There were no "clinically significant" elevations in eosinophil counts recorded during this trial (>1.25 x 10^3). For 24 patients, eosinophil counts increased to outside the normal range (>0.735 x 10^3), eight of these cases were in the placebo group. No other associated clinical findings were reported for any of these patients.

There were no subjects with "clinically significant" elevations in alkaline phosphatase (AP). There was a single patient in the FP 200 QD group who had an elevated AP at some point post-randomization. No additional information is available.

HPA Axis Assessment
The HPA axis was assessed at baseline and at study endpoint or early termination by means of unstimulated (basal) AM plasma cortisol levels. Any value <5 mcg/dl was considered abnormal. All samples were collected pre-dose.

Twenty-two (22; 7%) patients had one or more post-randomization plasma cortisol values which were abnormally low, defined as any value <5 mcg/dL. There were 6 in the placebo group, 4 in the FP 100 BID group, 5 in the FP 200 QD group, and 7 in the BDP group. Mean plasma cortisol levels were also determined for each group, and the change in cortisol levels between screening and the final visit was calculated. All groups had a net increase in basal AM cortisol, which was numerically similar among the four groups, 2.2 mcg/dL for placebo, 2.4 mcg/dl for FP 100 BID, 1.4 mcg/dl for the FP 200 QD groups, and 1.8 mcg/dL for the BDP group.

4.3.2.7.4.4 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.

4.3.2.8 Conclusions

4.3.2.8.1 Efficacy Conclusions:

Dry powder FP delivered from the Diskus multi-dose powder inhaler (MDPI) device at a dose of 100 mcg BID has been shown to be efficacious in the treatment of mild-to-moderate asthma in adult and adolescent patients, and to have efficacy similar to that of the comparator drug product BDP 168 mcg BID via MDI. FP 100 mcg BID via Diskus was statistically superior to placebo for the primary endpoint, FEV_1, as well as for four out of five of the secondary endpoints. It was also superior to placebo on the endpoint survival-in-study. These results were obtained using the 50 mcg/blister Diskus device. Although no analogous study has been submitted using the 100 mcg/blister device at a dose of 100 mcg BID, available *in vitro* and

comparative PK studies suggest its performance to be similar to that of the Diskhaler, for which 100 mcg administered as one 100 mcg blister BID has been shown to be efficacious in adults and adolescents.

Subgroup analysis showed no significant difference in efficacy based on the subject's gender. It is not scientifically sound to draw conclusions regarding the impact of ethnicity on efficacy, because the number of non-Caucasian enrollees was very small. All patients recruited for this study were inhaled CS-naïve, therefore no subgroup analysis based on this parameter is necessary. It is expected that this "BDT" study population ought to manifest a greater improvement in lung function and other efficacy endpoints than an "ICT" study population. This ICT group is the focus of a separate study, FLTA2004, which follows in this review.

FP 200 mcg QD via Diskus failed to show statistical superiority over placebo for the primary endpoint, mean change from baseline in pre-dose FEV_1, and for two out of five secondary endpoints. Although non-significant, the p-value for the primary endpoint was close to the cutoff, p=0.54. However, the numerical difference between once and twice daily FP, and once daily FP vs. twice daily BDP at a comparable dosage, was substantial for most endpoints (see first table under 4-6-7-3, above). The difference between once daily FP and twice daily BDP was itself statistically significant for the primary endpoint. The time-effect curve for once daily FP is also cause for concern, that is, an inhaled CS-naïve asthmatic must be treated for a far longer duration to achieve the same improvement in lung function as would be expected if he/she were initially started on a BID dosing schedule. Finally, there is no data regarding long-term efficacy of FP 200 mcg via Diskus administered once daily. From a clinical perspective, it is important to know whether once daily FP 200 mcg leads to more asthma instability over the course of a year, potentially leading to more systemic CS exposure to control these exacerbations.

4.3.2.8.2 Safety Conclusions:

Based upon Study FLTA2003, dry powder FP administered via the Diskus and dosed at 100 mcg BID or 200 mcg QD appeared to be safe when used to treat adults and adolescents with mild-to-moderate asthma for a period of 3 months, and there appeared to be no safety difference between the two dosing schedules. Conversely, it appeared there was no safety advantage of once daily compared to twice daily FP, whether measured by local adverse events such as sore throat or dysphonia or systemic effects, such as on HPA axis endpoints. Both dosing schedules of FP had safety profiles that were similar to the comparator product BDP 168 mcg BID.

By organ system, the most frequently occurring adverse events were in the ENT system, the most common of these being URTI. This was followed by the GI and Neurological systems, the most common AE between those two

being headache. The overall profile was not different from that described in the approved labeling for Flovent Rotadisk Diskhaler.

There were no deaths in the study. There were four serious adverse events, and a total of three withdrawals due to adverse events. There was one first trimester pregnancy, diagnosed during the 10th week of the study, which ended in miscarriage two weeks later.

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 drawn at baseline and at study endpoint. There were no conspicuous differences between placebo and the three active treatment arms, or between once daily and twice daily FP, on this relatively insensitive measure of adrenal function.

4.3.2.9 Labeling Considerations:

Comments relevant to labeling this product for use in adults and adolescents will be deferred until the end of this section of the review, following assessment of all four supportive trials FLTA2003, FLTA2004, FLTA2005 and FLTA2016.

4.3.3 FLTA2004:

"A randomized, double-blind, double-dummy, parallel-group, comparative trial of inhaled fluticasone propionate 100 mcg BID and 200 mcg QD via multi-dose powder inhaler, beclomethasone dipropionate 168 mcg via metered-dose inhaler, and placebo in adolescent and adult patients with mild to moderate asthma."

4.3.3.1 Background Information

See section 4.2.3.1

4.3.3.2 Objectives

The objectives of this study were to compare the efficacy and safety of FP 100 mcg BID and FP 200 mcg QD administered to ICT asthmatics (already stabilized on inhaled CS) via multi-dose powder inhaler (MDPI or Diskus), BDP 168 mcg BID via metered-dose inhaler (MDI) and placebo BID terms of the following:

- Efficacy: Primary efficacy variable: FEV_1; Secondary efficacy variables: survival in study, physician global assessment, patient-determined PEFR, symptom scores, rescue beta-agonist use, and nighttime awakenings requiring beta-agonist

- Safety: Physical examination, clinical laboratory, HPA-axis assessment via AM plasma cortisol, 12-lead ECGs, and adverse events
- Humanistic and Resource Utilization Assesments: Via quality-of-life questionnaires.

4.3.3.3 Setting

Conducted at 26 outpatient sites in the US between 12 April 1995 and 15 March 1996. Enrollment per center ranged from 1 (<1%) to 18 (6%), with a mean of 11 patients/center and a median of 12 patients/center.

4.3.3.4 Endpoints

4.3.3.4.1 Efficacy Endpoints:

- The primary efficacy variable was change from baseline in AM pre-dose FEV_1 determined at each clinic visit.
- Secondary efficacy variables:
  - Survival in study
  - 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 requiring β-agonist

4.3.3.4.2 Humanistic and Resource Utilization Assessment:

- Asthma QOL Questionnaire
- Asthma-specific role-physical
- Resource utilization assessment

4.3.3.4.3 Safety Endpoints

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

4.3.3.5 Design

FLTA2004 was a 12-week, randomized, double-blind, double dummy, placebo-controlled, multi-center clinical trial in adult and adolescent patients with mild to moderate chronic asthma managed on inhaled CS. Subjects were eligible if they had been receiving inhaled CS for at least 3 months prior to Visit 1, and had been maintained on a dose of at least 8 puffs/day of BDP or TAA for at least 2 weeks prior to Visit 1. 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 a conventional metered dose inhaler (MDI). In addition to becoming familiar with these two devices, all subjects were

switched from their usual β-agonist bronchodilator to Ventolin and were instructed to discontinue all other anti-asthma medications except for their present inhaled CS. The subgroup of patients receiving salmeterol and/or theophylline at baseline were also allowed to continue these medications, as long as they maintained a stable dose throughout the trial. At the end of the two week run-in period, eligible subjects entered the 12-week double-blind phase of the study. Subjects discontinued their own inhaled CS and were assigned randomly to one of 4 treatment groups, placebo, FP 100 mcg BID via DK, FP 200 mcg QD via DK, or BDP 168 mcg BID via MDI. 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).

