lead ECG. This monitoring, including AM cortisol as an assessment of the HPA axis, continued during the post-52 week open label extension.

4.1.1.5.3 Design:

FLTA2002 was a 52-week, randomized, double-blind, parallel-group, placebo-controlled trial of 111 CS-dependent asthmatics which had an open-label extension at the end of the 52-week period. Subjects who were discontinued during the double-blind phase were eligible to receive open label FP 1000 µg BID for the balance of the 52-week study. The study design was "corticosteroid-sparing," that is, its intent was to substitute inhaled study drug for prednisone in oral CS-dependent asthmatics while simultaneously maintaining asthma stability. The relative success of CS-weaning in the FP arms compared to placebo was the primary efficacy endpoint.

4.1.1.6 Summary of Protocol (includes all amendments):

4.1.1.6.1 Study Population

Inclusion Criteria

- Male or female; if female, non-pregnant/non-lactating, surgically sterile ^{or} post-menopausal ^{or} practicing acceptable contraception for at least one month prior to study
- Age ≥ 12 years
- Asthma by ATS standard definition with severity defined by the following criteria:
  - Duration > 6 months
  - Best FEV_1 between 40-80% after withholding short-acting β-agonists for 4 hours or long-acting β-agonists for 12 hours
  - FEV_1 reversibility of ≥ 15%

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3 Juniper EF et al *Thorax* 1992;47:76-83; Juniper EF et al *Am Rev Respir Dis* 1993;147:832-8381 Juniper EF et al *lin Epidem* 1994;47:81-87

4 Ware JE, Sherbourne CD *Medical Care* 1992;30:473-84; Ware JE et al, *NEMC in-house manual* 1993; Boston, MA

5 Boyer JG et al Annual Meeting *AAAAI 1992*

6 Glaxo in-house instrument

- Requirement for oral CS on a daily or qod basis for at least 6 months
- CS dose equivalent to prednisone 5-40 mg qd or 5-80 qod
- Documented unsuccessful attempts to reduce CS dose
- Requirement for a short-acting β-agonist to control symptoms

- Be willing to exchange current short-acting β-agonist for Ventolin® MDI

Exclusion Criteria:

- Asthma history with any of the following:
  - ER treatment or hospitalization for acute asthma in prior 4 weeks
  - Treatment with cromolyn sodium, nedocromil, ipratropium bromide, or atropine in prior 4 weeks
  - Treatment with any of the following CS-sparing agents in prior 12 weeks: methotrexate, gold salts, troleandomycin, azathioprine, or cyclosporine
- Significant concurrent co-morbid medical condition **including Cushing's syndrome or Addison's disease**

(Reviewer's Comment: This exclusion raises the question of whether the sponsor has excluded a population of CS-dependent asthmatics who are more sensitive to, or who are more likely to experience CS adverse side effects. It is unclear how this would affect the efficacy data, although it would likely improve the safety profile since there would be less risk of a subject experiencing "Addisonian crisis" on switch from oral to inhaled CS).

- Substance abuse
- Drug allergy
- Significant clinical laboratory abnormalities
- Abnormal CXR with abnormality not related to asthma
- Abnormal ECG
- Elevated PSA in male participants ≥ 50 years
- URI, lower respiratory tract infection, or influenza vaccination in prior 4 weeks
- Current smoking or tobacco use in excess of 10 pack-years
- Use of astemizole in prior 6 weeks
- Use of intranasal, ophthalmologic, dermatologic, or parenteral corticosteroids (CS) in prior one month
- Use of an investigational drug in prior 4 weeks
- Antibiotic use in prior 4 weeks

Concurrent Medication Exclusions (i.e. proscribed medications during the 52 week study)

- Anticonvulsants
- Antihistamines other than loratidine
- β-blockers
- Digitalis

- Phenothiazines
- Antidepressants
- Macrolide antibiotics
- Quinolone antibiotics
- Ketoconazole, fluconazole
- Any CS medication other than inhaled FP and oral prednisone

4.1.1.6.2 Treatment Arms and Dosing

FP 1000 µg BID: Device A 2 blisters FP 250 µg qAM
Device B 2 blisters FP 250 µg qAM
Device A 2 blisters FP 250 µg qPM
Device B 2 blisters FP 250 µg qPM

FP 500 µg BID: Device A 2 blisters FP 250 µg qAM
Device B 2 blisters placebo qAM
Device A 2 blisters FP 250 µg qPM
Device B 2 blisters placebo qPM

Placebo BID Device A 2 blisters placebo qAM
Device B 2 blisters placebo qAM
Device A 2 blisters placebo qPM
Device B 2 blisters placebo qPM

4.1.1.6.3 Treatment Assignment

Double-blind treatment--Phases 1 and 2: Patients were assigned to one of the three study treatments according to a code generated by the sponsor. Patients were given the lowest available treatment number in the chronological order of presentation to the investigator. Patients were not stratified by prior CS use or by any other variable. No specific attempt to balance treatment assignments among the 13 centers was mentioned.

Open-label treatment up to 52 weeks: Subjects who discontinued from double-blind treatment in either treatment phase were to receive open-label FP1000 BID for the balance of the 52-week study.

Open-label extension after 52 weeks: All patients who completed the 52-week study could elect to continue FP Diskus until inhaled FP MDI was commercially available. Starting dose was FP 1000 BID, but could be tapered to a minimum of FP 250 BID at the discretion of the investigators.

4.1.1.6.4 Study Sequence

One hundred eleven (111) oral CS-dependent asthmatics completed a 2-week screening period (Visit 1 to Visit 2) during which they continued to take all their baseline asthma medications including inhaled CS (if any), except that Ventolin® MDI was substituted for their usual short-acting β-agonist. If their oral CS was not prednisone, then prednisone in comparable doses was substituted for it at this point. Prednisone was not

reduced during this period, but could be increased if needed incrementally by a maximum of 10 mg/day. Baseline data was also gathered, such as FEV_1, PEFR, nighttime awakenings, rescue β-agonist use, etc (see "Assessments," below, and appended "Figures 1 and 2").

At the end of the two-week screening period, subjects were randomized to treatment arm and entered the first 16 weeks of the double-blind segment of the trial, or "phase 1." The first two weeks (Visit 2 to Visit 3) was a stabilization period during which subjects were to discontinue their own inhaled CS and to begin their assigned treatment with FP 500 BID, FP 1000 BID, or placebo BID. Again, prednisone could not be reduced but could be increased, if necessary. Thereafter, patients were seen at weekly intervals, and attempts were made to decrease the prednisone according to pre-specified criteria (see below), beginning with Visit 4.

In order for prednisone to be reduced, subjects had to meet the following stability criteria:

- $FEV_1 \geq 0.80$ x (mean of highest FEV_1's recorded during baseline)
- PEFR ≥ 0.80 x (mean AM PEFR recorded during 2nd week of baseline)
- # nighttime awakenings ≤ 1.5 x (# nighttime awakenings during 2nd week of baseline) and <3 nights/week
- Daily Ventolin use ≤ 1.5 x (mean daily Ventolin use during 2nd week of baseline) and <12 actuations/day

Weeks 17 to 52 were designated "phase 2" and were scored separately from phase 1, although the same prednisone reduction criteria were followed.

