

had no major protocol violations during the study. The decision to exclude a subject from the Efficacy Population was made prior to breaking the blind.

Reviewer's Comment: The results from the ITT and Efficacy Populations were usually very similar. Only the ITT population has been considered in this review, unless otherwise stated.

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

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

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

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

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

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

4.2.2.7 Results

4.2.2.7.1 Disposition

Nineteen (19) of the original 22 planned sites recruited subjects. A total of 331 children were screened during the preliminary 2-week baseline period. There were 69 withdrawals, most due to "other" (27 subjects, 39%) which included lost to follow-up, consent withdrawn, noncompliant with diary card, and incorrect PFT data. Other reasons for ineligibility included asthma exacerbation by defined criteria (16 subjects, 23%) and disallowed medication (13 subjects, 19%). Adverse events accounted for only 4 dropouts (3%). Subject distribution by site ranged from one

<1%) to 28 / — , 11% each). The mean number of subjects per site was 14 and the median was 15. Nearly half of all subjects were accounted for by six (32%) of the sites.

Reviewer's Comment: A somewhat more even distribution compared to FLTA2006, where half of all enrollees were at slightly more than one-fifth of the sites.

The 262 subjects who completed the screening period were randomized into one of three study groups and entered into the double-blind treatment phase of the trial. Of the 262 children who received at least one dose of study medication, 169 completed the study, for an overall dropout rate of 35%. The breakdown by treatment group and the reason(s) for discontinuation are shown in the table below. Most children withdrew for lack of efficacy (26%), most commonly because their PEFR fell below the stability limit defined at Visit 2. About 30% of the active treatment group overall withdrew, compared to 47% of the placebo group. Adverse events accounted for only six (2%) of the total study discontinuations. The category "other" included failure to return for follow-up, lack of compliance, and prohibited medication.

SUBJECT DISPOSITION*

	Placebo	FP 50 BID	FP 100 QD	Total
Enrolled	83	88	91	262
Completed	44 (53%)	63 (72%)	62 (68%)	169 (65%)
Withdrawn	39 (47%)	25 (28%)	29 (32%)	93 (35%)
Lack of Efficacy	29 (35%)	17 (19%)	23 (25%)	69 (26%)
Adverse Event	3 (4%)	2 (2%)	1 (1%)	6 (2%)
Failed to Return	2 (2%)	3 (3%)	3 (3%)	8 (3%)
Other	5 (6%)	3 (3%)	2 (2%)	10 (4%)

* From Volume 187, p.48

4.2.2.7.2 Demographics and Other Baseline Characteristics:

Treatment groups were demographically similar. About three-fifths were boys. The mean age across treatment groups was 7.6 to 8.0 years with very young children (4-5 years) comprising 20% (53 subjects). As a group, they were predominantly Caucasian (67%), although there were nearly twice as many minority enrollees compared with FLTA2006, accounted for primarily by an increase in Latino subjects (from 5% to 14%) rather than African American (from 13% to 17%). As might be expected among children in this age range, there was great variability in height and weight, mean=51.8 inches (range: 40.0-67.0 inches) and mean=74.6 lbs. (range: 32.0-160.0 lbs.), respectively, although there was no significant difference between treatment groups. The range for this variable was also smaller than for FLTA2006, as might be expected for a smaller study.

Asthma histories were similar. Slightly less than half of all enrollees used inhaled CS or cromolyn at baseline. Duration of asthma was comparable, and substantial relative to the age range of 4 to 11 years, with about half of the children reported as having had asthma for 5 years or more. Eighty percent (80%) reported no ER visits and 94% reported no hospitalizations in the prior 12 months. FEV1 and PEFR were also comparable across treatment groups, both as absolute numbers and when expressed as percent predicted at baseline.

The comparability of orally inhaled corticosteroid (ICT) use at baseline across groups reflects stratification by this variable. Beclomethasone dipropionate was the most commonly used CS, reported by 17% to 19% of children. Triamcinolone acetonide was the second most common, with use ranging from 8% to 15%. Cromolyn use was reported by 25-31%. Nedocromil and flunisolide were rarely used, reported by only 1-5% across treatment groups.

BACKGROUND CHARACTERISTICS*

	Placebo	FP 50 BID	FP 100 QD	Total
Number	83	88	91	262
Gender:				
Female	36	38	31	105 (40%)
Male	47	50	60	157 (60%)
Ethnicity:				
Black	13	14	17	44 (17%)
Latino	11	13	12	36 (14%)
Caucasian	58	59	61	178 (68%)
Other	1	2	1	4 (1%)
Age (yrs):				
Mean	7.8	8.0	7.6	7.8
% 4-5 yo	19%	20%	21%	20%
Inhaled CS use				
Yes	46%	47%	45%	46%
No	54%	53%	55%	54%
≥3 ER visits in prior 12 mos.	4%	7%	8%	6%
Baseline FEV1, L	1.44 L	1.46 L	1.37 L	
(% predicted)	(74.15%)	(74.33%)	(72.31%)	
Baseline PEFR, L/min	192.9 L/min	197.2 L/min	184.5 L/min	
(% predicted)	(76.34%)	(75.10%)	(73.82%)	

*From Vol.187, Tables 3-6, p.91-94

4.2.2.7.3 Efficacy Analysis

The population analyzed included all 262 subjects who received at least one dose of study medication (the ITT population). A subset analysis was performed using the 239-subject "efficacy population," comprised of the ITT subjects minus 23 children excluded because of major protocol violations: 6 in the placebo group, 10 in the FP 50 BID group, and 7 in the FP 100 QD group. The decision to exclude was to have been made prior to un-blinding.

4.2.2.7.3.1 Primary Efficacy Variable: FEV₁

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

The results of this analysis are shown in the table below and in the attached Figure 2 (p.83; Vol.187). There was no significant difference in FEV₁ at baseline across treatment groups. At endpoint, there was no statistically significant overall treatment effect in FEV₁, whether the difference was expressed as "liters" or as "% change from baseline" or as "change from baseline in %-predicted." There was also no significant difference in the pair-wise comparison between placebo and either the FP 100 mcg once daily or FP 50 mcg twice daily when measured at study endpoint. When examined on a week-by-week basis, the pair-wise comparison of change from baseline in FEV₁ did not achieve statistical significance for any week assessed during this 12-week study. Finally, as might be expected, given the failure to separate active from placebo, once daily dosing did not differ significantly from twice daily dosing of FP in this study.

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

	Placebo	FP 50 BID	FP 100 QD	Overall
N	70	73	78	221
Baseline FEV ₁ (L)	1.44	1.46	1.37	
N at Endpoint	68	72	78	218
FEV ₁ at Endpoint: Mean change (L)	0.05	0.13	0.08	
% change	5.70%	10.54%	8.4%	
p-value				
vs. placebo (Mean change)		0.753	0.844	0.867**
vs. placebo (% change)		0.573	0.617	0.573**

* Intent-to-Treat Population; From Tables 11-15; vol.187

** F-test

Reviewer's Comment: Unlike FLTA2006, this study apparently excluded FEV₁ data from children age 4 or 5 years. It would be interesting to know whether including the data from the very young children would influence the results on this endpoint. Given that FP 50 mcg BID is the lowest approved dose (for the Diskhaler), it is possible that this younger subset of children may have done better than the group as a whole on this endpoint at 50 mcg BID.

The failure of this study to replicate the statistically significant treatment effect of FP 50 mcg BID via Diskus compared to placebo that was demonstrated in FLTA2006 is of some concern. The baseline characteristics of subjects enrolled in FLTA2007 were

similar to those described in FLTA2006 with regard to PEFR, FEV₁, and overall disease severity as measured by ER visits and hospitalizations. Fewer subjects in the present study were receiving inhaled CS at baseline (45% vs. 55%). This would be expected to work in favor of a treatment effect, however, since the change from baseline in FEV₁ or PEFR would be greater. It would have been useful if this study also included a Diskhaler arm (i.e. FP 50 BID via the Diskhaler) similar to the previous study.

Mean change from baseline in FEV₁ also failed to show a statistically significant improvement when calculated using the efficacy population.