4.3.3.6 Summary of Protocol (includes all amendments)

4.3.3.6.1 Study Population

Inclusion Criteria

- Male or female
  If female, non-pregnant/non-lactating or 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 FEV_1 50-80% predicted (Crapo; or Polgar if age 12-17 years; multiplied by 0.88 if subject was African American)
- Variability of FEV_1 of 15% or increase in FEV_1 within 30' of 2-4 puffs albuterol
- Current use of inhaled CS for at least 3 months and use of BDP or TAA at 8 puffs/day for at least 2 weeks

Exclusion Criteria

- Life-threatening asthma
- Use of nonsteroidal immunosuppressive therapy for asthma, such as cyclosporine, methotrexate, or gold
- Use of orally inhaled cromolyn or nedocromil in prior 4 weeks
- URI or lower respiratory tract infection in prior 2 weeks
- Influenza vaccination in prior 2 weeks
- ~~>~~10 pack-year hx/o cigarettes and/or smoking any tobacco products in prior year
- 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
- AM plasma cortisol < 5 mcg/dL
- Glaucoma or posterior subcapsular cataracts (PSC)

- Clinically significant abnormality on CXR
- Prior participation in MDPI study (Diskhaler participation OK)

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
  - Any inhaled CS except study medication
- Specifically prohibited during the trial:
  - Anticholinergics
  - Anticonvulsants
  - Antidepressants, including polycyclics and MAOI's
  - Long acting antihistamines or antihistamine/decongestant combinations (astemizole must have been continued 6 weeks prior to Visit 1)
  - Long acting oral decongestants (— nasal spray was allowed for a 5-day period as needed)
  - All antihistamines except loratidine, if started prior to the study and continued throughout its duration without a change in regimen
  - Phenothiazines
  - Orally inhaled nedocromil or cromolyn (nasally inhaled, see below)
  - 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 prior to start of study), or salmeterol (if on a stable dose prior to start of study)

4.3.3.6.2 Treatment Arms and Dosing

Subjects were randomized to one of four treatment groups (see table below). Each subject received two DKs, Device A and Device B, and an MDI, Device C. A dose consisted of two blisters from DK Device A and four puffs from MDI Device C administered at 8:00 AM and 2 blisters from DK Device B and four puffs from MDI Device C administered at 8:00 PM. MDI Device C was exchanged every two weeks and DK Devices A and B were exchanged every four weeks until the end of the study.

TREATMENT ARMS AND DOSING STRATEGY

Treatment	Twice Daily Dosing AM and PM
FP 100 mcg BID	2 blisters FP 50 mcg via DK Device A (AM) 2 blisters FP 50 mcg via DK Device B (PM) 4 puffs placebo MDI Device C (AM and PM)
FP 200 mcg QD	2 blisters FP 100 mcg via DK Device A (AM) 2 blisters placebo via DK Device B (PM) 4 puffs placebo MDI Device C (AM and PM)
BDP 168 mcg BID	2 blisters placebo via DK Device A (AM) 2 blisters placebo via DK Device B (PM) 4 puffs BDP 42 mcg MDI Device C (AM and PM)
Placebo	2 blisters lactose via DK Device A (AM) 2 blisters lactose via DK Device B (PM) 4 puffs placebo MDI Device C (AM and PM)

Reviewer's Comment: As discussed during the review of FLTA2003, the 100 mcg BID dose was administered from the 50 mcg/blister device. It would have been of some value had the sponsor chosen to conduct one of these trials utilizing the 100 mcg/blister device for the FP 100 mcg BID arm (although it would have complicated the blind).

4.3.3.6.3 4-7-6-3 Treatment Assignment:

Subjects were given a number at Visit 1. Eligible subjects who completed the screening period and met randomization criteria were assigned to one of four treatment arms in accordance with a code. Eligible subjects were assigned the lowest available treatment number in the chronological order of presentation. Subject and treatment numbers were unique and could not be reassigned. No specific attempt to balance enrollment at individual centers was mentioned in the protocol.

4.3.3.6.4 4-7-6-4 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.109; p.98).

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 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, FEV_1 with reversibility testing, if appropriate, and PEFR.

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.

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 two placebo Diskus's, Device A and Device B, and one MDI, Device C. Subjects were encouraged to take their medication at the same time every day, two blisters from Device A and four puffs from Device C at 8:00 AM and two blisters from Device B and four puffs from Device C at 8:00 PM.

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). Subjects were also instructed to continue to take their baseline inhaled CS, BDP or TAA at 8 puffs/day or greater. Theophylline and salmeterol could both be continued during the baseline period as well as for the duration of the trial, if they had been used previously in the management of the patient's asthma. Doses must remain constant, however, throughout the study, and both medications were to be withheld prior to each clinic visit, salmeterol for at least 12 hours and theophylline for 12-36 hours. Subjects were also to withhold Ventolin for 6 hours and the AM dose of study medication on the morning of the scheduled clinic appointments.

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 "Randomization" criteria:

- Their asthma had been relatively stable. "Stable" was defined as having no day in the last 7 in which ≥12 puffs of Ventolin MDI was 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 met the following criteria:
    - Best FEV_1 50-80% predicted (Polgar for ages 12-17 years; Crapo for 18 years and older)
    - Best FEV_1 from Visit 2 within ±15% of Best FEV_1 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

At Visit 2, subjects exchanged their placebo devices for a 2- or 4-week supply of the appropriate Diskus (DK) and MDI devices, as determined by their randomization code. They were instructed to discontinue their own inhaled CS (TAA or BDP) for the duration of the trial. Again, salmeterol and theophylline could be continued for that subgroup of subjects who had been managed on each previously. Instructions regarding withholding medications prior to clinic visits were repeated (Ventolin-6 hours; salmetrol-12 hours; theophylline-12-36 hours).

Other assessments that occurred at Visit 2 can be found summarized on the attached Figure 1 (Vol.109; p.98). These included adverse event assessment, oropharyngeal exam, baseline PFTs, collect/dispense diary card, and have "Quality-of-Life" questionnaires administered.

Eligible subjects needed to meet additional criteria at each clinic visit to continue in the study. "Stability limits" were therefore defined at Visit 2 for PEFR and FEV_1:

- FEV_1 stability limit: 20% decrease from the best FEV_1 at Visit 2
- PEFR stability limit: 20% decrease from mean diary AM PEFR from the past 7 days

Subjects not meeting the following "continuation criteria" at each clinic visit (Visit 3 and beyond) were discontinued for lack of efficacy:

- No more than 2 days in the last 7 in which ≥12 puffs of Ventolin MDI was used
- No more than 3 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 $FEV_1 \geq$ the FEV_1 stability limit

A subject could also be discontinued for lack of efficacy if they experienced a clinical asthma exacerbation requiring emergency intervention or treatment with a proscribed medication. All data from subjects discontinued for lack of efficacy prior to the time of their discontinuation was included in the analysis, carried forward (LVCF) to endpoint as the last evaluable value. Termination procedures similar to Visit 10 (Week 12) study endpoint procedures were also conducted.

Visits were scheduled weekly for the first 4 weeks, then every other week until study endpoint at 12-weeks. At Visits 3-9 the following procedures were performed:

- Assess subject's compliance including withholding medication (required for PFTs and other procedures to be performed)

- Assess subject's "continuation criteria" (must be met or patient was terminated for lack of efficacy)
- Review previous diary cards and dispense new cards
- Adverse event assessment especially acute asthma exacerbation
- PFTs.
- Collect/dispense study medication (Diskus: Visit 2, Visit 6 or 4 weeks, and Visit 8 or 8 weeks; MDI: Visits 2, 4, 6, 7, 8, and 9: every 2 weeks)
- Oropharyngeal exam (Visits 6, 8, and 10)
- Clinical laboratory tests/plasma cortisol: (Visit 10 or endpoint)

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.), and the special assessments summarized in the bullet points above. 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. The "Quality-of-Life" questionnaires were again administered.

4.3.3.6.5 Efficacy Assessments

The primary efficacy variable was pre-dose FEV_1. FEV_1 was performed in triplicate using approved spirometric equipment according to ATS recommendations. The subject could be sitting or standing during the maneuver, but was required to be consistent throughout the study. If two FEV_1 readings were identical, the once with the highest FVC was recorded.

Secondary efficacy variables included all of the following:

- Survival in the study
- Diary AM and PM PEFR
  (Using a peak flow meter, AM before study medication and PM after study medication. The highest of three values was recorded. The AM/PM PEFR difference was also assessed as a secondary endpoint)
- Subject-rated daily symptom scores on a scale of 0 (none), 1 (mild), 2 (moderate), or 3 (continuous or disabling)
- Number of nighttime awakenings requiring Ventolin
- Rescue Ventolin use
- Humanistic and Resource Utilization Assessment
  These included 3 instruments, the Asthma Quality of Life Questionnaire, the Asthma-specific role-physical, and the Resource utilization assessment. Each of these surveys has been described in great detail previously in this review. The reader is referred to section *4-1-6-5 Efficacy Assessments* for clinical trial FLTA2002.

4.3.3.6.6 Safety Assessments

- Clinical Adverse Events (AE)
- Clinically significant changes in clinical laboratory values
- Clinically significant changes in physical examination, oropharyngeal exam, vital signs, or 12-lead ECG
- HPA-axis effects via basal AM cortisol

4.3.3.6.7 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 made and pair-wise p-values were interpreted only when the overall test among treatment groups was statistically significant.

Power Calculations: Mean and standard deviation of the primary endpoint was estimated based on prior studies conducted by the sponsor. Enrollment was planned to obtain 280 evaluable (70 per arm) subjects to provide >80% power of detecting a difference in FEV_1 of 0.25L between any two treatment groups, using a t-test with a significance level of 0.05. The proposed sample size would also provide >80% power to detect a difference in AE of 16% between any two treatment arms.

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 was a subgroup that included only those subjects who had no major protocol violations during the study, determined post hoc. The decision to exclude a subject from the Efficacy Population was to have been made prior to breaking the blind.

