

subsequent phases, when switchover to FP would have been more complete.

In contrast to AE's in general, serious AE's appeared to increase with time and duration of exposure. Unfortunately, there is no placebo arm available for comparison beyond phase 1, so it is unknown how many serious events the placebo group would have reported after 52 weeks of treatment or longer. It is of interest that the serious eosinophilic syndromes began to emerge with longer (and higher) exposure to FP, in fact, the first and only confirmed case of CSS was not reported until well into the open-label extension (although the patient with eosinophilia who had a (+) sural nerve biopsy fulfills CSS criteria, and he was reported during the pre-52 week open label phase). Whether this is a function of duration of exposure to FP, or simply a matter of total patient-days of exposure (i.e. would it have been identified earlier in a larger study?) cannot be determined at this point. The relationship with the higher dose of FP is probably accidental, since patients were randomized and not assigned to treatment by disease severity. The protocol specified that dropouts who continued in the open-label arm could only receive FP 1000 mcg BID, without adjustment in dose until the post-52 week extension, therefore the connection likely has more to do with the greater number of patients receiving the higher dose of FP than with the higher dose itself.

The question of whether the higher dose of FP leads to more AE's and/or AE's of greater severity is an important one, given the marginal efficacy advantage of FP1000 over FP500. With regard to serious AE's, recall that the only incident of adrenal suppression leading to discontinuation occurred in a 15 year old boy 57 days into treatment with FP 1000 mcg BID. Unfortunately, for reasons of study design, many more subjects received FP1000 than FP500, so a direct comparison between the two arms is limited to the double-blind phases only. Of the 11 serious AE's recorded during this period, there was no difference between the two treatment groups, with 6 occurring in the FP1000 arm and 5 in the FP500 group. Similarly, the overall number of AE's was not different between the two FP doses, with approximately 90% of each group experiencing at least one event. Not unexpectedly, specific events related to orally inhaled CS's, such as oropharyngeal candidiasis and dysphonia, were nearly twice as high in the FP1000 group compared to the FP500 group.

The question of whether starting at a lower dose of FP in the CS-dependent asthmatic is itself an important safety issue in itself. Although not uniformly coded as an adverse event (unless it was serious), acute asthma exacerbation leading to discontinuation is an event of interest. Only one such event could be located, which

occurred to a FP500 subject during phase 1. The subject suffered an asthma exacerbation following anaphylaxis to a NSAID, and was discontinued from the study. From a safety standpoint, it is reassuring that the overall occurrence of serious deterioration in asthma control was comparable between the two groups during the double-blind phases of the trial, arguing that starting a patient on the lower dose of FP for oral CS-sparing purposes would not necessarily jeopardize his or her safety.

Laboratory assessment of the HPA axis revealed that the majority of these oral CS-dependent asthmatics had substantial abnormalities in their baseline adrenal function, in spite of the relative insensitivity of the tools by which it was measured. In fact, it is unlikely that any one of them would have been "normal" had a more sensitive tool (low dose cosyntropin test or ON urinary free cortisol, for example) been selected. Nevertheless, many subjects in the double-blind phases of the trial who had been weaned off oral CS began to show improvements by 16 weeks, although even by the 52-week time-point, recovery was far from complete. Furthermore, there was a clear dose-response between the two FP groups, with all but 12% of the FP500 group testing normal for AM plasma cortisol, compared to 56% of the FP1000 group. Stimulated plasma cortisol showed a comparable discrepancy between the two dose levels, with abnormally low readings in 28% of the FP100 group compared to 6% of the FP500 group.

In conclusion, the safety analysis of this trial fails to show a disadvantage to using the lower dose of FP 500 mcg BID, as measured by frequency of acute exacerbation. It also fails to show a safety advantage to starting with the lower dose, as measured by clinical endpoints such as adverse events. However, it is very clear from HPA axis assessment that the lower dose is less adrenally suppressive than the higher dose. Although no definite clinical correlates were identified or discussed in this trial, adrenal suppression may be a marker for other systemic effects that are, as yet, unrecognized. Finally, there remains the nagging issue of the eosinophilic syndromes and Churg-Strauss vasculitis when Flovent is used in this manner. Although there is no scientific evidence impugning the higher dose at this point, caution is in order.

4.1.1.8 Conclusions and Comments Labeling Implications:

The sponsor has provided convincing evidence of the safety and efficacy of *Flovent Diskus* 500 or 1000 mcg BID over placebo in the treatment of oral CS-dependent asthma. While the superiority of this product over placebo is clear, unlike Flovent MDI, the superiority of one dose over the

other is not. The reasons are probably complex and remain to be determined.

The efficacy analysis showed both doses of FP to be significantly superior to placebo on the primary endpoint, oral prednisone reduction, but not different from each other. The majority of secondary endpoints also failed to show a significant difference, with the exception of FEV₁ and PEF, although there tended to be a non-significant numerical advantage to FP1000 on many endpoints. Subgroup analysis, although based on very small numbers, failed to show even a numerical trend in favor of the higher dose for female (surrogate for size?) and elderly subjects. Conversely, non-elderly, non-adolescent patients and male subjects did show a numerical advantage on most endpoints with the higher dose.

Besides acute adrenal insufficiency, the most consequential safety issue of tapering prednisone in CS-dependent asthmatics is status asthmaticus. There was no evidence presented in this clinical trial that exacerbation was any more likely to occur with the lower dose of FP than with the higher.

The adverse event profile was not substantially different between the two FP doses, as measured either by severity or by total number. Serious events such as the eosinophilic syndromes and Churg-Strauss were seen only with FP 1000 mcg BID, but association with the higher dose remains questionable because only the higher dose was used during the latter stages of this trial. Not unexpectedly, there were more local effects, such as thrush, associated with the higher dose.

Finally, by all measures of HPA axis function, the subjects randomized to the FP500 arm showed earlier and superior adrenal recovery than subjects randomized to the FP1000 arm, the majority of whom were still "suppressed" by the 52 week time point.

4.1.1.9 Labeling Implications:

With regard to labeling, the recommended starting dose of this product for oral CS-dependent asthmatics should read 500 - 1000 mcg BID. The highest recommended dose should continue to read 1000 mcg BID. Specific labeling recommendations are contained below:

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 This should be deleted, because it refers to the open-label, uncontrolled post-52 week extension, not the double-blind, placebo controlled period of the trial.
- Under **DOSAGE AND ADMINISTRATION**, the "Recommended Starting Dose" for adults and adolescents receiving oral corticosteroids should read 500-1000 mcg twice daily.

4.2 Clinical Trials conducted to support the pediatric indication:

4.2.1 FLTA2006

"A randomized, double-blind, double-dummy, parallel-group trial assessing the efficacy and safety of fluticasone propionate 50 or 100 mcg BID via the multi-dose powder inhaler, fluticasone propionate (FP) 50 or 100 mcg BID via the Diskhaler, and placebo in subjects aged 4 to 11 years with chronic asthma."

4.2.1.1 Background Information:

FLTA2006 was one of three clinical trials submitted as part of this application which included data generated by Dr. [redacted]. Because of DSI (Division of Scientific Investigations) concerns about the scientific validity of Dr. [redacted] data, the Pulmonary Division asked the sponsor to submit a reanalysis of these three trials. The supplement was submitted on 12 October 1998, and included the reanalysis of FLTA2006. Therefore, when the source of the data used in this review is taken from this particular supplement, and not from the original submission, a citation has been included.

FLTA2006 was conducted as a device comparison trial. Both the approved Diskhaler device and the Diskus dispense a dry powder formulation of FP, with several differences. First, the Diskus has been designed to hold up to one month's supply of medication, compared to only 4 doses for the Diskhaler. Second, the dry powder formulation of FP in the Diskus contains 12.5 mg lactose/dose compared to 25 mg lactose/dose in the Diskhaler. In this trial, the performance of the Flovent Diskus, at nominal doses of FP of 50 mcg BID or 100 mcg BID, is compared to that of the Diskhaler at the same nominal doses in a population of mild to moderate pediatric asthmatics, for which the Flovent Diskhaler has already been approved.

4.2.1.2 Objectives:

The objectives of this study were to compare two doses of dry powder fluticasone propionate (FP), 50 mcg BID or 100 mcg BID, each administered from two different devices, the Multi-Dose Powder Inhaler or Diskus and the Diskhaler, on the following parameters:

- Efficacy: FEV₁, PEF, survival in study, symptom scores
- Humanistic and Resource Utilization Outcomes: 3-item Sleep Scale-Child (SLP-C) and other "quality-of-life" assessments
- Safety: Physical examination, clinical laboratory, HPA-axis, 12-lead ECG, adverse events
- PK: Plasma FP concentrations at selected sites

4.2.1.3 Setting:

Conducted at 34 outpatient sites in the US between 20 March 1995 and 30 August 1996. The number of patients per center ranged from 1 to 37 (0-8%).

4.2.1.4 Endpoints:

4.2.1.4.1 Efficacy Endpoints:

- The primary efficacy variable was change from baseline in AM predose FEV₁ and PEFR determined at each clinic visit.
- Secondary efficacy variables:
 - Survival in study
 - Diary AM and PM PEFR
 - Symptom Scores
 - Rescue β -agonist use
 - Nighttime awakenings
 - QOL: SLP-C, device satisfaction, QOL questionnaire

4.2.1.4.2 Safety Endpoints

- Adverse events
- Clinical laboratory tests
- HPA axis: AM plasma cortisol, 24-hour urinary cortisol, and cosyntropin stimulation tests (at selected sites only)
- Physical examination
- VS
- 12-lead ECG

4.2.1.4.3 PK Endpoints

- Fluticasone propionate (FP)⁷ plasma concentration at 20 and 40 minutes after the AM dose during week 12 (or early termination)

4.2.1.5 Design

FLTA2006 was a 12-week, randomized, double-blind, double-dummy, placebo-controlled, multi-center clinical trial of 435 pediatric asthmatics stratified at baseline for inhaled corticosteroid (CS) use which was conducted to assess the safety and efficacy of fluticasone propionate at 50 or 100 mcg BID delivered from two different devices, the approved Diskhaler or the Diskus, relative to placebo.

