CLINICAL REVIEW

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Reviewer Name	Banu A. Karimi-Shah, MD
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Established Name	Mometasone Furoate
(Proposed) Trade Name	Asmanex® Twisthaler®
Therapeutic Class	Inhaled corticosteroid
Applicant	Schering Plough Corporation
Priority Designation	S
Formulation	110 mcg multiple-dose dry powder inhaler
Dosing Regimen	110 mcg QD PM
Indication	Asthma
Intended Population	Children 4-11 years of age

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The clinical recommendation for this application is **Approval**.

Schering-Plough Corporation submitted an efficacy supplement to extend the indication of mometasone furoate (MF) dry powder inhaler (DPI) to asthmatic children 4 to 11 years of age. The dose proposed for registration in this pediatric population was 110 mcg QD PM. MF DPI is already approved for the maintenance treatment of asthmatic patients 12 years of age and older, at total daily doses from 220 to 880 mcg. The efficacy of MF in this pediatric population is supported by three 12-week pivotal clinical trials; the safety of MF is also supported by the three pivotal trials, as well as a dedicated hypothalamic-pituitary-adrenal (HPA) axis study, and two one-year safety studies, one of which looked primarily at the effects of MF on growth velocity in children. The Applicant has adequately demonstrated the efficacy and safety of mometasone furoate dry powder inhaler in asthmatic children 4 to 11 years of age. In addition to the proposed dose of 110 mcg QD PM, the efficacy and safety of MF 110 mcg BID are also supported by this clinical development program.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

The clinical review does not identify concerns for which post-marketing risk management activities are recommended.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are sought for mometasone furoate dry powder inhaler 110 mcg QD PM.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Schering-Plough Corporation's product ASMANEX®TWISTHALER® (mometasone furoate) is currently indicated for the maintenance treatment of asthma in adults and adolescents 12 years of age and older. It is currently available as a multiple-dose, dry-powder inhaler, which dispenses 200 mcg of mometasone furoate per actuation (220 mcg of mometasone furoate ex-valve per actuation). The Applicant submitted this supplemental application to extend the

indication for Asmanex to include the treatment of asthma in children ages 4 to 11 years, using a reduced-strength MF DPI of 100 mcg per actuation (110 mcg of mometasone furoate ex-valve per actuation).

In support of this efficacy supplement, the Applicant submitted the clinical study reports of eight clinical studies, three of which were considered pivotal, and five supportive. The Applicant proposed the dosing regimen of 100 mcg QD PM for the maintenance treatment of asthma in patients 4 to 11 years of age. Based on the review of the pivotal studies, the efficacy and safety of MF 100 mcg QD PM is supported. Although 100 mcg QD PM was the only dose proposed for registration, review of other submitted dosing regimens revealed that the efficacy and safety of MF 100 mcg BID is also supported as summarized below.

1.3.2 Efficacy

Three pivotal clinical trials demonstrated the efficacy of MF in children with asthma 4 to l1 years of age. These trials were multicenter, randomized, double-blind, placebo-controlled, parallel group studies, that were 12 weeks in duration. Patients were randomized to various MF treatment regimens or placebo. There were eight scheduled visits: Screening, Baseline, Day 4, Weeks 1, 2, 4, 8, and 12. Efficacy was assessed via pulmonary function testing at each visit. The primary endpoint was the mean change in percent-predicted FEV1 from Baseline to Endpoint. Additionally, subjects recorded AM and PM peak expiratory flow rates (PEFR), asthma symptom scores, rescue medication use, and number of nocturnal awakenings in their patient diaries. Response to therapy, time to first asthma worsening, and incidence of clinical asthma exacerbations were also assessed as secondary endpoints.

In aggregate, the clinical trials evaluated four dosing regimens of MF: 100 mcg QD AM, 100 mcg QD PM, 100 mcg BID, and 200 mcg QD AM. The efficacy of MF 100 mcg QD PM was supported based on a statistically significant difference in the primary endpoint when compared with placebo in Study P01431.

Studies P01431 and C97-380 demonstrated that the dosing regimen of 100 mcg BID was also statistically superior to placebo based on the primary endpoint. Although the twice daily regimen was not statistically different when compared directly to the once daily regimen in Study P01431, there was a trend towards numerical benefit with the higher dose. Additionally, subgroup analysis of more severe asthma patients (FEV1 < 80%) revealed that there is a numerical trend towards benefit with twice daily dosing in this specific patient population.

Key secondary endpoints included the change from Baseline to Endpoint in AM/PM PEFR and use of rescue medication, which were captured by patients in daily diaries in each of the pivotal studies. Change in AM and PM PEFR from Baseline to Endpoint in the 100 mcg QD PM and 100 mcg BID treatment arms was statistically superior to placebo, however there were no significant differences between treatment groups. Rescue medication use was also significantly decreased in the 100 mcg QD PM and 100 mcg BID treatment arms versus placebo, although the numerical differences were small. Response to therapy and time to worsening of asthma in the 100 mcg QD PM and 100 mcg BID groups were statistically superior to placebo, but did not

differ significantly between treatment groups. In conclusion, these secondary efficacy outcomes were supportive of the efficacy of MF DPI 100 mcg QD PM and MF 100 mcg BID.

In summary, the results of P01431, though unreplicated, when considered in combination with the efficacy findings of MF in adults, provide adequate support for MF 100 mcg QD PM in the maintenance treatment of asthma in this pediatric population. Though there was no statistical difference between the 100 mcg QD PM and 100 mcg BID treatment groups, the 100 mcg BID arm trended towards being numerically superior in two studies. Further, subgroup analysis of more severe asthma patients (FEV1 < 80%) revealed that there was a numerical trend towards benefit with twice daily dosing in this specific patient population. Demonstration of the efficacy of MF 100 mcg BID in two clinical trials, numerical trend towards added benefit with the higher dose, the results of subgroup analysis in more severe asthma patients, and extrapolation from the current labeling which allows for increasing (doubling) the daily dose in adults and adolescents, taken together provide support for 100 mcg QD PM as the recommended starting dose, and 100 mcg BID as the highest daily recommended dose, in asthmatic patients 4 to 11 years of age

1.3.3 Safety

The safety of mometasone furoate in asthmatic children 4 to 11 years of age is supported by six clinical trials, the safety findings of MF in adults, and post-marketing safety data. In addition to safety data from the three pivotal trials, the applicant also assessed the effects of MF on HPA-axis function and growth velocity in children in two separate studies. A one-year long-term safety study was also conducted. A summary of the adverse events (AEs), HPA-axis effects, and growth effects is presented below.

This safety summary will focus on the two MF treatments of interest, 100 mcg QD PM and 100 mcg BID. However, since some of the studies utilized other doses of MF, those findings will be discussed when pertinent. There were no deaths throughout the course of this pediatric development program. There were few serious adverse events (SAEs) in the entire program; the SAEs did not suggest a new safety signal. The rates of overall AEs varied between treatment groups in the clinical trials. However, in general, overall AEs tended to be comparable between MF groups and placebo. The majority of AEs were mild in intensity. Withdrawals due to AEs tended to be higher in the placebo treatment groups. The incidence of clinical asthma exacerbations (CAEs) was low and generally less in the MF 100 mcg BID and 100 mcg QD PM treatment groups compared to placebo. Common AEs (≥2%) noted more frequently in the active treatment groups included fever, allergy, abdominal pain, diarrhea, nausea, vomiting, sinusitis, tooth abscess, upper respiratory tract infection, urinary tract infection, musculoskeletal pain, bruise, and epistaxis. These common AEs are consistent with clinical trials in pediatric patients with asthma and do not suggest a new safety signal. In addition, the vital sign, laboratory, and ECG data also do not suggest a new safety signal.

In the 52-week, open-label, long-term safety study (C97-385), treatment arms were MF 100 mcg BID, MF 200 mcg QD AM, and an active comparator budesonide dipropionate (BDP) 168 mcg BID. As expected with a study of longer duration, the overall reporting of adverse events increased in all groups. The most commonly reported AEs (> 20%) were consistent with findings

in the shorter pivotal studies and included allergy, fever, headache, viral infection, nasal congestion, pharyngitis, rhinitis, sinusitis, and upper respiratory tract infection. Of note, serious adverse events (SAEs) were reported in six patients – only 1 of which was in the 100 mcg BID group and was unlikely to be related to treatment. Three SAES were reported in the MF 200 mcg QD AM group, all three of which were asthma aggravated. Further, CAEs were reported in a higher percentage (35%) of patients in the MF 200 mcg QD AM group compared to the 100 mcg BID group (23%). The results of the long-term safety study support the safety of the MF 100 mcg BID treatment group.

The effect of MF on HPA axis function was assessed in a 29-day randomized, double-blind, placebo-controlled, parallel group study involving 50 asthmatic children 6 to 11 years of age. HPA axis function was primarily evaluated by 12-hour plasma cortisol $AUC_{0\text{-}12h}$ and 24-hour urinary free cortisol levels. Following four weeks of treatment, the placebo-corrected differences in plasma cortisol $AUC_{0\text{-}12h}$ change from baseline for the 100 mcg BID, 200 mcg BID and 400 mcg BID treatment groups were 3.4 mcg.hr/dL (95% CI: -14.0, 20.7), -16.0 mcg.hr/dL (95% CI: -33.9, 1.9), and -17.9 mcg.hr/dL (95% CI: -35.8, 0.0), respectively. For the 24-hour urinary free cortisol excretion, the placebo corrected differences in change from baseline were 3.1 mcg/day (95% CI: -3.3, 9.6), 3.3 mcg/day (95% CI: -3.0, 9.7), and -2.0 mcg/day (95% CI: -8.6, 4.6), respectively. Although the results of the plasma cortisol measurements suggest dose-related suppression of HPA axis function, the changes were not statistically different from placebo. The results of the HPA axis study will be included in the product label.

The effect of MF on growth velocity was evaluated in a 52-week, placebo-controlled, parallel-group study conducted in 187 children 4 to 9 years of age, with mild persistent asthma. Treatment groups included MF 100 mcg BID, MF 200 mcg QD AM, 100 mcg QD AM, and placebo. For each patient, an average growth rate was defined as the height change from baseline divided by the time period for the change. The mean growth rates, expressed as least-squares mean in cm/year, for MF 100 mcg BID, MF 200 mcg QD AM, MF 100 mcg QD AM, and placebo were 5.25, 5.90, 6.06, and 6.26, respectively. The placebo-corrected differences and the corresponding two-sided 95% CI of the mean growth rates for MF 100 mcg BID, MF 200 mcg QD AM, and MF 100 mcg QD AM were -1.01 (-2.20, 0.19), -0.36 (-1.50, 0.78), and -0.19 (-1.34, 0.95), respectively. MF 100 mcg BID demonstrated the greatest numerical effect in terms of growth suppression, but was not statistically different from placebo or from the other dosing regimens. The findings in the growth study will be included in the product label.

Since market introduction in January 2003, subject exposure to MF DPI is estimated to be about 31 million subject treatment days as of the end of May 2006 in over 20 countries.
During the period of March 30, 2005 to December 23, 2006, 427 cases were reported of which 38 were serious cases. Most of the reported AEs were classified to the body system/organ classes of general disorders and respiratory disorders. The types of individual AEs reported were consistent with those observed during clinical studies. A total of 38 serious cases have been reported, which include hypersensitivity and throat tightness. During the same period, in pediatric patients 4 to 11 years of age, there were 14 cases of AEs of which 2 cases were serious. The types of AEs were similar to that observed in adults. Overall there is no information in the post-marketing database that identifies any new safety issues.

In general, the adverse event profile of MF was consistent with known effects of inhaled corticosteroids, the safety findings of MF in adults, post-marketing experience with MF, as well as with what would be expected in an asthmatic population. HPA axis suppression and decreased growth velocity were suggested numerically by dose-related trends in the data, but no statistically significant differences were present for any of the active treatment groups versus placebo. It is of note that MF 100 mcg QD PM was not evaluated in the 52-week safety study, or for its effect on the HPA axis or growth velocity, although MF 100 mcg BID and higher doses were studied. In summary, the clinical trial results support the safety of mometasone furoate in asthmatic children 4 to 11 years of age. Review of the safety data indicates that the safety experience was consistent with current labeling and no new safety signals have been identified in this review.

1.3.4 Dosing Regimen and Administration

A dose of 100 mcg QD PM is recommended in children 4 to 11 years of age for the maintenance treatment of asthma. The dose may be increased to 100 mcg BID if patients are not adequately responding to the lower dose. The application does not alter the currently approved dosing regimens for patients 12 years of age and older with varying degrees of asthma.

1.3.5 Drug-Drug Interactions

The Applicant did not conduct any new investigations specifically evaluating drug-drug interactions as part of this supplemental NDA.

1.3.6 Special Populations

The Applicant did not conduct any new investigations specifically targeted towards any special populations as part of this supplemental NDA.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Mometasone furoate, the active component of Asmanex Twisthaler, is an inhaled corticosteroid with the chemical name 9,21 –dichloro-11(Beta), 17-dihydroxy-16 (alpha0-methylpregna-1,4-diene-3,20-dione 17-(2-furoate). Mometasone furoate is a white powder with an empirical formula of $C_{27}H_{30}Cl_2O_6$, and a molecular weight of 521,44 Daltons. It is approved for marketing in more than 50 countries, including the US and most EU member states, for the maintenance treatment of asthma in patients 12 years of age and older at total daily doses of 200 to 800 mcg.

2.2 Currently Available Treatment for Indications

Currently, the major pharmaceutical therapies available for the maintenance treatment of asthma in children 4 to 11 years of age include corticosteroids, beta-agonists, mast-cell stabilizers (cromolyn sodium), leukotriene modifiers, and theophylline.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, mometasone furoate, is currently approved and marketed in the United States and over 50 countries as the Asmanex Twisthaler, 220 mcg, dry powder inhaler. MF is also marketed in an aqueous nasal formulation for the treatment and prophylaxis of nasal symptoms of seasonal and perennial allergic rhinitis in adults and children, and for the treatment of nasal polyps, under the Nasonex® trade name. MF is also available in cream, ointment, and lotion formulations for dermatologic use (Elocon®, Elocom®, and Elomet®).

2.5 Pre-submission Regulatory Activity

Asmanex Twisthaler was approved in the US under NDA 21-067 in March 2005, with US market introduction in August 2005. The NDA 21-067 Approval Letter of March 30, 2005, stated that submission of data for the maintenance treatment of asthma in patients 4 to 11 years of age was a required post-marketing study commitment to be completed by April 1, 2007. This submission is in accordance with that commitment. Pre-sNDA discussions were held with the Division in 2004 regarding future post-approval submission of pediatric data. Protocols for pediatric clinical efficacy and safety studies included in this submission were reviewed by the Division prior to study conduct, and comments were incorporated into the final study designs. Study protocols C97-300, C97-380, C97-384, and C97-385 were submitted to IND 46,216 on March 27, 1998 (Serial No. 061), with FDA comments provided in a letter dated July 12, 1998. Written responses to comments and revised protocols were submitted to IND 46,216 on December 18, 1998 (Serial No. 090). The Division provided comments on protocol P01431 in a letter dated March 15, 2001, and responses were contained in the submission of April 13, 2001 (Serial No. 141).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

This pediatric efficacy supplement proposes a new, reduced dosage strength of Asmanex Twisthaler 110 mcg. The drug substance, mometasone furoate, is the same drug substance used in the marketed drug product Asmanex Twisthaler 220 mcg. Anhydrous lactose is the only excipient in the new dosage strength, and is identical to that used in the currently marketed 220 mcg Twisthaler.

Asmanex Twisthaler 110 mcg, like the 220 mcg dosage strength, is a cap-activated, inhalation-driven, multi-dose device that contains a reservoir filled with free-flowing powder agglomerates and a metering mechanism. Two presentations of Asmanex Twisthaler 110 mcg are proposed for commercialization; a 7-dose count unit and a 30-dose count unit. The manufacturing process (Kenilworth, NJ) and the packaging configuration are identical to the 220 mcg device except for a lower fill weight and smaller dosing hole designed to meter the agglomerate formulation for the reduced dosage-strength Asmanex Twisthaler 110 mcg. The nominal dose is 110 mcg MF (ex-valve) per actuation and 100 mcg MF is delivered to the patient per actuation.

The CMC review team is recommending an **Approval** action for this efficacy supplement. For a more complete analysis of CMC issues, see the CMC review of NDA 21-067/ S-003 by Dr. Stuart E. Zimmerman.

3.2 Animal Pharmacology/Toxicology

Schering submitted complete pre-clinical general toxicology studies with the original NDA submission. Studies addressing the reproductive toxicity, genotoxicity, and carcinogenicity of MF were submitted to and reviewed under the NDA for MF nasal spray (Nasonex®, NDA 20-762). The current product label includes the information form these non-clinical studies.

No new animal pharmacology/toxicology studies were performed for this efficacy application. The rat to human exposure ratios in children required revision for labeling purposes. Pending acceptance of this labeling revision by the Applicant, the Pharmacology/Toxicology review team is recommending an **Approval** action for this pediatric efficacy supplement. Refer to the Pharmacology/Toxicology review of NDA 21-067/S-003 by Dr. Virgil Whitehurst for further details.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The studies conducted by the Applicant and included in this application were the primary source of clinical data for this review. The application does not rely on reports in the medical literature or other sources of data. Additional clinical information that could not be located in the NDA, or data clarifications, were obtained from the Applicant in response to Information Requests made during the review process. In all cases, the Applicant provided the requested information in usable format and the information was incorporated into the review.

4.2 Tables of Clinical Studies

Table 1 Summary of Clinical Phase 3 Studies in sNDA-21-067

Study #	Study Type	Design	Treatment Groups	Population[a]	Duration	eCTD
Pivotal Clinical Trials						
C/I97-300	Efficacy/Safety	R, DB, PC, MC, //	MF DPI 100 mcg QAM MF DPI 200 mcg QAM Placebo	Asthma for ≥ 6 months ICS dependent, FEV1 ≥ 60% and ≤ 90% predicted **N = 290 (197)**	3 months	5.3.5.1
C97-380	Efficacy/Safety	R, DB, PC, MC, //	MF DPI 100 mcg BID MF DPI 100 mcg QAM MF DPI 200 mcg QAM Placebo	Asthma for ≥ 6 months ICS dependent, FEV1 ≥ 60% and ≤ 90% predicted **N = 349 (236)**	3 months	5.3.5.1
P01431	Efficacy/Safety	R, DB, PC, MC, //	MF DPI 100 mcg QPM MF DPI 100 mcg BID Placebo	Asthma for ≥ 6 months ICS dependent, FEV1 ≥ 60% and ≤ 85% predicted **N = 296 (197)**	3 months	5.3.5.1

Study #	Study Type	Design	Treatment Groups	Population[a]	Duration	eCTD
Supportive Clinical Trials						
C/96-361	Short-term safety/ HPA study	R, DB, PC, SC, //	MF DPI 100 mcg BID MF DPI 200 mcg BID MF DPI 400 mcg BID Placebo	Asthma for ≥ 6 months Age (yrs): 6-11 **N = 50 (38)**	29 days	5.3.5.1
	Growth Velocity	R, DB, PC, MC, // (ICS naïve)	MF DPI 100 mcg BID MF DPI 100 mcg QAM MF DPI 200 mcg QD Placebo	4 to 9 years old, asthma for ≥ 6 months, ≤ Tanner Stage 1 Age (yrs): 4-9 **N = 187 (142)**	52 weeks	5.3.5.1
C97-385	Long-term safety of 2 doses of MF DPI (100 mcg BID and 200 mcg QAM)	R,OL, AC, MC (ICS dependent)	MF DPI 100 mcg BID MF DPI 200 mcg QAM BDP 168 mcg BID	Moderately severe, ICS dependent, asthma for ≥ 6 months, FEV1 ≥ 60% predicted Age (yrs): 4-11 **N= 233 (152)**	52 weeks	5.3.5.1

R = randomized, DB = double blind, EB = evaluator blind, OL = open label, PC = placebo controlled, AC = active controlled, MC = multicenter, SC = single center, // = parallel group, CO = crossover
a. Numbers in parentheses are the numbers of subjects treated with MF.

4.3 Review Strategy

Six of the eight studies presented in Table 1 were reviewed, but emphasis on the studies varied. The [redacted] were not reviewed as the Applicant had provided a one-year growth study which was considered to be a more clinically relevant and meaningful way to evaluate the effect of mometasone furoate on growth velocity in children.

Of the three efficacy studies, the emphasis was placed on study P01431 and C97-380, which included the dosing regimens of interest. Study C97-300 was used to support the results of P01431.

The effect of MF on growth velocity was the primary variable reviewed in Study C97-384. The primary source of the effects of MF on HPA axis function was study C96-361, although HPA axis assessments were collected in other studies. Information about adverse events was reviewed in all the studies, with emphasis on those studies (P01431, C97-380, C97-385) that included the MF 100 QD PM and MF 100 mcg BID dosing regimens.

4.4 Data Quality and Integrity

Review of the data from the pivotal studies by the Biometrics reviewer (Dr. Feng Zhou) did not show any evidence of treatment-by-site interaction. DPAP did not request audits by the Division of Scientific Investigation (DSI). DSI audits were considered to be unnecessary because:

- this submission is an efficacy supplement of a drug with an established safety and efficacy profile in adults.
- no treatment-by-site interaction was detected on statistical analysis.
- each site enrolled relatively small numbers of patients, with no specific site showing a positive response that was driving the outcome of the trial.

4.5 Compliance with Good Clinical Practices

The Applicant stated that they did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with the application [*Module 1.3.3]*. Clinical studies were conducted in compliance with recognized Good Clinical Practices.

4.6 Financial Disclosures

The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this NDA application. The Applicant certifies that it did not enter into financial arrangements with any investigator whereby the value of compensation could be affected by the outcome of the study (Category 1), that no investigator received significant payments (Category 2), that none of the investigators disclosed a proprietary interest in the product (Category 3), or possessed a significant

equity interest in the Applicant (Category 4) as defined in 21 CFR 54 with the following exceptions. Two investigators were noted to have significant investments with the Applicant of greater than $50,000 : [redacted]. An assessment of each of the above investigators degree of participation in the clinical program demonstrated that their enrollment of subjects was not sufficient to alter the outcome of any trial or the program in general. Based on this information, as well as the multicenter nature and number of the clinical trials in the program, it is unlikely that financial interests could have influenced or biased the results of these studies.

5 CLINICAL PHARMACOLOGY

As mometasone furoate dry-powder inhaler is an approved product and its pharmacokinetics and pharmacodynamics are well characterized, no further clinical pharmacology information was provided, or warranted, for this application. Refer to the discussion of the HPA axis study as this is really a pharmacodynamic study.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

This pediatric efficacy supplement is submitted to extend the indication of mometasone furoate (MF) dry powder inhaler (DPI) to asthmatic children 4 to 11 years of age.

6.1.1 Methods

Each of the three 12-week pivotal efficacy studies evaluated the primary efficacy endpoint. This reviewer will emphasize the results of studies P01431 and C97-380, as these trials include the dosing regimens of interest, MF 100 mcg QD PM and MF 100 mcg BID.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint in all three studies was the change from Baseline to Endpoint in percent-predicted FEV1, an established endpoint for clinical studies in patients with asthma. Secondary efficacy endpoints included:

- Change from Baseline to Endpoint in FEV1, FVC, FEF_{25-75}
- Change from Baseline to Endpoint in AM and PM PEFR
- Change from Baseline to Endpoint in Asthma Symptom Scores
- Change from Baseline to Endpoint in Response to Therapy
- Change from Baseline to Endpoint in Rescue Medication Use
- Change from Baseline to Endpoint in Number of Nocturnal Awakenings
- Clinical Asthma Exacerbations: at any time point during the study
- Time to Worsening of Asthma

6.1.3 Study Design

The three pivotal trials had the same general design. All were phase III, multi-center, double-blind, placebo-controlled, parallel group trials in children 4 to 11 years of age, with a diagnosis of asthma for at least 6 months, using specified doses of inhaled corticosteroids for 30-60 days prior to screening. The duration of the treatment period in all three studies was 12 weeks.

Study P01431 began with a run-in period during which subjects remained on their prescribed inhaled corticosteroids, followed by a 12-week double-blind treatment phase. Subjects who met eligibility criteria were randomized at Baseline to one of three parallel treatment arms: MF DPI 100 mcg QD PM, 100 mcg BID, or placebo. There were eight scheduled visits: Screening, Baseline, Day 4, Weeks 1, 2, 4, 8, and 12. Efficacy was assessed via pulmonary function testing at each visit.

Study C97-380 began with a run-in period, followed by a 2-week open label treatment period where all subjects were treated with budesonide dipropionate (BDP) 168 mcg BID. Subjects who met eligibility criteria were subsequently randomized at Baseline to one of four parallel treatment arms: 100 mcg QD AM, 100 mcg BID, 200 mcg QD AM, or placebo.

Study C97-300 differed from Study P01431 in the treatment arms: 100 mcg QD AM, 200 mcg QD AM, or placebo.

The primary endpoint in each of the pivotal trials was the mean change in percent-predicted FEV1 from Baseline to Endpoint (last observation carried forward, LOCF). Additionally, subjects recorded AM and PM peak expiratory flow rates (PEFR), asthma symptom scores, rescue medication use, and number of nocturnal awakenings daily in their patient diaries. Response to therapy, time to first asthma worsening, and incidence of clinical asthma exacerbations were also assessed as secondary endpoints. The primary analysis was performed using all-randomized subjects (ITT population), while additional analyses were performed on an evaluable-efficacy subset.

6.1.4 Efficacy Findings

6.1.4.1 Study P01431

Demographics and Baseline Characteristics

Of the 296 patients randomized in Study P01431, 109 (37%) were women. The majority of patients (282, 95%) were in the 6 to 11 year old age group. One-hundred seventy nine patients (60%) were Caucasian. Of the non-Caucasian subjects, 39 (8%) were Black, 77 (26%) were Hispanic, 2 (<1%) were Asian, and 8 (3%) were classified as Other. The distribution of patients by age, sex, and race was comparable between treatment arms. The mean duration of asthma was 5.3-5.9 years. The mean baseline percent-predicted FEV1 was 77-79%. The mean AM PEFR was 210 – 237 L/min. The Baseline characteristics were comparable across the three treatment

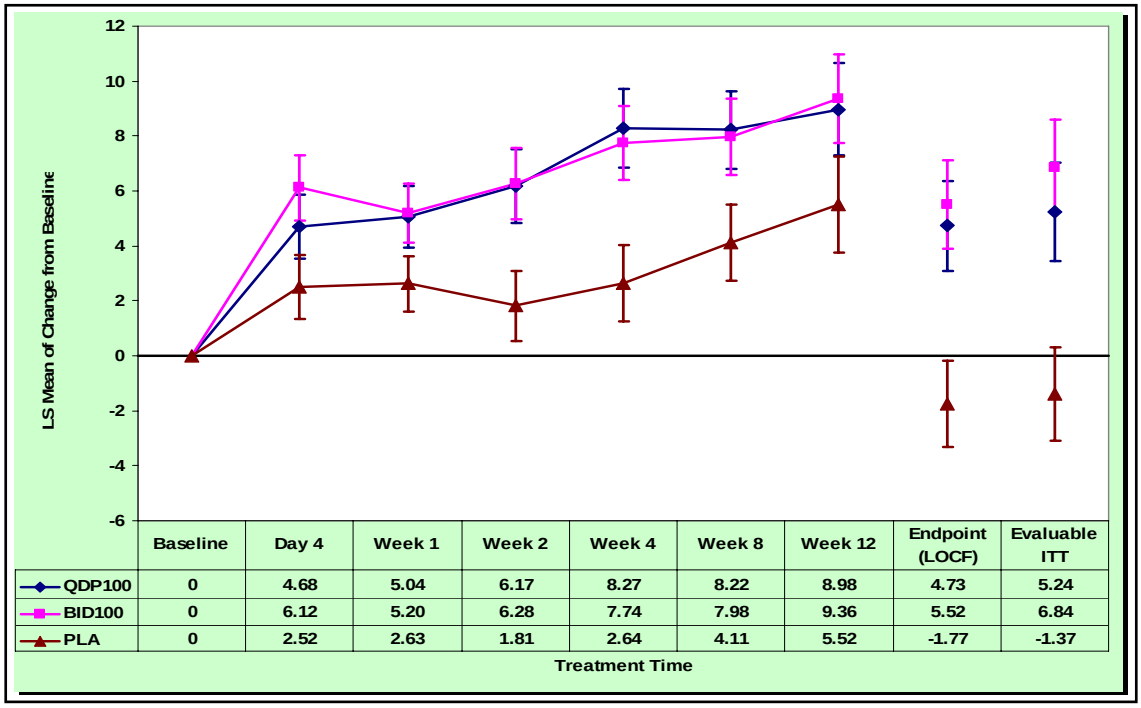
arms. Approximately 75% of patients completed the study, with more completers in the active treatment arms (79% to 81%) compared to the placebo arm (68%).

Primary Efficacy Endpoint

The primary efficacy endpoint was the change in percent-predicted FEV1 from Baseline to Endpoint (LOCF); the primary comparison was between the active treatment groups versus placebo. The results are summarized in Figure 1 below.

The mean change from Baseline to Endpoint (LOCF) in percent-predicted FEV1 was 4.73%, 5.52%, and -1.77% in the MF DPI 100 mcg QD PM, MF 100 mcg BID, and placebo groups, respectively. When the active treatment groups were compared to placebo, the treatment differences for mean change from baseline to endpoint in percent-predicted FEV1 were 6.50% for the 100 mcg QD PM group, and 7.29% for the 100 mcg BID group (See Figure 1).

Figure 1 Study P01431, Change from Baseline in % Predicted FEV1



	Baseline	Day 4	Week 1	Week 2	Week 4	Week 8	Week 12	Endpoint (LOCF)	Evaluable ITT
QDP100	0	4.68	5.04	6.17	8.27	8.22	8.98	4.73	5.24
BID100	0	6.12	5.20	6.28	7.74	7.98	9.36	5.52	6.84
PLA	0	2.52	2.63	1.81	2.64	4.11	5.52	-1.77	-1.37

[Source: Biometrics Review, NDA 21-067/S-003, Dr. Feng Zhou]

These data demonstrate that subjects treated with MF DPI 100 mcg QD PM had statistically significant improvement in mean % predicted FEV1 values from Baseline to Endpoint as compared with placebo (P=0.002). A similar treatment effect was seen with MF DPI 100 mcg BID as compared with placebo (P < 0.001). No significant differences between the two dosing schedules was observed, although there was a numerical trend towards added benefit with the 100 mcg BID dosing regimen.

6.1.4.2 Study C97-380

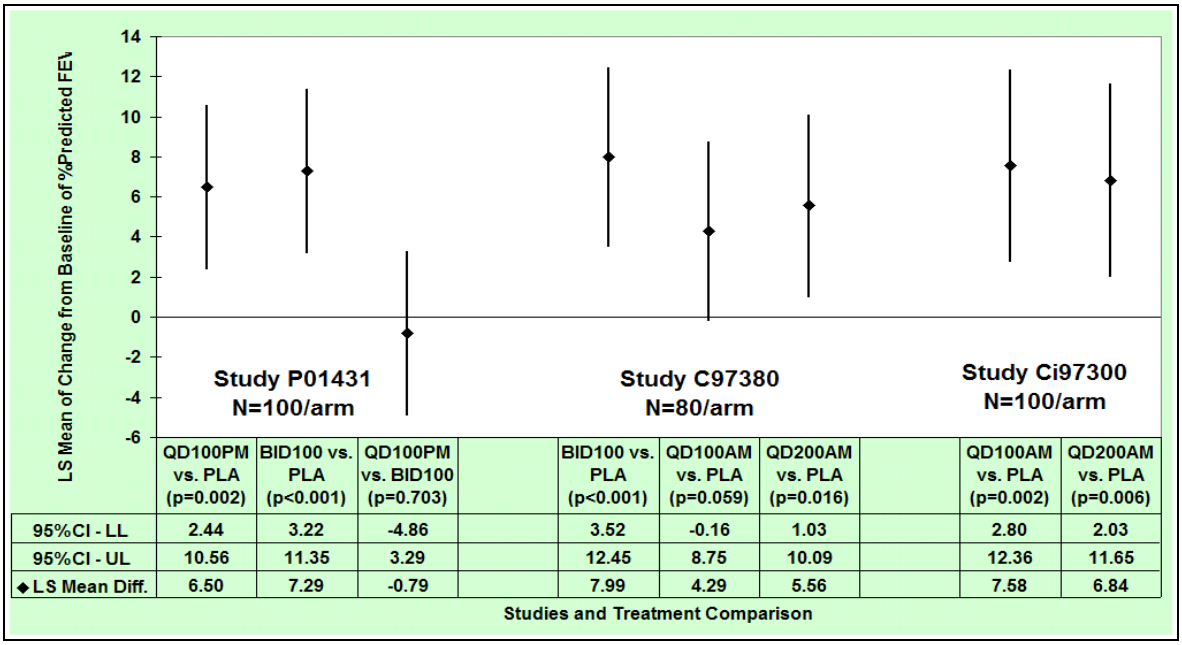
Demographics and Baseline Characteristics

Of the 316 patient randomized in Study C97-380, 112 (35%) were women. The majority of patients (291, 92%) were in the 6 to 11 year old age group. Two hundred thirty-seven patients (75 were Caucasian. Of the non-Caucasian subjects, 50 (16%) were Black, 15 (5%) were Hispanic, 2 (<1%) were Asian, and 12 (4%) were classified as Other. The distribution of patients by age, sex, and race was comparable between treatment arms. The mean duration of asthma was 5.0-5.7 years. The mean Baseline percent-predicted FEV1 was 80-81%. The mean AM PEFR was 233.5 – 257 L/min. The Baseline characteristics were comparable across the three treatment arms and to the treatment arms of Study P01431. Approximately 75% of patients completed the study, with more completers in the active treatment groups (100 mcg BID: 92%) compared with placebo (62%).

Primary Efficacy Endpoint

The primary efficacy endpoint was the change in percent-predicted FEV1 from Baseline to Endpoint (LOCF); the primary comparison was between MF 100 mcg BID and placebo.
The mean change from Baseline to Endpoint (LOCF) in percent-predicted FEV1 was 6.09% and -1.09% in the MF 100 mcg BID and placebo groups, respectively. The placebo-corrected difference in mean change from baseline to endpoint in percent-predicted FEV1 for MF 100 mcg BID was 7.99% (95% CI: 3.52, 12.45). Although not statistically different when compared across studies to 100 mcg QD PM (study P01431), there was a numerical trend towards added benefit (See Figure 2).

Figure 2 Studies P01431, C97-380, C97-300: % Predicted FEV1 Change from Baseline



	QD100PM vs. PLA (p=0.002)	BID100 vs. PLA (p<0.001)	QD100PM vs. BID100 (p=0.703)		BID100 vs. PLA (p<0.001)	QD100AM vs. PLA (p=0.059)	QD200AM vs. PLA (p=0.016)		QD100AM vs. PLA (p=0.002)	QD200AM vs. PLA (p=0.006)
95%CI - LL	2.44	3.22	-4.86		3.52	-0.16	1.03		2.80	2.03
95%CI - UL	10.56	11.35	3.29		12.45	8.75	10.09		12.36	11.65
◆ LS Mean Diff.	6.50	7.29	-0.79		7.99	4.29	5.56		7.58	6.84

[Source: Biometrics Review, NDA 21-067/S-003, Dr. Feng Zhou]

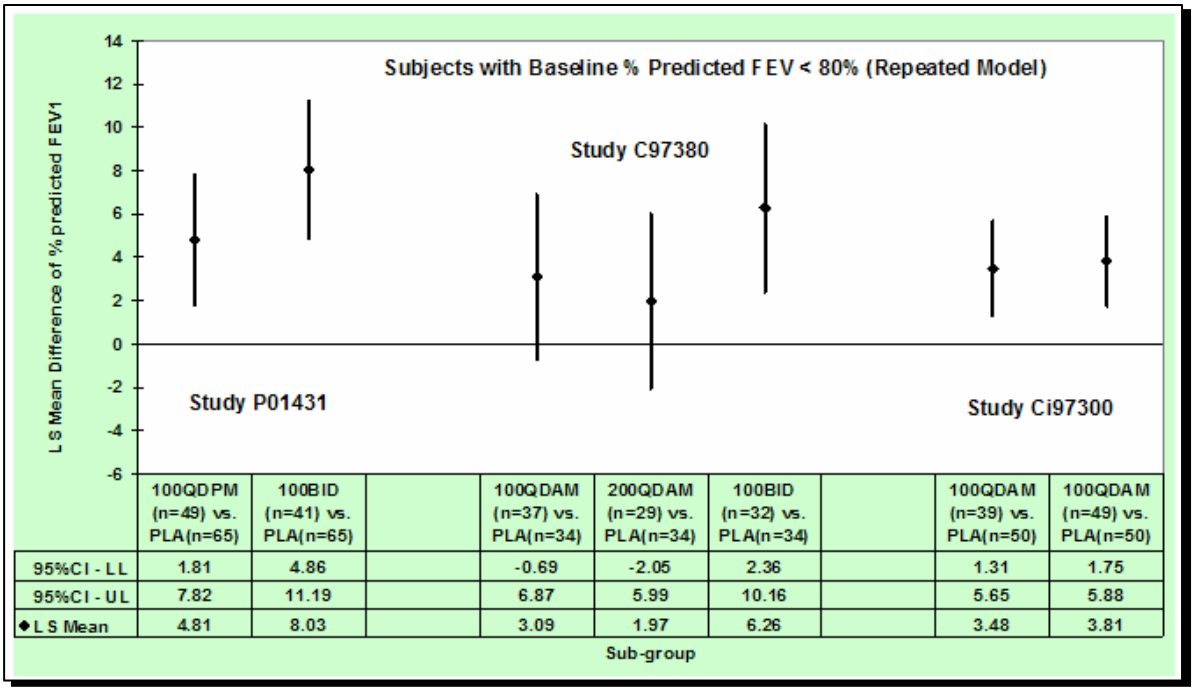
These data demonstrate that subjects treated with 100 mcg QD PM and 100 mcg BID had statistically significant improvements in mean percent-predicted FEV1 from baseline to endpoint as compared with placebo. The efficacy of 100 mcg QD PM was demonstrated in Study P01431, while the efficacy of 100 mcg BID was supported in both P01431 and C97-380. Although 100 mcg BID was not statistically different from 100 mcg QD PM, there was a numerical trend towards added benefit, which was not present for the 200 mcg QD AM dose (C97-380 and C97-300).

The results of P01431, though unreplicated, when considered in combination with the efficacy findings of MF in adults provide adequate support for the MF 100 QD PM dosing regimen. In addition, demonstration of the efficacy of MF 100 mcg BID in two clinical trials, numerical trend towards added benefit with the higher dose, the results of subgroup analysis in more severe asthma patients (See Figure 3), and extrapolation from the current labeling which allows for increasing (doubling) the daily dose in adults and adolescents, provided support for the approval of 100 mcg QD PM as the recommended starting dose, and 100 mcg BID as the highest daily recommended dose, in asthmatic patients 4 to 11 years of age.

6.1.4.3 Subgroup Analyses of the Primary Endpoint

Subgroup analysis by severity of asthma is presented in Figure 3 below.

Figure 3 Studies P01431, C97-380, C97-300, Subgroup Analysis by Severity of Asthma



[Source: Biometrics Review, NDA 21-067/S-003, Dr. Feng Zhou]

For the subgroup analysis in patients with FEV1 < 80%, the placebo-corrected difference in mean percent-predicted FEV1 from baseline to endpoint was 8.03% for the 100 mcg BID

treatment arm versus 4.81% in the 100 mcg QD PM treatment arm in Study P01431. In Study C97-380, the treatment difference was numerically highest (6.26%) for the 100 mcg BID treatment arm.

Both the 100 mcg QD PM and 100 mcg BID treatment arms demonstrated efficacy in a subgroup of asthma patients with percent-predicted FEV1 < 80% . Although the two treatment groups were not statistically different from each other, the results suggest a numerical trend towards added benefit in this subgroup with the 100 mcg BID dosing regimen.

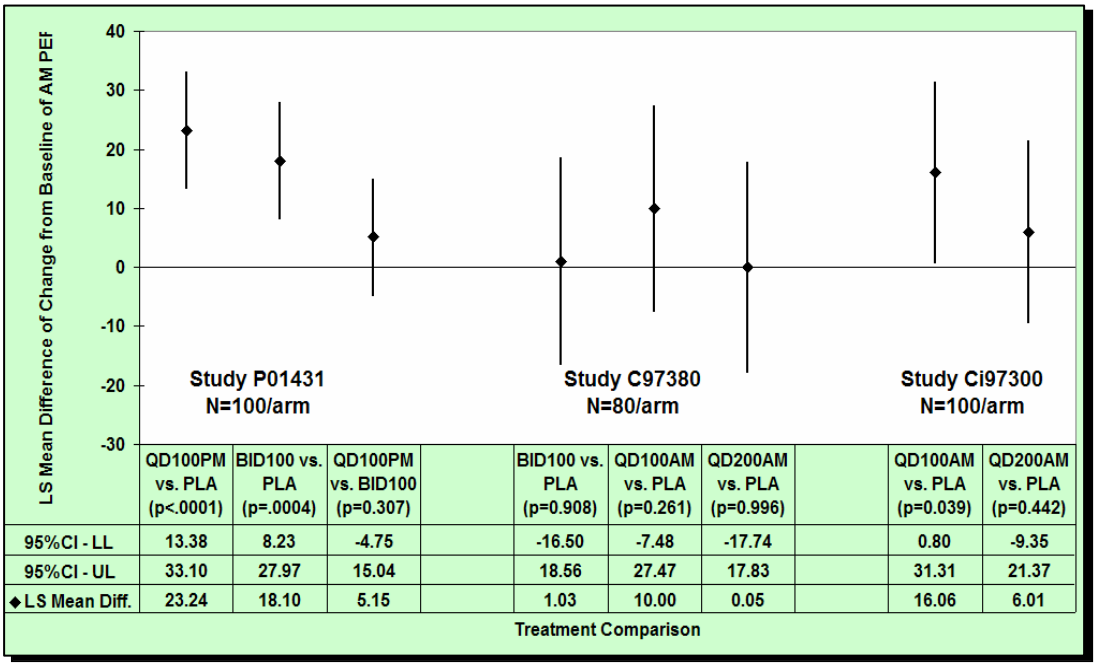
6.1.4.4 Secondary efficacy endpoints

Key secondary endpoints included AM/PM PEFR and use of rescue medication. As the Applicant has included these particular endpoints in the proposed labeling, this review will assess these endpoints in more detail. Although the secondary endpoint of FEV1 is related to the primary endpoint, it will also be addressed in some detail here to maintain consistency, as the previous adult and adolescent labeling uses this spirometry parameter, rather than % predicted FEV1, as the primary endpoint. The other relevant secondary efficacy endpoints of response to therapy and time to worsening of asthma will also be briefly reviewed here. (See Section 10 Appendices for a detailed review of all the secondary efficacy endpoints in the individual studies.) The secondary endpoints were evaluated in each of the three pivotal clinical studies, but this reviewer will emphasize the results of studies P01431 and C97-380, as these trials include the dosing regimens of interest.
Reviewer's Comment: Asthma symptom scores and nocturnal awakenings are not discussed here because the baseline values were low, and very little change occurred throughout the study in these endpoints. Therefore inferential analysis did not provide any meaningful results.

<u>AM and PM Peak Expiratory Flow Rates (PEFR)</u>
AM and PM PEFR were measured daily by patients and captured in patient diaries. In study P01431, the baseline AM and PM PEFR for MF 100 mcg QD PM were 237.0 L/min and 243.4 L/min, respectively. The baseline AM and PM PEFR for MF 100 mcg BID were 237.7 L/min and 244.3 L/min, respectively. The baseline AM and PM PEFR for the placebo group was 210.9 L/min and 218.6 L/min, respectively. All treatment groups were comparable at baseline. At endpoint, the mean change in AM and PM PEFR for MF 100 mcg QD PM was 16.3 L/min and 14.9 L/min, respectively. For 100 mcg BID, the mean change in AM and PM PEFR at endpoint was 11.2 L/min and 12.9 L/min. At endpoint, AM and PM PEFR in the placebo group decreased by 6.9 L/min and 5.6 L/min, respectively. The corresponding placebo-corrected treatment differences in mean change from baseline in AM PEFR for MF 100 QD PM and 100 mcg BID were 23.24 L/min (95% CI: 13.38, 33.10) and 18.10 L/min (95% CI: 8.23, 27.97), respectively. For PM PEFR, these values were 20.51 L/min (95% CI: 11.19, 29.83), and 18.50 L/min (95% CI: 9.18, 27.83), respectively (See Figure 4 and Figure 5).

In study C97-380, the baseline AM and PM PEFR for MF 100 mcg BID were 249.9 L/min and 253.1 L/min, respectively. The baseline AM and PM PEFR fro the placebo group were 233.5 L/min and 238.9 L/min, respectively. Baseline values were comparable in both groups. At endpoint, the mean change in AM and PM PEFR for MF 100 mcg BID was 6.03 L/min and 9.34 L/min, respectively. The placebo-corrected treatment differences in mean change from baseline to endpoint in AM and PM PEFR for MF 100 mcg BID were 1.03 L/min (95% CI: -16.50, 18.56) and -2.04 L/min (95% CI: -18.79, 14.72), respectively (See Figure 4 and Figure 5).