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

Efficacy: The primary efficacy parameter was AM pre-dose FEV_1 in the ITT population. Testing for the primary and for most (continuous) secondary efficacy parameters 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 due to lack of efficacy were evaluated using Kaplan-Meier estimates of survival, and overall and pair-wise treatment comparisons were based on the Log-rank test.

As stated above, continuous parameters such as PEFR measurements were tested with an ANOVA F-test controlling for investigator. Tests were performed on mean values over days within individual weeks. Parameters having discrete values such as symptom scores were analyzed using the non-parametric van Elteren test based on 7-day subject averages.

Reviewer's Comment: As for clinical trial FLTA2003, the mean number of diary entries required in a given week before data could be analyzed was not stated.

Humanistic and Resource Utilization: The primary assessment of health-related QOL was the Asthma Quality of Life Questionnaire (AQLQ; Juniper et al, 1993, *ARRD* 147: 832). A difference of 0.5 between treatment groups was considered clinically significant. Assuming a standard deviation of 1.1 on the AQLQ score, 70 subjects per treatment arm would provide >80% power of detecting a difference of 0.5, using a two-sided t-test with a significance level of 0.05. AQLQ results for an individual subject were included if at least 75% of the items were completed. The data for the Asthma Specific Role Physical (ASRP) was said to be handled in a similar manner, however, a clinically difference was not specified. Resource utilization data was to be used for descriptive purposes only.

Safety: All safety assessments were based on the ITT population. Adverse events were tabulated by organ system, treatment group, severity, and relation to study drug. Laboratory variables, ECG, VS, and physical exam were reported by presence and/or direction of change and whether or not abnormal. AM plasma cortisol results were tabulated by treatment group based on an abnormal value, defined as any basal (un-stimulated) reading <5 mcg/dL. No statistical tests were specified.

4.3.3.7 Results

4.3.3.7.1 Disposition

A total of 358 subjects were screened at 25 sites during the preliminary 2-week baseline period. There were 87 withdrawals, most due to failure to complete the Humanistic and Resource Utilization Questionnaires (38 subjects, 44%), followed by asthma exacerbation per randomization criteria (31 subjects, 36%) and "other," (27 subjects, 23%) including use of a proscribed medication and lack of reproducible lung function. Subjects may have had more than one reason for screening failure.

Reviewer's Comment: It is sobering to be told that nearly half of all screening failures were dropped from further participation because they found the QOL questionnaire too burdensome to fill out. This fact is especially striking when one considers that <3% of screening failures were due to noncompliance with medication (see Table ST-2; Vol.109).

If it is more acceptable to take 12 inhalations of possibly placebo medication every day for 2 weeks than to sit down and fill out a questionnaire on a single occasion, then there are serious problems with the utility of these QOL instruments, and the dropout of individuals reluctant to fill out the questionnaire leads to questions about the generalizability and validity of any data they have been used to gather.

The 271 subjects who completed the screening period were randomized and entered into the double-blind treatment phase of the trial, 69 into placebo, 65 into FP 100 mcg BID, 65 into FP 200 mcg QD, and 72 into BDP 168 BID. One hundred nineteen (44%) of these subjects discontinued prior to study endpoint, 62% of the placebo group, 35% of the FP 100 BID group, 45% of the FP 200 QD group, and 33% of the BDP 168 BID group. The reason(s) for discontinuation are given by the table below, the most common being lack of efficacy by pre-defined criteria (29% overall). Adverse events accounted for only one (<1%) of the total study discontinuations. The category "other" included protocol violations, noncompliance, prohibited medication use, and failure to meet inclusion/exclusion criteria. According to the sponsor, these latter patients should never have been randomized, and were discovered and discontinued late due to "untimely monitoring."

SUBJECT DISPOSITION*

	Placebo	FP100 BID	FP 200 QD	BDP 168 BID	Total
Enrolled	69	65	65	72	271
Completed	26	42	36	48	152 (56%)
Withdrawn	43	23	29	24	119 (44%)
Lack of Efficacy	33	12	21	12	78 (29%)
Adverse Event	1	0	0	0	1 (<1%)
Other	9	11	7	12	39 (14%)

* From Volume 109, Table 2, and p.51.

4.3.3.7.2 Demographics and Other Baseline Characteristics:

Treatment groups were demographically similar. About 60% of enrollees were male. The mean age was 36 years, with a range from 12 to 74 years. Most had never smoked (76%). As a group, they were overwhelmingly Caucasian (91%) with a vanishingly small representation by Black and Latino subjects, comprising 6% and 1% overall, respectively.

Reviewer's Comment: As a group, the subjects enrolled in this study were older than the subjects enrolled in any previously reviewed trial. Of interest, there were more patients age 12-17 years (38 subjects) and about the same number of individuals >64 years (9 subjects) as in the previous clinical trial, FLTA2003 (25 and 9 subjects, respectively). Otherwise, the preponderance of male, Caucasian subjects is typical of the previous studies.

Asthma histories were similar. Over half of the group (57%) reported a duration of asthma in excess of 15 years. Newly diagnosed asthmatics

(duration ≤1 year) comprised 2% of the total enrollees. Eighty percent (80%) reported no ER visits and 97% reported no hospitalizations in the prior 12 months. FEV_1 values were about 67.5% of predicted at baseline and comparable across treatment groups. Not shown in the table below is the S.E. for FEV_1, which was 0.06-0.07.

Concurrent anti-asthma medication included the inhaled β-agonist—albuterol (Ventolin), taken by 100% of subjects, as specified in the protocol. Similarly, all subjects were receiving inhaled CS at baseline, about half each TAA and BDP. Theophylline was taken by 22%, 32%, 18%, and 24% of the placebo, twice daily FP, once daily FP, and BDP groups, respectively. Daily doses and/or serum levels were not provided. Salmeterol was taken by 30%, 25%, 37%, and 33% of the placebo, twice daily FP, once daily FP, and BDP groups, respectively (Vol.109; Table 6). Both salmeterol and theophylline were taken by nearly twice as many subjects per treatment group for this study as for FLTA2003, which recruited only inhaled CS-naïve subjects. Concurrent non-asthma medications and related medical conditions were not appreciably different between the four groups (Tables 7-9; Vol.109), with allergic or atopic disorders heading the list.

BACKGROUND CHARACTERISTICS*

	Placebo	FP 100 BID	FP 200 QD	BDP 168 BID	Total
Number	69	65	65	72	271
Gender:					
Female	42%	52%	40%	50%	125 (46%)
Male	58%	48%	60%	50%	146 (54%)
Ethnicity:					
Black	4	3	4	5	16 (6%)
Latino	1	2	0	0	3 (1%)
Caucasian	61	57	61	67	246 (91%)
Other	3	3	0	0	6 (2%)
Age:					
Mean (yrs)	36	39	36	35	36 yrs
Range	12-69	14-71	12-73	12-74	12-74 yrs
12-17 years	12	4	11	11	25
>64 years	2	2	1	4	9
Smoking history:					
Never smoked	75%	77%	74%	78%	76%
Former smoker	25%	23%	26%	22%	24%
Asthma Duration:					
< 15 years	54%	35%	42%	40%	43%
≥ 15 years	32 (46%)	42 (65%)	38 (58%)	43 (60%)	155 (57%)
ER visits (one yr) :					
0	81%	77%	77%	83%	80%
≥3	3%	2%	3%	4%	3%
FEV_1 at Baseline:					
Liters (SE)	2.35 L	2.26 L	2.38 L	2.41 L	
% Predicted	67.87%	65.93%	66.06%	68.89%	

* From Tables 3, 4, and 5; vol.109

4.3.3.7.3 Efficacy Analysis

4.3.3.7.3.1 Populations and Compliance

The population analyzed included all 271 subjects who received at least one dose of study medication (the ITT population). A subset analysis was performed using the 252 subject "efficacy population," comprised of the ITT subjects minus 19 subjects excluded because of a post hoc determination that they had not met inclusion/exclusion criteria. Data from 9 additional subjects were "partially excluded" because of protocol violations, also found to have occurred post hoc. This review will only consider the ITT population in the efficacy analysis.

Compliance rates were defined as the percent of scheduled doses used from study drug dispensed at each visit. The study drug compliance rate for both devices was determined for Visits 2-10 based on blister count. MDI compliance could not be directly determined other than from diary data. Mean compliance rate exceeded 100% by these criteria for all four groups.

Reviewer's Comment: Compliance rates in excess of 100% by blister counts suggests some problem with the device, such as jamming or skipping, requiring the subject to re-administer the dose.

4.3.3.7.3.2 Primary Efficacy Variable: FEV_1

Mean AM pre-dose FEV_1 was calculated for each treatment group at baseline and compared to mean AM pre-dose FEV_1 for each at end-point. Comparisons were made as mean FEV_1, mean absolute change in FEV_1, percent change in FEV_1, and change in percent predicted FEV_1. An F-test for overall treatment effect was performed prior to any pair-wise statistical comparisons. The last-value-carried-forward principle was used to calculate endpoint FEV_1 for each treatment group, to avoid bias introduced by the dropout of "sicker" patients, especially among the placebo subjects.