4.2.1.6 Summary of Protocol (includes all amendments)

4.2.1.6.1 Study Population

Inclusion Criteria

- Male or premenarchal female
- Age 4 – 11 years and <12 years by visit 2

- Asthma by ATS criteria
- Use of pharmacotherapy for prior 3 months or more
- Effective use of both devices
- Mild to moderate asthma:
 - 4 – 5 years: PEFR \leq 85% predicted⁸
 - 6 – 11 years: FEV₁ 50 – 85% predicted
- Reversibility:
 - 4 - 5 years: PEFR checked pre- and post- β -agonist, but no criteria given
 - 6 – 11 years: \geq 15% increase with β -agonists
- Relatively stable asthma symptoms

Exclusion Criteria

- Life-threatening asthma
- Use of nonsteroidal immunosuppressive therapy for asthma, such as cyclosporine, methotrexate, or gold
- Intermittent or seasonal asthma
- Other significant concomitant disease
- Current chickenpox or exposure in prior 3 weeks
- URI in prior 2 weeks
- Tobacco use
- Allergy to corticosteroids (CS) or β -agonists
- Clinically significant abnormality on screening laboratory or 12-lead ECG
- Glaucoma or posterior subcapsular cataracts (PSC)
- Prior participation in Diskhaler (or other Diskus) study

Disallowed Medications

- At time of enrollment:
 - Any antibiotic in prior 2 weeks
 - Any investigational drug in prior 30 days
 - Oral, intranasal, or parenteral CS in prior month
 - If not already maintained on inhaled CS (\equiv continuous use at stable dose in prior 3 months), inhaled CS use in prior month
- Specifically prohibited during the trial:
 - Anticholinergics
 - Anticonvulsants
 - Antidepressants
 - Long acting antihistamines or antihistamine/decongestant combinations
 - Long acting decongestants
 - Phenothiazines

- Macrolide antibiotics
- Quinolone antibiotics
- β -blockers
- All anti-asthma medications except Ventolin MDI or Rotacaps (substituted for any other β -agonist), theophylline (if on a stable dose for at least 3 months prior), or inhaled CS other than FP (if on a stable dose for at least 3 months prior).

4.2.1.6.2 Treatment arms and dosing:

Subjects were randomized to one of five treatment groups. Each child received both devices, and used both devices for each of the two scheduled doses per day. Only one of the two devices carried study medication, the other contained matching placebo. Devices were exchanged at four-week intervals after the start of the study, that is, at Weeks 4, 8, and 12.

Treatment	Twice Daily Dosing AM and PM
FP 50 mcg BID via Diskus	1 blister FP 50 mcg via Diskus 1 blister Placebo via Diskhaler
FP 100 mcg BID via the Diskus	1 blister FP 100 mcg via Diskus 1 blister Placebo via Diskhaler
FP 50 mcg BID via Diskhaler	1 blister FP 50 mcg via Diskhaler 1 blister Placebo via Diskus
FP 100 mcg BID via the Diskhaler	1 blister FP 100 mcg via Diskhaler 1 blister Placebo via Diskus
Placebo	1 blister Placebo via Diskus 1 blister Placebo via Diskhaler

4.2.1.6.3 Treatment Assignment:

During run-in, subjects were stratified according to whether or not they were receiving inhaled "anti-inflammatories" that is, inhaled CS or inhaled cromolyn sodium (ICT), prior to study entry or were managed on bronchodilator therapy alone (BDT). After the two-week run-in, eligible BDT subjects were randomly assigned, in ascending order, a unique treatment number in the range of numbers 0001 through 0999 while the eligible ICT subjects were similarly assigned a unique treatment number in the range of 1001 through 1999. Each eligible child received the lowest number available for their stratification and chronology of presentation. Subject and treatment numbers were unique and could not be reassigned. No specific attempt to balance enrollment at individual centers was mentioned in the protocol.

4.2.1.6.4 Study Sequence

Screening Period (Visits 1- 2): Five hundred sixty-one (561) children who met the inclusion/exclusion criteria were screened over a two week, single blind period. Subjects could continue to take their baseline asthma

medication at this time, except that Ventolin (MDI or Rotacaps) was substituted for their own particular β -agonist. Once the device was selected, however, it was to be used consistently if the child was eligible to continue with the study. The Ventolin was to be used only to treat symptoms, and not taken on a regular basis (even if that was how it was previously taken).

The screening period was used to confirm eligibility, assess asthma stability, obtain baseline data, assess compliance, and instruct the children (and caregivers) in the use of all the devices and study procedures to be used during this trial. (See the attached "Figure 1" for a summary schedule of events).

Routine assessments performed at Visit 1 included medical history, physical examination, VS, clinical laboratory tests, AM cortisol, 12-lead ECG, and PEFR/spirometry. Urinary free cortisol was to be measured from a 24-hour urine specimen, therefore participants received a plastic container with instructions to return it to the clinic when it was complete.

On the first visit only, children age 4-5 years had the PEFR measured before and 30' after two puffs of Ventolin MDI to assess reversibility. Children age 6-11 years who did not have reversibility documented in their history also had their FEV₁ measured before and after Ventolin.

Children also received instructions on daily routine assessments and procedures they were to perform for the subsequent two weeks. Diary PEFR was to be measured twice daily in triplicate using a Peak Flow Meter, and the highest value recorded in the subject's diary. AM PEFR was to be measured before study medication but after other diary assessments. Clinic PEFR was to be measured in lieu of the child's home AM PEFR assessment, between 7:00 and 10:00 am for each scheduled visit. Children were instructed not to take any β -agonist for at least 6 hours prior to clinic testing. Every clinic visit was to include both FEV₁ (performed first) and PEFR assessment. Children age 4-5 years were asked to perform a PEFR only. Older children age 6-11 years were required to perform both FEV₁ and PEFR.

Children received diary cards at Visit 1, and were instructed to record their asthma symptoms, rescue β -agonist use, and nighttime awakenings daily throughout the study.

The screening period of this trial was single-blind. Each child received a two-week supply of (placebo) Diskus and Diskhaler-with instructions for their use until their next visit (Visit 2). They were told to dose themselves twice each day using one blister from each device, once in

the morning and in the evening, and perform all the assessment described above.

Treatment Period (Visits 2 – 10): Four hundred thirty-seven (437) eligible children completed the screening period and were found to be eligible for the study. In addition to meeting the Inclusion/Exclusion criteria above, these children had met the following “randomization criteria:”

- Their asthma had been relatively stable. “Stable” was defined as having no more than 3 days in the last 7 in which ≥ 12 puffs of Ventolin MDI (or 6 doses of Rotacaps) was used and No more than 3 mornings in the last 7 where the AM PEFR was decreased $>20\%$ from the prior PM PEFR and No more than 3 nights in the last 7 with awakenings requiring Ventolin.
- Their clinic spirometry/PEFR met the following criteria:
 - Best clinic PEFR $\leq 85\%$ predicted for ages 4-5 years
 - Best FEV₁ 50-85% predicted for ages 6-11 years
 - Best FEV₁ from Visit 2 within 25% of Best FEV₁ from Visit 1.
- Adequate compliance was demonstrated:
 - At least 70% of study medication had been used
 - Diary card had been completed
 - Anti-asthma medications had been withheld as required

Eligible children needed to meet additional criteria at each clinic visit to continue in the study. “Stability limits” were therefore defined for PEFR and FEV₁:

- FEV₁ stability limit: 15% decrease from the best FEV₁ at Visit 2
- PEFR stability limit: 20% decrease from mean diary AM PEFR from the past 7 days or 20% decrease from the best Visit 2 PEFR, whichever was higher

(The FEV₁ stability limit applied only to subjects age 6-11 years, PEFR stability limit applied to all subjects).

Children not meeting the following “continuation criteria” at each visit were discontinued for lack of efficacy:

- No more than 2 days in the last 7 in which ≥ 12 puffs of Ventolin MDI (or 6 doses of Rotacaps) was used
- No more than 2 days in the last 7 where the AM or PM PEFR was below the PEFR stability limit
- No more than 2 nights in the last 7 with awakenings requiring Ventolin.
- A clinic PEFR \geq the PEFR stability limit
- A clinic FEV₁ \geq the FEV₁ stability limit (ages 6-11 years only)

At Visit 2, subjects exchanged their placebo devices for the appropriate Diskus (DK) and Diskhaler (DH) devices, as determined by their randomization. Subjects who had been receiving inhaled CS or inhaled cromolyn were told to discontinue these medications for the remainder of the study. Subjects taking theophylline could continue to take it, but were told to withhold it for the 24-36 hours preceding the next clinic visit. All subjects completed baseline QOL questionnaires (see "assessments," below). Selected subjects (100/437) underwent a short cosyntropin stimulation test.

Reviewer's Comment: Baseline efficacy measurements would have been made using a mixed population of children, some receiving inhaled CS and some not. This would tend to raise the baseline, making it more difficult to show a difference with FP. On the other hand, children receiving inhaled CS at baseline randomized to placebo are likely to show a "CS washout" effect, thus flattening or lending a negative slope to the placebo change-from-baseline time-line and increasing the separation between treatment and placebo. These two effects may offset each other, especially since the study was stratified by baseline inhaled CS use.

The discontinuation of theophylline before clinic visits seems a bit odd, since clinic measurements may not reflect the preceding one or two weeks. Also, imbalance between treatment arms in this parameter could possibly affect safety or efficacy results.

At Visits 3-9 the following procedures were performed:

- Review previous diary cards and dispense new cards
- Adverse event assessment
- PFT's: PEFr, spirometry

Visits were scheduled weekly for the first 4 weeks, then every other week until study endpoint at 12-weeks. Devices were collected and new ones dispensed every 4 weeks. At the midpoint of the study, week 6 (Visit 7), an oropharyngeal exam was performed and a second QOL questionnaire was completed. Between the last 2 visits, a second 24-hour urine was collected for determination of urinary free cortisol.

At study endpoint (Visit 10) or early termination, the usual scheduled clinic assessments were made, in addition to the same as performed at baseline (physical exam, etc.). A subset of children completed a 2nd cosyntropin stimulation test. A different subset of children underwent PK testing, with plasma FP concentrations being determined 20' and 40' after the dose given in clinic.

Compliance was assessed by blister counts, completion of diary cards, and whether subject followed instructions to withhold medication on the morning of the clinic visit.

4.2.1.6.5 Efficacy Assessments

The two primary efficacy variables were AM predose FEV₁ and clinic visit PEFR. For the older children (6-11 years), FEV₁ was performed in triplicate using approved spirometric equipment according to ATS recommendations. The child could be sitting or standing during the maneuver, but was required to be consistent throughout the study. For all children in the study, PEFR was performed using the same hand-held — peak flow meter as they used at home. The highest of three determinations was recorded.

Secondary efficacy variables included all of the following:

- Survival in the study
- Diary AM and PM PEFR
- Subject-rated daily symptom scores on a scale of 0 (none), 1 (mild), 2 (moderate), or 3 (continuous or disabling)
- Number of nighttime awakenings requiring Ventolin
- Rescue Ventolin use
- “Humanistic and Resource Utilization Outcomes”
 - 3-Item Sleep Scale-Child (SLP-C)⁹
 - Device Satisfaction
 - Impact on Daily Activities¹⁰

4.2.1.6.6 Safety Assessments

- Adverse Events (AE)
- Clinically significant changes in clinical laboratory values
- Clinically significant changes in physical examination, VS, or 12-lead ECG
- HPA-axis effects
- Plasma concentrations of FP (also for PK purposes)

4.2.1.6.7 Statistical Methods

General Statements: All statistical tests were two-sided. Treatment differences at or below the 0.05 level were considered 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.

