

FP groups were also significant at study endpoint ($p < 0.001$ for each comparison vs. placebo). The numerical improvement from baseline was greater for the twice daily group (35 L/min) than for the once daily group (23 L/min), although the pair-wise comparison between the two was not significant. Similar to the primary endpoint FEV1, the placebo group showed a net deterioration in lung function as measured by this parameter (-15L/min).

The mean change from baseline in diary PM PEFR followed a pattern similar to diary AM PEFR (see table below). Baseline values were comparable between treatment groups and slightly higher than AM PEFR values. Change from baseline to endpoint was also quantitatively similar to AM PEFR, that is, -9L/min for placebo, 33 L/min for twice daily, and 20 L/min for once daily. There was a statistically significant overall treatment effect at endpoint ($p < 0.001$). Pair-wise comparison of each of the two FP arms to placebo was also significant ($p < 0.001$ for both), but comparison of the two FP arms to each other was not.

**CHANGE FROM BASELINE TO ENDPOINT IN AM/PM PEFR:
ITT***

	Placebo	FP 250 BID	FP 500 QD	Placebo vs. BID [†]	Placebo vs. QD [†]	QD vs. BID [†]
N	84	86	83			
Baseline AM PEFR (L/min)	416	408	400			
Δ from Baseline AM PEFR	-15	35	23	<0.001	<0.001	0.518
Baseline PM PEFR (L/min)	439	433	427			
Δ from Baseline PM PEFR	-9	33	20	<0.001	<0.001	0.179

* Tables 15-19; Vol.127

[†] P-values for pair-wise comparisons. Overall, $p < 0.05$ for both by F-test

**4.3.4.7.3.5 Secondary Endpoints: 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 slightly greater than 1.00. At endpoint, there was a statistically significant treatment effect for FP compared to placebo. The pair-wise comparison of FP group with placebo was also significant at endpoint, although the twice daily group showed numerical superiority over the once daily group. There was no significant difference between the two FP groups ($p = 0.549$).

Nighttime awakenings requiring Ventolin were also infrequent and similar across treatment groups, although the difference between twice daily FP and placebo was significant at baseline ($p=0.010$, see table below). A statistically significant treatment effect could be found at endpoint compared to baseline, however, this was driven primarily by deterioration in the placebo group (change from baseline= $+0.09$) rather than improvement in the FP-treated groups (minus 0.01 and minus 0.03 for once daily and twice daily, respectively). Pair-wise comparison with placebo was significant for both FP doses. There was no statistical difference between the two doses, however ($p=0.859$).

At baseline, daily use of Ventolin was similar between treatment groups, approximately 2 ½ to 3 puffs per day. There was a statistically significant treatment effect for this parameter at endpoint ($p<0.001$, see table below). The pair-wise comparison between placebo and each of the two FP groups was also significant at endpoint ($p<0.001$ for each comparison). The twice daily FP group had reduced their mean Ventolin use by approximately 1 puff per day (-1.05) and the once daily by 2/3rd puff per day (-0.67). The placebo group had increased their mean usage by nearly 1 puff per day ($+0.86$). Although the improvement for the once daily group was numerically smaller, there was no statistical difference between once and twice daily FP at endpoint.

CHANGE FROM BASELINE IN DIARY VARIABLES (ITT)*

	Placebo	FP 250 BID	FP 500 QD
N	84	86	83
Asthma symptom score:			
Baseline	1.10	1.13	1.10
Change	+0.16	-0.33	-0.32
p-value**		<0.001	<0.001
Nighttime Awakenings:			
Baseline	0.16	0.08 [†]	0.11
Change	0.09	-0.03	-0.01
p-value**		0.048	0.012
Ventolin use (puffs/day)			
Baseline	3.14	2.88	2.79
Change	0.86	-1.05	-0.67 ^{††}
p-value**		<0.001	<0.001

* From Tables 22-24; Vol.127.

** Compared to placebo

[†] $p=0.010$ vs. placebo

^{††} Pair-wise comparison for QD vs. BID, $p=0.030$

4.3.4.7.3.6 Efficacy by Demographic Subgroups

There was no indication that a difference in response to FP existed by gender or age (Tables ST-12 through 19; Vol 127). The number of non-Caucasian subjects was too small to make any scientifically valid

statement regarding the impact of ethnicity on FP efficacy. Subgroup analysis was performed only for the primary endpoint, FEV₁.

4.3.4.7.3.7 Efficacy by Inhaled Corticosteroid/Cromolyn use at Baseline

The subgroup using inhaled CS at baseline constituted about half of the study population. Baseline characteristics of the ICT population which differed from the BDT subjects included a lower mean FEV₁ at baseline, a slightly higher percentage of females (perhaps explaining the lower FEV₁), and a mean age that was approximately 5 years older (Tables ST 20-25).

Mean change from baseline in FEV₁ has been summarized by ICT and BDT strata and displayed in the table below. Endpoint data for these two subgroups were generally consistent with the overall ITT population, that is, the two FP groups showed more improvement than the placebo group, and the subjects in the twice daily group showed greater improvement than the subjects in the once daily group. BDT subjects in both FP treatment groups showed greater numerical improvement in FEV₁ than ICT subjects. Somewhat surprisingly, both ICT and BDT subjects treated with placebo experienced a net deterioration in lung function as measured by fall in FEV₁. The ICT group had a three-fold greater worsening than the BDT group, however, during the double-blind segment of the trial. No survival data for these strata have been provided, but inspection of Tables ST-24 and ST-25 show that the Week-12 FEV₁ was based on only 10 of the original 42 patients in the ICT placebo group, compared to 23 out of 42 for the BDT placebo group (76% dropout vs. 45%).

Mean Change from Baseline in FEV₁ by ICT/BDT Strata*

	Placebo		FP 250 BID		FP 500 QD	
	ICT	BDT	ICT	BDT	ICT	BDT
N	42	42	42	44	40	42
Baseline FEV ₁ Liters	2.37	2.53	2.25	2.58	2.17	2.75
Mean Change at Endpoint	-0.23	-0.08	0.37	0.47	0.09	0.19

*From Tables ST-22- 25, Vol.127

No p-values are provided for comparisons between treatment groups, because the study was not powered to detect differences among sample sizes this small.

Reviewer's Comment: As noted earlier in this review, this is another serious flaw with FLTA2005. The two mutually exclusive subgroups ICT and BDT behave differently in the analysis above. Although the difference between placebo and once daily FP at endpoint is very close for the two strata (0.27L for the BDT group and 0.32 L for the ICT group), the ICT difference is due primarily to deterioration by the placebo group while the BDT difference is attributable more to improvement by the FP-treated group.

labeling of 500 mcg once daily, it would be important to have adequately powered data to clarify whether this dosing strategy is advisable for BDT patients (i.e., those initiating steroids) vs. ICT patients (those already stable on steroids).

4.3.4.7.4 Humanistic and Resource Utilization

Tables 25 and ST-27 present individual and combined scores for the AQLQ. At endpoint, the Overall quality of life scores for both FP 250 mcg BID and FP 500 mcg BID were significantly higher than placebo (-0.22, 0.81, and 0.46 for placebo, twice daily, and once daily, respectively; $p < 0.001$). The change from baseline to endpoint score for twice daily exceeded the pre-specified clinically significant difference of 0.5 by itself. The change from baseline for the once daily group exceeded this threshold only in comparison to placebo. The pair-wise comparisons with placebo with each of the two FP arms was significant ($p < 0.001$ for each). The difference between once and twice daily was not significant ($P = 0.091$).

The ASRP and Resource utilization instruments did not have pre-specified clinically significant changes, and will not be discussed further in this review.

4.3.4.7.5 Safety Results

4.3.4.7.5.1 Extent of Exposure

A total of 253 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 BID-treated patients were exposed for approximately 80 days out of an 84-day trial. The once daily group received approximately 15 fewer days of exposure. The placebo patients received approximately 30 fewer days of exposure.

EXTENT OF EXPOSURE TO STUDY MEDICATION*

	Placebo	FP 250 BiD	FP 500 BID DH
Number			
Baseline	84	86	83
Completed	31 (37%)	74 (86%)	53 (64%)
Exposure(days):			
Mean	48.3	79.2	64.9
Median	50.0	85.0	84.0

* Table 28; Vol.127

4.3.4.7.5.2 Adverse Events (AE)

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

Overall, 46% of the placebo group reported at least one adverse event during this trial, compared to 51% in the once daily FP group and 65% in the twice daily FP group. This incidence is reasonably consistent with the overall extent of exposure shown in the table above.

By organ system, the most commonly reported AE's in all treatment groups were within the ENT system (25-4%) followed by GI (10-19%), and non-site specific (8-11%). In descending order of frequency, the most frequently reported AE's were URI (11-21%), throat irritation (3-8%), and sinusitis (1-3%).

Because of the substantial difference in extent of exposure, it is difficult to tease out those events more common in FP-treated subjects, or more common in one or the other FP dosing group. There is a suggestion that URTI may be more common among FP BID patients (21% vs. 12% for placebo and 11% for FP once daily). Sinusitis may be more common among once daily FP users (8% vs. 5% for placebo and 3% for FP BID). Combined candidiasis at an unspecified site and oral thrush was reported for 7 placebo subjects, 5 FP BID subjects, and 6 FP QD patients.

When analyzed by demographic subgroups, there was no apparent difference in overall numbers of AEs based upon gender or age. The number of non-Caucasian subjects was too small for scientifically meaningful differences to be detected.

There were no deaths in the double-blind phase of this study. Five subjects suffered serious AEs and three patients were withdrawn due to the AEs, two with SAEs. The 5 SAEs included 3 from the FP BID group, one from the once daily FP group, and one withdrawn prior to randomization. The FP BID subjects included a cholecystectomy, basal cell CA, and chest pain of unclear etiology. The FP QD subject developed appendicitis. The latter two patients were also withdrawn from the study due to these SAEs. The withdrawal which occurred to an FP QD subject and was not mentioned as an SAE was described as an "anxiety attack."

There were no pregnancies during this trial. No adverse event specifically coded as "HPA axis suppression" was reported.

4.3.4.7.5.3 Laboratory Data (excluding HPA-axis)

Blood samples for serum chemistry, LFT's, and hematology were obtained at baseline and at study endpoint. One subject was withdrawn for an abnormal baseline GGT. No abnormal laboratory value was reported as an adverse event. A few subjects (1% per group, maximum) had "clinically significant" laboratory values by pre-specified criteria reported at any time post-randomization (Table 32; Vol.127, p.140). Each of these patients was

further discussed in the text of the study report. A few more patients had laboratory values outside of the normal range, many of which were probably chance variation expected among a large group of patients. 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. These have been separately noted in this review (below).