Figure 4 Studies P01431, C97-380, C97-300. LS Mean Difference of Change from Baseline to Endpoint in AM PEFR

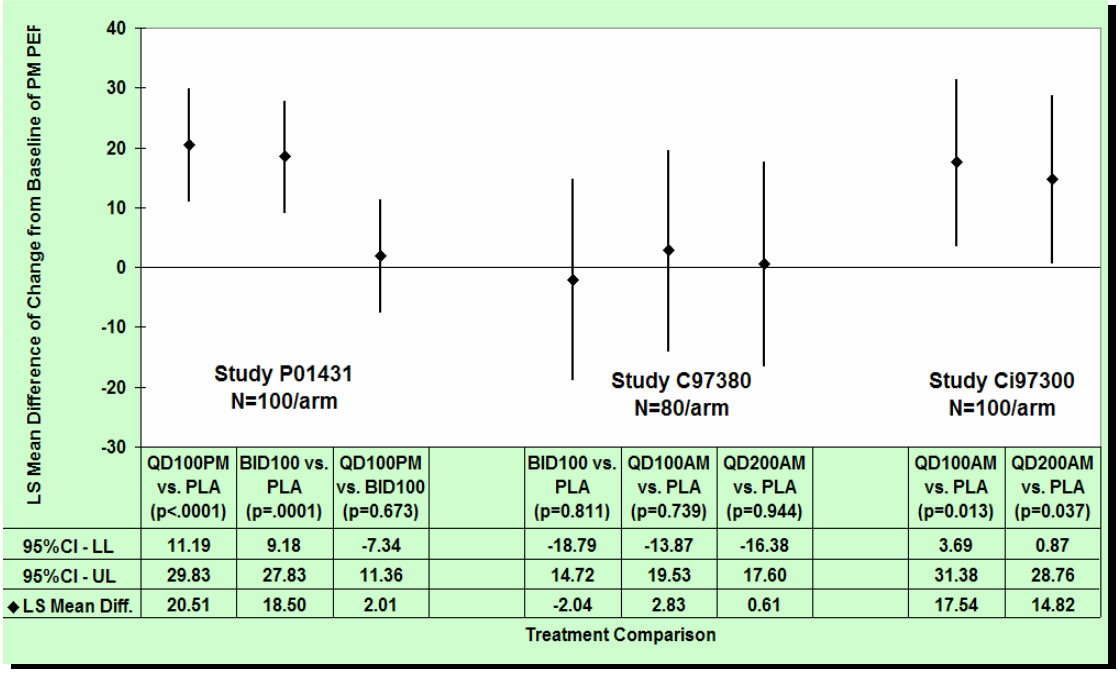


	QD100PM vs. PLA (p<.0001)	BID100 vs. PLA (p=.0004)	QD100PM vs. BID100 (p=0.307)		BID100 vs. PLA (p=0.908)	QD100AM vs. PLA (p=0.261)	QD200AM vs. PLA (p=0.996)		QD100AM vs. PLA (p=0.039)	QD200AM vs. PLA (p=0.442)
95%CI - LL	13.38	8.23	-4.75		-16.50	-7.48	-17.74		0.80	-9.35
95%CI - UL	33.10	27.97	15.04		18.56	27.47	17.83		31.31	21.37
◆ LS Mean Diff.	23.24	18.10	5.15		1.03	10.00	0.05		16.06	6.01

Treatment Comparison

[Source: Biometrics Review, NDA 21-067/S-003, Dr. Feng Zhou]

Figure 5 Studies P01431, C87-380, C97-300. LS Mean Difference of Change from Baseline to Endpoint of PM PEFR



	QD100PM vs. PLA (p<.0001)	BID100 vs. PLA (p=.0001)	QD100PM vs. BID100 (p=0.673)		BID100 vs. PLA (p=0.811)	QD100AM vs. PLA (p=0.739)	QD200AM vs. PLA (p=0.944)		QD100AM vs. PLA (p=0.013)	QD200AM vs. PLA (p=0.037)
95%CI - LL	11.19	9.18	-7.34		-18.79	-13.87	-16.38		3.69	0.87
95%CI - UL	29.83	27.83	11.36		14.72	19.53	17.60		31.38	28.76
◆LS Mean Diff.	20.51	18.50	2.01		-2.04	2.83	0.61		17.54	14.82

Treatment Comparison

[Source: Biometrics Review, NDA 21-067/S-003, Dr. Feng Zhou]

The results of study P01431 demonstrated that both MF DPI treatment groups were significant compared to placebo for change from baseline to endpoint in AM PEFR ($p < 0.001$) and PM PEFR ($P<0.001$). There was no statistical difference between 100 mcg QD PM and 100 mcg BID. In study C97-380, all treatments showed improvement in AM and PM PEFR at endpoint, but placebo-corrected treatment differences were not statistically significant. Change in AM and PM PEFR is generally supportive of the efficacy of MF 100 mcg QD PM and 100 mcg BID, but only in study P01431.

Reviewer's Comment: Statistically, the secondary efficacy endpoint of PEFR is supportive of the two dosing regimens in Study P01431. However, the clinical significance of the absolute numerical improvements is unclear.

Rescue Medication Use

Rescue medication use was recorded in patient diaries and the change in use of rescue medication from Baseline to Endpoint was evaluated. In study P01431, the mean number of daily inhalations of protocol-permitted rescue medication was 1.3 puffs for all groups at Baseline. Subjects treated with MF DPI 100 mcg QD PM and MF DPI 100 mcg BID reported decreased use of rescue medication over the course of the study, while subjects treated with placebo required an increase in the use of rescue medication. At Endpoint, the mean use of rescue medication had decreased by 0.4 to 0.5 inhalations/day in the MF DPI groups compared with an increase of 0.3 inhalations/day in the placebo group ($P \leq 0.006$). Rescue medication use was not inferentially analyzed in study C97-380 due to low usage at baseline and throughout the

study, which precluded meaningful results. The change in rescue medication use is generally supportive of the efficacy of MF 100 mcg QD PM and 100 mcg BID, but only in study P01431.

Reviewer's Comment: Statistically, the secondary efficacy endpoint of rescue medication use is supportive of the 100 mcg QD PM regimen, however the magnitude of the treatment difference described is unlikely to be clinically relevant.

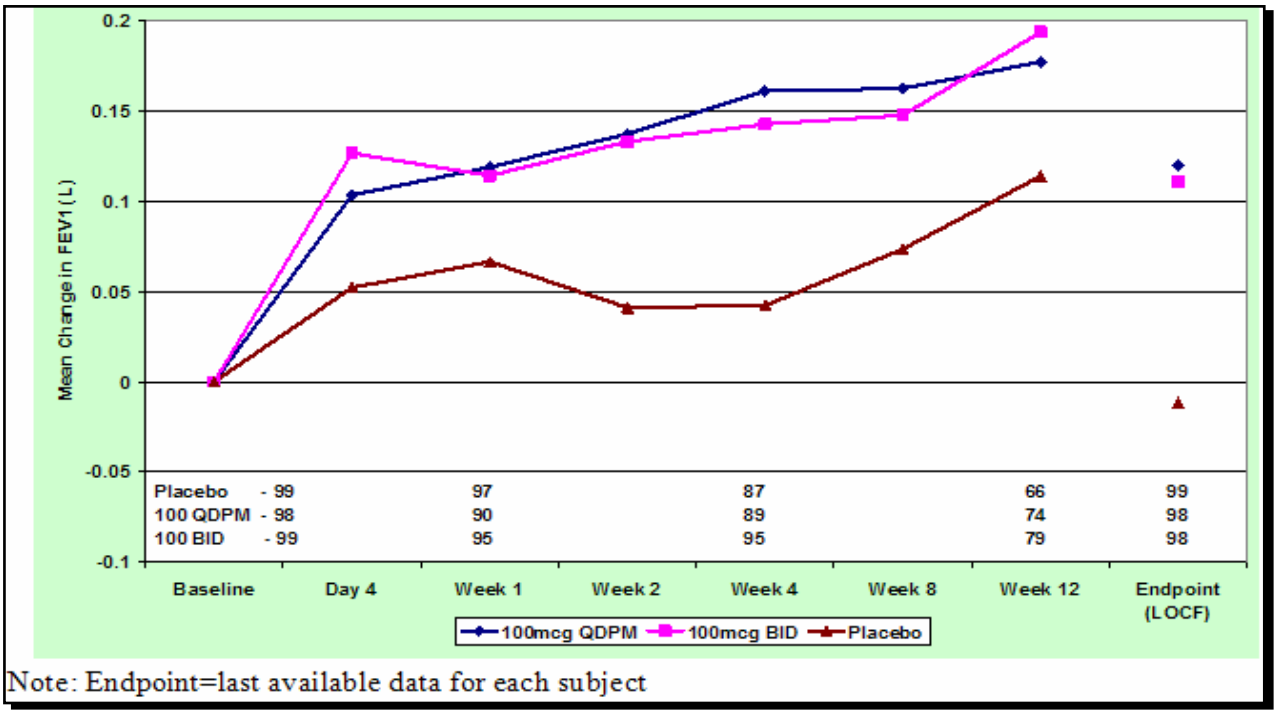
FEV1

The change in FEV1 from Baseline to Endpoint was evaluated in all three studies. As expected, the result of FEV1 analysis were comparable to that of the primary efficacy endpoint: change in percent-predicted FEV1 from Baseline to Endpoint. As an example,

Figure 6 represents the change in mean FEV1 from baseline to endpoint in Study P01431.

Reviewer's Comment: Although this figure is repetitive of data already presented in terms of percent predicted FEV1 (See Figure 1), [redacted] as the current labeling for adults and adolescents > 12 years of age includes figures presented in terms of FEV1. This will provide consistency in the way in which the data are presented across different patient populations.

Figure 6 Study P01431, Change from Baseline to Endpoint in FEV1 by Treatment Group



[Source: Biometrics Review, NDA 21-067/S-003, Dr. Feng Zhou]

Response to Therapy
At all visits, the physician or designee assessed the subject's response to therapy on a scale from 1 (much improved) to 5 (much worse). In study P01431, the percentage of subjects evaluated as improved (i.e. much improved or improved) was higher in the MF DPI 100 mcg QD PM and MF DPI 100 mcg BID groups (68% and 62%, respectively) than in the placebo group (44%). In study C97-380, the percentage of subjects evaluated as improved was higher in the MF DPI 100 mcg BID group than in the placebo group (84% vs. 51%). Mean response scores at endpoint were also significantly lower in the active treatment groups when compared with placebo in both studies. MF DPI 100 mcg QD PM and 100 mcg BID demonstrated a statistically significant improvement in response to therapy when compared to placebo. Overall, the secondary efficacy endpoint of response to therapy is supportive of the 100 mcg QD PM and 100 mcg BID dosing regimens.

Time to Worsening of Asthma
In study P01431, 79 subjects met one or more protocol-specified criteria for worsening of asthma: 17 subjects (17%) in the MF DPI 100 mcg QD PM group, 22 subjects (22%) in the MF DPI 100 mcg BID group, and 40 subjects (40%) in the placebo group. The most common criterion for asthma worsening was decrease in peak expiratory flow, followed by a clinical asthma exacerbation. Kaplan Meier survival curves of time to first asthma worsening demonstrate that all active treatments were better than placebo with a statistically significant separation ($P<0.001$). Although a similar trend was present in C97-380, the active treatment groups, including 100 mcg BID, were not statistically different from placebo. Overall, the secondary efficacy endpoint of time to worsening of asthma is supportive of the 100 mcg QD PM and 100 mcg BID dosing regimens.

6.1.5 Clinical Microbiology

Mometasone furoate is not an antimicrobial and therefore this section is not applicable.

6.1.6 Efficacy Conclusions

In support of this pediatric efficacy supplement, the Applicant submitted the clinical study reports of eight clinical studies, three of which were considered pivotal, and five supportive. The Applicant proposed the dosing regimen of 100 mcg QD PM for the maintenance treatment of asthma in patients 4 to 11 years of age. Based on the review of the pivotal studies, the efficacy of MF 100 mcg QD PM was supported. Although 100 mcg QD PM was the only dose proposed for registration by the Applicant, review of other submitted dosing regimens revealed that the efficacy of MF 100 mcg BID was also supported based on a statistically significant difference in the primary endpoint versus placebo. Though there was no statistical difference between the 100 mcg QD PM and 100 mcg BID treatment groups, the 100 mcg BID arm trended towards being numerically superior in two studies. Further, subgroup analysis of more severe asthma patients ($FEV1 < 80\%$) revealed that there may be a numerical trend towards benefit with twice daily dosing in this specific patient population. Demonstration of the efficacy of MF 100 mcg BID in two clinical trials, numerical trend towards added benefit with the higher dose, the results of subgroup analysis in more severe asthma patients, and extrapolation from the current labeling

which allows for increasing (doubling) the daily dose in adults and adolescents, taken together provide support for the approval of 100 mcg QD PM as the recommended starting dose, and 100 mcg BID as the highest daily recommended dose, in asthmatic patients 4 to 11 years of age.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The Applicant submitted eight studies in support of their pediatric development program. The relevant six studies are reviewed in depth in the Appendix of this review. The adverse event data summarized here will be primarily from those studies in which the dosing regimens of interest (100 mcg QD PM and 100 mcg BID) were included (Study P01431, C97-380, and C97-385). The Applicant assessed the effects of MF on growth velocity in a 52-week long-term safety study. The findings of the growth study will be presented in detail in *Section 7.1.15 Assessment of Effect on Growth*. The two knemometry studies have not been reviewed in detail and will not be discussed further, as the one-year study provides a more clinically relevant method by which to assess growth in children.

Finally, the Applicant also evaluated the effects of MF on the HPA axis in multiple studies. Study C96-361 provides the most rigorous collection of HPA axis data, and hence, will be emphasized in this review and presented in *Section 7.1.12 Special Safety Studies.*

7.1.1 Deaths

No subjects died during the studies nor were there any deaths reported within 30 days of the last dose of study medication.

7.1.2 Other Serious Adverse Events

In Study P01431, 6 subjects reported serious adverse events (SAEs), one prior to randomization during the screening period. The 5 SAEs during the treatment period included an SAE of second/third degree burns (MF 100 mcg QD PM), appendicitis (2 subjects, MF 100 mcg BID), spinal surgery scheduled prior to study enrollment (MF 100 mcg BID), and abdominal pain/vomiting/respiratory distress requiring hospitalization (placebo). None of the reported SAEs was likely to have been related to drug treatment. In the study C97-380, there were 3 SAES, none of which was reported in the 100 mcg BID treatment arm.

In the two 1-year safety studies, 10 SAEs were reported during the double-blind treatment period. A total of 2 SAEs in both studies occurred in the MF 100 mcg BID groups, one in each

study. In study C97-384, the SAE was hospitalization due to aggravated asthma and viral pneumonia. In study C97-385, the SAE was gastroenteritis requiring hospitalization.

The SAE data do not suggest a new safety signal for MF.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The dropout data from all three pivotal studies supports the safety and efficacy of MF in pediatric patients as there were fewer dropouts in the MF groups due to AEs and treatment failure compared to placebo. In study P01431, the incidence of withdrawals was 24%. Study discontinuation was more common in the placebo group than in the active treatment groups (32% placebo; 19% MF DPI 100 mcg BID; 21% in MF DPI 100 mcg QD PM. The most common reason for discontinuation was treatment failure, reported by 12% of patients. Twice as many patients in the placebo group discontinued secondary to treatment failure (18%) as compared with the active treatment groups (9%). Protocol violations and subjects deciding to withdraw accounted for a small proportion of the withdrawals in each group (2-4%). The results for Study C97-380 were similar to those described above, with an overall discontinuation of 24%, due mostly to treatment failure, reported more frequently in the placebo group.

In study C97-384, a total of 52 subjects (27%) withdrew from the study during the treatment period. The percentage of patients that discontinued from each active treatment arm was similar to placebo. Discontinuation due to adverse events occurred only in the active treatment groups (100 mcg BID, 5%; 200 mcg QD AM, 8%; 100 mcg QD AM 4%). Treatment failure was reported as a reason for discontinuation in 2% of 100 mcg BID patients as compared with 9% in the placebo group. In study C97-385, a total of 43 subjects (18%) withdrew from the study. The percentage of patients that discontinued from each treatment arm was similar.

7.1.3.2 Adverse events associated with dropouts

In Study P01431, 18 subjects (6%) withdrew secondary to adverse events (3 subjects in 100 mcg QD PM, 4 subjects in 100 mcg BID, and 11 subjects in the placebo group). In the MF DPI 100 mcg QD PM groups, the three AEs that led to discontinuation were skin burn (day 24), viral infection (Day 10), and laryngitis (Day 64). None of these adverse events is likely to be treatment related. In Study C97-380, 28 subjects (9%) did not complete double-blind study treatment secondary to AEs. Of these 28 subjects, only 1 subject in the 100 mcg BID group withdrew secondary to an AE. The most frequently reported adverse events leading to discontinuation were events that were classified to the respiratory system, such as upper respiratory tract infection. Overall, the frequency of withdrawal secondary to AEs was highest in the placebo group.

The two 1-year long-term safety studies did not demonstrate a higher number of withdrawals secondary to adverse events. Study C97-384 had 8 withdrawals (4%) secondary to AEs, with

the highest number of withdrawals in the 200 mcg QD AM group (4 subjects); study C97-385 had 6 withdrawals (3%) due to AEs, with the highest number of withdrawals also in the 200 mcg QD AM group (4 subjects) .

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the pediatric mometasone furoate development program, an AE was defined as "any physical or clinical change or disease experienced by the subject at any time during the course of the study, whether or not considered related to the use of the study drug". This included the onset of new illness and the exacerbation of pre-existing conditions, other than the indication under study. At each visit, subjects were questioned regarding the occurrence and severity of AEs, and AEs were recorded in the electronic case report form (eCRF). The questioning of subjects with regard to the possible occurrence of AES was generalized, such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs was not solicited from subjects. The diary cards were also reviewed and any relevant comments that referred to possible AEs were captured in the eCRF. Asthma symptoms of wheezing, difficulty breathing, cough, and chest tightness/ congestion were not considered AEs, unless they showed a clear temporal relationship to study drug administration or resulted in hospitalization.

Reviewer's comment: Although it is atypical that the applicant did not consider asthma symptoms to be AEs, clinical asthma exacerbations (defined as a worsening of asthma that resulted in hospitalization, treatment with asthma medication in addition to hose allowed in the protocol, or other emergency treatment) were captured. Monitoring and recording of CAEs provided an alternate means by which to gauge the presence of asthma symptoms in this development program.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The nomenclature for reported clinical AEs was standardized using a customized version of the World Health Organization Adverse Reaction Terminology (WHO-ART) dictionary, which is continuously maintained and updated as needed by the applicant's Drug Safety Surveillance department. Literal terms reported in each subject's eCRF were coded and translated into a preferred term that served to consolidate reports of a similar nature; both the literal and preferred terms were stored in the database.

7.1.5.3 Incidence of common adverse events

The adverse event profile of MF 100 mcg QD PM and 100 mcg BID was reviewed in studies P01431 and C97-380. The majority of AEs were categorized as mild in these two studies. In P01431, overall reporting of AEs was 54% in the 100 mcg QD PM arm, 59% in the 100 mcg

BID arm, and 51% in the placebo group. The most commonly reported AEs (> 10%) were fever, headache, and upper respiratory tract infection. Fever, allergy, abdominal pain, diarrhea, nausea, vomiting, sinusitis, tooth abscess, upper respiratory tract infection, urinary tract infection, musculoskeletal pain, bruise, and epistaxis were reported by ≥2% of subjects and more frequently in the active treatment groups versus placebo (See Table 2). AEs did not differ with regard to frequency or type between treatment groups. CAEs were similarly low in both treatment groups and less than placebo.

In study C97-380, overall reporting of AEs ranged from 72-84% of subjects, with the placebo group having the highest number of reported AEs (100 mc BID 73%, 100 mcg QD 72%, Placebo 81%). The most commonly reported AEs (≥10%) were fever, headache, allergy aggravated, viral infection, nasal congestion, pharyngitis, rhinitis, and upper respiratory tract infection. Allergy aggravated, leg cramps, edema, fatigue, fever, diarrhea, dyspepsia, gastroenteritis, oral candidiasis, musculoskeletal pain, viral infection, otitis, nasal congestion, rhinitis, and upper respiratory tract infection were reported by ≥ 3% of patients and more frequently in the active treatment groups versus placebo (See Table 3). The proportion of subjects reporting oral candidiasis was similar at MF DPI doses of 100 mcg BID (6%) and 100 mcg QD AM (4%) vs. 0 in the placebo group. CAEs were reported least frequently in the 100 mcg BID arm (5%) as compared with 25% of subjects in the placebo group.

In the 52-week, open-label, long-term safety study (C97-385), treatment arms were MF 100 mcg BID, MF 200 mcg QD AM, and an active comparator budesonide dipropionate (BDP) 168 mcg BID. As expected with a study of longer duration, the overall reporting of adverse events increased to 96-97% of subjects in all groups. The most commonly reported AEs (> 20%) were allergy, fever, headache, viral infection, nasal congestion, pharyngitis, rhinitis, sinusitis, and upper respiratory tract infection. CAEs were reported in 35% of patients in the MF 200 mcg QD AM group vs. 23% in 100 mcg BID group.

7.1.5.4 Common adverse event tables

Table 2 Summary of AEs from Study P01431 with an Incidence of ≥ 2% Of Patients and with Greater Frequency in the Active Treatment Group vs. Placebo

Number (%) of subjects			
Adverse Event	**MF 100 mcg QPM (n = 98)**	**MF 100 mcg BID (n = 99)**	**Placebo (n=99)**
Any Adverse Event	**54 (54)**	**59 (59)**	**51 (51)**
Fever	7 (7)	10 (10)	5 (5)
Allergy	4 (4)	6 (6)	3 (3)
Abdominal pain	6 (6)	6 (6)	2 (2)
Diarrhea	1 (1)	2 (2)	0 (0)
Nausea	1 (1)	2 (2)	1 (1)
Vomiting	3 (3)	2 (2)	2 (2)
Sinusitis	1 (1)	3 (3)	0 (0)
Tooth Abscess	0 (0)	2 (2)	0 (0)
Upper Respiratory Tract Infection	11 (11)	18 (18)	16 (16)
Urinary tract infection	2 (2)	1 (1)	0 (0)
Musculoskeletal Pain	1 (1)	4 (4)	0 (0)
Bruise	2 (2)	1 (1)	0 (0)
Epistaxis	1 (1)	2 (2)	1 (1)

Reviewer's Comment: A modified version of this table should be used for the label. Currently, the applicant does not have an AE listing for the pediatric studies in the label.

Table 3 Study C97-380. Adverse Events Reported by ≥ 3% of Patients and with Greater Frequency in the Active Treatment Group vs. Placebo.

	Number (%) of Subjects		
	MF DPI 100 mcg BID (n = 80)	**MF DPI 100 mcg QD AM (n=81)**	**Placebo (n=80)**
Any Event	**58 (73)**	**58(72)**	**65 (81)**
Allergy Aggravated	7 (9)	6(7)	5(6)
Leg Cramps	2 (3)	0 (0)	0 (0)
Edema	2 (3)	0 (0)	0 (0)
Fever	7 (9)	10(12)	9(11)
Diarrhea	0 (0)	3(4)	1(1)
Gastroenteritis	2 (3)	3(4)	2(3)
Earache	3 (4)	4(5)	1(1)
Musculoskeletal pain	3 (4)	4(5)	1(1)
Oral Candidiasis	5 (6)	3(4)	1 (1)
Viral Infection	10 (13)	8(10)	5(6)
Otitis Media	4 (5)	2 (2)	3 (4)
Nasal Congestion	7 (9)	13 (16)	9 (11)
Respiratory Disorder	2 (3)	0 (0)	0 (0)
Rhinitis	13 (16)	9 (11)	6(8)
Rhinitis aggravated	3 (4)	2 (2)	2 (3)
Sneezing	2 (3)	1 (1)	1 (1)
Upper Respiratory Tract Infection	7 (9)	14(17)	12 (15)
Dermatitis	1 (1)	3(4)	0
Fungal Skin Infection	2 (3)	0 (0)	0 (0)
Conjunctivitis	6 (8)	2 (2)	3 (4)

7.1.5.5 Identifying common and drug-related adverse events

The adverse events noted were typical of what is seen in asthma studies. It is often difficult to determine if the adverse events are drug-related, or related to the underlying disease process (i.e. coughing, hoarseness, etc.). Oral candidiasis is a known adverse event of inhaled corticosteroid use, and the incidence of this was relatively low in this development program.

7.1.6 Less Common Adverse Events

The uncommon AEs that are pertinent to this review are those related to local inhaled corticosteroid effects such oral candidiasis and hoarseness/dysphonia. Interestingly, there was no oral candidiasis or dysphonia reported in either of the active treatment groups in Study P01431. However, in study C97-380, oral candidiasis rose to the level of a common adverse event, being present in 6% of the patients in the 100 mcg BID group vs. 1 % in the placebo (See Table 3).

During Study C97-384, a one-year study, 1 subject in the MF DPI 200 mcg QD group in reported moderate dysphonia. It was reported in 2% of subjects overall, with 2 subjects in the 100 mcg BID group. In Study C97-385, also a one-year study, oral candidiasis occurred in 4% of the subjects in the 100 mcg BID group. The onset of oral candidiasis was noted after subjects received at least 3 months of treatment in the one-year studies. All cases were considered mild to moderate in severity.

Overall, the incidence of these well-characterized local adverse effects of inhaled corticosteroids was quite low in the 12-week studies, and did not increase significantly in the trials of longer duration.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine safety hematology and chemistry blood tests were performed and summarized by treatment regimen for subjects who had both a baseline and endpoint value for comparison (end of study or early withdrawal). In the 12-week pivotal trials, laboratory studies were performed at the screening and final visits. In the long-term safety study, C97-384, routine laboratory studies were performed at screening, Week 26, and the final visit. The HPA-axis was evaluated in study C96-361 and the timing of urinary and plasma cortisol sampling is described in Section 7.1.12.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Routine laboratory results were reviewed for each of the submitted studies. HPA axis function was assessed in three studies: a 29-day study (C96-361) in asthmatic children 6 to 11 years of age, and two one-year studies in asthmatic children 4 to 11 years of age (growth study C97-384 and safety study C97-385). In study C96-361, standard measurements including plasma cortisol AUC and 24-hour urinary free cortisol levels were assessed. For the purpose of HPA axis assessment, the two one-year studies were inadequate, as only AM plasma cortisol and 12-hour urinary cortisol were collected. These parameters are not generally considered sensitive enough to detect the systemic effect of inhaled corticosteroids on HPA axis function. Hence, the effect on HPA axis function was only reviewed in the dedicated HPA-axis study, Study C96-361 (See 7.1.12 Special Safety Studies).

7.1.7.3 Standard analyses and explorations of laboratory data

There were no clinically meaningful changes in the median percent change of any of the routine laboratory values. Laboratory associated AEs included urine white blood cells increased reported for one subject treated with placebo and SGOT and SGPT increased reported for one subject treated with MF DPI 100 mcg QD PM in Study P01431. In both cases, the events were mild, and the subjects required no additional therapy. These were likely unrelated to study treatment.

Results were evaluated as percent change from Baseline to Endpoint. Range and percent change from Baseline of the ranges at Endpoint were listed. Subjects who had clinically significant (pre-specified in the protocol) laboratory test results by regimen were listed. Clinically significant abnormalities were defined for all blood chemistry parameters as $\geq$ 2.6 times the upper limit of normal. Other, specific, abnormal values were: hemoglobin concentration $\leq$ 9.4 g/dL, platelet count $\leq$ 74,000 cells/µL, or white blood cell count $\leq 2.9 \times 10^3$ cells/µL. One or more of these criteria was met by 3 subjects in Study C97-300, 5 subjects in the C97-380 study, (3 in the MF DPI 100 mcg BID group and 2 in the placebo group), and 3 subjects in Study P01431. These outliers were reviewed (*Module 2, Summary of Clinical Safety, Table 41*), and none were considered to be clinically significant.

7.1.7.5 Special assessments

Ophthalmologic Exams

In Study C97-384 and C97-385, the one-year safety studies, ophthalmologic exams were performed at Screening and at the Final Treatment Visit. Overall, no clinically relevant cases of increased intra-ocular pressure were reported. One case of posterior subcapsular cataract was noted in the 100 mcg BID treatment group at Week 26 in Study C97-385. The subject had not had the cataract present at Screening. The cataract was less than 3% of axial opacity. *Reviewer's Comment: The Applicant did not consider the cataract to be a treatment-emergent AE because it was reported 40 days after treatment had been stopped for reasons unrelated to the cataract. However, it cannot be ruled out as an adverse event secondary to drug.*

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs, including systolic and diastolic blood pressure, temperature, pulse, and respirations were taken at all study visits. All of the submitted studies were reviewed for overall MF/placebo comparisons. Actual mean changes and mean percent changes from Baseline to treatment Endpoint were calculated for systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, and weight. Mean percent changes were minimal. There were no trends that would indicate an adverse effect of MF DPI on vital signs. The line-listings for those subjects who had

vital sign values representing a change from Baseline of ≥ 30% were reviewed for each study. Again, there were no trends to indicate an adverse effect of MF DPI on these vital signs, and for the most part, these changes were not clinically relevant.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

A 12-lead electrocardiogram was to have been obtained at the Screening Visit (if results from an ECG performed in the previous 30 days were not available). The ECG was required to be without clinically significant abnormalities. ECGs were not performed post-treatment.

7.1.9.4 Additional analyses and explorations

No additional analyses were performed as corticosteroids have a low potential to affect cardiac rhythm or function.

7.1.10 Immunogenicity

Immunogenicity is not applicable for an inhaled corticosteroid.

7.1.11 Human Carcinogenicity

Carcinogenicity was not formally assessed in this pediatric efficacy supplement, but it was examined in the original clinical development program. Per the approved product label, in a 2-year carcinogenicity study in Sprague Dawley rats, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 67 mcg/kg (approximately 8 times the maximum recommended daily inhalation dose in adults on an AUC basis and 2 times the maximum recommended daily inhalation dose in pediatric patients based on a mcg/m^2 basis). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 mcg/kg (approximately 10 times the maximum recommended daily inhalation dose in adults on an AUC basis and 3 times the maximum recommended daily inhalation dose in pediatric patients based on a mcg/m^2 basis).

Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary cell assay, but did not have this effect in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenic in the Ames test or mouse lymphoma assay, and was not clastogenic in an *in vivo* mouse micronucleus assay, a rat bone marrow chromosomal aberration assay, or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

7.1.12 Special Safety Studies

The effect of mometasone furoate (MF) on HPA axis function was assessed most rigorously in a 29-day randomized, double-blind, placebo-controlled, parallel group study involving 50 asthmatic children 6 to 11 years of age. HPA axis function was primarily evaluated by 12-hour plasma cortisol AUC_{0-12h} and 24-hour urinary free cortisol levels with additional analysis on plasma cortisol Cmin, Cmax, 8 AM levels, and Tmax. Following 4 weeks of treatment, the placebo-corrected differences in AUC_{0-12h} change from baseline for the 100 mcg BID, 200 mcg BID and 400 mcg BID treatment groups were 3.4 mcg.hr/dL (95% CI: -14.0, 20.7), -16.0 mcg.hr/dL (95% CI: -33.9, 1.9), and -17.9 mcg.hr/dL (95% CI: -35.8, 0.0), respectively. For the 24-hour urinary free cortisol excretion, the placebo corrected differences in changes from baseline for the 100 mcg BID, 200 mcg BID, and 400 mcg BID treatment groups were 3.1 mcg/day (95% CI: -3.3, 9.6), 3.3 mcg/day (95% CI: -3.0, 9.7), and -2.0 mcg/day (95% CI: -8.6, 4.6), respectively. The plasma cortisol Cmin and Cmax values for all doses showed dose-dependent decreases from baseline compared to placebo. The 8 AM cortisol concentrations are generally consistent with the AUC_{0-12h} finding where only the 200 mcg BID and 400 mcg BID groups showed dose-related decreases from baseline compared to placebo. Although dose dependent decreases in HPA axis function were suggested by the results of this study, none of the changes were statistically significant, even after the baseline was adjusted for as a covariate. See the Biopharmaceutics Review of Dr. Wei Qiu for a more detailed review of Study C96-361.

Reviewer's Comment: There were several limitations in this study. First, the proposed dose of 100 mcg QD PM was not assessed in this study. However, the 100 mcg QD PM dose was included in the 100 mcg BID dosing regimen. Secondly, the study population was smaller than what we typically see in these types of studies and the duration was short, 4 weeks rather than six. Finally, there was no active control which is now recommended for HPA axis studies. This may be less important in this study where somewhat of a numerical dose response was seen in the results. Although a dose-related trend in HPA axis effect is suggested by the results, the confidence intervals show that these values are not statistically significant for any of the doses.

Reviewer's Comment: It is important to note that the group that was dosed with 400 mcg BID was given 1 puff twice a day of the [redacted] *g strength Twisthaler.* [redacted] *The issue of dose proportionality was raised during the initial review of this application. Dr. Craig Bertha, who had reviewed the in vitro data for other batches of the* [redacted] *strength (see Chemistry Review by Dr. Craig Bertha, March 23, 1999) found that dose delivery of the* [redacted] *batches was reasonably close to target and met the Agency's acceptance criterion of 85-115% of the claimed emitted dose.*

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No special studies to investigate withdrawal phenomena and/or abuse potential were provided nor warranted for this efficacy supplement.

7.1.14 Human Reproduction and Pregnancy Data

The use of mometasone furoate in pregnancy and lactation was not evaluated in this efficacy supplement. There are no adequate studies in pregnant women. Studies in animals with MF, like other glucocorticoids, have shown reproductive toxicity, however. As of December 31, 2006, 44 pregnancy exposures were reported during clinical studies with MF DPI and MF MDI. No study medication-related effects were reported.

7.1.15 Assessment of Effect on Growth

The effect of MF on growth velocity was evaluated in a 52-week, placebo-controlled, parallel-group study conducted in 187 children 4 to 9 years of age, with mild persistent asthma. Treatment groups included MF 100 mcg BID, MF 200 mcg QD AM, 100 mcg QD AM, and placebo. For each patient, an average growth rate was defined as the height change from baseline divided by the time period for the change. The mean growth rates, expressed as least-squares mean in cm/year, for MF 100 mcg BID, MF 200 mcg QD AM, MF 100 mcg QD AM, and placebo were 5.25, 5.90, 6.06, and 6.26, respectively. The placebo-corrected differences and the corresponding two-sided 95% CI of the mean growth rates for MF 100 mcg BID, MF 200 mcg QD AM, and MF 100 mcg QD AM were -1.01 (-2.20, 0.19), -0.36 (-1.50, 0.78), and -0.19 (-1.34, 0.95), respectively. MF 100 mcg BID demonstrated the greatest numerical effect in terms of growth suppression, but was not statistically different from placebo or from the other dosing regimens. The 100 mcg QD PM dosing regimen was not evaluated in this study. See the Biometrics review of Dr. Qian Li for a more detailed review of Study C97-384.

7.1.16 Overdose Experience

One overdose was reported in Study P01431 without adverse effect. There is no data available on the effects of acute or chronic overdosage with Asmanex. Per the approved product label, the potential for acute toxic effects following overdose with the Asmanex Twisthaler is low. Because of low systemic bioavailability and an absence of acute drug-related systemic findings in clinical studies, overdose is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur. Single daily doses as high as 1200 mcg per day for 28 days were well tolerated and did not cause a significant reduction in plasma cortisol AUC (94% of placebo AUC). Single oral doses up to 8000 mcg have been studied on human volunteers with no adverse events reported.

7.1.17 Post-marketing Experience

Since market introduction in January 2003, subject exposure to MF DPI is estimated to be about 31 million subject treatment days as of the end of May 2006. Asmanex is marketed in 20 countries including Costa Rica, Denmark, Dominican Republic, El Salvador, Germany, Greece, Guatemala, Honduras, Iceland, Ireland, Nicaragua, Panama, Slovenia, Sweden, Switzerland, Turkmenistan, United Kingdom, Ukraine, Venezuela and the United States.

During the period of March 30, 2005 to December 23, 2006, 427 cases were reported of which 38 were serious cases. Most of the reported AEs were classified to the body system/organ classes of general disorders and respiratory disorders. The types of individual AEs reported were consistent with those observed during clinical studies. The most frequently reported AEs included dyspnea, drug ineffective, medication error, and headache. A total of 38 serious cases have been reported. Seventeen of the reported AEs were classified to the body system/organ class of respiratory and nine to general disorders. The most commonly reported AEs in these serious cases, although infrequent, include hypersensitivity and throat tightness. During the same period, in pediatric patients 4 to 11 years of age, there were 14 cases of AEs of which 2 cases were serious. The types of AEs were similar to that observed in adults. Overall there is no information in the post-marketing database that identifies any new safety issues.

7.2 Adequacy of Patient Exposure and Safety Assessments

The designs of the studies in this application, patient demographics, exposure of sub-populations, and duration of exposure to MF are sufficient to allow for an assessment of safety.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Table 1 Summary of Clinical Phase 3 Studies in sNDA-21-067 provides a summary of the studies that comprise the clinical development program. This table includes descriptive information on study type, treatment groups, design, patient population, subject numbers, dosing schedule, and indication.

7.2.1.2 Demographics

A summary of the demographic data for the three 3-month efficacy trials is presented in Table 4. In the 3-month studies, the treatment groups were similar with regard to age, race, sex, and baseline characteristics. There were more females than males, and more Caucasians. The majority of subjects were 6 to 11 years of age. Subjects enrolled into the three studies ranged from mild to moderate asthma; % predicted FEV1 ranged from a mean of 78.9 to 80.53%. Mean duration of asthma was similar across treatment groups. The demographic characteristics of the patient populations in the pivotal efficacy studies are representative of those in the HPA axis study and the one-year safety studies.

Table 4 Summary of Demographic Data for 12-Week Efficacy and Safety Studies (P01431, C97-300, C97-380)

	MF DPI 100 mcg QD PM (n = 98)	MF DPI 100 mcg QD AM (n =181)	MF DPI 200 mcg QD AM (n = 172)	MF DPI 100 mcg BID (n = 179)	Placebo (n = 272)
Sex (n, %)					
Female	41 (42)	64 (35)	64 (37)	66 (37)	104 (38)
Male	57 (58)	117 (65)	108 (63)	113 (63)	168 (62
Race (n, %)					
Caucasian	56 (57)	123 (68)	121 (70)	124 (69)	174 (64)
Non-caucasian	42 (43)	58 (32)	51 (30)	55 (31)	98 (36)
Am. Indian	1 (1)	0	0	2 (1)	0
Asian	1 (1)	2 (1)	0	1 (1)	1 (<1)
Black	16 (16)	18 (10)	22 (13)	23 (13)	34 (13)
Hispanic	22 (22)	35 (19)	28 (16)	24 (13)	58 (21)
Other	2 (2)	3 (2)	1 (1)	5 (3)	5 (2)
Age (yr)					
Mean (SD)	9.0 (1.8)	8.5 (2.0)	8.6 (2.1)	8.6 (1.8)	8.4 (1.8)
Age (n, %)					
4 - < 6	5 (5)	14 (8)	19 (11)	13 (7)	15 (6)
6 - < 12	93 (95)	167 (92)	153 (89)	166 (93)	257 (94)
Baseline % Predicted FEV1					
Mean (SD)	79.13 (7.0)	80.53 (8.3)	79.63 (8.2)	80.07 (8.2)	78.90 (8.0)
Range	60.0 – 97.8	59.7 – 112.2	54.3 – 96.3	51.3 – 99.6	58.5 – 99.4
Duration of Asthma (years)					
Mean (SD)	5.94 (2.8)	5.23 (2.6)	5.28 (3.0)	5.45 (2.7)	5.18 (2.7)
Range	0.6 – 11.0	0.5 – 11.0	0.5 – 11.0	0.6 – 11.0	0.5 – 11.0

Source: [(Section 1.3.1, Module 2, Summary of Clinical Safety)]

7.2.1.3 Extent of exposure (dose/duration)

In the eight pediatric clinical studies included in this program, 1479 subjects were randomized and 1035 (70%) subjects received at least one dose of MF. The protocol-prescribed treatment durations ranged from 14 days to 52 weeks in duration, but subjects actually took study medication from 2 to 412 days. Of these 1035 subjects, 314 (30%) were exposed to MF for a period of ≥ 3 months, 255 (25%) for a period of ≥ 6 months, 237 (23%) for ≥ 9 months, and 269 (26%) for ≥ 12 months. Overall, the numbers of subjects exposed to MF DPI met the International Conference on Harmonization (ICH) Guidance E1 for extent of population exposure to assess clinical safety. The total population exposed was 1035 patients and >100 patients received study drug for one year. However, only 255 patients received study treatment for > 6 months. This does not meet the ICH Guidance E1 recommendation of 300 to 600 patients exposed for > 6 months. Although the ICH Guidance E1 recommendation is not met for 6-month exposure, given the extensive post-marketing experience and relatively well-known safety profile of this drug, the extent of exposure is acceptable. (See Section 10 Appendices for exposure data for individual studies.)

7. 2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary clinical data sources were used to evaluate the safety of MF DPI in children ages 4 to 11 years.

7.2.3 Adequacy of Overall Clinical Experience

The study number, design, and duration are sufficient to assess the efficacy and safety of MF 100 mcg QD PM and MF 100 mcg BID in children ages 4 to 11 years old with asthma. All of the studies were double-blind, randomized, and placebo controlled (with the exception of C97-385, which was open-label, active controlled). All of the subjects had an appropriate diagnosis of asthma for at least 6 months and had been using inhaled corticosteroids for at least 30-60 days prior to Screening. Percent predicted FEV1, an accepted measure of efficacy in asthma, was used as the primary efficacy variable. The statistical analysis was appropriate. In addition, there were an adequate number of subjects exposed to the drug, although racial subsets were small to allow for an adequate assessment of safety in these subgroups.

Although the 100 mcg QD PM was evaluated in only one study, the absence of a new safety signal along with extrapolation from safety data in adults, adequately support the safety of MF in this pediatric population. It is also of note that the 100 mcg QD PM dosing regimen was not examined in the growth and HPA axis studies, however, the 100 mcg BID dose and higher dosing regimens were examined, which are also supportive of the safety of MF in this pediatric population 4 to 11 years of age.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal or in vitro studies were performed for this efficacy supplement.

7.2.5 Adequacy of Routine Clinical Testing

Adverse events were collected daily and reviewed by the investigators at all clinic visits, as were vital signs. Routine laboratory testing was performed at baseline and endpoint, and at Week 26 in the one-year studies. Given the mometasone furoate is in a class (corticosteroid) about which there is extensive information, and further is an approved product with significant post-marketing experience, this degree of safety monitoring is adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

These areas of evaluation were not necessary for this pediatric efficacy supplement.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

As mometasone furoate is not a new molecular entity or a new drug, this section is not applicable to this efficacy supplement.

7.2.8 Assessment of Quality and Completeness of Data

The quality of data available for a safety review was generally adequate. Narrative, CRTs, and CRFs were available, accessible, and complete.

7.2.9 Additional Submissions, Including Safety Update

There were no additional submissions.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The adverse event profile of mometasone furoate has been characterized in adults. Adverse events associated with MF DPI in patients ≥12 year old are listed in the currently approved product label and include headache, allergic rhinitis, pharyngitis, upper respiratory tract infection, sinusitis, oral candidiasis, dysmenorrhea, musculoskeletal pain, back pain, dyspepsia, myalgia, abdominal pain, and nausea.

In the pediatric population 4 to 11 years of age, the adverse event profile is similar. Known local AEs associated with inhaled corticosteroids, such as oral candidiasis and dysphonia, were infrequent in these studies.

The known effects of inhaled corticosteroids on HPA axis function and growth velocity were also examined in children. Although the HPA-axis study (study C96-361) failed to show an effect of mometasone furoate on the HPA axis function, there are important limitations to this data. First, the sample size was small and the study shorter than recommended in duration. Further, the proposed dose was not examined in this study, although higher dosing regimens were examined. There was a trend towards HPA axis suppression with increasing doses, however, due to small sample size and variability of the data, the effects were not statistically significant, except at the highest dose of 400 mcg BID, which was marginally statistically significant ($p = 0.05$).

The growth study, Study C97-384, examined MF DPI 100 mcg QD AM, 100 mcg BID, and 200 mcg QD AM. Again, there was a numerical trend towards decrease in growth velocity with increasing dose, but the only the 200 mcg QD AM dose showed a statistically significant effect on growth (-2.42 cm/yr, $p=0.05$). Although the exact dosing regimen of 100 mcg QD PM as not examined in the growth study, the absence of statistically significant effect in the 100 mcg QD AM group and the 100 mcg BID group are supportive.

Since market introduction in January 2003, subject exposure to MF DPI is estimated to be about 31 million subject treatment days as of the end of May 2006. During the period of March 30, 2005 to December 23, 2006, a total of 38 serious cases have been reported. Seventeen of the reported AEs were classified to the body system/organ class of respiratory and nine to general disorders. The most commonly reported AEs in these serious cases, although infrequent, include hypersensitivity and throat tightness. During the same period, in pediatric patients 4 to 11 years of age, there were 14 cases of AEs of which 2 cases were serious. The types of AEs were similar to that observed in adults.