Patients who experienced clinical asthma exacerbation could be treated with prednisone bursts (see below). Subjects who required more than three prednisone bursts during phase 1, or more than one prednisone burst during phase 2 to maintain stability were discontinued. Also, any exacerbation requiring hospitalization resulted in discontinuation.

Prednisone bursts were administered as follows: 60 mg for 1 day, taper by 5 mg/day until 2.5 mg above the dose at which exacerbation occurred, maintain this dose for at least 7 days before any further reductions.

Discontinued patients were eligible to receive open label FP 1000 mcg BID, as described above, but were still evaluated per prednisone reduction criteria.

Subject compliance was assessed by examination of diary card information at clinic visits. Drug compliance was assessed for FP by the study drug monitor by counting blisters. Compliance with prednisone

could not be assessed by pill count because subjects frequently used their own personal supplies. Diary card records were therefore used.

4.1.1.6.5 Efficacy Assessments:

The primary efficacy variable, prednisone reduction, was calculated as the difference between daily dose during the baseline period minus the lowest dose achieved that would maintain stability. Subjects on qod prednisone were calculated as daily equivalents.

All other efficacy assessments were considered secondary.

- Spirometry: FEV_1, FVC, and FEF_{25-75} were performed at each clinic visit in triplicate, with the highest value of the three attempts recorded in the CRF. Subjects were to withhold short-acting β-agonists for >4 hours and long-acting β-agonists for >12 hours prior to the study.

- Survival: The probability of a subject remaining in the study over time was determined from the numbers of subjects discontinued during phase 1 or 2 of the study for lack of efficacy.

- PEFR: Measured using a — Peak Flow Meter twice daily in triplicate and recorded on diary cards. The morning measurements were taken before study drug and the evening measurements after study drug.

(Reviewer's Comment: Although a minor point, the rationale for timing the AM and PM PEFR differently relative to study drug administration eludes this reviewer. Also, it is unclear whether subjects were instructed to withhold short-acting β-agonists until after the maneuver was performed.)

- Symptom score: Subjects were asked to rate the previous day's asthma symptoms on a 4-point scale where 0 = none, 1 = mild, 2 = moderate, 3 = continuous. Subjects were to rate symptoms prior to performing the AM PEFR.

- Number of nighttime awakenings requiring treatment: From the prior night. Recorded at the same time as the symptom score.

- Ventolin use: From the preceding 24 hours, also recorded in the AM.

- Asthma Quality of Life Questionnaire (AQLQ): A 32-question survey completed by the subjects at baseline and at endpoint. Questions covered four domains: activity limitation (11 items), symptoms (12 items), emotional function (5 items), and environmental stimuli (4 items). The response format consisted of a 7-point scale where "1" indicated maximum impairment and "7" indicated no impairment. A

difference of 0.5 between active and placebo groups at endpoint was considered a clinically significant difference.

- The Short Form-36 (SF-36): An instrument which assessed health-related quality of life in the following eight areas: physical functioning, bodily pain, limitations in role activities due to physical or emotional problems (2 domains), general health, vitality, mental health perceptions, and health status relative to one year ago. Scored and transformed onto a 100-point continuum with higher scores indicating superior health status.

- Three-Item Sleep Scale (SLP): Instrument which measured the impact of asthma on a subject's sleep quality and quantity. Scored and transformed onto a 100-point continuum with higher scores reflecting improved sleep.

- Asthma-Specific Role Physical (ASRP): Scale developed by Glaxo to measure the effect of treatment on the interference with work, daily, and leisure activities due to asthma. Scored from 1 to 5, this time lower score correlates with improved QOL.

- Device Satisfaction Questionnaire: Patients were asked to rate the Diskus on a 5-point scale concerning attributes such as ease of use, etc. Glaxo instrument.

4.1.1.6.6 Safety Assessments:

- Adverse Events: Recorded in subject's CRF at each clinic visit, including date of onset, frequency, severity, outcome, causality, action taken, and whether "Serious."

Please see appended "Figures 1 and 2" for timing of each safety monitoring procedure described below

- Laboratory evaluations: Clinical laboratory tests included complete blood count with platelets and differential, serum electrolytes, liver function tests, renal function tests, glucose, uric acid, AM plasma cortisol, and 6-hour cosyntropin stimulated plasma cortisol. All laboratory samples were drawn prior to AM dosing with prednisone or study drug. Female subjects also had serum β-HCG measured at baseline and at endpoint (or early discontinuation). Male subjects over 50 years had serum PSA performed.

- 12-lead ECG

- Physical examination including vital signs and oropharyngeal evaluation

- During the post-52-week open-label extension, subjects were monitored for continued asthma stability and safety through PFT, adverse event, and clinical laboratory assessments including AM plasma cortisol.

4.1.1.6.7 Statistical Methods:

Assessment of Efficacy Parameters:

General considerations: All statistical tests were two-sided. Treatment differences at or below the 0.05 level were considered statistically significant. Pair-wise comparisons were performed without adjusting p-values for the number of comparisons made and pair-wise p-values were interpreted only when the overall test among treatment groups was statistically significant.

Sample size: To achieve 80% power to detect a difference of 35% in the number of patients in the FP 500 BID group who eliminated oral prednisone, compared to the placebo group, a target sample size of 32 subjects per treatment group was determined.

The Intent-to-Treat population was defined as all subjects randomized to treatment who received at least one dose of blinded study drug.

The primary efficacy parameter was the percentage of patients in each of the following oral prednisone reduction categories:

- 100% reduction
- 50-99% reduction
- 1-49% reduction
- no change
- increase

The prednisone reduction was calculated as the difference between baseline dose and physician prescribed dose at the last clinic visit of each phase.

Reviewer's Comment: Last-value-carried-forward was used to determine the endpoint prednisone dose for dropouts in the final analysis, since discontinuation resulted in no placebo patients and barely half of the FP-treated patients "surviving" until study endpoint, see below.

Also, there are multiple comparisons here, with 5 categories divided over 2 phases and 2 doses adding up to 20 possibilities. For the sponsor to "win" in this trial, they must win strongly [i.e. very low p-values] on multiple primary endpoints. Note that the sponsor has stated above that no adjustments in p-values were made for multiple comparisons, although calculation of these p-values depended upon the overall test between treatment groups being significant.

There were many secondary endpoints, including alternative representations of prednisone dose, spirometry, diary data, and several

"Quality of Life" instruments.

The mean daily dose of prednisone was calculated as the maintenance dosage plus bursts, and was compared between treatment arms on a week-by-week basis. Differences between treatment arms for mean daily prednisone, spirometric measurements, asthma symptom scores, PEFR, nighttime awakenings, and rescue β-agonist use were each tested for statistically significant differences using an ANOVA model F-test that included investigator effects and treatment-by-investigator interaction. For PEFR, Ventolin use, nighttime awakenings, and symptoms scores this test was performed on mean values over days within individual weeks. For PFT's and prednisone, it was the last recorded value at the clinic visit.

The four "Quality of Life" questionnaires each had multiple domains that could be analyzed separately, although the results were considered to be for descriptive purposes only if the overall difference was not significant. Mean differences between treatment arms for each of the four scales were tested using the ANCOVA F-test with baseline as the covariate and a term to control for investigator. Numerical differences considered "significant" were based on the previously observed standard deviation for the instrument, and in the case of the AQLQ, by what was considered a "clinically significant" difference.