The results of this analysis are shown in the table below and in the attached Figure 3 (p.88; Vol.109). There was no significant difference in FEV_1 at baseline across treatment groups (p=0.567; see table above or below). At endpoint, there was a statistically significant treatment effect overall (p=0.002). Pair-wise comparisons between placebo and each of the three treatment groups showed statistical significance for both BID regimens ($p \leq 0.002$), but not for FP once daily, although the p-value was close (p=0.055; see table below). Inspection of the mean change from baseline in FEV_1 showed a substantial numerical difference at endpoint between FP once daily and each of the two BID arms, 0.27L for FP 100 BID and 0.25L for BDP 168 BID, compared to 0.11 L for FP 200 QD and -0.08L for placebo. The pair-wise comparison between once daily and

twice daily FP was not significant, although the p-value was close (p=0.079).

If the change from baseline in FEV_1 is calculated as mean % change or as mean change in percent predicted FEV_1, the results are unchanged. There is a statistically significant overall treatment effect at endpoint, but only the FP 100 BID and BDP 168 BID arms show significance in the pair-wise comparison with placebo, the FP 200 QD group does not (p=0.130 and 0.099, respectively). The pair-wise comparison between once and twice daily FP is again not significant in spite of the wide numerical difference, but it is close (p=0.057 for both).

The same analysis performed using the efficacy population demonstrated a mean change from baseline in FEV_1 which was not different from the ITT population for all groups but placebo, where lung function was found to decline less steeply, -0.02L. When tested for statistical significance, however, there was no overall treatment effect and none of the pair-wise comparisons was significant.

As expected among inhaled CS users, the absolute change for each of the three active treatments was smaller than for inhaled CS-naïve individuals, studied in FLTA2003. Also as expected, "washout" of baseline inhaled CS in the placebo group produced a negative slope for the time-effect line for the placebo group.

MEAN CHANGE FROM BASELINE IN FEV_1 (L): ITT*

	Placebo	FP 100 BID	FP 200 QD	BDP 168 BID	p vs. Placebo FP100	FP200	BDP
N	69	65	65	72			
Baseline FEV_1 (L)	2.35	2.26	2.38	2.41			
Mean change at Endpoint (L)	-0.08	0.27	0.11	0.25	<0.001	0.055	0.002
% change at Endpoint	-3.31%	11.89%	3.83%	10.77%	<0.001	0.130	0.003
Mean change in % Predicted	-2.10%	7.24%	2.59%	7.54%	0.001	0.099	0.002

* Intent-to-Treat Population; from Tables 11-14; vol.109

Figure 3 shows the mean change in FEV_1 over time, and Table 11 (Vol.109; p.109-110) shows the mean numerical value of FEV_1 at each clinic visit. The FP 100 BID group attains a statistically significant improvement at the end of one week of active treatment, a statistical difference which is maintained, with the exception of two intermediate time points, until the end of the trial and at endpoint. Not only does FP 200 QD fail to achieve statistical significance in this primary endpoint, but the numerical improvement in FEV_1 at endpoint for this group is less than the improvement registered by the FP 100 BID group at the end of the first week of treatment.

4.3.3.7.3.3 Secondary Endpoint: Survival in Study

There was a significant overall treatment effect on duration of study participation using the Log-rank test on Kaplan-Meier estimates of survival (p=0.001; see attach. 1 Figure 4; p.80; Vol.109; and Table 21). By the end of the study, 33 subjects (48%) in the placebo group had discontinued for lack of efficacy compared to 12 (18%) in the FP 100 BID group, 21 (32%) in the FP 200 QD group, and 12 (17%) in the BDP group. The overall dropout rate for all reasons was 62% for placebo, 35% for FP 100 BID, 45% for FP QD, and 44% for BDP 168 BID.

Reviewer's Comment: The remarkably high dropout rate of 62% among the subjects randomized to the placebo group, all of whom had been previously maintained on inhaled CS (by inclusion criteria), is indirect testimony to the efficacy of inhaled CS in controlling the symptoms of asthma.

Pair-wise comparisons of survival-in-study between placebo and each of the three treatment arms were statistically significant, p=0.001 for the two BID dosing arms, FP 100 BID and BDP 168 BID, and p=0.045 for the comparison of placebo with the once daily arm, FP 200 QD. The numerical difference between once daily FP and twice daily BDP was also statistically significant (p=0.046), but not between once daily and twice daily FP, although the p-value was close (p=0.075).

4.3.3.7.3.4 Secondary Endpoint: Diary PEFR

Mean AM PEFR, PM PEFR, and AM/PM PEFR differential were averaged weekly from diary card records of PEFR measured by subjects twice daily: before the AM dose of study medication and again after the PM dose. The change from baseline was calculated for each of these three variables at all post-randomization clinic visits and at endpoint (Tables 16-20; Vol.95).

Reviewer's Comment: As with the prior two studies FLTA2001 and FLTA2003, it is unclear how many of seven possible AM PEFR diary entries needed to be recorded during a given week for the data to be considered "evaluable." Likewise for PM PEFR.

Baseline AM PEFRs were similar across treatment groups at baseline, 396-429 L/min (see table, below). There was a statistically significant treatment effect at study endpoint (p<0.001) as well as significant pair-wise treatment comparisons between placebo and each of the two twice daily treatment groups at endpoint (p<0.001 for both FP twice daily and BDP) but not for once daily FP (p=0.153). The improvement from baseline was numerically greater for the two twice daily dosing groups (18 L/min for FP twice daily and 13 L/min for BDP twice daily) than for the FP once daily group, where lung function based on this parameter actually deteriorated (-3 L/min). As would be expected, the changes from baseline to endpoint for this parameter are smaller for this ICT subject population than for the inhaled CS-naïve BDT subject group studied in clinical trial

FLTA2003. The difference between once daily FP and twice daily FP was also significant (p=0.005) as was the difference between once daily FP and twice daily BDP (p=0.011).

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. Net improvement over time was more modest than for AM PEFR, with the final change from baseline to endpoint being 15 L/min for FP 100 BID and 2 L/min for BDP twice daily. This time the FP once daily arm had no change from baseline (ΔPEFR=0), while the placebo group deteriorated (ΔPEFR=-7). The overall treatment effect was significant at endpoint (p=0.006), but again only the twice daily arms were statistically significant in a pair-wise comparisons to placebo (p=0.002 for FP twice daily and p=0.049 for BDP twice daily; see table below).

CHANGE FROM BASELINE TO ENDPOINT IN AM/PM PEFR*

	Placebo	FP 100 BID	FP 200 QD	BDP 168 BID	p vs. placebo FP100	FP200	BDP
N	69	65	65	72			
Baseline AM PEFR (L/min)	408	396	421	429			
ΔAM PEFR	-12	18	-3	13	<0.001	0.153	<0.001
Baseline PM PEFR (L/min)	426	411	438	447			
ΔPM PEFR	-7	15	0	2	0.002	0.127	0.049
Baseline AM/PM PEFR Differential (L/min)	17	15	17	17			
ΔAM/PM PEFR Differential	6	-2	4	-7	0.078	0.980	0.013 **

* Tables 15-20; Vol. 109. ITT population

** The overall treatment effect was not significant (F-test p=0.53)

The AM/PM differentials for each subject were calculated at the various time-points by subtracting each AM PEFR from the previous evening's PM PEFR. A high AM/PM differential is considered indicative of asthma instability. These data are shown in Tables 19 and 20 (Vol.109). Mean change from baseline to endpoint in AM/PM differential is shown in the table above. There was a numerical decrease in AM/PM differential in the two twice daily arms, FP BID and BDP BID. Both placebo and FP once daily showed an increase (i.e. deterioration) in this parameter. There was no significant overall treatment effect.

4.3.3.7.3.5 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 approximately 1.00. At endpoint, there was a statistically significant treatment effect overall (p=0.003; see table below), with an absolute change in symptom scores of approximately 20% reduction for both twice daily arms, no net change for the once daily group, and an approximately 15% worsening in the placebo group. The pair-wise comparison of each treatment arm with placebo was significant at endpoint for all three active treatment groups. The difference between once daily and twice daily FP was also significant (p=0.025).

Nighttime awakenings requiring Ventolin were also infrequent and similar across treatment groups at baseline, ranging from approximately one night in ten to one night in 20 for each group (placebo, 0.08; FP BID, 0.06; FP QD, 0.07; BDP, 0.11). At study endpoint, there was no statistically significant treatment effect overall, nor were any of the pair-wise comparisons with placebo significant (see table below).

Use of rescue Ventolin was to be recorded daily in the diary as number of puffs of the MDI used. At baseline, daily use of Ventolin was similar between treatment groups, approximately 2 ½to 3 puffs per day. At study endpoint, all three active treatment arms had succeeded in reducing their daily Ventolin requirements. This amounted to slightly under ½ puff per day by the two twice daily groups compared to approximately $1/10^{th}$ puff per day by the once daily group. The placebo arm, in contrast, showed a net mean increase in Ventolin use in excess of one puff per day. There was a statistically significant treatment effect for this parameter when measured at study endpoint (p<0.001). The pair-wise comparisons between placebo and each of the three active treatment groups were also significant at study endpoint. There was no statistical difference between any two active treatment arms, however.