Power Calculations: Enrollment was planned to obtain 400 evaluable subjects to provide >80% power of detecting a difference in AM PEFR of 16 L/min between five treatment groups of 80 subjects each, assuming a standard deviation of 36 L/min. It was calculated that 75 subjects/treatment arm would be required to achieve 80% power of

⁹

Glaxo in-house instrument

¹⁰

Glaxo questionnaire for children and parents

detecting a difference in FEV1 of 0.25L between any two treatment groups, hence enrollment exceeded this minimum requirement.

Populations: The Intent-to-Treat (ITT) Population was used for most calculations, unless otherwise stated. The ITT Population included any subject who had received at least one dose of study medication. The Efficacy Population included only those subjects in the ITT group who had no major protocol violations during the study. The decision to exclude a subject from the Efficacy Population was made prior to breaking the blind.

Background Characteristics: Comparisons between treatment groups were based on ANOVA F-test controlling for investigator for age, height, and weight, and on the Cochran-Mantel-Haenszel test controlling for investigator for gender and ethnic origin.

Efficacy: Testing was first performed on data from all investigators combined, assessing investigator effects and treatment-by-investigator interactions at a significance level of 0.10. An ANOVA F-test was used to compare change-from-baseline for each of the time-dependent variables at endpoint (or at other selected time points). Endpoint was the last recorded value for the ITT population and the last evaluable value for the efficacy population.

Withdrawals from the study were evaluated using Kaplan-Meier statistics.

PEFR measurements were also tested with an ANOVA F-test controlling for investigator. Tests were performed on mean values over a minimum of 3 days (or 3 diary points) within individual weeks.

Overall and pair-wise analysis of symptom scores was performed using the van Elteren test based on 7-day subject averages.

Data for SLP-C were reported using descriptive statistics and compared using ANCOVA to control for baseline score. Within treatment change from baseline was analyzed using a paired t-test.

Safety: All safety assessments were based on the ITT population. Adverse events were tabulated by organ system, treatment group, severity, and relation to study drug. Laboratory variables, ECG, VS, and physical exam were reported by presence and/or direction of change and whether or not abnormal. No statistical tests were specified.

4.2.1.7 Results

4.2.1.7.1 Disposition

Thirty-four (34) of the original 38 planned sites recruited subjects. A total of 561 children were screened during the preliminary 2-week baseline period. There were 124 withdrawals, most due to failure to meet randomization criteria, for a total of 437 eligible children. Other reasons for ineligibility included noncompliance (8%), disallowed medication (8%), and adverse event (6%). Subject distribution by site ranged from one (<1%) to 37 (8.5%). The mean number of subjects per site was 12 and the median was seven. Nearly half of all subjects were accounted for by only eight (23%) of the sites.

The 437 subjects who completed the screening period were randomized into one of five study groups and entered into the double-blind treatment phase of the trial. Of the 437 children who received at least one dose of study medication, 319 completed the study. The breakdown by treatment group and the reason(s) for discontinuation are given by the table below. Most children withdrew for lack of efficacy, most commonly because their PEFR fell below the stability limit defined at Visit 2. About one-quarter of the active treatment group overall withdrew, compared to 55% of the placebo group. Adverse events accounted for only six (1%) of the total study discontinuations. The category "other" included failure to return for follow-up, dosing error, and prohibited medication.

SUBJECT DISPOSITION*

	Placebo	DK FP50 BID	DK FP100 BID	DH FP50 BID	DH 100 BID	Total
Enrolled	86	90	87	91	83	437
Completed	39 (45%)	69 (77%)	71 (82%)	77 (85%)	63 (76%)	319 (73%)
Withdrawn	47 (55%)	21 (23%)	16 (18%)	14 (15%)	20 (24%)	118 (27%)
Lack of Efficacy	40 (47%)	13 (14%)	7 (8%)	5 (5%)	13 (16%)	78 (18%)
Adverse Event	2 (2%)	1 (1%)	1 (1%)	2 (2%)	0	6 (1%)
Other	5 (6%)	7 (8%)	8 (9%)	7 (8%)	5 (6%)	32 (7%)

* From Volume 163, Table 2, p.126

4.2.1.7.2 Demographics and Other Baseline Characteristics:

Treatment groups were demographically similar. About two-thirds were boys. The mean age was 8.3 years with very young children (4-5 years) comprising slightly more than one in ten enrollees. As a group, they were predominantly Caucasian (79%) with African American and Latino comprising 13% and 5% overall, respectively. As might be expected among children in this age range, there was great variability in height and weight, 52.6 inches (range: 39.0-67.0 inches) and 74.6 lbs. (range: 28.0-191.0 lbs.), respectively, although there was no significant difference between treatment groups.

Asthma histories were also similar. Slightly more than half of all enrollees used inhaled CS or cromolyn at baseline. About half of each group reported a duration of asthma of 5 to 10 years or from one year to just under 5 years. Children whose duration exceeded 10 years or was under one year accounted for less than 10% of the total. Eighty percent (80%) reported no ER visits and 94% reported no hospitalizations in the prior 12 months. FEV1 and PEFr were also comparable across treatment groups, when expressed as percent predicted at baseline.

The comparability of orally inhaled corticosteroid (ICT) use at baseline across groups reflects stratification by this variable. Beclomethasone dipropionate was the most commonly used CS within the ICT group, reported by 17% to 29% of children. Triamcinolone acetonide was the second most common, with usage ranging from 11% to 19%. Cromolyn use was reported by 19-23%. Nedocromil and flunisolide were rarely used, reported by only 1-4% across treatment groups.

BACKGROUND CHARACTERISTICS*

	Placebo	FP 50 BID DK	FP 100 BID DK	FP 50 BID DH	FP 100 BID DH	Total
Number	86	90	87	91	83	437
Gender:						
Female	25	37	28	41	33	164 (38%)
Male	61	53	59	50	50	273 (62%)
Ethnicity:						
Black	9	14	13	9	13	58 (13%)
Latino	2	7	5	5	4	23 (5%)
Caucasian	72	68	66	74	65	345 (79%)
Other	3	1	3	3	1	11 (3%)
Age (yrs):						
Mean	8.6	8.3	8.1	8.2	8.1	8.3
% 4-5 yo	7 (8%)	11 (12%)	14 (16%)	13 (14%)	12 (14%)	57 (13%)
Inhaled CS use						
Yes	56%	53%	54%	54%	53%	54%
no	44%	47%	46%	46%	47%	46%
>=3 ER visits in prior 12 mos. (%)	5%	4%	1%	3%	2%	3%
Baseline FEV1 (% predicted)	72.9%	73.2%	73.5%	72.9%	71.9%	
Baseline PEFr (%predicted)	79.0%	78.4%	79.5%	80.5%	76.8%	

* From Tables 3, 4, 5 and 6; vol.163, pp.128-132

4.2.1.7.3 Efficacy Analysis

The population analyzed included all 437 subjects who received at least one dose of study medication (the ITT population). A subset analysis was performed using the 417-subject "efficacy population," comprised of the

ITT subjects minus 21 children excluded because of major protocol violations: 4 in placebo, 4 in DK 50 BID, 7 in DK 100 BID, and 3 each from the two DH groups. The decision to exclude was to have been made prior to unblinding.

4.2.1.7.3.1 Primary Efficacy Variable: FEV₁

Mean AM pre-dose FEV₁ was calculated for each treatment group at baseline and compared to mean AM pre-dose FEV₁ at each subsequent clinic visit and at end-point. Comparisons were made as mean absolute change in FEV₁ or as change in percent predicted. An F-test for overall treatment effect was performed prior to any pair-wise statistical comparisons.

The results of this analysis are shown in the table below and in the attached Figure 2 (p.119; Vol.163). There was no significant difference in FEV₁ at baseline across treatment groups. At endpoint, there was a statistically significant improvement in FEV₁ in each FP treatment group compared to placebo, whether the difference is expressed as "liters" or as "% change from baseline." There was no difference in the pair-wise comparison between any two FP groups at endpoint, regardless of doses and/or devices being compared. Not included in the table below is the standard error for the change from baseline to endpoint in FEV₁, which was reported as 0.03 for each treatment group.

MEAN CHANGE FROM BASELINE IN FEV₁ (L): ITT*

	Placebo	FP 50 BID DK	FP 100 BID DK	FP 50 BID DH	FP 100 BID DH	Overall
N	83	81	76	80	72	437
Baseline FEV ₁ (L)	1.47	1.45	1.47	1.48	1.38	
N at Endpoint	83	80	76	80	72	436
FEV ₁ at Endpoint:						
Mean change	0.10	0.22	0.24	0.24	0.23	
% change	7.0%	15.8%	17.9%	17.9%	18.6%	
p-value vs. placebo		0.006	0.003	0.001	0.023	0.005**

* Intent-to-Treat Population; From Tables 11, 12, 13; vol.163

** F-test

Reviewer's Comment: The "N" at endpoint must have included most if not all of the fifty-seven 4 year-olds and 5 year-olds. Although a minor point, the sponsor does not explain the unexpected success in coaxing children this young to perform spirometry reproducibly, nor how reliable the numbers from such FEV₁ maneuvers were. Since the sponsor did not prospectively plan to include these young children in this analysis, it would be interesting (but not critical to this application) to see their data alone and/or the FEV₁ results from this trial without them included.

The mean numerical improvement in FEV₁ reported for the two Diskhaler groups for this trial was greater than the improvement reported for pediatric clinical trial FLIT85 (NDA #20-770 Flovent Diskhaler). However, In FLIT85, change in FEV₁ was prospectively identified as a secondary endpoint rather than primary because of concern that 4 and 5 year-olds could not perform an acceptable FEV₁. In FLIT85, change in FEV₁ was 0.07L for placebo, 0.17L for FP 50 BID DH and 0.25L for FP 100 BID DH. Only the difference between FP100 and placebo was significant.

When expressed as percent predicted FEV₁, results were similar. The mean change in % predicted FEV₁ for placebo was 4.72% (72.92% of predicted at baseline and 77.64% of predicted at endpoint). For the FP groups, the results were 11.25%, 12.53%, 12.26%, and 12.74% for FP 50 BID DK, FP 100 BID DK, FP 50 BID DH, and FP 100 BID DH.