Questionnaires were given only to subjects who remained in the double-blind cohort, and were administered at baseline, at other defined intervals (see Figure 1, 2) or at discontinuation. Seventy-five (75%) of each questionnaire had to be completed for the data to be included in the analysis.

Reviewer's Comment: In general for all of these instruments, the analysis based on the standard deviation indicated that a sample size in the range of 32 per treatment arm would be required to provide 80% power to detect a difference between treatment arms. The substantial number of subjects who discontinued, and the limitations placed on using incomplete questionnaires, suggests that the study was too underpowered by the analysis stage to make sense of any of the results from these instruments.

Assessment of Safety Parameters:

Safety assessments were based upon adverse events, clinical laboratory tests, HPA axis assessments, physical examinations including vital signs, and the12-lead ECG. The Intent-to-Treat population formed the basis for these assessments. Although ANOVA was planned to detect treatment effects for each of these parameters, no statistical tests were performed due to the small number of placebo subjects (n=4) who remained in the study at Visit 18 (week 16). However, the proportion of subjects with abnormal tests was reported by treatment group for each parameter.

4.1.1.7 Results:

4.1.1.7.1 Efficacy Results

4.1.1.7.1.1 Disposition of Subjects

One hundred eleven (111) subjects met randomization criteria at Visit 2 and were assigned to a treatment arm. The disposition of subjects who were enrolled in phase 1 (the first 16 weeks) is shown in the table below. There were 48 subjects who discontinued during this phase, and all of them elected to continue in the open-label FP 1000 BID arm. Overwhelmingly, the reason for withdrawal was lack of efficacy, which included worsening of asthma as defined by hospitalization, (third) burst of prednisone, or increased additional asthma medication. The "other" category included noncompliance, protocol violations, and request to leave the study.

SUBJECT DISPOSITION (PHASE 1)

	Placebo	FP500 BID	FP1000 BID	Total
Enrolled	34	41	36	111
Completed	4 (12%)	29 (71%)	30 (83%)	63 (57%)
Withdrawn	30 (88%)	12 29%)	6 (17%)	48 (43%)
Lack of Efficacy	27 (79%)	5 (12%)	3 (8%)	35 (32%)
Adverse Events	2 (6%)	3 (7%)	0	5 (5%)
Other	1 (3%)	4 (10%)	3 (8%)	8 (7%)

Phase 2: Sixty-three (63) subjects continued into phase 2 in the double-blind group, 4 in placebo, 29 in FP500 BID, and 30 in FP1000 BID. By the end of the 52-week study, all 4 placebo patients, 11 of the FP500 BID group, and 12 subjects from the FP1000 BID group had discontinued and entered the open label option. As in phase 1, the primary reason for withdrawal was "lack of efficacy."

Open-Label Phase: Seventy-one (71) subjects entered the Open-Label Phase of the study after withdrawing from double-blind study treatment during phase 1 or phase 2. During this phase, all subjects were to receive open-label FP 1000 BID for the balance of the 52 weeks. Sixty-five (65) subjects completed the open-label therapy phase for a total of 52 weeks of study treatment. Of the six subjects (8%) who withdrew, three had worsening asthma, two had an adverse event, and one was noncompliant.

Reviewer's Comment: Things get confusing at this point. There were subjects who "continued in the study," but who no longer received FP. For example, open-label FP was discontinued for subject #2103 because of eosinophilic pneumonia, but she continued in the study on oral prednisone.

4.1.1.7.1.2 Demographics and Other Baseline Characteristics:

As shown in the table below, the three treatment arms were not significantly different from each other at baseline. Approximately 40% were male and one-fifth were minorities. Subjects ranged in age from 12

to 77 years with a mean age of 49 to 50 years. With regard to severity, percent predicted FEV_1 was approximately 60% predicted overall. On average, one out of five subjects in each treatment group had been hospitalized at least once in the prior year for asthma exacerbation.

BACKGROUND CHARACTERISTICS*

	Placebo	FP500 BID	FP1000 BID	Total
Number	34	41	36	111
Gender:				
Female	21 (62%)	25 (61%)	21 (58%)	67 (60%)
Male	13 (38%)	16 (39%)	15 (42%)	44 (40%)
Ethnicity:				
Black	6 (18%)	6 (15%)	5 (14%)	17 (15%)
Hispanic	2 (6%)	0	1 (3%)	3 (3%)
Caucasian	26 (76%)	35 (85%)	30 (83%)	91 (82%)
Age (years):				
Mean	48.5	48.8	50.0	49.1
Range	16-74	12-77	15-76	12-77
Prior Tobacco Use	10	8	8	26
	29%	20%	22%	23%
Asthma Duration ≥ 15 years	18	28	20	66
	53%	68%	56%	59%
Hospitalizations in prior 12 months**:				
0	28 (82%)	34 (83%)	27 (75%)	89 (80%)
1	5 (15%)	3 (7%)	7 (19%)	15 (14%)
≥ 2	1 (3%)	4 (10%)	2 (6%)	7 (6%)
Baseline prednisone dose in mg/day	13.03	15.44	13.58	
Baseline FEV_1:				
Mean (±SE)	1.87 L/min (0.11)	1.81 L/min (0.10)	1.90 L/min (0.11)	
% predicted	61%	60%	62%	

*Data pooled from Tables 4, 5, and 6; volume 54, pp.197-9.

**For asthma exacerbation. Pattern for ER visits due to asthma is very similar to hospitalization data.

Concurrent asthma medication use at baseline differed somewhat by treatment group. Theophylline was used by approximately two thirds of all patients (61-68%), and was similar across groups. In contrast, use of salmeterol and inhaled CS's differed considerably between patients and across treatment groups. At baseline, 23 or 68% of placebo, 20 or 49% of FP500, and 13 or 36% of FP1000 were receiving salmeterol for their asthma. Similarly with regard to inhaled CS, 22 placebo (65%), 35 FP500 (85%), and 26 FP1000 (72%) subjects were receiving these drugs at baseline (Table ST-2, vol.55, pp.11-13). The proprietary inhaled CS listed were Beclovent, Azmacort, Aerobid, and Vanceril, with doses ranging from 4 to 24 actuations/day.

Reviewer's Comment: Inhaled CS use at baseline may be a marker for more severe asthma among patients who are already receiving oral CS. More subjects in the FP500 group received inhaled CS, and the average baseline prednisone dose taken by this group as a whole was also somewhat higher than the other two groups. These data suggest that

the FP500 group may have been more severely affected than the FP1000 or placebo subjects

Phase 2: The demographics and background characteristics of subjects who entered phase 2 were not substantially different from those who were enrolled in phase 1 at the start of the study, except that the percentage of African American subjects who continued in the double-blind treatment was somewhat lower (10%) than the overall percentage enrolled at the start of the study (15%).

Open-Label Phase: As might be expected, demographic and background characteristics of the subjects in the open-label phase were not substantially different from subjects who enrolled in phase 1, except that the percentage of African Americans was higher (20%) reflecting the dropouts from the double-blind phases.