4.2.2.7.3.2 Primary Efficacy Variable: AM Clinic PEFR:

The co-primary efficacy endpoint in this trial was mean change from baseline in AM PEFR, the subject's first effort of the morning measured in clinic and prior to dosing with study medication. These data are summarized in the table below and shown graphically on the attached Figure 3 (p.84; Vol.187). There was no overall statistically significant treatment effect for the endpoint clinic AM PEFR, whether measured as absolute change in L/min, % change, or change in % predicted. Pairwise comparisons between placebo and twice daily or once daily FP were also performed, in spite of the absence of overall significance. When measured as change in % predicted, the BID treatment group reached a "significant" p-value (p=0.038) compared to placebo. However, it was not different from once daily dosing, nor was once daily dosing significant in the pairwise comparison with placebo.

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

	Placebo	FP 50 BID	FP 100 QD	Overall
N	83	88	91	262
Baseline PEFR (L/min)	203.5	201.3	193.8	
N at Endpoint	80	87	91	258
PEFR at Endpoint:				
Mean change	10.73 L/min	38.53 L/min	26.0 L/min	
% change	8.99%	24.40%	14.95%	
p-value vs. placebo:				
Mean change		0.030	0.267	0.123**
% change		0.060	0.454	0.172**

* Intent-to-Treat Population; From Tables 16, 17, and 18; Volume 187

** F-test

When the same analysis was performed using the efficacy population in place of the intent-to-treat, mean change from baseline in AM clinic PEFR was 13.97 L/min., 34.92 L/min, and 28.96 L/min for placebo, FP 50 BID, and FP 100 QD, respectively. Again, the overall treatment effect was not significant (p=0.213), nor were the pair-wise comparisons between placebo and BID dosing (p=0.115) or QD dosing (p=0.140).

Figure 3 (p.84; Vol.187). There was no overall statistically significant treatment effect for the endpoint clinic AM PEFR, whether measured as absolute change in L/min, % change, or change in % predicted. Pairwise comparisons between placebo and twice daily or once daily FP were also performed, in spite of the absence of overall significance. When measured as change in % predicted, the BID treatment group reached a "significant" p-value ($p=0.038$) compared to placebo. However, it was not different from once daily dosing, nor was once daily dosing significant in the pair-wise comparison with placebo.

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4.2.2.7.3.3 Secondary Endpoint: Survival in Study

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

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

4.2.2.7.3.4 Secondary Endpoints: Diary Data

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

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

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

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

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

Subjects recorded their asthma-related symptoms daily on their diary cards using a 0-3 severity scale, as described earlier in this review for study FLTA2006. Using this scale, symptoms were similar and relatively mild at baseline across treatment groups, from 0.77 to 0.84, also similar to baseline symptoms in study FLTA2006. At study endpoint, symptom scores had decreased by -0.30 for twice daily and -0.24 for once daily, compared to -0.08 for placebo. There was no statistically significant treatment effect overall, nor were either of the two pair-wise comparisons with placebo significant. For the FP 50 BID group, the absolute change relative to placebo in symptom score was less than 2/3rds of the change observed for the two BID arms in FLTA2006.

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

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

CHANGE FROM BASELINE IN DIARY VARIABLES*

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

*From Table on p.7; Vol.187

** No BID vs. QD comparisons achieved statistical significance

4.2.2.7.3.5 Efficacy by Demographic Subgroups

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

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

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

4.2.2.7.3.6 Efficacy by Inhaled Corticosteroid/Cromolyn use at Baseline

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

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

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

4.2.2.7.4 Safety Results:

4.2.2.7.4.1 Extent of Exposure

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

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4.2.2.7.4.2 Adverse Events (AE)

The adverse events identified in this trial are not substantially different from those described for clinical trial FLTA2006, or for clinical trial FLIT85 (NDA 20-770), which have already been incorporated into the ADVERSE REACTIONS section of the approved product labeling for Flovent™ Rotadisk.

Overall, 70% of the placebo group reported at least one adverse event during the double-blind treatment phase of this trial, compared to 59% in the FP 50 BID group and 65% of the FP 100 QD group. By system, the most commonly reported AE's in all treatment groups were within the ENT system (43-49%) followed by GI (14-22%; e.g. nausea/vomiting) and non-site specific (13-16%; e.g. fever). The top five ENT AE's were: URI (17-23%), throat irritation (5-13%), ENT infection (2-11%), upper resp. inflammation (4-6%) and sinusitis (2-7%). Headaches, which tend to be common in this population, occurred in 11% of placebo subjects, 9% of the twice daily group, and 14% of the once daily group.

There did not appear to be much difference between the two FP groups in the incidence of local side effects, although the overall occurrence of ENT AE's was greater in the once daily group (49%) compared to the twice daily group (45%).

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

There were no deaths in this study. There were four serious AE's and six withdrawals due to AE, three with SAE's and three with non-serious AE's. The serious AE's included 2 episodes asthma exacerbation associated with pneumonia (both placebo), appendicitis (FP 50 BID), and N/V with otitis media and dehydration (FP 50 BID). All four events required hospitalization, and the first three resulted in study withdrawal. The three additional withdrawals were accounted for by chickenpox (placebo), behavior changes (FP 50 BID), and worsening Tourette's syndrome and ADD (FP 100 QD).

There was one report of thrush (FP 50 BID). No adverse event specifically coded as "HPA axis suppression" was reported.

4.2.2.7.4.3 Laboratory Data (excluding HPA-axis)

Blood samples for serum chemistry, LFT's, and hematology were obtained at baseline and at study endpoint. No subject was withdrawn for abnormal laboratory values. A few subjects (1-5% per group, maximum)

had "clinically significant" laboratory values by pre-specified criteria reported at any time post-randomization.

Clinical laboratory tests of special interest include eosinophil count, alkaline phosphatase (AP), glucose, potassium, and bicarbonate. No subjects were reported as having clinically significant abnormalities in glucose, potassium, or bicarbonate post-randomization. There were six clinically significant elevations in eosinophil count (defined as $>1.25 \times 10^3$ /L), 3 in placebo and 3 in the FP groups. The maximum count was 1.62×10^3 recorded for a child enrolled in the placebo group. There were 9 clinically significant elevations in AP (defined as >400 u/L), 4 in placebo and 5 in the FP groups. No elevation occurred in a subject with concomitant elevations in other LFT's, so its source was likely bone. The maximum elevation, 887 u/L, was recorded from an 11 yo boy enrolled in the once daily FP arm. It would not be unreasonable to assume this increased AP had something to do with a "growth spurt" in this child. The relevance of AP in general to other aspects of bone turnover and metabolism remain to be determined.

4.2.2.7.4.4 HPA Axis Assessment

The HPA axis was assessed by means of basal AM plasma cortisol drawn at baseline and compared across treatment groups to basal AM plasma cortisol drawn at study endpoint.

These data were analyzed as change in *mean* basal cortisol level or as *percentage* of subjects with an abnormally low basal cortisol level at baseline vs. endpoint.

A value of 5 mcg/dl was selected as the lower limit of normal for basal AM plasma cortisol for all subjects except for boys age 9 through 12 years of age. Using this cutoff, 39 children (15%) of the ITT population had an abnormal cortisol at the start of the study: 15 (18%) in placebo, 10 (11%) in the FP 50 BID group, and 14 (15%) in the FP 100 QD group. At study endpoint using the above criteria, the percentages of subjects with abnormal cortisol levels (34%) was not appreciably different, nor was the distribution across treatment groups: 16%, 11%, and 12%, respectively in the placebo, twice daily, and once daily groups. It was not stated whether the same children who had abnormalities at baseline also had them at endpoint.

Mean AM basal plasma cortisol ranged from 9.3 to 9.9 mcg/dl at baseline across treatment groups and had not changed appreciably by the end of the 12-week study for any of the three treatment groups.

Reviewer's comment: The same flaws which so seriously compromised the HPA-axis analysis used in FLTA2006 are repeated here (see "Reviewer's Comment" in previous trial). Basal AM plasma cortisol is a very insensitive

instrument, and again there is wide variability in the accepted "normal" range of plasma cortisol among children in this age range.

4.2.2.7.4.5 Other Safety Evaluations

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

4.2.2.8 Conclusions

4.2.2.8.1 Efficacy Conclusions:

Dry powder FP delivered from the Diskus device at doses of 50 mcg BID or 100 mcg QD was numerically superior to placebo in the treatment of mild-to-moderate asthma in pediatric patients age 4-11 years. Unfortunately, there was no significant treatment effect for either of the two primary endpoints, FEV₁ and clinic AM PEFR, and none for three out of five of the secondary endpoints. For the remaining two secondary endpoints showing significant treatment effect relative to placebo, PM PEFR and nighttime awakenings, there was no statistical difference between the once or twice daily FP groups.