There were no reported clinically significant elevations in bicarbonate. For glucose, there was one placebo subject who had a clinically significant high plasma glucose value.

One FP BID subject had clinically significant hypokalemia ($k=2.9$, no further information is available).

No clinically significantly elevated eosinophil count was reported for this study.

There were no subjects with "clinically significant" elevations in alkaline phosphatase (AP).

4.3.4.7.5.4 HPA Axis Assessment

The HPA axis was assessed at baseline and at study endpoint by means of unstimulated (basal) AM plasma cortisol levels. Any value <5 mcg/dl was considered abnormal. All samples were collected pre-dose. Mean plasma levels for each group were determined and compared at baseline and endpoint.

Eighteen patients had abnormal plasma cortisol values at screening, 4 in placebo, 6 in FP BID, and 8 in FP QD. Twenty-two subjects had plasma cortisol levels that were abnormally low drawn at some point after randomization, 1 in placebo, 12 in FP BID and 11 in FP QD. (see supporting table ST-38, Vol.127)..

With regard to change from baseline to endpoint in mean plasma cortisol level, the placebo group had a mean change of -0.1 mcg/dL compared to -0.5 mcg/dL for the FP 250 BID group and -0.6 mcg/dL for FP 500 QD.

Once daily dosing had no advantage in this regard, despite the AM cortisol being more distal to the prior dosing

4.3.4.7.5.5 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 between the two FP treatment groups relevant to this application.

4.3.4.8 Conclusions

4.3.4.8.1 Efficacy Conclusions:

Dry powder FP delivered from the Diskus multi-dose powder inhaler (MDPI) device at a dose of 250 mcg BID has been shown to be efficacious in the treatment of mild-to-moderate asthma in adult and adolescent patients. Efficacy was demonstrated for the primary endpoint, change from baseline in AM pre-dose FEV₁. Efficacy was supported by the results of all five of the secondary endpoints, in addition to survival-in-study.

Subgroup analysis showed no significant difference in efficacy based on the subject's gender or age. There were too few non-Caucasian subjects to make a scientifically sound determination based on ethnicity. With regard to inhaled corticosteroid use at baseline compared to inhaled bronchodilator use only, (ICT vs. BDT), both subgroups showed numerical improvement in the primary endpoint, however, the BDT subgroup showed a greater improvement than the ICT, not unexpectedly. Also as expected, the ICT placebo group did generally show a deterioration in lung function, as expected upon withdrawal of inhaled corticosteroids, although the BDT placebo group had a minor deterioration, as well.

Once daily FP 500 mcg via Diskus did show a statistically significant difference on the primary endpoint, FEV₁, in the pair-wise comparison with placebo. The numerical change from baseline was approximately three-fold less than the improvement in FEV₁ shown by the FP BID arm, however, and statistical significance was driven primarily by the deterioration in the placebo group. The numerical change from baseline to endpoint in FEV₁ was 0.11 L, a very small improvement (<5%) with questionable or borderline clinical significance. Subgroup analysis taking inhaled CS usage at baseline into account reinforced the substantial difference between these two groups when treated with inhaled CS,

FP 500 mcg once daily
via Diskus is not recommended for approval at this time

4.3.4.8.2 Safety Conclusions:

Based upon Study FLTA2005, dry powder FP 250 mcg BID and FP 500 mcg QD administered via the Diskus appeared to be safe when used to treat adults and adolescents with mild-to-moderate asthma, and there appeared to be no safety difference between the two dosing schedules.

The most frequently occurring adverse events were in the ENT system, the most common being URTI, followed by GI and non-site specific. Because

of the substantial difference in extent of exposure between treatment groups, it is difficult to identify adverse events more common for one group over another, however, URTI and throat irritation were more common among FP-treated patients. Once daily dosing did not appear to provide any safety advantage with regard to AE profile than twice daily, however. The overall profile was not different from that described in the approved labeling for Flovent Rotadisk Diskhaler.

There were no deaths in the study, five serious adverse events, and a total of three withdrawals due to adverse events.

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. There were 24 patients who had abnormally low plasma cortisol levels post-randomization, 12 in the FP BID group, 11 in the FP QD group, and one in the placebo group.

Although this trial did not identify any individual switched from twice daily inhaled CS to once daily FP who experienced an acute asthma exacerbation, the trial was specifically designed to discontinue subjects early if their asthma became unstable by predefined criteria, often in the absence of symptoms.

4.3.4.9 Labeling Considerations: See next section 4.3.5.

4.3.5 FLTA2016:

“A stratified, randomized, double-blind, parallel-group, comparative trial of inhaled fluticasone propionate via the multi-dose powder inhaler 100 mcg QD, 200 mcg QD, 500 mcg QD and placebo in adolescents and adult subjects with chronic asthma.”

A detailed analysis of this clinical trial will not add substantially to the information already contained in this NDA review. Neither FP 200 mcg QD via Diskus nor FP 100 mcg QD via Diskus have been shown to be efficacious based on the pre-specified primary endpoint FEV₁ (FLTA2003 and FLTA2004) and co-primary endpoints FEV₁ and AM clinic PEFr (FLTA2008). Indeed, review of data from this trial again demonstrates lack of efficacy based on the primary endpoint, FEV₁. With regard to once daily FP 500 mcg for treatment of mild to moderate asthma in adults and adolescents, FLTA2005 did demonstrate a statistically significant difference between placebo and FP 500 mcg QD via Diskhaler for the primary endpoint FEV₁. However, the issues from that trial were the

absence of long-term data on the safety and efficacy of once daily dosing (particularly in reference to systemic safety in comparison of the same nominal daily dose given twice daily), a treatment effect which was marginally significant from a clinical standpoint, and the under-powering of the study to detect differences in response to once daily dosing among the two separate inhaled CS subpopulations, the ICT and the BDT. This current dose-ranging trial for once daily dosing, 2016, adds nothing to address these crucial issues.

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5 INTEGRATED SUMMARY OF EFFICACY¹³

The patient population studied in pivotal controlled trials with Flovent Diskus exceeded 2600 patients, with over 1,100 receiving active formulation. The results to date support the efficacy of the Flovent DPI over a range of asthma severity from mild to severe at doses of 100 to 2,000 µg/day administered on a BID schedule to patients ages 4 – 11 (doses of 50 – 100 mcg BID) and 12 and above (doses of 100 to 1000 mcg/BID), with the data supporting once daily administration being relatively mixed (with only the 500 mcg QD dose having clear evidence of efficacy, albeit without sufficient data on appropriate patient populations and what doses of BID FP may be comparable to 500 QD).

The review of the ISE will be relatively brief, due to the prior review of Flovent products, and will mainly focus on product specific comparisons and the novel QD indication sought.

5.1 Onset of Efficacy

Onset of efficacy was tracked by means of daily diary scores for symptoms, Ventolin use, nighttime awakenings and PEFR. By PEFR, symptoms and Ventolin use, onset was within 1 – 2 days for many of the adult/adolescent studies with BID dosing (2004, 2005, 2001), with FEV₁ (its first assessment) showing improvement by the first week in many studies as well. The pediatric study data are somewhat less convincing of effect within the first few days, but show convincing trends by a week. Overall, there appears to be adequate data with the Diskus (in addition to those from the Rotadisk), to support the statement that onset may be seen as early as 1 – 2 days, but full effects may take 1 – 2 weeks or longer. It is notable that the QD data often took several weeks to months to achieve a net improvement similar to that seen with BID dosing in the first week.

5.2 Duration of Efficacy

The open label extensions of the adult trial 2005 and the pediatric trial 2008 provide some data, albeit not adequately controlled, supporting the long-term stability of asthma in subjects treated with the Flovent Diskus, assessed by measures such as spirometry and PEFRs. In all treatment categories, improvements in these airflow measures seen with active drug were maintained or further improved through the course of the 1 year follow-up. Confounding the interpretation of these data in comparison to the double-blind baseline, however, is the number of subjects not entering into the extension (21% in the adult trial), and the drop out occurring during the safety study. Study 2002, the prednisone sparing study, had a longer double-blind period, though only a small number (4 subjects) remained on placebo out to a year. The data in this longer-term phase of 2002 showed evidence of continuing effectiveness. The interpretation of these longer term data were also somewhat confounded (see the 2002

¹³

review). However, there are no data in this NDA or prior FP NDAs to suggest a waning of activity over time.

5.3 Dose - Response Characteristics

NDA 20-833 contains few trials that examined multiple and/or large ranges of doses from the Flovent Diskus in a single study (often studying either one or two BID doses). Therefore, the sponsor performed cross-study comparisons within dosing regimens to address dose response. When this was done, numerical trends do emerge, but these data must be viewed with all the caveats related to cross-study comparisons. Twice daily data from adult/adolescent trials 2001, 2003, 2004 and 2005 were pooled by the sponsor in these post-hoc examinations. These pooled data are tabularly summarized below:

	Placebo		FP100 BID		FP250 BID		FP500 BID	
	N	mean	N	mean	N	mean	N	mean
Predose FEV ₁	296	2.46	138	2.44	86	2.44	64	2.44
Mean change at endpoint	291	0.00	138	0.39	86	0.42	63	0.52
Withdrawals due to lack of efficacy	122/296 (41%)		17/138 (12%)		7/86 (8%)		3/63 (5%)	

Similar trends were seen for separate pooling of ICT or BDT subsets, although the dose-response relationship for the BDT subjects was less convincing on both FEV₁ and withdrawal endpoints.

Of particular note, however, is to consider the same data for the QD dosing (arising from the single dose ranging 2016 trial) in patients ages 12 and above. There is much less of an apparent numerical trend in the FEV₁ data between 100, 200 and 500 QD, and the differential between active and placebo is smaller (approximately of 0.25 L for FEV₁ compared to approximately 0.45 L for BID). The withdrawals due to lack of efficacy were in the range of 29% (100 QD) to 14% (500 QD) compared to a placebo rate of 44%. All three of these FP QD treatment group rates were higher than any of the BID rates (shown above).

As previously discussed in this review, the 2002 prednisone sparing study showed no statistical separation of doses, but numerically, most endpoints favored the 1,000 mcg BID dose over the 500 mcg BID dose. This is in contrast to the MDI oral steroid sparing study where there was clear separation of a small dose spread (880 mcg BID vs. 660 mcg BID). The reasons for this disparity are not clear.