4.1.1.7.1.3 Efficacy Analysis

In the submission, the sponsor has chosen to analyze and present this clinical trial as if it were three separate trials. Safety and efficacy data from phase 1 are presented completely before data from phase 2 are analyzed. Likewise with the data from the group who received open-label FP1000 BID for variable periods of time.

This review is organized somewhat differently. The efficacy data, first primary and then secondary, are analyzed consecutively from all three periods before the safety data is analyzed. This approach is intended to preserve the logic and continuity of this trial, and especially what happens with its primary endpoint, prednisone reduction, over time. Ideally, it may also permit a better sense of how adverse events are related to duration of study drug exposure. For purposes of this review, however, analysis of the first 16-weeks of this trial will be considered primary, because this time period was the only segment of the study which had a concurrent placebo arm.

4.1.1.7.1.4 Primary Endpoint (Phase 1): Prednisone Reduction

The sponsor presents the prednisone reduction data using several different analyses, including proportion of patients weaned off of prednisone, the proportion of patients in each dose reduction category, the average daily dose of prednisone, and the absolute reduction (in mg) in prednisone dose. As a general statement, each one of these analyses support the efficacy of FP over placebo as an oral CS-sparing agent. There is no discernable dose-response, however, as the efficacy data from the FP500 BID group is not significantly different from the FP1000 BID group on this endpoint, although there are small numerical differences in favor of the higher dose.

The change in oral prednisone maintenance dose by response category at endpoint for the intent-to-treat population is shown in the table below (Volume 54, p.70). At the end of 16 weeks, the distribution of subjects among the 5 reduction categories was significantly different by treatment groups ($p<0.001$). Pair-wise comparisons were significant for FP500 BID and FP1000 BID compared to placebo ($p<0.001$), but not for FP500 BID compared to FP1000 BID ($p=0.285$).

PREDNISONE REDUCTION (Phase 1)

% Reduction by Category	Placebo N=33	FP500 BID N=40	FP1000 BID N=36
100%	3 (9%)	30 (75%)	32 (89%)
50-99%	10 (30%)	4 (10%)	3 (8%)
1-49%	6 (18%)	5 (13%)	1 (3%)
No change	6 (18%)	0	0
Increase	8 (24)	1 (3%)	0

Mean change from baseline in maintenance prednisone dose also showed a statistically significant treatment effect at the phase 1 endpoint ($p<0.001$; see Table 12, vol.54, p.210). The mean maintenance dosage decreased by 12.0 mg and 13.0 mg, respectively, for the FP500 and FP1000 groups, but by only 5.19 mg for placebo. Final maintenance doses were 7.84, 3.41, and 0.63 for placebo, FP500, and FP1000, respectively. Again, the pairwise comparisons showed statistical significance for each FP group relative to placebo ($p<0.001$) but not between the two FP groups ($p=0.470$).

The daily dose of prednisone was calculated as maintenance plus any "bursts" that a patient was taking, based on data recorded in each subject's diary. The mean daily dose ± SE was reported for each treatment group by week, based on the average for that week (Table 13, vol.54, p.211). "Endpoint" is based on the last recorded diary entry prior to discontinuation (last value carried forward: LVCF):

MEAN DAILY DOSE PREDNISONE

	Placebo			FP500 BID			FP1000 BID		
	N	mg pred	(SE)	N	mg pred	(SE)	N	mg pred	SE
Baseline	34	12.7	(1.5)	41	16.6	(1.6)	36	13.4	(1.3)
Week 16	6	14.0	(5.2)	31	1.8	(0.9)	30	0.4	(0.3)
Endpoint	34	19.9	(2.6)	41	6.9	(2.1)	36	1.0	(0.5)

The average daily prednisone dose decreased from baseline by 14.8 mg and 13.0 mg for the FP500 BID and FP1000 BID groups, respectively, by the 16th week of the study, compared to an increase of 2.7 mg for placebo. A similar trend is seen when study endpoint is used (no p-values were provided).

4.1.1.7.1.5 Primary Endpoint (Phase 2): Prednisone Reduction

Sixty-three subjects completed phase 1 and entered phase 2, four in the placebo group, 29 in the FP500 BID group, and 30 in the FP 1000 BID group. Of this total, three in the placebo group, two in FP500, and five in FP1000 were apparently discontinued from the study with no maintenance dose recorded. Therefore, the analysis is based upon the 53 remaining double-blind subjects. The change in oral prednisone maintenance dosage by response category at phase 2 endpoint is shown in the table below (Table 51, vol.54). All FP-treated subjects had a 100% reduction in dosage from baseline (visit 2) to phase 2 endpoint (week 52 or early withdrawal).

PREDNISONE REDUCTION (Phase 2)

% Reduction by Category	Placebo N=1	FP500 BID N=27	FP1000 BID N=25
100%		27 (100%)	25 (100%)
50-99%			
1-49%	1 (100%)		
No change			
Increase			

Reviewer's Comment: The data become very misleading here. If you look at the subject disposition during phase 2 (two tables above), 11/29 of the FP500 group and 12/30 of the FP1000 group are discontinued, most for "lack of efficacy," yet 100% of each group have achieved "100% reduction" in maintenance prednisone. The only way to interpret this is to assume that subjects are tapered to "0" on their maintenance prednisone, but soon thereafter exacerbate. They are then placed on "burst" doses of prednisone and are discontinued (recall patients are dropped from phase 2 for only one exacerbation). Although "CS-spared", by no means are these patients "CS-free" (see below).

Mean reduction from baseline in maintenance prednisone use was 10.8 mg for FP500 and 13.0 mg for FP1000 and, as indicated by the above table, maintenance dose for both FP treatment arms was 0 mg. One placebo-treated subject reduced his daily maintenance prednisone dosage by 25% before being withdrawn. Average daily prednisone use (maintenance plus bursts) at phase 2 endpoint was 3.10 mg for the FP500 and 8.51 mg for the FP1000 group.

4.1.1.7.1.6 Primary Endpoint (Open-label Phase): Prednisone Reduction

Seventy-one (71) subjects who discontinued one of the double-blind phases were eligible to receive open label FP 1000 BID for the duration of the 52-week trial. They were allowed unlimited bursts for exacerbation, but tapering of maintenance prednisone continued as per protocol. At study endpoint, the mean decrease in maintenance prednisone was 11.3 mg, with 57 (80%) discontinuing maintenance prednisone, 8 (11%) reducing it by 50 to 99%, 2 (3%) reducing it by

<50%, and 4 (6%) requiring increases to retain stability (data taken from Table 86, vol.54).

Reviewer's Comment: The sponsor provides no data on the average daily dose of prednisone for this open-label group (other than recorded in individual CRFs). This dose could have been substantial because unlimited bursts were permitted, and most subjects were in this phase because of "lack of efficacy" of double-blind treatment.

4.1.1.7.1.7 Secondary Endpoint: Survival

The probability of remaining in the study over time without being withdrawn for lack of efficacy significantly favored the two FP arms over placebo during both phase 1 and phase 2. At the end of phase 1, 27 subjects (79%) had discontinued for lack of efficacy compared with 5 subjects (12%) in the FP500 BID group and 3 subjects (8%) in the FP1000 BID group (p=0.001 by logrank test on Kaplan-Meier estimates of survival). The two FP groups did not differ significantly for probability of survival in phase 1 (p=0.512; see Figure 7, attached).