Survival analysis did show a statistically significant ($p=0.037$) difference across treatment groups in the number of subjects withdrawn due to lack of efficacy over time. The largest percentage of withdrawals due to lack of efficacy occurred in the placebo group, 35%, compared to 25% for the once daily FP group and 19% for the twice daily group. The two FP arms did not differ from each other.

Subgroup analysis suggested that female gender and African American ethnicity improved the likelihood of a salutary effect on asthma of FP via Diskus. The difference between the subgroup and the ITT was numerically greater when the FP was dosed as 100 mcg once daily than when dosed as 50 mcg BID. Definitive conclusions cannot be made, however, because the study was not powered to detect a difference among subgroups of this size. With regard to the ICT vs. BDT strata, the BDT subgroup tended to show a numerically greater improvement in measurements of lung function than the ICT group, as would have been expected.

The marginal efficacy of FP 50 mcg BID via Diskus in this study is disconcerting, compared to the very solid efficacy it showed in study FLTA2006. There was numerical improvement for all endpoints, however, and even though there was no significant treatment effect for clinic AM PEFR, the pair-wise comparison of FP 50 BID to placebo was significant ($p=0.037$). Unfortunately, this was not corroborated by diary AM PEFR ($p=0.271$ vs. placebo).

Although numerically superior to placebo on all endpoints, FP 100 mcg QD via Diskus was numerically inferior to twice daily dosing on survival analysis and for all endpoints, except PM PEFR. The latter suggests an end-of-dosing-interval effect is important, that is, while FP 100 mcg may be efficacious for the initial 12 hours after dosing, this efficacy wanes at some point between 12 and 24 hours, as demonstrated by both clinic and diary AM PEFR.

In conclusion, FP 50 mcg BID via Diskus shows marginal efficacy and FP 100 mcg QD via Diskus is ineffective for the treatment of pediatric patients age 4-11 years with mild to moderate asthma.

4.2.2.8.2 Safety Conclusions

Based upon study FLTA2007, FP 50 mcg BID or 100 mcg QD administered via the Diskus appeared to be safe when used to treat children 4-11 years old with mild-to-moderate asthma. The most frequently occurring adverse events were in the ENT system. There were no deaths in the study, four serious adverse events, and six withdrawals due to adverse events. Subgroup analysis by gender and ethnicity did not identify any group more prone to adverse events or other safety issues. The adverse event profile did not appear to be substantially different from that already ascertained from study FLTA2006, reviewed earlier.

Also of importance with regard to safety, once daily FP did not appear to pose a safety risk as measured by acute asthma exacerbations for children with mild to moderate asthma.

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 HPA axis was assessed via basal AM plasma cortisol, a very insensitive test, the analysis of which was seriously flawed. Although FP 100 mcg QD was ineffective in this study, it nevertheless would have provided some useful data had the sponsor chosen to ascertain the difference, if any, of once vs. twice daily FP on HPA axis function in children. An assay more sensitive than basal AM cortisol would have been required, however.

4.2.2.8.3 Labeling Considerations

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

4.2.3 FLTA2008:

"A randomized, double-blind, parallel-group trial assessing the efficacy and safety of fluticasone propionate via the multi-dose powder inhaler 100 mcg BID, 200 mcg QD, and placebo in subjects aged 4 to 11 years with chronic asthma."

4.2.3.1 Background Information

As with FLTA2007, FLTA2008 was conducted to compare once daily to twice daily dosing of FP via Diskus. Because the sponsor has not requested once daily dosing for the pediatric age group, this trial will be analyzed primarily as supportive of the safety and efficacy of FP 100 mcg BID via Diskus for the pediatric indication.

4.2.3.2 Objectives

The objectives of this study were to compare the efficacy and safety of FP 100 mcg BID or 200 mcg QD with placebo in children aged 4 to 11 years with chronic asthma in terms of the following:

- Efficacy: FEV₁, PEFR, survival in study, symptom scores
- Safety: Physical examination, clinical laboratory, 12-lead ECGs, and adverse events

4.2.3.3 Setting

Conducted at 21 outpatient sites in the US between 1 August 1994 and 5 April 1996. The number of patients per center ranged from 1 to 28 (0-12%).

4.2.3.4 Endpoints

4.2.3.4.1 Efficacy Endpoints:

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

4.2.3.4.2 Safety Endpoints

- Adverse events
- Clinical laboratory tests
- Basal AM plasma cortisol
- Physical examination
- Vital Signs

4.2.3.5 Design

FLTA2008 was a 12-week, randomized, double-blind, placebo-controlled, multi-center clinical trial which was later amended to permit open-label use of FP during a 12-month extension. Enrollment was planned at a minimum of 14 centers to obtain 280 evaluable pediatric asthmatics, however, this was amended to 295 to provide adequate numbers of subjects for the open-label extension. Subjects were stratified at baseline for inhaled corticosteroid or inhaled cromolyn use (ICT) or use of bronchodilator therapy alone (BDT). At the end of a 2-week, single-blind, placebo screening period, eligible subjects were assigned in a 1:1:1 ratio to one of three double-blind treatment groups, placebo, DK FP 100 BID, or DK FP 200 QD. Assessments occurred weekly during the first 4 weeks of the 12-week dosing period, then biweekly until the end of the study. Except for the doses of FP selected, design, recruitment, inclusions, and assessments were identical to FLTA2007.

Reviewer's Comment: Only the double-blind, 12-week trial has been included in the sponsor's analysis. The open-label extension was not used for safety or efficacy data in this study report, although Amendment 01 (16 August 1994) included as its rationale for the extension "to obtain long-term safety data on FP." Perhaps because of inadequate recruitment to cover anticipated dropouts over the one year extension, the planned efficacy analysis was dropped (see Statistical Methods, below), but this should not have impacted safety data.

4.2.3.6 Summary of Protocol (includes all amendments)

4.2.3.6.1 Study Population

Inclusion Criteria

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

Exclusion Criteria

- Life-threatening asthma
- Use of nonsteroidal immunosuppressive therapy for asthma, such as cyclosporine, methotrexate, or gold
- Intermittent or seasonal asthma
- Other significant concomitant disease

- Current chickenpox or exposure in prior 3 weeks
- URI in prior 2 weeks
- Tobacco use
- Allergy to corticosteroids (CS) or β -agonists
- Clinically significant abnormality on screening laboratory or 12-lead ECG
- Glaucoma or posterior subcapsular cataracts (PSC)
- Prior participation in Diskhaler (or other Diskus) study

Disallowed Medications

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

4.2.3.6.2 Treatment Arms and Dosing

Subjects were randomized to one of three treatment groups. Each child received three devices, A, B, and C, two (A and B) to be used for AM dosing and one (C) for PM dosing. For DK 100 BID, A and C contained active medication. For DK 200 QD, A and B contained FP. For the placebo arm, all three devices contained matching placebo. Devices were exchanged at six-weeks and at 12-weeks after the start of the study.

Reviewer's Comment: As in FLTA2007, six weeks would not constitute life-of-device for a once daily indication (42 doses utilized out of a possible 60 doses=60 days of QD dosing or 8 weeks plus 4 days).

Treatment	Twice Daily Dosing AM and PM
FP 100 mcg BID	1 blister FP 100 mcg via Device A (AM) 1 blister Placebo via Device B (AM) 1 blister FP 100 mcg via Device C (PM)
FP 200 mcg QD	1 blister FP 100 mcg via Device A (AM) 1 blister FP 100 mcg via Device B (AM) 1 blister Placebo via Device C (PM)
Placebo	1 blister Placebo via Device A (AM) 1 blister Placebo via Device B (AM) 1 blister Placebo via Device C (PM)

4.2.3.6.3 Treatment Assignment:

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

4.2.3.6.4 Study Sequence

Screening Period (Visits 1-2): Twenty-one investigators screened 316 children who met the inclusion/exclusion criteria over a two week, single blind period. Subjects could continue to take their baseline asthma medication at this time, except that Ventolin (MDI or Rotacaps) was substituted for their own particular β_2 -agonist. Once selected, however, either the MDI or the DPI Ventolin was to be used consistently throughout the remainder of the study. The Ventolin was to be used only to treat symptoms, and not taken on a regular basis (even if that was how it was previously taken).

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

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

On the first visit only, children age 4-5 years had their PEFr measured before and 30' after two puffs of Ventolin MDI to assess reversibility.