Finally, the pediatric BID studies suggest that 100 mcg BID provides somewhat more benefit than the 50 mcg BID dose. While these separations between active doses are not often statistically significant, there are times in these studies where the 100 mcg dose separates from placebo, while the 50 mcg dose does not.

Overall, the data available support the dosing recommendations that the sponsor proposes in the labeling for the BID doses, with the caveat that all patients should be titrated to their lowest effective dose.

5.4 Efficacy in Subgroups of Asthmatic patients

Gender, Age and Race / Ethnic Subgroups are addressed in the sponsor's application. Unfortunately, with the racial/ethnic subgroups and the age over 65 subgroups, there are few individuals contributing to the data, so any conclusions cannot be made with confidence. However, for the gender and age groupings (adolescent vs. adult), there is no signal of important differences in clinical responses. [see table on page 75, vol. 242]. In particular, overall males and females appear to experience comparable results. Notable for adolescents is that none of the QD dosing groups separate very much from placebo for FEV₁ (placebo = 0.22 L improvement, FP100 QD = 0.23, FP200 QD = 0.27 and FP500 QD = 0.27). However, the BID differential from placebo for this age group looks comparable to that seen with BID dosing in adults.

The data for ethnic subgroups and those patients over 65 is quite variable, due to low numbers in each treatment arm. It is notable, however, that the largest active treatment enrollment for those over age 65 was to the FP200 QD treatment (8 subjects) and in that group, the FEV₁ response was even lower than placebo, at - 0.17 L vs. - 0.12 L.

For the pediatric data, there were more non-Caucasians studied proportionately than in adults. A male predominance typical of the population of 4 - 11 year olds was also seen. Here again, males and females showed no important differences in response. For the Black, non-Black - non-Caucasians and Caucasians subgroups, there were no trends of differences seen, particularly for those treatment arms represented by adequate numbers.

5.5 Medication Co-Administration Subgroups

5.5.1 Salmeterol

The only co-administered drug analyzed by the sponsor was salmeterol, a long-acting inhaled bronchodilator. Four of the adult/adolescent studies allowed its fixed use, and 24% of subjects were indeed on it. No important differences were seen on the primary endpoint in those patients receiving salmeterol vs. those who did not. On average, the improvement in FEV₁ with FP therapy appeared to be somewhat better in those who did not than those who continued on salmeterol.

5.6 "Humanistic" Measures of Efficacy

The AQLQ instrument of Juniper et.al. was used in a number of these studies, with adequate planning in the protocols. In study 2004, a study of

ICT patients, the overall results of the AQLQ for the FP100 BID dosing showed an improvement from baseline of 0.40, with a change in placebo of - 0.16 (a net difference of 0.56). While the mean difference between active and placebo exceeds the 0.5 MID (minimally important difference) validated for this instrument, the improvement in the active group did not exceed its own baseline by 0.5.

Study 2005 enrolled a mix of BDT and ICT patients treated with 250 BID or 500 mcg QD. This study showed clear, striking results for the AQLQ against placebo and baseline for the 250 mcg BID dose, with an overall improvement of 0.81 points (with individual domains being between 0.87 and 0.55) from baseline. Placebo had a decrement of - 0.22 points overall, and between - 0.04 and - 0.38 for the various domains. In this study, the FP500 QD group also showed improvements from baseline approaching the MID (overall 0.46), but exceeding placebo by the MID in all but the environmental exposure domain. This study provides more convincing AQLQ results, but the sponsor does not give subgroup results (BDT vs. ICT) to clarify the issue raised by 2004, and the findings are not replicated for dose/population.

Study 2002 produced the most convincing results by the AQLQ, and are tabulated below:

Dimension	Placebo (n ≈ 30)	FP500 (n ≈ 36)	FP1000 (n ≈ 34)	Overall p-value
Overall	-0.38	0.84	1.29	< 0.001
Activity limitation	-0.04	0.90	1.04	< 0.001
Asthma symptoms	-0.52	0.78	1.52	< 0.001
Emotional Function	-0.42	1.08	1.50	< 0.001
Environmental Exposure	-0.13	0.82	1.02	< 0.001

The sponsor has presented data supporting an improvement in asthma and its impact on the asthmatic patient for the high dose, oral corticosteroid indication (but the results are not replicated). In that regard, it should be mentioned that these differences are more striking than those seen in the similar MDI study. Study 2005's results also support an improvement in asthma and its impact on the asthmatic patient as assessed by the AQLQ in a population of patients, but with a different dose and different population/indication. The data from 2004 appears least convincing, since the improvement from baseline arguably matters more for this study since the placebo group represents patients in whom therapy was withdrawn. For both 2004 and 2005, there was a large number of patients screened

who did not enroll secondary apparently related to the burden of taking the humanistic instruments. The population left, therefore, also raises generalizability issues.

In total, these data are all supportive of the more traditional efficacy endpoints.

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6 OVERVIEW OF SAFETY

**Source: Integrated Safety Summary for NDA's 20-833
120 day Safety Update - submitted 7-23-98**

The data that forms the basis of this safety summary are taken from the Integrated Summary of Safety (ISS) originally supplied to the Flovent Diskus NDA, as well as from the 120 day safety update submitted in July 1998.

It is worth noting that in addition to the clinical trials and post-marketing database for the Flovent Diskus itself, the consideration of safety for this product includes the other approved inhalation forms of Flovent – the metered-dose inhaler and the Rotadisk DPI. Given the similarities in formulation (i.e., fluticasone propionate blended with lactose albeit at differing proportions) and pharmacokinetics between the Flovent Diskus and Rotadisk products, much of the original ISS data reviewed for NDA 20-549 hold for this device as well. Furthermore, the Diskus device is approved for the inhaled administration of salmeterol, so issues of device performance as they relate to safety are less for this application than for a novel DPI device. In many ways, although developed under a full clinical program, this NDA has a number of parallels to a “switch” development program. The safety issues, therefore, are not so much about the safety of this formulation, this substance or this device, but how does the safety of all three combined differ from the prior approved formulations/devices. Therefore, the ISS review will be abbreviated compared to an NME, a new drug substance for inhalational use, or a new device/formulation.

The 120-day safety update, which covers the period from November 30, 1997 through March of 1998. No new studies were completed during this reporting period (two on-going studies remained on-going by March 31, 1998)

6.1 Demographics of Population Exposed – Diskus Clinical Trials (20-833)
6.1.1 Demographics of Population Exposed –US Diskus Standard Efficacy Trials

A summary of demographics from the US trials for the Flovent Diskus is presented below, excluding the CS-sparing study:

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(derived from table 3.1 of ISS, vol 244, pg 244)

	Placebo	FP 50 µg BID	FP 100 µg QD	FP 100 µg BID	FP 200 µg QD
Total # patients	627	178	170	305	307
Gender					
female	242 (39)	75 (42)	59 (35)	116 (38)	120 (39)
n (%)					
male	385 (61)	103 (58)	111 (65)	189 (62)	187 (61)
Age (yrs) - Mean (range)	25 (4 - 78)	8(4 - 11)	20(4 - 72)	21(4 - 71)	29(4 - 73)
Ethnic Origin					
Caucasian	525 (84%)	127 (71%)	128 (75)	261 (86)	262 (85)
Black	46 (7)	28 (16)	20 (12)	24 (8)	22 (7)
Other	56 (9)	23 (13)	22 (13)	20 (7)	23 (7)
	FP 250 µg BID	FP 500 µg QD	FP 500 µg BID		
Total # patients	86	169	64		
Gender					
female	42 (49)	73 (43)	28 (44)		
n (%)					
male	44 (51)	96 (57)	36 (56)		
Age (yrs) - Mean (range)	38(12 - 66)	37(12 - 75)	32(13 - 62)		
Ethnic Origin					
Caucasian	81 (94%)	147 (87%)	50 (78)		
Black	3 (3)	6 (4)	4 (6)		
Other	2 (2)	16 (9)	10 (16)		

Overall, the demographics showed a reasonable gender balance, a wide variety of ages studied (including pediatrics down to age 4), and some racial/ethnic mix, though the proportion of minorities overall is certainly not fully reflective of the general US population.

Although not included in the table, for these studies, the mix of subjects entering the trials who were utilizing ICS at entry versus bronchodilators alone was approximately 50% in all groups except the FP 500 BID group, where 63% of the group was not using ICS at the time of study entry. As with the Rotadisk, the sponsor has restricted the use of Flovent in studies of children less than 12 years of age \leq 200 µg daily dose. Clearly, the safety of a higher dose in this age group has not therefore been established.

Also, in addition to these Diskus arms, the sponsor conducted comparative trials to the Rotadisk formulation and to BDP. The demographics and safety data from these groups will not be detailed in the ISS, but may be cited as appropriate for reasons of comparisons and contrasts to the formulation/device under review.

The sponsor separately considered the CS-sparing trial FLTA2002 due to differences in population and study design from the above studies. This separation is reasonable and since this is only a single study which was previously reviewed in this document, these data will not be fully commented upon in this ISS review.

Also reported separately by the sponsor is the FLTA2008 open label safety trial in children ages 4 – 11. These data are not detailed here, but it should be pointed out that only 19 of the 192 subjects (10%) were 4 – 5, so the majority of these open-label data come from 6 – 11 year olds.

6.1.2 Demographics of Population Exposed – Non-US Diskus Clinical Trials

	FP 50 µg BID	FP 100 µg BID	FP 250 µg BID	FP 500 µg BID
Total # patients	166	164	320	172
Gender				
female	62 (37)	62 (38)	137 (43)	96 (56)
male	104 (63)	102 (62)	183 (57)	76 (44)
n (%)				
Age				
Mean	8	8	48	47
Years				
range	4 – 13	4 – 11	18 – 81	18 – 80
Ethnic				
Caucasian	158 (95%)	155 (95%)	316 (<1)	168 (98)
Origin				
Black	0 (0)	1 (<1)	1 (12)	0 (0)
Other	8 (5)	8 (5)	3 (<1)	4 (2)

A few points on differences between the US and non-US demographics. Not atypically, there are very few blacks in these trials (as is often the case for studies based in Europe). Also, the adult trials did not have any adolescents, so the non-US controlled trial safety data provides no information on patients older than 13 but younger than 18.

6.2 Duration of Exposure

6.2.1 US Diskus Efficacy Studies, all age ranges, all indications (excluding study FLTA2002):

	Placebo	FP Diskus
Number of Patients (> 1 dose exposure)	627	1279
1 - 21 days	174 (28)	123 (10)
22 - 42 days	63 (10)	709 (8)
43 - 63 days	47 (7)	61 (5)
64 - 84 days	124 (20)	294 (23)
>84 days	219 (35)	705 (55)
Treatment days		
Mean	56	72
Median	74	85

Since the mean and median exposure duration is substantially shorter for placebo than for active drug, this will need to be taken into account in the assessment of rates of occurrences of adverse events.