In summary, no new safety signals are identified from the data provided. Although the 100 mcg QD PM was evaluated in only one study, the absence of a new safety signal along with extrapolation from safety data in adults, adequately support the safety of MF in this pediatric efficacy supplement. It is also of note that the 100 mcg QD PM dosing regimen was not examined in the growth and HPA axis studies, however, the 100 mcg BID dose and higher dosing regimens were examined, which also support the safety of MF in this pediatric population 4 to 11 years of age.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Data were not pooled across studies, as the dosing regimens examined in each study were different.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Multiple doses were examined across the eight clinical studies submitted in this application. Overall, there were no meaningful difference in adverse events with increasing doses of MF DPI. However, there appeared to be a numerical trend towards dose dependency on the pharmacodynamic effect of MF on the HPA axis and the growth velocity of children (See Sections 7.1.12 Special Safety Studies and 7.1.15 Assessment of Effect on Growth)

7.4.2.2 Explorations for time dependency for adverse findings

In general, there were more adverse events reported in the 52-week safety trial than in the shorter efficacy trials. This is not unexpected as longer exposure generally results in more adverse events being reported. No other relevant effect of duration of exposure was noted on incidence of adverse findings in this development program.

7.4.2.3 Explorations for drug-demographic interactions

There were no significant differences noted in adverse events when subsets were analyzed according to age, sex, and race. However, it should be noted that the age group of 4-5 year old as well as the non-Caucasian population may have been too small to rule out differing effects on adverse events in these populations.

7.4.2.4 Explorations for drug-disease interactions

The population of subjects in the clinical development program for MF was generally healthy other than the presence of asthma and allergic rhinitis, so no specific drug-disease interactions were assessed.

7.4.2.5 Explorations for drug-drug interactions

Explorations for drug-drug interaction were not conducted during this pediatric development program.

7.4.3 Causality Determination

There were no unusual or rare adverse events that required a causality determination. All of the common adverse events observed were those commonly seen in this class of drug, in this patient population, and in this mode of administration.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

A dose of 100 mcg QD PM is recommended in children 4 to 11 years of age for the maintenance treatment of asthma. The dose may be increased to 100 mcg BID if patients are not adequately responding to the lower dose. The application does not alter the currently approved dosing regimens for patients 12 years of age and older with varying degrees of asthma.

8.2 Drug-Drug Interactions

The Applicant did not conduct any new investigations specifically evaluating drug-drug interactions as part of this supplemental NDA.

8.3 Special Populations

The Applicant did not conduct any new investigations specifically targeted towards any special populations as part of this supplemental NDA.

8.4 Pediatrics

The treatment of children 4 to 11 years of age is covered in the body of this application, and MF is already approved for children 12 years of age and older. The applicant requested and has been granted a waiver for studies in children < 4 years of age.

8.5 Advisory Committee Meeting

A Pulmonary Allergy Advisory Committee was neither held nor required for this efficacy supplement.

8.6 Literature Review

Other than the study reports already included in this application, there were no additional relevant published reports when this reviewer searched the MEDLINE database on November 20, 2007.

8.7 Post-marketing Risk Management Plan

A post-marketing risk management plan was neither submitted nor required for this pediatric efficacy supplement.

9 OVERALL ASSESSMENT

9.1 Conclusions

9.2 Recommendation on Regulatory Action

The regulatory action recommended for this application is **Approval**.

9.3 Recommendation on Post-marketing Actions

None.

9.3.1 Risk Management Activity

Not applicable.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

This reviewer performed a line-by-line review of the product label as submitted by the Applicant in the new PLR format. As of the completion of this review, line-by-line revision of the product label is ongoing. An overview of the proposed major changes to the label is as follows:

Warnings and Precautions (Section 5)
This section will be modified to re-order the warnings and precautions by clinical relevance and importance. The results of the growth study will be added to Section 5.4.

Adverse Reactions (Section 6)
An adverse reaction table for the approved pediatric dosing regimens will be added. Additionally, results of the one-year safety study and post-marketing experience will be summarized.

Clinical Pharmacology (12.2)
The results of the 29-day HPA axis study in children will be added to this section.

Clinical Studies (14)
The results of study PO1431 will be added to this section. The language will be modified to include the treatment effect sizes with confidence intervals, rather than percentage change, as presented by the Applicant.. A figure depicting the change in FEV1 from baseline to endpoint will be included in the label to maintain consistency with the other figures in the Clinical Studies section, even though absolute FEV1 was not the primary endpoint. Study P01431 was chosen as the representative study given its inclusion of both supported dosing regimens (100 mcg QD PM and 100 mcg BID).

9.5 Comments to Applicant

This reviewer has no comments to the Applicant at the time of completion of this review.

10 APPENDICES

10.1 Study P01431, Placebo-Controlled Efficacy and Safety Study of Mometasone Furoate Administered Via Dry Powder Inhaler in the Treatment of Asthma in Children Previously Maintained on Inhaled Corticosteroids

Protocol #:	P01431
Title:	Placebo-Controlled Efficacy and Safety Study of Mometasone Furoate Administered Via Dry Powder Inhaler in the Treatment of Asthma in Children Previously Maintained on Inhaled Corticosteroids
Study Dates:	Initiated January 11, 2001. Completed April 2, 2002.
Sites:	34 sites in the United States; 5 sites in Latin America
Investigators:	3 Principal Investigators
IRB:	The protocol, protocol amendments, and subject informed consent form were reviewed by an Institutional Review Board for each center.
Ethical Considerations:	The investigators conducted this study according to the principles of Good Clinical Practices (GCP).

10.1.1 Study Design/Protocol

Objectives

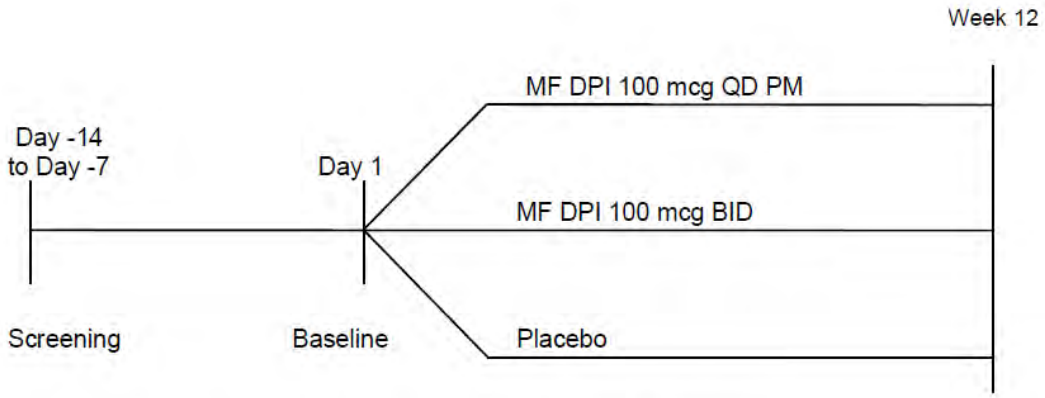
The primary objective of this study was to evaluate the efficacy and safety of MF DPI 100 mcg BID and MF DPI 100 mcg QPM compared with placebo in children with asthma who were previously maintained on inhaled corticosteroids. A secondary objective was to evaluate the relative efficacy and safety of MF DPI 100 mcg QD PM compared with 100 mcg BID.

Description

This was a Phase III, 12-week, multi-center, randomized, double-blind, placebo-controlled, parallel group study evaluating the efficacy and safety of MF DPI, particularly addressing the efficacy of once-daily dosing in relation to placebo and twice-daily dosing. Following a 2-week run-in period during which subjects remained on their prescribed inhaled corticosteroids, the

patients were randomized to one of three parallel treatment arms for 12 weeks: MF 100 mcg QD PM, MF 100 mcg BID, or placebo (See Figure 7).

Figure 7 Study P01431, Study Design Diagram



Postbaseline visits were conducted on Day 4 and Weeks 1, 2, 4, 8, and 12.

Population

The study was designed to recruit 9-12 subjects at each of approximately 35 centers to ensure at least 315 subjects who met the criteria for the evaluation of the primary efficacy endpoint. The inclusion and exclusion criteria used for the study follow:

- Inclusion Criteria

Patients were eligible for study entry if:

1. they were 4 years of age through 11 years of age, of either gender, and of any race
2. they had a diagnosis of asthma of at least 6 months
3. they had a FEV1 at Screening (visit 1) and Baseline (visit 2) of at least 60% and no more than 85% of predicted normal when all restricted medications were withheld for the specified intervals
4. they demonstrated evidence of an increase in absolute FEV1 of ≥ 12% after reversibility testing at Screening or within the past 12 months.
5. they were using inhaled corticosteroids for at least 60 days prior to Screening. For the two weeks prior to Screening, subjects must have been on a stable regimen of one of the following within the ranges specified below:
    a. Flunisolide: 500-1000 mcg/day
    b. Triamcinolone acetonide: 200-800 mcg/day
    c. Beclomethasone dipropionate: 84-336 mcg/day
    d. Budesonide: 200-800 mcg/day
    e. Fluticasone propionate: 88-220 mcg/day
6. if their clinical laboratory tests (CBC, chemistries, and urinalysis) were within normal limits or clinically acceptable to the sponsor/investigator.

7. they were free of any clinically significant disease (other than asthma) that would interfere with the study evaluations
8. they (and/or parents/guardians) gave consent and able to adhere to the protocol
9. they had informed their usual treating physician (if other than the study investigator) of their participation in the study
10. they were premenarchal girls. If a girl began menstruating during the study, a serum pregnancy test was to be done at the next study visit. In order to continue in the study, the subject and parent/guardian must have consented to the subject using a double-barrier method of contraception should she become sexually active during the remainder of the study.

- Exclusion Criteria

Patients were excluded from the study if:

1. their clinical condition required daily use of nebulized beta agonists, or any use of long-acting beta agonists
2. they required in-patient hospitalization for asthma control within the previous 3 months
3. they had required ventilator support for respiratory failure secondary to their asthma within the last 5 years
4. they had used more than 15 days of systemic corticosteroids in the 6 months prior to Screening
5. they had been admitted to the hospital for management of airway obstruction on 2 or more occasions within the last 6 months
6. they had demonstrated an increase or decrease in FEV1 of 20% or more between the Screening and Baseline visits
7. they had required the use of >12 inhalations per day of rescue medication (or three nebulizer treatments) on any two consecutive days between the Screening and Baseline visits
8. they had experienced an upper or lower respiratory tract infection (viral or bacterial) within the previous 2 weeks prior to either the Screening or Baseline Visits.
9. they were receiving escalating doses of immunotherapy, oral immunotherapy, or short course (rush) immunotherapy for treatment of rhinitis.
10. they were allergic to corticosteroids or beta agonists.
11. they had clinical evidence of bronchiectasis or cystic fibrosis
12. they had a significant history of renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, respiratory, gastrointestinal, cerebrovascular, psychiatric, immunologic, or other significant medical illness or disorder which, in the judgment of the investigator, could have interfered with the study, or required treatment that might have interfered with the study (i.e. glaucoma, cataracts, IDDM, cancer, active hepatitis). Other conditions which were well-controlled and stable, and on appropriate medications may have been allowed upon consultation with the sponsor.
13. they had clinically significant abnormal vital signs at Baseline
14. they had clinically significant abnormal ECG at Screening or within previous 30 days.
15. they had clinically significant abnormalities on chest x-ray at Screening or within the previous year

16. they had evidence of clinically significant oropharyngeal candidiasis
17. they had been taking any of the restricted medications prior to the Screening Visit
18. they could not adhere to the concomitant medication prohibitions (see below)
19. they were unable to use the DPI device
20. they were unable to effectively use a peak flow meter

- Withdrawal Criteria

Any subject whose health or well-being would have been threatened by study continuation was to be withdrawn from the study by the investigator. Subjects who experienced a worsening of asthma during the study may have been discontinued depending on their symptoms and/or the judgment of the investigator. Subjects who experienced either of the following criteria MUST have been discontinued from the study:

1. A 20% or greater decrease in FEV1 (absolute value) from the value at the Baseline Visit
2. A clinical asthma exacerbation (CAE) which was defined as a deterioration of asthma that resulted in: hospitalization, treatment with asthma medications prohibited by the protocol, or any other emergency treatment.

Other asthma worsenings which may have contributed to withdrawing of the patient from the study included:

1. A 25% or greater decrease in AM or PM peak flow from the mean AM Baseline value (obtained between Screening and Baseline) on any 2 consecutive days
2. Clinically significant increase in use of bronchodilator (e.g., use of >12 inhalation or > 3 nebulizer treatments of Proventil-HFA® per day for 2 consecutive days).

If a premenarchal girl began menstruating during the study, a serum pregnancy test was to be performed at the next study visit. A positive pregnancy test would also be criteria for study withdrawal.

Treatments

- Study Treatments

At the Baseline visit, subjects meeting the eligibility criteria were randomized to 12 weeks of treatment with one of the following (see below):

Table 5 Study P01431, Treatment Groups

Treatment Group	AM Dose	PM Dose	Total MF (mcg/day)
Group 1	Placebo	100 mcg MF DPI	MF 100 mcg
Group 2	100 mcg MF DPI	100 mcg MF DPI	MF 200 mcg
Group 3	Placebo	Placebo	Placebo (0 mcg)

Each treatment kit contained 2 DPI devices, one AM device and one PM device. Proventil HFA or another albuterol inhaler was provided for rescue medication use.

- Permitted Therapies

The following medications were permitted during the study:

- Proventil-HFA metered dose inhaler (MDI; with at least a 6 hour withhold period prior to any study visit).

- Nebulized beta-agonists (with at least a 6-hour withhold prior to any study visit). For the purposes of this study, one nebulized treatment was regarded as equivalent to four inhalations of Proventil HFA MDI.
- Oral antihistamines (except astemizole)
- Short-acting decongestants, alone or in combination with antihistamines (1 day washout prior to study visit)
- Topical nasal or ocular decongestants, nasal or ocular cromolyn, nasal or ocular antihistamines, intranasal anticholinergics
- Immunotherapy if they were on a stable maintenance schedule for at least one month prior to the screening visit
- Influenza vaccines and childhood immunizations
- Mild potency topical corticosteroids for dermatologic conditions
- Otic mild-potency corticosteroids
- Over the counter pain relief medications
- Antibiotics for indications other than lower respiratory tract infections
- Topical antimicrobials
- OTC pain relief medications
- Ritalin® (methylphenidate hydrochloride)

- Excluded Therapies

Table 6 provides the prohibited medications and the exclusionary time period prior to Screening for each. In addition, no patients could receive any medications linked with clinically significant incidence of hepatotoxicity or which might cause significant liver enzyme induction.

Table 6 Study P01431, Excluded Therapies

Excluded Medication	Washout Period
Methotrexate, cyclosporine, gold and other cytotoxic agents	3 months
Investigational drugs	1 month
Investigational antibodies for asthma or rhinitis	3 months
Beta-adrenergic bronchodilators (syrups, tablets)	1 day
Bronchodilators, short-acting inhaled	6 hours
Beta-adrenergic bronchodilators, nebulized	6 hours
Beta-adrenergic bronchodilators, long-acting	1 week
Theophylline	2 weeks
Cromolyn sodium, nedocromil, inhaled	2 weeks
Ipratropium bromide, aerosol or nebulized or combination with albuterol	6 hours
Leukotriene modifiers	2 weeks
Any systemic bursts of oral, iv, or short-acting intramuscular corticosteroids (not more than 15 days in the 6 months prior to the Screening Visit)	1 month
Corticosteroids, nasal or ocular	2 weeks
Corticosteroids, intramuscular or long acting depot	3 months
Corticosteroids, mid-strength, potent, or superpotent dermatologicals, plain and/or combination	1 month
Astemizole	3 months
Antihistamines	3 days
Oral decongestants (long-acting)	3 days
Oral decongestants (short-acting)	1 day
Immunotherapy for rhinitis	1 day

- Compliance

Compliance was assessed by questioning the subject and/or parent guardian, reviewing the patient diaries for times of medication usage, and recording the counter number from the DPI counter at ach visit. Rescue medication use was assessed in a similar manner.

Conduct

This Phase III, multi-center, randomized, double-blind, placebo-controlled, parallel group study consisted of a run-in period of 1-2 weeks, during which subjects remained on their prescribed ICS. The run-in period was followed by a 12 week double-blind treatment phase. Subjects who met eligibility criteria were randomized at Baseline in a 1:1:1 ratio to one of three parallel treatment arms: MF DPI 100 mcg QD PM, 100 mcg BID, or placebo. The population was stratified according to age (4-5 years and 6-11 years).

There were eight scheduled visits: Screening, Baseline, Day 4, and Weeks 1, 2, 4, 8, and 12. Efficacy was assessed via Pulmonary Function Testing at each visit. Additionally, subjects recorded PEF, symptom scores, rescue medication use, and number of nocturnal awakenings in their patient diaries. Safety assessments included monitoring of adverse events, vital signs, clinical laboratory tests, and physical examinations. The study schedule appears in Table 7.

Table 7 Study P01431, Study Flow Chart

	Screening	Treatment Period						
	Visit 1	Baseline Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Days -14 to -7	Day 1	Day 4 (±1 day)	Week 1 Day 8 (±2 days)	Week 2 Day 15 (±2 days)	Week 4 Day 29 (±2 days)	Week 8 Day 56 (±3 days)	Week 12 Day 84 (±3 days)
Obtain Informed Consent and Informed Assent where appropriate(a)	X							
Review Inclusion/Exclusion Criteria	X	X						
Medical/Disease History	X							
Concomitant Medications Review	X	X	X	X	X	X	X	X
Physical Examination	X							X
Height	X							
Weight	X							X
Vital Signs (Temp, Blood Pressure, Pulse, Respiration)	X	X	X	X	X	X	X	X
Pulmonary Auscultation	X	X	X	X	X	X	X	X
Pulmonary Function Tests	X	X	X	X	X	X	X	X
Reversibility Test	X							
Hematology, Blood Chemistry, Urinalysis	X	Review						X
Electrocardiogram(b)	X	Review						
Chest x-ray(c)	X	Review						
Dispense Peak Flow Meter	X							
Dispense Diary	X	X	X	X	X	X	X	
Retrieve/Review Diary		X	X	X	X	X	X	X
Dispense/Retrieve Rescue Medication, as needed	X	X	X	X	X	X	X	X
Dispense Study Inhaler(s)		X						
Administer First Dose of Study Drug in Office		X						
Evaluation of Response to Therapy			X	X	X	X	X	X
Adverse Events/Intercurrent Illness Evaluation		X	X	X	X	X	X	X
Review Compliance		X	X	X	X	X	X	X
Review DPI Technique(d)	X	X	X	X	X	X	X	
Collect Study Inhaler(s)								X
Quality of Life Assessment		X					X	X

Efficacy Assessments

- Pulmonary Function Testing: spirometry was performed at all visits and three measurements were done. The largest FEV1 and FVC were recorded. Reversibility testing was performed at screening. Reversibility was initially defined in the protocol as an increase in absolute FEV1 of at least 12% over the prebronchodilator value. Prior to unblinding of the data, the criteria was widened to include an increase in absolute FEV1 of 10%. Spirometry was performed to meet the ATS standards.
- Evaluation of Response to Therapy: the investigator or designee assessed the patient's response to therapy from Visit 3 to the final visit using the following scale:
    - 1 = much improved
    - 2 = improved

- 3 = no change
- 4 = worse
- 5 = much worse

- Quality of Life Assessment: a parent/guardian-reported health-related quality of life (HQOL) questionnaire that comprised the Child Health Questionnaire and a modified version of the Usherwood asthma-specific module done at Visit 2, Visit 7, and final visit.
- Peak Expiratory Flow Rate (PEFR): each patient was given a diary and a [redacted]t Peak Flow Meter. Triplicate PEFR measurements were done twice a day before taking asthma medication and the best of the three values at each time point were recorded in the diary. The evening PEFR was to be done approximately 12 hours after the morning PEFR. An average PEFR was determined at Baseline using data from the previous 7 days. This average PEFR value was used to determine if there was a 25% decrease in PEFR from average (safety criteria for clinical evaluation).
- Asthma symptoms: Every morning and evening prior to dosing, patient evaluated three asthma symptoms of wheezing, difficulty breathing, and cough which were scored according to the following scale and recorded in the diary:
  - 0 = None
  - 1 = Noticeable but did not bother me or interfere with normal daily activities/sleep
  - 2 = Annoying and may have interfered with daily activities/sleep
  - 3 = Very uncomfortable and interfered with most of or all of normal daily activities/sleep
- Nocturnal awakenings: patients recorded the number of times during the night that he/she was awakened by asthma symptoms AND required use of rescue medication.
- Rescue Medication Use: patients were also required to record the number of inhalations of rescue medication and/or nebulized beta-agonist treatments used in each 24-hour period.

Safety Assessments

- Physical Examination: at Screening and at final visit
- Vital signs: all visits
- Concomitant Medication Review: all visits
- Laboratory Tests: Screening and final visits (CBC, Chemistry 18 including LFTs, Urinalysis with microscopic examination, serum pregnancy test for girls who become menarchal while on study)
- 12-Lead ECG: Screening
- Chest X-ray: Screening
- Clinical Asthma Exacerbations (CAEs): defined by the sponsor as a deterioration of asthma that resulted in hospitalization, treatment with asthma medication in addition to that allowed in the protocol, or any other emergency treatment. Subjects who experienced a CAE were withdrawn from the study.
- Adverse Events: All visits

Reviewer's Comment: The sponsor states that any asthma symptoms of wheezing, difficulty breathing, cough, and chest tightness or congestion were not considered adverse events, unless they showed a clear temporal relationship to study drug administration or resulted in hospitalization. Although this is atypical in that these symptoms are recorded as AEs in asthma programs, the sponsor has captured clinical asthma exacerbations, so there is some record of these symptoms.

Statistical Plan

- Data Sets Analyzed

The sponsor analyzed two data sets: the intent-to-treat and evaluable subjects. The intent-to-treat set included all subjects randomized to the study. The evaluable data set included all treated subjects who met key eligibility criteria. The primary analysis sample was the ITT population.

- Sample Size Determination

The study was designed to enroll 315 subjects with 105 subjects per treatment arm. The sample size was chosen to detect a treatment difference of 7% or more in the %predicted FEV1 mean change from Baseline (the primary efficacy variable) between any active treatment group and placebo with 90% power and two-sided 5% significance level, assuming a pooled standard deviation of 14.3 for % predicted FEV1 change from baseline.

- Definition of Baseline

The baseline period included the interval of time that began 7 days prior to the Baseline Visit and ended on the day of the Baseline visit, before the first dose of treatment was given

- Primary Efficacy Analyses

The primary efficacy endpoint was change from Baseline to Endpoint in %predicted FEV1. Endpoint was defined as the last post-baseline non-missing observation. The primary objective of the study was to compare the efficacy of MF DPI 100 mcg BID and 100 mcg QD PM versus placebo.

The primary efficacy analysis at Endpoint was based on a test for non-decreasing response with increasing MF DPI dose (0, 100, 200 mcg) using a linear contrast of the treatment means, obtained from a two-way ANOVA to account for treatment and center interactions. In addition to this test of trend, treatment differences were evaluated using the same two-way ANOVA. Specifically, if the test for non-decreasing response with increasing dose was significant, all pair-wise comparisons were made using the least square means from the ANOVA model without adjustments for the multiple comparisons.

- Secondary Efficacy Analyses

The secondary efficacy endpoints were:

- FEV1
- FEF 25%-75% and FVC
- AM and PM PEFR
- Asthma symptom scores
- Use of rescue medication
- Nocturnal awakenings due to asthma
- Response to therapy
- Time to worsening
- Health-Related Quality of Life

All key secondary efficacy variables (except for response to therapy, clinical asthma exacerbations, and time to worsening of asthma) were to be analyzed at each time point using the main-effects two-way ANOVA model noted above for the primary efficacy endpoint. The evaluation of response to therapy was analyzed using the Fisher's exact test. Clinical asthma exacerbation and worsening were summarized and tabulated. For time to worsening of asthma, Kaplan-Meier estimates were calculated and the treatment groups compared using Log-Rank statistics.

- Protocol Amendments

One general amendment was issued on June 21, 2001. The pertinent change instituted by this amendment was to include comparison of the 100 mcg QD PM dose to the 100 mcg BID dose. Other changes were minor, including clarification of inclusion and exclusion criteria and laboratory tests. There was one center-specific amendment which clarified the FEV1 inclusion criteria.

10.1.2 Results

Patient Disposition

A total of 296 subjects were randomized at 39 centers, and all randomized subjects received at least one dose of study medication. The number of subjects randomized to each of the treatment groups is as follows:

- MF DPI 100 mcg QD PM: 98 subjects
- MF DPI 100 mcg BID: 99 subjects;
- Placebo: 99 subjects.

Discontinuations from the study were more common in the placebo treatment group than in the active treatment groups. A total of 72 subjects (24%) discontinued from the study: 32 subjects (32%) in placebo, 19 subjects (19%) in MF DPI 100 mcg BID, and 21 subjects (21%) in MF DPI

100 mcg QD PM. The most common reason for discontinuation was treatment failure, reported by 36 subjects (8.2%). More patients in the placebo group discontinued secondary to treatment failure (18 subjects, 6%) as compared to the MF active treatment groups. Discontinuation secondary to adverse events was greater in the placebo treatment group (11%) vs. the active treatment groups (3-4%). Other less common reasons for study discontinuation were non-compliance, protocol violations, and withdrawal of consent. The patient disposition results are summarized in Table 8.

Table 8 Study P01431, Patient disposition

	MF DPI 100 mcg QD PM (n=98)	MF DPI 100 mcg QD BID (n=99)	Placebo (n=99)
Subjects Randomized	98 (100)	99 (100)	99 (100)
Subjects Completed	77 (79)	80 (81)	67 (68)
Subjects Discontinued	21 (21)	19 (19)	32 (32)
Reason for Discontinuation			
Treatment Failure	9 (9)	9 (9)	18 (18)
Adverse Event	3 (3)	4 (4)	11 (11)
Non-compliance	4 (4)	2 (2)	1 (1)
Did not meet protocol eligibility	4 (4)	2 (2)	0
Did Not Wish to Continue	1 (1)	2 (2)	2 (2)

- Protocol Violations

A total of 25 subjects had a protocol violation. Nine (9) subjects had violations in the MF DPI 100 mcg QD PM group, 11 subjects had violations in the 100 mcg BID group, and 5 subjects had violations in the placebo group. Most protocol deviations were subjects who did not meet entry criteria and in most cases, the subject entered the study with a %predicted FEV1 of >89%. Other protocol violations included non-compliance with study treatment (defined as <75% of the specified doses taken) and use of an unacceptable concomitant medication.

Demographics and Other Baseline Characteristics

- Demographics

Generally, treatment groups were fairly similar at baseline with respect to sex, age, race, weight, and most baseline characteristics. The greatest percentage of subjects was in the 6-11 year age group, ranging from 93-95%. There were more males in the study compared to females, ranging from 57-67% in a given treatment group. The subjects were primarily Caucasian; of the non-Caucasians, 20% were Hispanic. The results are summarized in Table 9.

Table 9 Study P01431, Demographics and Baseline Characteristics

	MF DPI 100 mcg QD PM	MF DPI 100 mcg BID	Placebo
	n = 98	n=99	n=99
Age (years)			
Mean	9.0	8.7	8.2
Range	4 – 11	4-11	4-11
Age Distribution [n (%)]			
4-5 years	5 (5.1%)	5 (5.1%)	4 (4.0%)
6-11 years	93 (94.9%)	94 (94.9%)	95 (96.0%)
Sex			
Female	41 (41.8%)	32 (32.3%)	36 (36.4%)
Male	57 (58.2 %)	67 (67.7 %)	63 (63.6 %)
Race			
Caucasian	56 (57.1%)	63 (63.6%)	60 (60.6%)
Non-Caucasian	42 (42.9%)	36 (36.4%)	39 (39.4%)
Black	16 (16%)	11 (11%)	12 (12%)
Hispanic	22 (22%)	22 (22%)	24 (24%)
Asian	1(1%)	1(1%)	0 (0%)
Other	2 (2%)	2 (2%)	3 (3%)
Height (cm)			
Mean	136.14	134.77	132.53
Range	102.0-159.7	104.1 – 164.9	98.0 – 175.2
Weight (kg)			
Mean	35.42	35.19	33.73
Range	15.0-81.8	15.9-79.5	15.0-90

- Baseline Disease/Other Characteristics

The mean duration of asthma and baseline FEV1 % predicted were similar across all groups. The mean duration of asthma ranged from 5.4 to 6 years, with the range being 1 to 11 years in all groups. The mean % predicted FEV1 at baseline was between 77-79% in all treatment groups. Notable differences between the groups included a lower mean Baseline AM PEF in the placebo group (210.9 L/min) compared to the MF DPI groups (237.0 and 237.7 L/min) and a greater number of subjects (60 subjects) in the MF DPI 100 mcg BID group using fluticasone at

Baseline than subjects in either of the other groups (MD DPI 100 mcg QPM, 48 subjects, and placebo, 52 subjects). These characteristics are summarized in Table 10.

Table 10 Study P01431, Baseline Disease Characteristics

	MF DPI 100 mcg QD PM	MF DPI 100 mcg BID	Placebo
	n = 98	n=99	n=99
Duration of disease (years)			
Mean	5.9	5.8	5.3
Range	1-11	1-11	1-11
Baseline FEV1 % predicted			
Mean	79.21	79.67	77.31
AM PEF			
Mean	237.0	237.7	210.9
Baseline ICS Use *			
Fluticasone			
n	48	60	52
Mean (mcg/day)	161.4	173.4	172.7

* Flunisolide, Triamcinolone, Beclomethasone, and Budesonide were without significant differences between treatment groups.

- Baseline Concomitant Medications and Medical History

The sponsor did not summarize baseline concomitant medications or medical history. This reviewer reviewed the line listings for concomitant medications and the reasons for the medications to provide some information on baseline medical history. In general, the concomitant medications and baseline medical history appear comparable among the treatment groups. The most common baseline medications were asthma-related (steroids and beta-agonists) and the most common concomitant diseases were asthma and allergic rhinitis.

Compliance

Compliance was measured based on the number of doses documented in the diary cards. Study treatment non-compliance was defined as the use of < 75% of > 110 % of the protocol specified dose. The sponsor states that the majority of subjects (99%) were compliant with the dosing

regimen. Four subjects (MF DPI 100 mcg QD PM, one subject; MF DPI 100 mcg BID, two subjects; and placebo, one subject) took <75% of the overall doses specified.
Reviewer's Comment: At the time of finalization of this review, we are awaiting response to an information request to the sponsor regarding a more detailed summary of their compliance data.

Efficacy Outcomes

Efficacy analyses were based on pulmonary function testing, diary cards, investigator assessments, and global evaluation. The sponsor performed analyses on all randomized subjects (the ITT population) and all efficacy-evaluable subjects. There were a total of 25 subjects excluded from the efficacy-evaluable population. The primary reason for exclusion from the efficacy population was primarily due to not meeting entry criteria. This reviewer will focus on the ITT population, as this was the primary population of interest. Analysis of variance was used to compare treatment means with factors for center and treatment interactions. A two-sided t-test was used for pair-wise comparisons between the different treatment groups.

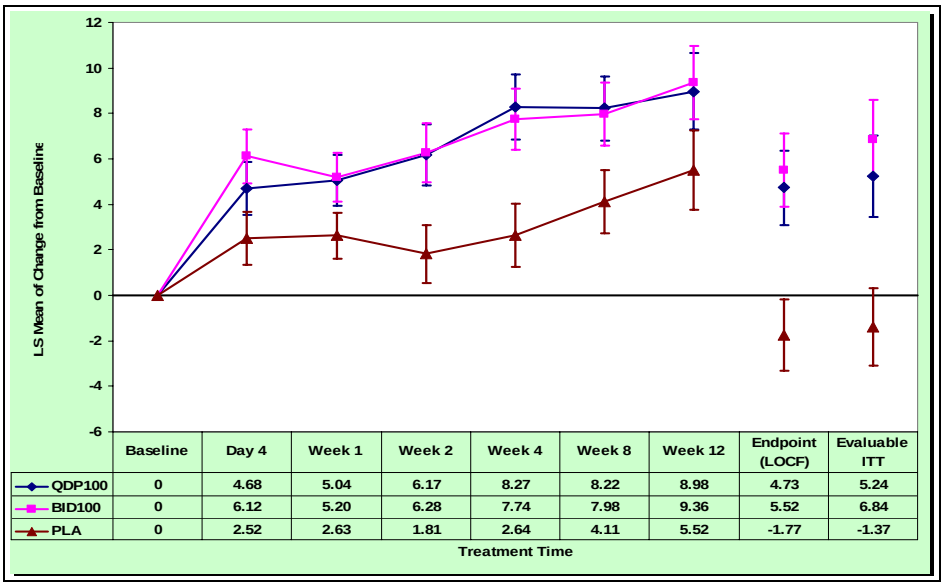
- Primary Efficacy Analysis

The primary efficacy endpoint was the change in % predicted FEV1 from Baseline to Endpoint and the primary comparison was between the active treatment groups versus placebo. The primary objective of this study was to compare the efficacy of the active treatment groups to placebo. Table 11 presents the LS mean of the change from baseline to endpoint in % predicted FEV1. In the active treatment groups, the LS mean change ranged from 4.73% to 5.52%. The LS Mean change for the placebo group was -1.77. These data are graphically represented in Figure 8.

Table 11 Study P01431, Efficacy Measures Summary: Baseline LS Mean % Predicted FEV1 and Change from Baseline LS Mean % Predicted FEV1 in ITT Population

	MF DPI 100 mcg QPM		MF DPI 100 mcg BID		MF DPI Placebo	
	LS Mean	**n**	**LS Mean**	**n**	**LS Mean**	**n**
Baseline	79.21	98	79.67	99	77.31	99
Change from Baseline						
Day 4	4.68	89	6.12	84	2.52	86
Week 1	5.04	90	5.20	95	2.63	97
Week 2	6.17	91	6.28	94	1.81	93
Week 4	8.27	89	7.74	95	2.64	87
Week 8	8.22	79	7.98	83	4.11	76
Week 12	8.98	74	9.36	79	5.52	66
Endpoint	**4.73**	**98**	**5.52**	**99**	**-1.77**	**99**

Figure 8 Study P01431, Change from Baseline to Endpoint in Mean Percent Predicted FEV1

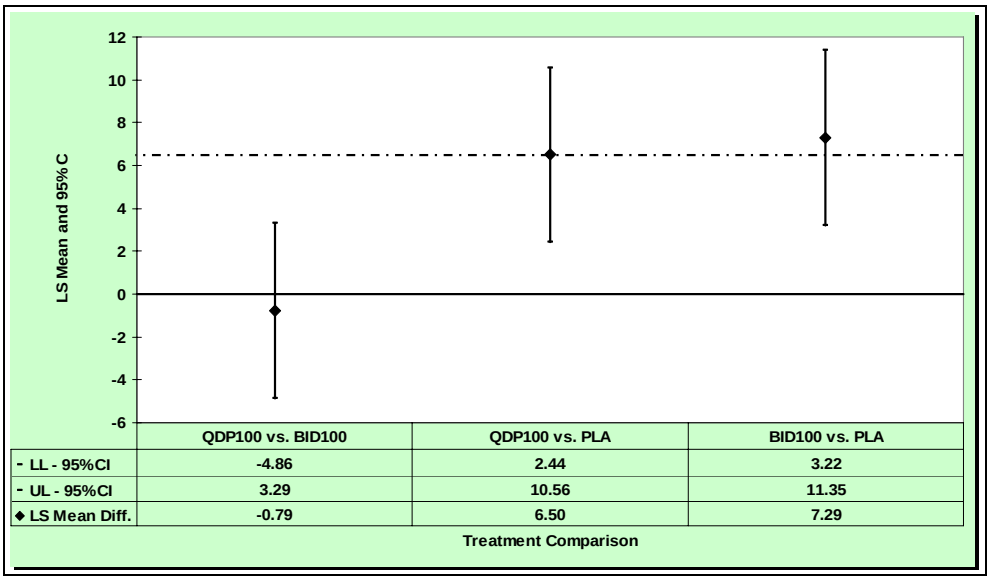


	Baseline	Day 4	Week 1	Week 2	Week 4	Week 8	Week 12	Endpoint (LOCF)	Evaluable ITT
QDP100	0	4.68	5.04	6.17	8.27	8.22	8.98	4.73	5.24
BID100	0	6.12	5.20	6.28	7.74	7.98	9.36	5.52	6.84
PLA	0	2.52	2.63	1.81	2.64	4.11	5.52	-1.77	-1.37

[Source: Biometrics Review, NDA 21-067/S-003, Dr. Feng Zhou]

Figure 9 shows the placebo-corrected differences in mean change in percent-predicted FEV1 from baseline to endpoint for 100 mcg QD pm and 100 mcg BID to be 6.50 (95% CI: 2.44, 10.68) and 7.29 (95% CI: 3.22, 11.35), respectively. These data demonstrate statistically significant increases in mean percent-predicted FEV1 from baseline to endpoint for both MF 100 mcg QD PM and 100 mcg BID ($p = 0.002$ and $p < 0.001$, respectively). The slight difference between the MF DPI groups was not statistically significant, but there was a numerical trend towards benefit with the higher dose.

Figure 9 Study P01431, Change from Baseline to Endpoint in Mean Percent Predicted FEV1



	QDP100 vs. BID100	QDP100 vs. PLA	BID100 vs. PLA
- LL - 95%CI	-4.86	2.44	3.22
- UL - 95%CI	3.29	10.56	11.35
◆ LS Mean Diff.	-0.79	6.50	7.29

[Source: Biometrics Review, NDA 21-067/S-003, Dr. Feng Zhou]

In summary, the primary efficacy analysis was the change in percent-predicted FEV1 from baseline to endpoint. Both active treatment groups were statistically different from placebo, however there was no significant difference between groups.

- Subgroup Analyses by Sex, Age, and Race

The Sponsor analyzed % predicted FEV1 with respect to sex, age, and race. Analysis by sex demonstrated similar mean changes in % predicted FEV1 over time for males and females, Caucasians and non-Caucasians. The sponsor was unable to perform a meaningful subgroup analysis with respect to children younger than 6 years of age (n = 14) because of too few subjects.

- Secondary Efficacy Analyses

The primary analysis sample for secondary efficacy measures was the ITT population, and the primary analysis time point was Endpoint. Secondary efficacy measures included the following:

- FEV1 (L)
- FVC and $FEF_{25-75\%}$
- AM and PM PEFR
- Asthma Symptom Scores
- Response to Therapy
- Use of Rescue Medication
- Number of Nocturnal Awakenings
- Clinical Asthma Exacerbations
- Time to Worsening of Asthma
- Health-Related Quality of Life

FEV1 in Liters

The change from Baseline to Endpoint in FEV1 favored the active treatments over placebo. The baseline LS Mean FEV1 ranged from 1.46 to 1.60 L and was similar in all treatment groups. For the active treatment groups, the change in FEV1 from baseline to endpoint was 0.09L, and -0.04 L in the placebo group. Similar to percent-predicted FEV1, both active treatment groups were statistically superior to placebo ($p < 0.001$).

FVC and $FEF_{25-75\%}$

The LS Mean FVC was similar between all treatment groups at Baseline, ranging from 1.88 to 2.01 liters. Statistically significant differences in mean change in FVC from Baseline to Endpoint were noted for both 100 mcg QD PM and 100 mcg BID compared with placebo (treatment differences: 0.10, p=0.033 and 0.10, p=0.036, respectively).
Similarly, $FEF_{25-75\%}$ was significantly better in active treatment groups, with placebo-corrected differences in mean change from baseline to endpoint for 100 mcg QD PM and 100 mcg BID of 0.26 L ($p<0.001$) and 0.31 L ($p<0.001$), respectively. There was no statistical difference between active treatment groups. FEV1, FVC, $FEF_{25-75\%}$ provide support for the efficacy of both active treatment groups.

AM and PM PEFR

Subjects recorded measured PEF in the morning and evening in diaries. At Baseline, the mean AM PEF ranged between 210.9 L/min to 237.7 L/min per group. The change from Baseline to Endpoint in LS Mean AM PEF ranged from 11.2 to 16.3 L/min for the active treatment groups, compared with -6.9 L/min for the placebo arm. Interestingly, 100 mcg QPM had a greater numerical change in AM PEF as compared with 100 mcg BID, although there was no statistical difference between active treatment groups. Similarly, the change from Baseline to Endpoint in LS mean PM PEF ranged from 12.9 to 14.9 L/min, compared with -5.6 L/min for placebo. Again, the numerical value was greater for once/day dosing. These results are summarized in Table 12.

Table 12 Baseline AM and PM PEFR (L/min) and Change from Baseline in AM and PM PEFR (L/min) by Treatment Group

	MF DPI 100 mcg QPM		MF DPI 100 mcg BID		MF DPI Placebo	
	LS Mean	n	LS Mean	n	LS Mean	n
AM PEFR (L/min)						
Baseline	237.0	98	237.7	99	210.9	99
Change at Endpoint	16.3	98	11.2	99	-6.9	99
Treatment difference (95% CI) p-value	23.2 (13.4, 33.1) P < 0.001		18.1 (8.2, 28.0) P < 0.001			
PM PEFR						
Baseline	243.4	98	244.3	99	218.6	99
Change at Endpoint	14.9	98	12.9	99	-5.6	99
Treatment difference (95% CI) p-value	20.5 (11.2, 29.8) P < 0.001		18.5 (9.2, 27.8) P < 0.001			

The secondary efficacy endpoints of AM and PM PEFR support the efficacy of 100 mcg QD and 100 mcg BID.

Reviewer's Comment: The PEFR data is supportive of the active treatment groups. However, the clinical significance of a difference between treatment groups of 18.5 and 20.5 L/min is questionable.

Asthma Symptom Scores

Subjects recorded AM and PM symptom scores for wheezing, cough, and shortness of breath, each rated on a scale of 0-3. The mean symptom scores were generally low (<1) at Baseline and

most subjects continued to report no or low symptom scores throughout treatment. Because of these low scores, and small changes, the sponsor did not perform inferential analysis of the data. Though the numerical changes were small for all three categories, symptom scores generally decreased in the active treatment groups at Endpoint, and increased at Endpoint in the placebo group. Decrease in asthma symptom scores is generally supportive of the efficacy of both MF dosing regiments.

Response to Therapy

At all visits from Day 4 through Week 12, the physician or designee assessed the subject's response to therapy on a scale from 1 (much improved) to 5 (much worse) at endpoint as compared to baseline. Most patients were rated in the *improved category*, 35.7% to 43.9% in the active treatment groups compared with 30% in the placebo arm. The percentages of patients that were categorized as *much improved* were greater in the active treatment groups compared to placebo (24.5% to 26.5% vs. 14.1% for placebo). Also, 5.1% to 6.1% of subjects in the active treatment groups were characterized as *much worse*, as compared with 14.1% of patients in the placebo arm. In terms of mean scores, significant differences in response to therapy were noted at Week 1 through Week 12 and at Endpoint between placebo and both MF DPI groups. However, the MF DPID BID vs. placebo comparison was not significant at Week 12. There was no significant difference between the active treatment groups. Overall, it appears that the subjects in the active treatment groups had more favorable responses to therapy as compared to placebo.

Use of Rescue Medication

Subjects recorded the number of inhalations of protocol-permitted rescue medication used each day throughout the study period. Mean daily inhalations of protocol-permitted rescue medication were 1.3 in all groups at Baseline. At Endpoint, mean use of rescue medication had decreased by 0.4 to 0.5 inhalations/day in the MF DPI groups compared with an increase of 0.3 inhalations/day in the placebo group. These changes reached statistical significance, though the numerical values were small. There was no difference between the two active treatment arms. For nebulized treatments, all treatment groups showed an increase in nebulizer treatments at Endpoint; however, the active treatment groups had a smaller increase (0 to 0.02) compared to a mean increase of 0.10 for the placebo group.

Number of Nocturnal Awakenings

Subjects recorded the number of times during the night that they were awakened by asthma symptoms requiring rescue medication. The number of nocturnal awakenings at Baseline was low so the data is presented as raw means and no inferential analysis of the data was performed by the Sponsor. At Endpoint, only the MF DPI 100 mcg QPM group showed a mean decrease of -0.03 in the number of nocturnal awakenings, compared to a mean increase of 0.03 with 100 mcg BID and 0.09 with the placebo group. The low prevalence of nocturnal awakenings and the minimal change seen from baseline to endpoint make it difficult to draw any meaningful conclusions from the data.

Clinical Asthma Exacerbations

The sponsor defined clinical asthma exacerbation (CAE) as a deterioration of asthma that results in hospitalization, treatment with asthma medication in addition to those allowed in the protocol, e.g., treatment with a long-acting oral or inhaled beta-agonist or oral steroids, or other emergency treatment. CAEs were reported for 59 subjects, and determined by the sponsor as being present by definition in 54 of the subjects. Of these 54 subjects, the breakdown according to treatment arm is as follows:

- Placebo: 27 subjects
- MF DPI 100 mcg QD: 15 subjects
- MF DPI 100 mcg BID: 12 subjects

The most common reason for recording a CAE was additional asthma medications required. These results demonstrate that CAEs occurred more in placebo-treated patients than those administered active treatment.