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CHANGE FROM BASELINE IN DIARY VARIABLES (ITT)*

	Placebo	FP 100 BID	FP 200 QD	BDP 168 BID
N	69	65	65	72
Asthma symptom score:				
Baseline	0.96	0.96	0.90	0.87
Change	0.14	-0.23	-0.03	-0.17
p-value**		0.001	0.035	0.011
Nighttime Awakenings:				
Baseline	0.08	0.06	0.07	0.11
Change	0.07	-0.01	-0.01	-0.03
p-value**		0.318	0.156	0.315
Ventolin use (puffs/day)				
Baseline	2.62	2.91	2.62	2.55
Change	+1.29	-0.43	-0.11	-0.37
p-value**		<0.001	0.003	<0.001

* From Tables 22-24; Vol.109.
** Compared to placebo

4.3.3.7.3.6 Efficacy by Demographic Subgroups

There was no indication that a difference in the primary endpoint existed by gender, age, or ethnicity, although the number of subjects in the non-Caucasian subgroup was too low to make a scientific determination.

4.3.3.7.4 Humanistic and Resource Utilization Results

For the AQLQ, change from baseline at endpoint for the overall score was -0.16 for placebo, 0.40 for FP 100 BID, 0.09 for FP 200 QD, and 0.32 for BDP 168 BID. Within groups, none of these values reached the "clinically significant" change of 0.5. Relative to placebo, however, the twice-daily FP group exceeded this threshold, the twice-daily BDP group was very close, and the once daily FP arm fell short by at least a two-fold margin. Statistical analysis performed by the sponsor showed a significant overall treatment effect (p=0.004) and statistical significance for each of the three pair-wise comparisons with placebo (see p. 63, Vol.109; also ST-20).

Reviewer's Comment: Although statistically significant, most of these differences with placebo in pair-wise analyses fall short of achieving the pre-specified level for clinical significance. About the best conclusion which can be drawn from these data is that an asthmatic receiving twice daily inhaled CS is better off by the assessment of the AQLQ being switched to Flovent than being placed on placebo.

Unlike the AQLQ, a clinically significant difference for the ASRP instrument was not declared prospectively, and the instrument will therefore not be discussed further. This is also true for the Resource Utilization Assessment, which also had no statistical tests planned.

Reviewer's Comment: For the ASRP, this could give rise to a situation in which a statistically significant difference between treatment groups has been identified, but its clinical meaning is completely obscure.

4.3.3.7.5 Safety Results

4.3.3.7.5.1 Extent of Exposure

A total of 271 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 patients who received FP or BDP BID were exposed for approximately 70 days out of an 84-day trial. In contrast, subjects in the FP QD group received approximately 10 fewer days of exposure, while the placebo patients received approximately 20 fewer days of exposure.

EXTENT OF EXPOSURE TO STUDY MEDICATION*

	Placebo	FP 100 BID	FP 200 QD	BDP 168 BID
Number				
Baseline	69	65	65	72
Completed	26 (38%)	42 (65%)	36 (55%)	48 (67%)
Exposure(days):				
Mean	51.7	70.4	61.5	69.2
Median	55.0	84.0	83.0	84.5

* Table 28 and p.65; Vol.109

4.3.3.7.5.2 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 not be discussed in great detail in this review.

Overall, 54% of the placebo group reported at least one adverse event during this trial, which was somewhat less than in the active-treatment groups, consistent with the overall exposure. Among the active treatment group, 74% of FP 100 BID, 65% of FP 200 QD, and 76% of the BDP BID group reported at least one adverse event. By organ system, the most commonly reported AE's in all treatment groups were within the ENT system (38-51%) followed by Neurologic (15-20%), Lower Respiratory (9-19%), non-site specific (9-18%), and GI (6-22%). In descending order of frequency, the top ENT AE's were URTI (14-33%), throat irritation (8-14%), nasal congestion (4-8%), sinusitis/sinus infection (4-8%), sinusitis (1-9%), and upper respiratory inflammation (3-5%).

Among the AEs which were more common in the FP-treated subjects were nasal congestion/blockage, 6% of the placebo group compared to 8% each of the FP BID and QD groups, and 4% among the BDP group; viral respiratory infection, occurring in 4%, 5%, 6%, and 1% of placebo, FP 100 BID, FP 200 QD, and BDP QD patients, respectively; any GI complaint, reported by 6%, 22%, 17%, and 5% of placebo, FP 100 BID, FP 200 QD, and BDP QD patients, respectively; diarrhea, reported by 0%, 6%, 8%, and 0% of the placebo, FP 100 BID, FP 200 QD, and BDP QD patients, respectively; and

nausea/vomiting , reported by 0%, 6%, 8%, and 0% of the placebo, FP 100 BID, FP 200 QD, and BDP QD patients, respectively.

Events more commonly reported among once daily compared to twice daily inhaled CS users, or vice versa, include URTI, more common among thetwice daily CS users (reported by 14% of FP 200 QD patients compared to 22% of the FP BID group and 33% of the BDP group); throat irritation, more common among the twice daily inhaled CS-users (reported by 8% of FP 200 QD patients compared to 12% of the FP BID group and 14% of the BDP group); headaches, more common among the twice daily CS users (reported by 12% of FP 200 QD patients compared to 15% of the FP BID group and 17% of the BDP group); and Musculoskeletal system events, primarily muscle and joint pains, more common among the once daily users (occurring in 11% of the FP once daily group compared to 5% of the FP 100 BID group and 8% of the BDP group). Local CS effects such as dysphonia or pharyngitis did not appear to differ between the once and twice daily groups.

Events of particular interest include oropharyngeal candidiasis or candidiasis unspecified site, which was reported for 1 placebo subject, 5 FP 100 BID subjects, 1 FP 200 QD subjects, and 4 BDP subjects, respectively. Not unexpectedly, there were no reports of cataracts, glaucoma, or osteopenia in this 12-week trial. No adverse event specifically coded as "HPA axis suppression" was reported. There was one pregnancy, reported for a subject in the BDP group, occurring at day 86 after starting study drug. No further information is available.

When analyzed by demographic subgroups, there were no apparent differences in the overall number or nature of AEs based upon gender, age or ethnicity. The number of non-Caucasian subjects was very small, however, as were the number of enrollees at each end of the age spectrum.

There were no deaths during this study. Five patients experienced serious AEs and one patient was withdrawn due to an AE. One SAE occurred during screening (enlarged submandibular lymph node later found to be a malignant neuroendocrine tumor), and the subject was dropped 15 days after having been randomized to the placebo group. The other four SAEs included one FP 100 BID patient with appendicitis, one FP 100 BID subject with squamous cell CA and intradermal nevus, one FP 200 QD subject with *asthma exacerbation,* and one BDP subject with theophylline overdose. The subject withdrawn due to an AE was the patient described above with the malignant submandibular mass.

4.3.3.7.5.3 Laboratory Data (excluding HPA-axis)

Blood samples for serum chemistry, LFT's, and hematology were obtained at baseline and at study endpoint. No subject was withdrawn for an

abnormal laboratory test, and no laboratory abnormality was coded as an AE.

A few subjects (1-3% per group, maximum) had "clinically significant" laboratory values by pre-specified criteria reported at any time post-randomization (Table 33; Vol.109). These are summarized by test in Table 36 and specific values appear in Table ST-32 (Vol.109). 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. These are summarized in "shift" tables, and appear in Tables 34-35 (Vol.109). Abnormalities of relevance to this review, either because of known side-effects of CS or because of post-marketing surveillance, would include bicarbonate, potassium, glucose, eosinophil count, and alkaline phosphatase. These have been separately noted below.

There were no reported "clinically significant" (>40 meq/L) elevations in bicarbonate. There were no reported "clinically significant" decreases in potassium (<3.0). The shift tables (Tables 34-35; Vol.109) similarly showed noshift to high abnormal values for bicarbonate. There was one shift from normal to low for potassium, occurring in the BDP group.

There was one reported case of "clinically significant" elevation in plasma glucose (>175 mg/dL), occurring in a patient in the FP 200 QD group. This latter patient (— 7704) had a normal glucose at baseline (79 mg/dL; nml range 65-115 mg/dL), and an elevated reading of 182 mg/dL at endpoint. Shift tables showed 10 patients whose glucose went from normal to elevated during the trial, 1 in placebo, 2 in FP 100 BID, 4 in FP 200 QD, and 3 in the BDP group. No further information is available about these patients.

There were three "clinically significant" elevations in eosinophil counts recorded during this trial (>1.25 x 10^3), one each in the three active treatment groups. Although these 3 patients are listed in Table ST-32 — #7711, — #7935, — #7803), the eosinophil counts are not. For 46 patients, eosinophil counts increased to outside the normal range (>0.735 x10^3). Eleven of these cases were in the placebo group and 13, 11, and 11 in the FP 100 BID, the FP 200 QD, and the BDP 168 BID groups, respectively. No other associated clinical findings were reported for any of these patients.

There were no subjects with "clinically significant" elevations in alkaline phosphatase (AP). There was a single patient in the FP 100 BID group who had an elevated AP at some point post-randomization. No additional information is available.