By the end of phase 2, 100% of the remaining placebo patients (n=4) had discontinued for lack of efficacy compared to 24% (n=7) of the FP500 and 30% (n=9) of the FP1000group.

4.1.1.7.1.8 Secondary Endpoint: Spirometry

Changes from baseline in subjects' FEV_1, FVC, and FEF_{25-75} were compared across treatment arms at the end of phase 1 and phase 2. At the end of the first 16 weeks, there was a statistically significant treatment effect for mean change in FEV_1(see "Demographics" table, above, for baseline FEV_1). Pairwise treatment comparisons indicated that the improvement in FEV_1 was significantly greater for the FP1000 group (0.41L) compared to placebo (-0.06L; p<0.001). Statistical significance was not found in the change from baseline in FEV_1 for the FP500 group (0.13L) compared to placebo. On this particular endpoint, the improvement seen in the FP1000 group was significantly greater than that seen in the FP500 group (p=0.012). Change from baseline for the other two endpoints, FVC and FEF_{25-75}, each showed a significant treatment effect. Pairwise comparisons demonstrated statistical significance for both FP500 and FP1000 compared to placebo, although they were not significantly different from each other.

For these same variables during phase 2, the change from baseline in FEV_1 for was 0.22L for FP500 and 0.27L for FP1000. The change for the placebo arm at endpoint was 0.29L, however, this was based on only 4 patients, 3 of whom discontinued during the first week of phase 2 and the 4th by week 8.

4.1.1.7.1.9 Secondary Endpoints: Diary entries (PEFR, Symptom scores, β-

agonist use, and Nightime awakenings)

For phase 1, change from baseline in AM PEFR was –23 L/min for placebo. 23 L/min for FP500, and 48 L/min for FP1000. For PM PEFR, the mean changes from baseline were as follows: -9 L/min for placebo, 3 L/min for FP500, and 48 L/min for FP1000. For FP1000, both the AM and the PM PEFR were significantly different from placebo ($p<0.001$ for both comparisons) and from FP500 ($p=0.006$ for AM and $p=0.001$ for PM). The numerical improvement shown by the FP500 group was significant relative to placebo for AM but not PM PEFR.

For phase 2, mean change from baseline in AM PEFR was 6 L/min for placebo, 36 L/min for FP500, and 34 L/min for FP1000. For PM PEFR, the mean changes from baseline were as follows: 4 L/min for placebo, 9 L/min for FP500, and 21 L/min for FP1000. No p-values were provided, although it would appear that both FP arms were superior to placebo for AM PEFR , and not different from each other. For PM PEFR, this could only be said about the FP1000 arm.

Subjects rated their asthma symptoms (cough, wheeze, SOB) daily in the morning prior to PEFR determination using a scale from 0 (no symptoms) to 3 (continuous and interfering with activities). Baseline mean symptom scores were 0.81, 0.75, and 0.95 for placebo, FP500, and FP1000, respectively, indicating mild symptoms, and were not significantly different between groups. At phase 1 endpoint, symptom scores had changed by 0.26 for placebo, -0.26 for FP500, and -0.47 for FP1000, a statistically significant improvement for both FP arms compared to placebo. The difference between FP500 and FP1000 approached but did not reach significance ($p=0.069$). By the end of phase 2, the difference from baseline in mean symptom scores had improved to –0.43 for FP500 and –0.63 for FP1000. As with PEFR scores, no p-values were provided.

Mean daily Ventolin use was recorded as number of actuations used in the previous 24 hours. One nebule was considered 4 actuations. At baseline, Ventolin use was 5.17, 5.83, and 5.49 actuations/24 hours for placebo, FP500, and FP1000. Mean change from baseline to phase 1 endpoint was 1.30, -2.06, and -3.13 actuations/24 hours, indicating worsening of symptoms for the placebo group compared to relative improvement for the two FP groups. This was statistically significant for both FP arms compared to placebo ($p<0.001$ for each pairwise comparison), but not for FP500 compared to FP1000 ($p=0.279$). At phase 2 endpoint, the mean difference from baseline in daily Ventolin use had declined further to –2.41 and –3.20 actuations/24 hours for FP500 and FP1000, respectively.

The baseline number of nighttime awakenings requiring treatment with Ventolin were 0.46, 0.41, and 0.52 episodes/night for placebo, FP500, and FP1000, respectively. Mean change from baseline to phase 1 endpoint was 0.26, -0.19, and –0.42 awakenings/night for placebo, FP500, and FP1000, respectively, indicating worsening of symptoms in the placebo group compared to improvement for the two FP arms. The difference between placebo and FP1000 was significant (p=0.009), but not between placebo and FP500. At phase 2 endpoint, the mean difference from baseline in nighttime awakenings remained about the same as at phase 1 timepoint for FP500 (-0.20 awakenings/night), but worsened numerically for the FP1000 group relative to phase 1 (-0.29).

4.1.1.7.1.10 Quality of Life Assessments

The Asthma Quality of Life Questionnaire (AQLQ) showed improvement in overall scores at phase 1 endpoint relative to baseline for both FP groups (0.84 and 1.29, respectively, for FP500 and FP1000) but not for placebo, which showed a decline relative to baseline (-0.38). The absolute improvement exceeds what is generally accepted as a clinically significant change in AQLQ score, that is , 0.5. The four individual domains of this instrument (emotional function, for example) showed comparable changes in direction and magnitude as for the overall score. Pair-wise comparisons for the overall change showed statistical significance for each FP group relative to placebo ($p<0.001$ for both), but no difference between FP500 and FP1000. At phase2 endpoint, change from baseline in the overall score was –0.07 for placebo, 1.24 for FP500, and 1.31 for FP1000. As for other phase 2 secondary endpoints, these numbers are reported for descriptive purposes only, because too few placebo patients (n=4) remained to calculate meaningful statistical values.

The Short Form 36 (SF-36) assessed changes from baseline in nine psychosocial and other aspects of asthma, such as mental health, vitality, and bodily pain. At phase 1 endpoint, numerical changes in all nine of these domains favored both FP groups over placebo, but the change was statistically significant in only six of these nine assessments. In five of the six significant domains, there was no difference between the two doses of FP. At phase 2 endpoint, in general, these 9 domains continued to numerically favor active treatment over placebo.

The 3-Item Sleep Scale (SLP) showed numerical improvement in sleep quality at phase 1 endpoint compared to baseline for both FP groups compared to a decline in the placebo arm. Pairwise comparisons showed statistical significance for each FP group compared to placebo, but no significant difference between FP500 and FP1000. From

baseline to phase 2 endpoint, compared to the value at phase 1 endpoint, FP500 improved numerically by approximately 35% and FP1000 by about 5%. Ironically, the group which improved the most was placebo, which made a not-fully-explained change from negative to positive and which had an absolute change in value of 15.81 units (compared to 5.41 for FP500 and 1.23 for FP1000).

Reviewer' Comment: Which calls into question not only the value of the phase 2 analysis, but also the relative merit of these "quality-of-life" instruments, if whatever it is they are measuring is not sustained over time.