Time to Worsening of Asthma

Seventy-nine subjects met one or more protocol-specified criteria for worsening of asthma: 17 subjects – MF DPI 100 mcg QPM; 22 subjects- MF DPI 100 mcg BID; 40 subjects in placebo. The most common criterion for asthma worsening was decrease in PEF (28 of 79 subjects), followed by CAE (15 of 79 subjects). Kaplan-Meier Survival Curves of time to first asthma worsening demonstrate that all active treatments were better than placebo with a distinct separation between the active treatment groups and placebo. Although median time to worsening of asthma in the placebo group was 89 days, the median times to worsening could not be determined in the active treatment groups because less than half the subjects experienced asthma worsening.

Health Related Quality of Life

The HQOL was administered to all randomized subjects at Baseline, Week 8, Week 12, and Endpoint and completed by parents or guardians. The primary HQOL variables were the change from Baseline in the physical summary score of the CHQ-PF 28 and the disability domain of the asthma-specific questionnaire. At Baseline, all treatment groups were comparable with mild-moderate effect of asthma on HQOL. At endpoint, both MF active treatment groups generally reported better HQOL than placebo.

In summary, the efficacy data demonstrate that subjects treated with MF DPI 100 mcg QD PM had statistically significant improvement in mean % predicted FEV1 values from Baseline to Endpoint as compared with placebo (P=0.002). A similar treatment effect was seen with MF DPI 100 mcg BID as compared with placebo ($P < 0.001$). No significant differences between the two dosing schedules was observed, although there was a numerical trend towards added benefit with the 100 mcg BID dosing regimen. In general, the secondary endpoint were also supportive of the efficacy of both treatment arms.

Safety Outcomes

- Exposure

The extent of exposure was generally similar between the active treatment groups and placebo, with 73-75% completing the 12 week study as compared with 69% in the placebo group. The extent of exposure was satisfactory to allow for safety assessments (See Table 13).

Table 13 Study P01431, Extent of Exposure

	Number (%) Subjects		
Length of Exposure	**MF 100 mcg QD PM (n = 98)**	**MF 100 mcg BID (n = 99)**	**Placebo (n = 99)**
Days 1-7	98 (100)	99 (100)	99 (100)
Days 8 -14	94 (95.9)	95 (96)	94 (94.9)
Days 15-28	90 (91.8)	95 (96)	87 (87.9)
Days 29-56	86 (87.8)	90 (90.9)	82 (82.8)
Days 57-84	82 (83.7)	83 (83.8)	74 (74.7)
> 84 Days	22 (22.4)	23 (23.2)	21 (21.2)
Mean (SD)	72 (24.5)	75 (21.7)	68 (27.5)

- Adverse Events

Most Commonly Reported Adverse Events

In general, adverse events were more common in the active treatment arms as compared with placebo. Adverse events were reported in 54-59% of patients in the active treatment groups as compared with 51% in the placebo arm. The most frequently reported adverse events during double-blind treatment with study drug were fever, headache, and upper respiratory tract infection (See Table 14).

Table 14 Study P01431, Adverse Events Occurring in ≥ 10% of Subjects in Any Treatment Group

	MF DPI 100 mcg QD PM N = 98	**MF DPI 100 mcg BID N = 99**	**Placebo N = 99**
Fever	7%	10%	5%
Headache	5%	12%	14%
Upper Respiratory Tract Infection	11%	18%	16%

See Table 15 below for a listing of adverse events reported in at least 2% of subjects in Study P01431. Highlighted adverse events are those which occurred in the active treatment groups at a greater frequency than in the placebo group. Fever, allergy, abdominal pain, diarrhea, nausea, vomiting, sinusitis, tooth abscess, upper respiratory tract infection, urinary tract infection, musculoskeletal pain, bruise, and epistaxis occurred more in the active treatment groups when compared with placebo.

Table 15 Study P01431, Incidence of Adverse Events Reported in at Least 2% of Subjects

	MF 100 mcg QPM (n = 98)	MF 100 mcg BID (n = 99)	Placebo (n=99)
Subjects Reporting any Adverse Event	**54**	**59**	**51**
Body as a Whole/General Disorders	**11**	**24**	**16**
Fatigue	0	2	3
Fever	7	10	5
Headache	5	12	14
Disorders of Blood and Lymphatic System	**0**	**0**	**3**
Lymphadenopathy cervical	0	0	2
Disorders of the Ear and Labyrinth	**2**	**3**	**3**
Earache	1	2	2
Disorders of the Immune System	**7**	**11**	**8**
Allergy	4	6	3
Allergy aggravated	4	5	5
Gastrointestinal System Disorders	**13**	**17**	**8**
Abdominal pain	6	6	2
Diarrhea	1	2	0
Nausea	1	2	1
Vomiting	3	2	2
Infections and Infestations	**27**	**26**	**29**
Infection viral	2	1	33
Otitis media	2	1	6
Pharyngitis	9	5	9
Sinusitis	1	3	0
Tooth abscess	0	2	0
Upper Respiratory Tract Infection	11	18	16
Urinary tract infection	2	1	0

	MF 100 mcg QPM (n = 98)	MF 100 mcg BID (n = 99)	Placebo (n=99)
Arthralgia	0	0	2
Musculoskeletal Pain	1	4	0
Platelet, Bleeding, and Clotting Disorders	**2**	**1**	**0**
Bruise	2	1	0
Respiratory System Disorders	**5**	**7**	**11**
Coughing	1	2	2
Epistaxis	1	2	1
Nasal congestion	1	1	4
Rhinitis	1	1	2

The majority of the AEs reported in this study were categorized as mild. The applicant did present a table of severe AEs, (study report P01431, Table 29). Twenty-one (7%) subjects reported severe AEs; no life-threatening AEs were reported. The overall incidences of severe AEs was similar in the two MF DPI groups and slightly higher in the placebo group: MF DPI 100 QD PM 4 (4%); MF DPI 100 mcg BID 6 (6%); and placebo 11(11%). Most severe AEs were reported by only one subject.

Local Adverse Events

Corticosteroids are commonly implicated as causes of local adverse events such as pharyngitis, oral candidiasis, and hoarseness/dysphonia. Pharyngitis was reported by 23 (8%) of subjects overall; 14 (7%) in the active treatment groups (PM, 9; BID 5) and 9% in the placebo group. All cases of pharyngitis were considered mild to moderate in severity. No cases of pharyngitis led to the discontinuation of a subject from the study.

Interestingly, oral candidiasis was only reported by one subject receiving placebo, who experienced moderate oral candidiasis from Day 59 to Day 66. Pharyngitis was reported in 5-9% of subjects receiving active treatment, and 9% of subjects receiving placebo.

Reviewer's Comment: Overall, the incidence of the well-known local adverse events of inhaled corticosteroids seems low in this study, especially oral candidiasis.

Subgroup Analysis of Adverse Events

The sponsor attempted to address any differential in adverse events noted in different genders, races, or age. Although there were more boys (n=27 to 39) than girls (n= 20 to 27) in each group, the incidence of AEs was somewhat higher per group in girls than boys; among girls,

66%, 63%, and 56% of those treated with 100 mcg QPM, 100 mcg BID, and placebo, respectively, reported AEs, compared with 47%, 58%, and 49% of boys, respectively. There were only slight differences, however, between girls and boys in the incidence of the more common AEs of upper respiratory tract infection and headache. There were more Caucasian subject per treatment group (n=56 to 63) than non-Caucasian (n = 36 to 42) subjects. The overall incidence of AEs per treatment group was higher among Caucasians than non-Caucasians; 59%, 63%, and 62% of Caucasians treated with 100 mcg QPM, 100 mcg BID, and placebo, respectively, reported AEs, compared with 50%, 53%, and 36% on non-Caucasians, respectively. There were no apparent differences, however, between Caucasians and non-Caucasians in the incidence of the more common AEs of upper respiratory tract infection (11%-18% of Caucasians; 12%-19% of non-Caucasians) and headache (4%-17% of Caucasians; 7-17% of non-Caucasians). AEs were also sub-grouped by age (4-5 year olds and 6-11 year old), but there were not enough subjects in the younger age group (n = 14) to provide meaningful assessment of AEs based on age stratum.

- Deaths, Serious Adverse Events, and Pregnancies

There were no deaths reported during the study period or within 30 days of the last dose of the study drug.

Serious adverse events were reported in six patients; one in the MF 100 mcg QD PM group, three in the MF 100 mcg BID group, and one in the placebo group. One additional patient had an SAE during the Screening period, prior to randomization. A brief summary of these SAEs follows:

- Subject P01431-08/S08913, was a 10-year old male, who during the Screening period of the study and was exposed to “super fart spray”. He had a history of asthma since 1993 triggered by exercise, allergen, infections, odors, perfumes, smoke, and pollutants. As a result of exposure to this odor, he developed an acute flare of asthma symptoms. His doctor prescribed prednisone and nebulized albuterol at home, but his condition worsened and he required 2 days of hospitalization secondary to status asthmaticus. The sponsor states that these events are unlikely related to treatment, and this reviewer agrees with this assessment.

- Subject P01431-21/0120, was an 11-year old male with history of asthma, scoliosis, and spinal fusion who received MF DPI 100 mcg QD PM. On Day 23 of treatment, the subject was hospitalized for second- and third-degree burns to his extremities which he sustained accidentally in a garage fire. He required intubation for inhalation injury and multiple trips to the operating room for escharatomy and wound debridement. This event is unlikely to be related to treatment.

- Subject P01431-27/0071, was an 11-year old male with a history of asthma who received MF DPI 100 mcg BID. The patient developed acute abdominal pain and fever on Day 65, was diagnosed with appendicitis, and subsequently required appendectomy. This event is unlikely to be related to treatment.

- Subject P01431-34/0540, was an 8-year old female receiving MF DPI 100 mcg BID who was hospitalized on Day 56 of treatment with acute appendicitis requiring appendectomy. This event is also unlikely to be related to treatment.

- Subject P01431-36/0502, was a 6-year old male with a history of grade-4 myelomeningocele who was receiving MF DPI 100 mcg BID. The patient underwent spinal surgery for anchored spinal cord that had been scheduled prior to trial entrance. Treatment with blinded study medication continued and the subject was discharged without incident. The investigator considered this event unrelated to study drug.

- Subject P01431-36/0505, was a 7-year old female who had been receiving placebo with 2 reported SAEs: hospitalization and overdose. The patient was hospitalized approximately 2 months after study enrollment with respiratory distress, abdominal pain, vomiting, and chest pain. She was treated with albuterol, antibiotics, ranitidine, hydrocortisone, oxygen, and chest physiotherapy after a CXR showed questionable atelectasis. She was discharged after 3 days of hospitalization. Additionally, this patient had mistakenly doubled the dose of the study medication. The investigator considered the hospitalization unrelated to study drug.

- Withdrawals Secondary to Adverse Events

Eighteen subjects (6%) withdrew from the study secondary to adverse events, three subjects (3%) in the MF DPI 100 mcg QD PM group, four (4%) in the MF DPI 100 mcg BID group, and eleven (11%) in the placebo treatment group. The most commonly reported AE leading to study discontinuation was upper respiratory tract infection.

In the MF DPI 100 mcg QD PM group, the three subjects that withdrew from the study were reported as having skin burn (Day 24), viral infection (Day 10), and laryngitis (Day 64). In the MF DPI 100 mcg BID group, the four discontinuations were for upper respiratory tract infection (Days 57 and 25), abdominal pain (Day 68), and anorexia/fatigue/irritability (Day 21). All but two of the discontinuations in the placebo treatment arm were due to upper respiratory tract infection. The other two AEs reported in the placebo group were allergy (Day 20) and atelectasis (day 66).

Reviewer's Comment: With the exception of anorexia/fatigue/irritability, none of the other AEs are likely to be treatment related. In terms of anorexia/fatigue/irritability, the possibility of association is present; however, the few number of subjects with these AEs leading to discontinuation makes any attribution to causality difficult. No clinically meaningful safety concerns have arose from review of this section.

- Laboratory Evaluation

Laboratory evaluation did not reveal any clinically meaningful results. There was one subject in the MF DPI 100 mcg QD PM treatment group who had increased ALT/AST on Day 95 to

209/141 respectively from normal at screening. However, repeat values on follow up (Day 95) were normal.

- Vital Signs

No clinically meaningful changes in vital signs were noted after review of the line listings.

10.1.3 Conclusions

This was a 12-week, multicenter, randomized, double blind, parallel group study evaluating the efficacy and safety of mometasone dry powder inhaler (MF DPI) in 296 patients ages 4-11 years with asthma of at least 6 months duration.

A total of 296 subjects were randomized to 39 centers, and all randomized subjects received at least one dose of study medication. The number of subjects randomized to each of the treatment groups was comparable. Discontinuation from the study was more common in the placebo group as compared with the treatment groups. A total of 72 subjects (24%) discontinued from the study: 32 subjects (32%) in placebo, 19 subjects (19%) in MF DPI 100 mcg BID, and 21 subjects (21%) in MF DPI 100 mcg QD PM. More patients in the placebo group discontinued secondary to treatment failure (18 subjects, 6%) as compared to the MF DPI active treatment groups. Discontinuation secondary to adverse events was greater in the placebo group (11%) vs. the active treatment groups (3-4%).

The mean duration of asthma, FEV1 % predicted, AM PEF, and baseline ICS use were similar across all groups. The mean duration of asthma ranged from 5.4 to 6.0 years, with the range being 1-11 years in all treatment groups. The mean FEV1% predicted at baseline was between 77.3% and 79.7% for all treatment groups. The mean AM PEF ranged from 210 to 237 in all treatment groups. Mean baseline ICS use ranged from 161 µg in the placebo group to 173 µg in the 100 mcg BID treatment arm.

The primary efficacy endpoint was the change in % predicted FEV1 from Baseline to Endpoint and the primary comparison was between the active treatment groups and placebo. Baseline percent-predicted FEV1 LS Means were fairly comparable between treatment groups, ranging from 77.3 – 79.2%. In the active treatment groups, the LS Mean changes in % predicted FEV1 ranged from 4.73% to 5.52% for 100 mcg QD PM and 100 mcg BID, respectively, as compared to -1.77% for placebo. The placebo-corrected differences in mean change in percent-predicted FEV1 from baseline to endpoint for 100 mcg QD pm and 100 mcg BID to be 6.50 (95% CI: 2.44, 10.68) and 7.29 (95% CI: 3.22, 11.35), respectively. These data demonstrate statistically significant increases in mean percent-predicted FEV1 from baseline to endpoint for both MF 100 mcg QD PM and 100 mcg BID ($p = 0.002$ and $p < 0.001$, respectively). The slight difference between the MF DPI groups was not statistically significant, but there was a numerical trend towards benefit with the higher dose. Secondary endpoints, for the most part, trended towards favoring the active treatments as well.

The extent of exposure was generally similar between the active treatment groups and placebo, with 73-75% of subjects completing the 12 week study as compared with 69% in the placebo group. The extent of exposure was satisfactory to allow for safety assessments.

In general, adverse events were more common and of similar incidence in the active treatment groups as compared to placebo. Adverse events were reported in 54-59% of patients in the active treatment groups as compared to 51% in the placebo arm. Viral infection, upper respiratory tract infection, fever, headache, and abdominal pain were the most commonly reported adverse events. It is of note that local adverse events typically attributed to corticosteroid use were not seen in this study, with the exception of pharyngitis. Pharyngitis was reported by 23 subjects (8%) overall; 14 (7%) in the active treatment groups (PM 9; BID 5) and in 9% of the placebo group. There were no cases of dysphonia, hoarseness, or oral candidiasis in the active treatment groups. No new safety concerns arose from review of adverse events, as the general incidence of AEs was comparable between active treatment groups, and the types of reported AEs were not unexpected for corticosteroids or this asthma population. There were no deaths reported during the study period or within 30 days of the last dose of the study drug. Serious adverse events were reported in six patients, one in the MF 100 mcg QD PM group, three in the MF 100 mcg BID group, and one in the placebo group. One additional patient had an SAE during the Screening period, prior to randomization. It is unlikely that any of the reported SAEs were due to treatment. Additionally, no clinically meaningful changes in vital signs, laboratory tests, or physical examination were noted.

In conclusion, this study supports the safety and efficacy of the MF 100 mcg QD PM and MF 100 mcg BID dosing regimens. There were no clinically significant differences in the safety or efficacy profile between the two dosing regimens, although there was a numerical trend towards added benefit with twice-daily dosing.

10.2 Study C97-380, Placebo-Controlled Efficacy and Safety Study of Mometasone Furoate Dry Powder Inhaler (MF DPI) in the Treatment of Asthma in Children Previously Maintained on Beclomethasone Dipropionate (Vanceril® 84 mcg double strength)

Protocol #:	C97-380
Title:	Placebo-Controlled Efficacy and Safety Study of Mometasone Furoate Dry Powder Inhaler (MF DPI) in the Treatment of Asthma in Children Previously Maintained on Beclomethasone Dipropionate (BDP) [Vanceril® 84 mcg double strength]
Study Dates:	Initiated May 21, 1998. Completed September 1, 1999
Sites:	25 evaluable US centers

IRB:	The protocol, protocol amendments, and subject informed consent form were reviewed by an Institutional Review Board for each center.
Ethical Considerations:	The investigators conducted this study according to the principles of Good Clinical Practices (GCP).

10.2.1 Study Design/Protocol

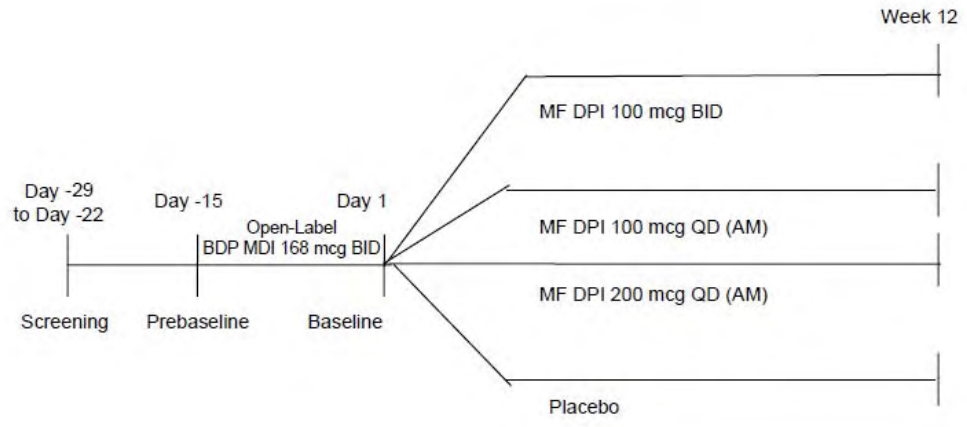
Objectives

The primary objective of this study was to evaluate the efficacy and safety of MF DPI 100 mcg BID compared to placebo. The secondary objective was to evaluate the relative efficacy and safety of MF DPI 100 mcg QD AM and 200 mcg QD AM compared to placebo and MF DPI 100 mcg BID, 100 mcg QD AM, and 200 mcg QD AM compared to each other.

Description

This was a Phase III, multicenter, 4-arm, randomized, double-blind, placebo-controlled, parallel group study evaluating the efficacy and safety of MF DPI in the treatment of asthma in children previously maintained on inhaled corticosteroids. Open-label treatment with BDP 168 mcg BID was used to stabilize and maintain subjects on one standard dose of an inhaled corticosteroid during a 2 week run-in period. The patients were then randomized to one of four parallel treatment arms for 12 weeks: MF DPI 100 mcg BID, MF DPI 100 mcg QD AM, MF DPI 200 mcg QD AM, and placebo (See Figure 10).

Figure 10 Study C97-380, Study Design Diagram



Population

The study was designed to recruit 12-16 subjects at each of approximately 26 centers to ensure at least 400 subjects who met the criteria for the evaluation of the primary efficacy endpoint. The inclusion and exclusion criteria used for the study follow:

- Inclusion Criteria

Patients were eligible for study entry if:

1. they were 4 years of age through 11 years of age, of either gender, and of any race
2. they had a diagnosis of asthma of at least 6 months
3. they had a FEV1 at Screening (visit 1) and Baseline (visit 2) of at least 60% and no more than 90% of predicted normal when all restricted medications were withheld for the specified intervals
4. they demonstrated evidence of an increase in absolute FEV1 of ≥ 12% after reversibility testing at Screening or within the past 12 months.
5. they were using inhaled corticosteroids for at least 30 days prior to Screening. For the two weeks prior to Screening, subjects must have been on a stable regimen of one of the following within the ranges specified below:
    a. Flunisolide: 500-1000 mcg/day
    b. Triamcinolone acetonide: 200-800 mcg/day
    c. Beclomethasone dipropionate: 84-336 mcg/day
    d. Budesonide: 200-800 mcg/day
    e. Fluticasone propionate: 88-220 mcg/day
    f. Vanceril 84 mcg DS: 84-336 mcg/day
    g. Flovent Rotadisk DPI: 100-250 mcg/day
6. if their clinical laboratory tests (CBC, chemistries, and urinalysis) were within normal limits or clinically acceptable to the sponsor/investigator.
7. they were free of any clinically significant disease (other than asthma) that would interfere with the study evaluations
8. they (and/or parents/guardians) gave consent and able to adhere to the protocol
9. they had informed their usual treating physician (if other than the study investigator) of their participation in the study
10. they were premenarchal girls.

- Exclusion Criteria

Patients were excluded from the study if:

1. their clinical condition required daily use of nebulized beta agonists, or any use of long-acting beta agonists
2. they required in-patient hospitalization for asthma control within the previous 3 months
3. they had required ventilator support for respiratory failure secondary to their asthma within the last 5 years
4. they had been admitted to the hospital for management of airway obstruction on 2 or more occasions within the last 6 months
5. they had demonstrated an increase or decrease in FEV1 of 20% or more between the Screening and Baseline visits or between pre-baseline and Baseline visits.

6. they had required the use of >12 inhalations per day of rescue medication (or three nebulizer treatments) on any two consecutive days between the Screening and Baseline visits
7. they had experienced an upper or lower respiratory tract infection (viral or bacterial) within the previous 2 weeks prior to either the Screening or Baseline Visits.
8. they were receiving escalating doses of immunotherapy, oral immunotherapy, or short course (rush) immunotherapy for treatment of rhinitis.
9. they were allergic to corticosteroids or beta agonists.
10. they had clinical evidence of bronchiectasis or cystic fibrosis
11. they had a significant history of renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, respiratory, gastrointestinal, cerebrovascular, psychiatric, immunologic, or other significant medical illness or disorder which, in the judgment of the investigator, could have interfered with the study, or required treatment that might have interfered with the study (i.e. glaucoma, cataracts, IDDM, cancer, active hepatitis). Other conditions which were well-controlled and stable, and on appropriate medications may have been allowed upon consultation with the sponsor.
12. they had clinically significant abnormal vital signs at Baseline
13. they had clinically significant abnormal ECG at Screening or within previous 30 days.
14. they had clinically significant abnormalities on chest x-ray at Screening or within the previous year
15. they had evidence of clinically significant oropharyngeal candidiasis
16. they had been taking any of the restricted medications prior to the Screening Visit
17. they could not adhere to the concomitant medication prohibitions (see below)
18. they were unable to use the DPI device
19. they were unable to effectively use a peak flow meter
20. they were unable to use a metered dose inhaler without a spacer device.
21. they had clinically significant psychological/psychiatric disturbances such as depression, anorexia, or bulimia
22. they were known to be HIV positive (HIV testing was not performed at Screening).

- Withdrawal Criteria

Any subject whose health or well-being would have been threatened by study continuation was to be withdrawn from the study by the investigator. Subjects who experienced a worsening of asthma during the study may have been discontinued depending on their symptoms and/or the judgment of the investigator. Subjects who experienced either of the following criteria MUST have been discontinued from the study:

1. A 20% or greater decrease in FEV1 (absolute value) from the value at the Baseline Visit
2. A clinical asthma exacerbation (CAE) which was defined as a deterioration of asthma that resulted in: hospitalization, treatment with asthma medications prohibited by the protocol, or any other emergency treatment.

Other asthma worsenings which MAY have contributed to withdrawing of the patient from the study included:

1. A 25% or greater decrease in AM or PM peak flow from the mean AM Baseline value (obtained between Screening and Baseline) on any 2 consecutive days

2. Clinically significant increase in use of bronchodilator (e.g., use of >12 inhalation or > 3 nebulizer treatments of Proventil-HFA® per day for 2 consecutive days).

If a premenarchal girl began menstruating during the study, a serum pregnancy test was to be performed at the next study visit. In order to continue in the study, the subject and parent/guardian must have consented to the subject using a double-barrier method of contraception should she become sexually active during the remainder of the study. Another serum pregnancy test was performed at the Final visit. A positive pregnancy test would also be criteria for study withdrawal, and the pregnancy was to be followed to resolution.

Treatments

- Study Treatments

During the Screening Phase (between Screening Visit 1 and Pre-baseline Visit 2), all subjects were to continue to take their prescribed inhaled corticosteroid. The last dose of prescribed inhaled corticosteroid was to be taken the evening prior to the Pre-baseline visit. Following the initial 1-to-2 week Screening period, all eligible subjects returned for the Pre-baseline visit, at which time they were switched to an open-label BDP MDI 168 mcg BID regimen (Vanceril 84 mcg Double Strength MDI) for an additional 2 weeks of treatment. The patients received their first dose of BDP MDI in the investigator's office, and subsequently were instructed to take it in the morning and evening at home. At the Baseline visit, subjects meeting the eligibility criteria were randomized to 12 weeks of treatment with one of the following in a 1:1:1:1 ratio (See Table 16):

Table 16 Study C97-380, Treatment Groups

Treatment Group	AM Dose	PM Dose	Total MF (mcg/day)
MF DPI 100 mcg BID	100 mcg x 1 inhalation	100 mcg x 1 inhalation	MF 200 mcg
MF DPI 100 mcg QD AM	100 mcg x 1 inhalation	Placebo x 1 inhalation	MF 100 mcg
MF DPI 200 mcg QD AM	200 mcg x 1 inhalation	Placebo x 1 inhalation	MF 200 mcg
Placebo	Placebo x 1 inhalation	Placebo x 1 inhalation	Placebo (0)

Each treatment kit contained 2 DPI devices, one AM device and one PM device. Proventil HFA or another albuterol inhaler was provided for rescue medication use.

- Permitted Therapies

The following medications were permitted during the study:

- Proventil-HFA metered dose inhaler (MDI; with at least a 6 hour withhold period prior to any study visit).

- Nebulized beta-agonists (with at least a 6-hour withhold prior to any study visit). For the purposes of this study, one nebulized treatment was regarded as equivalent to four inhalations of Proventil HFA MDI.
- Oral antihistamines (except astemizole or terfenadine)
- Short-acting decongestants, alone or in combination with antihistamines (1 day washout prior to study visit)
- Topical nasal or ocular decongestants, nasal or ocular cromolyn, nasal or ocular antihistamines, intranasal anticholinergics
- Immunotherapy if they were on a stable maintenance schedule for at least one month prior to the screening visit
- Influenza vaccines and childhood immunizations
- Mild potency topical corticosteroids for dermatologic conditions
- Otic mild-potency corticosteroids
- Over the counter pain relief medications
- Antibiotics for indications other than lower respiratory tract infections
- Topical antimicrobials
- OTC pain relief medications
- Ritalin® (methylphenidate hydrochloride)

- Excluded Therapies

Table 17 provides the prohibited medications and the exclusionary time period prior to Screening for each. In addition, no patients could receive any medications linked with clinically significant incidence of hepatotoxicity or which might cause significant liver enzyme induction.

Table 17 C97-380, Excluded Therapies

Excluded Medication	Washout Period
Methotrexate, cyclosporine, gold and other cytotoxic agents	3 months
Investigational drugs	1 month
Investigational antibodies for asthma or rhinitis	3 months
Beta-adrenergic bronchodilators (syrups, tablets)	1 day
Bronchodilators, short-acting inhaled	6 hours
Beta-adrenergic bronchodilators, nebulized	6 hours
Beta-adrenergic bronchodilators, long-acting	1 week
Beta-adrenergic bronchodilators, sustained release	

Excluded Medication	Washout Period
Cromolyn sodium, nedocromil, inhaled	2 weeks
Ipratropium bromide, aerosol or nebulized or combination with albuterol	6 hours
Leukotriene modifiers	2 weeks
Any systemic bursts of oral, iv, or short-acting intramuscular corticosteroids (not more than 15 days in the 6 months prior to the Screening Visit)	1 month
Corticosteroids, nasal or ocular	2 weeks
Corticosteroids, intramuscular or long acting depot	3 months
Corticosteroids, mid-strength, potent, or superpotent dermatologicals, plain and/or combination	1 month
Twelve (12) selected sites collecting MF samples: Any dermatologic or nasal preparation of MF	1 month
Astemizole	3 months
Terfenadine	48 hours
Influenza Vaccine	2 weeks
Theophylline	2 weeks
Antidepressants (tricyclic, serotonin uptake inhibitors, MAO-I)	3 months

The following medications were prohibited after the Screening Visit and for the duration of the study:

- any medication linked with clinically significant incidence of hepatotoxicity (e.g., methotrexate, 17α-alkylsteroids) or which may cause significant liver enzyme induction (e.g., barbiturates).
- Beta blockers (oral or non-selective ophthalmic preparations)
- Nasal, ocular, intra-articular, intramuscular, oral, intravenous, and inhaled corticosteroids, except for the subject's previous ongoing inhaled corticosteroid therapy, which is to be continued through the Screening - pre-Baseline phase only.
- Any dermatological corticosteroids other than the mild category
- Oral decongestants (except for short-acting pseudoephedrine formulations)
- Oral or inhaled bronchodilators (other than Proventil_ or nebulized short-acting beta-agonists).
- Theophylline
- Ipratropium bromide in combination with albuterol (Combivent®)
- Cromolyn sodium or nedocromil (inhaled)
- Astemizole or terfenadine

- Leukotriene modifiers
- Oral immunotherapy or short-course (rush) immunotherapy, for rhinitis
- Other investigational drugs
- Monoamine oxidase inhibitors
- Tricyclic antidepressants
- Antidepressant selective serotonin reuptake inhibitors such as fluoxetine hydrochloride (Prozac) and sertraline hydrochloride (Zoloft)

- Compliance

Compliance was assessed by questioning the subject and/or parent guardian, reviewing the patient diaries for times of medication usage and number of inhalations, and recording the counter number from the DPI counter at ach visit. Rescue medication use was assessed in a similar manner.

Conduct

This Phase III, multi-center, randomized, double-blind, placebo-controlled, parallel group study consisted of a run-in period of 1-2 weeks, during which subjects remained on their prescribed ICS. The run-in period was followed by a 2 week open-label treatment period with BDP 168 mcg BID. The open-label treatment period was followed by a 12-week double-blind treatment phase. Subjects who met eligibility criteria were randomized at Baseline in a 1:1:1:1 ratio to one of four parallel treatment arms: MF DPI 100 mcg QD AM, 100 mcg BID, 200 mcg QD AM, or placebo. There were eight scheduled visits: Screening, Pre-Baseline, Baseline, Day 4, and Weeks 1, 2, 8, and 12. Efficacy was assessed via Pulmonary Function Testing at each visit. Additionally, subjects recorded PEF, symptom scores, rescue medication use, and number of nocturnal awakenings in their patient diaries. Safety assessments included monitoring of adverse events, vital signs, clinical laboratory tests, and physical examinations. The study schedule appears in Table 18.

Table 18 Study C97-380, Study Schedule

	Study C97-380							
	Screening Visit 1	Pre-Baseline Visit 2	Baseline Visit 3	Visit 4	Visit 5	Visit 6	Visits 7/8	Visit 9
	Days -29 to -22	Day -15	Day 1	Day 4 ±1 day	Day 8 ±2 days	Day 15 ±2 days	Day 29/ Week 8 ±2 days	Week 12 ±3 days
Obtain informed consent	X							
Review Inclusion/Exclusion Criteria	X	X	X					
Medical/Disease History	X							
Concomitant Medications Review	X	X	X	X	X	X	X	X
Physical Examination	X							X
Height, Weight	X							
Vital Signs	X	X	X	X	X	X	X	X
Oropharyngeal Exam	X	X	X	X	X	X	X	X
Pulmonary Auscultation	X	X	X	X	X	X	X	X
Pulmonary Function Tests	X	X	X	X	X	X	X	X
Reversibility Test	X							
Hematology, Blood Chemistry, Urinalysis	X	Review						X
Electrocardiogram	X							
Chest X-ray	X							
Dispense Peak Flow Meter	X							
Dispense Diary	X	X	X	X	X	X	X	
Retrieve/Review Diary		X	X	X	X	X	X	X
Dispense/Retrieve Rescue Medication, as needed	X	X	X	X	X	X	X	X
Dispense open label BDP MDI		X						
Collect open label BDP MDI			X					
Dispense Study Inhalers			X					
Administer First Dose of Drug in Office		X	X					
Evaluation of Response to Therapy				X	X	X	X	X
Adverse Events/Intercurrent Illness Evaluation		X	X	X	X	X	X	X
Review Compliance		X	X	X	X	X	X	X
Collect Study Inhalers								X
Quality of Life Assessment			X					X

a: Earlier than Day -14 if longer medication washouts are required. Informed consent must be signed prior to any study-related procedures, including required washout of medications.
b: If not done within the last 30 days.
c: If not done within last year.

Efficacy Assessments

- Pulmonary Function Testing: spirometry was performed at all visits and three measurements were done. The largest FEV1 and FVC were recorded. Reversibility testing was performed at screening. Reversibility was initially defined in the protocol as an increase in absolute FEV1 of at least 12% over the prebronchodilator value. Spirometry was performed to meet ATS standards.
- Evaluation of Response to Therapy: the investigator or designee assessed the patient's response to therapy from Visit 4 to the final visit using the following scale:
    - 1 = much improved
    - 2 = improved
    - 3 = no change
    - 4 = worse
    - 5 = much worse
- Quality of Life Assessment: Visit 3 and Final Visit; a parent-reported health-related quality of life (HQOL) questionnaire which is comprised of the Child Health Questionnaire and a modified version of the Usherwood asthma-specific module

Each subject was given a diary card at Screening and at each subsequent visit, not including the Final Visit. The following information was recorded daily in the diary: morning and evening peak expiratory flow, total daily number of Proventil inhalations, nebulized beta-agonist

treatment (if any), symptoms of asthma, number of nocturnal awakenings due to asthma requiring Proventil use, adverse events, and use of study drug and concomitant medications

- Peak Expiratory Flow Rate (PEFR): At the Screening visit, subjects were given a [redacted] Peak Flow Meter and were instructed in its proper use. Subjects were instructed to perform triplicate PEFR measurements in the morning and the evening before taking their asthma medication. The highest of the three values was recorded in the diary. Also, the average peak flow rate over the 7 days prior to the baseline visit was used to calculate a 25% decline in PEFR. Subjects were instructed to contact the study staff immediately should the AM or PM PEFR be at or below the 25% decrease value on any two consecutive days.
- Asthma symptoms: Every morning and evening prior to dosing, patient evaluated three asthma symptoms of wheezing, difficulty breathing, and cough which were scored according to the following scale and recorded in the diary:
    - 0 = None
    - 1 = Noticeable but did not bother me or interfere with normal daily activities/sleep
    - 2 = Annoying and may have interfered with daily activities/sleep
    - 3 = Very uncomfortable and interfered with most of or all of normal daily activities/sleep
- Nocturnal awakenings: patients recorded the number of times during the night that he/she was awakened by asthma symptoms that required use of Proventil.
- Daily Medication Record: From the pre-baseline visit onward, the subject recorded the time of dosing of study medication twice daily in the diary. In addition, the total number of inhalations of Proventil and/or nebulized beta-agonist treatments used as rescue medication in each 24-hour period was recorded. The subject also recorded any other medications, including over-the-counter preparations.

Safety Assessments

- Medical History: Visit 1
- Physical Examination: Visit 1 and Final Visit
- Oropharyngeal Examination: all visits
- Vital signs: all visits
- Concomitant Medication Review: all visits
- Laboratory Tests: Visit 1 and Final Visit (CBC, Chemistry 18 including LFTs, Urinalysis with microscopic examination, serum pregnancy test for girls who become menarchal while on study)
- 12-Lead ECG: Visit 1
- Chest X-ray: Visit 1
- Adverse Events: At all visits subjects were instructed to accurately record the type and day on which an adverse occurred in their diary. Additionally, the patients were questioned and/or examined at each visit regarding the possible occurrence of adverse events. Adverse events were recorded on the case report form.
    - Clinical Asthma Exacerbations (CAE): defined by the sponsor as a deterioration of asthma that resulted in hospitalization, treatment with asthma medication in addition

to that allowed in the protocol, or any other emergency treatment. Subjects who experienced a CAE were withdrawn from the study.

Reviewer's Comment: The sponsor states that any asthma symptoms of wheezing, difficulty breathing, cough, and chest tightness or congestion were not considered adverse events, unless they showed a clear temporal relationship to study drug administration or resulted in hospitalization. This is not typical. We usually do see these types of symptoms reported as AEs, especially since inhalers can cause paradoxical effects. However, significant deterioration of asthma led to withdrawal per the protocol. Therefore, a careful assessment of subject withdrawal due to asthma will be important. Further, CAEs were also captured as a means to assess the asthma symptoms that were not recorded as AEs.

Statistical Plan

This was a randomized, multi-center, parallel group study of the use of MF DPI in subjects with moderate asthma. There were 4 treatment groups: MF DPI 100 mcg BID, 100 mcg QD AM, 200 mcg QD AM, and placebo. The primary objective of the study was to evaluate the efficacy of MF 100 mcg BID compared to placebo. The null hypothesis was that there was no difference in efficacy between MF 100 mcg BID and placebo.

- Data Sets Analyzed

The sponsor analyzed two data sets: (Section 11.1)

- All Treated Subjects: This data set included all subjects randomized who received at least one dose of double-blind study medication (intent-to-treat principle). All efficacy analyses and summaries of safety were based on all treated subjects.
- Efficacy-Evaluable Subjects: This data set included all subjects randomized who met the key eligibility and evaluability criteria defined below. Confirmatory analyses of the primary parameter, % predicted FEV1, and AM PEFR were based on this subset.

This review will focus on the intent-to-treat data set.

- Sample Size Determination

The study was designed to enroll 400 subjects with 100 subjects per treatment arm. The sample size was chosen to detect a treatment difference of 7% or more in the %predicted FEV1 mean change from Baseline (the primary efficacy variable) between any active treatment group and placebo with 90% power and two-sided 5% significance level, assuming a pooled standard deviation of 13.5 for % predicted FEV1 change from baseline.

Reviewer's Comment: In June 1999, the sponsor notified FDA that, because of observed and significant departures from GCP, the participation of Center 04 was being terminated. The data from Center 04 were excluded from all efficacy and pooled safety analyses. However, listings of safety data from this center are included in this report.

- Primary Efficacy Analyses

The primary efficacy endpoint was change from Baseline to Endpoint in % predicted FEV1. Endpoint was defined as the last post-baseline non-missing observation. The primary objective of the study was to compare the efficacy of MF DPI 100 mcg BID versus placebo.

The primary efficacy analysis at Endpoint was based on the comparison of MF DPI 100 mcg BID vs. placebo using least squares means, obtained from two-way ANOVA that extracted sources of variation due to treatment and center. If this comparison was significant at the 0.05 significance level, then all pair-wise comparisons were to be made using the least squares means from the ANOVA model without adjustment for the multiple comparisons. Summary statistics for the primary variable at Endpoint were provided for the following patient subgroups: Gender, Age(4-5, 6-11), and Race (Caucasians, non-Caucasians).

In addition to the analysis at Endpoint, all six pair-wise comparisons among the four treatment groups were made with respect to the change from Baseline in % predicted FEV1 for each scheduled visit, using the two-way ANOVA model as above. The p-values were not adjusted for multiple comparisons.

- Secondary Efficacy Analyses

At each post-Baseline visit and at Endpoint, the change from Baseline in the following efficacy variables was evaluated:

- FEV1
- FVC
- FEF 25%-75%
- Evaluation of response to therapy

The following efficacy variables obtained from the subject's daily diary card were averaged for Baseline (across 2 days prior to the start of double blind treatment) and at 7-day intervals post-Baseline and analyzed at each time point using two-way ANOVA.

- AM and PM PEFR
- Discontinuations due to worsening of asthma
- Health-Related Quality of Life (Child Health Questionnaire and the Asthma Specific Module)

The following secondary efficacy variables were summarized by each treatment group, at each time interval using only descriptive statistics:

- Asthma symptom scores
- Use of rescue medication, both Proventil HFA MDI and nebulized treatments
- Nocturnal awakenings requiring Proventil

Reviewer's Comment: The protocol had specified that ANOVA was to be done on these secondary efficacy variables as well. However, the symptom scores, use of rescue medication, and nocturnal awakenings were very low at Baseline. As a result, the Sponsor decided to summarize these endpoints using descriptive statistics.

All of the secondary efficacy variables listed above were analyzed at each time point using two-way ANOVA. The evaluation of response to therapy as the percentage of subjects demonstrating improvement or much improvement from Baseline was analyzed using Fisher's exact test. Clinically significant asthma exacerbations and worsenings leading to discontinuation were summarized and tabulated. For time to discontinuation due to worsening asthma, Kaplan-Meier estimates were calculated and the treatment groups compared using Log-Rank statistics. No interim analyses were planned or done.

- Safety Analyses

Frequency tabulations and summary statistics were provided for the following safety parameters.

- Incidence of treatment-emergent adverse events
- Discontinuation due to adverse events
- Changes from Baseline in vital signs
- Changes from Baseline in laboratory tests

- Protocol Amendments

One general amendment was issued on October 12, 1998. The major changes reflected in C97-380, Amendment 1 include:

- Modification of the inclusion criteria to include Vanceril 84 mcg Double Strength, and Flovent Rotadisk DPI as permitted inhaled corticosteroids prior to Screening
- A modification under prohibited medications that resulted in a reduction of the washout period of systemic bursts of oral, intravenous, or short acting intramuscular corticosteroids, from three months to one month.
- A modification of the number of Proventil MDI treatments which were considered equivalent to one nebulized treatment, from six inhalations to four
- Expansion of the discussion of Quality of life data under statistical methods and considerations

In addition, a site specific amendment (site 2) was issued on May 15, 1998. This amendment specified that female subjects who experience the onset of menses at any time during the study would be immediately discontinued from the study.

10.2.2 Results

Patient Disposition

With the exclusion of Center 04, a total of 349 subjects at 25 centers entered the open-label treatment phase, of which 316 were randomized to double-blind study medication. All randomized subjects received at least one dose of study medication. The number of subjects randomized to each of the treatment groups is as follows:

- MF DPI 100 mcg BID: 80 subjects
- MF DPI 100 mcg QD AM: 81 subjects;
- MF DPI 200 mcg QD AM: 75 subjects;
- Placebo: 80 subjects

There were 33 subjects treated during the open-label treatment who were not randomized to double blind treatment. Not meeting protocol eligibility (19 subjects) was the most common reason for discontinuation during open-label treatment. Discontinuation from the study was most common in the placebo treatment group, and lower in the active treatment groups. A total of 76 subjects (24%) discontinued from the study: 30 subjects (38%) in placebo, 20 subjects (27%) in MF DPI 200 mcg QD AM, and 18subjects (22%) in MF DPI 100 mcg QD AM, and 8

subjects (10%) in MF DPI 100 mcg BID. The most common reasons for discontinuation were treatment failure and adverse events. More patients in the placebo group discontinued secondary to treatment failure (16%) as compared to the MF active treatment groups (4-11%). Discontinuation secondary to adverse events was somewhat greater in the placebo treatment group (15%) vs. the active treatment groups (1-11%). The patient disposition results are summarized in the Table 19.

Table 19 Study C97-380, Patient disposition

	Number (%) of Subjects				
	Open-Label	Double-Blind			
	BDP 168 mcg BID (n=349)	MF DPI 100 mcg BID (n=80)	MF DPI 100 mcg QD (n=81)	MF DPI 200 mcg QD (n=75)	Placebo (n=80)
Completed	316 (91)	72 (90)	63 (78)	55 (73)	50 (63)
Final Status Not Available	3 (<1)[a]	0	0	0	0
Discontinued	30 (9)	8 (10)	18 (22)	20 (27)	30 (38)
Reasons for Discontinuation					
Adverse Event	6 (2)	1 (1)	7 (9)[b,c]	8 (11)	12 (15)
Treatment Failure	0	3 (4)	8 (10)[b,c]	8 (11)	13 (16)
Did Not Continue For Reasons Unrelated To Treatment	1 (<1)	2 (3)	1 (1)	1 (1)	2 (3)
Noncompliant With Protocol	4 (1)	1 (1)	2 (2)	2 (3)	2 (3)
Did Not Meet Entry Criteria	19 (5)[d,e]	1 (1)	0	0	1 (1)
Administrative	0	0	0	1 (1)	0

Reviewer's Comment: Superscripts in the above table refer to some individual subjects who may have been misclassified as to reason for discontinuation. However, the individual changes made by the sponsor did not change the fact that more subject discontinued from the placebo group for AEs and treatment failure than any of the active treatment groups.

- Protocol Violations

In addition to the 33 subjects that were not randomized to double-blind treatment, 46 randomized subjects had one or more major protocol deviations. Fifteen subjects had violations in the MF DPI 100 mcg BID group, 8 subjects in the 100 mcg QD AM group, 11 subjects in the 200 mcg QD AM group, and 12 subjects in the placebo group. Most protocol deviations were subjects who did not meet entry criteria and in most cases, the subject entered the study with a %predicted FEV1 outside the specified range. Other protocol violations included non-compliance with study treatment and FEV1 values exceeding criteria for variability (≥20%) between Pre-baseline and Baseline. Eleven subjects had a first worsening of asthma due to CAE or decrease in FEV1 and were not discontinued, which was considered a protocol deviation. Subjects who were not appropriately discontinued from the study were not excluded from the efficacy-evaluable data set.