4.3.3.7.5.4 HPA Axis Assessment

The HPA axis was assessed at baseline and at study endpoint or early termination 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 cortisol levels for each treatment group were also calculated (see Tables 31, 32 and ST-31; Vol.109).

Twenty-three (23; 8%) patients had one or more post-randomization plasma cortisol values which were abnormally low, defined as any value <5 mcg/dL. There were 8 in the placebo group, 1 in the FP 100 BID group, 6 in the FP 200 QD group, and 8 in the BDP group. Mean plasma cortisol levels were also determined for each group, and the change in cortisol levels between screening and the final visit was calculated. Except for the BDP group, each group had a net increase in basal AM cortisol, which was numerically greatest for the FP 100 BID subjects. The placebo group had a mean increase of 0.5 mcg/dL compared to 2.5 mcg/dl for FP 100 BID, 1.7 mcg/dl for the FP 200 QD group, and -0.7 mcg/dL for the BDP group.

4.3.3.7.5.5 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.

4.3.3.8 Conclusions

4.3.3.8.1 Efficacy Conclusions:

Dry powder FP delivered from the Diskus multi-dose powder inhaler (MDPI) device at a dose of 100 mcg BID has been shown to be efficacious in the treatment of mild-to-moderate asthma in adult and adolescent patients, and to have efficacy similar to that of the comparator drug product BDP 168 mcg BID via MDI. FP 100 mcg BID via Diskus was statistically superior to placebo for the primary endpoint, FEV_1, as well as for four out of five of the secondary endpoints. It was also superior to placebo on the endpoint survival-in-study. As with the preceding controlled clinical trial FLTA2003, these results were obtained using the 50 mcg/blister Diskus device. Although no analogous study has been submitted using the 100 mcg/blister device at a dose of 100 mcg BID, available *in vitro* and comparative PK studies suggest its performance to be similar to that of the Diskhaler, for which 100 mcg administered as one 100 mcg blister BID has been shown to be efficacious in adults and adolescents.

Subgroup analysis showed no significant difference in efficacy based on the subject's gender. It is not scientifically sound to draw conclusions regarding ethnicity, because the number of non-Caucasian enrollees was very small. All patients recruited for this study used inhaled CS at baseline, therefore no subgroup analysis predicated on this parameter is necessary. As would have been expected, subjects receiving active medication in this "ICT" study population manifested only a modest improvement in lung function compared to inhaled CS-naïve patients, as seen in clinical trial FLTA2003,

comprised solely of a "BDT" study population. Inhaled CS "washout" in the placebo group lead to a net deterioration in lung function among this group, which was substantially responsible for the significant overall "treatment effect" seen for many efficacy endpoints in this study.

FP 200 mcg QD via Diskus failed to show statistical superiority over placebo for the primary endpoint, mean change from baseline in AM pre-dose FEV_1. It also failed on three out of five secondary endpoints. For most of these efficacy endpoints, the numerical difference between once daily and twice daily FP was substantial, on the order of two-fold or greater. For one secondary endpoint, AM PEFR, the difference between once daily and twice daily FP was itself statistically significant, and the once daily FP group actually showed a net worsening compared to baseline on this parameter (-3 L/min for once daily compared to 18 L/min for twice daily). Finally, there was the suggestion that patients previously managed on twice daily inhaled CS may be at risk for asthma instability when switched to once daily (see Safety Conclusions, below). For this reason, the absence of data regarding long-term efficacy of FP 200 mcg via Diskus administered once daily is a serious flaw in this application.

4.3.3.8.2 Safety Conclusions:

Based upon Study FLTA2004, dry powder FP administered via the Diskus and dosed at 100 mcg BID or 200 mcg QD appeared to be safe when used to treat adults and adolescents with mild-to-moderate asthma for a period of 3 months, and there appeared to be no safety difference between the two dosing schedules. Conversely, it appeared that there was no safety advantage of once daily compared to twice daily FP, whether measured by local adverse events such as sore throat or dysphonia or systemic effects, such as on HPA axis endpoints. Both dosing schedules of FP had safety profiles that were similar to the comparator product BDP 168 mcg BID.

By organ system, the most frequently occurring adverse events were in the ENT system, the most common of these being URTI. This was followed by the Neurological and Lower Respiratory systems, the most common AE between those two being headache. The overall profile was not different from that described in the approved labeling for Flovent Rotadisk Diskhaler.

There were no deaths in the study. There was one pregnancy, diagnosed after the final week of the study, which occurred in a subject receiving BDP. There were five serious adverse events and one withdrawal due to an adverse event. The latter is of particular concern because it occurred to a subject enrolled in the once daily FP arm — #8066). This 15 year old male experienced a fall in FEV_1 to 32% of predicted and worsening symptoms 20 days after starting once daily FP. He required hospitalization and parenteral CS and was withdrawn from the study. Although this AE was the only identified serious asthma exacerbation among subjects in the once daily FP

group, by design, this trial was structured to avoid serious deterioration by discontinuing patients whose asthma had begun to destabilize based on objective measurements, even if subjectively they remained asymptomatic. It further suggests that some patients may not tolerate a switch from twice daily to once daily inhaled CS treatment. At stake is not simply lack of efficacy, but a potentially serious safety issue.

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 drawn at baseline and at study endpoint. There were no conspicuous differences between placebo and the three active treatment arms, or between once daily and twice daily FP, on this relatively insensitive measure of adrenal function.

4.3.3.9 Labeling Considerations:

Comments relevant to labeling this product for use in adults and adolescents will be deferred until the end of this section of the review, following assessment of all four supportive trials FLTA2003, FLTA2004, FLTA2005 and FLTA2016.

4.3.4 FLTA2005:

"A randomized, double-blind, double-dummy, parallel-group, comparative trial of inhaled fluticasone propionate multi-dose powder inhaler250 mcg BID, 500 mcg QD, and placebo in adolescent and adult patients with mild to moderate asthma."

4.3.4.1 Background Information

Unlike the two clinical trials submitted to support the once daily indication for FP 200 mcg QD, FLTA2005 combines the inhaled CS-naïve subjects and inhaled CS users into a single trial. It is unlikely this trial will have sufficient power to assess efficacy in each of these subgroups by themselves.

4.3.4.2 Objectives

The objectives of this study were to compare the efficacy and safety of FP 250 mcg BID via multi-dose powder inhaler (MDPI or Diskus), FP 500 mcg QD via Diskus, and placebo in terms of the following:

- Efficacy: The primary efficacy variable wasAM, pre-dose FEV_1. The secondary efficacy variables were: survival in study, patient-determinedAM/PM PEFR, symptom scores, rescue beta-agonist use, and nighttime awakenings requiring beta-agonist
- Humanistic and Resource Utilization Assesments: Via quality-of-life questionnaires.

- Safety: Physical examination, clinical laboratory, HPA-axis assessment, 12-lead ECGs, and adverse events

4.3.4.3 Setting

The study was conducted at 15 outpatient sites in the US between 11 April 1995 and 28 February 1996.

4.3.4.4 Endpoints

4.3.4.4.1 Efficacy Endpoints:

- The primary efficacy variable was change from baseline in AM pre-dose FEV_1 determined at each clinic visit.
- Secondary efficacy variables:
  - Survival in study
  - 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

4.3.4.4.2 Humanistic and Resource Utilization Assessment:

- Asthma QOL Questionnaire of Juniper et al.
- Asthma-specific role-physical
- Resource utilization assessment

4.3.4.4.3 Safety Endpoints

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

4.3.4.5 Design

FLTA2005 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 three different Diskus (DK) devices. In addition to becoming familiar with this device, 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. Subjects receiving theophylline or salmeterol could continue them at their baseline dosage for the duration of the study. 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 250 mcg BID, or FP 500 mcg QD. 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). An open-label extension of 12-months was added via amendment on 5 January 1995. There would be no placebo arm, all subjects would receive either FP 250 mcg BID or FP 500 mcg QD.

4.3.4.6 Summary of Protocol (includes all amendments)

4.3.4.6.1 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 FEV_1 50-80% predicted (Crapo; or Polgar if age 12-17 years)
- Variability in FEV_1 of 15% or increase in FEV_1 of at least 15% within 30' of 2-4 puffs albuterol

Exclusion Criteria

- Life-threatening asthma
- Use of nonsteroidal immunosuppressive therapy for asthma, such as cyclosporine, methotrexate, or gold
- Orally inhaled 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 (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 loratidine, if started prior to the study and continued throughout its duration without a change in regimen
- 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) or salmeterol (if on a stable dose for at least 3 months).
- 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 Visit1.
- Cromolyn nasal solution for allergic rhinitis could be used as needed as long as it had been started prior to Visit 1, and was held for at least 12 hours prior to each visit.

4.3.4.6.2 Treatment Arms and Dosing

Subjects were randomized to one of three treatment groups (see table below). Each subject received three Diskus devices, two for use in the morning and once for evening dosing. A dose consisted of one blister from device A and one blister from device B administered at 8:00 AM and one blister from device C administered at 8:00 PM. Blisters contained 250 mcg FP or matching placebo (lactose). Devices were exchanged at Week 6 and Week 12.