Mean change from baseline in FEV₁ was also calculated using the efficacy population. The results were not substantially different from those described above, except that the Diskus FP 100 mcg BID group failed to achieve a statistically significant improvement in FEV₁ in the pairwise comparison to placebo.

4.2.1.7.3.2 Primary Efficacy Variable: AM Clinic PEFr:

The co-primary efficacy endpoint in this trial was mean change from baseline in AM PEFr, the subject's first effort of the morning measured in clinic and prior to dosing with study medication. As summarized in the table below and shown graphically on the attached Figure 3 (p.120; Vol.163), there was an endpoint increase from baseline in PEFr of approximately 50 L/min for each one of the active treatment groups, which is an approximately 30% improvement. Compared to placebo, the overall treatment effect was statistically significant by ANOVA F-test ($p < 0.001$). The pair-wise comparisons with placebo were significant for both devices, at both doses. There was no significant difference between any of the FP groups by pair-wise analysis. Not shown in the table are the standard errors for the change from baseline in PEFr, which ranged from 4.8 L/min to 6.2 L/min.

**APPEARS THIS WAY
ON ORIGINAL**

MEAN CHANGE FROM BASELINE IN CLINIC AM PEFR (L/min): ITT*

	Placebo	FP 50 BID DK	FP 100 BID DK	FP 50 BID DH	FP 100 BID DH	Overall
N	86	90	87	91	83	437
Baseline PEFR (L/min)	226.0	216.5	216.2	222.3	204.9	
N at Endpoint	85	88	87	91	82	433
PEFR at Endpoint: Mean change	21.55	50.80	47.93	55.49	51.89	
% change	13.79%	26.16%	26.76%	30.34%	33.36%	
p-value vs. placebo		0.001	0.006	0.001	0.001	<0.001**

* Intent-to-Treat Population; From Tables 16, 17, and 18; Volume 163

** F-test

Mean change from baseline in PEFR was also calculated using the efficacy population. The results were not substantially different from those described for the ITT population.

When expressed as change from baseline in percent predicted AM PEFR, the placebo group improved from 78.91% to 86.55% of predicted for an absolute change of 7.64%. The change for each treatment group was 19.55%, 19.50%, 22.57%, and 23.18% for FP 50 BID DK, FP 100 BID DK, FP 50 BID DH, and FP 100 BID DH, respectively. The overall treatment effect was statistically significant by ANOVA F-test ($p \leq 0.001$), as were each of the pair-wise comparisons between placebo and FP ($p = 0.027$ to 0.001). There was no significant difference between any two FP groups by pair-wise analysis.

Reviewer's Comment: Unlike the data for FEV₁, the absolute change, percent change, and change in percent predicted PEFR for this trial are very similar to data reported for pivotal trial FLIT85 (NDA 20-770, see comment above). In that trial, placebo PEFR improved from 207 to 224 L/min (Δ 17 L/min), for FP 50 BID DH, $\Delta = 50$ L/min, and for FP 100 BID DH, $\Delta = 57$ L/min.

4.2.1.7.3.3 Secondary Endpoint: Survival in Study

There was a significant overall treatment effect on duration of study participation using the Log-rank test on Kaplan-Meier estimates of survival ($p < 0.001$; see attached Figure-5; p122; Vol.163). By the end of the study, 40 subjects (47%) in the placebo group had discontinued for lack of efficacy compared to 13 (14%) in the Diskus 50 BID group, 7 (8%) in the Diskus 100 BID group, 5 (5%) in the Diskhaler 50 BID, and 13 (16%) in the Diskhaler 100 BID. Pair-wise comparisons of survival-in-study between placebo and each of the four FP arms were statistically significant ($p < 0.001$ for each comparison). There was no significant difference in survival between any two FP arms.

4.2.1.7.3.4 Secondary Endpoint: Diary PEFR

Change from baseline in mean diary AM PEFR was calculated at the end of each study week based on entries from the preceding week. At least three of seven possible AM pre-dose PEFR diary entries were required for the mean AM PEFR to be considered evaluable. The comparator was baseline mean diary AM pre-dose PEFR, which was calculated from diary data recorded during the final week of the two week baseline period. Change from baseline in mean diary PM PEFR was similarly calculated, except that PM PEFR was always measured after study medication had been given.

There was a statistically significant treatment effect for FP compared to placebo at study endpoint for AM diary PEFR, as shown in the table below ($p < 0.001$). Pair-wise treatment comparisons between placebo and each of the 4 FP groups were also significant ($p < 0.001$ for each comparison; see also Figure 4, attached). The improvement from baseline was numerically smaller for the Diskus 50 BID group than for the other 3 FP groups, and the pair-wise comparison between the Diskus 50 BID and the Diskhaler 50 BID statistically favored the latter ($p = 0.030$). There were no significant differences between any other two FP groups by pair-wise analysis.

The mean change from baseline in diary PM PEFR followed a pattern similar to diary AM PEFR (see table below). There was a statistically significant treatment effect at endpoint ($p < 0.001$). Pair-wise comparisons were significant between placebo and each FP group. The Diskus 50 BID group showed a numerically smaller improvement in PM PEFR than the other three FP arms, and pair-wise comparison with the Diskhaler 50 BID group showed a significant difference ($p = 0.023$). There were no significant differences between any other two FP-groups by pair-wise analysis.

**APPEARS THIS WAY
ON ORIGINAL**

DIARY CHANGE FROM BASELINE IN AM/PM PEFR*

	Placebo	FP 50 BID DK	FP 100 BID DK	FP 50 BID DH	FP 100 BID DH	Overall (F-test)
N at Baseline	86	90	87	91	83	
AM PEFR Baseline (L/min)	234	229	220	232	213	
AM: Change at Endpoint	13	34	40	41	42	
AM: p vs. placebo		<0.001	<0.001	<0.001	<0.001	<0.001
PM PEFR Baseline (L/min)	245	243	233	244	227	
PM: Change at Endpoint	12	26	34	36	36	
PM: p vs. placebo		0.003	0.003	<0.001	<0.001	<0.001

* Tables 21-24; Vol. 163.

Another planned secondary analysis was change in AM/PM PEFR differential, as a measure of asthma stability. No significant treatment effect was found for this endpoint.

4.2.1.7.3.5 Secondary Endpoints: Diary Symptom Scores, Nighttime Awakenings, and Rescue Ventolin Use

Subjects recorded their asthma-related symptoms daily on their diary cards using a 0-3 severity scale, as described earlier in this review. Using this scale, symptoms were similar and relatively mild at baseline across treatment groups, all being <1.00. Statistically significant improvements in symptoms scores were found at endpoint compared to baseline for all FP treatment groups compared to placebo except for the Diskus 50 BID group (p=0.074; see table below).

Nighttime awakenings requiring Ventolin were infrequent and similar across treatment groups at baseline, ranging from under one night in ten for the DH 100 BID group (0.09) to one night in twenty for the DK and DH 50 BID groups (0.05). A statistically significant improvement in nighttime awakenings at endpoint compared to baseline was found for all four FP treatment groups compared to placebo. There was no difference between any two FP treatment groups (see table below).

Use of rescue Ventolin was to be recorded daily in the diary as number of puffs of the MDI or number of Rotacaps used. The reported value was normalized to puffs of Ventolin MDI, where 1 Rotacap=2 puffs MDI. At baseline, daily use of Ventolin ranged from approximately 1 ½ puffs to 2 puffs per day. There was a statistically significant reduction in Ventolin use by all four FP groups compared to placebo at study endpoint compared

to baseline, although the improvement for the DH 50 BID group was numerically smaller (see table below).

CHANGE FROM BASELINE IN DIARY VARIABLES*

	Placebo	FP 50 BID DK	FP 100 BID DK	FP 50 BID DH	FP 100 BID DH
N at Baseline	85**	90	87	91	83
Asthma symptom score:					
Baseline	0.72	0.81	0.80	0.86	0.76
Change	-0.02	-0.36	-0.41	-0.41	-0.36
p-value***		0.074	<0.001	0.002	0.036
Nighttime Awakenings:					
Baseline	0.06	0.05	0.08	0.05	0.09
Change	0.07	-0.03	-0.06	-0.04	-0.06
p-value***		0.019	<0.001	<0.001	0.003
Ventolin use					
Baseline	1.42	1.61	1.96	1.73	1.61
Change	0.08	-0.75	-1.04	-1.02	-0.90
p-value***		0.002	<0.001	<0.001	<0.001

* From Tables 28-31; Vol.163.

** N=86 for Nighttime awakenings and Ventolin use

*** Compared to placebo

4.2.1.7.3.6 Efficacy by Demographic Subgroups

There was no indication that a difference in response to FP existed by gender subgroup on either of the two primary endpoints. This appeared to be true by ethnic subgroup, as well, however the number of non-Caucasian subjects was very small (see "Results: Demographics; also Tables ST 15-24; Vol.163).

4.2.1.7.3.7 Efficacy by Inhaled Corticosteroid/Cromolyn use at Baseline

The study population was stratified by use of these agents at baseline (the ICT group) or whether they were managed on bronchodilator therapy alone (the BDT group). The ICT group constituted 54% of the study population overall compared to 46% for the BDT group (see "Results: Demographics").

When these two subgroups were compared by their results on the two primary endpoints, the BDT group tended to have a slightly greater change from baseline in FEV1 than the ICT group, as might be expected. The difference was more marked for the placebo group (0.05L for ICT vs. 0.16L for BDT) than any of the FP groups, although the DH 50 BID group changed in the opposite direction (0.26L for ICT vs. 0.22L for BDT). The other primary endpoint, change from baseline in clinic AM PEFr, was notably different between the two groups only at the higher doses. The change from baseline in clinic AM PEFr was greater for the BDT group than the ICT group at FP 100 BID (both DK and DH), whereas at FP 50

BID (both DK and DH), the changes from baseline were nearly the same (see first table, p.87; Vol.163).

With regard to the secondary endpoint change from baseline in Diary AM PEFr, the BDT group consistently showed a greater change from baseline for all treatment groups.

Reviewer's Comment: The differences were numerically small but consistent for most FP treatment groups, but relatively greater for the placebo group because the overall change from baseline was smaller. It is possible that an imbalance in BDT vs. ICT patients in the placebo arm could have tipped the results in either direction, favorable or unfavorable, hence baseline stratification by this variable was probably important.

With regard to the secondary endpoint of study survival, the same proportion of ICT subjects discontinued for lack of efficacy (19%) as BDT subjects (16%), more in the placebo groups, as would be expected.

4.2.1.7.3.8 Efficacy by "Humanistic and Resource Utilization"

The 3-Item Sleep Scale-Child (SLP-C) showed a statistically significant improvement at endpoint compared to baseline for all FP groups compared to placebo.