Children age 6-11 years who did not have reversibility documented in their history also had their FEV₁ measured before and after Ventolin.

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

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

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

Treatment Period (Visits 2 – 10): Two hundred forty-two (242) eligible children completed the screening period and were found to be eligible for the study. In addition to meeting the Inclusion/Exclusion criteria above, these children had met the following "randomization criteria:"

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

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

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

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

Reviewer's Comment: It was not discussed why the "stability limit" for FEV₁ was "20% decrease from best FEV₁ at Visit 2," rather than "15% decrease from best FEV₁ at Visit 2" used for FLTA2006 and FLTA2007. The protocol was primarily written using the 15% stability limit (Vol.197; p.353), and no amendment changing this limit at a later time could be located (Vol.197; p.402-429). If added prospectively, this change should decrease the overall number of dropouts due to pre-specified "lack of efficacy" criteria and should not favor any one group in particular. If this change was not pre-specified in the protocol, however, this is a problem and the data must be recalculated using the pre-specified 15% limit.

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

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

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

At Visits 3-9 the following procedures were performed:

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

Visits were scheduled weekly for the first 4 weeks, then every other week until study endpoint at 12-weeks. Devices were collected and new ones dispensed at the midpoint of the study, week 6 (Visit 7) and at the end of

the double-blind period, week 12. An oropharyngeal exam was also performed at week 6.

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

4.2.3.6.5 Efficacy Assessments

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

Secondary efficacy variables included all of the following:

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

4.2.3.6.6 Safety Assessments

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

4.2.3.6.7 Statistical Methods

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

Power Calculations: Enrollment was planned (via amendment) to obtain 295 evaluable subjects to provide >80% power of detecting a difference in AM PEFR of 16 L/min between any two treatment groups of 80 subjects each, assuming a standard deviation of 36 L/min. It was also calculated

that 75 subjects/treatment arm would be required to achieve 80% power of detecting a difference in FEV1 of 0.25L between any two treatment groups. Actual enrollment was 78 to 84 subjects per treatment group, with a total enrollment of 242 subjects.

Reviewer's Comment: The amendment was included to increase enrollment so that adequate numbers of subjects (≥ 80 per arm) would be available for analysis after the duration of the study was increased by the addition of a 12-month "open label" extension. Unfortunately, it appears that enrollment was barely adequate to provide power to detect the pre-specified treatment effect for the original 12-week trial. Furthermore, this study had a substantial dropout rate (41% overall, see results, below), which may therefore be cause for concern.

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

Reviewer's Comment: In this study, the results from the ITT and Efficacy Populations were usually very similar for the twice daily group, but tended to be disparate on the once daily. The Efficacy Population also had 10 fewer subjects than the ITT, not expedient for a study with already marginal enrollment. Only the ITT population has been considered in this review, unless otherwise stated.

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

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

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

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

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

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

4.2.3.7 Results

4.2.3.7.1 Disposition

Twenty-one (21) of the planned sites recruited subjects. A total of 316 children were screened during the preliminary 2-week baseline period. There were 74 screening failures, leaving 242 subjects eligible for randomization: 78 to placebo, 80 to FP, and 84 to FP 200 mcg QD. The most common reason for screening failure was not meeting the randomization criteria at Visit 2. The mean number of subjects per site was 12 and the median was 12. Nearly half of all subjects were accounted for by six (29%) of the sites.

Of the 242 subjects enrolled, 142 completed the study and 100 were withdrawn, for an overall dropout rate of 41%. Most were discontinued due to lack of efficacy by predefined criteria (83 subjects; 83% of withdrawals, 34% of ITT). Only 3 subjects were withdrawn because of adverse events. The remaining 14 were accounted for by failure to return or "other," which included use of a disallowed medication, protocol violation, and noncompliance. The breakdown by treatment group and the reason(s) for discontinuation are shown in the table below. The breakdown by lack of efficacy (Table 2, Vol. 198; p.90) included falling below the FEV₁ stability limit (15%), falling below the clinic PEFR stability limit (14%), or falling below one of the other diary stability criteria (1-16%). Some subjects fulfilled more than one lack of efficacy criteria.

SUBJECT DISPOSITION*

	Placebo	FP 100 BID	FP 200 QD	Total
Enrolled	78	80	84	242
Completed	32 (41%)	58 (73%)	52 (62%)	142 (59%)
Withdrawn	46 (59%)	22 (28%)	32 (38%)	100 (41%)
Lack of Efficacy	42 (54%)	16 (20%)	25 (30%)	83 (34%)
Adverse Event	1 (1%)	0 (0%)	2 (2%)	3 (1%)
Failed to Return	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Other	2 (3%)	6 (8%)	5 (6%)	13 (5%)

* From Volume 198, pp.47, 90

4.2.3.7.2 Demographics and Other Baseline Characteristics:

Treatment groups were demographically similar. About two-thirds were boys. As a group, the children enrolled in this trial were older than in either FLTA2006 or 2007, with the mean age across treatment groups

being 8.5 to 8.8 years. Very young children (4-5 years) comprised only 9% (21 subjects), compared to 13% and 21% in the two former studies, respectively. As a group, they were predominantly Caucasian (83%), with only 8% African Americans and 7% Latino representation, also the lowest of the three studies. Again, as might be expected, there was great variability in height and weight, mean=53.1 inches (range: 40.0-65.0 inches) and mean=75.4 lbs. (range: 33.0-166.0 lbs.), respectively, although there was no significant difference between treatment groups.

Asthma histories were similar. Slightly more than half of all enrollees used inhaled CS or cromolyn at baseline. Duration of asthma was comparable, and substantial relative to the age range of 4 to 11 years, with about half of the children reported as having had asthma for 5 years or more. Seventy-eight percent (78%) reported no ER visits and 93% reported no hospitalizations in the prior 12 months. Percent predicted FEV₁ and PEFR were not significantly different between treatment groups at baseline.

The comparability of orally inhaled corticosteroid (ICT) use at baseline across groups reflects stratification by this variable. Beclomethasone dipropionate was the most commonly used CS, reported by 22% to 25% of children. Triamcinolone acetonide was the second most common, with use ranging from 11% to 18%. Cromolyn use was reported by 19-24%. Nedocromil and flunisolide were the least frequently used, reported by only 1-8% across treatment groups.

BACKGROUND CHARACTERISTICS*

	Placebo	FP 100 BID	FP 200 QD	Total
Number	78	80	84	242
Gender:				
Female	21	23	25	69 (29%)
Male	57	57	59	173 (71%)
Ethnicity:				
Black	5	7	8	20 (8%)
Latino	9	4	5	18 (7%)
Caucasian	63	67	71	201 (83%)
Other	1	2	0	3 (1%)
Age (yrs):				
Mean	8.8	8.5	8.5	8.6
% 4-5 yo	5%	8%	13%	9%
Inhaled CS use				
Yes	60%	59%	54%	57%
No	40%	41%	46%	43%
≥3 ER visits in prior 12 mos. (%)	4%	8%	2%	5%
Baseline FEV₁, L (% predicted)	1.51 L (73.14%)	1.36 L (70.49%)	1.40 L (70.19%)	
Baseline PEFR, L/min (% predicted)	209.5 L/min (75.22%)	202.6 L/min (75.32%)	203.2 L/min (74.42%)	

*From Vol.198, Tables 3-6, p.92-95

4.2.3.7.3 Efficacy Analysis

The population analyzed included all 242 subjects who received at least one dose of study medication (the ITT population). A subset analysis was performed using the 232-subject "efficacy population," comprised of the ITT subjects minus 10 children excluded because of major protocol violations: 2 in the placebo group, 4 in the FP 100 BID group, and 4 in the FP 200 QD group. The decision to exclude was to have been made prior to un-blinding.

4.2.3.7.3.1 Primary Efficacy Variable: FEV₁

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

The results of this analysis are shown in the table below and in the attached Figure 2 (p.83; Vol.198). There was no significant difference in FEV₁ at baseline across treatment groups. At endpoint, there was a statistically significant overall treatment effect in FEV₁, ($p < 0.001$) in mean change from baseline. In the pair-wise comparison with placebo, there was also a significant difference in mean change from baseline in FEV₁ for each of the two FP groups ($p < 0.001$ for each). There was no significant difference between the two FP arms.