As with the other four instruments discussed above, the Asthma Specific Role Physical (ASRP) showed a numerical change which was in the direction of improvement and was of a magnitude to make it "statistically significant" for both FP groups relative to placebo at phase 1 endpoint, compared to baseline. The difference between the two FP doses was again not significant. For the phase 2 endpoint, the absolute direction of change relative to baseline for all three arms remained the same, that is, placebo remained (+) and both FP arms (-). However, all three arms did show modest improvement in the "quality-of-life" for phase 2 only.

4.1.1.7.1.11 Device Satisfaction

The sponsor measured "satisfaction scores" (defined as comfort with the device) for subjects at baseline and at the end of phase 1 and found they had improved.

4.1.1.7.1.12 Subgroup Analysis

A descriptive subgroup analysis was performed for the primary endpoint, maintenance prednisone reduction, by categorizing the ITT population by gender, ethnic origin, and age. These data are shown in the table below (Vol.54, p, 75). Recall that this is a relatively small clinical trial, therefore a subgroup analysis that further divides each treatment arm is unlikely to be of sufficient power to draw any definite conclusions.

In data drawn from the trial as a whole, FP was superior to placebo in oral CS-sparing efficacy. The higher dose, FP 1000 BID, was numerically better but not statistically superior to FP 500 BID on the primary endpoint. Looking at the various subgroups, it is of interest that one of the largest of these groups, female subjects, had a near equal probability of being weaned off maintenance prednisone whether they were in the FP500 (83%) or the FP1000 (81%) treatment groups. The same could be said about the subjects whose age was ≥65 years, although this category included only 18 subjects. On the other hand, a dose response favoring FP1000 over FP500 could be found in the male

subgroup (n=33), African Americans (n=17), and the "adult" subgroup (18-64 years, excluding adolescents and the "elderly").

PERCENT OF SUBGROUP WITH 100% PREDNISONE REDUCTION

	Placebo	FP500 BID	FP1000 BID
All Subjects	N=33 3 (9%)	N=40 30 (75%)	N=36 32 (89%)
Gender			
Female	N=21 1(5%)	N=24 20 (83%)	N=21 17 (81%)
Male	N=12 2 (17%)	N=16 10 (63%)	N=15 15 (100%)
Ethnicity			
Caucasian	N=25 1 (4%)	N=34 28 (82%)	N=30 27 (90%)
African American	N=6 1 (17%)	N=6 2 (33%)	N=5 4 (80%)
Non-Caucasain, non-black	N=2 1 (50%)	0	N=1 1 (100%)
Age			
18-64 years	N=26 3 (12%)	N=32 22 (69%)	N=30 27 (90%)
≥65 years	N=6 0	N=7 7 (100%)	N=5 4 (80%)
12-17 years	N=1 0	N=1 1(100%)	N=1 1 (100%)

4.1.1.7.1.13 Efficacy Analysis of Doses

The dose response and/or most efficacious dose for FP in this oral CS-sparing clinical trial is by no means as clear as was reported from clinical trial FLI210 (NDA 20-548: Flovent MDI). On the primary endpoint, both FP 500 BID and FP 1000 BID are superior to placebo, but are not significantly different from each other. The same can be said for many secondary endpoints, such as survival in study, asthma symptom scores, β-agonist use, and nighttime awakenings. On the other hand, there were a few secondary endpoints where FP1000 was significantly better than FP500 (FEV_1 and PEFR), and, in general, FP1000 was very often numerically superior to FP500 even if the difference did not achieve statistical significance.

The incomplete data available from the subgroup analysis, above, suggests that a dose-response may be more likely in certain groups of CS-dependent asthmatics, in particular, male patients and "non-elderly" subjects. The percent of subjects attaining 100% reduction in prednisone use was numerically greater for the FP 1000 mcg BID dose than for the 500 mcg BID dose, and the difference between the two doses was greater than for the ITT population. Whether this difference

now attains statistical significance cannot be determined because this study was not sufficiently powered to detect differences in subgroups this small.

In summary, the most efficacious dose of FP for the oral CS-sparing indication is not entirely clear at this point. Recommendations relevant to labeling will be settled by a careful review of the safety data.

4.1.1.7.2 Safety Results

4.1.1.7.2.1 Safety Analysis

The safety profile of *Flovent Diskus* is very similar to the description provided in the MO review of clinical trial FLI210 submitted with NDA 20-548 *Flovent MDI*, the primary difference being the duration of the *Diskus* trial well beyond 16 weeks. This review of clinical trial FLTA2002 will be presented in four parts: 1) Phase 1 (Weeks 1-16) in the greatest detail; 2) Phase 2 (Weeks #17-52) 3) Open-Label Phase (before the 52-week endpoint) 4) Open-Label Extension (after 52 weeks).

4.1.1.7.2.2 Phase 1 (Weeks 1-16)

4.1.1.7.2.3 Extent of Exposure

One hundred eleven (111) subjects received at least one dose of study medication, 34 in placebo, 41 in FP500, and 36 in FP1000. Mean exposure to study drug was 75 days for placebo, 103 days for FP500, and 104 days for FP1000. Forty-four (44%), 85%, and 89%, respectively, of each group received at least 12 weeks of study treatment. Completion rates of the 16-week study were 12%, 71%, and 83%. This wide discrepancy is reflected in the absolute numbers of adverse events (below).

4.1.1.7.2.4 Adverse Events (AE's)

The table below summarizes the most frequently reported adverse events in phase 1(vol.54, p.83; defined as >=3 subjects or 7% in either FP group).

The most common AE's by body system were categorized as ENT(Ear, Nose, and Throat) and tended to occur in all three treatment groups, as might be expected for an asthmatic population. Hoarseness/dysphonia was only reported among the FP patients, also not unexpected. Notable among the GI/non-site specific category was oropharyngeal candidiasis, predominant among the FP subjects, again not surprising. Arthralgia and articular pain within the Musculoskeletal category was more frequently reported by FP patients, which

may have been a consequence of systemic corticosteroid withdrawal. Overall, adverse events relating to the eye were reported more frequently in the FP treatment groups (11-17%) compared to placebo (0), although each event was reported in only one or two subjects. Events included eye pain, eye irritation and itching, and eye hemorrhage. There was one report of a cataract, which was surgically removed 5 days into the study.