Demographics and Other Baseline Characteristics

- Demographics

Generally, treatment groups were fairly similar at baseline with respect to sex, age, race, weight, and most baseline characteristics. The greatest percentage of subjects was in the 6-11 year age group, ranging from 87-96%. There were more males in the study compared to females, ranging from 52-70% in a given treatment group. The patients were primarily Caucasian. The results are summarized in Table 20.

Table 20 Study C97-380, Demographics and Baseline Characteristics

	BDP-Only	MF DPI 100 mcg BID	MF DPI 100 mcg QD AM	MF DPI 200 mcg QD AM	Placebo
	n=33	n=80	n = 81	n = 75	n=80
Age (years)					
Mean	8.1	8.5	8.8	8.5	8.7
Range	5-11	4-11	4-11	4-11	4-11
Age Distribution [n (%)]					
4-5 years	4 (12)	8 (10)	4 (5)	10 (13)	3 (4)
6-11 years	29 (88)	72 (90)	77 (95)	65 (77)	77 (96)
Sex					
Female	9 (27)	34 (43)	26 (32)	22 (29)	30 (38)
Male	24 (73)	46 (57)	55 (68)	53 (71)	50 (62)
Race[n (%)]					
Caucasian	23 (70)	61 (76)	58 (72)	60 (80)	58 (73)
Non-Caucasian	10 (30)	19 (24)	23 (28)	15 (20)	22 (27)
Black	9 (27)	12 (15)	15 (19)	11(15)	12 (15)
Hispanic	---	2(3)	4 (5)	2 (3)	7 (9)
Asian	---	---	1 (1)	---	1 (1)
Other	1 (3)	5(6)	3 (4)	2 (3)	2 (3)
Weight (kg)					
Mean	32.4	35.8	35.1	36.6	36.8
Range	18.0-56.0	16.0-84.0	17.0-73.0	17.0-79.0	15.0-74.0

Reviewer's Comment: The Sponsor has not provided the composition of the "non-caucasian" subset of patients. The breakdown of the non-caucasian subset was compiled by this reviewer from the line listings in section 14.1.3.

- Baseline Disease/Other Characteristics

The mean duration of asthma and baseline FEV1 % predicted were similar across all groups. The mean duration of asthma ranged from 5.0 to 6.0 years, with the range being 0.67 to 11 years in all groups. The mean % predicted FEV1 at baseline was between 80.6% and 79% in all treatment groups. Notable differences between the groups included a lower mean Baseline AM PEF in the placebo group (210.9 L/min) compared to the MF DPI groups (237.0 and 237.7 L/min) and a greater number of subjects (60 subjects) in the MF DPI 100 mcg BID group using fluticasone at Baseline than subjects in either of the other groups (MF DPI 100 mcg QPM, 48 subjects, and placebo, 52 subjects). These characteristics are summarized in **Table** 21.

Table 21 Study C97-380 Baseline Disease/Other Characteristics

	BDP-Only	MF DPI 100 mcg BID	MF DPI 100 mcg QD AM	MF DPI 200 mcg QD AM	Placebo
	n=33	n=80	n = 81	n = 75	n=80
Duration of disease (years)					
Mean	6.0	5.0	5.7	5.3	5.2
Range	2.0-11.0	0.67-11.0	1.83-11.0	0.67-11.0	0.5-11.0
Baseline FEV1 % predicted					
Mean	NA	80.6	80.8	81.2	81.4
AM PEF (l/min)					
Mean	NA	249.9	252.8	257.5	233.5
Pre-Baseline ICS Use					
BDP					
no. of subjects	14	47	36	39	40
Mean mcg/day	225.1	236.8	231.9	220.8	212.9
Range	128-336	42-336	84-336	84-336	84-336
Budesonide					
no. of subjects	4	4	6	3	3
Mean mcg/day	350.0	300	333.3	333.3	333.3
Range	200-400	200-400	200-400	200-400	200-400
Flunisolide					
no. of subjects	1	4	3	2	2
Mean mcg/day	250	625	1000	750	1000
Range	250-250	500-1000	1000-1000	500-1000	1000-1000

Fluticasone Propionate					
no. of subjects	5	15	18	15	21
Mean mcg/day	269.6	173.3	189.6	189.3	191.6
Range	176-440	88-220	88-440	88-440	100-220
Triamcinolone Acetonide					
no. of subjects	9	10	18	16	14
Mean mcg/day	377.8	390	505.6	450	557.1
Range	200-400	200-600	300-800	200-800	400-800

- Baseline Concomitant Medications and Medical History

The sponsor did not summarize baseline concomitant medications or medical history. This reviewer reviewed the line listings for concomitant medications. The concomitant medications were divided into asthma/allergy related and unrelated medications. Among the most common concomitant medications used to treat asthma/allergy were short acting b2-agonists, antihistamines, inhaled/nasal corticosteroids, cromolyn, ipratropium, oral corticosteroids, and decongestants. Many subjects were also receiving immunotherapy. Of the asthma/allergy unrelated concomitant medications, the most common drugs were acetaminophen, ibuprofen, antibiotics, and over-the-counter cough/cold preparations.

Compliance

Compliance was measured based on the number of doses documented in the diary cards. Study treatment non-compliance was defined as the use of < 75% of > 125 % of the protocol-specified dose. Fifteen subjects were considered to have been non-compliant with study medication (< 75% of doses taken), and were excluded from the Efficacy-Evaluable subset. Eleven subjects were non-compliant with BDP during the open-label treatment and the remaining four subjects (MF DPI 100 mcg BID, 2 subjects; MF DPI 200 mcg QD AM, 1 subject; Placebo, 1 subject) had an overall compliance of <75%. All non-compliant subjects were included in the intent-to-treat analysis. No subject took > 125% of the doses specified.
Reviewer's Comment: An information request was submitted to the company on November 6, 2007, to attain complete compliance data in a tabular format.

Efficacy Outcomes

Efficacy analyses were based on pulmonary function testing, diary cards, investigator assessments, and global evaluation. The sponsor performed analyses on all randomized subjects (the ITT population) and all efficacy-evaluable subjects. There were a total of 79 patients excluded from the efficacy-evaluable population. The primary reasons for exclusion from the efficacy-evaluable population were: no valid visits, noncompliance with the protocol, and not meeting entrance criteria. This reviewer will focus on the ITT population, as this was the primary population of interest. Analysis of variance was used to compare treatment means with factors

for center and treatment interactions. A two-sided t-test was used for pair-wise comparisons between the different treatment groups.

- Primary Efficacy Analysis

The primary efficacy endpoint was change from Baseline to Endpoint in % predicted FEV1. The use of Endpoint data adjusts for the discontinuation of subjects over time. The primary objective of the study was to compare the efficacy of MF DPI 100 mcg BID versus placebo. The primary efficacy analysis at Endpoint was based on the comparison of MF DPI 100 mcg BID vs. placebo using least squares means, obtained from two-way ANOVA that extracted sources of variation due to treatment and center. If this comparison was significant at the 0.05 significance level, then all pair-wise comparisons were to be made using the least squares means from the ANOVA model without adjustment for the multiple comparisons.

In addition to the analysis at Endpoint, all six pair-wise comparisons among the four treatment groups were made with respect to the change from Baseline in % predicted FEV1 for each scheduled visit, using the two-way ANOVA model as above. The p-values were not adjusted for multiple comparisons.

Table 22 presents the LS Mean of the change from baseline to endpoint in % predicted FEV1. In the active treatment groups, the LS Mean changes in % predicted FEV1 ranged from 2.40 in the MF DPI 100 mcg QD AM group to 6.09 in the MF DPI 100 mcg BID group. The LS Mean change in the % predicted FEV1 from baseline in the placebo group was -1.90. These data as presented in Table 23 demonstrate statistically significant increases in mean % predicted FEV1 values from baseline to endpoint for both MF DPI 100 mcg BID and MF DPI 200 mcg QD AM, compared with placebo. Increases in mean % predicted FEV1 from Baseline to Endpoint were not significantly different between the MF DPI treatment groups and the MF DPI 100mcg QD AM compared with placebo. These data are graphically represented in Figure 11.

Figure 11 Study C97-380, % Predicted FEV1 – Change from Baseline by Treatment Group (All treated Subjects): LS Mean +/- SE

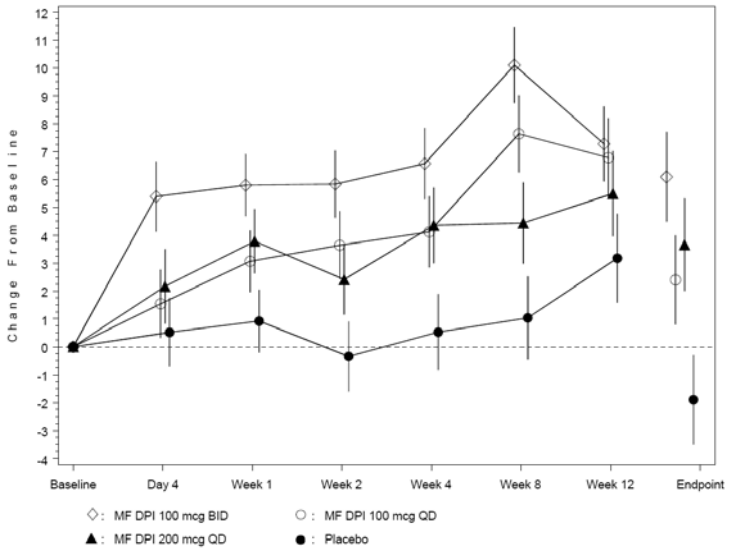


Table 22 Study C97-380, Baseline LS Mean % Predicted FEV1 and Change from Baseline to Endpoint LS Mean % Predicted FEV1 in ITT Population

	100 mcg BID		100 mcg QD AM		200 mcg QD AM		Placebo	
	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
Baseline	80	80.55	81	80.82	75	81.15	80	81.35
Change from Baseline								
Day 4	63	5.38	67	1.54	56	2.16	66	0.52
Week 1	78	5.79	78	3.07	72	3.78	76	0.92
Week 2	78	5.83	76	3.64	72	2.41	72	-0.34
Week 4	75	6.57	75	4.12	66	4.35	65	0.53
Week 8	71	10.09	68	7.63	61	4.43	58	1.04
Week 12	70	7.27	63	6.78	54	5.49	50	3.18
Endpoint	80	6.09	81	2.40	75	3.66	80	-1.90

Table 23 Study C97-380, % Predicted FEV1 LS Mean Difference of Pair-wise Comparisons

	100 mcg BID vs. PLA	100 mcg BID vs. 100 mcg QD AM	100 mcg BID vs. 200 mcg QD AM	100 mcg QD AM vs. 200 mcg QD AM	100 mcg QD AM vs. PLA	200 mcg QD vs. PLA
LS Mean Difference	7.99	3.69	2.43	-1.26	4.29	5.56
P-value	**<0.001**	0.103	0.293	0.585	0.059	**0.016**

Although the change from Baseline to Endpoint was the primary variable of interest, results at other time points were also reviewed. The range of improvement in LS Mean % predicted FEV1 from Baseline to any given time point ranged between 1.54 and 10.09 for all active treatment groups, compared to between -0.34 and 3.18 for placebo (See Table 22).

In summary, the primary efficacy analysis was the change of % predicted FEV1 from Baseline to Endpoint. The primary comparison was between MF DPI 100 mcg BID vs. placebo. MF DPI 100 mcg BID was superior to placebo with a treatment difference (LS Mean) of 7.99, P <0.001. In other comparisons, MF DPI 200 mcg QD was also superior to placebo with a treatment difference of 5.56, P=0.016. There were no statistically significant differences between the active treatment groups.

- Subgroup Analyses of the Primary Efficacy Variables

Response by Sex, Age, and Race

The Sponsor analyzed % predicted FEV1 with respect to sex, age, and race. Analysis by sex demonstrated similar mean changes in % predicted FEV1 over time for males and females, Caucasians and non-Caucasians. The sponsor did not conduct an analysis to further differentiate

the response by race as the number of non-Caucasians was limited. The sponsor was unable to perform a meaningful subgroup analysis with respect to children younger than 6 years of age (n = 14) because of too few subjects.

Response by Baseline Severity of Asthma

Response to therapy was evaluated in subjects whose Baseline % predicted FEV1 was < 75% of the predicted value (more severe asthma) versus those whose Baseline % predicted FEV1 was ≥ 75% of the predicted value (less severe asthma). The majority of the patients enrolled in this study were less severe asthmatics with FEV1 % predicted at Baseline ≥ 75%. Numerically, the greatest difference was observed in the MF DPI 100 mcg BID treatment group of the less severe asthmatics (See Table 24).

Table 24 Study C97-380, % Predicted FEV1 - Change from Baseline to Endpoint by Treatment group in Patients with FEV1 < 75% vs. ≥ 75%

	100 mcg BID		100 mcg QD AM		200 mcg QD AM		Placebo	
	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
< 75% at Baseline (More Severe)								
Baseline	22	70.08	19	70.22	18	70.06	17	68.85
Change from Baseline to Endpoint	22	5.21	19	8.42	18	5.99	17	5.32
≥ 75% at Baseline (Less Severe)								
Baseline	58	84.44	62	83.82	57	84.45	63	84.45
Change from Baseline to Endpoint	58	6.97	62	0.83	57	3.49	63	-3.41

- Secondary Efficacy Analyses

The primary analysis sample for secondary efficacy measures was the ITT population, and the primary analysis time point was Endpoint. Secondary efficacy measures included the following:

- FEV1 (L)
- FVC and $FEF_{25-75\%}$
- AM and PM PEFR
- Asthma Symptom Scores
- Response to Therapy
- Use of Rescue Medication
- Number of Nocturnal Awakenings
- Clinical Asthma Exacerbations

- Time to Worsening of Asthma
- Health-Related Quality of Life

FEV1 in Liters

Table 25 Study C97-380, FEV1 (L) – Change from Baseline by Treatment Group (All treated subjects)

	100 mcg BID		100 mcg QD AM		200 mcg QD AM		Placebo	
	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
Baseline	80	1.59	81	1.61	75	1.60	80	1.62
Change from Baseline								
Day 4	63	0.11	67	0.03	56	0.05	66	0.01
Week 1	78	0.11	78	0.06	72	0.08	76	0.02
Week 2	78	0.11	76	0.07	72	0.04	72	0.00
Week 4	75	0.13	75	0.08	66	0.07	65	0.01
Week 8	71	0.19	68	0.14	61	0.07	58	0.02
Week 12	70	0.14	63	0.13	54	0.10	50	0.06
Endpoint	80	0.11	81	0.05	75	0.06	80	-0.04

Table 26 Study C97-380, FEV1 (L) LS Mean Difference of Pair-wise Comparisons

	100 mcg BID vs. PLA	100 mcg BID vs. 100 mcg QD AM	100 mcg BID vs. 200 mcg QD AM	100 mcg QD AM vs. 200 mcg QD AM	100 mcg QD AM vs. PLA	200 mcg QD AM vs. PLA
LS Mean Difference	0.15	0.06	0.05	-0.01	0.09	0.10
P-value	**<0.001**	0.104	0.226	0.702	**0.035**	**0.014**

Similar to % predicted FEV1, there were no differences in baseline measurements. The baseline LS Mean FEV1 ranged from 1.59 to 1.61 L (See Table 25). The treatment differences for change in baseline to endpoint in absolute FEV1 are shown in Table 26. Similar to the primary efficacy analysis, MF DPI 100 mcg BID and 200 mcg QD AM are both significantly better than placebo. However, when the analysis is conducted with FEV1, instead of % predicted FEV1, MF DPI 100 mcg QD AM is also significantly superior to placebo.
Reviewer's comment: Although the p-value was on the borderline of being significant when the analysis was conducted using % predicted FEV1, it is unclear why the p-value is significant for 100 mg QD AM (<0.05) when the analysis is conducted using the absolute FEV1 in liters. Because the percent predicted are based upon population standards whereas the FEV1 is an absolute value, there are differences between the variables that affect the outcome of the

analysis. However, the two efficacy variables are correlated and numerically show similar trends.

FVC and $FEF_{25-75\%}$

There were no significant differences among treatment groups at Baseline in either FVC or $FEF_{25-75\%}$. Statistically significant differences in mean change in FVC from Baseline were noted at Endpoint for both MF DPI 100 mcg BID and MF DPI 200 mcg QD AM compared with placebo. (Treatment differences: 0.10 L, P=0.046 and 0.10 L, P=0.035, respectively).

Statistically significant differences in mean change in $FEF_{25-75\%}$ from Baseline were noted at Endpoint for all MF DPI treatment groups compared with placebo ($p \leq 0.029$). Comparison among the treatment groups showed that MF DPI 100 mcg BID was significantly better than both MF DPI 100 mcg QD AM and MF DPI 200 mcg QD AM. In conclusion, the secondary endpoints of FEV1, FVC, and $FEF_{25-75\%}$ are supportive of the efficacy of MF 100 mcg BID and 200 mcg QD AM.

AM and PM PEFR

No statistically significant differences in response at Endpoint were detected for either AM or PM PEFR between the active treatment groups and placebo. The results for the AM PEFR are presented below in Table 27 and Table 28. While the AM PEFR numerically favored the active treatment groups (primarily the 100mcg BID and the 100mcg QAM groups), there was no statistically significant difference between the active treatment groups and placebo. The change from baseline for the PM PEFR was 9.34, 14.20, 11.99, and 11.38 for the 100mcg BID, 100mcg QD AM, 200mcg QD AM, and placebo groups, respectively. There were no statistically significant differences between treatment groups. Numerically, the 100mcg BID treatment group had the smallest improvement.

Table 27 Study C97-380. AM PEFR (L/min) – Change from Baseline to Endpoint by Treatment Group (All treated subjects)

	100 mcg BID		100 mcg QD AM		200 mcg QD AM		Placebo	
	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
AM PEFR								
Baseline	80	249.9	81	252.8	75	257.5	80	233.5
Change from Baseline to Endpoint	80	6.03	81	14.99	75	5.04	80	5.00

Table 28 Study C97-380, AM PEFR (L/min)- LS Mean Difference of Pair-wise Comparisons

	100 mcg BID vs. PLA	100 mcg BID vs. 100 mcg QD AM	100 mcg BID vs. 200 mcg QD AM	100 mcg QD AM vs. 200 mcg QD AM	100 mcg QD AM vs. PLA	200 mcg QD vs. PLA
LS Mean Difference	1.03	-8.96	0.99	9.95	9.99	0.04
P-value	0.908	0.313	0.914	0.272	0.261	0.996

In conclusion, although the trends were favorable, the secondary endpoint of PEFR did not statistically support the efficacy of MF in this study.

Asthma Symptom Scores

Subjects recorded AM and PM symptom scores for wheezing, cough, and shortness of breath, each rated on a scale of 0-3. The mean symptom scores were generally low (0.2 to 0.3) at Baseline and most subjects continued to report no or low symptom scores throughout treatment. Because of these low scores, and small changes, the sponsor did not consider it meaningful to conduct statistical analyses of these data.

Generally, morning and evening scores for wheezing, difficulty breathing, and cough were maintained throughout the study and at Endpoint for all active treatment groups. At Endpoint, symptom scores tended to increase (worsen) in all treatment groups.

Reviewer's Comment: Per the Sponsor, the increases in the MF DPI treatment groups in the primary efficacy variable (Change from Baseline to Endpoint in % predicted FEV1) are considered clinically meaningful because subjects entered the study using prescribed doses of various inhaled corticosteroids as maintenance therapy, were switched to BDP 168 mcg BID during open-label treatment, and were then randomized to double-blind treatment at Baseline. Therefore, these increases suggested not only continued maintenance of the previous effect, but improvement in effect over the active treatments taken earlier. However, it is interesting that the same does not hold true for asthma symptom scores or PEFR.

Response to Therapy

At all visits following the Baseline visit, the physician or designee assessed the subject's response to therapy by comparing the current level of symptoms with those noted at Baseline on a scale of 1 (much improved) to 5 (much worse). At Endpoint, the proportion of subjects evaluated as "improved" or "much improved" was higher in the MF DPI groups (all doses, 64% to 84%) than subjects receiving placebo (51%). Results of the Fisher's exact test indicated a significant difference among the active treatment groups compared to placebo in the number of subjects rated as having improved or not having improved.

Table 29 Study C97-380, Response To Therapy (LS Mean scores at Day 4 and Endpoint)

	100 mcg BID		100 mcg QD AM		200 mcg QD AM		Placebo	
	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
Day 4	63	2.39	67	2.77	58	2.69	65	2.62
Endpoint	80	2.01	81	2.40	75	2.32	80	2.74

Table 30 Study C97-380, Response to Therapy (Pair-wise Comparisons)

	100 mcg BID vs. PLA	100 mcg BID vs. 100 mcg QD AM	100 mcg BID vs. 200 mcg QD AM	100 mcg QD AM vs. 200 mcg QD AM	100 mcg QD AM vs. PLA	200 mcg QD vs. PLA
P-value	**<0.001**	**0.019**	0.068	0.632	**0.043**	**0.014**

At Endpoint, mean response scores were significantly lower for all active-treatment groups compared to placebo. In addition, subjects in the MF DPI 100 mcg BID treatment group demonstrated significantly lower mean scores at Endpoint than the MF DPI 100 mcg QD AM treatment group, but was not significantly different from the MF DPI 200 mcg QD AM treatment group (See Table 29 and Table 30).

Overall, it appears that the subjects in the active treatment groups had more favorable responses to therapy as compared to placebo.

Use of Rescue Medication

Subjects recorded the number of inhalations of protocol-permitted rescue medication used each day along with the number of short-acting beta-agonist nebulizer treatments throughout the study period. The majority of subjects did not use rescue medication either at Baseline or during double-blind treatment; therefore, the Sponsor did not consider it meaningful to perform statistical analyses of these data.

Overall, the use of rescue medication both by MDI and nebulization was low at baseline and changed very little at Endpoint. The low prevalence of rescue medication use and the minimal change seen from baseline to endpoint make it difficult to draw any meaningful conclusions from this data.

Number of Nocturnal Awakenings

Subjects recorded the number of times during the night that they were awakened by asthma symptoms requiring rescue medication. The number of nocturnal awakenings at Baseline was low so the data was presented as raw means and no inferential analysis of the data was

performed by the Sponsor. All treatment groups began with ≤ 0.14 nocturnal awakenings. Although the changes were small (0.02-0.11), it is interesting to note that nocturnal awakenings increased in all treatment groups at Endpoint, although less of an increase was noted in the active treatment groups than with placebo. The low prevalence of nocturnal awakenings and the minimal change seen from baseline to endpoint make it difficult to draw any meaningful conclusions from the data.

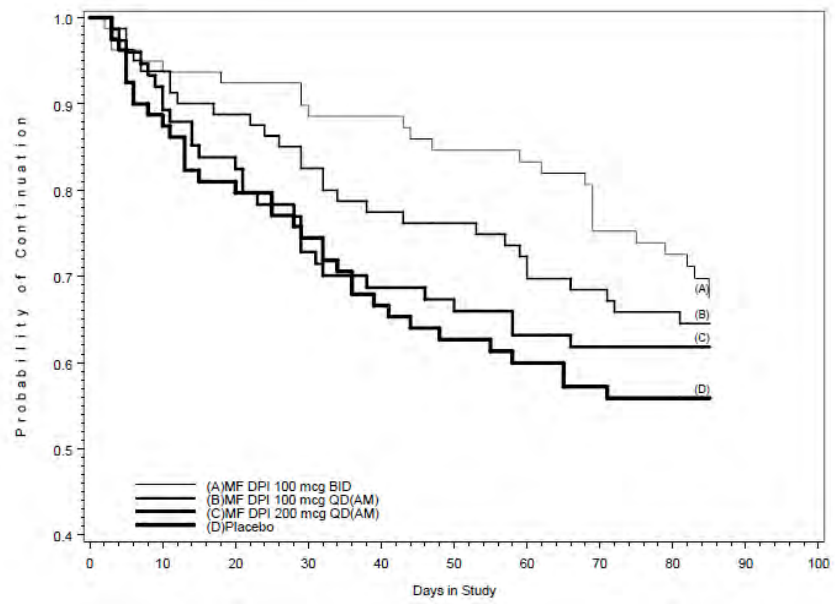
Time to First Asthma Worsening

One-hundred-sixteen subjects met one or more criteria for asthma worsening:

- MF DPI 100 mcg BID: 25 subjects
- MF DPI 100 mcg QD AM: 28 subjects
- MF DPI 200 mcg QD AM: 28 subjects
- Placebo: 35 subjects

The most common reason for worsening of asthma was a decrease in PEFR, followed by a decrease in FEV1 and clinical asthma exacerbation. Survival curves of time to first asthma worsening are shown in Figure 12. Although the active treatment groups appear distinguishable from placebo, they were not statistically different (p=0.24) based on the log-rank test of equality.

Figure 12 Study C97-380, Time to First Asthma Worsening (All-treated subjects)



The secondary endpoint of time to first asthma worsening trended towards support of the efficacy of 100 mcg BID, but did not statistically show a difference from placebo.

Clinical Asthma Exacerbations

The sponsor defined clinical asthma exacerbation (CAE) as a deterioration of asthma that results in hospitalization, treatment with asthma medication in addition to those allowed in the protocol, e.g., treatment with a long-acting oral or inhaled beta-agonist or oral steroids, or other emergency treatment.

Of 316 subjects randomized to double-blind treatment, 48 (15% of total subjects) experienced a protocol-defined CAE sometime during the study. During the double-blind treatment phase, CAEs were reported most often in the placebo group (21 subjects) followed by MF DPI 200 mcg QD (11 subjects) and MF DPI 100 mcg QD AM (12 subjects). CAEs occurred least frequently in the MF DPI 100 mcg BID (4 subjects) group.

These results demonstrate that CAEs occurred more in placebo-treated patients than those administered active treatment. Among the active treatment, MF DPI 100 mcg BID had the least number of CAEs. The secondary endpoint of clinical asthma exacerbations supports that primary efficacy endpoint.

Health Related Quality of Life (HRQOL)

HRQOL in this study was measured using the general health questionnaire, CHQ-PF28, plus an asthma-specific module. Together, these questionnaires assess physical and emotional functioning and how much the asthma interrupts a child's life. The CHQ-PF28 can be summarized by using two summary scores for physical and psychosocial impact. There were no differences between treatment groups for either of the summary scores. Similarly, there was no statistical differences between treatment groups as measured by the asthma specific module.

In summary, statistically significant increases in mean % predicted FEV1 values from baseline to endpoint were noted in both MF DPI 100 mcg BID and MF DPI 200 mcg QD AM groups when compared with placebo. The efficacy of MF DPI was supported by the following secondary endpoints: FEV1, FVC, $FEF_{25-75\%}$, decreased CAEs, and physician's assessment of response to therapy. HRQOL was in favor of MF DPI but did not demonstrate statistical superiority. PEFR, asthma symptom scores, use of rescue medications, and nocturnal awakenings were numerically, although not statistically favorable in support of the efficacy of MF 100 mcg BID and 200 mcg QD AM.. Asthma symptom scores were not supportive of the efficacy, and rescue medication use and nocturnal awakenings were inconclusive.

Safety Outcomes

- Exposure

Sixty-four percent to 80% of subjects in the active treatment groups received treatment for at least 12 weeks. The extent of exposure was satisfactory to allow for safety assessments. This information is summarized in the Table 31.

Table 31 Study C97-380, Extent of Exposure

	Number (%) Subjects			
Length of Exposure	**MF DPI 100 mcg BID N=80**	**MF DPI 100 mcg QD N=81**	**MF DPI 200 mcg QD N=75**	**Placebo N=80**
≥ 1 dose	80 (100)	81 (100)	75 (100)	80 (100)
≥ 4 days	80 (100)	81 (100)	74 (99)	79 (99)
≥ 1 week	79 (99)	79 (98)	74 (99)	75 (94)
≥ 2 weeks	77 (96)	76 (94)	71 (95)	69 (86)
≥ 4 weeks	76 (95)	74 (91)	65 (87)	65 (81)
≥ 8 weeks	73 (91)	67 (83)	62 (83)	58 (73)
≥ 12 weeks	64 (80)	52 (64)	53 (71)	45 (56)

- Adverse Events

Overall, adverse events were reported in 72-84% of subjects during the 12 week double-blind treatment phase (MF DPI 100 mcg BID: 73%, MF DPI 100 mcg QD: 72%, MF DPI 200 mcg QAM: 84%, and Placebo: 81%).

The most frequently reported (≥10%) adverse events during double-blind treatment with study drug were fever, headache, allergy aggravated, viral infection, nasal congestion, pharyngitis, rhinitis, and upper respiratory tract infection (See Table 32).

Table 32 Study C97-380, Adverse Events Occurring in ≥ 10% of subjects in any Treatment Group

	MF DPI 100 mcg BID	MF DPI 100 mcg QD	MF DPI 200 mcg QD	Placebo
Fever	9%	12%	9%	11%
Headache	8%	10%	17%	24%
Allergy aggravated	9%	7%	11%	6%
Viral Infection	13%	10%	11%	6%
Nasal congestion	9%	16%	13%	11%
Pharyngitis	10%	14%	11%	14%
Rhinitis	16%	11%	12%	8%
Upper Respiratory Tract Infection	9%	17%	15%	15%

See Table 33 below for a full listing of adverse events reported in this study. In Table 34, following the full listing, this reviewer has compiled those adverse events which occurred with greater frequency in any of the active MF DPI treatment groups when compared with placebo.

Table 33 Study C97-380, Incidence of Adverse Events Reported in at Least ≥3% of Subjects in Any Treatment Group by Body System/Organ Class (*Table 30, C97-380 study report)*

	Number (%) of Subjects[a]				
	Open-Label	Double-Blind			
Adverse Event	BDP MDI 168 mcg BID (n=349)	MF DPI 100 mcg BID (n=80)	MF DPI 100 mcg QD (n=81)	MF DPI 200 mcg QD (n=75)	Placebo (n=80)
NO. OF SUBJECTS (%) WITH ANY AE	**124 (36)**	**58 (73)**	**58 (72)**	**63 (84)**	**65 (81)**
Autonomic Nervous System Disorders	**1 (<1)**	**2 (3)**	**0**	**0**	**1 (1)**
Lacrimation	0	2 (3)	0	0	0
Body as a Whole-General Disorders	**42 (12)**	**24 (30)**	**23 (28)**	**31 (41)**	**33 (41)**
Allergy	3 (<1)	3 (4)	5 (6)	6 (8)	6 (8)
Allergy Aggravated	2 (<1)	7 (9)	6 (7)	8 (11)	5 (6)
Chest Pain	1 (<1)	1 (1)	1 (1)	0	2 (3)
Cramps Legs	1 (<1)	2 (3)	0	0	1 (1)
Edema	0	2 (3)	0	0	0
Fatigue	0	0	0	3 (4)	1 (1)
Fever	8 (2)	7 (9)	10 (12)	7 (9)	9 (11)
Headache	27 (8)	6 (8)	8 (10)	13 (17)	19 (24)
Gastrointestinal System Disorders	**19 (5)**	**10 (13)**	**11 (14)**	**12 (16)**	**11 (14)**
Diarrhea	2 (<1)	0	3 (4)	1 (1)	1 (1)
Dyspepsia	4 (1)	0	3 (4)	5 (7)	4 (5)
Gastroenteritis	1 (<1)	2 (3)	3 (4)	3 (4)	2 (3)
Nausea	2 (<1)	1 (1)	1 (1)	0	2 (3)
Toothache	1 (<1)	1 (1)	0	2 (3)	1 (1)
Vomiting	6 (2)	3 (4)	4 (5)	2 (3)	4 (5)
Hearing and Vestibular Disorders	**0**	**3 (4)**	**4 (5)**	**2 (3)**	**1 (1)**
Earache	0	3 (4)	4 (5)	2 (3)	1 (1)
Musculo-Skeletal System Disorders	**7 (2)**	**6 (8)**	**7 (9)**	**2 (3)**	**3 (4)**
Musculo-Skeletal Pain	3 (<1)	3 (4)	4 (5)	2 (3)	1 (1)
Resistance Mechanism Disorders	**8 (2)**	**17 (21)**	**15 (19)**	**14 (19)**	**8 (10)**
Candidiasis, Oral	0	5 (6)	3 (4)	0	1 (1)
Infection Viral	2 (<1)	10 (13)	8 (10)	8 (11)	5 (6)
Otitis Media	2 (<1)	4 (5)	2 (2)	5 (7)	3 (4)
Respiratory System Disorders	**61 (17)**	**38 (48)**	**46 (57)**	**41 (55)**	**39 (49)**
Bronchitis	0	2 (3)	2 (2)	3 (4)	2 (3)
Coughing	6 (2)	7 (9)	4 (5)	4 (5)	7 (9)
Nasal Congestion	12 (3)	7 (9)	13 (16)	10 (13)	9 (11)
Pharyngitis	9 (3)	8 (10)	11 (14)	8 (11)	11 (14)
Pneumonia	0	0	0	2 (3)	1 (1)
Respiratory Disorder	1 (<1)	2 (3)	0	0	0
Rhinitis	17 (5)	13 (16)	9 (11)	9 (12)	6 (8)
Rhinitis Aggravated	3 (<1)	3 (4)	2 (2)	3 (4)	2 (3)
Rhinorrhea	3 (<1)	5 (6)	5 (6)	6 (8)	5 (6)
Sinusitis	6 (2)	7 (9)	7 (9)	6 (8)	7 (9)
Sneezing	4 (1)	2 (3)	1 (1)	3 (4)	1 (1)

	Number (%) of Subjects[a]				
	Open-Label	Double-Blind			
Adverse Event	BDP MDI 168 mcg BID (n=349)	MF DPI 100 mcg BID (n=80)	MF DPI 100 mcg QD (n=81)	MF DPI 200 mcg QD (n=75)	Placebo (n=80)
Stridor	0	0	0	1 (1)	2 (3)
Upper Respiratory Tract Infection	5 (1)	7 (9)	14 (17)	11 (15)	12 (15)
Skin and Appendages Disorders	**14 (4)**	**9 (11)**	**8 (10)**	**5 (7)**	**8 (10)**
Dermatitis	2 (<1)	1 (1)	3 (4)	1 (1)	0
Skin Infection, Fungal	0	2 (3)	0	0	0
Vision Disorders	**1 (<1)**	**6 (8)**	**2 (2)**	**1 (1)**	**3 (4)**
Conjunctivitis	0	6 (8)	2 (2)	1 (1)	3 (4)

a: Number (percentage) of subjects having at least one event in the indicated category. Body system/organ class entries are the number (percentage) of subjects having at least one event within that category. Some subjects may have reported more than one adverse event.

Source Data: Section 14.3.1.1..

Table 34 Study C97-380, Adverse events reported by ≥ 3% of Patients and with Greater Frequency in the Active Treatment Groups as Compared with Placebo

	MF DPI 100 mcg BID N=80	MF DPI 100 mcg QD N=81	MF DPI 200 mcg QD N=75	Placebo N=80
Allergy Aggravated	7(9)	6(7)	8(11)	5(6)
Cramps (Legs)	2(3)	0	0	1(1)
Edema	2(3)	0	0	0
Fatigue	0	0	3(4)	1(1)
Fever	7(9)	10(12)	7(9)	9(11)
Diarrhea	0	3(4)	1(1)	1(1)
Dyspepsia	0	3(4)	5(7)	4(5)
Gastroenteritis	2(3)	3(4)	3(4)	2(3)
Toothache	1(1)	0	2(3)	1(1)
Earache	3 (4)	4(5)	2(3)	1(1)
Musculoskeletal pain	3 (4)	4(5)	2 (3)	1(1)
Oral Candidiasis	5 (6)	3(4)	0	1 (1)
Viral Infection	10(13)	8(10)	8(11)	5(6)
Otitis Media	4(5)	2(2)	5(7)	3(4)
Bronchitis	2(3)	2(2)	3(4)	2(3)
Nasal Congestion	7 (9)	13 (16)	10 (13)	9 (11)
Pneumonia	0	0	2 (3)	1(1)
Respiratory disorder	2 (3)	0	0	0
Rhinitis	13(16)	9 (11)	9(12)	6(8)
Rhinitis aggravated	3 (4)	2(2)	3(4)	2(3)
Rhinorrhea	5(6)	5(6)	6 (8)	5(6)
Sneezing	2 (3)	1 (1)	3 (4)	1 (1)
URTI	7 (9%)	14(17%)	11(15%)	12 (15%)

Dermatitis	1(1)	3(4)	1(1)	0
Fungal Skin Infection	2(3%)	0	0	0
Conjunctivitis	6 (8%)	2(2%)	1(1%)	3(4%)

**Highlighted cells represent those treatment groups in which the AE was more frequent than placebo.

The adverse events noted above are consistent with adverse events typically seen in clinical studies in children with asthma. Most adverse events were categorized as mild to moderate in severity. No life-threatening adverse events were reported. Overall, severe adverse events were reported by 24 subjects (8%) of randomized subjects during the double-blind treatment period. No single severe adverse event was reported by more than two subjects in a treatment group, and overall, the frequency of severe adverse events was higher in the placebo group (14%) vs. the active treatment groups (MF DPI 100 mcg BID: 9%; MF DPI 100 mcg QD AM: 4%; MF DPI 200 mcg QD AM: 4%).

Local Adverse Events

Oral candidiasis was reported by 9 subjects (3%) during double-blind treatment.
The proportion of subjects reporting oral candidiasis were similar at MF DPI doses of 100 mcg BID (6%) and 100 mcg QD (4%), but collectively higher than in the MF DPI 200 mcg QD AM (0%) or placebo (1%) groups. All cases were considered mild to moderate in severity.

Subgroup Analysis of Adverse Events

Per the Sponsor, there were no indications of a differential response to treatment between males and females and there were too few subjects 4 to 5 years of age to provide meaningful analysis by age. A greater proportion of Caucasian subjects reported adverse events across treatment groups (Caucasians, 72% to 90%; non-Caucasians, 57%to 74%).

- Deaths and Serious Adverse Events

There were no deaths reported during the study period or within 30 days of the last dose of the study drug. Serious adverse events were reported in three patients; one in the MF 100 mcg QD AM group, one in the MF DPI 200 mcg QD AM group, and one in placebo. All SAEs occurred at one center. A brief summary of these SAEs follows (Section 14.3.3):

- Subject 08/323 was 8 year old, female, non-caucasian who was randomized to MF DPI 100 mcg QD AM. She presented to the ER with hypoxia and wheezing approximately 1 month into study treatment. The patient was diagnosed with strep pharyngitis and asthma exacerbation. The patient was discontinued from the study, admitted to the hospital, and treated with oxygen, prednisone 60 mg QD, Pulmicort, Nasacort nasal inhaler, antibiotics, and albuterol nebulizers. She switched to Solumedrol intravenously, and gradually improved upon discharge 4 days later.
- Subject 08/326 was an 8 year old, male who was randomized to receive placebo. Six days into study treatment, the patient's mother noted cough and wheeze, but stable PEFR.

After insufficient relief with rescue medication, and visit to his physician, the patient was admitted to the hospital with an asthma exacerbation, URI, and pneumonia. The patient was treated successfully with oral corticosteroids and discharge from the hospital 5 days later.

- Subject 08/378 was a 5-year old male patient who was randomized to receive MF DPI 200 mcg QD AM. Approximately 1 month into treatment, the patient fell while climbing into a tree house and suffered a supracondylar fracture. The patient was hospitalized to set the arm and to repair the muscle and vascular damage. It is unlikely that this SAE is related to study medication.

- Withdrawals Secondary to Adverse Events

A total of 36 subjects did not complete treatment because of adverse events, 28 of these subjects during the double-blind treatment phase of the study:

- MF DPI 100 mcg BID: 1 subject (1%)
- MF DPI 100 mcg QD AM: 7 subjects (9%)
- MF DPI 200 mcg QD AM: 8 subjects (11%)
- Placebo: 12 subjects (15%)

The most frequently reported adverse events leading to discontinuation were events that were classified to the Respiratory System, such as upper respiratory tract infection, bronchitis, allergy, asthma exacerbation, sinusitis, pharyngitis, and pneumonia.

Overall, the frequency of withdrawal secondary to adverse events was highest in the placebo group. In summary, no clinically meaningful safety concerns have arisen from review of this section. The adverse events that have been reported are known to occur with inhaled corticosteroids and in asthmatic populations.

- Laboratory Evaluation

Laboratory evaluation did not reveal any clinically meaningful results for the analysis of central tendency (median). There were 5 patients with notable laboratory changes: 3 in the MF 100mcg BID group and 2 in the placebo group. In the MF group, there were two subjects with elevation of liver enzymes – one due to viral hepatitis and one during treatment. The third MF subject had elevation in platelets. In the placebo group one patient was found to have elevated creatinine and another elevated liver enzyme.
Reviewer's comment: These results do not suggest a safety signal with regards to laboratory evaluation.

- Vital Signs

No clinically meaningful changes in vital signs were noted after review of the line listings.

10.2.3 Conclusions

This was a Phase III, multicenter, 4-arm, randomized, double-blind, placebo-controlled, parallel group study evaluating the efficacy and safety of MF DPI in the treatment of asthma in children previously maintained on inhaled corticosteroids. Open-label treatment with BDP 168 mcg BID was used to stabilize and maintain subjects on one standard dose of an inhaled corticosteroid during a 2 week run-in period. The patients were then randomized to one of four parallel treatment arms for 12 weeks: MF DPI 100 mcg BID, MF DPI 100 mcg QD AM, MF DPI 200 mcg QD AM, and placebo.

A total of 349 subjects at 25 centers entered the open-label treatment phase, of which 316 were randomized to double-blind study medication. All randomized subjects received at least one dose of study medication. The number of subjects randomized to each of the treatment groups was comparable. Discontinuation from the study was most common in the placebo treatment group, and lower in the active treatment groups. A total of 76 subjects (24%) discontinued from the study: 30 subjects (38%) in placebo, 20 subjects (27%) in MF DPI 200 mcg QD AM, and 18subjects (22%) in MF DPI 100 mcg QD AM, and 8 subjects (10%) in MF DPI 100 mcg BID. The most common reasons for discontinuation were treatment failure and adverse events. More patients in the placebo group discontinued secondary to treatment failure (16%) as compared to the MF active treatment groups (4-11%). Discontinuation secondary to adverse events was somewhat greater in the placebo treatment group (15%) vs. the active treatment groups (1-11%). Baseline demographic and disease characteristics were generally similar across groups.

The primary objective of this study was to evaluate the efficacy and safety of MF DPI 100 mcg BID compared to placebo. The secondary objective was to evaluate the relative efficacy and safety of MF DPI 100 mcg QD AM and 200 mcg QD AM compared to placebo and MF DPI 100 mcg BID, 100 mcg QD AM, and 200 mcg QD AM compared to each other.

The primary efficacy endpoint was the change of % predicted FEV1 from Baseline to Endpoint. The primary comparison was between MF DPI 100 mcg BID vs. placebo. MD DPI 100 mcg BID was superior to placebo with a treatment difference (LS Mean) of 7.99, P <0.001. In other comparisons, MF DPI 200 mcg QD was also superior to placebo with a treatment difference of 5.56, P=0.016. The efficacy of MF DPI 100 mcg BID and 200 mcg QD AM was supported by the following secondary endpoints: FEV1, FVC, $FEF_{25-75\%}$, decreased CAEs, and physician's assessment of response to therapy. PEFR, use of rescue medication, and nocturnal awakenings were generally in favor of the efficacy of MF DPI, but not statistically supportive.

Sixty-four percent to 80% of subjects in the active treatment groups received treatment for at least 12 weeks. The extent of exposure was satisfactory to allow for safety assessments. Overall, adverse events were reported in 72-84% of subjects during the 12 week double-blind treatment phase (MF DPI 100 mcg BID: 73%, MF DPI 100 mcg QD: 72%, MF DPI 200 mcg QAM: 84%, and Placebo: 81%). The most frequently reported adverse events (≥10%) during double-blind treatment with study drug were fever, headache, allergy aggravated, viral infection, nasal congestion, pharyngitis, rhinitis, and upper respiratory tract infection. Most adverse events

were categorized as mild to moderate in severity. No life-threatening adverse events were reported. Overall, severe adverse events were reported by 24 subjects (8%) of randomized subjects during the double-blind treatment period. No single severe adverse event was reported by more than two subjects in a treatment group, and overall, the frequency of severe adverse events was higher in the placebo group (14%) vs. the active treatment groups (MF DPI 100 mcg BID: 9%,; MF DPI 100 mcg QD AM: 4%; MF DPI 200 mcg QD AM: 4%). Oral candidiasis was reported by 9 subjects (3%) during double-blind treatment. The proportion of subjects reporting oral candidiasis were similar at MF DPI doses of 100 mcg BID (6%) and 100 mcg QD (4%), but collectively higher than in the MF Dpi 200 mcg QD AM (0%) or placebo (1%) groups. All cases were considered mild to moderate in severity.

There were no deaths reported during the study period or within 30 days of the last dose of the study drug. Serious adverse events were reported in 3 patients, two in the MF DPI treatment groups, and 1 in the placebo group. There were no clinically meaningful changes in vital signs, laboratory tests, or physical examination. There were no unusual or unexpected safety concerns noted.