Treatment	Twice Daily Dosing 8:00 AM and 8:00 PM
Diskus FP 250 mcg BID	1 blister FP 250 mcg via DK (Device A) (AM) 1 blister Placebo (Device B) (AM) 1 blister FP 250 mcg via DK (Device C) (PM)
Diskus FP 500 mcg QD	1 blister FP 250 mcg via DK (Device A) (AM) 1 blister FP 250 mcg via DK (Device B) (AM) 1 blister Placebo (Device C) (PM)
Placebo BID	1 blister Placebo (Device A) (AM) 1 blister Placebo (Device B) (AM) 1 blister Placebo (Device C) (PM)

4.3.4.6.3 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.

4.3.4.6.4 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 pertinent to this trial. (See the attached "Figure 1" for a summary schedule of events: Vol.127; p.84).

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 patients who could present an acceptable CXR obtained 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, FEV_1, and a baseline humanistic and resource utilization questionnaire.

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.

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 Diskus devices A, B, and C 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.

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). Subjects managed on inhaled CS could continue to take this medication during the single blind period, but were required to discontinue it the evening before clinic Visit 2. All subjects receiving salmeterol or theophylline at baseline could continue to take it throughout the single-blind period and the remainder of the study, following their same baseline regimen.

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 "randomization 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 havr met the following criteria:
    - Best FEV_1 50-80% predicted (Polgar for ages 12-17 years; Crapo for 18 years and older; African American subjects had predicted FEV_1 multiplied by 0.88)
    - Best FEV_1 from Visit 2 within ±15% of Best FEV_1 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 6-week supply of the appropriate Diskus (A, B, and C) 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, and to start taking study medication daily at 8:00 AM and 8:00 PM. They 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.

Subjects taking theophylline and/or salmeterol could continue taking these medications, but without changing the dosages for the duration of the study. Those receiving theophylline were instructed to withhold this medication for 12-36 hours prior to each clinic visit, and those receiving salmeterol to withhold it for at least 12 hours prior to clinic visits.

Other assessments that occurred at Visit 2 can be found summarized on the attached Figure 1 (Vol.127; p.84). These included an adverse event assessment, oropharyngeal exam, baseline PFTs, collect/dispense diary

card, and collect the Humanistic and Resource Utilization questionnaire.

Eligible subjects needed to meet additional criteria at each clinic visit subsequent to Visit 2 in order to continue in the study. "Stability limits" were therefore defined at Visit 2 for PEFR and FEV_1:

- FEV_1 stability limit: 20% decrease from the best FEV_1 at Visit 2
- PEFR stability limit: 20% decrease from mean diary AM PEFR___ calculated from the 7 days preceding Visit 2.

Subjects not meeting the following "continuation criteria" at each clinic visit (Visit 3 and beyond) were discontinued for lack of efficacy:

- No more than 2 days in the last 7 in which ≥12 puffs of Ventolin MDI were used
- No more than 3 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 $FEV_1 \geq$ the FEV_1 stability limit

Visits were scheduled weekly for the first 4 weeks, then every other week until study endpoint at 12-weeks. At Visits 3-9 the following procedures were performed:

- Assess subject's compliance including withholding medication (required for PFTs and other procedures to be performed)
- Assess subject's "continuation criteria" (must be met or patient was terminated for lack of efficacy)
- Review previous diary cards and dispense new cards
- Adverse event assessment especially acute asthma exacerbation
- Collect/dispense study medication (Visits 7 and 10)
- Oropharyngeal exam (Visits 6, 8, and 10)
- Clinical laboratory tests/plasma cortisol (Visit 10)
- Complete humanistic and resource utilization questionnaire (Visit 10)

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.), and the special assessments summarized in the bullet points above. 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.

An open-label extension of 12-months was added via amendment on 5 January 1995. There would be no placebo arm, all subjects would receive either FP 250 mcg BID or FP 500 mcg QD.

4.3.4.6.5 Efficacy Assessments

The primary efficacy variable was AM pre-dose FEV_1. FEV_1 was performed in triplicate using approved spirometric equipment according to ATS recommendations. The subject could be sitting or standing during the maneuver, but was required to be consistent throughout the study. If two FEV_1 readings were identical, the once with the highest FVC was utilized.

Secondary efficacy variables included all of the following:

- "Survival" in the study
- Diary AM and PM PEFR
  (Using a peak flow-meter, AM before study medication and PM after study medication. The highest of three values was recorded. The AM/PM PEFR difference was also assessed as a secondary endpoint)
- 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
- Reversibility: performed at baseline and endpoint for the BDT subgroup only, in order to compare reversibility before and after the chronic use of inhaled CS.

4.3.4.6.6 Humanistic and Resource Utilization

- Asthma Quality of Life Questionniare (AQLQ): The Juniper et al instrument discussed extensively in earlier segments of this review
- Asthma-Specific Role-Physical (ASRP): Glaxo in-house instrument discussed earlier in this review
- Resource utilization assessment: Glaxo in-house instrument to assess "subject productivity" via days missed from work or school due to asthma symptoms

4.3.4.6.7 Safety Assessments

- Clinical Adverse Events (AE)
- Clinically significant changes in clinical laboratory values
- Clinically significant changes in physical examination, oropharyngeal exam, vital signs, or 12-lead ECG
- HPA-axis effects via basal AM cortisol

4.3.4.6.8 Statistical Methods

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

Power Calculations: Mean and standard deviation of the primary endpoint was estimated based on prior studies conducted by the sponsor. Enrollment was planned to obtain 210 evaluable (70 per arm) subjects to provide >80% power of detecting a difference in FEV_1 of 0.25L between any two treatment groups, using a t-test with a significance level of 0.05. The proposed sample size would also provide >80% power to detect a difference in AEs of 16% between any two treatment arms.

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 was a subgroup that excluded any subject found post hoc to have had a major protocol violation during the study. The decision to exclude a subject from the Efficacy Population was to have been made prior to breaking the blind.

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

Efficacy: The primary efficacy parameter was AM pre-dose FEV_1 in the ITT population. Testing for the primary and for most (continuous) secondary efficacy parameters was first performed on data from all investigators combined, assessing investigator 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 due to lack of efficacy were evaluated using Kaplan-Meier estimates of survival, and overall and pairwise treatment comparisons were based on the Log-rank test.

As stated above, continuous parameters such as PEFR measurements were tested with an ANOVA F-test controlling for investigator. Parameters having discrete values such as symptom scores were analyzed using the non-parametric van Elteren test based on 7-day subject averages.

Tests were performed on mean values over days within individual weeks. Mean values from diary card records required a minimum of 3 days out of 7 to be averaged for that week. The endpoint measurement was an average from the last complete week of diary data collected, defined by a minimum of 7 days

Safety: All safety assessments were based on the ITT population, including the dropped site, which was analyzed separately. Adverse events were tabulated by organ system, treatment group, severity, and relation to study drug. Laboratory variables, ECG, VS, and physical exam were reported by presence and/or direction of change and whether or not abnormal. AM plasma cortisol results were tabulated by treatment group based on an abnormality, defined as any basal (un-stimulated) reading <5 mcg/dL. No statistical tests were specified.

"Quality of life": The change from baseline to endpoint in the AQLQ score was considered primary in this aspect of the analysis, and the ASRP was considered supportive. For the AQLQ, treatment group differences of 0.5 or more were considered clinically significant, consistent with the approach of Juniper et al of using 0.5 as the smallest difference which the subjects perceive as beneficial. No clinically significant difference was defined for the ASRP or for the Resource utilization parameter.

4.3.4.7 Results

4.3.4.7.1 Disposition

A total of 335 subjects were screened at 16 sites and entered into the preliminary 2-week baseline period. There were 82 withdrawals, most due to lack of reproducible lung function (46%), for a total of 253 eligible subjects. Other reasons for ineligibility included failure to meet all inclusion/exclusion criteria (32%), FEV_1 <50% or >80% predicted on Visit 2 (32%), and failure to complete the humanistic resource utilization questionnaire (23%). There was only one reported discontinuation for an AE (asthma exacerbation). Subject distribution by site ranged from 8 (— , 3%) to 23 (— , 9%), with a mean of 17 patients/center and a median of 17 patients/center.

Reviewer's Comment: There could have been >1 reason for study discontinuation for each withdrawn subject. Again, filling out the humanistic/QOL questionnaires may have been a particularly onerous task, since 23% of the subjects preferred to be dropped rather than do it, compared to only 5% who failed to take at least 70% of the doses of their study medication.

The 253 subjects who completed the screening period were randomized and entered into the double-blind treatment phase of the trial, 84 into placebo, 86 into FP 250 mcg BID, and 83 into FP 500 mcg QD. Ninety-five (38%) of these 253 subjects discontinued prior to study endpoint, 63% in the placebo group, 14% in the FP BID group, and 36% in the DH group. The reason(s) for discontinuation are given by the table below, the most common being lack of efficacy by pre-defined criteria (29% overall). Adverse events accounted for only three (1%) of the total study discontinuations. The category "other" included investigator discretion, Failure to return, noncompliance, and prohibited medication.