ADVERSE EVENTS, PHASE 1

# with >=1 AE	**Placebo n=30/34 88%**	**FP 500 BID n=38/41 93%**	**FP 1000 BID n=33/36 92%**
Mean Exposure to Study Drug (days)	75	103	104
ENT	**15 (44%)**	**32(78%)**	**27 (75%)**
URTI	8 (24%)	13 (32%)	11 (31%)
Sinusitis	2 (6%)	9 (22%)	6 (17%)
Sinus infection	2 (6%)	5 (12%)	6 (17%)
Rhinitis	3 (9%)	8 (20%)	2 (6%)
Nasal congestion	0	7 (17%)	5 (14%)
Throat irritation	3 (9%)	6 (15%)	2 (6%)
Dysphonia	0	3 (7%)	4 (11%)
Non-site specific	**14 (41%)**	**20 (48%)**	**15 (42%)**
Candidiasis	7 (21%)	7 (17%)	8 (22%)
Malaise	3 (9%)	8 (20%)	4 (11%)
Edema	3 (9%)	5 (12%)	2 (6%)
Pain	1 (3%)	4 (10%)	4 (11%)
Musculoskeletal	**9 (26%)**	**12 (29%)**	**12 (33%)**
Arthralgia	1 (3%)	7 (17%)	6 (17%)
Pain	5 (15%)	3 (7%)	2 (6%)
Muscle pain	0	3 (7%)	6 (17%)
GI	**5 (15%)**	**12 (29%)**	**15 (42%)**
Thrush	0	3 (7%)	6 (17%)
N/V	0	4 (10%)	3 (8%)
Diarrhea	1 (3%)	1 (2%)	3 (8%)
GI pain	0	4 (10%)	0
Abd. Pain	0	3 (7%)	0
Neurology	**7 (21%)**	**9 (22%)**	**12 (33%)**
H/A	7 (21%)	7 (17%)	8 (22%)
Lower respiratory	**8 (24%)**	**7 (17%)**	**11 (31%)**
Cough	1 (3%)	4 (10%)	3 (8%)
Viral infection	2 (6%)	1 (2%)	6 (17%)
Lower resp. sx	0	0	3 (8%)
Skin	**4 (12%)**	**10 (24%)**	**7 (19%)**
Rash	1 (3%)	4 (10%)	2 (6%)
Pruritus	0	4 (10%)	1 (3%)
Drug interact., OD, Trauma	**4 (12%)**	**4 (10%)**	**5 (14%)**
Muscle injury	1 (3%)	3 (7%)	1 (3%)

Subgroups by gender, age, and ethnicity did not appear to have significantly different AE profiles than the study population as a whole, but numbers were very small. Patients older than 65 years (n=18) numerically had more AE's and more AE's classified as

"severe" by the sponsor than the overall group. Thrush, for example, was reported in 0 placebo, 1 (14%) FP500, and 3 (60%) FP1000 subjects, but again these are very small numbers.

There were no deaths during this phase of the study.

There were 8 serious AE's, 3 in placebo (asthma exacerbation, reflux esophagitis, status asthmaticus), 4 in FP500 (tachycardia, cystitis, otitis media and sinusitis, anaphylaxis due to NSAID), and 1 in FP1000 (avascular necrosis of the right hip).

Adverse events related to systemic CS effects not already described above included the following:

- A 15-year old subject randomized to FP1000 who developed adrenal suppression during therapy (day 57 of double-blind treatment).
- Glaucoma—The same patient who underwent cataract extraction 5 days into double-blind therapy had been diagnosed with glaucoma during the screening period prior to study medication administration.
- Eosinophilia—One subject in the FP500 arms developed elevated eosinophils in the 2.5 x 10^3 after 57 days of study drug.

4.1.1.7.2.5 Laboratory Analysis Including HPA Axis:

HPA-axis was assessed by by unstimulated AM plasma cortisol and by stimulated plasma cortisol peak and AUC following a 6-hour cosyntropin (250 mcg) infusion (Table 37,38; vol.54; see also Tables 1,2, attached).

Reviewer's Comment: The 6-hour ACTH infusion, which may detect clinically significant adrenal suppression, is generally not sensitive for more subtle adrenal abnormalities.

Ninety-eight (98) subjects were tested at baseline and 54 of these 98 at 16-weeks. Each of the three arms, including placebo, showed a mean improvement in each of the above parameters by study endpoint. Differences across treatment groups were not significant on any of these measurements, except that there was a trend at Week 16 toward greater change from baseline in stimulated peak plasma cortisol in the FP500 group compared to the other two groups (p=0.056; Table 38; vol. 54).

As might be expected, the percentage of patients at baseline who had abnormal peak responses to cosyntropin infusion was very high, 74% of placebo, 59% of FP500, and 73% of FP1000 (assuming an abnormal peak response as anything <18 mcg/dl). By study endpoint,

2/4 remaining placebo patients had abnormal responses compared to 4 (14%) FP500 subjects and 9 (36%) patients in the FP1000 group. All subjects with abnormal stimulated or unstimulated plasma cortisol concentrations or responses were found to have had abnormal baseline tests, with the exception of three patients: one in the placebo group and two in the FP1000 group.

Unstimulated AM plasma cortisol was low at baseline in 77%, 56%, and 52%, respectively, of placebo, FP500, and FP1000 subjects (where abnormal was anything <5 mcg/dl). At the 16-week endpoint, abnormal values were found in one out of four (25%) placebo patients, 7 of 25 (28%) FP500 subjects, and 12 of 22 (55%) of the FP1000 group.

Small numbers of subjects had changes in other laboratory parameters consistent with systemic CS effects, or withdrawal from systemic corticosteroids:

- Four subjects (10%) in the FP500 group and two (6%) in the FP1000 group had significantly elevated eosinophil counts post-randomization (1.25 - 2.37 $x10^3$/ul vs. Normal <0.58$x10^3$/ul). Four of six of these subjects had normal counts before the trial. One of these patients was reported earlier in this review.
- Three FP500 subjects and one FP1000 subject had elevated glucose levels, compared to one in the placebo group. For three of the five, including the placebo subject, these elevations preceded the trial.
- Slightly more placebo than FP patients were found to have elevated cholesterol, potassium, and BUN post-randomization.

There were no significant changes in physical exam, VS, or ECG directly attributable to study drug which have not already been discussed in this review.

4.1.1.7.2.6 Phase 2 (Weeks 17-52)

4.1.1.7.2.7 Extent of Exposure

There were 63 patients who received double-blind treatment medication in phase 2, 4 placebo, 29 FP500, and 30 FP1000. Only 36 completed the final 36-weeks, none in placebo 18 (62%) in FP500, and 18 (60%) in FP1000.

Mean exposure to study drug was 34 days for placebo, 197 for FP500, and 195 for FP1000. Median days of exposure were

28, 251, and 247, respectively. Twenty each of FP500 and FP1000 received >32 weeks of treatment during phase 2 and therefore had a cumulative exposure of >48 weeks.

4.1.1.7.2.8 Adverse Events

The overall pattern and frequency of adverse events was not substantially different during the 2nd phase of the study compared with the 1st. Ninety percent (90%) of FP500 and 83% of FP1000 subjects experienced at least one AE. Adverse events linked to CS withdrawal (e.g. myalgia) or to local effects (e.g. thrush) were also similar in frequency. Overall, 5 (21%) of FP500 and 10 (33%) of FP1000 subjects were coded as having experienced "candidiasis."

There were no deaths during phase 2.

There were six serious adverse events (vol.54, p.101), one in the FP500 group and five in the FP1000 group. Although not coded as treatment-related, three events were consistent with known systemic effects of CS's: Distal tibial prolapse (FP500), Staph infection of the thigh (FP1000), and Depression (FP1000).

4.1.1.7.2.9 Laboratory Analysis Including HPA Axis:

There were 57 subjects who underwent 6-hour cosyntropin testing at phase 2 start and 35 who completed a repeat assessment after 36 weeks on the study. Of these 35, there were 17 FP500 and 18 FP1000. There were no significant cross-treatment differences at start of phase 2. However, at week 52, the mean peak plasma cortisol was 27.0 mcg/dl and 21.7 mcg/dl for FP500 and FP1000, respectively. The FP500 group also had higher mean values for unstimulated AM plasma cortisol and plasma cortisol AUC.