6.2.2 Non-US Diskus studies

Not represented by a table, these data show that on average, the duration of exposure to active drug was much shorter in the non-US studies, and these studies were not placebo-controlled. The mean duration of active drug exposure was most often in the 28-day range, rather than the mean of 72 shown above. Since these exposures were more limited in duration and not

placebo-controlled, they will be reviewed mainly for safety signals, rather than for trying to assess occurrence rates of adverse events in relation to placebo.

6.2.3 Patient Disposition

6.2.3.1 Patient Disposition, US¹⁴

Summary table: disposition of patients in US Diskus studies excluding FLTA2002

Dose	Placebo	FP50 BID	FP100 QD	FP100 BID	FP200 QD	FP250 BID	FP500 QD	FP500 BID
Number	627	178	170	305	307	86	169	64
Completed	N 284 (45)	132 (74)	107 (83)	228 (75)	205 (67)	74 (86)	119 (70)	54 (84)
Withdrawn (%)	343 (55)	46 (26)	63 (37)	77 (25)	102 (33)	12 (14)	50 (30)	10 (16)
Reason for withdrawal								
Lack of efficacy	270 (43)	30 (17)	46 (27)	40 (13)	73 (24)	7 (8)	33 (20)	3 (5)
Adverse event	12 (2)	3 (2)	3 (2)	1 (<1)	4 (1)	1 (1)	3 (2)	1 (1)
Failure to return	4 (<1)	3 (2)	3 (2)	0	3 (<1)	2 (2)	2 (1)	1 (2)
Other	57 (9)	10 (6)	11 (6)	36 (12)	22 (7)	2 (2)	12 (7)	5 (8)

The numbers of drop-outs for adverse events is low and fairly even for all groups. This likewise holds for the failure to return and other categories. Not surprisingly, given the study design, the drop-outs due to lack of efficacy are not evenly distributed and occur in what is largely a dose-dependent manner. Notable once again from these data is that the BID dosing is consistently better in controlling asthma by this "efficacy" measure than is the QD dosing regimen (regardless of dose). Note that there was no dose-trend in the withdrawals due to adverse events.

6.2.3.2 Patient Disposition, non-US¹⁵

Perhaps due to the shorter duration and differences in design and conduct, the non-US disposition data shows that well over 90% of the subjects completed the studies in all dosage groups, and none were reported to have discontinued for lack-of-efficacy. The withdrawals due to adverse events ranged from <1% to 4% and, unlike the US data, trended towards higher occurrences with higher Diskus doses.

6.2.4 Adverse Event Reports / Drug Reactions

Note: There will also be a separate discussion of significant and/or serious events and of deaths under section 10.4.

¹⁴ Taken from Table 4.1, page 260-1, vol. 244
¹⁵ Table 4.9 of ISS, page 269; vol. 244

6.2.4.1 All Adverse Events –US study population (adult and pediatric)

Included in this table are any events occurring at a percentage 2% or higher in one of the FP Diskus groups compared to that in placebo, or that are an AE of interest for an inhaled corticosteroid, or a likely ENT/Respiratory event in this population. (Note that although certain trauma events met the criterion to be included, they are not depicted due to causality considerations). No attempt is made in the tabulation to correct for rate, i.e., that placebo patients had a lower duration of exposure.¹⁶

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¹⁶ Table 5.1 of ISS, page 272; vol. 244

	Dose (BID)	Placebo	FP50 BID	FP100 QD	FP100 BID	FP200 QD	FP250 BID	F500 QD	FP500 BID
# taking more than 1 dose		627	178	170	305	307	86	169	64
Number of pts with any AE		396 (63)	121 (68)	107 (63)	218 (71)	204 (66)	56 (66)	103 (61)	42 (66)
Pulmonary	Viral Resp, Infect.	26 (4)	8 (4)	11 (6)	16 (5)	16 (5)	1 (1)	10 (6)	1 (2)
	Cough	54 (9)	24 (13)	15 (9)	39 (13)	33 (11)	3 (3)	19 (11)	14 (22)
	Bronchitis	11 (2)	3 (2)	4 (2)	8 (3)	7 (2)	0 (0)	4 (2)	5 (8)
	Asthma	11 (2)	1 (<1)	0	0	1 (<1)	0	0	0
ENT	URI	105 (17)	35 (20)	36 (21)	54 (18)	64 (21)	18 (21)	33 (20)	9 (14)
	Throat Irritation	24 (4)	5 (3)	9 (5)	16 (5)	13 (4)	1 (1)	4 (2)	3 (5)
	Sinusitis	31 (5)	13 (7)	10 (6)	23 (8)	17 (6)	3 (3)	7 (4)	4 (6)
	Upper Respiratory Inflammation	19 (3)	9 (5)	5 (3)	16 (5)	11 (4)	0 (0)	1 (<1)	3 (5)
	Rhinitis	12 (2)	7 (4)	4 (2)	9 (3)	3 (<1)	1 (11)	0 (0)	1 (2)
	Hoarseness/Dysphonia/Laryngitis	4 (<1)	3 (2)	0 (0)	3 (<1)	3 (<1)	3 (3)	4 (2)	4 (6)
	Epistaxis	5 (<1)	6 (3)	1 (<1)	3 (<1)	1 (<1)	0 (0)	1 (<1)	0 (0)
	Unspec. Oropharyngeal plaques	2 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	3 (3)	1 (<1)	0 (0)
GI	Nausea/vomiting	24 (4)	14 (4)	11 (6)	13 (4)	9 (3)	1 (1)	6 (4)	1 (2)
	Diarrhea	9 (1)	3 (2)	2 (1)	8 (3)	16 (5)	1 (1)	3 (2)	0 (0)
	Viral GI infections	8 (1)	7 (4)	3 (2)	9 (3)	9 (3)	3 (3)	5 (3)	3 (5)
	Oral Candidiasis	17 (3)	0 (0)	0 (0)	12 (4)	12 (2)	2 (2)	2 (1)	2 (3)
General	Fever	21 (3)	13 (7)	12 (7)	22 (7)	14 (5)	1 (1)	3 (2)	1 (2)
	Malaise/fatigue	4 (<1)	5 (3)	2 (1)	1 (<1)	8 (3)	0 (0)	0 (0)	1 (2)
	Chest symptoms	6 (<1)	1 (<1)	1 (<1)	4 (1)	2 (<1)	3 (3)	2 (1)	1 (2)
	Candidiasis, site unspec.	19 (3)	1 (<1)	0 (0)	14 (5)	7 (2)	3 (3)	4 (2)	1 (2)
	Viral infections	14 (2)	4 (2)	8 (5)	6 (2)	5 (2)	0 (0)	4 (2)	3 (5)
Neuro	Headache	47 (7)	22 (12)	20 (12)	36 (12)	40 (13)	2 (2)	10 (6)	9 (14)
Musculoskeletal (MS)	MS Pain	14 (2)	8 (4)	3 (2)	9 (3)	6 (2)	2 (2)	9 (5)	3 (5)
Skin	Rashes	7 (1)	6 (3)	0 (0)	6 (2)	2 (<1)	0 (0)	0 (0)	2 (3)

Other notable events reported at a higher percentage than placebo for at least one active Diskus arm, but by less than 2% above placebo include: gastrointestinal pain, and dizziness.

It is notable in all these data that some of the common AEs associated with inhalation drug products, particularly steroids (including Flovent), are quite low in percentages of reports. For instance, even with lumping dysphonia/hoarseness and laryngitis, the highest reported occurrence was 6% in the 500 BID study. Similarly, the occurrence of oral candidiasis was

reasonably low (see below). Overall, it appears that this product (excluding the data related to oral-corticosteroid sparing) is quite well tolerated in terms of local events. The profile of the events reported overall is quite similar to those seen in the Flovent MDI and DPI trials.

The sponsor also represented the reporting percentages from these same studies for throat irritation, pharyngitis/throat infection summed.¹⁷ The percentage in placebo was 11% and ranged from 3% in FP 250 BID to 22% in FP500 BID, with all the active treatment arms other than FP 250 BID exceeding placebo. Due to the design of these trials (where the placebo was lactose alone), the contribution of inhaling lactose to the overall reports of these AEs cannot be fully assessed. However, the percentage of reports for these summed AEs in the BDP aerosol treated groups was 19%, suggesting the throat symptoms resulting from the Flovent Diskus are quite similar to that of an MDI corticosteroid.

The sponsor similarly summed the reporting percentages for oral candidiasis and unspecified-site candidiasis.¹⁸ The percentage for placebo was 6% and that in the FP groups ranged from 0 (FP 100 QD) to 9% (FP 100 BID). Curiously, only this latter group had a higher percentage of reports than placebo. It is not clear why the placebo group had such a high percentage, but may relate to prior corticosteroid exposure in this group.

As can be seen from the above table, and as came out of the review of the AE data, relatively few AE reports indicated significant systemic events in these trials. However, the caveat to that statement is that these data exclude the oral corticosteroid-sparing study and are of limited duration (generally 12 weeks).

6.2.4.2 AE reporting by demographic subgroups - US study population

The sponsor tabulated AEs by demographic subgroups, including gender, ethnic/racial groups, and age ranges.¹⁹

For gender, there was an apparent increase in reporting rate of AEs overall for females compared to males in the adolescent and adult population (males ranged between 55% for placebo and 58-69% in the FP Diskus groups, females between 62% for placebo and 46 - 75% for FP Diskus). The patterns seen did not suggest any important differences based on gender.

For ethnic-racial subgroups, these studies were conducted in populations that were very much weighted towards Caucasians. The percentages of Blacks ranged from 2 - 16% in the various dosing groups. Given the relatively small numbers, little confidence could be given to any conclusions based on observed differences. However, the overall AE experience does not appear to be importantly different across racial/ethnic groups.