In conclusion, study C97-380 supports the efficacy and safety of the MF DPI 100 mcg BID and 200 mcg QD AM dosing regimens.

10.3 Study C97-300 Placebo-Controlled Efficacy and Safety Study of Mometasone Furoate Dry Powder Inhaler (MF DPI) in the Treatment of Asthma in Children Previously Maintained on Inhaled Corticosteroids

Protocol #:	C97-380
Study dates:	Initiated April 27, 1998. Completed May 28, 1999.
Sites:	20 centers (15 United States, 5 Central/South America)
IRB:	The protocol, protocol amendments, and subject informed consent Form were reviewed by an Institutional Review Board for each Center.
Ethics:	The investigators conducted this study according to the principles of Good Clinical Practices (GCP).

10.3.1 Study Design/Protocol

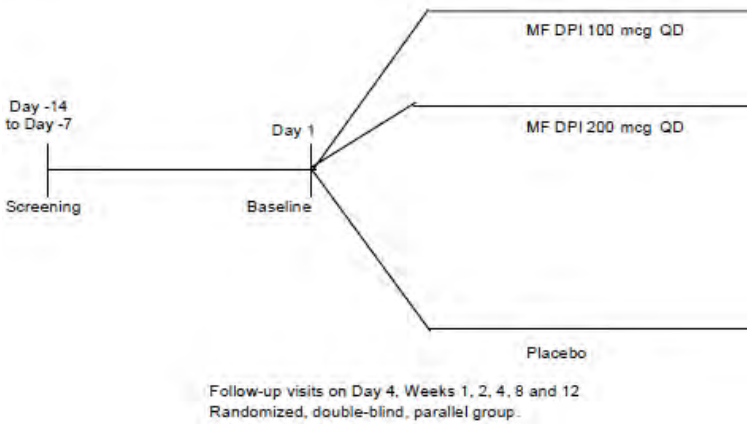
Objectives

The primary objective of this study was to evaluate the efficacy and safety of MF DPI 200 mcg QD compared to placebo. The secondary objective was to evaluate the relative efficacy and safety of MF DPI 100 mcg QD and 200 mcg QD compared to placebo.

Description

This was a Phase III, multicenter, randomized, placebo-controlled, double-blind, parallel-group efficacy and safety study of MF DPI in the treatment of asthma in children previously maintained on inhaled corticosteroids. The study began with a 1-2 week run-in period in which subjects continued on their prescribed inhaled corticosteroids. The subjects were then randomized to one of three parallel treatment arms for 12 weeks: MF DPI 100 mcg QD, MF DPI 200 mcg QD, and placebo (See Figure 13).

Figure 13 Study C97-300, Study Design Diagram.



Population

This study was designed to recruit 12-16 subjects at each of approximately 20 centers to ensure 300 subjects would meet the criteria for the evaluation of the primary efficacy endpoint. The inclusion, exclusion, and withdrawal criteria for this study were the same as those used in Study C97-380 (See 10.2.1 Study Design/Protocol).

Treatments

- Study Treatments

During the run-in period (between Screening and Baseline visits, all subjects were to continue to take their prescribed inhaled corticosteroids. The last dose of prescribed inhaled corticosteroid was to be taken the evening prior the Baseline visit. At the Baseline visit, subjects meeting eligibility criteria were randomized to 12 weeks of treatment with one of the following in a 1:1:1 ratio (See Table 35):

Table 35 Study C97-300, Treatment Groups

Treatment Group	AM Dose	Total MF (mcg/day)
MF DPI 100 mcg QD	100 mcg x 1 inhalation	MF 200 mcg
MF DPI 200 mcg QD	200 mcg x 1 inhalation	MF 100 mcg
Placebo	Placebo x 1 inhalation	Placebo (0)

Each subject was to take one inhalation from the dry powder inhaler every morning.

- Permitted Therapies (See Study C97-380,10.2.1 Study Design/Protocol)
- Prohibited Therapies (See Study C97-380,10.2.1 Study Design/Protocol)
- Compliance (See Study C97-380,10.2.1 Study Design/Protocol)

Conduct

This Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel group study consisted of a run-in period of 1 to 2 weeks, during which subjects remained on their prescribed ICS. Subjects who met eligibility criteria were randomized at the Baseline visit in a 1:1:1 ratio to one of three parallel treatment arm (see Table 1). There were eight scheduled visits: Screening, Baseline, Day 4, Week 1, Week 2, Week 4, Week 8, and Week 12. Efficacy was assessed via Pulmonary Function Testing at each visit. Additionally, subjects recorded PEF, symptom scores, rescue medication use, and number of nocturnal awakenings in their patient diaries. Safety assessments included monitoring of adverse events, vital signs, clinical laboratory tests, and physical examinations. The study schedule appears in Table 36.

Table 36 Study C97-300, Study Schedule

	(Screening) Visit 1	Treatment Period (Baseline) Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	-14 to -7	Day 1	Day 4 (±1 day)	Week 1 Day 8 (±2 days)	Week 2 Day 15 (±2 days)	Week 4 Day 29 (±2 days)	Week 8 (±3 days)	Week 12 (±3 days)
Obtain Informed Consent[a]	X							
Review Inclusion/ Exclusion Criteria	X	X						
Medical/Disease History	X							
Concomitant Medications Review	X	X	X	X	X	X	X	X
Vital Signs (temperature, Blood pressure, pulse, respiration rate)	X	X	X	X	X	X	X	X
Physical Examination	X							X
Height, Weight	X							
Oropharyngeal Exam	X	X	X	X	X	X	X	X
Hematology, Blood Chemistry, Urinalysis	X	Review						X
Pulmonary Auscultation	X	X	X	X	X	X	X	X
Pulmonary Function Tests	X	X	X	X	X	X	X	X
Reversibility Test	X							
Electrocardiogram[b]	X	Review						
Chest X-Ray[c]	X	Review						
Dispense Peak Flow Meter	X							
Dispense Diary	X	X	X	X	X	X	X	
Retrieve/Review Diary		X	X	X	X	X	X	X
Dispense/Retrieve Rescue Medication, As Needed	X	X		X	X	X	X	X
Dispense Study Inhalers		X						
Administer First Dose of Study Drug in Office		X						
Evaluation of Response to Therapy			X	X	X	X	X	X
Adverse Events/Intercurrent Illness Evaluation		X	X	X	X	X	X	X
Review Compliance		X	X	X	X	X	X	X
Collect/Count Study Inhalers								X
Quality of Life Assessment[d]		X						X

a: Earlier than Day -14 if longer medication washouts were required. Informed consent must have been signed prior to any study-related procedures, including required washout of medications.
b: If not done within the last 30 days.
c: Or within last year.
d: At C97-300 (U.S.) centers only.

Efficacy Assessments

The primary efficacy variable for Study C97-300 was change from baseline in % predicted FEV1 and the primary time point was Endpoint (last visit.) Secondary efficacy variables included FEV1, FEV25-75%, FVC, AM and PM PEFR, asthma symptom scores, Proventil/Ventolin use, nighttime awakening due to asthma which required Proventil/Ventolin, time to first worsening of asthma, assessment of response to therapy, the number of nebulized beta-agonist treatment recorded daily, and quality of life assessments. See Study C97-380, for description of efficacy assessments.

Safety Assessments

See Study C97-380, Section 10.2.1.7 for description of safety assessment. See Table 2, C97-300, Study Schedule for timing of these safety assessments.

Statistical Plan

- Data Sets Analyzed (See Study C97-380, 10.2.1 Study Design/Protocol)

- Sample Size Determination

The study was designed to enroll 300 subjects with 100 subjects per treatment arm. The sample size was chosen to detect a treatment difference of 7% or more in the %predicted FEV1 mean change from Baseline (the primary efficacy variable) between any active treatment group and placebo with 90% power and two-sided 5% significance level, assuming a pooled standard deviation of 13.5 for % predicted FEV1 change from baseline.

- Primary Efficacy Analysis

The statistical plan is identical to that in Study C97-380. (See Study C97-380, Section 10.2.1) In this study, the primary efficacy analysis at endpoint was based on the comparison of MF DPI 200 mcg QD compared to placebo. If this comparison was significant, all pairwise comparisons were to be made without adjust for the multiple comparisons. The primary efficacy variable was defined in the protocol as the change from Baseline in % predicted FEV1, and the primary time point was the Endpoint (last visit).

- Secondary Efficacy Analyses (see Study C97-380, Section 10.2.1)

- Safety Analyses (see Study C97-380, section 10.2.1)

- Protocol Amendments

Two general amendments were issued February 2, 1998 and March 31, 1998. The major changes reflected in C97-300 by these two amendments included:

  - Addition of the MF DPI 100 mcg QD dose group, modification of the primary objective, and subsequent addition of a secondary objective which was to evaluate the relative efficacy and safety of MF DPI 100 mcg QD and 200 mcg QD compared to placebo.
  - Modification of the permissible limits for inhaled corticosteroids prior to Screening.
  - Separation of criteria for significant worsening of asthma into two categories: (1) criteria that require a subject to be discontinued and (2) criteria that may have contributed to discontinuation of a subject for asthma worsening.
  - Inclusion of theophylline, terfenadine, and short-acting intramuscular corticosteroids (not more than 15 days in the 6 months prior to screening) in the list of medication restriction
  - Addition of study restrictions.

The protocol was amended the final time on August 25, 1998. The major changes reflected in the protocol included:

- Modification to the inclusion criteria to include Vanceril 84 mcg Double Strength and Flovent Rotadisk DPI as permitted inhaled corticosteroids prior to Screening.
- Modification of the number of Proventil/Ventolin MDI treatments which were considered equivalent to one nebulization, from six inhalations to four.

10.3.2 Results

Patient Disposition

There were 290 subjects randomized at 20 study centers. All randomized patients received at least one dose of study medication. The number of subjects randomized and treated in the three groups are as follows:

- MF DPI 100 mcg QD: 100 subjects
- MF DPI 200 mcg QD: 97 subjects
- Placebo: 93 subjects

A total of 73 subjects (25%) discontinued from the study prior to scheduled completion. The occurrence of discontinuation was lowest for subjects receiving MF DPI 100 mcg QD, 16 subjects (16%), and highest for subjects receiving placebo 36 subjects (39%). Treatment failure was the most common reason for discontinuation (50 subjects, 17%). The proportion of subjects in each active treatment group reporting treatment failure as the reason for discontinuation was similar, and lower than in the placebo group (11% to 13% in the active treatment groups vs. 27% in the placebo. In general, it appears that the subjects in the placebo group were more likely to discontinue from the study than subjects in either of the active treatment groups. See Table 37 for details of patient disposition.

Table 37 C97-300, Patient Disposition

	Number (%) of Subjects			
	MF DPI 100 mcg QD (n=100)	MF DPI 200 mcg QD (n=97)	Placebo (n=93)	Total (n= 290)
Subjects Who Completed	84 (84)	76 (78)	57 (61)	217 (75)
Subjects Who Discontinued	16 (16)	21 (22)	36 (39)	73 (25)
Reason for Discontinuation				
Adverse Event	2 (2)	7 (7)	3 (3)	12 (4)
Treatment Failure	13 (13)	11 (11)	26 (27)	50 (17)
Lost to Follow-up	0 (0)	0 (0)	1 (1)	1 (<1)
Did Not Continue for Reasons Unrelated to Treatment	1 (1)	2 (2)	4 (4)	7 (2)
Did Not Meet Protocol Eligibility	0 (0)	1 (1)	0 (0)	1 (<1)
Noncompliance with Protocol	0 (0)	0 (0)	2 (2)	2 (<1)

- Protocol Violations

Twenty (20) subjects with one or more protocol deviations were excluded from the Efficacy Evaluable data set. Protocol deviations were noted for 4 subjects treated with MF DPI 100 mcg QD, 7 subjects treated with 200 mcg QD, and 9 subjects treated with placebo. Most protocol deviations were subjects who did not meet entry criteria and in most cases, the subject entered the study with a %predicted FEV1 outside the specified range. Other protocol violations included non-compliance with study treatment, FEV1 values exceeding criteria for variability (≥20%) between Screening and Baseline, and prohibited concomitant medications/insufficient washout of medication.

In addition, 53 subjects who experienced one or more of the criteria for asthma worsening were not discontinued from the study. Based upon the protocol-defined criteria, 15 of these subjects should have been discontinued but were not.

Demographics and Other Baseline Characteristics

- Demographics

Generally, treatment groups were fairly similar at baseline with respect to sex, age, race, weight and Baseline disease characteristics. The greatest percentage of subjects was in the 6-11 year age group, ranging from 90-91%. There were more males in the study compared to females, ranging from 57-62% in a given treatment group. The patients were primarily Caucasian. Of the non-caucasian patients, 77% were Hispanic, 22% Black, and < 1% were Asian. The demographic information is summarized in Table 38.

Table 38 Study C97-300, Demographics and Baseline Characteristics

	MF DPI 100 mcg QD AM	MF DPI 200 mcg QD AM	Placebo
	n = 100	n = 97	n=93
Age (years)			
Mean	8.2	8.7	8.4
Range	4.0-11.0	4.0-11.0	4.0-11.0
Age Distribution [n (%)]			
4-5 years	10 (10)	9 (9)	8 (10)
6-11 years	90 (90)	88 (91)	85 (90)
Sex			
Female	38 (38)	42 (43)	38 (41)
Male	62 (62)	55 (57)	55 (59)
Race[n (%)]			
Caucasian	65 (65)	61 (63)	56 (60)
Non-Caucasian	35 (35)	36 (37)	37 (40)
Black	3 (3)	11 (11)	10 (11)
Hispanic	31 (31)	25 (26)	27 (29)
Asian	1 (1)	0 (0)	0 (0)
Weight (kg)			
Mean	32.4	36.9	32.0
Range	16.0 – 74.0	16.0-83.0	15.0-68/0

- Baseline Disease and Other Characteristics

The mean duration of asthma and baseline FEV1 % predicted were fairly similar across all groups. The mean duration of asthma ranged from 4.8-5.2 years, with the range being 0.5-11.0 years. The mean % predicted FEV1 at baseline was between 78.5% and 80.4%. Notable differences included a higher baseline AM PEF in the MF DPI 200 mcg QD AM group (232.7 l/min) compared with the MF DPI 100 mcg QD group (206.4 l/min) and placebo (213.7 l/min). Baseline ICS use was similar among treatment arms (See Table 39).

Table 39 Study C97-300, Baseline Disease/Other Characteristics

	MF DPI 100 mcg QD AM	MF DPI 200 mcg QD AM	Placebo
	n = 100	**n = 97**	**n=93**
Duration of disease (years)			
Mean	4.8	5.2	5.0
Range	0.5-11.0	0.5-11.0	0.6-11.0
Baseline FEV1 % predicted			
Mean	80.4	78.5	78.9
AM PEF (l/min)			
Mean	206.4	232.7	213.7
BDP			
no. of subjects	56	53	56
Mean mcg/day	230	239	246
Range	84-400	84-500	84-500

	MF DPI 100 mcg QD AM	MF DPI 200 mcg QD AM	Placebo
Budesonide			
no. of subjects	15	10	11
Mean mcg/day	387	360	400
Range	200-400	200-400	400-400
Flunisolide			
no. of subjects	3	8	2
Mean mcg/day	1000	594	1000
Range	1000-1000	500-1000	1000-1000
Fluticasone Propionate			
no. of subjects	21	17	15
Mean mcg/day	178	220	194
Range	88-440	88-440	88-440
Triamcinolone Acetonide			
no. of subjects	5	9	9
Mean mcg/day	400	400	533
Range	400-400	200-600	200-800

- Baseline Concomitant Medications and Medical History

The sponsor did not summarize baseline concomitant medications or medical history. This reviewer reviewed the line listings for concomitant medications. The concomitant medications were divided into asthma/allergy related and unrelated medications. Among the most common concomitant medications used to treat asthma/allergy were short acting beta2-agonists, antihistamines, inhaled/nasal corticosteroids, cromolyn, ipratropium, oral corticosteroids, and decongestants. Many subjects were also receiving immunotherapy. Of the asthma/allergy unrelated concomitant medications, the most common drugs were acetaminophen, ibuprofen, antibiotics, and over-the-counter cough/cold preparations.

Compliance

Study medication non-compliance was defined as use of <75% or >125% of the protocol-specified doses. Four subjects (2 in the MF DPI 200 mcg QD group and 2 in the placebo group) had overall compliance of <75% and were excluded from the Efficacy Evaluable subset. All of these subjects were included in the intent-to-treat analysis and safety analyses. No subject took >125% of the doses specified.

Efficacy Outcomes

- Primary Efficacy Outcome

The primary efficacy endpoint was change from Baseline to Endpoint in % predicted FEV1. The use of Endpoint data adjusts for the discontinuation of subjects over time. The primary objective of this study was to compare the efficacy of MF DPI 200 mcg QD vs. placebo. The primary efficacy analysis at endpoint was based on the comparison of MF DPI 200 mcg QD vs. placebo using least squares means, obtained from two-way ANOVA that extracted sources of variation due to treatment and center. If this comparison was significant at the 0.05 significance level, then all pair-wise comparisons were to be made using the least squares means from the ANOVA model without adjustment for the multiple comparisons.

In addition to the analysis at Endpoint, all six pair-wise comparisons among the four treatment groups were made with respect to the change from Baseline in % predicted FEV1 for each scheduled visit, using the two-way ANOVA model as above. The p-values were not adjusted for multiple comparisons.

Table 40 presents the LS Mean of the change from Baseline to Endpoint in % predicted FEV1. In the active treatment groups, the LS Mean changes in % predicted FEV1 were 5.74 and 5.00 for the 200 mcg and 100 mcg groups, respectively. The LS mean change in the % predicted FEV1 from baseline to endpoint in the placebo group was -1.84. This data is graphically represented in Figure 14 Study C97-300, % Predicted FEV1 – Change from Baseline by Treatment Group (All treated Subjects): LS Mean +/- SE.

Figure 14 Study C97-300, % Predicted FEV1 – Change from Baseline by Treatment Group (All treated Subjects): LS Mean +/- SE

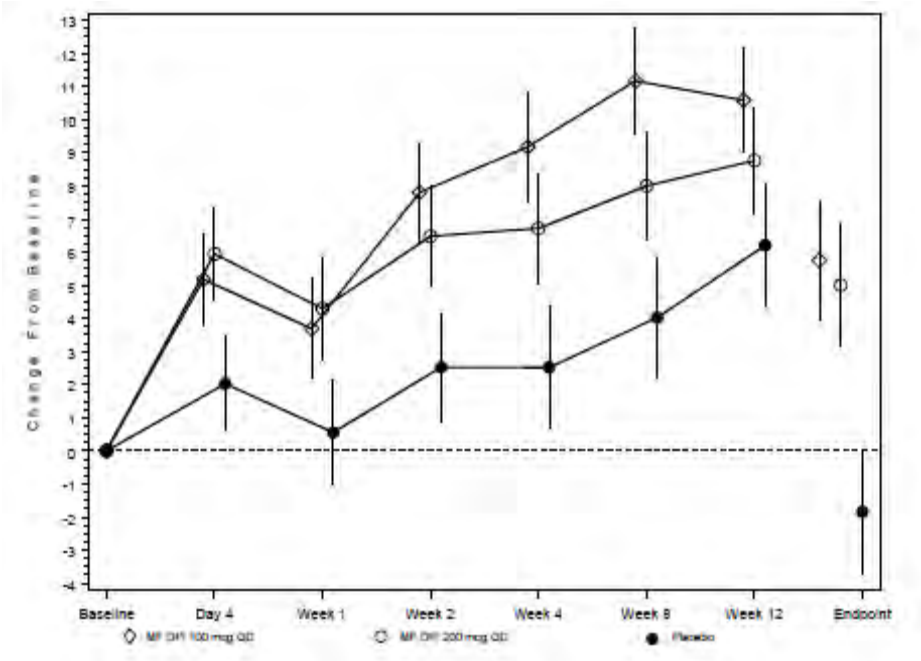


Table 40 Study C97-300, Baseline LS Mean % Predicted FEV1 and Change from Baseline to Endpoint LS Mean % Predicted FEV1 in ITT Population

	100 mcg QD		200 mcg QD		Placebo	
	N	LS Mean	N	LS Mean	N	LS Mean
Baseline	100	80.44	97	78.51	93	78.88
Change from Baseline						
Day 4	84	5.17	86	5.94	81	2.02
Week 1	98	3.69	96	4.29	89	0.55
Week 2	96	7.80	93	6.47	81	2.52
Week 4	88	9.17	89	6.71	73	2.51
Week 8	81	11.16	80	7.99	65	4.02
Week 12	79	10.58	77	8.76	57	6.20
Endpoint	100	5.74	97	5.00	93	-1.84

These data tabulated in Table 41 demonstrate statistically significant increases in mean % predicted FEV1 values from Baseline to Endpoint for both MF DPI 100 mcg QD and 200 mcg QD, compared with placebo. Increases in mean % predicted FEV1 from Baseline to Endpoint were not significantly different between the MF DPI treatment groups.

Table 41 Study C97-300, % Predicted LS Mean Difference of Pair-wise Comparisons

	200 mcg QD vs. PLA	100 mcg QD vs. 200 mcg QD	100 mcg QD vs. PLA
LS Mean Difference	6.84	0.74	7.58
P-value	**<0.01**	0.76	**<0.01**

Although the change from Baseline to Endpoint was the primary variable of interest, results at other time points were also reviewed. The range of improvement in LS Mean % predicted FEV1 from Baseline to any given time point in the active treatment groups ranged from 3.69 to 11.16, compared with 0.55 to 6.20 for placebo (See Table 40).

In summary, the primary efficacy analysis was the change of % predicted FEV1 from Baseline to Endpoint. The primary comparison was between MF DPI 200 mcg QD vs. placebo. MF DPI 200 mcg QD was superior to placebo with a LS Mean treatment difference of 6.84, $p < 0.01$. In other comparisons, MF DPI 100 mcg QD was also superior to placebo with a LS Mean treatment difference of 7.58, $p < 0.01$. There was no significant difference between active treatment groups.

- Subgroup Analyses of the Primary Efficacy Variable

Response by Sex, Age, and Race
Analysis of change in % predicted FEV_1 by sex indicated that response over time and at Endpoint was generally similar for male (n=172) and female (n=118) subjects and resembled the overall study population. However, the mean percent increase in % predicted FEV_1 at Endpoint among male subjects receiving MF DPI 100 mcg QD (11.7%) was greater than among the female subjects in the same treatment group (0.7%). In contrast, the mean percent increase in % predicted FEV_1 at Endpoint among female subjects receiving MF DPI 200 mcg QD (9.2%) was greater than among the male subjects in the same treatment group (5.8%).

Too few subjects were aged 4 to 5 years (27 subjects) for meaningful comparisons; however, no age-related differential response to therapy was apparent for subjects aged 6 to 11 years compared with the response of the overall study population. The majority of subjects in this study were Caucasian (182 subjects; 63%) and the mean change in % predicted FEV_1 for Caucasian subjects were similar to those of the overall population. Because the remaining 108 subjects (37% of the total) were divided among other race categories, differentiation of response by race was not performed. At Endpoint, non-Caucasian subjects as a whole showed a greater mean percent change in both active treatment groups (MF DPI 100 mcg 11.6%; MF DPI 200 mcg 9.2%) compared to Caucasian subjects (MF DPI 100 mcg 5.4%; MF DPI 200 mcg 6.1%). However, both Caucasian and non-Caucasian subjects receiving MF DPI showed a greater improvement in % predicted FEV_1 over placebo.

Response by Baseline Severity of Asthma
Response to therapy was evaluated in subjects whose Baseline % predicted FEV1 was < 75% of the predicted value (more severe asthma) versus those whose Baseline % predicted FEV1 was ≥ 75% of the predicted value (less severe asthma). The majority of the patients enrolled in this study were less severe asthmatics with FEV1 % predicted at Baseline ≥ 75%. Numerically, the greatest difference was observed in the MF DPI 100 mcg QD treatment group of the more severe asthmatics. However, these data are difficult to interpret as the placebo treatment arm in the more severe asthmatics had a treatment response that was comparable to that of the treatment groups in the less severe subset (See Table 42).

Table 42 Study C97-300, % Predicted FEV1 - Change from Baseline to Endpoint by Treatment group in Patients with FEV1 < 75% vs. ≥ 75%

	100 mcg QD AM		200 mcg QD AM		Placebo	
	N	**LS Mean**	**N**	**LS Mean**	**N**	**LS Mean**
< 75% at Baseline (More Severe)						
Baseline	24	67.93	29	68.17	39	70.41
Change from Baseline to Endpoint	24	7.58	29	7.26	39	4.25
≥ 75% at Baseline (Less Severe)						
Baseline	76	84.40	68	83.02	54	85.13
Change from Baseline to Endpoint	76	5.41	68	4.62	54	-5.24

- Secondary Efficacy Outcomes

The primary analysis sample for secondary efficacy measures was the ITT population, and the primary analysis time point was Endpoint. Secondary efficacy measures included the following:

- FEV1 (L)
- FVC and $FEF_{25-75\%}$
- AM and PM PEFR
- Asthma Symptom Scores
- Response to Therapy
- Use of Rescue Medication
- Number of Nocturnal Awakenings
- Clinical Asthma Exacerbations
- Time to Worsening of Asthma
- Health-Related Quality of Life

FEV1 in Liters

Table 43 Study C97-300, FEV1 (L) – Change from Baseline by Treatment Group (All treated subjects)

	100 mcg QD AM		200 mcg QD AM		Placebo	
	N	LS Mean	N	LS Mean	N	LS Mean
Baseline	100	1.46	97	1.55	93	1.45
Day 4	84	0.07	86	0.12	81	0.04
Week 1	98	0.06	96	0.08	89	0.01
Week 2	96	0.12	93	0.12	81	0.05
Week 4	88	0.15	89	0.13	73	0.06
Week 8	81	0.18	80	0.15	65	0.07
Week 12	79	0.18	77	0.17	57	0.13
Endpoint	100	0.09	97	0.11	93	-0.02

Table 44 Study C97-300, FEV1 (L) LS Mean Difference of Pairwise Comparisons of Change from Baseline to Endpoint in FEV1 (L/s)

	200 mcg QD vs. PLA	100 mcg QD AM vs. 200 mcg QD AM	100 mcg QD AM vs. PLA
LS Mean Difference	0.13	0.02	0.11
P-value	**<0.01**	0.56	**0.02**

Similar to % predicted FEV1, there were no differences in baseline measurements. The baseline LS Mean FEV1 ranged from 1.46-1.55 L. The treatment differences for change in baseline to endpoint in absolute FEV1 are shown in Table 43. As expected from the primary efficacy analysis, MF DPI 100 mcg QD and 200 mcg QD are both significantly better than placebo (See Table 44). The secondary outcome of FEV1 is supportive of the efficacy of 100 mcg QD AM and 200 mcg QD AM.

FVC and FEF25-75%

There were no significant differences among treatment groups at Baseline for either FVC or $FEF_{25-75\%}$. Baseline FVC ranged from 1.79 to 1.81. Change at Endpoint ranged from 0.03 in the placebo group to 0.13 in the MF DPI 200 mcg QD group. No statistically significant differences were noted between active treatment group at Endpoint. $FEF_{25-75\%}$ was significantly improved from Baseline to Endpoint in both active treatment arms ($p \leq 0.05$).

In conclusion, statistically significant improvements in $FEF_{25-75\%}$, but not FVC, support the primary efficacy endpoint in this study. However, FVC numerically trended in support of the active treatment groups.

AM and PM PEFR

Significant differences were noted among treatment groups at Baseline for both AM and PM PEFR. Further exploration of the data indicated that the protocol-specified ANOVA was still appropriate. Results for PM PEFR were similar to AM PEFR, therefore, only the results for AM PEFR are presented here.

At Endpoint, MF DPI 100 mcg QD was statistically superior to placebo for both AM and PM PEFR MF DPI 200 mcg QD was statistically superior to placebo but only for PM PEFR. There were no statistically significant differences between active treatment groups (See Table 45 and Table 46). In conclusion, the statistical analysis of AM and PM PEFR is somewhat supportive of the primary efficacy outcome.

Table 45 Study C97-300. AM PEFR – Change from Baseline to Endpoint by Treatment Group (All treated subjects)

	100 mcg QD AM		200 mcg QD AM		Placebo	
	N	LS Mean	N	LS Mean	N	LS Mean
Baseline	100	206.44	97	232.67	93	213.72
Change from Baseline to Endpoint	100	25.81	97	15.76	93	9.75

Table 46 Study C97-300, AM PEFR- LS Mean Difference of Pair-wise Comparisons

	200 mcg QD vs. PLA	100 mcg QD AM vs. 200 mcg QD AM	100 mcg QD AM vs. PLA
LS Mean Difference	6.01	10.05	16.06
P-value	0.44	0.19	**0.04**

Asthma Symptom Scores

Subjects recorded AM and PM symptom scores for wheezing, cough, and shortness of breath, each rated on a scale of 0-3. The mean symptom scores were generally low at Baseline. Although general improvements were noted in both morning and evening scores for wheezing, difficulty breathing, and cough throughout the study at and Endpoint for both active treatment groups, no statistically significant differences were found when active treatment groups were compared to each other or to placebo.

Response to Therapy

At all visits following the Baseline visit, the physician or designee assessed the subject's response to therapy by comparing the current level of symptoms with those noted at Baseline on a scale of 1 (much improved) to 5 (much worse). At Endpoint, the proportion of subjects

evaluated as improved (i.e. much improved or improved) was higher in both the MF DPI 100 mcg QD and 200 mcg QD groups (63% and 61%, respectively) than subjects receiving placebo (44%). Per the Sponsor's analysis, results of the Fisher's exact test indicated a significant (p=0.02) difference between groups in the percentage of subjects rated as having improved or not improved._At endpoint, both active treatment groups reported significant improvement (p <0.01) over placebo. There were no statistical differences in response to therapy between active treatment groups. (See Table 47 and Table 48).

Table 47 Study C97-300, Response To Therapy (LS Mean scores at Day 4 and Endpoint)

	100 mcg QD AM		200 mcg QD AM		Placebo	
	N	LS Mean	N	LS Mean	N	LS Mean
Baseline	84	2.44	86	2.42	81	2.72
Change from Baseline to Endpoint	100	2.16	97	2.37	93	2.91

Table 48 Study C97-300, Response to Therapy – Pair-wise Comparisons

	200 mcg QD vs. PLA	100 mcg QD AM vs. 200 mcg QD AM	100 mcg QD AM vs. PLA
LS Mean Difference	-0.54	-0.21	-0.75
P-value	**< 0.01**	0.23	**< 0.01**

Use of Rescue Medication

Subjects recorded the number inhalations of Proventil/Ventolin they used each day. There were no significant differences in rescue medication use at Baseline. Baseline rescue medication use ranged from 1.54 to 1.88 puffs/day. Subjects treated with MF DPI 100 mcg QD and MF DPI 200 mcg QD experienced an overall decrease of 0.49 puffs/day and 0.34 puff/day, respectively, compared to an increase of 0.08 puffs/day for placebo. Although both active treatment groups recorded decreases in Proventil use throughout the study, only the MF DPI 100 mcg QD treatment group used significantly less rescue medication than the placebo group (p=0.02). When nebulizer treatments were evaluated together with Proventil/Ventolin MDI use, the results were similar to that of the MDI use alone, in that the 100 mcg QD treatment group used significant less Proventil/Ventolin and nebulizer treatments that the placebo group at Endpoint (p=0.04). Subjects treated with MF DPI 100 mcg QD experienced an overall decrease of 0.50 puff/day compared to an increase of 0.32 puff/day for placebo. MF DPI 200 mcg was not significantly different form either MF DPI 100 mcg or placebo. Overall, the secondary endpoint of rescue medication use is supportive of the efficacy of MF 100 QD AM and 200 MF 200 QD AM.

Reviewer's Comment: When evaluating the use of rescue medication, it is difficult to know what magnitude of reduction in use is a clinically significant finding. The trend may be more important than the actual values.

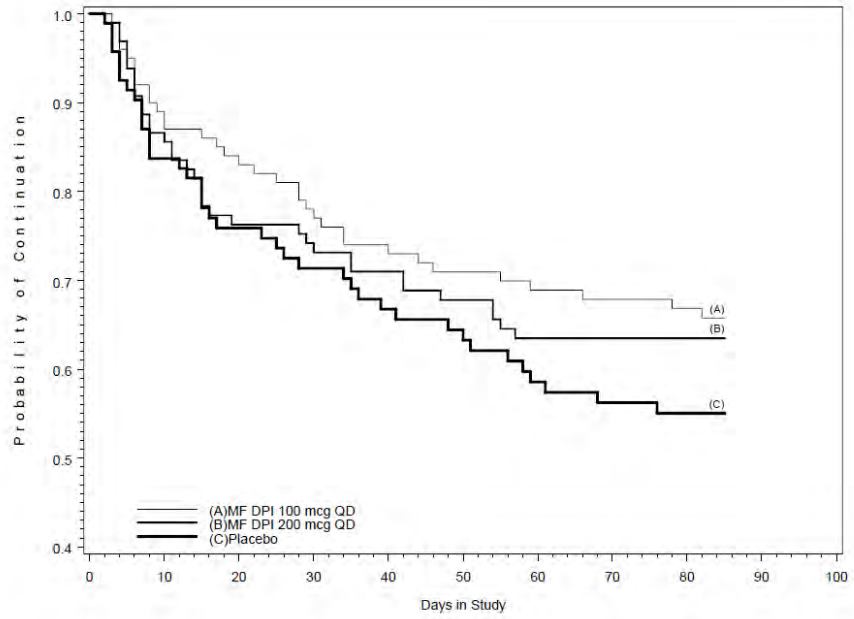
Number of Nocturnal Awakenings

Subjects recorded the number of times during the night that they were awakened by asthma symptoms requiring rescue medication. For the analysis, all nocturnal awakenings were included regardless of Proventil/Ventolin use. In general, the number of nocturnal awakenings per night was low at Baseline (≤0.15 awakenings/night) in all treatment groups. There were no significant differences at Baseline among the treatment groups. The number of nocturnal awakenings decreased between Baseline and Endpoint to a greater extent in the MF DPI treatment groups (-0.05 awakenings/night), while awakenings increased slightly (0.12 awakenings/night) in the placebo group. There was a statistically significant difference between both MF DPI treatment groups and placebo at Endpoint ($p \leq 0.03$). Statistically, the decrease in the number of nocturnal awakenings is supportive of the primary endpoint in this study, however the clinical meaning of these findings is unclear given the extremely small numerical changes.

Time to First Asthma Worsening

One-hundred eleven subjects met one or more criteria for asthma worsening (MF DPI 100 mcg Qd, 35 subjects; MF DPI 200 mcg Qd, 35 subjects and placebo, 41 subjects). The greatest number of subjects experiencing asthma worsening were in the placebo group. The most common reasons for worsening of asthma was a decrease in FEV1 and PEFR. Survival curves of time to first asthma worsening are shown in Figure 15. Results of log-rank tests shoed the two active treatment groups different from placebo.

Figure 15 Study C97-300, Time to First Asthma Worsening (All Treated Subjects)



The secondary endpoint of time to first asthma worsening was supportive of the efficacy of the active MF treatments.

Clinical Asthma Exacerbations

The sponsor defined clinical asthma exacerbation (CAE) as a deterioration of asthma that results in hospitalization, treatment with asthma medication in addition to those allowed in the protocol, e.g., treatment with a long-acting oral or inhaled beta-agonist or oral steroids, or other emergency treatment. CAEs were infrequent in study C97-300. Thirty-two (32) subjects experienced a protocol-defined CAE sometime during the study. CAEs were reported more often in the placebo (12 subjects) and MF DPI 200 mcg QD (14 subjects) than in the MF DPI 100 mcg QD (6 subjects). The secondary endpoint of clinical asthma exacerbation does not fully support the primary efficacy endpoint, but it is difficult to interpret since the occurrence of CAEs was infrequent in this 12 week study.

Health-Related Quality of Life (HRQOL)

HRQOL in this study was measured using the general health questionnaire, CHQ-PF28, plus an asthma-specific module. Together, these questionnaires assess physical and emotional functioning and how much the asthma interrupts a child's life. The CHQ-PF28 can be summarized by using two summary scores for physical and psychosocial impact. Both dose levels of MF DPI were significantly different from placebo for the physical summary score. In addition to the improved HRQOL observed in the physical function summary score of the CHQ-PF28, statistically significant differences (after adjustment for multiplicity) were also observed between placebo and both dose levels of MF DPI for the disability domain of the asthma specific questionnaire.

In summary, FEV1, $FEF_{25-75\%,}$ Response to Therapy, Use of Rescue Medication, Time To Asthma Worsening, and HRQOL were supportive of the primary efficacy endpoint in this study. Nocturnal awakenings and PEFR were equivocal, whereas FVC, asthma symptom scores, and CAES did not statistically support the efficacy of the active treatment groups but did show favorable numerical trends.

Safety Outcomes

- Exposure

Sixty-eight to 75% of patients in the active treatment groups received treatment for at least 12 weeks. The extent of exposure was satisfactory to allow for safety assessments. This information is summarized in Table 49.

Table 49 Study C97-300, Extent of Exposure

Length of Exposure	MF DPI 100 mcg QD N=100	MF DPI 200 mcg QD N=97	Placebo N=93
≥ 1 dose	100 (100)	97 (100)	93 (100)
≥ 4 days	99(99)	97(100)	91(98)
≥ 1 week	98(98)	96(99)	85(91)
≥ 2 weeks	96(96)	93(96)	80(86)
≥ 4 weeks	92(92)	88(91)	71(76)
≥ 8 weeks	84(84)	80(82)	65(70)
≥ 12 weeks	75(75)_	66(68)	51(55)

- Adverse Events

Overall adverse events were reported in 69% of subjects in each MF DPI group and 75% of subjects in the placebo group. The most frequently reported adverse events during double-blind treatment with study drug were fever, headache, allergy aggravated, viral infection, pharyngitis, rhinitis, and upper respiratory tract infection (See Table 50).

Table 50 Study C97-300, Adverse Events Occurring in ≥ 10% of subjects in any Treatment group

	MF DPI 100 mcg QD	MF DPI 200 mcg QD	Placebo
Fever	19%	20%	12%
Headache	21%	22%	13%
Allergy aggravated	12%	11%	10%
Viral Infection	13%	16%	17%
Pharyngitis	13%	6%	6%
Rhinitis	11%	11%	9%
Upper Respiratory Tract Infection	11%	8%	5%

See Table 51 below for a full listing of adverse events reported in this study. In Table 52, following the full listing of adverse events, this reviewer compiled those adverse events which occurred with greater frequency in any of the active MF DPI treatment groups when compared with placebo.

Table 51 Study C97-300, Incidence of Adverse Events Reported in at Least ≥ 3% of Subjects in Any Treatment Group by Body System/Organ Class

	Number[a] (%) of Subjects		
	MF DPI 100 mcg QD (n=100)	MF DPI 200 mcg QD (n=97)	Placebo (n=93)
No. of Subjects (%) With Any Adverse Event	**69 (69)**	**67 (69)**	**70 (75)**
Body as a Whole – General Disorders	**41 (41%)**	**44 (45%)**	**28 (30%)**
Allergy Aggravated	12 (12)	11 (11)	9 (10)
Fever	19 (19)	19 (20)	11 (12)
Headache	21 (21)	21 (22)	12 (13)
Gastrointestinal System Disorders	**16 (16)**	**21 (22)**	**14(15)**
Abdominal pain	2 (2)	4 (4)	2 (2)
Diarrhea	2 (2)	1 (1)	3 (3)
Dyspepsia	5 (5)	7 (7)	3 (3)
Nausea	3 (3)	3 (3)	2 (2)
Tooth disorder	3 (3)	0 (0)	2 (2)
Vomiting	3 (3)	7 (7)	1 (1)
Hearing and Vestibular Disorders	**5 (5)**	**2 (2)**	**3(3)**
Earache	5 (5)	2 (2)	3 (3)
Musculo-Skeletal System	**6(6)**	**2(2)**	**1(1)**
Musculo-skeletal pain	3 (3)	0 (0)	0 (0)
Reproductive Disorders, Female	**1 (3)**	**0 (0)**	**1 (3)**
Vaginitis[b]	1 (3)	0 (0)	1 (3)
Resistance Mechanism Disorders	**23(23)**	**21(22)**	**25(27)**
Infection viral	13 (13)	16 (16)	16 (17)
Otitis media	8 (8)	7 (7)	7 (8)
Respiratory System Disorders	**48(48)**	**43(44)**	**35(38)**
Coughing	5 (5)	3 (3)	2 (2)
Epistaxis	3 (3)	2 (2)	2 (2)
Nasal congestion	9 (9)	12 (12)	5 (5)
Pharyngitis	13 (13)	6 (6)	6 (6)
Rhinitis	11 (11)	11 (11)	8 (9)
Rhinitis aggravated	1 (1)	5 (5)	2 (2)
Rhinorrhea	5 (5)	3 (3)	5 (5)
Sinusitis	4 (4)	9 (9)	3 (3)
Upper respiratory tract infection	11 (11)	8 (8)	5 (5)
Skin and Appendages Disorders	**11(11)**	**8(8)**	**6(6)**
Rash	4 (4)	1 (1)	2 (2)
Vision Disorders	**6(6)**	**1(1)**	**2(2)**
Conjunctivitis	5 (5)	0 (0)	1 (1)

a: Number of subjects reporting adverse events at least once during the study. Some subjects may have reported more than one adverse event.

b: Percent calculated based on the total female population.

Table 52 Study C97-300, Adverse events reported by ≥ 3% of Patients and with Greater Frequency in the Active Treatment Groups as Compared with Placebo

	MF DPI 100 mcg QD N=100	**MF DPI 200 mcg QD N=97**	**Placebo N=93**
Allergy Aggravated	12 (12)	11(11)	9(10)
Fever	19(19)	19(20)	11(12)
Headache	21(21)	21(22)	12(13)
Abdominal pain	2(2)	4(4)	2(2)
Dyspepsia	5(5)	7(7)	3(3)
Nausea	3(3)	3(3)	2(2)
Tooth disorder	3(3)	0(0)	2(2)
Earache	5(5)	2(2)	3(3)
Musculoskeletal pain	3(3)	0(0)	0(0)
Coughing	5(5)	3(3)	2(2)
Epistaxis	3(3)	2(2)	2(2)
Nasal Congestion	9(9)	12(12)	5(5)
Pharyngitis	13(13)	6(6)	6(6)
Rhinitis	11(11)	11(11)	8(9)
Rhinitis aggravated	1(1)	5(5)	2(2)
URTI	11(11)	8(8)	6(6)
Rash	4(4)	1(1)	2(2)
Conjunctivitis	5(5)	0(0)	1(1)

**Highlighted cells represent those treatment groups in which the AE was more frequent than placebo.

Most adverse events in this study were categorized as mild to moderate in severity. Twenty-six subjects reported severe/life-threatening adverse events; 12 subjects treated with MF DPI 100 mcg QD, 9 treated with MF DPI 200 mcg QD, and 5 treated with placebo. Upper respiratory tract infection was reported by 4 subjects in the 100 mcg QD group. No single severe adverse event was reported by more than 2 subjects in a treatment group, with the exception of headache which was reported by 3 patients in the MF DPI 200 mcg QD group. The life-threatening AE was an asthma exacerbation in the placebo group. Overall, there did not appear to be any notable differences in the occurrence of severe/life-threatening AEs between treatment groups. One

severe AE led to interruption of treatment and three led to the discontinuation of a subject from the study.

Local Adverse Events

Pharyngitis was reported by 25 (9%) overall: 13 subjects in the MF DPI 100 mcg QD group, 6 subjects in MF DPI 200 mcg QD group, and 6 treated with placebo. Most cases of pharyngitis were considered to be mild to moderate in severity. No case of pharyngitis led to interruption of treatment or discontinuation of a subject from the study. Oral candidiasis was uncommon in this study, being reported by only 5 subjects overall (1.7%); 2 subjects treated with MF DPI 100 mcg QD, 1 treated with MF DPI 200 mcg QD, and 2 treated with placebo. No case of oral candidiasis led to interruption of treatment or the discontinuation of a subject from the study.

Subgroup Analysis of Adverse Events

Per the Sponsor, there were no indications of a differential response to treatment between males and females. There were too few subjects 4 to 5 years of age to provide meaningful analysis by age. A greater proportion A greater proportion of Caucasian subjects reported adverse events across treatment groups (Caucasians, 75% to 88%; non-Caucasians, 47% to 57%). These differences were largely events that were classified into the body systems/organ classes of Body as a Whole, and Respiratory System Disorders.