The number of subjects with abnormally low stimulated plasma cortisol (<18 mcg/dl) was higher in the FP1000 group (5 subjects; 28%) than in the FP500 group (1 subject; 6%). Similarly, two (12%) of the FP500 and 9 (56%) of the FP1000 subjects were found to have abnormally low unstimulated plasma cortisol levels (<5 mcg/dl) at 52 weeks. Both of the FP500 and 4 of the FP1000 subjects had AM cortisol <5 mcgdl at baseline.

Reviewer's Comment: These results are consistent with the observation that time until improvement in adrenal function can be prolonged after systemic corticosteroids, and that lower doses of inhaled CS, as might be expected, are permissive of a faster return.

There were no new, clinically relevant changes in routine laboratory values that were not already covered in phase 1. There was no

accelerated appearance of hyperglycemia, hypokalemia, eosinophilia, etc. compared to phase 1 in spite of the longer duration of phase 2.

There were no clinically relevant changes in physical exam, VS, or ECG not already covered.

4.1.1.7.2.10 Open-Label Phase (before 52 weeks)

4.1.1.7.2.11 Extent of Exposure

Seventy one (71) subjects received open label FP for the balance of the 52-week study after withdrawal. All but one received FP 1000 BID. Mean and median exposure to study medication was 229 and 259 days, respectively.

4.1.1.7.2.12 Adverse Events

Ninety-three percent (93%) of subjects in the open-label phase experienced an adverse event. Mean exposure was greater here than during either phase 1 or phase 2, therefore the frequency of AE's by body system is slightly higher. However, the overall pattern is not different.

There were no deaths in the open label phase.

Thirteen FP1000 patients experienced a serious AE, three of which lead to study drug discontinuation: Eosinophilic pneumonia (see below), eosinophilia (see below), and asthma exacerbation. The other serious AE's included duodenal ulcer, RLL pneumonia, CHF, post-surgical abdominal pain, esophageal candidiasis, thyroiditis, asthma exacerbation with URTI, right hip degeneration, gastroenteritis, and bronchitis.

- Eosinophilic pneumonia: Occurred in a 28 yo wf who received 4 weeks of double-blind FP 1000 BID and 6 months after starting the open label phase. She developed a migratory, non-resolving right-sided infiltrate with an effusion. Bronchoscopy eventually revealed eosinophilic infiltrate. The infiltrate resolved with prednisone.
- Eosinophilia (possible Churg-Strauss Vasculitis): Occurred in a 49 yo wm who received approximately 10 weeks of FP 1000 BID. He developed eosinophilia and peripheral neuropathy. Sural nerve biopsy was (+) for eosinophilic non-necrotizing vasculitis. The event responded to systemic CS and other agents.

4.1.1.7.2.13 Laboratory Analysis Including HPA Axis

During the open-label phase, blood samples were obtained at 16 weeks, 52 weeks, or at early withdrawal from open label.

Compared to baseline, mean unstimulated plasma cortisol and mean stimulated plasma cortisol values (peak and AUC) had improved by week 52, as might be expected.

Clinical laboratory studies revealed no new adverse events of significance which have not been previously reported and discussed as part of this trial.

Physical examination, VS, and ECG similarly provided no new information regarding the safety of *Flovent Diskus*.

4.1.1.7.2.14 Open-Label Extension (after 52 weeks)

Information is somewhat limited for this phase of the study, since it was added via amendment to the original protocol very soon before it was to begin. Laboratory data, including adrenal assessment, would have been useful given the prolonged follow-up, but unfortunately was not drawn.

4.1.1.7.2.15 Extent of Exposure

One hundred (100) subjects participated in the extension. Seventy (70) subjects had received FP 500 mcg or 1000 mcg BID for 52 weeks prior to entering into the extension. Mean exposure to FP in the post-52-week extension was 152 days. Fifty-four (54) subjects were exposed for >140 days.

4.1.1.7.2.16 Adverse Events

Eighty percent (80%) of subjects in the extension experienced an AE. The nature and frequency of these AE's were similar to those already reported in this review.

Seven FP-treated subjects experienced a serious adverse event in the extension and two of these were withdrawn. One of these subjects died of a MI and the other developed Churg-Strauss vasculitits:

- Fatal myocardial infarction: This 65 yo wm participated in the double-blind portion of the study for one year at FP 500 mcg BID. At the end of 52 weeks, he received FP 1000 mcg BID as part of the open label extension. Three months into the extension, he collapsed and died while golfing. Cause of death was reported as MI. No autopsy was performed.
- Churg-Strauss Vasculitis: A 48 yo wf received FP 1000 mcg BID for 3 months during the extensions phase. She began to have increased symptoms, including cough and sputum, and was placed on antibiotics. After 1 months, w/u showed peripheral eosinophilia and bilateral pulmonary infiltrates. She was hospitalized and received antibiotics. FP was continued, there is no mention of systemic CS therapy at that time. Upon

hospital discharge, the patient soon returned with altered mental status and worsening pulmonary symptoms. Brain MRI showed multiple small CVAs consistent with vasculitis. She was diagnosed with CSS and with drawn from the study. No further information is available due to lack of patient cooperation.

4.1.1.7.2.17 Laboratory Analysis Including HPA Axis

During the open label extension, laboratory studies were obtained every 4 months, at study endpoint, or at the investigator's discretion.

Thirteen percent (13%) of the extension participants were found to have an abnormally low (<5 mcg/dl) unstimulated AM cortisol at some point during the extension.

Five subjects had a "clinically significant" increase in eosinophil counts. (>1.25 x 10^3). One of these subjects was later diagnosed with Churg-Strauss (see above). A second had levels as high as 6.26 x 10^3, but remained without clinical sequelae and continued FP. Both of these cases were reported as AE's. There were a few other abnormal laboratory tests also reported as AE's. These included: two subjects with hypokalemia, one with hyperglycemia, and one with abnormal LFT's (elevated ALT, AST, and alk.phos.)

No safety issues were identified in physical examinations or VS during the extension.

4.1.1.7.3 Safety Conclusions:

In general, FP Diskus is safe and well-tolerated for the oral corticosteroid sparing indication, similar to the Division's conclusions for Flovent MDI (NDA 20-548) three years ago. Since that time, however, several new safety concerns have been brought to light through post-approval monitoring by the sponsor and by the Agency. These include the eosinophilic syndromes, most importantly Churg-Strauss vasculitis, and a greater appreciation of the systemic effects of these "locally acting" corticosteroids. Although these are important considerations, they of course should be balanced against the known adverse effects of long-term oral/systemic CS to control severe asthma, particularly when given for this indication.

Adverse events (AE's) were similar across the three treatment groups in phase 1, 88%, 93%, and 92% for placebo, FP 500 mcg BID (FP500), and FP 1000 mcg BID (FP1000). ENT events were most frequently reported, followed by events related to the local effects of orally inhaled CS (dysphonia, pharyngitis, thrush). Events related to withdrawal of systemic CS were also prominent, such as malaise, myalgia, nausea, and fatigue. Because of the timing of oral CS withdrawal, a lower overall frequency of AE's were reported during