The "device satisfaction" questionnaire showed that parents or caregivers gave a "favorable" rating to each device at the end of the trial, based upon the sponsor's interpretation of their own 5-question survey. No between-device comparison was mentioned.

The "resource utilization" instrument showed little or no impact of asthma on the child's or the parent's activities, either at baseline or at endpoint, for any of the five treatment groups.

Reviewer's Comment: Even if these instruments had detected a difference among treatment groups, these assessments would add nothing to the data recorded by the subjects on their diary cards, which were pre-specified secondary endpoints.

4.2.1.7.4 Safety Results

4.2.1.7.4.1 Extent of Exposure

A total of 437 patients received at least one dose of study medication and therefore have been included in the safety analysis. Their extent of exposure is shown in the table below. On average, the FP-treated patients were exposed for approximately 75 days out of an 84-day trial. The placebo patients received approximately 20 fewer days of exposure.

EXTENT OF EXPOSURE TO STUDY MEDICATION*

	Placebo	FP 50 BID DK	FP 100 BID DK	FP 50 BID DH	FP 100 BID DH
Number					
Baseline	86	90	87	91	83
Completed	39	69	71	77	63
Exposure(days):					
Mean	54.6	76.6	75.8	77.5	72.2
Median	71.0	85.0	85.0	85.0	84.0

* Table 31 and p.91; Vol.163

4.2.1.7.4.2 Adverse Events (AE)

The adverse events identified in this trial are not substantially different from those reported in clinical trial FLIT85 and already incorporated into the ADVERSE REACTIONS section of the approved product labeling for Flovent™ Rotadisk. These common adverse events will therefore not be repeated in great detail in this review.

Overall, 72% of the placebo group reported at least one adverse event during this trial, which was comparable to the FP-treated groups, 77% in DK 50 BID, 72% in DK 100 BID, 75% in DH 50 BID, and 75% in DH 100 BID. By system, the most commonly reported AE's in all treatment groups were within the ENT system (43-58%) followed by GI (21-25%; e.g. nausea/vomiting) and non-site specific (13-19%; e.g. fever). In descending order of frequency, the top five ENT AE's were: URI (14-19%), throat irritation (8-14%), ENT infection (5-12%), sinusitis (8-10%), and rhinitis (2-8%). Headaches, which tend to be common in this population related to concomitant conditions, occurred in 5 (6%) of placebo patients, but in proportionately more FP-treated subjects. There were 16% of the DK 50 BID, 9% of the DK 100 BID, 5% of the DH 50 BID, and 13% of the DH 100 BID groups each complaining of headache at least once.

When analyzed by demographic subgroups, there were no apparent differences between the genders, and the AE profile of the Caucasian subgroup resembled the profile of the group as a whole. Representation by other ethnic subgroups was too low to detect true or possible differences. No subgroup analysis based on age was provided.

There were no deaths in this study. There were three serious AE's and six withdrawals due to AE, including two with serious AE's for a total of seven: 2 placebo, 1 DK 50 BID, 2 DK 100 BID, and 2 DH 50 BID. The serious AE's included asthma exacerbation (placebo), pneumonia with N/V and hypokalemia (DH 50 BID), and viral gastroenteritis. All three events required hospitalization, and the first two resulted in study withdrawal. The four additional withdrawals were accounted for by

hoarseness/pharyngitis (placebo), behavior changes (DH 50 BID), and two episodes of chickenpox (DK 50 BID and DK 100 BID) that occurred at different sites at 67 days and 43 days, respectively, into double-blind treatment.

There were three reports of thrush, one each in the placebo, DH 50 BID, and DK 100 BID groups. Not unexpectedly, there were no reports of cataracts, glaucoma, or osteopenia in this 12-week pediatric trial. No adverse event specifically coded as "HPA axis suppression" was reported.

4.2.1.7.4.3 Laboratory Data (excluding HPA-axis)

Blood samples for serum chemistry, LFT's, and hematology were obtained at baseline and at study endpoint. No subject was withdrawn for abnormal laboratory values. A few subjects (1-4% per group, maximum) had "clinically significant" laboratory values by pre-specified criteria reported at any time post-randomization. Abnormalities of relevance to this review, either because of known side-effects of CS or because of post-marketing surveillance, would include glucose, bicarbonate, potassium, eosinophil count, and alkaline phosphatase.

There were no reported clinically significant elevations in glucose or bicarbonate, although a few children from each group had a low value. There was one episode of clinically significant hypokalemia in the DH 50 BID group (see serious adverse events, above).

There were 6 children with abnormally high eosinophil counts, one in the placebo arm and 5 in any FP group. The group included four boys and two girls ranging in age from 6 to 11 years old. The highest recorded eosinophil count was 3.70×10^3 that occurred in a child receiving placebo. The other five children, one child in the DK 50 BID group, two in the DK 100 BID group, and two in the DH 50 BID group, had relatively modest elevations in eosinophil counts ranging from 1.28 to 1.53×10^3 . One of these five children already had a clinically significant elevation at baseline, which did not increase during the study. There was no specific mention of concomitant symptoms or other physical or laboratory findings of significance in these children. None were discontinued from the study as a direct consequence of their eosinophil counts.

There were 7 children with "clinically significant" elevations in alkaline phosphatase (AP), none of whom were receiving placebo. There were 3 children from the DH 100 BID group, 2 from DK 100 BID, and one each from DK or DH 50 BID. Their ages ranged from 6 to 11 years and the group included 4 girls and 2 boys. Although listed under "LFT's," the source of the AP was more likely bone than liver given that there were no concomitant elevations in other liver enzymes in any of these children. The elevations were modest, the highest being 506 U/L ("clinically

significant" was defined as >400 U/L), and most of these children had borderline high or slightly elevated AP at baseline. It's safety significance remains somewhat unclear.

Reviewer's Comment: Whether the elevated AP could be construed as a marker of abnormally high turnover of bone in these growing children is highly debatable, since AP is a relatively imprecise and nonspecific measurement. Osteopenia associated with prolonged inhaled CS use does remain an issue of concern, however, and more sensitive tools to follow bone accretion and/or turnover in children and to predict final bone density are needed for all inhaled CS.

4.2.1.7.4.4 HPA Axis Assessment

The HPA axis was assessed at baseline and at endpoint (or early discontinuation) by means of three different tests. Unstimulated (basal) AM plasma cortisol, was conducted in all subjects. A subset of children at selected sites underwent a "short" cosyntropin stimulation test (standard dose infused over minutes rather than 6 hours). A 24-hour urine sample was measured for cortisol excretion for another subset of patients.

The AM plasma cortisol data was presented as *change in mean basal cortisol level* or as *percentage of subjects with an abnormally low basal cortisol level* at baseline vs. endpoint. These data were then compared across treatment groups. A separate analysis was performed for the ICT vs. the BDT subgroups.

Reviewer's comment: Tables 36, 37, and 38 (Vol.163) summarize mean change in AM basal plasma cortisol level across treatment groups and by inhaled CS use at baseline (ICT vs. BDT). The treatment group headings for all three tables read "Diskus 100 mcg QD" rather than "Diskus 100 mcg BID" and "Diskhaler 100 mcg QD" rather than "Diskhaler 100 mcg BID." This reviewer has assumed that this is an error, and the three tables do refer to Clinical Trial #FLTA2006, and not to a comparison between once and twice daily dosing. (addendum 26 March 1999; confirmed via telecon with sponsor).

A value of 5 mcg/dl was selected as the lower limit of normal for basal AM plasma cortisol and all values <5 mcg/dl were classified as abnormally low. Using this cutoff, 41 of the 236 ICT subjects (17%) and 24 of the 201 BDT subjects (12%) were classified as abnormal at the start of the study. At study endpoint, both groups were found to have fewer subjects with abnormally low cortisols, 10 (4%) of the ICT subjects and 9 (4%) of the BDT subjects.

Mean AM basal plasma cortisol was also calculated for each treatment group at baseline and at study endpoint. As shown in Table 38 for the intent-to-treat population, for every treatment group there was an increase in basal plasma cortisol levels: 1.7 mcg/dl for placebo (8.4 mcg/dl baseline to 10.3 mcg/dl endpoint), 2.0 mcg/dl for FP 50 DK, 2.0 mcg/dl for FP 100 DK, 2.3 mcg/dl for FP 50 DH, and 3.1 mcg/dl for FP 100 DH.

The pattern was not substantially different for the ICT and BDT subgroups, that is, there was an increase in basal AM cortisol in all 5 treatment groups for each of the two subgroups.

Reviewer's comment: There are significant problems with the sponsor's analysis. First, the selection of <5 mcg/dl as the lower limit for normal basal AM cortisol is questionable since the lower limit for children in this age range can vary between 4 and 9 mcg/dl depending upon age and gender (Vol.163; Table 44; p. 208). It is unclear whether this variability was prospectively considered (Vol.164; p.77). Second, the reference range for the upper and lower limits of normal for basal AM cortisol showed variability not fully explained by the age/gender adjustment shown in Table 44 (Vol 163; p.208). The data listings (Vol.170-177) present individual cortisol levels along with the lab's normal reference range. For example, placebo patient #5743 (Vol.171, p.73) had a normal baseline AM cortisol of 7 mcg/dl on 7 October 1995 when the normal range was listed as 4 to 8 mcg/dl (Table 44: M, 10-12 yr). This same placebo subject had an endpoint AM cortisol of 5 mcg/dl on 12 January 1996 at a time when the normal range was given as 8 to 14 mcg/dl (Table 44;M, <6 yr?). Not only is this reference range not given in Table 44, but this endpoint result illustrates the problem with the cutoff value of <5 mcg/dl, since it appears quite abnormal by the lab reference range but would still fit the sponsor's criteria of "normal." Patient #5389 (FP 50 BID DH; Vol.175; p.19) also illustrates both of these problems. Baseline AM cortisol was recorded as 3 mcg/dl, abnormal by both the sponsor's cutoff value of <5 and by the stated reference of 4 to 8 mcg/dl. Endpoint AM cortisol was 6 mcg/dl, normal by the <5 mcg/dl cutoff but abnormal by the stated reference range of was 8 to 14 mcg/dl. This child would have been one of the subjects who "normalized" their basal cortisol, in some cases paradoxically, while receiving active study medication. There are several other subjects where there is inconsistency between the <5 mcg/dl normal cutoff and the subject's age/gender-adjusted normal range. There are also other examples of reference ranges in the data listings for which there is no corresponding "Normal Range" in Table 44.