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

	Placebo	FP 100 BID	FP 200 QD	Overall
N	78	80	84	242
Baseline FEV ₁ (L)	1.51	1.36	1.40	P=0.065
N at Endpoint	75	77	76	228
FEV ₁ at Endpoint:				
Mean change (L)	-0.04	0.23	0.12	
% change	-2.60%	18.13%	9.5%	
p-value				
vs. placebo (Mean change)		<0.001	<0.001	<0.001**
vs. placebo (% change)		<0.001	0.004	<0.001**

* Intent-to-Treat Population; From Tables 11-15; vol.198

** F-test

Reviewer's Comment: The "treatment effect" was +0.27 L for twice daily but only +0.16 L for once daily. This latter difference is less than the 0.25 L difference between treatment groups specified in the statistical section of the protocol. The power analysis this number was based on was ≥ 80 subjects per treatment arm, a recruitment goal this study failed to achieve. While this endpoint does show a statistically significant treatment effect for once daily dosing, it is not entirely convincing that this statistically significant difference of only 0.16 L between placebo and once daily equals a clinically significant difference.

4.2.3.7.3.2 Primary Efficacy Variable: AM Clinic PEFR:

The co-primary efficacy endpoint in this trial was mean change from baseline in clinic AM PEFR. These data are summarized in the table below and shown graphically on the attached Figure 3 (p.84; Vol.198). There was no overall statistically significant treatment effect, whether measured as absolute change from baseline in L/min or as % change. Pair-wise comparisons between placebo and twice daily or once daily FP were also performed, in spite of the absence of overall significance. When measured as mean change or as % change, the BID treatment group reached a "significant" p-value ($p=0.002$; 0.007 , respectively) compared to placebo. However, it was not different from once daily dosing, nor was once daily dosing significant in the pair-wise comparison with placebo.

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

	Placebo	FP 100 BID	FP 200 QD	Overall
N	78	80	84	242
Baseline PEFR (L/min)	219.3	208.0	207.5	
PEFR at Endpoint:				
Mean change	19.32	42.11	32.67	
% change	L/min 10.83%	L/min 22.54%	L/min 18.46%	
p-value vs. placebo:				
Mean change		0.002	0.321	0.081**
% change		0.007	0.383	0.189**

* Intent-to-Treat Population; From Tables 16, 17, and 18; Volume 198

** F-test

When the same analysis was performed using the efficacy population in place of the intent-to-treat, mean change from baseline in AM clinic PEFR was 19.28 L/min, 47.01 L/min., 38.17 L/min, and for placebo (74 subjects), FP 100 BID (74 subjects), and FP 200 QD (77 subjects), respectively. The overall treatment effect was significant ($p=0.003$), as were the pair-wise comparisons between placebo and BID dosing ($p<0.000$) and placebo and QD dosing ($p=0.018$), but not between once and twice daily dosing.

Reviewer's Comment: Although the data from the Efficacy Population is at odds with the ITT, as stated earlier, the ITT population is preferred for regulatory reasons, usually for reasons similar to the ones which follow. In this case, the endpoint efficacy analysis excluded data from 17 subjects, and it remains unclear which of the 28 subjects "eligible" for data exclusion (10 "completely excluded" and 18 "partially excluded") nonetheless had their data incorporated into the analysis. Also, there remains the problem with the FEV₁ stability limits, the point at which the change from 15 to 20% occurred, and whether the change was applied post hoc.

Figure 3 shows the week-by-week PEFR means of study survivors and does not reflect the LVCF analysis used to determine endpoint. Because of the substantial dropout

rate in this study (41% overall), this figure bears little resemblance to study endpoint and is confusing.

4.2.3.7.3.3 Secondary Endpoint: Survival in Study

Using the logrank test on Kaplan-Meier estimates of survival, a significant overall treatment effect on survival in study could be shown ($p=0.001$; see table below). At study endpoint, the percentage of subjects withdrawn due to lack of efficacy was 54% for placebo, 20% for twice daily, and 30% in the once daily groups. The difference was significant for the twice daily group compared to placebo ($p=0.001$) as well as for the once daily group compared to placebo ($p=0.001$). There was no significant difference between once and twice daily FP.

4.2.3.7.3.4 Secondary Endpoints: Diary Data

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

The diary PEFR data reported for FLTA2008 showed improvement in lung function for both FP groups, which numerically favored twice daily dosing. There was a statistically significant treatment effect for both change from baseline in AM PEFR as well as for change from baseline in PM PEFR. For the AM PEFR endpoint, the change from baseline in L/min for the placebo group was 14, compared to 24 L/min for the once daily arm ($p=0.019$) and 34 L/min for the twice daily arm ($p=0.001$). There was no difference between the two FP doses. Change from baseline in PM PEFR was also significant for both doses. In addition, the numerical superiority of twice daily compared to once daily was smaller than for the AM PEFR endpoint, 27 L/min for FP 100 BID compared to 24 L/min for FP 200 QD and 11 L/min for placebo. Again, there was no significant difference between the two FP doses. Finally, although not a prospectively declared endpoint, the AM-PM PEFR differential is one measure of asthma stability. At baseline, the difference for placebo, twice daily, and once daily were 10 L/min, 11 L/min, and 14 L/min, respectively. At endpoint, the difference had decreased to 4 L/min for twice daily dosing compared to 6 L/min for placebo and 11 L/min for once daily. Although not significant, there was greater numerical improvement for the twice daily arm than for the once daily arm, in which the change was less than for placebo.

Subjects recorded their asthma-related symptoms daily on their diary cards using a 0-3 severity scale. Using this scale, symptoms were similar and relatively mild at baseline across treatment groups, from 0.85 to 0.93. Although a cross-study comparison, the baseline scores were slightly higher by about 10% than for FLTA2006 or FLTA2007. At study endpoint, symptom scores had decreased by -0.38 for twice daily and -

0.24 for once daily, compared to -0.01 for placebo. There was a statistically significant treatment effect overall ($p < 0.001$). The pair-wise comparisons between twice daily and placebo ($p < 0.001$) as well as between once daily and placebo ($p < 0.001$) were significant. There was no difference between the two FP arms.

Nighttime awakenings requiring Ventolin were infrequent and decreased further in both active treatment groups (0.04 for placebo, -0.06 for twice daily, and -0.04 for once daily, $p = 0.010$ overall). The pair-wise comparison with placebo demonstrated a statistically significant improvement in nighttime awakenings at endpoint compared to baseline for twice daily ($p < 0.001$) but not for once daily ($p = 0.114$). There was no difference between the two FP groups.

Use of rescue Ventolin at study endpoint compared to baseline improved significantly for the twice daily group only (-0.65 puffs/day; $p = 0.007$), although the once daily group showed numerical improvement (-0.45 puffs/day; $p = 0.223$). There was no significant treatment effect overall for this endpoint, although the p-value was close ($p = 0.061$; see table below).

CHANGE FROM BASELINE IN DIARY VARIABLES*

Δ baseline in:	Placebo	FP 100 BID	FP 200 QD	Overall p-value	p-value vs. Placebo**	
					BID	QD
Diary AM PEFr (L/min)	14	34	24	0.002	<0.001	0.019
Diary PM PEFr (L/min)	11	27	24	0.041	0.013	0.034
Asthma Symptom Score	-0.01	-0.38	-0.24	<0.001	<0.001	<0.001
Rescue Ventolin Use (puffs/day)	0.03	-0.65	-0.45	0.061	0.007	0.223
Nighttime Awakenings	0.04	-0.06	-0.04	0.010	<0.001	0.114
Subjects withdrawn for lack of efficacy	54%	20%	30%	0.001		

* From Table on p.5; Vol.198

** No BID vs. QD comparisons achieved statistical significance

4.2.3.7.3.5 Efficacy by Demographic Subgroups

A subgroup analysis by gender and ethnicity was performed for the two primary endpoints (Tables ST15-19 for FEV₁ and ST21-24 for PEFr; vol.198, p.207-216). Numbers were too limited to draw conclusions based on ethnicity. Gender appeared to have little discernible impact on the efficacy of FP via Diskus.

4.2.3.7.3.6 Efficacy by Inhaled Corticosteroid/Cromolyn use at Baseline

The study population was stratified by use of these agents at baseline (the ICT group) or whether they were managed on bronchodilator therapy

alone (the BDT group). The ICT group constituted 57% of the study population overall compared to 43% for the BDT group.