- Deaths and Serious Adverse Events

There were no deaths reported ruing the study, or within 30 days of the last dose of study medication. Serious adverse events were reported by 6 subjects (2%), two during the Screening period prior to randomization, and four during the double-blind treatment phase with study medication. Of those occurring during treatment, one occurred during treatment with MF DPI 100 mcg QD, two during treatment with MF DPI 200 mcg QD, and one during treatment with placebo. A brief summary of these SAEs that occurred during the treatment period follows:

- Subject 15/176 was a 10-year-old female who was randomized to MF DPI 100 mcg QD. One month into study treatment, she was hospitalized with an asthma exacerbation and right lower lobe atelectasis, later diagnosed as *M. pneumoniae* pneumonia. The subject was treated and discharged from the hospital four days later, and discontinued from the study.
- Subject 10/006 was an 11-year-old male who was randomized to MF DPI 200 mcg QD. Approximately 2 weeks into study treatment, she experienced progressive respiratory distress and was admitted to the hospital in status asthmaticus. The subject was discontinued from the study at this time and was discharged from the hospital after 1 week of treatment.
- Subject 05/056 was a 7-year-old male randomized to receive MF DPI 200 mcg QD. Approximately 1 month into study treatment, he was admitted to hospital for shortness of breath, cough, and palpitations. The subject was discontinued from the study.
- Subject 02/034 was a 10-year-old female who was randomized to receive placebo. Approximately 12 days into study treatment, she experienced a diminished AM PEFR and increasing cough, dyspnea, and wheezing. Increased albuterol administration failed to alleviate her symptoms. She then received treatment in the emergency room, without

admittance, for a life-threatening asthma exacerbation. The subject was discontinued from the study at this time.

Reviewer's Comment: The three SAEs that occurred in the active treatment groups were all respiratory in nature. It is unlikely that any of these SAEs were caused by the drug itself, but it is possible that they were caused due to lack of effect. It is difficult to draw any definite conclusions with such small numbers of SAEs.

- Withdrawals Secondary to Adverse Events

A total of 12 subjects (4%) did not complete treatment because of adverse events.

- MF DPI 100 mcg QD: 2 subjects (2%)
- MF DPI 200 mcg QD: 7 subjects (7%)
- Placebo: 3 subjects (3%)

Withdrawal secondary to AEs was more common in the active treatment groups versus placebo. The AEs that led to withdrawal in the MF DPI groups were mostly classified as Respiratory System Disorders, and included: upper respiratory tract infection, asthma aggravated, atelectasis, pneumonia, rhinitis aggravated, sinusitis, and status asthmaticus. Two patients withdrew secondary to viral infection and somnolence.

- Laboratory Evaluation

Median changes in laboratory test values from Baseline to Endpoint were evaluated for changes for each treatment group. Evaluation of these population-based results revealed no clinically relevant change in median values. However, there were 3 individuals who met the criteria for clinically significant abnormalities, 2 subjects in the MF DPI 100 mcg QD group, and 1 in the placebo group. One subject in the MF DPI 100 mcg QD group and 1 in the placebo group both had significant elevations in their alkaline phosphatase values (4-5x ULN), and 1 subject in the MF DPI group had an elevation in LDH to 2.5x the ULN. The clinical significance of these abnormalities is unknown.

- Vital Signs

No clinically meaningful changes in vital signs were noted after review of the line listings.

In summary, MF DPI treatment was well tolerated with no unusual or unexpected safety concerns arising from review of the safety data in Study C97-300. The adverse events that been reported are known to occur with this class of medications and in this patient population with asthma.

10.3.3 Conclusions

This was a Phase III, multicenter, randomized, placebo-controlled, double-blind, parallel-group efficacy and safety study of MF DPI in the treatment of asthma in children previously maintained on inhaled corticosteroids. The study began with a 1-2 week run-in period in which subjects continued on their prescribed inhaled corticosteroids. The subjects were then randomized to one of three parallel treatment arms for 12 weeks: MF DPI 100 mcg QD, MF DPI 200 mcg QD, and placebo.

There were 290 subjects randomized at 20 study centers. All randomized patients received at least one dose of study medication. The number or subjects randomized to each of the treatment groups was comparable. A total of 73 subjects (25%) discontinued from the study prior to scheduled completion. The occurrence of discontinuation was lowest for subjects receiving MF DPI 100 mcg QD, 16 subjects (16%), and highest for subjects receiving placebo 36 subjects (39%). Treatment failure was the most common reason for discontinuation (50 subjects, 17%). The proportion of subjects in each active treatment group reporting treatment failure as the reason for discontinuation was similar, and lower than in the placebo group (11% to 13% in the active treatment groups vs. 27% in the placebo. In general, it appears that the subjects in the placebo group were more likely to discontinue from the study than subjects in either of the active treatment groups.

The primary objective of this study was to evaluate the efficacy and safety of MF DPI 200 mcg QD compared to placebo. The secondary objective was to evaluate the relative efficacy and safety of MF DPI 100 mcg QD and 200 mcg QD compared to placebo. The primary efficacy analysis was the change of % predicted FEV1 from Baseline to Endpoint. The primary comparison was between MF DPI 200 mcg QD vs. placebo. MF DPI 200 mcg QD was superior to placebo with a LS Mean treatment difference of 6.84, $p < 0.01$. In other comparisons, MF DPI 100 mcg QD was also superior to placebo with a LS Mean treatment difference of 7.58, $p < 0.01$. There was not difference between active treatment groups. The efficacy of MF DPI 100 mcg QD and 200 mcg QD was supported by the following secondary endpoints: FEV1, $FEF_{25-75\%}$, Response to Therapy, Use of Rescue Medication, Time to Asthma Worsening, and HRQOL.

Sixty-eight to 75% of patients in the active treatment groups received treatment for at least 12 weeks. The extent of exposure was satisfactory to allow for safety assessments. Overall adverse events were reported in 69% of subjects in each MF DPI group and 75% of subjects in the placebo group. The most frequently reported adverse events during double-blind treatment with study drug were fever, headache, allergy aggravated, viral infection, pharyngitis, rhinitis, and upper respiratory tract infection. There were no deaths reported during the study period or within 30 days of the last dose of the study drug. Serious adverse events were reported in 4 randomized patients, three in the MF DPI treatment groups, and 1 in the placebo group. There were no clinically meaningful changes in vital signs, laboratory tests, or physical examination. There were no unusual or unexpected safety concerns noted.

In conclusion, study C97-300 supports the efficacy and safety of MF DPI 100 mcg QD AM and 200 mcg QD AM dosing regimens.

10.4 Study C97-384: One-Year, Double-Blind Study of the Effects of Mometasone Furoate Dry Powder Inhaler (MF DPI) Versus Placebo on Growth of Children with Asthma

Protocol #:	C97-384
Title:	One-Year Double Blind Study of the Effects of Mometasone Furoate Dry Powder Inhaler (MF DPI) versus Placebo on Growth of Children with Asthma
Study Dates:	Initiated May 28, 1998. Completed July 28, 2000.
Sites:	29 centers in the United States
IRB:	The protocol and subject informed consent form were reviewed by the institutional review boards for each center.
Ethics:	The investigators conducted this study according to the principles Good Clinical Practices (GCP).

10.4.1 Study Design/Protocol

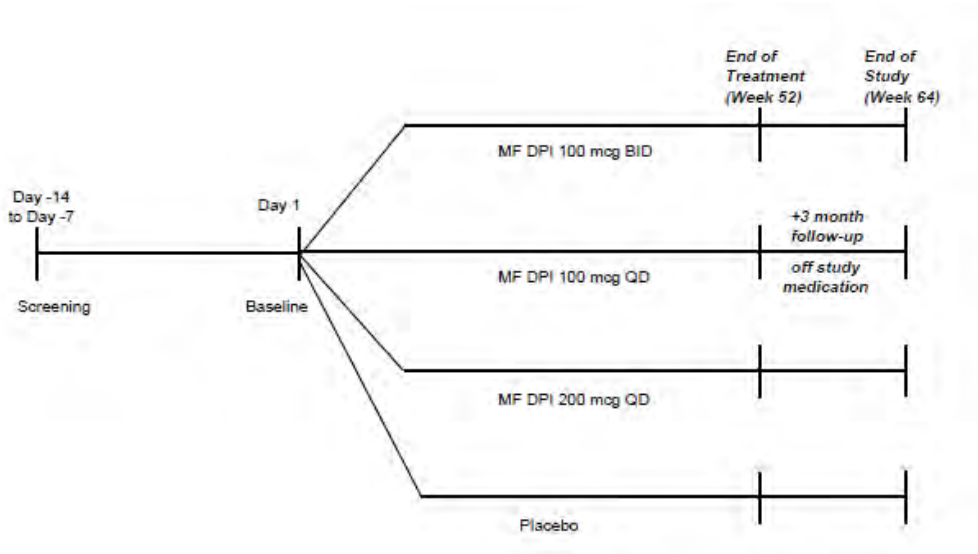
Objectives

The primary objective of this study was to determine whether MF DPI had any effect on growth velocity of pediatric subjects (4-9 years of age) with asthma. The secondary objective was to evaluate the effect of MF DPI on the HPA axis using 8 AM plasma cortisol and 12-hour urinary cortisol measurements.
Reviewer's Comment: HPA axis data collection was not as rigorous as in study C96-361. Therefore, the HPA axis data will only be reviewed in study C96-361.

Description

This was a Phase III, 52 week, 4-arm, multicenter, randomized, placebo-controlled, parallel group, double-blind, long-term safety study of MF DPI in children aged 4 to 9 years with asthma. This study was designed to assess the effect of treatment with MF DPI on growth velocity. After a run-in period of 1 to 2 weeks, subjects were randomized in a 1:1:1:1 ratio to MF DPI 100 mcg QD AM, MF DPI 100 mcg BID, MF DPI 200 mcg QD AM, or placebo. Subjects received study drug for 52 weeks. On completion of the treatment period, subjects were followed monthly for 3 months. (See Figure 16).
Reviewer's Comment: The dosing regimen that has been submitted for registration is not studied in this trial (i.e. 100 mcg QD PM.)

Figure 16 Study C97-384, Study Design Diagram



Population

- Inclusion Criteria

Patients were eligible for study entry if ALL of the following applied:

1. Between the ages of 4 and 9 years, of either gender, and of any race. Boys: no more than 9 years 6 months of age at the Baseline visit. Girls: no more than 9 years of age, in order to reasonably ensure that they were still prepubescent following 12 months of treatment
2. Height as measured by stadiometer was within normal limits with respect to age and gender.
3. Subjects must have had one stadiometer height measurement taken at least 3 months and no more than 24 months prior to Screening which fell between the 5th and 95th percentile on standard growth charts. This height measurement must not have deviated more than 10 percentiles from the Screening height measurement as evaluated on the growth chart. Alternatively, subjects may have had two non-stadiometer height measurements within the 3-24 months prior to Screening which must have both fallen between the 5th and 95th percentiles. These height measurements must not have deviated more than 15 percentiles from the Screening height measurement.
4. Each subject must have been at a stage no greater than Stage 1 in the Tanner Classification of Sex Maturity (pre-adolescent penis and testes in boys; pre-adolescent pubic hair and breasts in girls).
5. Skeletal age as determined by left hand-wrist x-rays must have been within 2 years of chronological age.
6. Subjects must have had a diagnosis of asthma for at least 6 months, which required physician-prescribed pharmacotherapy with at least one asthma medication for the 6 months preceding the Screening visit.

7. The subject's FEV1 must have been greater than or equal to 75% of predicted normal at both the Screening (Visit 1) and Baseline (Visit 2) visits, when all restricted medications had been withheld for the specified intervals. Alternatively, for children 4 or 5 years of age, the subject may have qualified for the study if he/she demonstrated either ≥75% of predicted normal FEV1 for any one value, irrespective of consistency with the other efforts, or, ≥75% of predicted average morning peak expiratory flow for that age group, utilizing a morning average peak flow value obtained at the Screening visit, plus the average of the
   last 7 morning peak flow values recorded in the subject's diary and reviewed at Baseline. For 4-5 year olds unable to qualify using spirometry, the subject's morning average PEF must have been ≥75% of predicted normal at both Screening and Baseline visits to qualify.
8. Subjects must demonstrate evidence of an increase in absolute FEV1 of at least 12% after reversibility testing at Screening, or historically within the past 12 months. Alternatively, for children 4 or 5 years of age, if every best effort has been made and documented to achieve reversibility utilizing spirometry, without success, and historical reversibility is unavailable, then a subject may be qualified for the study if the Investigator has determined and documented that the subject has met the NHLBI criteria for the diagnosis and treatment of asthma for this age group.
9. Subjects at selected centers must have had a morning (8 AM +/- 1 hour) plasma cortisol level of at least 5 mcg/dL.
10. Clinical laboratory tests (CBC, blood chemistries, urinalysis) must have been within normal limits or clinically acceptable to the Investigator/SPRI.
11. Subjects must have been free of any clinically significant disease (other than asthma), that would have interfered with the study evaluations.
12. Subjects and parents/guardians must have been willing to give written informed consent and able to adhere to dose and visit schedules and meet study requirements.
13. Subjects and parents/guardians must have agreed to inform their usual treating physician (if other than study Investigator) of their participation in this study.
14. Female subjects must have been pre-menarchal.

- Exclusion Criteria

Patients were excluded from the study if ANY of the following applied:

1. Subjects who had been taking any of the restricted medications prior to Screening.
2. Subjects who could not adhere to the concomitant medication prohibitions.
3. Subjects whose clinical condition required daily use of nebulized beta-agonists, or any use of long-acting inhaled beta-agonists. Use of long-acting beta-agonists (e.g., salmeterol) was prohibited for the duration of the study.
4. Subjects who were unable to use the MF DPI device.
5. Subjects who were unable to effectively use a peak flow meter.
6. Subjects with the following clinical conditions/demography were excluded:
   a. asthma that required chronic use of inhaled or systemic corticosteroids
   b. history, or evidence of, abnormal growth
   c. any disease or condition which might substantially affect growth, or required concomitant steroid therapy

d. evidence of gross malnutrition
e. Subjects who were allergic to corticosteroids or beta-agonists.
f. Subjects who required inpatient hospitalization for asthma control within the previous 3 months.
g. Subjects who required ventilator support for respiratory failure secondary to their asthma within the last 5 years.
h. Subjects who were admitted to the hospital for management of airway obstruction, on two or more occasions within the last six months.
i. Subjects with clinically significant evidence of bronchiectasis or cystic fibrosis.
j. Subjects with a significant history of renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, respiratory, gastrointestinal, cerebrovascular, or other significant medical illness or disorder which, in the judgment of the investigator, could have interfered with the study, or required treatment which might have interfered with the study. Specific examples include insulin dependent diabetes mellitus, cancer, active hepatitis. Other conditions which were well-controlled and stable, and on appropriate medications may be allowed upon consultation with the SPRI.
k. Subjects who demonstrated an increase or decrease in FEV1 of ≥20% between Screening and Baseline visits.
l. Subjects who required the use of >12 puffs per day of Proventil_ on any 2 consecutive days between Screening and Baseline.
m. Subjects who experienced an upper or lower respiratory tract infection (viral or bacterial) within the previous 2 weeks prior to Screening and Baseline visits.
n. Subjects with any clinically relevant abnormal Baseline vital sign.
o. Subjects with a clinically significant abnormal ECG at the Screening Visit or within the previous 30 days.
p. Subjects who had clinically significant abnormalities on chest x-ray at the Screening Visit or within the previous year.
q. Subjects with evidence (on physical examination) of clinically significant oropharyngeal candidiasis.
r. Subjects with history and/or presence of posterior subcapsular cataracts.
s. Subjects with clinically significant psychological/psychiatric disturbances such as depression, anorexia or bulimia.
t. Subjects who were known to be human immunodeficiency virus (HIV) positive (HIV testing will not be done at Screening).

- Withdrawal Criteria

Any subject whose health or well-being would have been threatened by study continuation was to be withdrawn from the study by the investigator. Subjects who experienced a clinically significant worsening of their asthma during the study (as defined by the following criteria) were to have been discontinued from the study:

<u>During the Treatment Period</u>

1. Oral steroid treatment or equivalent (intravenous or short-acting intramuscular preparations: each day's administration was considered equivalent to one day's treatment with oral steroids) for more than 15 days. There must have

been an interval of at least 4 weeks between the last dose of steroid and 8 AM plasma cortisol and 12-hour urinary cortisol testing.
2. Hospitalized for asthma on more than two occasions during the study.
3. Required ventilator support for asthma.
4. Required chronic treatment with additional ICS.

During the 3-Month Follow-Up Period

1. Required use of any oral, intramuscular, intra-articular, inhaled, ocular or nasal corticosteroid.

Other criteria which may have contributed to the physician's decision to discontinue a subject included any of the following:

A. 20% or greater decrease in FEV_1 (absolute value) from the value at the Baseline Visit.
B. 25% or greater decrease in AM or PM peak flow from the mean AM Baseline value (obtained between the Screening and Baseline Visits) on any 2 consecutive days.
C. Clinically significant increase in use of bronchodilator (e.g. use of>12 puffs of short-acting beta-agonist MDI or >2 treatments with nebulized beta-agonists on any 2 consecutive days).
D. A clinical asthma exacerbation (CAE) requiring emergency treatment for asthma, hospital admission, or treatment with additional asthma medication, other than short-acting inhaled beta agonists.

If a pre-menarchal girl began menstruating during the study, a serum pregnancy test was to be performed. In order to continue in the study, the subject and parent/guardian must have consented to the subject using double-barrier method of contraception should she become sexually active during the remainder of the study. Another serum pregnancy test was performed at the Final Treatment Visit. Subjects who became pregnant during the study were to be discontinued, and the pregnancy followed to resolution.

Treatments

- Study Treatments

Run-in phase (Between Screening and Baseline Visits)

A primed Proventil MDI was provided at the Screening visit as rescue mediation. Patients could also be taking nebulized beta-agonists. Subjects who were taking theophylline as part of their current therapeutic regimen were permitted to continue to take this medication during the run-in period and throughout the study, provided the dose remained constant.

Double-blind Treatment Phase

At the Baseline Visit, subjects meeting the eligibility criteria were randomized to 52 weeks of treatments with one of the following double-blind treatments (See Table 53):

Table 53 Study C97-384, Treatment Groups

Treatment Group	AM Dose	PM Dose	Total mcg/day
MF DPI 100 mcg BID	100 mcg x 1 inhalation	100 mcg x 1 inhalation	200 mcg
MF DPI 100 mcg QD AM	100 mcg x 1 inhalation	Placebo x 1 inhalation	100 mcg
MF DPI 200 mcg QD AM	200 mcg x 1 inhalation	Placebo x 1 inhalation	200 mcg
Placebo	Placebo x 1 inhalation	Placebo x 1 inhalation	0 mcg

Each treatment kit contained 2 DPI devices, one AM and one PM device.

- Permitted Therapies

The permitted therapies are similar to those in Study C97-385. See Section 10.6.1 Study C97-385, Study Design/Protocol.

- Excluded Therapies

The excluded therapies are similar to those in Study C97-385. See Section 10.6.1 Study C97-385, Study Design/Protocol. In this study, Ritalin® and Periactin® are additionally excluded with washout periods of 3 months prior to Screening.

- Compliance

Compliance was evaluated by asking subjects and/or parent/guardians whether all medications had been taken as instructed. Further, patient diaries were reviewed at each visit.
Reviewer's comment: At the time of the completion of this review, there is an information request pending to the applicant requesting a more detailed summary of compliance data.

Conduct

This was a Phase III, 52 week, 4-arm, multicenter, randomized, placebo-controlled, parallel group, double-blind, long-term safety study of MF DPI in children aged 4 to 9 years with asthma. This study was designed to assess the effect of treatment with MF DPI on growth velocity. After a run-in period of 1 to 2 weeks, subjects who met eligibility criteria were randomized in a 1:1:1:1 ratio to MF DPI 100 mcg QD AM, MF DPI 100 mcg BID, MF DPI 200 mcg QD AM, or placebo. Subjects received study drug for 52 weeks. On completion of the treatment period, subjects were followed monthly for 3 months. There were eleven scheduled visits: Screening, Baseline, Weeks 1, 2, 4, 8, 12, 16, 26, 38, and 52. The study schedule appears in Table 54.

Table 54 Study C97-384. Study Flow Chart

Procedure	Screening Visit 1 -14 to -7	Treatment Period[a] Baseline Visit 2 1	Visit 3 Week 1 ±2 days	Visit 4 Week 2 ±2 days	Visit 5 Week 4 ±3 days	Visit 6 Week 8 ±1 week	Visit 7 Week 12 ±1 week	Visit 8 Week 16 ±1 week	Visit 9 Week 26 ±1 week	Visit 10 Week 38 ±1 week	Visit 11 Week 52 ±1 week
Obtain Informed Consent[b]	X										
Review Inclusion/Exclusion Criteria	X	X									
Medical/Disease History	X										
Concomitant Medications Review	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X								X		X
Body Weight and Height (by Harpenden stadiometer)	X	X		X	X	X	X	X	X	X	X
Vital Signs (temperature, blood pressure, pulse, respiratory rate)	X	X	X	X	X	X	X	X	X	X	X
Oropharyngeal Exam	X	X	X	X	X	X	X	X	X	X	X
Pulmonary Auscultation	X	X	X	X	X	X	X	X	X	X	X
Pulmonary Function Tests	X	X	X	X	X	X	X	X	X	X	X
Reversibility Test	X										
Ophthalmic Examination	X										X
Hematology, Blood Chemistry plus 8 AM cortisol, Urinalysis	X	Review							X		X
12-hour Urine Collection		x							X		X
Mometasone Furoate Plasma Concentration[e]									X		X
Electrocardiogram[c]	X										
Chest X-Ray[d]	X										
Left Hand-Wrist X-Ray	X	Review									X
Dispense Diary	X	X	X	X	X	X	X	X	X	X	

Procedure	Screening Visit 1 -14 to -7	Treatment Period[a] Baseline Visit 2 1	Visit 3 Week 1 ±2 days	Visit 4 Week 2 ±2 days	Visit 5 Week 4 ±3 days	Visit 6 Week 8 ±1 week	Visit 7 Week 12 ±1 week	Visit 8 Week 16 ±1 week	Visit 9 Week 26 ±1 week	Visit 10 Week 38 ±1 week	Visit 11 Week 52 ±1 week
Retrieve/Review Diary		X	X	X	X	X	X	X	X	X	X
Dispense Peak Flow Meter	X										
Dispense/Retrieve Rescue Medication (as needed)	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Medication		X					X		X	X	
Administration of First Dose in Office		X									
Evaluation of Response to Therapy			X	X	X	X	X	X	X	X	X
Adverse Events/Intercurrent Illness Evaluation		X	X	X	X	X	X	X	X	X	X
Review Compliance		X	X	X	X	X	X	X	X	X	X
Collect Study Inhalers							X		X	X	X

a: Telephone Contact: Weeks 20, 32, 42 and 48.

b: Earlier than Day -14 if longer medication washouts were required. Informed consent must have been signed prior to any study-related procedures, including required washout of medications.

c: If not done within previous 30 days.

d: If not done within previous year.

e: Not at sites in Latin America

Efficacy Assessments

This was primarily a long-term safety study. As such, no primary efficacy variables were defined in the protocol. Efficacy variables pertaining to pulmonary function, response to therapy, clinical asthma exacerbations, peak expiratory flow, and nocturnal awakening were

considered supplementary variables to confirm that asthma did not worsen, and as another means of assessing compliance. The study was not designed to show differences in efficacy between treatment groups.

Safety Assessments

The primary variable for safety was the growth velocity over the one-year Treatment Period. Other safety assessments included:

- Medical History: Visit 1
- Physical Examination: Visit 1, Visit 9, and Final Visit
- Vital signs: All visits
- Concomitant Medication Review: All visits
- Oropharyngeal examination: All visits
- Ophthalmic Examination: Visit 1 and Final Visit
- Laboratory Tests: Visit 1, Visit 9, and Final Visit
    - CBC
    - Blood Chemistry : sodium, potassium, chloride, BUN, creatinine, liver enzymes, total protein, albumin, calcium, inorganic phosphorous, LDH
    - Serum pregnancy tests on all females who became menarchal while on study
    - Complete urinalysis
    - 8AM plasma cortisol and 12 hour urinary free cortisol : Weeks 1, 9, 11
    - Blood samples for MF : Visit 9, 11
- 12-Lead ECG: Visit 1
- Chest X-ray: Visit 1
- Telephone Contacts: Weeks 20, 32, 42, 48
- Left Hand-Wrist X-Ray: Visits 1 and 11
- Adverse Events: All visits

> *Reviewer's Comment: The sponsor states that any asthma symptoms of wheezing, difficulty breathing, cough, and chest tightness or congestion were not considered adverse events, unless they showed a clear temporal relationship to study drug administration or resulted in hospitalization. This is atypical. These events are usually reported as adverse events as inhalers can have paradoxical effects, such as bronchospasm which may mimic asthma symptoms.*

Statistical Plan

Reviewer's Comment: At the time of this review, the Division's biometric reviewer has not completed the final analysis of the growth data in this study. See the Biometrics Review by Dr. Qian Li for the Division's analysis of the growth data in this study.

- Data Sets Analyzed

The sponsor analyzed to following data sets:

- All-treated subjects: included all subjects randomized into the study who had received at least one dose of study medication. All summaries of safety day (excluding growth data) were based on all treated subjects (intent-to-treat principle).

- Full Analysis Subset**:** included all treated subjects with at least one follow-up evaluation. Summaries of growth and efficacy were based upon this dataset.

- Sample Size Determination

Assuming a pooled standard deviation of 2.6 cm/yr in growth velocity, it was anticipated that with a sample size of 44 subjects per treatment group and at a 0.05 level of significance, there would be at least 90% power to detect a mean treatment difference of approximately 1.8 cm/yr in growth velocity or more between a pair of treatment groups. This sample size also allows differences of 0.9 cm in actual growth to be detected with the same power assuming a pooled standard deviation of 1.0 cm. A difference between groups of less than 30% of yearly growth was not considered clinically significant.

- Primary Safety Analyses

The primary safety variable was defined in the protocol as the growth velocity during the one-year treatment period. The growth velocity of the one-year treatment period was defined as the slope (rate of change) obtained from a linear regression standing height vs. time (i.e. the number of days from the Baseline Visit at which the height was obtained) for each subject. These individual growth velocities were analyzed by two-way ANOVA. Treatment comparisons were based on the LS means from ANOVA, using a 5% two-sided significance level. The full analysis subset (pooled across centers) was to be included in the analyses.
Reviewer's Comment: Due to poor estimation of early drop outs, the Sponsor determined that the above planned statistical analysis would not be the optimal way to evaluate the growth data. The Sponsor decided, prior to unblinding, to change the method of the primary analysis to one based on a longitudinal random slope model. For the same reason, the analysis of change in standing height from Baseline was not performed.

- Analysis of Secondary Safety Variables

For the additional 3-month Follow-up Period, the growth velocity was to be defined as the slope (rate of change) to be obtained from a linear regression of standing height vs. time (i.e, number of days post-treatment of stadiometer evaluation of standing height) for each subject. These post-treatment growth velocities were to be analyzed by the same two-way ANOVA described above for the primary variable.

The changes in standing height at each post Baseline Visit (Treatment and Follow-up Periods) from the Baseline of the Treatment Period were also to be compared.

- Analysis of Secondary Efficacy Variables

All continuous efficacy variables were to be analyzed at each time point using the same two-way ANOVA noted above. This included % predicted FEV1, FVC, FEF25-75%, and the response to therapy at scheduled visits, as well as subject evaluations recorded on the diary (averaged over each7-day interval) including PEFR, nocturnal awakenings, the amount of Proventil used (including equivalent doses for nebulizer use of 4 puffs), and separately, the number of nebulized beta-agonist treatments. The evaluation of response to therapy as the percentage of subjects

demonstrating improvement or much improvement from Baseline was to be analyzed using Fisher.s exact test. Clinical asthma exacerbations and worsenings (discontinuation) were to be summarized and tabulated. Kaplan-Meier estimates were to be calculated to assess time to discontinuation due to asthma worsening. Subjects who met the criteria for worsening asthma were to be included in this analysis, regardless of whether or not the Investigator actually discontinued the subject.
Reviewer's Comment: Evaluation of the time to discontinuation due to asthma worsening was changed to an evaluation of the time to first asthma worsening.

Protocol Amendments
Three general amendments and one center specific amendment were made to the original protocol:

- Amendment No. 1: September 25, 1998. The major changes instituted by this amendment include:
    - Modification of the inclusion criteria to include Vanceril 84 mcg Double Strength, and Flovent Rotadisk DPI as permitted inhaled corticosteroids prior to Screening
    - Daytime and nighttime symptom scores were removed as a secondary endpoint.
    - All references to Cortrosyn testing were removed and replaced with 8 AM plasma cortisol and 12-hour urinary cortisol testing at 11 centers
    - 6-month interim analysis was removed
    - Weight was added as a safety evaluation
    - Assessment of skeletal age at Visit 11 to assess changes in bone age, and a 3 month follow-up period for off-treatment observation to look for changes in growth rate that might occur once treatment was discontinued were added
    - **The primary variable was amended to be growth velocity during the one-year treatment period, not change in standing height as originally planned.**
- Amendment No. 2: January 20, 1999. The major changes instituted by this amendment include:
    - Change in inclusion criteria for children 4-5 years of age to allow children to qualify for the study if, alternatively, he/she demonstrated either $\geq$ 75% of predicted normal FEV1 or $\geq$75% of predicted average PEF for that age group.
    - Ventolin was added as rescue medication to be used at the Latin American Centers.
- Amendment No. 3: May 16, 2000. The major changes instituted by this amendment include:
    - Removal of the blinded interim analysis at the end of the treatment period. The study was to continue to the end of the post-treatment follow-up independent of treatment period results.

In addition, a site specific amendment (site 05) was issued on May 12, 1998. This amendment specified that female subjects who experience the onset of menses at any time during the study would be immediately discontinued from the study.

10.4.2 Results

Patient Disposition

A total of 187 subjects were randomized at 29 US study centers. All randomized subjects received at least one dose of study medication. The number of subjects randomized to each of the treatment groups is as follows:

- MF DPI 100 mcg BID: 44 subjects
- MF DPI 200 mcg QD AM: 50 subjects
- MF DPI 100 mcg QD AM: 48 subjects
- Placebo: 45 subjects

Of the 187 randomized subjects, 135 (72%) completed the treatment period. A total of 52 subjects discontinued from the study during the Treatment Period. The percentage of patients that discontinued from each treatment group ranged from 21% (100 mcg QD AM) to 33% (Placebo). The two most common reasons for study discontinuation during the treatment period were: discontinuation unrelated to treatment and subject lost to follow-up. Discontinuation due to adverse events occurred only in the active treatment groups, and was notably lowest in the 100 mcg QD AM group (4%). Treatment failure was reported as a reason for discontinuation in 2% of MF DPI 100 mcg BID, 4% of MF DPI 200 mcg QD AM, and 6% of MF DPI 100 mcg QD AM treated patients, vs. 9% in placebo. See Table 55 for details of patient disposition.

Table 55 Study C97-384, Patient Disposition

	Number (%) of Subjects			
	MF DPI 100 mcg BID	MF DPI 200 mcg QD AM	MF DPI 100 mcg QD AM	Placebo
Treatment Period				
Number of Subject Enrolled for Treatment	44	50	48	45
Completed	33 (75)	34 (68)	38 (79)	30 (67)
Discontinued	11 (25)	16 (32)	10 (21)	15 (33)
Reasons for Discontinuation				
Adverse Event	2 (5)	4 (8)	2 (4)	0
Treatment Failure	1 (2)	2 (4)	3 (6)	4 (9)
Lost to Follow-up	2 (5)	4 (8)	1 (2)	6 (13)
Did Not Continue For Reasons Unrelated To Treatment	3 (7)	6 (12)	2 (4)	3 (7)
Noncompliance With Protocol	3 (7)	0	2 (4)	2 (4)
Follow-up Period				
Number of Subject Enrolled for Follow-up	30	30	37	25
Completed	28 (93)	25 (83)	32 (86)	23 (92)
Discontinued	2 (7)	5 (17)	5 (14)	2 (8)
Reasons for Discontinuation				
Adverse Event	0	1 (3)	0	1 (4)
Lost to Follow-up	0	1 (3)	1 (3)	0
Did Not Continue For Reasons Unrelated To Treatment	0	1 (3)	2 (5)	0
Noncompliance With Protocol	1 (3)	1 (3)	1 (3)	1 (4)
Did Not Meet Protocol Eligibility	1 (3)	1 (3)	1 (3)	0

Source Data: Section 14.4.3. and Section 16.2.1..

- Protocol Violations

Two sets of protocol violations were identified in this study:

- One patient was not discontinued at the time of asthma worsening as was dictated by protocol-defined criteria
- 49 patients had exposure to excessive prohibited medication. Analysis with and without these patients showed that inclusion of these patients did not impact the analysis. A subset analysis of patients who used more than 15 days of systemic or additional inhaled corticosteroids, more than 84 days of nasal corticosteroids, or growth hormone confirmed the analysis of the full analysis subset, and hence these patients were also not excluded from the final analysis.

Demographics and Other Baseline Characteristics

- Demographics

Demographic data for the study population are presented in Table 56. The randomized treatment groups were generally similar with regard to age, sex, race, asthma duration, and baseline % predicted FEV1. There was a higher proportion of males than females in each treatment group and the majority of the subjects were Caucasian. Of the 37 non-Caucasians in the study, 70% were black, and 30% were Hispanic. The mean duration of asthma was 3.6 to 4.5 years and the baseline % predicted FEV1 was 42-49%.

Table 56 Study C97-384, Demographics and Baseline Characteristics

	MF DPI 100 mcg BID (n=44)	MF DPI 200 mcg QD AM (n=50)	MF DPI 100 mcg QD AM (n=48)	Placebo (n=45)
Age (years)				
Mean	6.3	6.6	6.4	6.6
Median	6	7	7	7
Min-Max	4-9	4-9	4-9	4-9
Distribution of Subjects in Age Categories				
4 to 5 years	15	13	14	11
6 to 9 years	29	37	34	34
Sex				
Female	16	17	14	9
Male	28	33	34	36
Race				
Caucasian	33	37	40	40
NonCaucasian	11	13	8	5
Weight (kg)				
Mean	25.4	26.5	25.3	27.6
Median	24	25	25	25
Min-Max	15-43	17-49	12-43	15-67
Height (cm)				
Mean	120.3	122.1	120.6	123.3
Median	118.9	124.15	122.05	124.0
Min-Max	99.6-139.3	102.7-138.5	95.6-143.4	96.1-141.9
Asthma Duration (years)				
Mean	4.0	3.6	3.8	4.5
Median	4	4	4	5
Min-Max	0.83-9.0	0.42-8.0	0.67-8.0	0.50-8.0
Theophylline Use				
Yes	1	0	0	0
No	43	50	48	45
Baseline % Predicted FEV_1				
no. of subjects[a]	42	49	47	43
Mean	89.3	89.5	87.2	85.4
Median	88.3	88.3	86.8	84.1
Min-Max	74.9-111.3	47.5-112.1	61.0-115.3	61.4-115.3

a: Subject C97-384-12/034, C97-384-17/267, C97-384-25/273, C97-384-23/221, C97-384-12/142, and C97-384-27/006 had missing Baseline values. They qualified for the study using entry PEF criteria for 4-5 year olds.

- Baseline Concomitant Medications

The sponsor did not summarize baseline concomitant medications or medical history. This reviewer reviewed the line listings for concomitant medications. The concomitant medications were divided into asthma/allergy related and unrelated medications. Among the concomitant medications used to treat asthma/allergy were short acting b2-agonists, antihistamines, inhaled/nasal corticosteroids, cromolyn, ipratropium, oral corticosteroids, and decongestants. Of the asthma/allergy unrelated concomitant medications, the most common drugs were acetaminophen, ibuprofen, and antibiotics.

Compliance

Table 57 Study C97-384, Summary of Treatment Compliance

Percent of Compliance	MF DPI 100 mcg BID n=44	MF DPI 200 mcg QD AM n=50	MF DPI 100 mcg QD AM n=48	Placebo n=45
100%	4 (9)	2 (4)	3 (6)	4 (9)
90% - <100%	29 (66)	37 (74)	37 (77)	36 (80)
75% - <90%	8 (18)	7 (14)	5 (10)	4 (9)
50% - <75%	1 (2)	4 (8)	2 (4)	1 (2)
<50%	0	0	1 (2)	0
MISSING	2 (5)	0	0	0

Note: Treatment compliance was based upon diary data.
Source Data: Section 14.1.4. and Section 16.2.5.

Compliance was generally good in this study and similar across treatment groups. Treatment non-compliance, defined as the use of less than 75% or greater than 125% of the protocol specified doses, occurred in only 11 subjects and all were due to use of less than 75% of protocol specified doses (9 subjects) or missing diary data (2 subjects). The majority of subjects were at least 90% compliant. A summary of percent treatment compliance based on diary data is provided in Table 57. PK samples were also collected as a means of assessing compliance. PK was assessed pre-dose at Week 26 and 52. No subject in the PBO group had detectable MF. Most subjects in active tx groups had MF concentration below LOQ (50pg/mL). One-three subjects in each tx group had detectable MF concentration.

Efficacy outcomes

Because this study was primarily a safety study, efficacy evaluations were considered secondary. The study was not designed nor powered to detect differences between treatment groups. A brief summary of selected efficacy results are as follows:

- **% predicted FEV1**: all treatment groups demonstrated improvement over baseline, but there were no statistically significant differences among treatment groups or placebo. Even though there was no statistically significant difference there was a numerical trend favoring the MF treatment groups over placebo.

- **AM and PM PEFR:** AM and PM PEFR were better at most time points with 200 mcg total daily dose of MF DPI than with MF DPI 100 mcg or placebo, however, no statistically significant differences between the MF DPI treatment groups or between any dose of MF DPI and placebo were observed. Even though there was no statistically significant difference there was a numerical trend favoring the MF treatment groups over placebo.
- **Response to therapy:** all MF DPI treatments produced slightly better mean physician evaluated response scores compared to placebo at most time points. At the endpoint of treatment, the mean response scores were significantly lower (better) for MF DPI 100 mcg BID compared to placebo.
- **Use of Rescue Medication:** all treatment groups recorded a decrease in rescue medication at all time points, however there were no statistical differences between groups.
- **Time to Worsening of Asthma:** MF DPI treatment groups had a smaller proportion of subjects with asthma worsening, and the median time to first asthma worsening was delayed.
- **Clinical Asthma Exacerbations:** were reported in a total of 48/187 (26%) of subjects. CAEs were most common in the placebo group (17 subjects) followed by subjects treated with MF DPI 100 mcg QD AM (13 subjects.).

In summary, this study was not powered to show differences in efficacy results among treatment groups. However, the efficacy data did suggest a trend in favor of the MF treatment groups.

Safety Outcomes

Reviewer's Comment: Many different variables were studied as secondary endpoints in this one year growth study. Growth was the primary safety variable. This reviewer will focus on the growth velocity and adverse events as a part of the safety review of this study. Other variables (such as HPA axis effects) have been examined in a more rigorous manner in other studies and hence will not be reviewed in detail here.

- Exposure

Of the 187 subjects enrolled in the study, 131 subjects (70%) received treatment for at least 50 weeks: MF DPI 100 mcg BID, 75%; MF DPI 200 mcg QD AM, 66%; MF DPI 100 mcg QD AM, 79%; Placebo, 60%. Thus the extent of exposure was adequate to assess long-term safety in this population of subjects (See Table 58).

Table 58 Study C97-384, Extent of Exposure

Length of Exposure	MF DPI 100 mcg BID (n=44)	MF DPI 200 mcg QD AM (n=50)	MF DPI 100 mcg QD AM (n=48)	Placebo (n=45)
≥1 dose	44	50	48	45
≥1 week	42	50	48	45
≥2 weeks	42	49	47	44
≥4 weeks	42	49	47	43
≥8 weeks	41	46	46	41
≥12 weeks	39	45	45	39
≥16 weeks	38	43	44	37
≥20 weeks	37	42	43	35
≥26 weeks	36	41	42	33
≥32 weeks	35	37	41	33
≥38 weeks	33	35	40	33
≥42 weeks	33	34	39	31
≥50 weeks	33	33	38	27
≥52 weeks	17	25	26	19

Source Data: Section 14.5..

- Growth Velocity

Reviewer's Comment: At the time of this review, the Division's biometric reviewer has not completed the final analysis of the growth data in this study. See the final Biometrics review for the Division's analysis of the growth data in this study. The outline presented here is per the Sponsor's statistical analysis of the data and may change with the final statistical review and for labeling purposes. The data reflected in the Executive Summary and the NDA template contains the data from the Biometrics Review, by Dr. Qian Li.

The primary endpoint for this study was growth velocity at one year of treatment. The growth velocity for the one year treatment period was defined as the slope (rate of change) obtained from a linear regression of standing height vs. time (i.e., number days from the Baseline Visit at which height was obtained) for each subject. The results of the analysis are listed in Table 59.

Table 59 Study C97-384, Growth-Velocity

C97-384: Growth				
	MF DPI			
	100 mcg BID	200 mcg QD(AM)	100 mcg QD(AM)	Placebo
On-Treatment Velocity (N)	5.88 (42)	5.82 (49)	6.42 (48)	6.52 (45)
Δ from Placebo± Standard Error (p-value)	-0.64 ±0.39 (0.10)	-0.70±0.29 (0.02)	-0.10±0.31 (0.76)	0
Follow-Up Phase Velocity (N)	5.96 (36)	4.50 (34)	7.66 (40)	6.91 (30)
Δ from Placebo	-0.95±1.51 (0.53)	-2.42±1.18 (0.05)	0.75±1.76 (0.67)	0

Growth velocity for the MF DPI 200 mcg QD treatment group was significantly less than placebo (p=0.02), and the difference between MF DPI 100 mcg BID and placebo achieved borderline significance (p=0.10). Comparisons between active treatments showed that growth velocity for the MF DPI 200 mcg QD AM treatment group was significantly lower than for the MF DPI 100 mcg QD AM treatment group (p=0.04).

Estimates of the mean velocities during the 3-month Follow-up Period should be interpreted with caution. This analysis uses three months of growth data (or in some cases less) from each subject, which may be too little time to accurately measure growth. This analysis was based upon 140 subjects due to the large number of subjects that either did not wish to continue into the follow-up phase or dropped out after starting the follow-up phase.
In general, growth velocities decreased with increasing age across treatment groups. There were too few non-Caucasians and too few females to make the assessments of growth velocity by sex and race. When growth velocity was examined for the 135 subjects that completed one year of treatment, the results supported the primary analysis.

- Adverse Events

Overall, the incidence of all treatment-emergent adverse events was similar among the four treatment groups ranging from 91% to 98%. The most frequently reported adverse event in this study was upper respiratory tract infection, reported by 40% to 52% of MF DPI treated subjects and 56% of placebo subjects. Other commonly reported adverse events (≥ 20% of subjects in any one treatment group) included viral infection, headache, pharyngitis, fever, otitis media, nasal congestion, allergy, allergy aggravated, coughing, sinusitis, and dyspepsia. Table 60 presents the adverse events that were reported by ≥ 3% of patients and with greater frequency in the active treatment groups as compared with placebo.

Table 60 Study C97-384, Adverse events reported by ≥ 3% of Patients and with Greater Frequency in the Active Treatment Groups as Compared with Placebo

	MF DPI 100 mcg BID N=44	MF DPI 200 mcg QD N=50	MF DPI 100 mcg QD N=48	Placebo N=45
Abdominal Pain	2 (5)	1 (2)	3 (6)	0
Allergy Aggravated	9(20)	9(18)	9(19)	4 (9)
Bronchitis	8 (18)	4 (8)	6 (13)	5 (11)
Candidiasis, oral	2 (5)	0	1 (2)	0
Coughing	8 (18)	11 (22)	8 (17)	4 (9)
Cramps (Legs)	2 (5)	0	1 (2)	2(4)
Dental procedure	2 (5)	0	0	0
Dermatitis	0	2 (4)	2 (4)	0
Dermatitis, contact	3 (7)	0	2 (4)	1 (2)
Diarrhea	3 (7)	3 (6)	2 (4)	2 (4)
Dysuria	2 (5)	0	0	0
Ecchymoses	0	0	2 (4)	0
Eczema aggravated	0	1 (2)	2 (4)	0
Epistaxis	2 (5)	1 (2)	5 (10)	2 (4)
Face Edema	1 (2)	2 (4)	0	0
Fever	16 (36)	15(30)	14 (29)	10(22)
Gastritis	0	1 (2)	2 (4)	0
Gastroenteritis	3 (7)	3 (6)	4 (8)	1 (2)
Headache	17 (39)	12 (24)	16 (33)	14 (31)
Hyperkinesia	1 (2)	2 (4)	0	1 (2)
Influenza-like sx	0	3 (6)	0	0

Insomnia	1 (2)	0	2 (4)	0
Joint Sprain	2 (5)	0	1 (2)	0
Laceration, skin	1 (2)	0	3 (6)	0
Malaise	2 (5)	0	2 (4)	0
Mouth ulceration	0	2 (4)	0	0
Myalgia	1 (2)	3 (6)	0	1 (2)
Nausea	0	0	3(6)	2 (4)
Otitis Externa	2 (5)	1 (2)	2 (4)	2 (4)
Otitis Media	9 (20)	8 (16)	16 (33)	6 (13)
Pruritis	0	0	2 (4)	1 (2)
Rash	2 (5)	4 (8)	3 (6)	3 (7)
Rhinitis	10 (23)	8 (16)	12 (25)	8 (18)
Rhinorrhea	5 (11)	4 (8)	2 (4)	3 (7)
Sinus congestion	0	1 (2)	2 (4)	1 (2)
Skin Trauma	0	2 (4)	1 (2)	1 (2)
Sneezing	0	2 (4)	1 (2)	0
Stridor	2 (5)	0	2 (4)	0
Surgical procedure, skin	0	0	2 (4)	0
Tooth Abscess	1 (2)	2 (4)	0	0
Urinary Tract Infection	1 (2)	0	2 (4)	0
Urticaria	2 (5)	0	1 (2)	1 (2)
Vaginal disorder	0	0	1 (7)	0
Varicella	1 (2)	2 (4)	1 (2)	1 (2)
Viral Infection	16 (36)	19 (38)	20 (42)	11 (24)

Most adverse events reported during this study were categorized as mild to moderate in severity. No life-threatening adverse events were reported. Overall, severe adverse events were reported by 25 subjects (13%) and was highest in the MF DPI 100 mcg QD AM group (19%) compared with MF DPI 100 mcg BID (7%), MF DPI 200 mcg QD AM (16%) and Placebo (11%). Pharyngitis and upper respiratory tract infection were the most frequently reported severe

adverse events. No single severe adverse event was reported by more than 3 subjects in a treatment groups.