The fact that a normal basal AM cortisol varies so widely in the pediatric population calls into question the validity of the sponsor's analysis of mean cortisol levels across time and between treatment groups. By analogy, FEV₁ and PEF_R also vary, but data can be normalized by using percent predicted value in addition to the raw data. Unlike FEV₁ and PEF_R, however, AM cortisol does not systematically increase with age but seems to follow a more complex pattern. This makes the value of raw data questionable (e.g.the normal range for a 10 yo girl, 9-14 mcg/dl, does not even overlap the normal range for a 10 yo boy, 4-8 mcg/dl).

There is one further concern about the analysis of the AM basal cortisol data, that is, does the absence of a "Normal Range" in Table 44 corresponding to the reference range given in the data listings mean that the lab's assay conditions or test sensitivity has changed? If so, this would throw further doubt on the validity of these data.

Because of these problems, the AM basal plasma cortisol data from this study cannot be unambiguously interpreted. These data cannot be used to support product labeling or promotional claims regarding the HPA axis effect of Flovent Diskus.

A subset of subjects collected 24-hour urine from which total urinary cortisol was determined, 322 at baseline and 253 at endpoint (Tables 39-

41; Vol.163; p.202-4). Table 39 shows a summary of the raw data by treatment group, Table 40 shows a pair-wise comparison of the log transformed data, and Table 41 the mean percent change from baseline by treatment group. Individual patient data is reported in Appendix 8, Vol. 165. Data listings include total urinary cortisol only, without the subject's corresponding total urine volume or urinary creatinine. Data were extremely variable both across and within treatment groups, with 24-hr urinary cortisol ranging from 0.8 mcg/24 hr to 91.4 mcg/24 hr at baseline. The means varied from 10.2 mcg/24 hrs to 12.8 mcg/24 hrs and had standard deviations in the same range as the means.

When these values were log transformed and compared in a pair-wise fashion between treatment groups, p-values were found to be insignificant (Table 39). When expressed as percent change from *median* pre-treatment baseline for the ICT subgroup (Table 41), urinary cortisol decreased in placebo, DH 50, and DH 100 groups (-13.6%, -15.00%, -24.55%, respectively) and increased in both DK groups (11.95% for DK 50 and 5.85% for DK 100). For the BDT subgroup, the direction of change was the same, except for the DK 100 group, but the magnitude was less. From these data, the sponsor concludes that FP treatment leads to similar or even lesser effects on urinary cortisol than placebo.

Reviewer's Comment: The variability in 24-hr urinary cortisol over several logs remains unexplained, raising the question of an incomplete collection. No total urinary volume is given in the laboratory data listings in Appendix 8 (Vol.165), and an incomplete 24-hr urine collection must be assumed, especially among children as young as 4 or 5 years who are outpatients. No other data supporting a complete collection, such as correction for creatinine, have been provided. Normal or expected ranges with an age/gender correction, if appropriate, were not given, which also would have helped to exclude incomplete collections based on physiologically improbable data.

In the opinion of this reviewer, complex analyses and transformations of unreliable data, such as shown in Tables 40 and 41, are superfluous. The choice of the data analysis shown in Table 40 begs the question of the wide variability in the 24-hour urinary cortisol values. The variability has been extinguished using log transformation rather than explained. In the analysis shown in Table 41, it has not been explained why the median and not the arithmetic mean have been selected for determination of change from baseline for each treatment group. Finally, the argument supporting changes in urinary cortisol excretion ranging from +11.95% to -24.55% as not significantly different has not been presented. It is therefore illogical to conclude there is no effect of FP on 24-hr urinary cortisol.

As with the analysis of the basal AM plasma cortisol levels above, these urinary cortisol excretion data cannot be used to support product labeling or promotional claims regarding the HPA axis effect of Flovent Diskus.

A subset of 100 children had "short" cosyntropin (ACTH) stimulation testing at baseline. Sixty-nine (69) of these children had repeat testing at study endpoint or early withdrawal. "Short" testing was conducted using

the standard adult dose of cosyntropin, 250 mcg, administered as a bolus injection rather than as a 6-hour infusion. Ten minutes after cosyntropin was given, subjects were dosed with study drug. Plasma cortisol, which had also been drawn at baseline, was drawn 20 minutes later. A normal response was defined as a plasma cortisol level of ≥ 18 mcg/dl and/or an increase of ≥ 7 mcg/dl over baseline cortisol.

Reviewer's Comment: The rationale for the interposition of study medication dosing 10 minutes after cosyntropin and 20 minutes before blood sampling was not explained.

Standard dose cosyntropin testing is useful in diagnosing clinically significant adrenal insufficiency, however, the 250 mcg dose of ACTH is supra-physiologic and therefore very insensitive to more subtle levels of adrenal suppression. This lack of sensitivity seriously limits the usefulness of this test and the conclusions that can be drawn from a "negative" result.

FREQUENCY OF PLASMA CORTISOL ABNORMALITIES: SHORT COSYNTROPIN STIMULATION TEST

	Placebo	FP 50 BID DK	FP 100 BID DK	FP 50 BID DH	FP 100 BID DH
N	12	13	16	17	11
Baseline AM Cortisol <5mcg/dL	1 (8%)	1 (8%)	1 (6%)	1 (6%)	0
Last Visit AM Cortisol <5mcg/dL	0	1 (8%)	0	0	0
Post-Stimulation change <7 mcg/dL	0	1 (8%)	1 (6%)	0	1 (9%)
Post-Stimulation cortisol <18 mcg/dL	0	0	0	0	2 (18%)
Post-Stimulation change <7 mcg/dL and Post-Stimulation cortisol <18 mcg/dL	0	0	0	0	1 (9%)

The table summarizing the results of this testing is shown above, reproduced from p.97, Vol.163. At baseline, one placebo subject and one each in three of the four FP groups had an abnormal AM plasma cortisol. At study endpoint, no placebo subject tested was found to have an abnormality in basal or stimulated plasma cortisol (0/12; 0%), compared to 7 in the combined FP groups (7/57; 12%).

Reviewer's Comment: According to the text, the DH 100 BID subject with the combined abnormality was not counted in more than one category.

4.2.1.7.4.5 Other Safety Evaluations

These assessments included oropharyngeal examinations, vital signs, physical examinations, and ECG's. There were no clinically significant differences between placebo and treatment groups or among different FP treatment groups relevant to this application.

4.2.1.7.5 Comparative Pharmacokinetics: Diskus vs. Diskhaler

For a full discussion of the clinical pharmacology of the Diskus in the pediatric population, the reader is referred to the Biopharmacologist's review of this application.

A subset of children enrolled in this trial had FP plasma levels assayed following the last AM dose at the final clinic visit. Samples were drawn 20 and 40 minutes after the final dose. The following table shows the C_{max} data for each treatment group including the standard deviation. Using a Hodges-Lehmann estimate of the median difference, a treatment-by-treatment comparison is shown below the table.

FP C_{MAX} VALUES FOLLOWING LAST AM DOSE (pg/mL)

	DK 50 BID	DK 100 BID	DH 50 BID	DH 100 BID
N	31	30	37	26
Median	BQL	BQL	BQL	34.3
Range				
Mean	5.4	7.8	13.4	30.3
SD	17.3	16.4	21.7	29.0

TREATMENT COMPARISON	p-value
DH 50 BID vs DH 100 BID	0.015
DK 50 BID vs. DK 100 BID	0.389
DK 50 BID vs. DH 50 BID	0.069
DK 100 BID vs. DH 100 BID	0.001

These data strongly suggest that the two devices differ in their delivery of FP to the lungs of children with mild to moderate asthma, at least when measured at this particular time-point in the life of each device (6 weeks since having been dispensed). It appears that more FP is delivered to a (pulmonary) site where it can be readily absorbed using the approved Diskhaler device than when using the Diskus.

4.2.1.8 Conclusions

4.2.1.8.1 Efficacy Conclusions:

Dry powder FP delivered from the Diskus device at doses of 50 mcg BID or 100 mcg BID was shown to be efficacious in the treatment of mild-to-moderate asthma in pediatric patients age 4-11 years. Efficacy was demonstrated for both doses for both of the two primary endpoints, FEV₁ and AM clinic PEF. Efficacy was supported for both doses on all but one of the diary secondary endpoints. No dose-response was apparent in this study, that is, although there was numerical superiority of the DK 100 mcg BID dose relative to the DK 50 mcg BID dose on many efficacy endpoints, the difference did not achieve statistical significance.

In comparison with the approved Diskhaler device, there was no significant difference between the Diskhaler and the Diskus at the same

nominal dose, 50 or 100 mcg BID, on either of the two primary endpoints, on survival, and on most of the secondary endpoints.

Subgroup analysis showed no significant difference in efficacy based on the subject's gender or ethnicity, although there were relatively few non-Caucasian subjects. With regard to inhaled corticosteroid (or cromolyn) use at baseline compared to inhaled bronchodilator use only, (ICT vs. BDT), the BDT subgroup showed a greater improvement on most efficacy endpoints, not unexpectedly. Somewhat surprisingly, however, the ICT placebo group did not generally show a deterioration in lung function, as would have been expected upon withdrawal of inhaled corticosteroids. The explanation for this finding is unclear, but it is unlikely to have impacted the results of this study in favor of efficacy.

Efficacy analysis based upon "humanistic" assessments was generally favorable for all FP-treated subjects compared to placebo, however, these assessments did not add anything unique to the analysis not already covered by diary secondary endpoints.

4.2.1.8.2 Safety Conclusions:

Based upon Study FLTA2006, dry powder FP 50 or 100 mcg BID administered via the Diskus appeared to be safe when used to treat children 4-11 years old with mild-to-moderate asthma. The most frequently occurring adverse events were in the ENT system. There were no deaths in the study, three serious adverse events, and six withdrawals due to adverse events. The adverse event profile of the Diskus 50 or 100 mcg BID in the pediatric population did not appear to be substantially different from that already ascertained from study FLIT85 and incorporated into the approved product labeling for the Diskhaler 50 or 100 mcg BID.

Routine clinical laboratory assessments, physical examinations, ECG's, and vital signs did not disclose any unique or unexpected safety issue relevant to this product.

The assessments of HPA axis function included basal AM plasma cortisol, the analysis of which was seriously flawed, 24-hour urinary cortisol, for which an adequate collection was not documented, and standard dose cosyntropin stimulation testing, which is a very insensitive test of adrenal suppression. These assessments cannot be used to support or refute the sponsor's argument that

These data are therefore inadequate to support labeling or promotional claims.

4.2.2.7.3.3 Secondary Endpoint: Survival in Study

Using the logrank test on Kaplan-Meier estimates of survival, a significant overall treatment effect on survival could be shown ($p=0.037$; see table below). At study endpoint, the percentage of subjects withdrawn due to lack of efficacy was 35% for placebo, 19% for twice daily, and 25% in the once daily groups. The difference was significant for the twice daily group compared to placebo ($p=0.014$), but not for the once daily group compared to placebo ($p=0.095$). There was no significant difference between once and twice daily FP.