¹⁷ page 79 of ISS, vol. 244

¹⁸ page 80 of ISS, vol. 244

¹⁹ Tables 5.3 - 5.10 of ISS, pages 308-445

Age-based considerations are important, but a comparison of the pediatric groups, particularly the 4 – 11 group²⁰, to the adult experience are confounded by differences in total daily dosing, differential background rates of URIs and other common childhood illnesses, and the probability of proxy (parental) reporting for many of the occurrences. That stated, as might be expected, many of the ENT-related complaints were more frequently reported in the 4 – 11 year olds. One exception to this is dysphonia, which was seen at percentages of 2% or below in all groups. However, oral candidiasis, an AE that does not suffer all the above confounding factors, was seen in more patients of this age range, with a reported percentage in placebo patients of 4% and with active drug ranging between 0 and 12%. Interestingly, this 12% was reported for the 200 mcg QD dosing, whereas the 100 mcg BID had a reported percentage of oral candidiasis of only 1%. Other non-ENT events that occurred at notable percentages include nausea/vomiting, gastrointestinal pain, diarrhea, and fevers. Again, these might be expected to occur at a somewhat higher rate in this demographic group and none of these appeared to have a strong relationship to dose.

For the “elderly” – those patients at or above the age of 65, the number of patients represented are quite small, amounting to 33 subjects within the FP Diskus active treatment and placebo arms (with 21 patients in one of 5 active treatment arms). Therefore, no reasonable conclusions can be drawn from these data other than to say that no events atypical of the younger subjects were seen, excluding radiation disorders, post-operative complications and tremor. All of these, with the possible exception of the post-operative complication, would be implausibly linked to drug.

6.2.4.3 *AE experience in long-term safety studies (other than FLTA2002)*²¹

FLTA2005E was an open-label long-term study comparing FP250 BID versus FP500 QD in a population 12 and above. The percentage reporting of AEs was similar between the two groups (84% for the BID group, 81% for the QD group). The reporting percentages favored the QD group for oral candidiasis (6% BID vs. 1% in QD) and with respect to dysphonia (6% vs. 2%). Otherwise, the overall type of reports seen and the distribution between the two groups is largely unremarkable.

FLTA2008E was an open-label long-term study comparing FP100 BID versus FP200 QD in a pediatric population. Here the percentage is high (over 90% in both groups), but this likely stems from the expected occurrences of usual illnesses in this population over a prolonged period. Again, few notable differences between the groups or between these data and the controlled trials data are seen. The percentage of reported candidiasis is similar and reasonably low (2% BID vs. 4% QD); pharyngitis and throat irritation were reported by 18% of the BID, 28% of

²⁰

Table 5.13 of ISS, vol. 245, pages 19 - 28

²¹

Tables 5.24, 5.26 of ISS, vol. 245, pages 116 – 121; 124 – 128.

the QD, largely due to a nearly 2 fold increased reporting of throat irritation in the QD group.

6.2.4.4 *AE experience in non-US studies*²²

These data will not be extensively commented upon here as they add little to the AE discussion, particularly since there are no placebo percentages to use as a comparison of rate, and since in many cases the exposures were shorter than the US studies. However, the overall pattern of reported events, the types of events reported and the comparison to the budesonide product reveals no patterns or surprises.

6.2.5 Summary of Adverse Events

The adverse event experience for this product appears very much in keeping with the other Flovent formulations and with ICS products in general. The sponsor has proposed a reasonable tabulation of events for inclusion in labeling on page 95 of volume 244. However, this table

6.3 Deaths / Serious / Potentially Significant Adverse Events

6.3.1 Deaths

6.3.1.1 *Deaths in US Trials*

There was one death in the US trials for the FP Diskus, involving a patient in study FLTA2002 – the oral steroid sparing trial during the open label treatment portion of the study. This 65 year old patient had been on 1000 mcg BID and suffered a fatal myocardial infarction.

There were 4 additional deaths in studies of other formulations. FLTA4021 was a post-marketing study of FP versus triamcinolone. One death occurred in a triamcinolone treated patient (a 31 year old who died with urosepsis and a pulmonary embolism). The other occurred in a 77-year old female being treated with FP 88 mcg BID and salmeterol. She developed a dissecting aortic aneurysm and died of subsequent complications.

A patient in study FLTQ5001, another post-marketing study, died of a motor vehicle accident. He had been randomized to zafirlukast. Finally, a patient receiving the FP MDI at a dose of 88 mcg BID during the run-in for study SLGA5021 died in an MVA.

None of these deaths was felt by investigators to be related to study treatment, and indeed none seem plausibly causally linked.

6.3.1.2 *Deaths in non-US Trials*

There was one death in a non-US Diskus trial involving a 63 year old male (B000) who also suffered a fatal MI during treatment with FP250 BID.

²²

Table 5.28 of ISS, vol. 245, pages 130-147

FP is being studied for COPD in FLIT78, where 11 deaths have occurred, 8 in subjects on FP at 500 mcg BID, 3 in placebo. These 8 deaths were a 72 year old male, attributed to an MI (B0044086); a 64 year old male, attributed to an MI (B0049770); a 75 year old male who died of progressive COPD/pneumonia/cor pulmonale (B0043319); a 70 year old male who died of COPD and aspergillosis/pneumonia (B0044737); a 74 year old male who died of an exacerbation of COPD (B0044741); a 70 year old male who died of lung cancer (B0044792); a patient of unspecified gender and age who died of pneumonia (B049256); and finally a 72 year old male who collapsed and died with a coronary artery disorder (B0049635). Though some of these deaths in this COPD trial do raise some concerns (such as the pneumonias and the aspergillosis), no such deaths were seen in trials for asthma and most of these cases were deemed as unlikely related to study drug by the investigators.

6.3.1.3 Deaths in local studies

There were six deaths reported in various local studies, all non-US. Two were due to or related to GI hemorrhage not otherwise detailed, one was due to a choking episode and likely aspiration, one was due to bronchial neoplasm one year after completing an FP study, one was a remote asthma death well after discontinuing brief participation in an FP trial due to asthma instability, and one due to cardiac failure.

6.3.1.4 Deaths in spontaneous reporting system

There were 3 deaths reported by the SRS during the 11 months prior to the ISS being closed. One was a female patient, age 42, who was receiving 660 mcg FP via the MDI for oral-corticosteroid sparing purposes and developed hypereosinophilic syndrome (not clearly Churg-Strauss) including eosinophilic myocarditis, and died. This death appears more likely related to the circumstances of use for the Flovent (as an oral steroid sparing agent) than a direct causality, but this cannot be fully sorted out. Labeling related to Churg-Strauss and serious eosinophilic conditions has recently been added to the approved Flovent products and should be included for the Diskus as well. There was a 60 year old male who was receiving FP 1000 BID and experienced massive liver failure (no autopsy). Finally, there was a 30 year old male on FP MDI who had sudden death with no other details available. The latter two cases have insufficient detail to speak to likelihood of causality, although there has been no indication of hepatic effects of systemically absorbed FP.

6.3.2 Serious / Potentially Significant Adverse Events

6.3.2.1 Serious Adverse Events - US Diskus Trials

A total of 20 of the subjects treated with the Diskus or placebo in the US trials (excluding the corticosteroid sparing study and long-term studies) suffered AEs that met the regulatory definition of serious. Reassuringly, whereas there were 6 cases of serious AEs classified as asthma and 2 cases of pneumonia in the placebo group, there was only one case each in the

Diskus groups – the asthma case in FP 200 QD treatment and the pneumonia case in FP50 BID. These data not only do not raise a concern over the respiratory safety of the product, but in the case of asthma exacerbations, actually support efficacy. There were three cases of appendicitis in the FP groups, with none in the placebo, an unusual occurrence noted previously for some ICS safety reviews in apparent higher percentage with active drug – including the original Flovent NDAs. Otherwise the events are sporadic and not suggestive of drug effect, but of unusual events occurring at a background rate in the population.

In study 2002, exposure during each “phase” of the study was considered a separate exposure. Therefore, there were 31 subjects (35 exposures) resulting in 56 serious adverse events. Focusing on the randomized, placebo-controlled blinded ‘phase I’ portion of this trial, there were 3 patients in placebo, 4 patients in FP 500 and 1 patient in FP1000 who experienced serious AEs. This included 3 patients with asthma episodes (2 in placebo, 1 in FP500), and a case of anaphylactic shock (FP500). Notable for the open-label phase of the study is the occurrence of an eosinophilic pneumonia – Churg-Strauss vasculitis and a case of candidal esophagitis, both in the FP1000 group.

Finally, in FLTA2005E and 2008E, there were 9 subjects and 3 subjects respectively who experienced serious AEs. Notable among these is a pneumonia episode and an asthma exacerbation in the FP250 BID group of study 2005E, and an asthma exacerbation and a psychotic depressive episode in study 2008E (the pediatric long-term safety study).

6.3.2.2 *Serious Adverse Events non-US Diskus Trials*

Since these trials did not include placebo comparators, it is not possible to related overall or individual occurrences to the placebo rate. However, the percent of subjects with serious AEs ranged from 0 – 2% in the Diskus groups, 0 – 2% in the Rotadisk groups, and was 1% in the Pulmicort group. Most AEs were predictable for the population, but some are worth noting, including 2 patients receiving FP500 Diskus with ‘abnormal adrenal hormone levels,’ 1 with appetite disturbance (FP500 BID), and 1 with menstrual symptoms (FP250 BID). These cases are suggestive of some systemic effects of the inhaled FP. However, due to the design of the trials, the low cortisol levels were reported as serious AEs, although they would not otherwise meet the regulatory definition of serious. (A further episode of low cortisol was observed in the run-in period of a trial in a patient previously receiving FP 500 BID – formulation not specified).

6.3.2.3 *Spontaneously Reported Serious Adverse Events for FP Diskus*

There were 5 cases reported, specific to the Diskus product (and therefore non-US in origin), during the reporting period included in this ISS. These include a ‘permanently’ disabling (but improving) aphonia/dysphonia judged likely related to FP by the reporter in a patient with pre-existing vocal cord disease, a case of anaphylaxis with a positive FP scratch and intradermal test, a device failure with lack-of-efficacy (device appeared to

advance, but in fact the dosing strip did not), and a case of HPA axis suppression. The device failure resulted in an asthma exacerbation. The last case mentioned was a 5 year old girl placed on 1000 mcg daily of FP Diskus, notably higher than the recommended dosing. This subject developed excess hair growth, tiredness, weight loss, and other signs of exogenous hypercortisolism, including a non-measurable serum cortisol. FP was eventually stopped when it was decided the girl in fact did not have asthma. It was noted in the report that at follow-up the girl's bone age was 1 year below her chronologic age.