More subjects in the ICT group (40%) discontinued because of lack of efficacy than in the BDT group (27%). However, within these strata, the subjects who discontinued were more likely to be receiving placebo (62% for ICT and 42% for BDT) than active treatment. When these two subgroups were compared by their results on the two primary endpoints, the BDT group tended to have a slightly greater change from baseline in the two FP-treated groups for FEV₁ than the ICT group, as might be expected. For the PEF_R endpoint, the difference between the BDT and ICT groups was greatest for the FP 100 BID dose (15 L/min), as in FLTA2007, but negligible and paradoxically in favor of the ICT subgroup for the FP 200 QD arm (-4 L/min). For the secondary endpoint, AM diary PEF_R, the difference between the two strata was minimal for the BID arm (1 L/sec) and slightly larger (-7 L/sec) and in favor of the ICT subgroup for the once daily arm.

In conclusion, baseline inhaled CS use appeared to have a smaller and/or more neutral impact on the various primary and secondary endpoints, and differences between treatment arms, in this clinical trial than demonstrated for the two other pediatric clinical trials FLTA2006 or FLTA2007.

4.2.3.7.4 Safety Results

4.2.3.7.4.1 Extent of Exposure

A total of 242 subjects received at least one dose of study medication (the ITT population); all have been included in the safety analysis. The mean exposure to study drug was 48.3 days for the placebo group (32/78 subjects completed), 72.2 days for the FP 100 BID group (58/80 subjects completed), and 65.5 days for the FP 200 QD group (52/84 subjects completed).

4.2.3.7.4.2 Adverse Events (AE)

The adverse events identified in this trial are not substantially different from those described for clinical trial FLTA2007, or for clinical trial FLIT85 (NDA 20-770), which have already been incorporated into the ADVERSE REACTIONS section of the approved product labeling for FloventTM Rotadisk.

Overall, 73% of the placebo group reported at least one adverse event during the double-blind treatment phase of this trial, compared to 76% in the FP 100 BID group and 76% of the FP 200 QD group. By system, the most commonly reported AE's in all treatment groups were within the ENT system (44-51%). The top 5 AE's in this category across treatment groups were: URI (15-20%), throat irritation (9-13%), sinusitis (8-13%), ENT infection (6-9%), and upper resp. inflammation (4-8%). A slightly higher

incidence of upper respiratory tract infection, throat irritation, and sinusitis occurred in the active treatment groups compared with placebo.

Other commonly reported systems included non-site specific (24-29%) followed by GI (14-30%). Among non-site specific events, candidiasis of unspecified site (7-21%) and fever (1-13%) were the most common, fever being more common among FP-treated children. Among GI events, oral thrush (10-13%) was the most common, followed by GI discomfort and pain (1-5%). Among the two candidiasis categories, oropharyngeal candidiasis was more common in the FP treated groups while candidiasis of unspecified site was more common among placebo children. Other events included headache (6-13%), cough (4-8%) and viral respiratory infections (4-6%).

Overall, there did not appear to be a greater incidence of local side effects among one FP group compared to the other, although selected AEs, such as URTI, showed a higher incidence among the once daily group.

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

There were no deaths in this study. There were two serious AE's and three withdrawals due to AE, one with a SAE and two with non-serious AE's. The 2 serious AE's included one episode acute appendicitis occurring during the run-in period in a subject subsequently randomized to FP 200 QD and acute asthma exacerbation requiring hospitalization occurring in a placebo subject. The two additional withdrawals were accounted for by chickenpox (FP 200 QD) and pneumonia FP 200 QD.

With regard to adverse events of special interest, the relatively high incidence of candidiasis reported in this study is likely explained by the fact that baseline oropharyngeal cultures were taken from all patients at the randomization visit (Visit 2). The majority (95%) of patients in whom candidiasis of the mouth and throat was reported as an adverse event had positive cultures at randomization but had no clinical evidence of oropharyngeal candidiasis. No subjects in the placebo group, and only 1 (<1%) of patients in the FP 100 mcg BID group, and 2 (2%) of patients in the FP 200 AD group had clinical evidence of oropharyngeal candidiasis.

Throat irritation and sinusitis occurred more often in the FP treatment groups (10-13%) than in the placebo group (8-9%). Cough was also more frequent among FP subjects (8%) compared to placebo (4%).

No adverse event specifically coded as "HPA axis suppression" was reported.

4.2.3.7.4.3 Laboratory Data (excluding HPA-axis)

Blood samples for serum chemistry, LFT's, and hematology were obtained at baseline and at study endpoint. No subject was withdrawn for abnormal laboratory values. A few subjects (1-4% per group, maximum) had "clinically significant" laboratory values by pre-specified criteria reported at any time post-randomization.

Clinical laboratory tests of special interest include eosinophil count, alkaline phosphatase (AP), glucose, potassium, and bicarbonate. No subjects were reported as having clinically significant abnormalities in glucose post-randomization. Based on the known systemic effects of CS, an elevated bicarbonate or a decreased potassium would be of interest. There was one subjects with an abnormal (elevated) potassium in the FP 200 QD group and two subjects with abnormal (decreased) bicarbonate, neither of clear pharmacologic interest. There were five clinically significant elevations in eosinophil count (defined as $>1.25 \times 10^3 /L$), 2 in placebo and 3 in the FP groups. The maximum count was 2.49×10^3 recorded for a child enrolled in the placebo group. There were 3 clinically significant elevations in AP (defined as $>400 \text{ u/L}$), 2 in FP 100 BID and 1 in FP 200 QD. The maximum elevation, 494 u/L, was recorded from a 9 yo boy enrolled in the twice daily FP arm. This child's AP was elevated at baseline (473 u/L), at which time he also had a borderline elevated AST (41 u/L; nml=11-36 u/L), which persisted until study endpoint (42 u/L). It is unlikely that this child's laboratory abnormalities were related to study medication. The remaining two AP elevations were not associated with other abnormal LFT's, and their significance is unclear, but could be related to bone turnover and metabolism.

4.2.3.7.4.4 HPA Axis Assessment

The HPA axis was assessed by means of basal AM plasma cortisol drawn at baseline and at study endpoint. A value of 5 mcg/dl was selected as the lower limit of normal for all subjects, and abnormally low plasma cortisol readings were identified using this cutoff and then compared across treatment arms at study endpoint. Data were not further analyzed, but were then presented descriptively.

Table 34 (Vol.198; p. 133) shows the results. By the sponsor's criteria, 22 subjects (9%) had low plasma cortisol abnormalities at endpoint: 9 (12%) in the placebo group, 7 (9%) in the FP100 BID group, and 6 (7%) in the FP 200 QD group.

Reviewer's comment: The same problems identified during review of clinical trials FLTA2006 and FLTA2007 have been repeated here. Again, plasma AM cortisol is not a sensitive test for HPA axis suppression, and the somewhat arbitrary selection of 5 mcg/dl

as the cutoff diminishes its sensitivity still further. Table ST-45 (Vol.198; p. 302) shows the numerical values for plasma cortisol and Table 35 (Vol.198; p.135) identifies the normal ranges for all laboratory values used in this study. The normal range of basal AM plasma cortisol is from 4 to 17 mcg/dl, depending upon age and gender and "<4 mcg/dl" is identified as a clinically significant abnormality. If 4 mcg/dl rather than 5 mcg/dl is used as the cutoff, then only 2 out of 9 placebo subjects (2.6%), 3 out of 7 FP 100 BID subjects (3.8%), and 2 out of 6 FP 200 QD subjects (2.4%) have abnormalities at endpoint.

4.2.3.7.4.5 Other Safety Evaluations

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

4.2.3.8 Conclusions

4.2.3.8.1 Efficacy Conclusions:

Dry powder FP delivered from the Diskus device MDPI at doses of 100 mcg BID or 200 mcg QD was numerically superior to placebo in the treatment of mild-to-moderate asthma in pediatric patients age 4-11 years. Unfortunately, there was no significant overall treatment effect for one of the two primary endpoints, clinic AM PEF, as well as no significant treatment effect for two out of five of the secondary endpoints, rescue β -agonist use and nighttime awakenings. The lack of an overall significant treatment effect reflects the generally poor performance of FP 200 mcg QD, rather than FP 100 mcg BID, since BID appeared solidly effective in this population. Not only was FP 200 QD consistently numerically inferior to FP 100 BID, but even an endpoint which registered as a "win" for once daily, such as FEV₁, showed a numerical improvement from baseline which was half the magnitude of the improvement attributable to the twice daily arm. The lack of a statistical separation between once and twice daily on this and on other endpoints is probably related to the substantial dropout rate for this study.