Reviewer's Comment: The differences are not nearly as striking as in the preceding study, FLTA2006, in which 47% of placebo, 14% of FP 50 BID Diskhaler, and 5% of FP 50 BID Diskus discontinued for lack of efficacy.

4.2.2.7.3.4 Secondary Endpoints: Diary Data

Secondary endpoints included change from baseline in AM or PM PEFR, and change from baseline in asthma symptom scores, rescue Ventolin use, and night-time awakenings (see table below).

The diary PEFR data is very informative. AM PEFR was recorded each morning prior to dosing, therefore it represents an end-of-dosing-interval measurement for both the once as well as the twice daily FP Diskus dose. The change from baseline in L/min for the placebo group was 12, compared to 21 L/min for the once daily arm and 25 L/min. for the twice daily arm. For neither of the two did change from baseline to endpoint reach statistical significance.

Reviewer's Comment: Perhaps implying two different things, that the 24-hr dosing interval was too long for FP 100 QD DK, and that even when dosed twice daily, the efficacy of FP 50 BID DK might wane near the end of the dosing interval (which was probably >12 hrs since the drug was given BID, not Q12 hrs). Again, in comparison with the previous trial, the change in PEFR was much smaller, 34 L/min for FP 50 BID DK and 41 L/min for FP 50 BID DH compared to the placebo group's change of 13 L/min.

In contrast to AM PEFR, change from baseline for PM PEFR was significant for both doses. The improvement for once daily was numerically greater than for twice daily, 25 L/min compared to 20 L/min for twice daily, although the difference did not reach statistical significance.

Reviewer's Comment: In some sense, one could think of the PM PEFR for the FP 100 mcg QD group as reflecting the efficacy of FP 100 mcg BID measured at the end-of-dosing-interval.

Subjects recorded their asthma-related symptoms daily on their diary cards using a 0-3 severity scale, as described earlier in this review for study FLTA2006. Using this scale, symptoms were similar and relatively mild

at baseline across treatment groups, from 0.77 to 0.84, also similar to baseline symptoms in study FLTA2006. At study endpoint, symptom scores had decreased by -0.30 for twice daily and -0.24 for once daily, compared to -0.08 for placebo. There was no statistically significant treatment effect overall, nor were either of the two pair-wise comparisons with placebo significant. For the FP 50 BID group, the absolute change relative to placebo in symptom score was less than 2/3rds of the change observed for the two BID arms in FLTA2006.

Nighttime awakenings requiring Ventolin were infrequent and decreased further in both active treatment groups (0.05 for placebo, -0.04 for twice daily, and -0.03 for once daily, $p=0.014$). The pair-wise comparison with placebo demonstrated a statistically significant improvement in nighttime awakenings at endpoint compared to baseline for both FP treatment groups. There was no difference between the two groups, however (see table below).

Use of rescue Ventolin at study endpoint compared to baseline improved significantly for the twice daily group only (-0.98 puffs/day; $p=0.047$), although the once daily group showed numerical improvement (-0.56 puffs/day; $p=0.235$). There was no significant treatment effect overall for this endpoint, although the p-value was close ($p=0.067$; see table below).

CHANGE FROM BASELINE IN DIARY VARIABLES*

Δ baseline in:	Placebo	FP 50 BID	FP 100 QD	Overall p-value	p-value vs. Placebo**	
					BID	QD
Diary AM PEFR (L/min)	12	21	25	0.386	0.271	0.200
Diary PM PEFR (L/min)	9	20	25	0.025	0.048	0.008
Asthma Symptom Score	-0.08	-0.30	-0.24	0.249	0.119	0.725
Rescue Ventolin Use (puffs/day)	0.07	-0.98	-0.56	0.067	0.047	0.235
Nighttime Awakenings	0.05	-0.04	-0.03	0.014	0.009	0.039
Subjects withdrawn for lack of efficacy	29 (35%)	17 (19%)	23 (25%)			

* From Table on p.7; Vol.187

** No BID vs. QD comparisons achieved statistical significance

4.2.2.7.3.5 Efficacy by Demographic Subgroups

A subgroup analysis by gender and ethnicity was performed for the two primary endpoints (Tables ST15-19 for FEV₁ and ST10-14 for PEF_R; vol.187, p.210-219). Although the subgroups lack sufficient power to draw definitive conclusions, and no p-values have been provided, there is some indication that once daily FP may have better efficacy for girls and for African American children (see table below).

CHANGE FROM BASELINE IN FEV₁ AND AM CLINIC PEFR, BY SUBGROUP

Endpoint	Placebo		FP 50 BID		FP 100 QD	
	FEV ₁	PEFR	FEV ₁	PEFR	FEV ₁	PEFR
ITT	N 80 0.05 L	N 81 10.73 L/min	N 87 0.13 L	N 87 38.53 L/min	N 91 0.08 L	N 91 26.00 L/min
Boys	N 46 0.06 L	N 46 4.80 L/min	N 50 0.11 L	N 50 36.92 L/min	N 60 0.04 L	N 60 23.18 L/min
Girls	N 34 0.05 L	N 35 18.34 L/min	N 37 0.17 L	N 37 40.70 L/min	N 31 0.17 L	N 31 31.31 L/min
Caucasian	N 57 0.05 L	N 57 14.98 L/min	N 58 0.14 L	N 58 35.31 L/min	N 61 0.05 L	N 61 19.97 L/min
African American	N 12 0.09 L	N 13 5.31 L/min	N 14 0.11 L	N 14 42.50 L/min	N 17 0.19 L	N 17 37.36 L/min
Other	N 11 0.01 L	N 11 -4.55 L/min	N 15 0.10 L	N 15 47.27 L/min	N 13 0.05 L	N 13 38.92 L/min

4.2.2.7.3.6 Efficacy by Inhaled Corticosteroid/Cromolyn use at Baseline

The study population was stratified by use of these agents at baseline (the ICT group) or whether they were managed on bronchodilator therapy alone (the BDT group). The ICT group constituted 46% of the study population overall compared to 54% for the BDT group.

When these two subgroups were compared by their results on the two primary endpoints, the BDT group tended to have a slightly greater change from baseline in the two FP-treated groups for both FEV₁ and PEFR than the ICT group, as might be expected. This difference was most marked for the primary endpoint FEV₁, where the improvement over baseline for the BDT subgroup was nearly 3 to 4-fold greater than for the ICT group. For PEFR, the difference was more modest, less than a 2-fold difference between the two subgroups for the BID arm and near equality for the once daily arm. This pattern was similar for the secondary endpoint, AM diary PEFR.

Reviewer's Comment: There were nearly 25% more BDT subjects in this trial than in FLTA2006, which is why it seems surprising that FP 50 BID DK was not statistically different from placebo on both primary and most secondary endpoints for this trial (while this same arm was consistently statistically superior to placebo in FLTA2006).

4.2.2.7.4 Safety Results:**4.2.2.7.4.1 Extent of Exposure**

A total of 262 subjects received at least one dose of study medication (the ITT population); all have been included in the safety analysis. The mean exposure to study drug was 63.7 days for the placebo group (44/83 subjects completed), 74.6 days for the FP 50 BID group (63/88 subjects completed), and 74.7 days for the FP 100 QD group (62/91 subjects completed).

Pharmacokinetic studies performed on a subset of subjects suggest that less dry powder FP is delivered to the airways of asthmatic children using the Diskus than delivered with the same nominal dose of the Diskhaler.

4.2.1.9 Labeling Considerations:

Comments relevant to labeling this product for use in children will be deferred until the end of the pediatric section of the review, following the two supportive trials FLTA2007 and FLTA2008.

4.2.2 FLTA2007

“A stratified, randomized, double-blind, parallel-group trial assessing the efficacy and safety of fluticasone propionate via the multi-dose powder inhaler, 50 mcg BID, 100 mcg QD, and placebo in subjects aged 4 to 11 years with chronic asthma.”

4.2.2.1 Background Information:

FLTA2007 was conducted to compare once daily to twice daily dosing of FP via Diskus. However, the sponsor has not requested once daily dosing for the pediatric age group. This trial will be analyzed primarily as supportive of the safety and efficacy of FP 50 mcg BID via Diskus for the pediatric indication.

4.2.2.2 Objectives:

The objectives of this study were to compare the efficacy and safety of FP 50 mcg BID or 100 mcg QD with placebo in children aged 4 to 11 years with chronic asthma in terms of the following:

- Efficacy: FEV₁, PEFR, survival in study, symptom scores
- Safety: Physical examination, clinical laboratory, and adverse events

4.2.2.3 Setting:

Conducted at 19 outpatient sites in the US between 3 July 1995 and 18 September 1996. The number of patients per center ranged from 1 to 28 (0-11%).

4.2.2.4 Endpoints:

4.2.2.4.1 Efficacy Endpoints:

- The primary efficacy variable was change from baseline in AM pre-dose FEV₁ and PEFR determined at each clinic visit.
- Secondary efficacy variables:
 - Survival in study
 - Diary AM and PM PEFR
 - Symptom Scores
 - Rescue β -agonist use
 - Nighttime awakenings

4.2.2.4.2 Safety Endpoints:

- Adverse events
- Clinical laboratory tests
- Physical examination
- VS

4.2.2.5 Design:

FLTA2007 was a 12-week, randomized, double-blind, placebo-controlled, multi-center clinical trial of 269 pediatric asthmatics stratified at baseline for inhaled corticosteroid or inhaled cromolyn use (ICT) or use of bronchodilator therapy alone (BDT). Subjects were assigned one of three double-blind treatments, placebo, DK FP 50 BID, or DK FP 100 QD, at the end of a 2-week, single-blind, placebo screening period. Assessments occurred weekly during the first 4 weeks of the 12-week dosing period, then biweekly until the end of the study. Except for the number of active treatment groups, design, recruitment, inclusions, and assessments were identical to ALTA2006.

Reviewer's Comment: Note that the protocol for FLTA2007 which follows is nearly identical to the protocol for pivotal trial FLTA2006, just reviewed above. It was also conducted concurrently and used unique numbers from the same ICT/BDT-specific randomization codes. FLTA2007 had fewer endpoints and no "humanistic" assessments, however, in addition to a few other minor differences such as the time points at which study devices were collected or exchanged. With this in mind, the reader could use the attached "Figure 1" (Vol.187, p.82) is an adequate summary while reviewing the "Results."