6.3.2.4 Spontaneously-reported Serious Adverse Events, other formulations

There were 48 such events reported for the period covered in the ISS for all the non-Diskus formulations. These reports vary considerably in character, but include 13 cases of HPA perturbations (e.g., low cortisol, cushingoid appearance, etc) – at least 5 of which were related to doses in excess of recommended doses for the US (several summaries list no dose). Other AEs that might signal systemic steroid effects include a case of cataracts (in a woman without concomitant oral steroids, but with an unclear prior exposure), depression, psychotic suicidal ideation, exacerbated hypertension, elevated glucose, a pathologic fibula fracture, and growth suppression (included also in the HPA disturbance count above in a 4.5 year old dosed at 1500 mcg BID).

Other notable events include drug rashes and/or local allergic reactions, dysphonia, cough, several cases of serious eosinophilia (including a fatal case of hypereosinophilia), several fetal malformations, and two cases of immediate bronchospasm in patients exposed to the MDI.

6.3.2.5 Pregnancies

6.3.2.5.1 Diskhaler Study Pregnancies – US and non-US

There were 3 pregnancies in the Diskus clinical trials, all in the US studies. Of the 3, one resulted in a normal birth, one ended in spontaneous abortion (apparently 1st trimester), and the last case has no outcome detailed.

6.3.2.5.2 Study Pregnancies with other formulations – US and non-US

Although there are a number of other pregnancies reported by the sponsor in non-US trials of other formulations/indications, the majority of these have insufficient information related to outcome to be informative.

6.3.3 Adverse Events Leading to Withdrawal (US trials)

Below is a tabulation of the percent of subjects withdrawing due to AEs in the safety and efficacy trials for the Diskus in the US – excluding 2002 which is commented upon below.

Dose	Placebo	FP50 BID	FP100 QD	FP100 BID	FP200 QD	FP250 BID	FP500 QD	FP500 BID
N	627	178	170	305	307	86	169	64
# withdrawn due to AE (%)	12 (2)	3 (2)	3 (2)	1 (<1)	4* (1)	1 (1)	3 (2)	1 (2)

* one patient was listed as withdrawing for an AE, but the AE was not listed by the PI. The sponsor therefore reported 3 patients in their version of this table.

The percentages of withdrawals due to AEs was relatively equal between groups and certainly no higher with active than placebo, given the lower mean exposure duration in the placebo group. The events that lead to withdrawals included occurrences that would be common in this patient population – such as viral infections, URI's, pneumonia, and asthma events. The occurrence of pneumonia was as frequent in placebo as active drug. Notably, there was a withdrawal for psychiatric disturbance in a Diskus 50 BID patient (with an additional subject in the Diskhaler group dosed at 50 BID), and a patient in the Diskus 100 BID treatment who developed cognitive dysfunction and “tics.” Also notable were the appendicitis cases from an FP50 BID patient in trial 2007, and a patient in 2005.

During the randomized, double-blind 16-week initial portion of Study 2002, the steroid sparing study, study drug was stopped due to an AE in 6 patients – 3 in placebo, 3 in active treatment (all in the FP500 BID group). These events included asthma exacerbations, GERD, tachycardia and eczema exacerbation. Additionally, 3 more subjects withdrew in phase 2 of this study for events originally noted as having an onset in phase 1, including an adrenal suppression (FP1000 BID), and a cataract procedure (FP500).

In the long-term safety studies (2005 and 2008), events which bear noting include a withdrawal due to tics/anxiety, candidiasis/throat irritation, and hair loss/alopecia – all in the adolescent/adult study (2005), and withdrawal due to psychosis, mood disorder, and decreased cortisol in the pediatric (2008) trial. There were also some withdrawals for more common events in such populations, including viral infections, and asthma.

The withdrawal percentage, pattern and types of events for the non-US Diskus studies was similar and does not add substantively to the safety discussion (see table 5.62 of ISS, volume 245, page 326-334).

6.4 Laboratory Results²³

The sponsor provides two main analyses of clinical laboratory results from the clinical trials - shift analyses (change from baseline to final treatment visits) and values that met the sponsor's predefined criteria of abnormality.

6.4.1 Laboratory Results – Diskus US studies

Routine laboratories were conducted at baseline and end-of-study, including CBCs with differential counts, LFTs, Renal function tests, electrolytes, glucose, calcium, phosphorus, total serum protein and albumin, and cholesterol. The sponsor, appropriately, only analyzed the results of the US studies due to an extensive analysis of all laboratories,

²³

Normal ranges are found in table 6.1 of volume 245, pages 343-344.

foreign and domestic, in the original MDI and DPI. This latter analysis revealed no apparent pattern of drug-related adverse laboratory changes.

Hematology – As in the prior NDAs for Flovent products, the one apparent shift in laboratories that was related to drug exposure (and showed a dose-relationship) was changes in eosinophil counts. Beginning at doses of FP250 BID and above, there were fewer patients with shifts to high eosinophils and more patients with shifts to low eosinophil counts in active treatment than with placebo or lower FP doses. For the FP500 BID group, only 2% showed an increase in eosinophils and 7% a decrease, compared to 13% and 5% respectively in the placebo group. This sponsor makes the point that the downward shifts seen were due to patients going from high levels to normal (note that this would have to be the case, since the normal range for eosinophils includes 0). This appears to signal at least a subtle systemic effect occurring at doses of 500 mcg/day and above.

There were no remarkable findings in the analysis of abnormal hematology values, with the occurrence rates being very similar for active versus treatment.

Liver Related Laboratories – The majority of subjects were normal at baseline and remained normal at the end of the study in all dosage groups. Predictably for these tests, the ALT and AST were most likely to vary. In the placebo group for the adolescent/adult studies, 3% of subjects had an increase in AST and 5% in ALT (with somewhat lower percentages in the younger pediatric studies). Two active groups had higher percentages – 5%/9% in the FP250 BID and 3%/8% in the FP500 QD groups. However, this was not seen in the FP500 BID group and examining these data overall, there was no apparent dose-relationship. There was also a higher percentage of upward shifts in the bilirubin in the FP100 QD group compared to all others, but since this dose represents one of the lowest daily exposures, it is unlikely to be an effect of the FP. In the younger pediatric studies, there were 12% of the children receiving FP100 QD who experienced an upward shift in their alkaline phosphatase (compared to 4% in placebo). However, both of the higher daily doses FP200 QD and FP100 BID had rates below that of placebo, suggesting this to be a spurious rise.

Serum electrolytes, Calcium/phosphorus – The data for electrolytes and the inorganic ions were perhaps more variable than the LFTs. However, there was no discernable pattern of shifts or abnormalities in either the adult/adolescent studies nor in the studies conducted in the younger pediatric patients.

Glucose – Generally, there is little indication of a hyperglycemic effect of FP from these trials, although in the adult/adolescent studies at FP500 BID, there were 12% of subjects who's glucoses shifted upwards compared to 7% of placebo. However, there were also more downward shifts in this same treatment group (7%) than placebo (4%), with the ratio between the

two shifts being similar. In the pediatric studies, there was actually a more prominent downward shift in the upper daily dose compared to placebo.

Renal Function Tests – As with the other serum chemistries, there were no remarkable trends in abnormalities nor shifts that bear comment in either the adult/adolescent studies or the pediatric studies.

Study 2002 – During the placebo-controlled portion of this study, there are a few laboratory changes worth comment. The first is that there were more upward shifts of eosinophils in FP patients compared to placebo. Similarly, there were fewer upward shifts in serum glucose with active treatment compared to placebo. Finally there were more downward shifts in neutrophil counts. All of these effects might be anticipated, given that FP patients more often successfully stopped prednisone. There were no surprising patterns seen, however, either in the placebo-controlled or later portions of this study (as previously mentioned, one patient did experience a serious AE of hypereosinophilia/Churg-Strauss in this trial and a second was withdrawn for eosinophilia).

6.5 Special Studies

Among the most significant issues with a new inhaled corticosteroid product are the pharmacologic effects other than the asthma ameliorative effects. Specifically, the systemic effects such as suppression of the HPA axis, bone metabolic effects and growth effects. Many of these have been at least in part addressed by Glaxo Wellcome in their previous development programs for the Flovent line of products. In many cases, these programs went above and beyond what might be required for the registration of a new inhaled corticosteroid. In some respects, therefore, part of the question for this product is how it relates to the approved MDI and Rotadisk products. The PK data for this product in comparison to the approved products is somewhat mixed, and little of it comes from direct head-to-head PK studies (since this Diskus program is more of a “stand-alone” program than a “switch” in its design). However, by utilizing cross-study comparisons, one can conclude that the systemic exposure resulting from the Diskus is similar to that Rotadisk, and both are lower than that from the MDI when the MDI is used in a controlled setting by trained individuals. There are very few data to suggest a significantly higher exposure from the Diskus compared to the Rotadisk, and therefore the long-term systemic data (growth, bone effects, ophthalmologic effects,...) may be reasonably applied to this product as well.

6.5.1 HPA axis

In NDA 20-549, it appeared that clinically important systemic events in adults (i.e., where growth effects are not a consideration) appeared to occur in some patients at doses above 250 mcg BID for the Rotadisk. In the NDA under review, HPA axis was variably assessed – including a.m. cortisol, stimulated serum cortisol and timed urinary/serum collections for cortisol. However, the examination of a.m. cortisol was the most

common assessment of the HPA axis function in these studies, providing the least informative data.

In study 2001, patients were treated with either 500 mcg BID from the Diskus, from the Diskhaler or placebo for 12 weeks. Measures of a.m. cortisol were done, as was 12-hour cortisol AUCs. The morning cortisol data suggest an effect of both the Diskus and Diskhaler product as seen below:

	Placebo	Diskus (500 BID)	Diskhaler (500 BID)
Subjects	70	64	79
Low cortisol at screen (< 5 mcg/dl)	4 (6%)	1 (2%)	4 (5%)
Subjects with low cortisol post-randomization	1 (1%)	4 (6%)	6 (8%)

Overall, there was a higher rate of at least one low post-randomization cortisol in the FP groups compared to placebo and the change from baseline is towards a higher percentage in both FP groups, compared to a decrease in placebo subjects. However, the 12-hour plasma cortisol AUC data done in a subset of individuals (approximately 50%) at weeks 0, 1 and 4 showed no patterns of active versus placebo either in absolute terms nor in change from baseline. By this more sensitive measure, there does not appear to be a clear systemic effect of these doses of FP on the adrenal output of cortisol.