Survival analysis did show a statistically significant ($p=0.001$) difference across treatment groups in the number of subjects withdrawn due to lack of efficacy over time. The largest percentage of withdrawals due to lack of efficacy occurred in the placebo group, 54%, compared to 30% for the once daily FP group and 20% for the twice daily group. The two FP arms did not differ from each other.

Subgroup analysis did not favor one gender over the other or identify a particular ethnic group more likely to show benefit, but there were too few non-Caucasian subjects for a meaningful analysis. With regard to the ICT vs. BDT strata, neither subgroup demonstrated a consistently greater numerical improvement in measurements of lung function than the other, unlike in clinical trial FLTA2007.

Unlike the marginal efficacy of FP 50 mcg BID via Diskus demonstrated in clinical trial FLTA2007, FP 100 mcg BID was very solidly effective in this study. As noted above, the lack of a significant treatment effect for one primary and two secondary endpoints was due to the FP 200 mcg QD arm. Although not technically interpretable under these circumstances, the p-values for both primary and all five secondary endpoints for FP 100 BID were well below the usual significance cutoff level of $p=0.05$.

Although numerically superior to placebo on all endpoints, FP 200 mcg QD via Diskus was inferior to twice daily dosing on survival analysis and for all endpoints. In most cases, such as FEV_1 discussed above, the difference was substantial and on the order of two-fold.

In conclusion, FP 100 mcg BID via Diskus MDPI shows clear efficacy while FP 200 mcg QD via Diskus is ineffective for the treatment of pediatric patients age 4-11 years with mild to moderate asthma.

4.2.3.8.2 Safety Conclusions

Based upon study FLTA2008, FP 100 mcg BID or 200 mcg QD administered via the Diskus MDPI appeared to be safe when used to treat children 4-11 years old with mild-to-moderate asthma. The most frequently occurring adverse events were in the ENT system. There were no deaths in the study, two serious adverse events, and three withdrawals due to adverse events. Subgroup analysis by gender and ethnicity did not identify any group more prone to adverse events or other safety issues. The adverse event profile did not appear to be substantially different from that already ascertained from study FLTA2007, reviewed earlier.

Also of importance with regard to safety, once daily FP did not appear to pose a safety risk as measured by acute asthma exacerbations for children with mild to moderate asthma. There also did not appear to be a substantially increased risk of local side effects for once daily FP, although this group did report more URTI than twice daily.

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 HPA axis was assessed via basal AM plasma cortisol, a very insensitive test, the analysis of which was seriously flawed.

4.2.3.8.3 Labeling Considerations (Includes comments pertinent to all three pediatric clinical trials, FLTA2006, FLTA2007, and FLTA2008).

1. Under the **Pharmacodynamics** subsection of the **CLINICAL PHARMACOLOGY** section, lines 134-138. The short cosyntropin stimulation test performed on a subset of subjects during clinical trial FLTA2006 is described. The HPA axis testing of this product for the pediatric indication was marginal, at best. The tests selected were either relatively insensitive measures of HPA axis suppression (i.e. basal plasma AM cortisol or high dose ["standard dose"] cosyntropin stimulation testing, either short or 6-hr. infusion) or were hampered by quality control problems and/or questionable analysis (i.e. 24-hour urinary cortisol and tallies of "abnormal" basal AM cortisol or group mean shifts in cortisol levels). Although not ideal, the test described in the labeling is probably the best of the lot.
2. In the *Pediatric Experience* subsection of the **Clinical Trials** section, lines 215-222. Supportive pediatric clinical trials FLTA2007 and FLTA2008 are described. FLTA2008 clearly demonstrated the efficacy of FP 100 mcg BID via Diskus because it showed statistically significant improvement on both co-primary and all five secondary endpoints. In contrast, FLTA2007 failed to show clear efficacy for FP 50 mcg BID via Diskus because statistically significant improvement was shown for only one of the two co-primary endpoints and only three out of five secondary endpoints. The final sentence should be deleted because it implies that
only FLTA2008 was extended from 12-weeks to one year by amendment.
3. Under **DOSAGE AND ADMINISTRATION**, the Division is in agreement with the sponsor that once daily dosing of fluticasone propionate via Diskus is not appropriate for pediatric patients age 4-11 years.
4. 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, 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."

4.3 Trials supporting the efficacy in asthma in adults and adolescents

4.3.1 FLTA2001:

"A randomized, double-blind, double-dummy, parallel-group, comparative trial of inhaled fluticasone propionate Rotadisk via Diskhaler 500 mcg BID, multi-dose powder inhaler 500 mcg BID, and placebo in adolescent and adult patients with mild to moderate asthma."

4.3.1.1 Background Information

Similar to pediatric clinical trial FLTA2006, this trial was conducted as a device comparison study, in order to provide a clinical "bridge" to compare the approved Diskhaler to the new Diskus MDPI. There is no once daily arm, and the dose selected, 500 mcg BID, is the highest approved maintenance dose for this product outside of the oral CS-sparing indication.

4.3.1.2 Objectives

The objectives of this study were to compare the efficacy and safety of FP 500 mcg BID via multi-dose powder inhaler (MDPI or Diskus), FP 500 mcg BID Rotadisk via Diskhaler, and placebo BID terms of the following:

- Efficacy: The primary efficacy variable was FEV₁. The secondary efficacy variables were: survival in study, physician global assessment, FEF₂₅₋₇₅, FVC, patient-determined PEF, symptom scores, rescue beta-agonist use, and nighttime awakenings requiring beta-agonist
- Safety: Physical examination, clinical laboratory, HPA-axis assessment, 12-lead ECGs, and adverse events
- Pharmacokinetics: Primary objective was to compare systemic exposure. Secondary objectives were to detect gender influences, drug interactions, compare PD effect on plasma cortisol, time to steady state, and FP accumulation with repeat dosing.
- Device Satisfaction: Compare patient preference

4.3.1.3 Setting

The study was conducted at 16 outpatient sites in the US between 14 April 1994 and 15 January 1995. Prior to unblinding, one center was dropped due to questions about data reliability, leaving a total of 15 centers. Enrollment per center ranged from 4 (2%) to 31 (15%), with a mean of 14 patients/center and a median of 16 patients/center.

Reviewer's Comment: Some information regarding this dropped center was provided in the "Statistical Methods" of this submission, and safety data from the patients were included, but analyzed separately from the remainder of the ITT. It is unclear why these data were considered "unreliable." The PI at the site was not Dr. —

4.3.1.4 Endpoints

4.3.1.4.1 Efficacy Endpoints:

- The primary efficacy variable was change from baseline in AM predose FEV₁ determined at each clinic visit.
- Secondary efficacy variables:
 - Survival in study
 - Physician-rated global assessment (scale of 0-3 where 0=ineffective and 3=very effective)
 - Pre-dose FVC and FEF25-75
 - "Onset of Action" FEV₁ was performed on a subset of patients at 3 selected sites at baseline and at one week and four weeks after initiation of therapy. Measurements were made *pre-dose*, then for a 12-hour period after study drug administration at the following time points: 20 minutes, 40 minutes, 1 hour, 2, 3, 4, 5, 6, 8, 10, and 12 hours *post-dose*.
 - Diary AM and PM PEFR
 - Patient-rated Symptom Scores (scale of 0-3 where 0=ineffective and 3=very effective)
 - Rescue β -agonist use
 - Nighttime awakenings

4.3.1.4.2 Safety Endpoints

- Adverse events
- Clinical laboratory tests
- Basal AM plasma cortisol
- Physical examination
- Vital Signs
- 12-lead ECG

4.3.1.4.3 Pharmacokinetic endpoint

Population-based pharmacokinetics were obtained to assess:

- FP levels (plasma fraction from heparinized blood)
- Terfenadine interactions
- Possible gender effects

4.3.1.5 Design

FLTA2001 was a 12-week, randomized, double-blind, double dummy, placebo-controlled, multi-center clinical trial in adolescents and adult patients with a diagnosis of chronic asthma. After an initial screening visit, subjects entered a 2-week, single blind, double-dummy run-in period with placebo dispensed from two different devices, the Diskus (DK) and the Diskhaler (DH). In addition to becoming familiar with these two

devices, all subjects were switched from their usual β -agonist bronchodilator to Ventolin. Subjects receiving inhaled corticosteroids (ICT) were instructed to continue BDP or TAA at a dose of ≥ 8 puffs/day. Only the subjects receiving inhaled corticosteroids at baseline were allowed to continue to take theophylline, if they were also receiving it at baseline; subjects on bronchodilators alone (BDT) were not. At the end of the two-week run-in period, eligible subjects entered the 12-week double-blind phase of the study. Subjects were stratified at baseline for inhaled corticosteroid or inhaled cromolyn use (ICT) or use of bronchodilator therapy alone (BDT) and assigned randomly to one of 3 treatment groups, placebo, FP 500 mcg BID via DK, or FP 500-mcg BID via DH. Assessments occurred weekly during the first 4 weeks of the 12-week dosing period, then biweekly until the end of the study (Weeks, 0, 1, 2, 3, 4, 6, 8, 10, and 12).