4.2.2.6 Summary of Protocol (includes all amendments)

4.2.2.6.1 Study Population

Inclusion Criteria

- Male or premenarchal female
- Age 4 – 11 years and <12 years by visit 2
- Asthma by ATS criteria
- Use of pharmacotherapy for prior 3 months or more
- Effective use of Diskus device
- Mild to moderate asthma:
 - 4 – 5 years: PEFR \leq 85% predicted³
 - 6 – 11 years: FEV₁ 50 – 85% predicted³
- Reversibility:
 - 4 - 5 years: PEFR checked pre- and post- β -agonist, but no criteria given
 - 6 – 11 years: \geq 15% increase with β -agonists
- Relatively stable asthma symptoms

Exclusion Criteria

- Life-threatening asthma

- Use of nonsteroidal immunosuppressive therapy for asthma, such as cyclosporine, methotrexate, or gold
- Intermittent or seasonal asthma
- Other significant concomitant disease
- Current chickenpox or exposure in prior 3 weeks
- URI in prior 2 weeks
- Tobacco use
- Allergy to corticosteroids (CS) or β -agonists
- Clinically significant abnormality on screening laboratory or 12-lead ECG
- Glaucoma or posterior subcapsular cataracts (PSC)
- Prior participation in Diskhaler (or other Diskus) study

Disallowed Medications

- At time of enrollment:
 - Any antibiotic in prior 2 weeks
 - Any investigational drug in prior 30 days
 - Oral, intranasal, or parenteral CS in prior month
 - If not already maintained on inhaled CS (\equiv continuous use at stable dose in prior 3 months), inhaled CS use in prior month
- Specifically prohibited during the trial:
 - Anticholinergics
 - Anticonvulsants
 - Antidepressants
 - Long acting antihistamines or antihistamine/decongestant combinations
 - Long acting decongestants
 - Phenothiazines
 - Macrolide antibiotics
 - Quinolone antibiotics
 - β -blockers
- All anti-asthma medications except Ventolin MDI or Rotacaps (substituted for any other β -agonist), theophylline (if on a stable dose for at least 3 months prior), or inhaled CS other than FP (if on a stable dose for at least 3 months prior).

4.2.2.6.2 Treatment arms and dosing:

Subjects were randomized to one of three treatment groups. Each child received two devices, one to be used for AM dosing and the other for PM dosing. For DK 50 BID, both devices contained active medication. For DK 100 QD, only the device to be used in the morning contained FP. For the placebo arm, both devices contained matching placebo. Devices were exchanged at six-weeks and at 12-weeks after the start of the study.

Reviewer's Comment: Six weeks would not constitute life-of-device for a once daily indication (42 doses utilized out of a possible 60 doses=60 days of QD dosing or 8 weeks plus 4 days).

Treatment	Twice Daily Dosing AM and PM
FP 50 mcg BID	1 blister FP 50 mcg via Device A (AM) 1 blister FP 50 mcg via Device B (PM)
FP 100 mcg QD	1 blister FP 100 mcg via Device A (AM) 1 blister Placebo via Device B (PM)
Placebo	1 blister Placebo via Device A (AM) 1 blister Placebo via Device B (PM)

4.2.2.6.3 Treatment Assignment:

During run-in, subjects were stratified according to whether or not they were receiving inhaled "anti-inflammatories" that is, inhaled CS or inhaled cromolyn sodium (ICT), prior to study entry or were managed on bronchodilator therapy alone (BDT). After the two-week run-in, eligible BDT subjects were randomly assigned, in ascending order, a unique treatment number in one unique range (of numbers) while the eligible ICT subjects were similarly assigned a unique treatment number in a different, non-overlapping range. Subject and treatment numbers were unique and could not be reassigned. No specific attempt to balance enrollment at individual centers was mentioned in the protocol.

4.2.2.6.4 Study Sequence

Screening Period (Visits 1- 2): Nineteen investigators screened 331 children who met the inclusion/exclusion criteria over a two week, single blind period. Subjects could continue to take their baseline asthma medication at this time, except that Ventolin (MDI or Rotacaps) was substituted for their own particular β -agonist. Once selected, however, either the MDI or the DPI Ventolin was to be used consistently throughout the remainder of the study. The Ventolin was to be used only to treat symptoms, and not taken on a regular basis (even if that was how it was previously taken).

The screening period was used to confirm eligibility, assess asthma stability, obtain baseline data, assess compliance, and instruct the children (and caregivers) in the use of all the devices and study procedures to be used during this trial. (See the attached "Figure 1" for a summary schedule of events).

Routine assessments performed at Visit 1 included medical history, physical examination, VS, clinical laboratory tests, AM plasma cortisol and PEFR/spirometry.

On the first visit only, children age 4-5 years had their PEFR measured before and 30' after two puffs of Ventolin MDI to assess reversibility. Children age 6-11 years who did not have reversibility documented in their history also had their FEV₁ measured before and after Ventolin.

Children also received instructions on daily routine assessments and procedures they were to perform for the subsequent two weeks. Diary PEFr was to be measured twice daily in triplicate using a Peak Flow Meter, and the highest value recorded in the subject's diary. AM PEFr was to be measured before study medication but after other diary assessments. Clinic PEFr was to be measured in lieu of the child's home AM PEFr assessment, between 7:00 and 10:00 am for each scheduled visit. Children were instructed not to take any β -agonist for at least 6 hours prior to clinic testing. Every clinic visit was to include both FEV₁ (performed first) and PEFr assessment. Children age 4-5 years were required to perform a PEFr only. FEV₁ was optional but encouraged and therefore usually performed. Older children age 6-11 years were required to perform both FEV₁ and PEFr.

Children received diary cards at Visit 1, and were instructed to record their asthma symptoms, rescue β -agonist use, and nighttime awakenings daily throughout the study.

The screening period of this trial was single-blind. Each child received a two-week supply of placebo Diskus devices and were instructed in the proper dosing: one blister from Device A inhaled in the morning and one blister from Device B inhaled in the evening.

Treatment Period (Visits 2 - 10): Two hundred sixty-two (262) eligible children completed the screening period and were found to be eligible for the study. In addition to meeting the Inclusion/Exclusion criteria above, these children had met the following "randomization criteria:"

- Their asthma had been relatively stable. "Stable" was defined as having no more than 3 days in the last 7 in which ≥ 12 puffs of Ventolin MDI (or 6 doses of Rotacaps) was used and No more than 3 mornings in the last 7 where the AM PEFr was decreased $>20\%$ from the prior PM PEFr and No more than 3 nights in the last 7 with awakenings requiring Ventolin.
- Their clinic spirometry/PEFr met the following criteria:
 - Best clinic PEFr $\leq 85\%$ predicted for ages 4-5 years
 - Best FEV₁ 50-85% predicted for ages 6-11 years
 - Best FEV₁ from Visit 2 within 25% of Best FEV₁ from Visit 1.
- Adequate compliance was demonstrated:
 - At least 70% of study medication had been used
 - Diary card had been completed
 - Anti-asthma medications had been withheld as required

Eligible children needed to meet additional criteria at each clinic visit to continue in the study. "Stability limits" were therefore defined for PEFr and FEV₁:

- FEV₁ stability limit: 15% decrease from the best FEV₁ at Visit 2
- PEFR stability limit: 20% decrease from mean diary AM PEFR from the past 7 days or 20% decrease from the best Visit 2 PEFR, whichever was higher

(The FEV₁ stability limit applied only to subjects age 6-11 years, PEFR stability limit applied to all subjects).

Children not meeting the following "continuation criteria" at each visit were discontinued for lack of efficacy:

- No more than 2 days in the last 7 in which ≥ 12 puffs of Ventolin MDI (or 6 doses of Rotacaps) was used
- No more than 2 days in the last 7 where the AM or PM PEFR was below the PEFR stability limit
- No more than 2 nights in the last 7 with awakenings requiring Ventolin.
- A clinic PEFR \geq the PEFR stability limit
- A clinic FEV₁ \geq the FEV₁ stability limit (ages 6-11 years only)

At Visit 2, subjects exchanged their placebo devices for the appropriate Diskus (DK) devices, as determined by their randomization. Subjects who had been receiving inhaled CS or inhaled cromolyn were told to discontinue these medications for the remainder of the study. Subjects taking theophylline could continue to take it, but were told to withhold it for the 24-36 hours preceding the next clinic visit.

At Visits 3-9 the following procedures were performed:

- Review previous diary cards and dispense new cards
- Adverse event assessment
- PFT's: PEFR, spirometry

Visits were scheduled weekly for the first 4 weeks, then every other week until study endpoint at 12-weeks. Devices were collected and new ones dispensed at the midpoint of the study, week 6 (Visit 7) and at the end of the double-blind period, week 12. An oropharyngeal exam was also performed at week 6.

At study endpoint (Visit 10) or early termination, the usual scheduled clinic assessments were made, in addition to the same as performed at baseline (physical exam, etc.). Study devices were collected, and overall compliance with study procedures was assessed by blister counts, completion of diary cards, and whether subject followed instructions to withhold medication on the morning of the clinic visit. "Adequate" compliance was defined as use of at least 70% of the blister doses.

4.2.2.6.5 Efficacy Assessments

The two primary efficacy variables were AM predose FEV₁ and clinic visit PEF_R. For the older children (6-11 years), FEV₁ was performed in triplicate using approved spirometric equipment according to ATS recommendations. The child could be sitting or standing during the maneuver, but was required to be consistent throughout the study. For all children in the study, PEF_R was performed using the same hand-held — peak flow meter as they used at home. The highest of three determinations was recorded.

Secondary efficacy variables included all of the following:

- Survival in the study
- Diary AM and PM PEF_R
- Subject-rated daily symptom scores on a scale of 0 (none), 1 (mild), 2 (moderate), or 3 (continuous or disabling)
- Number of nighttime awakenings requiring Ventolin
- Rescue Ventolin use

4.2.2.6.6 Safety Assessments

- Adverse Events (AE)
- Clinically significant changes in clinical laboratory values
- Clinically significant changes in physical examination, VS, or oropharyngeal exam

4.2.2.6.7 Statistical Methods

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

Reviewer's Comment: The final sentence of this paragraph should be borne in mind when assessing the "significance" of the primary endpoints for each FP arm vs. placebo.

Power Calculations: Enrollment was planned to obtain 240 evaluable subjects to provide >80% power of detecting a difference in AM PEF_R of 16 L/min between any two treatment groups of 80 subjects each, assuming a standard deviation of 36 L/min. It was also calculated that 75 subjects/treatment arm would be required to achieve 80% power of detecting a difference in FEV₁ of 0.25L between any two treatment groups. Actual enrollment was 83 to 91 subjects per treatment group, with a total enrollment of 262 subjects.

Populations: The Intent-to-Treat (ITT) Population was used for most calculations, unless otherwise stated. The ITT Population included any subject who had received at least one dose of study medication. The Efficacy Population included only those subjects in the ITT group who