The long-term systemic effect study with the Rotadisk formulation – 2 year placebo controlled study of 500 mcg BID – showed some minimal signs of an adrenal effect of this dose, particularly when the sponsor corrected the definition of abnormality to account for the insensitivity of the assay utilized for that study (peak of <35 mcg/dL considered abnormal compared to <18 mcg/dL). By this standard, there were 5 such subjects in the FP group, compared to 1 in placebo. Additionally, there were assessments of 8 hour serum cortisol AUCs in this study. These data again showed an apparent effect on the HPA axis of the 500 mcg BID dose from the Diskhaler device. These results are tabulated below:

	Placebo	FP 500 BID	p-value
Week 52			
mean (SE)			
8 hour AUC	269.6 (13.2)	291.0 (10.5)	0.318
Change in AUC from baseline	-15.5 (14.5)	-62.8 (12.3)	0.044
C _{max} cortisol	48.6 (2.1)	45.2 (1.5)	0.079
Change in C _{max} from baseline	-1.3 (2.2)	-11.0 (2.1)	0.013
Week 104			
8 hour AUC	346.5 (9.8)	311.0 (14.0)	0.020
Change in AUC	19.3 (12.0)	-48.8 (15.9)	0.007
C _{max} cortisol	55.1 (1.6)	49.4 (2.2)	0.021
Change in C _{max}	2.2 (2.3)	-8.0 (2.7)	0.021

There were a number of studies done of lower daily doses, either administered BID or QD, mostly with assessments of morning cortisol.

The data from these various studies do not show any consistent pattern suggestive of an HPA effect at these lower doses, although in study 2016 where once-daily doses of 100, 200, 500 mcg vs. placebo were studied, in the subjects who were not on ICS for 3 months prior to study entry, the 500 mcg dose had more subjects who failed to increase their cortisol in response to cosyntropin by 7 mcg/dL or had an inadequate peak (<18 mcg/dL) than in either placebo or lower dose FP groups. This difference was most pronounced for the inadequate peak – 3 subjects (9%) in FP500 compared to 1 (3%) in placebo.

The oral corticosteroid sparing study is somewhat difficult to interpret in this regard. However, while the majority of patients entering had abnormal cosyntropin tests (since they were on prednisone at entry), using the standard criteria for abnormal response for this test, the minority were still abnormal at week 16. This suggests that most patients could undergo some recovery of HPA function while on higher dose FP by Diskus as their oral prednisone is tapered and stopped. However, in the long-term extensions of these studies, the percentage of people who had abnormal cosyntropin testing at FP1000 appeared to remain in the 30% range, though only 1 subject (6%) in the FP500 group showed an abnormal response in the second phase of this study. This supports the 500 mcg BID dose of being at or below the cusp of where important HPA axis effects may occur in some subjects.

The pediatric studies, which examined lower doses of ≤ 200 mcg/day showed that these younger children more often had low a.m. cortisols, but no pattern to suggest an important effect to FP at these doses on measures of HPA axis function. While this is reassuring, FDA has seen other data to strongly suggest that short and medium-term suppression of growth velocity occurs at lower exposure levels than that required to suppress morning cortisol or standard cosyntropin response.

Finally, GW included numerous literature reprints of journal articles examining the HPA axis effects of FP – primarily utilizing pharmacodynamic assessments, rather than effects in clinical use/trial settings. These include a knemometry/urinary cortisol study by Pedersen et al, comparing the Pulmicort Turbuhaler to the Flovent Diskhaler,²⁴ a study by Lipworth et al comparing the adrenal suppressive effects of budesonide and fluticasone in adult asthmatics,²⁵ a comparative study of budesonide and fluticasone on the 24-hour serum cortisol AUC,²⁶ a pharmacodynamic study of the FP Diskhaler vs. the Turbuhaler utilizing plasma cortisols,²⁷ a PK/PD study of FP IV vs. the Diskhaler,²⁸ another study by Lipworth's group on the relative HPA effects of fluticasone via the MDI vs.

²⁴ Eur Respir J 1997; 10:1507-1512

²⁵ Thorax 1997; 52:55-58

²⁶ Am J Respir Crit Care Med 1997; 156:1746-51

²⁷ Eur J Clin Pharmacol 1997; 52: 261-267

²⁸ Br J Clin Pharmacol 1997; 43: 155-161

triamcinolone MDI,²⁹ and finally another report from Lipworth's group of a study comparing FP to triamcinolone over a dose-range for the HPA effects.³⁰

- Pedersen's study – utilizing knemometry and urinary cortisols – examined equal nominal doses (200 mcg and 400 mcg daily) of FP and budesonide from their dry powder devices in a cross-over study with treatment periods of 2.5 weeks and 2 week washout periods. This study showed effects of the 400 mcg daily dose of both products by knemometry and urinary cortisol (when corrected for creatinine), with FP 200 mcg daily also showing statistical suppression of urinary cortisol/creatinine, but not of knemometry measured growth rate. Like many of these studies, this study fails to establish that these nominal doses are equally effective, so the relevance of the comparative information is questionable. However, with all the caveats about knemometry, these data do show some measurable effect of the top approved dose of FP Diskhaler (for children 4-11) of 100 mcg BID by urinary cortisol assessment, but not for growth as assessed by knemometry. These data provide some indication that well done urinary cortisol assessments may be sufficiently sensitive for systemic exposure to predict growth effects (though this is by no means definitively shown).
- The other articles have variable relevance to this application due to considerations of formulations (MDI vs. Diskhaler – none with the Diskus), and populations (often, healthy volunteers were used rather than patients). None of the comparative data are useful, since there is no attempt to adequately choose equi-effective doses of FP versus the comparators. However, these data suggest that utilizing sensitive indicators of systemic effects (timed urinary and/or serum cortisols), nominal doses of FP from either the MDI or Diskhaler formulations (not always the US formulations at that) may have significant effects at doses of 440 mcg BID and upwards in adults. These data are consistent with what has been seen in Glaxo's clinical trials and clinical pharmacology studies.

6.5.2 Growth

There were no controlled growth data submitted with this application. Since there appears to be comparable exposures resulting from the Diskus and Rotadisk for Diskhaler formulations, it is reasonable to assume that the data from FLD-220, reviewed under NDA 20-549, would be applicable to this application and therefore should be represented in labeling. This study showed in the ITT population that placebo subjects had a mean growth velocity of 6.32 cm/yr, FP50 BID had a growth rate of 6.07 cm/yr and FP100 BID of 5.66 cm/yr.

²⁹ Eur J Clin Pharmacol 1997; 52: 444-448

³⁰ Am J Respir Crit Care Med 1997; 156:1274-77

6.5.3 Other Corticosteroidal Systemic Effects

Bone density studies have been performed for FP Rotadisk (FLTA3017). This study also included ophthalmologic endpoints and was reviewed previously by this medical officer for NDA 20-549. This study did not show any clear evidence of important ophthalmologic effects for FP at a dose of 500 mcg BID via the Diskhaler device over a 2-year treatment period. However, it did at least suggest some potential effects on bone mineralization for this relatively high dose of FP given over 2 years. Although the primary analysis of the bone densitometry – that was based on the AP view of the L1-L4 spine did not show any statistical difference between placebo and FP500 BID, the retrospectively quality assured femoral neck analysis showed a trend towards decreased bone mineralization compared to placebo at both 1 and 2 years.

	Placebo			FP 500 BID			p value
	N	Mean (SE)	Range	N	Mean (SE)	Range	
L1 - L4 AP Spine (Primary endpoint)							
Week 26	28	-0.001 (0.005)	-0.056 to 0.046	29	0.003 (0.007)	-0.069 to 0.093	.891
Week 52	22	-0.001 (0.006)	-0.059 to 0.038	25	-0.003 (0.009)	-0.083 to 0.065	.757
Week 104	17	-0.007 (0.010)	-0.071 to -0.071	21	-0.006 (0.008)	-0.110 to 0.064	.836
Femoral Neck (Retrospectively QA'd)							
Week 26	28	-0.004 (0.007)	-0.088 to 0.061	31	-0.007 (0.011)	-0.132 to 0.153	.605
Week 52	21	0.007 (0.007)	-0.041 to 0.075	28	-0.017 (0.010)	-0.133 to 0.121	.055
Week 104	18	-0.011 (0.010)	-0.113 to -0.061	21	-0.036 (0.012)	-0.140 to 0.097	.066

Though not statistically significant and not the a priori defined primary analysis, these data at least raise the concern that long term dosing of FP in a dry powder formulation may have detrimental effects on bone mineralization. This would not be totally surprising, given that the 500 mcg BID dose was shown in clinical trials to have some definable HPA axis effects, at least in a portion of subjects. In this same study, for instance, the change from baseline in 8-hour serum cortisol AUCs were significantly lower in the FP500 BID group at weeks 52 and 104 than with placebo. An important caveat to interpreting these data is that very few sponsors of inhaled or intranasal corticosteroids have performed such carefully controlled studies of the long-term systemic effects of their products. Since there are data that show that many of the ICS affect the HPA axis at doses within their recommended ranges, it is also likely that as a class these agents may have the potential in sensitive individuals to adversely impact on bone mineralization. Finally, the data from

FLTA3017/FLD-220 were obtained with a similar formulation – the Rotadisk product for use with the Diskhaler. The clinical and PK data available suggest comparable delivery from this product and the Diskus, but certainly “bioequivalent” pharmacokinetics cannot be assumed. Therefore, it is reasonable to view these data as useful for the Diskus product in evaluating approval and labeling, but not definitive in terms of characterizing the systemic effects of the Diskus formulation.

6.6 120-Day Safety Update

There were no new completed or newly started clinical studies with the Flovent Diskus in patients with asthma to report for the period covered in this document (November 30, 1997 to March 31, 1998).

6.6.1 Deaths

There were 3 deaths in clinical trials that occurred during the safety update reporting period, all from FLIT-78, a COPD study in largely elder adults. Two of these were on active drug (500 mcg BID) – one of myocardial failure after 3 years of treatment, the other of stomach cancer. Neither seem likely to be related to fluticasone treatment.

There was one SRS death reported during the safety update period for all the Flovent products, a 76-year old male receiving salmeterol and fluticasone (formulation/dose not specified) for asthma. No other details were available, so cause and likely relation to FP are not assessable.

6.6.2 Serious Adverse Events

There were no serious adverse events reported from the Diskus studies during the reporting period.

There were 21 serious AEs reported from controlled trials of the MDI formulation. Of these, 15 were receiving FP. One zafirlukast case is notable because it was a case of appendicitis (which previous in this ISS review had been cited as a notable occurrence in Flovent and other ICS trials). There was a case of “ruptured appendix” in the FP treated patients, a 23 year old male on Flovent MDI at 220 mcg BID for 85 days, with causality assessed by the PI as not related. Other notable events include 4 exacerbations of asthma, only one of whom was receiving FP (and had a character of inadequate effect), a pneumonia episode (which was treated and resolved on study drug), a case of zoster, a spontaneous rupture of the achilles tendon in a 36 year old male while playing handball (on FP MDI at 500 mcg BID and Flonase) and a miscarriage at 5-weeks of gestation in

a 33 year old woman exposed to FP prior to and during gestation. None of these events was assessed by the investigators as likely to be related to FP treatment.