4.3.1.6 Summary of Protocol (includes all amendments)

4.3.1.6.1 Study Population

Inclusion Criteria

- Male or female
 - If female, surgically sterilized, post-menopausal or practicing acceptable contraception
- Age 12 years or older
- Diagnosis of asthma by ATS criteria for at least 6 months
- Best FEV₁ 50-80% predicted (Crapo; or Polgar if age 12-17 years)
- Variability of FEV₁ of 15% or increase in FEV₁ within 30' of 2-4 puffs albuterol of at least 15%

Exclusion Criteria

- Life-threatening asthma
- Use of nonsteroidal immunosuppressive therapy for asthma, such as cyclosporine, methotrexate, or gold
- Cromolyn or nedocromil use in prior 4 weeks
- Other significant concomitant disease or medical condition
- Mentally challenged
- Concomitant psychiatric disorder
- History of alcohol or substance abuse
- Allergy to corticosteroids (CS) or β -agonists
- Clinically significant abnormality on screening laboratory or 12-lead ECG
- Glaucoma or posterior subcapsular cataracts (PSC)
- Clinically significant abnormality on CXR

Disallowed Medications

- At time of enrollment:
 - Any antibiotic in prior 2 weeks

- ☐ Any investigational drug in prior 90 days
- ☐ Oral, intranasal, or parenteral CS in prior month
- ☐ If not already maintained on inhaled CS ($\equiv$ continuous use at stable dose in prior 3 months), inhaled CS use in prior month
- Specifically prohibited during the trial:
 - ☐ Anticholinergics
 - ☐ Anticonvulsants
 - ☐ Antidepressants
 - ☐ Long acting antihistamines or antihistamine/decongestant combinations
 - ☐ Long acting oral decongestants — nasal spray was allowed for a 5-day period as needed)
 - ☐ All antihistamines except terfenadine, if started prior to the study and continued throughout its duration
 - ☐ Phenothiazines
 - ☐ Macrolide antibiotics
 - ☐ Quinolone antibiotics
 - ☐ β -blockers
 - ☐ digitalis
 - ☐ ketoconazole, fluconazole
- All anti-asthma medications except Ventolin MDI (substituted for any other β -agonist), theophylline (if on a stable dose for at least 3 months prior and receiving inhaled CS concurrently), or inhaled CS other than FP.
- Subjects receiving inhaled CS at baseline must have been on a stable dose of either BDP or TAA at 8 or more puffs/day for at least 3 months prior to Visit 1.

4.3.1.6.2 Treatment Arms and Dosing

Subjects were randomized to one of three treatment groups (see table below). Each subject received both a DK and a DH device, one containing active medication while the other contained matching placebo comprised of lactose. In the case of the placebo arm, each device contained matching placebo only. A dose consisted of two blisters from each device administered at 8:00 AM and at 8:00 PM. Devices were exchanged every two weeks until the end of the study.

Treatment	Twice Daily Dosing AM and PM
Diskus FP 500 mcg BID	2 blisters FP 250 mcg via DK plus 2 blisters Placebo via DH
Diskhaler FP 500 mcg BID	2 blisters FP 250 mcg via DH plus 2 blisters Placebo via DK
Placebo BID	2 blisters Placebo via DK plus 2 blisters Placebo via DH

4.3.1.6.3 Treatment Assignment:

During the run-in period, subjects were stratified according to whether or not they were receiving inhaled CS (ICT) prior to study entry or were managed on bronchodilator therapy alone (BDT). After the two-week run-in, eligible subjects were randomly assigned by strata to one of three treatment groups based on chronological order of presentation to the investigator. Subject and treatment numbers were unique and could not be reassigned. No specific attempt to balance enrollment at individual centers was mentioned in the protocol.

4.3.1.6.4 Study Sequence

Screening Period (Visits 1- 2): The screening period was used to confirm eligibility, assess asthma stability, obtain baseline data, assess compliance, and instruct the subjects in the use of all the devices and study procedures to be used during this trial. (See the attached "Figure 1" for a summary schedule of events: Vol.33; p.92).

With the exception of the CXR, all screening and baseline tests indicated on Figure 1 were to be completed at Visit 1 in order to be available at Visit 2. A CXR was optional for adolescents or for patients who could present an acceptable CXR performed in the prior 12 months. Other routine assessments performed at Visit 1 included medical history, physical examination, vital signs, oropharyngeal exam, clinical laboratory tests, pregnancy test if applicable, AM plasma cortisol, spirometry including FEV₁ and other PFTs, and a patient survey of device satisfaction.

Subjects received instructions on daily routine assessments and procedures they were to perform for the subsequent two weeks. Diary PEFR was to be measured twice daily in triplicate using a — Peak Flow Meter, and the highest value recorded in the subject's diary. AM PEFR was to be measured at 8:00 AM before study medication but after other diary assessments. PM PEFR was to be measured at 8:00 PM after study medication had been given.

Reviewer's Comment: The timing of PEFR assessment and diary symptom score recording is important, to prevent a subject's PEFR results from biasing the symptoms score.

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

The screening period of this trial was single-blind. Each subject received a two-week supply of placebo DK and DH devices and were instructed in the proper dosing: two blisters each from DK and DH inhaled in the morning and two blisters each from DK and DH inhaled in the evening.

Subjects could continue to take their baseline asthma medication at this time, except that Ventolin was substituted for their own particular β -agonist. The Ventolin was to be used only to treat symptoms, and not taken on a regular basis (even if that was how it was previously taken). BDT subjects were to have discontinued their theophylline, if they were using it, 72 hours before Visit 1 and to remain off of it for the remainder of the trial. ICT subjects could continue to take their BDP or TAA at 8 or more puffs/day during the single blind period. The ICT subjects could also continue to take their theophylline, if they were receiving it previously, throughout the single-blind period and the study.

Treatment Period (Visits 2 – 10): To be eligible for the study, in addition to meeting the Inclusion/Exclusion criteria above, subjects had to have met the following criteria:

- Asthma stability. "Stable" was defined as having no day in the last 7 in which ≥ 12 puffs of Ventolin MDI were used **and** No more than 4 mornings in the last 7 where the AM PEFR was decreased $>20\%$ from the prior PM PEFR **and** No more than 2 nights in the last 7 with awakenings requiring Ventolin.
- Their clinic spirometry were to have met the following criteria:
 - Best FEV₁ 50-80% predicted (Polgar for ages 12-17 years; Crapo for 18 years and older)
 - Best FEV₁ from Visit 2 within $\pm 15\%$ of Best FEV₁ from Visit 1.
- Adequate compliance was demonstrated:
 - At least 70% of single blind medication had been used
 - Diary card had been completed
 - Anti-asthma medications had been withheld as required

At Visit 2, subjects exchanged their placebo devices for a 2-week supply of the appropriate Diskus (DK) and Diskhaler (DH) devices, as determined by their randomization. Subjects who had been receiving inhaled CS were told to discontinue this medication for the remainder of the study. Subjects taking theophylline who had also been receiving inhaled CS could continue their theophylline, but were told not to change the dose for the duration of the study. Subjects were to dose themselves daily at 8:00 AM and 8:00 PM, DK first followed by DH. All were instructed to withhold their 8:00 AM dose of study medication on the morning of the next clinic visit, and to withhold Ventolin, if possible, for 6 hours prior to testing.

Other assessments that occurred at Visit 2 can be found summarized on the attached Figure 1 (Vol.33; p.92). These included a patient survey, adverse event assessment, oropharyngeal exam, baseline PFTs, collect/dispense diary card, and physician global assessment. In