SUBJECT DISPOSITION*

	Placebo	FP 250 BID	FP 500 QD	Total
Enrolled	84	86	83	253
Completed	31 (37%)	74 (86%)	53 (64%)	158 (62%)
Withdrawn	53 (63%)	12 (14%)	30 (36%)	95 (38%)
Lack of Efficacy	45 (54%)	7 (8%)	21 (25%)	73 (29%)
Adverse Event	0	1 (1%)	2 (2%)	3 (1%)
Other	8 (10%)	2 (2%)	6 (7%)	16 (6%)

* From Volume 33, Table 2, p.99

4.3.4.7.2 Demographics and Other Baseline Characteristics:

Treatment groups were demographically similar. About 56% were male, their mean age was 37 years with a range from 12 to 69 years. As a group, subjects were predominantly Caucasian (94%) with African American and Latino comprising a miniscule 2% and 4% overall, respectively. Most had never smoked (68%).

Asthma histories were also similar. Over half of the members of each group reported duration of asthma that were in excess of 15 years. Newly diagnosed asthmatics (duration <1 year) comprised <1% of the total enrollees. Only 49% of the group used inhaled CS at baseline. Eighty-three percent (83%) reported no ER visits and 95% reported no hospitalizations in the prior 12 months. Mean FEV_1 values were about 67% of predicted at baseline and comparable across treatment groups.

The comparability of orally inhaled corticosteroid (ICT) use at baseline across groups reflects stratification by this variable. Approximately 54% of these subjects used TAA, 35% used BDP, and 19% used flunisolide. Prednisone was used by four subjects each in the placebo and once daily groups and by three subjects in the twice daily group (Table 6; Vol.127; p.97). Concurrent non-asthma medications and related medical conditions were not appreciably different between the three groups (Tables 7-9; Vol.127; p.98-105), with allergic or atopic disorders heading the list.

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BACKGROUND CHARACTERISTICS*

	Placebo	FP 250 BID	FP 500 QD	Total
Number	84	86	83	253
Gender:				
Female	42%	49%	41%	111 (44%)
Male	58%	51%	59%	142 (56%)
Ethnicity: number				
Black	0	3%	1%	4 (2%)
Latino	7%	2%	4%	11 (4%)
Caucasian	92%	81%	95%	237 (94%)
Other	1%	1%	0	1 (<1%)
Mean age (yrs)	37	38	37	37 years
Range	12-66	12-66	13-69	12-69
Smoking history				
Never smoked	69%	72%	64%	173 (68%)
Former smoker	31%	28%	36%	80 (32%)
Inhaled CS use				
Yes (ICT)	50%	49%	49%	125 (49%)
No (BDT)	50%	51%	51%	128 (51%)
ER visits (12 mos.)				
0	87%	78%	83%	209 (83%)
≥3	2%	1%	0	3 (1%)
FEV_1 at Baseline				
Liters	2.45	2.42	2.46	
% Predicted	67.15%	67.75%	65.40%	
SE (L)	(0.06)	(0.07)	(0.08)	

* From Tables 3, 4, and 5; vol.127

4.3.4.7.3 Efficacy Analysis

4.3.4.7.3.1 Populations and Compliance

The population analyzed included all 253 subjects who received at least one dose of study medication (the ITT population). A subset analysis was performed using the 242-subject "efficacy population," comprised of the ITT subjects minus 11 subjects excluded because of a post hoc determination that major protocol violations had occurred. This review will only consider the ITT population in the efficacy analysis.

The study drug compliance rate was assessed using blister counts and diary data. The mean compliance rate was found to be in excess of 93% of doses. Fewer than 10% of subjects had an assessed compliance rate of < 80%.

4.3.4.7.3.2 Primary Efficacy Variable: FEV_1

Mean AM pre-dose FEV_1 was calculated for each treatment group at baseline and compared to mean AM pre-dose FEV_1 for each at end-point. Comparisons were made as mean FEV_1, mean absolute change in FEV_1, percent change in FEV_1, and change in percent predicted FEV_1. An F-test for overall treatment effect was performed prior to any pair-wise statistical comparisons. The last-value-carried-forward principle was used to

calculate endpoint FEV_1 for each treatment group, to avoid bias introduced by the dropout of "sicker" patients, especially among the placebo subjects.

The results of this analysis are shown in the table below and in the attached Figure 3 (p.98; Vol.127). There was no significant difference in FEV_1 at baseline across treatment groups, which was 2.45L for placebo, 2.42L for the FP 250 BID group, and 2.46L for the FP 500 QD. At endpoint, there was a statistically significant improvement in FEV_1 in each FP treatment group, 0.42L for the twice daily group and 0.14L for the once daily group, compared to placebo, -0.15L ($p<0.001$). The significant difference could be demonstrated whether the difference was calculated as "liters," as "change from baseline in % predicted", or as "% change from baseline. The three-fold numerical difference between once and twice daily FP is substantial, however, and the pair-wise comparison between the two FP groups at endpoint was also significant at $p<0.001$, a finding that was also independent of the way the difference in FEV_1 was calculated. The difference between the two FP treatment arms is well-seen on Figure 3 (attached) and in the time vs. effect data displayed in Tables 11, 12, and 14 (Vol. 127).

MEAN CHANGE FROM BASELINE IN FEV_1 (L): ITT*

	Placebo	FP 250 BID	FP 500 QD	Placebo vs. BID†	Placebo vs. QD†	QD vs. BID†
N (††)	84 *(78)*	86 *(81)*	83 *(75)*			
Baseline FEV_1 (Liters) % Predicted (SE in Liters)	2.45 67.15% (0.06)	2.42 67.75% (0.07)	2.46 65.40% (0.08)			
FEV_1: Mean change at Endpoint (L) (††)	-0.15 *(-0.15)*	0.42 *(0.42)*	0.14 *(0.11)*	<0.001 *(<0.001)*	<0.001 *(<0.001)*	<0.001 *<0.001)*
FEV_1: % change at Endpoint	-6.87%	18.47%	6.47%	<0.001	<0.001	<0.001
FEV_1: Mean change in % Predicted	-4.24%	12.05%	4.17%	<0.001	<0.001	<0.001

* Intent-to-Treat Population (From Tables 10-14; vol.127)
† Overall Treatment effect was <0.05 (F-test)
†† Excluding Dr. ——— data

Reviewer's Comment: The once daily FP arm did not achieve sustained improvement in FEV_1 until Visit 9 (Week 10), compared to Week 1 for twice daily. Furthermore, the once daily group did not achieve the same numerical improvement in FEV_1 at study endpoint as seen in the twice daily FP group by the end of Week 1.

Although the numerical improvement in FEV_1 at endpoint for the once daily group achieved statistical significance compared to placebo, the numerical value of 0.14L is scarcely a 5% improvement over baseline, depending upon how the data is

analyzed. It is debatable whether such a change can be called clinically significant. This problem is further compounded by recalculation of the change from baseline, excluding data provided by Dr. — which yields a numerical improvement in FEV_1 of only 0.11L (see entries in bold-italic in table above).

This trial was powered to detect a difference in FEV_1 of 0.25L between any two treatment groups, from which it can be inferred that 0.25L is the minimal change considered to be of clinical importance. Therefore, statistical significance for the twice daily FP group was driven primarily by improvement in FEV_1 at endpoint compared to baseline. In contrast, the statistical significance for the once daily group was driven more by the deterioration of the placebo group (FEV_1= -0.15) than by improvement in the once daily treatment group, probably reflecting "washout" of inhaled CS in the placebo group. This difference in attribution makes analysis of the ICT vs. BDT subgroups crucial.

4.3.4.7.3.3 Secondary Endpoint: Survival in Study

As described earlier under "Disposition," all-cause withdrawals from this study totaled 95 subjects (38%), including 53 (63%) in the placebo group, 12 (14%) in the FP twice daily group, and 30 (36%) in the FP once daily group. Survival analysis was performed only on the subgroup withdrawn for lack of efficacy, however.

There was a significant overall treatment effect on duration of study participation based on continued efficacy using the Log-rank test on Kaplan-Meier estimates of survival ($p<0.001$). By the end of the study, 45 subjects (54%) in the placebo group had discontinued for lack of efficacy compared to 7 (8%) in the FP 250 BID group and 21 (25%) in the FP 500 QD group. Pair-wise comparisons of survival-in-study between placebo and each of the two FP arms were statistically significant ($p<0.001$ for each comparison). There was also a significant difference in survival between the two FP arms, $p=0.001$, which is well-illustrated in Figure 4 by the distinct separation of lines beginning after the first week (see attached; p.87; Vol.127).

4.3.4.7.3.4 Secondary Endpoint: Diary PEFR

Mean AM and PM PEFR were determined weekly based on data recorded on subjects' diary cards. At least 3 time-points out of 7 were required for a subject's data to be included. Week-by-week changes and change from baseline to endpoint in AM or PM PEFR are shown in Tables 15-18 (Vol. 127).

Baseline AM PEFRs were similar across treatment groups at baseline, 400-416 L/min (see table, below). There was a statistically significant treatment effect for FP compared to placebo at study endpoint ($p<0.001$), and pair-wise treatment comparisons between placebo and each of the two