There were 18 SRS cases of serious adverse events reported for all formulations of FP during the safety update reporting period, including the death described above. Seven of these were for HPA axis effects – though one was considered a 'skin' system report by the sponsor because the report was for striae. Many of these were either confounded by co-administered drugs or concomitant diseases, or involved inappropriately high dosing. However, 2 of the cases in adults were administered doses within the recommended range (albeit high dose 750 – 1000 mcg BID) and appeared likely related to FP. The case with striae was a 16 year old girl on 880 mcg BID – a labeled dose, but the appropriateness of this dose (i.e., whether it was being used as a oral steroid-sparing agent) is not certain. There was one case of a probable Churg-Strauss syndrome in a 41 year old male given FP as a corticosteroid sparing agent. Other notable cases include a case of dysphonia, and 3 cases of immediate bronchospasm (one of these with a character of an immediate hypersensitivity reaction), a bleeding peptic ulcer, and a cataract occurrence. This cataract was noted in a man with pre-existing disease after only 19 days of treatment. Finally, there was a case of anaphylactic shock in relation to fluticasone and/or salmeterol.

6.6.3 Literature Reports of AEs/Adverse Effects of Fluticasone

The sponsor provided two articles from the literature related to FP – one a PD study in mild asthmatics comparing similar nominal doses of FP and budesonide. The second was a case report of two individuals treated with inhaled FP who developed HPA axis suppression and cushingoid changes. The remarkable feature of these cases is they occurred at somewhat lower doses than many of the spontaneous reports. The first was an 8 year old girl who's stable dose of FP was 250 mcg/day (formulation not provided) for 5 months and the second was a 32 year old woman with an FP dose of 500 mcg/day for 8 months. The former was therefore on a somewhat higher dose than currently recommended for that age group, the latter was on what appears to be an appropriate dose from the case report, well within the label range. These cases suggest that for particularly sensitive individuals, adrenal suppression may occur even at fairly low doses, albeit higher than recommended in the case of the 8 year old. It is also notable, though not surprising that this latter child also experienced apparent growth effects.

6.7 Summary / Conclusion

The safety data for the Flovent Diskus appear very similar in character to those seen with the Flovent Rotadisk and MDI formulations and quite typical for an inhaled corticosteroid. This review did not concentrate on demographic subgroup analyses outside of age groups, because both these data and prior data do not show any particular pattern related to

demographic-safety interactions (by gender, race, and ethnicity). The local and systemic events appear very similar to those seen in NDAs 20-548 and 20-549, and in the clinical studies where head-to-head comparisons to beclomethasone and budesonide were conducted, very similar to other ICS. Hence, like the other Flovent product previously reviewed, the safety appears to be acceptable, given the benefit. It is notable that the QD vs. BID safety data do not show any clear advantage of the QD dosing. Therefore, an approval of QD dosing will have to be based on a clear efficacy finding, since the safety data add no support to such an approval (nor do they add any concern).

Labeling review will need to assure that the safety tabulations and listings concur with the data presented in the ISS. Additionally, adequate discussions of potential for anaphylaxis, local allergic reactions, immediate bronchospasm and, importantly, potential for adrenal suppression will all need to be assured in the labeling. Additionally, with the growth data available and the class labeling request by the FDA subsequent to filing, incorporation of the precautions related to growth suppression need to be incorporated as well.

7 LABELING COMMENTS

The following section contains general comments:

1. A sentence should be added to the paragraph in the description section describing the dose delivery in relation to the in vivo and in vitro flow-rates making it clear that the actual amount of drug delivered will depend on patient factors, including inspiratory flow-rates.
2. The mention of the _____ in the description sentence should be removed, as this information is not pertinent to the description of this product.
3. The description of the 2 year safety study conducted with the Flovent Rotadisk should be amended to make it clear that it utilized the Rotadisk device (not the Diskus, since both can generally be referred to as fluticasone propionate inhalation powder), and to _____
4. The presentation of the _____ s inappropriate and should be removed.
5. The approvability of once-daily dosing as an alternative to BID dosing is currently not acceptable both due to the paucity of significant, replicated clinical data, as well as the CMC issue of _____

Therefore, all references to _____ should be removed from the labeling.

6. The tabulation of the adverse events data should be revised to refer only to the twice daily dosing, and the headers modified accordingly.

The following comments referring to clinical trial FLTA2002, for the oral CS-sparing indication:

- Under **DOSAGE AND ADMINISTRATION** : 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. A footnote should be added to the table which conveys the following information: "A controlled clinical study of 111 oral corticosteroid dependent asthmatics showed _____ between the two doses of FLOVENT DISKUS on _____ safety and efficacy endpoints. However, inability to decrease the dose of oral corticosteroids further during corticosteroid reduction may be indicative of the need to increase the dose of fluticasone propionate."
- Under **Clinical Trials** section, Lines 187-192 state that _____ by the end of the study. These statements should be deleted because they refer to the open-label, uncontrolled 52-week extension, not the placebo-controlled, double-blind segment of the trial and are misleading.
- Under **Clinical Trials** section, Lines 193-202 and the accompanying Figure _____ should be eliminated.

The following comments refer to clinical trials FLTA2006, 2007, and 2008 for the pediatric indication:

- Under the **Pharmacodynamics** subsection, lines 134-139 refer to the short cosyntropin stimulation test performed on a subset of subjects during clinical trial FLTA2006. The description should be amended to _____

- Also under **DOSAGE AND ADMINISTRATION**, because of the discordant results regarding the efficacy of FP 50 mcg BID via Diskus in the two pediatric trials during which it was studied (FLTA2006 and 2007), information similar to that conveyed by the following statement should be added: "Because individual responses may vary, children previously maintained on fluticasone propionate Rotadisk 50 or 100 mcg BID may require dosage adjustments upon transfer to Flovent Diskus."

8 CONCLUSIONS (RISK/BENEFIT ASSESSMENT):

The general safety and efficacy of inhaled fluticasone propionate (FP) for the treatment of asthma has been well established in the four years since its initial approval. The current NDA is a dry powder presentation of FP similar but not identical to the formulation contained in the recently approved (November, 1997) Flovent Rotadisk. This product was shown to be safe and effective in the maintenance treatment of asthma for children age 4-11 years at 50 or 100 mcg BID, and for adults at 100 to 500 mcg BID, (with labeling to include the oral corticosteroid sparing indication based on MDI data). The subject of this NDA, Flovent Diskus[®], is a multi-dose powder inhaler (MDPI) containing 60 blisters of drug per device. Although the sponsor could have chosen a "switch" program for this drug product's development, this NDA is a "stand-alone" submission, comprised of 9 pivotal placebo-controlled clinical trials in support of 5 separate indications. A brief risk/benefit for each indication follows:

Data presented in clinical trial FLTA2002 has demonstrated that Flovent Diskus at 500 or 1000 mcg BID is safe and effective for the oral CS-sparing indication. The superiority of inhaled over systemic CS in the management of asthma is widely accepted, but the risk/benefit ratio is different for severe asthma. The adverse event profile seen in FLTA2002 did not differ across treatment groups, but the impact on the HPA axis clearly favored Flovent Diskus. This should be considered a surrogate for other long-term consequences of chronic oral CS usage, such as osteoporosis, infections, diabetes, and ocular pathology. The efficacy of Flovent Diskus was also clearly demonstrated during the initial placebo-controlled, double blind phase of the trial. Of importance, there was no statistical difference between FP 500 mcg BID or FP 1000 mcg BID on the primary endpoint of oral CS reduction.

Data presented in clinical trials FLTA2006, FLTA2007, and FLTA2008 support the safety and efficacy of twice daily Flovent 50 mcg or 100 mcg BID via Diskus for the maintenance treatment of asthma for children age 4-11 years. Both doses were shown to be solidly effective in clinical trial FLTA2006. Supportive clinical trial 2008 replicated the efficacy of 100 mcg twice daily, but 50 mcg BID was not nearly as effective in clinical

trial FLTA2007. A pharmacokinetic study performed on a subset of children in FLTA2006 suggested that delivery of dry powder FP via the Diskus to the lung was less efficient than FP via the Diskhaler. Further *in vitro* studies may be advisable to settle this issue. This potential for clinical differences between the two devices in children should be incorporated into the labeling. With regard to safety, no new or unique issues were identified with this product. However, the sponsor missed a valuable opportunity to study the impact of once daily dosing on the systemic safety endpoints, such as growth velocity, bone age/density and HPA axis. Chronotropic effects of dosing at different times of day on these endpoints could also have been addressed. With regard to once daily dosing, FP 100 mcg QD and FP 200 mcg QD via Diskus failed to demonstrate efficacy for the pediatric population, and therefore this once daily indication is not recommended for approval.

Data presented in clinical trials FLTA2001, FLTA2003, FLTA2004, and FLTA2005 support the safety and efficacy of twice daily Flovent 100 mcg, 250 mcg, or 500 mcg BID via Diskus for the maintenance treatment of asthma for adults and adolescents. The efficacy of each of these doses was solid in the population of patients studied. No new or unique safety issues not adequately covered in the approved product labeling for Flovent Rotadisk were identified. With regard to once daily dosing of this product, FP 200 mcg QD failed to demonstrate efficacy on the primary endpoint for three adult (not to mention one pediatric) controlled clinical trials, FLTA2003, FLTA2004 and FLTA2016, and is not recommended for approval. FP 500 mcg QD did demonstrate a statistically significant change in the primary endpoint FEV₁ during two trials: FLTA2005 and FLTA2016. However, the numerical improvement was marginal and of questionable clinical significance, the duration of the trials was inadequate to address long-term safety and efficacy concerns regarding once daily dosing, and it is unclear how to label this product, that is, for inhaled CS-naïve asthmatics for initial therapy and/or as a switch from twice daily therapy (and from what BID dose). Neither trial provided adequate power to sort out the questions regarding these two subgroups. Finally, FP 500 QD is numerically inferior to BID dosing, not only at the same total daily dose, but likely at a lower BID daily dose, although this was not directly tested. This is another problematic labeling issue. For these reasons, in addition to

_____, FP 500 mcg QD via Diskus is not recommended for approval at this time.

**APPEARS THIS WAY
ON ORIGINAL**