Local Adverse Events

One subject in the MF DPI 200 mcg QD AM group reported moderate dysphonia. Pharyngitis was reported by 56 (30%) subjects overall, 27% to 31% in the active treatment groups as compared with 31% in the placebo group. Oral candidiasis was noted upon oropharyngeal examination in three subjects (2%) overall, 2 in the 100 mcg BID group and 1 in the 100 mcg QD AM group. The onset of oral candidiasis was noted after subjects received at least 3 months of treatment. All cases were considered mild to moderate in severity.

Subgroup Analysis of Adverse Events

Per the Sponsor, there were no indications of a differential response to treatment between males and females and there were too few subjects 4 to 5 years of age to provide meaningful analysis by age. There were also too few non-Caucasian subjects to allow a meaningful analysis of adverse events by race.

- Deaths and Serious Adverse Events

There were no deaths reported during the study period or within 30 days of the last dose of the study drug. Serious adverse events were reported in 5 subjects. Neither the number nor the nature of the serious adverse events reported suggested a differential risk of serious adverse events among the treatment groups. A brief summary of the SAEs follows:

- Subject C97-384-07/162, a 5-year-old male, was randomized to receive MF DPI 100 mcg BID on 29 July 1998. He was admitted to the hospital on [redacted] with a diagnosis of viral pneumonia, allergic rhinitis and aggravated asthma. Subject was discharged, upon recovery on [redacted] Study medication was continued.
- Subject C97-384-10/152, an 7-year-old female with a history of febrile seizures, was randomized to MF DPI 200 mcg QD AM on 04 March 1999. On [redacted], the mother reported that the subject had suffered a seizure while actively playing on a hot day. The pediatric neurologist ruled out a seizure since the subject had remained conscious with full memory and recall of the event. There were no further sequelae. Study medication was continued.
- Subject C97-384-10/158, a 7-year-old male, was randomized to receive placebo on 20 August 1998. Subject was seen in the emergency room on [redacted] for increased asthma symptoms and was subsequently admitted. Upon discharge on [redacted], the subject was discontinued from the study.
- Subject C97-384-20/257, a 5-year-old male, was randomized to receive MF DPI 200 mcg QD AM on 27 February 1999. On [redacted], the subject experienced cough, sore throat, shortness of breath and decrease in PEF. Study medication was interrupted and the subject was hospitalized. Upon recovery, the subject was discharged on [redacted] and study medication re-instituted on 16 April 1999.
- Subject C97-384-06/093, a 6-year-old male, was randomized to receive

placebo on 29 October 1998. The study completed treatment on 03 November 1999 and entered the Follow-up Period of the study. On [redacted], the subject was hospitalized for 2 days for an asthma exacerbation.

- Withdrawals Secondary to Adverse Events

A total of 8 subjects did not complete treatment because of adverse events, 28 of these subjects during the double-blind treatment phase of the study:

- MF DPI 100 mcg BID: 2 subject (5%)
- MF DPI 100 mcg QD AM: 2 subjects (5%)
- MF DPI 200 mcg QD AM: 4 subjects (8%)
- Placebo: 0 subjects

The most frequently reported adverse events leading to discontinuation were events that were classified to the Respiratory System, such as upper respiratory tract infection, bronchitis, sinusitis, and pharyngitis.

In summary, no clinically meaningful new safety concerns have arisen from review of this section. The adverse events that have been reported are known to occur with inhaled corticosteroids and in a patient population with asthma.

- Laboratory Evaluation

Laboratory evaluation did not reveal any clinically meaningful results.

- Ophthalmologic Exams

The findings of ophthalmologic exams were reviewed. Although limited in nature, no safety signal is indicated by the results of these exams.

- Vital Signs

No clinically meaningful changes in vital signs were noted after review of the line listings.

10.4.3 Conclusions

This was a Phase III, 52 week, 4-arm, multicenter, randomized, placebo-controlled, parallel group, double-blind, long-term safety study of MF DPI in children aged 4 to 9 years with asthma. This study was designed to assess the effect of treatment with MF DPI on growth velocity. After a run-in period of 1 to 2 weeks, subjects were randomized in a 1:1:1:1 ratio to MF DPI 100 mcg QD AM, MF DPI 100 mcg BID, MF DPI 200 mcg QD AM, or placebo. Subjects received study drug for 52 weeks. On completion of the treatment period, subjects were followed monthly for 3 months.

A total of 187 subjects were randomized at 29 US study centers. All randomized subjects received at least one dose of study medication. The number of subjects randomized to each of the treatment groups was comparable. Of the 187 randomized subjects, 135 (72%) completed the treatment period. A total of 52 subjects discontinued from the study during the Treatment

Period. The percentage of patients that discontinued from each treatment group ranged from 21% (100 mcg QD AM) to 33% (Placebo). The two most common reasons for study discontinuation during the treatment period were: discontinuation unrelated to treatment and subject lost to follow-up. Discontinuation due to adverse events occurred only in the active treatment groups, and was notably lowest in the 100 mcg QD AM group (4%). Treatment failure was reported as a reason for discontinuation in 2% of MF DPI 100 mcg BID, 4% of MF DPI 200 mcg QD AM, and 6% of MF DPI 100 mcg QD AM treated patients, vs. 9% in placebo.

Sixty-six to seventy-nine percent of subjects in the active treatment groups received treatment for more than 50 weeks. The extent of exposure was satisfactory to allow for safety assessments.

The primary endpoint for this study was growth velocity at one year of treatment. The growth velocity for the one year treatment period was defined as the slope (rate of change) obtained from a linear regression of standing height vs. time (i.e., number days from the Baseline Visit at which height was obtained) for each subject. Growth velocity for the MF DPI 200 mcg QD treatment group was significantly less than placebo (p=0.02), and the difference between MF DPI 100 mcg BID and placebo achieved borderline significance (p=0.10). Comparisons between active treatments showed that growth velocity for the MF DPI 200 mcg QD AM treatment group was significantly lower than for the MF DPI 100 mcg QD AM treatment group (p=0.04).

Overall, the incidence of all treatment-emergent adverse events was similar among the four treatment groups ranging from 91% to 98%. The most frequently reported adverse event in this study was upper respiratory tract infection, reported by 40% to 52% of MF DPI treated subjects and 56% of placebo subjects. Other commonly reported adverse events (≥ 20% of subjects in any one treatment group) included viral infection, headache, pharyngitis, fever, otitis media, nasal congestion, allergy, allergy aggravated, coughing, sinusitis, and dyspepsia. Most adverse events reported during this study were categorized as mild to moderate in severity. No life-threatening adverse events were reported. There were not deaths. Overall, severe adverse events were reported by 25 subjects (13%) and was highest in the MF DPI 100 mcg QD AM group (19%) compared with MF DPI 100 mcg BID (7%), MF DPI 200 mcg QD AM (16%) and Placebo (11%). Pharyngitis and upper respiratory tract infection were the most frequently reported severe adverse events. No single severe adverse event was reported by more than 3 subjects in a treatment groups. One subject in the MF DPI 200 mcg QD AM group reported moderate dysphonia. Pharyngitis was reported by 56 (30%) subjects overall, 27% to 31% in the active treatment groups as compared with 31% in the placebo group. Oral candidiasis was noted upon oropharyngeal examination in three subjects (2%) overall, 2 in the 100 mcg BID group and 1 in the 100 mcg QD AM group. The onset of oral candidiasis was noted after subjects received at least 3 months of treatment.

In conclusion, MF 200 mcg QD AM appears to cause a statistically significant reduction in growth velocity. MF 100 mcg BID shows numerical trends towards growth suppression.

Reviewer's Comment: At the time of finalization of this review, the analysis of the growth study by our biometrics reviewer has not been finalized. See the Biometrics Review by Dr. Qian Li for the Division's analysis of the growth data.

10.5 Study C96-361, Multiple Dose Safety Study of Mometasone Furoate Dry Powder (MF-DPI) in Asthmatic Children

Protocol #:	C96-361
Title:	Multiple Dose Safety Study of Mometasone Furoate Dry Powder (MF-DPI) in Asthmatic Children
Study Dates:	Initiated June 3, 1997. Completed September 7, 1997.
Sites:	Single center in the United States.
Investigators:	Thomas Haverty, MD and Keith Nolop, MD
IRB:	The protocol and subject informed consent form were reviewed by an Institutional Review Board.
Ethical Considerations:	The investigators conducted this study according to the principles of Good Clinical Practices (GCP).

10.5.1 Study Design/Protocol

Objectives

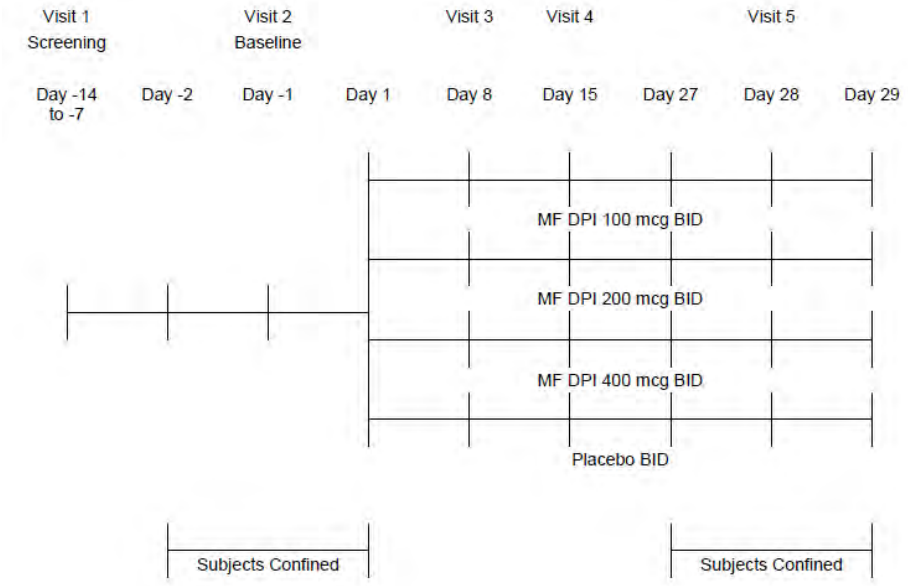
The primary objective of this study was to determine the systemic effects of mometasone furoate dry powder inhaler on HPA-axis function as assessed by 12-hour multiple nocturnal plasma cortisol measurements, cosyntropin stimulation, and 24-hour urinary free cortisol concentrations. The study was conducted in children 6 to 11 years of age with mild asthma, during treatment with MF DPI 100, 200, 400 mcg BID, or placebo.

Description

This was a 29-day, Phase 1, single center, randomized, placebo-controlled, double-blind, parallel group study of the effects of MF DPI on HPA-axis function in 50 children with mild asthma. After a screening period of 1-2 weeks, subjects were to be treated with double-blind study drug for 29 days. Each subject was randomized to one of four treatment groups in a 1:1:1:1 ratio: MF DPI 100 mcg BID, 200 mcg BID, 400 mcg BID or placebo. Plasma cortisol measurements were taken during periods of confinement at Baseline and at the Final Visit (Figure 17).

Reviewer's comment: The duration of this study is shorter then the current guidance document would recommend, i.e. six weeks. However, it is noted that the study was completed before the guidance was available. Also, this study did not include an active control group which is useful for interpreting assay sensitivity.

Figure 17 Study C96-361, Study Design Diagram



Population

- Inclusion Criteria

1. Subjects must have been between the ages of 6 and 11 years, of either sex and of any race.
2. Subjects must have had a diagnosis of childhood asthma for at least 6 months.
3. Subjects must have been using inhaled β2 adrenergic agonists on an as-needed basis only, and must not have required any regular controlling therapy.
4. The subject's Screening FEV1 must have been greater than or equal to 80% of predicted when all restricted medications had been withheld for the specified intervals.
5. Clinical laboratory tests (CBC, blood chemistries, urinalysis) must have been within normal limits or clinically acceptable to the investigator/sponsor.
6. Subjects must have been free of any clinically significant disease (other than asthma), that would interfere with the study evaluations.
7. Subjects and parents/guardians must have been willing to give written informed consent and must have been able to adhere to dose and visit schedules and meet study requirements.
8. Female subjects must have been pre-menarchal.
9. Subjects must have had normal growth development within the preceding year, as defined by either of the following criteria:

- Each subject's height must have been within normal limits (i.e., within 2 standard deviations of mean height for age and sex on standard height charts provided);
- Subjects must have had growth rates previously documented to be normal (i.e., 2 previous measurements taken at least 3 months apart that are within the 3 to 24 months preceding the Screening visit). These two historical height measurements must both have been within the same standard deviation from the mean as the Screening height (i.e., if the Screening height was 1 standard deviation from the mean then each of the two historical height measurements should also have been 1 standard deviation from the mean).

10. Subjects must have had a morning plasma cortisol value of ≥5 mcg/dL and must have demonstrated an increase in cortisol level of at least 7 mcg/dL, 30 minutes after Cortrosyn injection with an absolute stimulated plasma cortisol value exceeding 18 mcg/dL.

- Exclusion Criteria

1) Subjects with a history of multiple drug allergies (>2 different classes of medications) or who were allergic to corticosteroids or beta agonists.
2) Subjects who required the use of >4 puffs per day of Proventil on ≥2 consecutive days during the seven days prior to Baseline.
3) Subjects who had an active URI at the time of Screening and/or Baseline, or who had an upper respiratory tract or sinus infection that required antibiotic therapy within the previous 2 weeks, or who had a viral upper respiratory tract infection of more than 5 days duration within 14 days prior to Screening.
4) Subjects who had required inpatient hospitalization for asthma control within the last year.
5) Subjects with significant renal, gastrointestinal, neurologic, cardiovascular, hematologic, metabolic, hepatic, cerebrovascular, respiratory (other than mild asthma), or other significant medical illness or disorder which, in the judgment of the investigator, could have interfered with the study or required treatment which might interfere with the study.
6) Subjects with any clinically relevant abnormal vital sign or any laboratory test result outside the normal range for that laboratory that is:
    - not due to a known underlying disease and considered by the investigator and Schering monitor to contraindicate study participation or,
    - in the investigator's judgment, clinically significant, based on clinical evaluation and other tests with clinical relevance to the abnormal laboratory test.
7) Subjects with clinically significant psychological disturbances such as anorexia or bulimia.
8) Subjects with clinically significant enuresis.
9) Subjects unable to use the MF DPI device.
10) Subjects who had used any investigational drug in the past 30 days.
11) Subjects on immunotherapy (desensitization therapy) unless on a stable maintenance schedule for at least one month prior to Screening.

- Withdrawal Criteria

A subject who experienced a significant clinical asthma exacerbation was to be discontinued from the study. A significant clinical asthma exacerbations was defined as a worsening of asthma that resulted in emergency treatment, hospitalization, or treatment with asthma medication in addition to those allowed in the protocol.

In addition, subjects could have been removed from the study whenever considered necessary for their welfare, and subjects could discontinue at any time at their discretion, and at the discretion of the investigator. Non-compliance with the protocol or the occurrence of a significant adverse event, including a significant laboratory abnormality.

Treatments

- Study Treatments

At the Baseline visit, subjects meeting the eligibility criteria were randomized in a 1:1:1:1 ratio to 29 days of treatment with one of the following (See Table 61):

Table 61 Study C96-361, Treatment Groups

Treatment Group	AM Dose	PM Dose	Total MF (mcg/day)
Group A	100 mcg MF DPI	100 mcg MF DPI	MF 200 mcg
Group B	200 mcg MF DPI	200 mcg MF DPI	MF 400 mcg
Group C	400 mcg MF DPI	400 mcg MF DPI	MF 800 mcg
Group D	Placebo	Placebo	Placebo (0 mcg)

Each treatment kit contained 2 DPI devices, one AM device and one PM device. Proventil HFA or another albuterol inhaler was provided as rescue medication use.

Reviewer's Comment: An active control arm was NOT included in the study. In addition, the study did not include the dosing regimen proposed for registration.

- Permitted Therapies

The following medications were permitted during the study:

- OTC pain relief medications.
- Antibiotics for indications other than lower respiratory tract infections.
- Topical antimicrobials.
- Proventil inhalation aerosol (with 6-hour withhold prior to study visits).
- Nasal or ocular decongestants, nasal or ocular cromolyn, nasal ipratropium bromide, ocular antihistamines.
- Short-acting pseudoephedrine formulations (30 mg), up to a total daily dose of 120 mg/day; a 24-hour washout should be observed before each study visit.
- Oral antihistamines such as terfenadine, loratadine or chlorpheniramine (but not long-acting decongestant combination products of these medications) were permitted for subjects who

experienced allergy symptoms while on-study. If any of these medications was used in a PRN manner, the subject was to observe an appropriate washout period prior to any study visit. If a subject was using such medications on a daily basis prior to Screening, he was to continue this dosing regimen and no washout was necessary. Subjects were to refrain from using astemizole while on-study.

- Subjects could receive immunotherapy treatments during the study if they were on a stable maintenance schedule for at least one month prior to the Screening visit. However, doses were not to be given within 24 hours prior to a study visit. Subjects could receive their immunotherapy dose while in the office for a study visit, after all protocol-specified procedures had been completed.
- Mild potency topical corticosteroids for dermatological use only (excluding Elocon, all doses and formulations), for use in controlling eczema, hives, etc..

- Excluded Therapies

Table 62 provides the prohibited medications and the exclusionary time period prior to Screening for each.

Table 62 Study C96-361, Excluded Therapies

Excluded Medication	Washout Period
Investigational drugs	1 month
Beta-adrenergic bronchodilators (syrups, tablets, SR tablets)	1 day
Bronchodilators, short-acting inhaled	6 hours
Beta-adrenergic bronchodilators, long-acting (Salmeterol)	1 week
Theophylline	2 weeks
Cromolyn sodium, nedocromil, (all forms)	2 weeks
Leukotriene modifiers (Zafirlukast)	2 weeks
Zileuton	2 weeks
Corticosteroids, inhaled, nasal or ocular	3 months
Corticosteroids, intramuscular or long acting depot	6 months
Corticosteroids, high potency topical	1 month
Astemizole	3 months
Systemic Antibiotics	2 weeks
Immunotherapy	1 day

The following medications were prohibited after the Screening visit and for the duration of the study:

- Medications linked with a clinically significant incidence of hepatotoxicity or which may cause significant liver enzyme induction
- Inhaled, nasal, ocular, oral, intramuscular, intra-articular, intravenous corticosteroids
- High potency topical corticoids (Class 3, 2, or 1, Stoughton-Cornell Scale)
- Any medication for asthma other than Proventil
- Oral decongestants (except for short-acting pseudoephedrine formulations
- Astemizole
- Other investigational drugs.

- Compliance

Compliance was evaluated at each return visit by checks of protocol compliance, reviewing diary card data, and by use of the subject's drug supply. Plasma MF levels were also obtained.

Conduct

This 29-day, Phase I, single-center, randomized, double-blind, placebo-controlled, parallel group study consisted of a screening period of 1-2 weeks, followed by a 29 day treatment phase. Subjects who met eligibility criteria were randomized at Baseline in a 1:1:1:1 ratio to one of four parallel treatment arms: MF DPI 100 mcg BID, 200 mcg BID, 400 mcg BID, or placebo. There were five scheduled visits: Screening, Baseline (Days -2 to 1), Day 8, Day 15, Final Visit (Days 27-29)and Weeks 1, 2, 4, 8, and 12. Patients were confined for the purposes of complete urine collection and serial plasma cortisol measurement at the Baseline and Final Visits. The study schedule appears in the following table (See Table 63).

Table 63 Study C96-361, Schedule of Study Procedures and Evaluations

	Screening Visit 1	Baseline Visit 2			Visit 3	Visit 4	Final Visit 5		
Treatment Days	-14 to -7	-2	-1	1	8	15	27	28	29
Obtain Informed Consent	X								
Review Inclusion/Exclusion Criteria	X	X							
Subjects Confined		X[a]	X	X[b]			X[a]	X	X[b]
Concomitant Medications Review	X	X			X	X	X		
Medical/Disease History	X								
Vital Signs (temperature, blood pressure, pulse, respiration rate)	X			X	X	X			X
Physical Examination	X								X
Body Weight and Height	X								
Oropharyngeal Examination	X			X	X	X			X
Pulmonary Function Tests	X			X	X	X			X
Complete Blood Count	X			Review					X
Blood Chemistry	X			Review					X
Urinalysis	X			Review					X
12-lead Electrocardiogram	X			Review					
Initiate 24-Hour Urine Collection (10 AM)			X					X	
Complete 24-Hour Urine Collection (10 AM)				X					X
Plasma Cortisol (10 PM)			X					X	
Multiple Plasma Cortisols (10 PM, 12 midnight, 3,5,6,7,8,9 and 10 AM)				X					X
MF Plasma Concentrations								X	X
Cortrosyn®Test	X								X
Dispense Study Drug				X					
Administration of Study Drug in Office				X					
Dispense Subject Diary Cards/ Provide Instructions	X			X	X	X			
Dispense Peak Flow Meter/Provide Instructions	X								
Dispense Rescue Medication (Proventil®)	X								
Assessment of Response to Therapy					X	X			X
Collect and Review Diary Cards				X	X	X			X
Review Compliance				X	X	X			X
Adverse Events Evaluation				X	X	X			X
Collect Study Drug and Rescue Medication									X

a: by 4 PM

b: discharged before 12 noon

Efficacy Assessments

Although efficacy variables were measured, they were secondary evaluations as this study was designed to evaluate the safety of MF DPI in pediatric patients with respect to effect on HPA axis function. Efficacy assessments were measured to ensure that patients were not experiencing a worsening of their asthma symptoms during the course of the study.

- Pulmonary Function Testing: spirometry was performed at all visits and three measurements were done. The largest FEV1 and FVC were recorded. Spirometry was performed to meet the ATS standards.
- Assessment of Response to Therapy: the investigator or designee assessed the patient's response to therapy by comparing their current level of symptoms with those noted at the Baseline visit. The response to therapy was evaluated from Visits 3 to 5 using the following scale:
    - 1 = much improved
    - 2 = improved
    - 3 = no change
    - 4 = worse

- 5 = much worse

Each subject was given a diary card at Screening, Baseline, and Visits 3 and 4. The following information was recorded daily in the diary: morning and evening peak expiratory flow, total number of Proventil inhalations, symptoms of asthma, number of nocturnal awakening due to asthma requiring Proventil use, adverse events, and use of study drug and concomitant medications

- Peak Expiratory Flow Rate (PEFR): At the Screening visit, subjects were given a [redacted] Peak Flow Meter and were instructed in its proper use. Subjects were instructed to perform triplicate PEFR measurements in the morning and the evening before taking their asthma medication and/or Proventil, if need at that time. The highest of the three values was recorded in the diary. Also, the average peak flow rate over the 7 days prior to the baseline visit was used to calculate a 25% decline in PEFR. Subjects were instructed to contact the study staff immediately should the AM or PM PEFR be at or below the 25% decrease value on any two consecutive days.
- Asthma symptoms: Every morning and evening prior to dosing, patients evaluated three asthma symptoms of wheezing, difficulty breathing, and cough which were scored according to the following scale and recorded in the diary:
  - 0 = None
  - 1 = Noticeable but did not bother me or interfere with normal daily activities/sleep
  - 2 = Annoying and may have interfered with daily activities/sleep
  - 3 = Very uncomfortable and interfered with most of or all of normal daily activities/sleep
- Nocturnal awakenings: patients recorded the number of times during the night that he/she was awakened by asthma symptoms that required use of Proventil.
- Daily Medication Record: From the Baseline visit onward, the subject recorded the time of dosing of study medication twice daily in the diary. In addition, the total number of inhalations of Proventil used as rescue medication in each 24-hour period was recorded. The subject also recorded any other medications, including over-the-counter preparations.

Safety Assessments

- Medical History: Screening Visit
- Physical Examination: Visit 1 and Visit 5
- Vital signs: all visits
- Oropharyngeal Examination: all visits
- 12-lead ECG: Visit 1
- Concomitant Medication Review: all visits
- Laboratory Tests: Visit 1 and Visit 5 (CBC, Chemistry 18 including LFTs, Urinalysis with microscopic examination, serum pregnancy test for girls who become menarchal while on study)
- Adverse Events: All visits

The subjects were instructed to accurately record the type and day on which an adverse occurred in their diary. Additionally, the patients were questioned and/or examined at each visit regarding the possible occurrence of adverse events. Adverse events were recorded on the case report form.

Reviewer's Comment: The sponsor states that any asthma symptoms of wheezing, difficulty breathing, cough, and chest tightness or congestion were not considered adverse events, unless they showed a clear temporal relationship to study drug administration or resulted in hospitalization. This is not typical. We typically do see these types of symptoms reported as AEs, as inhalers have been known to cause paradoxical bronchospasm. However, CAEs have been recorded during this pediatric development program, so asthma symptoms that are not regarded as AEs are still captured.

- **Cortisol Measurements**

Subjects were confined to the research facility by 4 PM of Day -2 (two days prior to Baseline), as well as on Day 27 (two days prior to Day 29/Final Visit) for environmental acclimatization and heparin lock insertion. Urine and blood was collected at serial time points from the domiciled patients. (See Table 64).

Table 64 Study C96-361, Blood Sampling and Associated Study Drug Administration and Testing

(Study No. C96-361)

Procedure	Day -1													Day 1 (Baseline)										
Time (hour)	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10
AM/PM	AM		PM												AM										
Blood Samples for Plasma Cortisol													X		X			X		X	X	X	X	X	X
24-hour Urine Collection	<----------Continuous----------																								
Spirometry																								X[a]	
First Dose of Study Medication																									X[a]

Procedure	Day 28													Day 29 (Final)										
Time (hour)	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10
AM/PM	AM		PM												AM										
Blood Samples for Plasma Cortisol													X		X			X		X	X	X	X	X	X
Blood Samples for MF concentration													X										X	X	X
24-hour Urine Collection	<----------Continuous----------																								
Spirometry																								X[a]	
Administration of Study Medication											X												X[a]		
Cortrosyn® test																									X

a: after the blood sample.

- 24-hour urine collection for Urinary Free Cortisol: Visits 2 and 5

Urine was collected over a period of 24 hours during the Baseline and Final Visits for determination of urinary free cortisol. One 50 mL aliquot, obtained from each well-mixed 24-hour sample, was sent to central laboratory for testing. The total urine volume was recorded on the specimen container.

Reviewer's Comment: The study report does not specify that urine creatinine or other means of ensuring complete collection were also recorded.

- Plasma cortisol measurements: Visits 2 and 5

Blood samples were collected at serial timepoints during the Baseline (Day -1 to Day 1) and Final Visits (Day 28 to Day 29) for determination of plasma cortisol content.

- Cortosyn® Testing: Visits 1 and 5

Cortrosyn® testing began at approximately 10 AM on Visit 1 (Screening) and Visit 5. A blood sample was taken to determine the basal plasma cortisol level, which must have been ≥ 5 mcg/dL at Screening. At Visits 1 and 5, an IV injection of 0.25 mg of cosyntropin was administered following the last blood sample that was taken at 10 AM. A second blood sample was taken 30 minutes post-cosyntropin injection for the measurement of plasma cortisol. At Visit 1, subjects must have demonstrated an increase in cortisol level of at least 7 mcg/dL with an absolute level exceeding 18 mcg/dL following cosyntropin administration.

- Blood samples for Plasma Mometasone Furoate Determination: Visit 5

On Days 28 and 29, an additional 2 mL of blood was collected and the plasma was assayed for MF concentration.

Statistical Plan

- Data Sets Analyzed

The following data sets were used for evaluation and analysis in this study.

- All Treated Subjects: included all subjects randomized into the study who received ≥ 1 dose of treatment.
- Primary Analysis Subset: included all treated subjects who had sufficient plasma cortisol measurements to permit reliable calculation of AUC, and who had AUC measurements at both Baseline and Day 29.

Reviewer's Comment: The primary analysis subset was defined after the study was completed. The protocol defined analysis group had originally been All Treated Subjects. The primary analysis subset was defined by the sponsor as those patients which had >33% of the timepoints available to calculate a what they believe to be a reliable AUC.

The distribution of subjects used for the evaluation and analysis of the primary safety variable is presented in Table 65.

Table 65 Study C96-361, Distribution of Subjects Analyzed

Distribution of Subjects Analyzed

	Number of Subjects				
	MF DPI 100 mcg BID	MF DPI 200 mcg BID	MF DPI 400 mcg BID	Placebo	Total
All Treated Subjects	13	13	12	12	50
Primary Analysis Subset	12	12	11	7	42

- Sample Size Determination

The target sample size was to be 12 subjects per treatment group, for a total of 48 patients. The sample size was chosen to detect (with 80% power and 5% significance level) a clinically meaningful treatment difference for the Day 29 12-hour (Day 28, 10 PM to Day 29, 10 AM) plasma cortisol AUC.

- Definition of Baseline

Comparability of the treatment groups at baseline was assessed by comparing the four treatment groups with respect to demographic characteristics sex, race, age, weight) and Baseline cortisol levels (12- hour plasma cortisol AUC and 24-hour urinary free cortisol AUC).

- Primary Safety Analyses

The primary safety variable was defined as the Day-29 12 hour plasma cortisol AUC. The primary safety variable was to be analyzed for all randomized subjects using a one-way analysis of variance (ANOVA) which included an effect due to treatment. The primary pairwise comparison was between MF DPI 400 mcg BID and placebo. This comparison was made using the least squares means from the ANOVA model. If this test result was significant, the other five pairwise comparisons would also be made at the 5% level without adjustment for multiple comparisons to control overall alpha level. In addition, pairwise treatment (mean) differences would be estimated, and 95% confidence intervals calculated, based on the ANOVA model. In addition to the absolute AUC values, the change from Baseline to Day 29 in the 12-hour AUC was also to be analyzed using the same model.

- Secondary Safety Analyses

24-hour urinary free cortisol was also to be analyzed using the same ANOVA model as described from Day 29 12 hour plasma cortisol AUC. For the Screening and Final visits, the plasma cortisol concentrations for the Cortrosyn stimulation tests were listed for each subject and summarized for each treatment group. The results were used to help interpret the clinical relevance of any effects of MF DPI on 12-hour plasma cortisol AUC identified by the analysis described above.

- Summary of Other Safety Data and Efficacy Variables

Frequency tabulations and summary statistics were provided for the following additional safety parameters:

- Incidence of treatment-emergent adverse events
- Discontinuations due to adverse events
- Changes from Baseline in vital signs
- Changes in laboratory tests
- Physical and oropharyngeal examination results

Summaries of the following efficacy variables were also provided:

- FEV1
- % predicted FEV1
- FVC
- FEF 25%-75%
- Physician's evaluation of response to treatment
- AM and PM PEFR
- Asthma symptom scores
- Nocturnal awakenings due that required Proventil®

- Changes in the Planned Statistical Analyses

The analyses prospectively identified in the protocol were carried out as planned along with some additional analyses. The following variables were analyzed by ANOVA:

- Minimum, maximum, and 8 AM plasma cortisol concentrations
- Time of maximum plasma cortisol concentration
- Plasma concentrations for the Cortrosyn® stimulation tests
- FEV1 and % predicted FEV1
- AM and PM PEFR

Due to an imbalance in the Baseline AUC, an analysis of covariance (ANCOVA) was done rather than the ANOVA which had been specified in the protocol. In addition, the protocol specified that adjustments to the p-values would be made if the 400 mcg BID versus placebo comparison was not statistically significant ($p < 0.05$). In this case, the result for this comparison was marginally significant ($p = 0.05$). Despite this, the significance level was not changed for subsequent comparisons in order to remain conservative in this safety study.

Protocol Amendments

No protocol amendments were made.

10.5.2 Results

Patient Disposition

A total of 50 subjects were randomized, and all randomized subjects received at least one dose of study medication. The number of subjects randomized to each of the treatment groups is as follows:

- MF DPI 100 mcg BID: 13 subjects
- MF DPI 200 mcg BID: 13 subjects;
- MF DPI 400 mcg BID: 12 subjects,
- Placebo: 12 subjects.

Four subjects discontinued the study prior to completion. The reasons for discontinuation are summarized in Table 66.

Table 66 Study C96-361, Patient disposition

	Treatment Group				
	MF DPI 100 mcg BID (n=13)	MF DPI 200 mcg BID (n=13)	MF DPI 400 mcg BID (n=12)	Placebo (n=12)	Total (n=50)
Number (%) Completed	12 (92%)	12 (92%)	12 (100%)	10 (83%)	46 (92%)
Reason for Discontinuation					
Lost to Follow-up	0	1 (8%)	0	1 (8%)	2 (4%)
Did not Wish to Continue	0	0	0	1 (8%)	1 (2%)
Noncompliance with Protocol	1 (8%)	0	0	0	1 (2%)
TOTAL NUMBER (%) DISCONTINUING	1 (8%)	1 (8%)	0	2 (17%)	4 (8%)

- Protocol Violations

Three subjects in the placebo treatment group and one subject in the MF DPI 400 mcg BID group had missing plasma cortisol measurements at three or more (≥ 33%) of the time points, and were therefore excluded from all plasma cortisol analyses. Seven subjects (2 placebo, 1 MF DPI 100 mcg BID, 2 MF DPI 200 mcg BID, and 2 MF DPI 400 mcg BID) who had abnormal cortisol values (<5.0 pre-and/or <18.0 post-Cortrosyn) at Screening should not have been randomized, as they did not meet the protocol defined entry criteria. Of these seven, 2 were excluded from the analyses due to missing plasma cortisol concentration data, and five had pre-Cortrosyn values close to 5.0 (5.7-4.9 mcg/dL).

Demographics and Other Baseline Characteristics

- Demographics

Pooled demographic data for the study population are shown in Table 67. The treatment groups were similar with regard to demographic characteristics.

Table 67 Study C96-361, Demographics and Baseline Characteristics

	MF DPI 100 mcg BID	MF DPI 200 mcg BID	MF DPI 400 mcg BID	Placebo
	n = 13	**n=13**	**n=12**	**n=12**
Age (years)				
Mean	8.8	9.1	8.1	8.3
Range	7 – 11	6-11	6-11	6-11
Gender				
Female	8 (60.2%)	4 (30.1%)	3 (25%)	4 (33.3%)
Male	5 (39.8 %)	9 (69.9%)	9 (75%)	8 (66.7%)
Race				
White	4 (30.1%)	4 (30.1%)	4 (33.3%)	4(33.3%)
Black	9 (69.9%)	9 (69.9%)	8 (66.7%)	8(66.7%)
Height (cm)				
Mean	135	137	133	133
Range	122-152	104-152	118-163	115-145
Weight (lb)				
Mean	79	84	74	77
Range	59-117	40-146	44-145	43-135

Compliance

Subjects recorded daily use of investigational treatment in their diaries. At each visit, subjects were questioned regarding proper use of study medications. Forty-five of the 50 subjects (90%) used at lest 75% of their prescribed study medication.

Plasma mometasone furoate concentrations were also obtained on Days 28 and Days 29 of the study. These data are unhelpful to assess compliance, as the concentrations were generally below or only slightly above the limit of quantitation (LOQ = 50 pg/mL). (Section 12.4.3)

Reviewer's Comment: The Division has commented in the past regarding the poor sensitivity of the assay used to measure plasma MF concentrations. In this study, where an effect on HPA axis is observed, it is less important that we are unable to measure MF concentrations in the plasma, but the ability to do so would provide corroborative data.

Safety Outcomes

- Exposure

The majority of the subjects (92%) received the full 29 days of treatment. The extent of exposure was satisfactory to allow for safety assessments.

- 12-Hour Plasma Cortisol AUC

Three placebo-treated subjects (#021, 043, 045) and one 400 mcg BID MF DPI-treated subject (#028) had missing plasma cortisol measurements at three or more time points. The Sponsor decided that the remaining measurements would not accurately represent the AUC. In addition, two placebo treated subjects (#036, 037), one 100 mcg MF DPI-treated subject (# 050), and one 200 mcg BID MF DPI-treated subject (#014) did not complete the study. In summary, the total number of subjects excluded from the primary analysis subset are as follows:

- Placebo: 5 subjects
- MF DPI 100 mcg BID: 1 subject
- MF DPI 200 mcg BID: 1 subject
- MF DPI 400 mcg BID: 1 subject

The primary endpoint in this study was the Day 29 12-hour plasma cortisol AUC. See Table 68.

Table 68 Study C96-361, Mean Plasma Cortisol AUC (Primary Analysis Subset)

	MF DPI 100 mcg BID (n=12)	MF DPI 200 mcg BID (n=12)	MF DPI 400 mcg BID (n=11)	Placebo (n=7)
	AUC (mcg•hr/dL);			
Baseline	66.85	79.45	73.15	57.70
Day 29				
Actual Mean[a]	68.68	55.34	50.46	60.93
Adjusted Mean[b] (p-value)[c]	70.47 (0.698)	51.08 (0.078)	49.23 (0.050)	67.11
Change from Baseline	1.83	-24.11	-22.69	3.23

a: Mean of actual values; p=0.24 for overall treatment differences based on ANOVA of AUC.
b: Adjusted for imbalance in baseline AUC; p=0.02 for overall treatment differences based on ANCOVA.
c: P-value from ANCOVA for differences between specified treatment group and placebo.

The baseline values of the AUC showed large differences among treatment groups (Placebo: 57.70; MF DPI 400 mcg BID: 73.15; MF DPI 200 mcg BID: 79.45; MF DPI 100 mcg BID: 66.68). For this reason, an ANCOVA was done on Day 29 AUC data, with baseline AUC as a covariate (which was significant at $p < 0.01$). The mean value of 12-hour plasma cortisol AUC was adjusted for the imbalance in baseline AUC. The adjusted mean values for the treatment groups as compared with placebo are as follows:

- MF DPI 100 mcg BID: 70.47
- MF DPI 200 mcg BID: 51.08
- MF DPI 400 mcg BID: 49.23

Table 69 shows the treatment difference when the MF DPI groups are compared with placebo.

Table 69 Study C96-361, Comparison of Treatment Differences in Adjusted Mean Plasma Cortisol AUC at Day 29 versus Placebo.

	Adjusted Mean Plasma Cortisol AUC Day 29[1] (mcg·hr/dL)	Difference vs. Placebo
100 BID	70.47	+ 3.36
200 BID	51.08	-16.03
400 BID	49.23	-17.88
Placebo	67.11	-----

[1] Adjusted for imbalance in baseline AUC.

Reviewer's Comment: Negative values indicate that the treatment group had a lower plasma cortisol AUC when compared with placebo indicating at least a trend towards a suppressive effect on the HPA axis.

MF DPI 200 mcg BID and 400 mcg BID appeared to have an effect on the HPA axis, with mean 12-hour plasma cortisol AUCs of 51.08 mcg·hr/dL and 49.23 mcg·hr/dL, respectively, compared with 67.11 mcg·hr/dL for placebo. The mean AUCs for the 200 mcg BID and 400 mcg BID groups were 24% and 27% less than the placebo mean AUC, respectively.

Reviewer's Comment: Per the Sponsor's calculations the differences between MF DPI 200 mcg BID and 400 mcg BID and the placebo group are not statistically significant. However, it is the opinion of this reviewer that despite this, the numerical trend suggests a suppressive effect of the MF DPI 200 mcg BID and 400 mcg BID groups on the HPA axis, and according to this data, an effect on the HPA axis cannot be ruled out.

Reviewer's Comment: The three subjects that did not complete the study to Day 29 were appropriately excluded from the analysis as they had no data to contribute to the primary endpoint (Day 29 12-hour plasma cortisol AUC). However, the Sponsor did not do an analysis including the subjects that had "insufficient" data points to calculate AUC because they determined that if more than 33% of the measurements were missing, the calculation would not be reliable and should not be done. It would be more complete to include all the patients regardless of missing time points and then compare the two analyses.

- Plasma Cortisol Concentrations in Response to Cosyntropin

Change in plasma cortisol concentration in response to cosyntropin stimulation was evaluated at Screening and at Day 29. All subjects had responses to cosyntropin that were > 7 mcg/dL. Although, individual plasma cortisol concentrations were occasionally abnormal, most abnormalities were low pre-stimulation values (14 subjects: 2 placebo, 4 in each of the MF DPI groups). There were no significant differences between treatment groups at either time point (See Table 70).

Table 70 C96-361, Mean AM Plasma Cortisol Concentrations (mcg/dL) -All treated subjects with baseline and Day 29 data

(Study No. C96-361)

	MF DPI 100 mcg BID		MF DPI 200 mcg BID		MF DPI 400 mcg BID		Placebo	
	N	Mean	N	Mean	N	Mean	N	Mean
Screening								
Pre-Cortrosyn®	13	9.72	12	9.08	12	8.28	10	7.60
Post-Cortrosyn®	13	27.92	12	26.12	12	26.63	10	25.26
Difference Between Pre and Post	13	18.19	12	17.05	12	18.35	10	17.66
Day 29								
Pre-Cortrosyn®	13	8.47	12	7.80	11	6.33	10	9.47
Post-Cortrosyn®	12	26.14	12	24.89	11	24.43	10	25.46
Difference Between Pre and Post	12	17.75	12	17.09	10	18.14	10	15.99
Change from Screening (Post-Pre)	12	-0.72	12	0.04	10	-0.14	10	-1.67

Source Data: Sections 16.2.8.3. and 14.3.5.3.2..

Reviewer's Comment: The Sponsor's analysis does not reveal an effect on the HPA axis with the measurement of pre- and post-cosyntropin plasma cortisol values. Although I have presented the data here, it is the Division's current thinking that cosyntropin stimulation test is not the most sensitive way to evaluate for HPA axis suppression in response to inhaled corticosteroids. Hence, we rely more heavily on the plasma cortisol AUC as a measure of HPA axis function.

- Urinary Free Cortisol

Per the sponsor, individual urinary cortisol measurements were highly variable in this analysis. A summary of urinary free cortisol values from 24-hour urine sample at Baseline and Day 29 is presented in Table 71.

Table 71 Study C96-361, Mean Urinary Free Cortisol (mcg/24 hr) – All treated subjects with baseline and Day 29 data

Table 19 Mean Urinary Free Cortisol (mcg/24 hr)(All Treated Subjects with Baseline and Day 29 Data)

(Study No. C96-361)

	MF DPI 100 mcg BID		MF DPI 200 mcg BID		MF DPI 400 mcg BID		Placebo	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	12	19.02	12	14.28	12	21.26	10	11.41
Day 29	12	15.65	12	14.88	12	10.94	10	10.95
Change from Baseline	12	-3.37	12	0.60	12	-10.32	10	-0.46

Source Data: Sections16.2.8.5. and 14.3.5.3.3.

As calculated by the protocol specified ANOVA, the Sponsor reports no statistical differences in changes from Baseline between treatment groups.

Reviewer's Comment: The baseline 24 hour urinary free cortisol measurements are highly variable between treatment groups. It does not appear that the sponsor has adjusted for baseline as a covariate. It would appear that ANCOVA, rather than the protocol specified ANOVA, would be a more appropriate statistical test for this data as well, if the baseline value was indeed a significant covariate. Although the sponsor reports no statistical differences in changes from Baseline between treatment groups, numerically, a suppressive effect of MF DPI 400 mcg BID on the HPA axis cannot be ruled out.

Efficacy Outcomes

Pulmonary function was assessed primarily for safety reasons, per the Sponsor, to ensure that subjects with mild persistent asthma were not experiencing a worsening of asthma. There were no significant differences between groups with respect to FEV1, % predicted FEV1, and PEFR. None of the efficacy parameters showed a significant change from baseline to endpoint.

Reviewer's Comment: Although lack of efficacy in an HPA-axis study might raise questions regarding compliance with inhaled corticosteroid use, it is less important in this study in which a positive effect on the axis was observed. Further, these patients were all mild asthmatics who may lack a robust response to ICS.

Adverse Events

Overall, adverse events were reported for 38% to 62% of subjects in the MF DPI treatment groups compared with 42% of subjects in the placebo group. The most frequently reported events were headache, allergy aggravated, pharyngitis, chest pain and fever. The most common adverse event, headache, was reported more often by subjects who received MF DPI 400 mcg BID (25%) than those who received MF DPI 100 mcg BID (0%) or 200 mcg BID (8%) or placebo. Respiratory system disorders as a whole appeared to occur with greater frequency in the active treatment groups versus placebo. Other adverse events were reported by less than 1 or 2 subjects in any group. (See Table 72).

Table 72 Study C96-361, Adverse Events by Treatment Group and Body System/Organ Class (All treated subjects)

	MF DPI 100 mcg BID (n = 13)	MF DPI 200 mcg BID (n = 13)	MF DPI 400 mcg BID (n=12)	Placebo (n=12)
Subjects Reporting any Adverse Event	**8**	**5**	**6**	**5**
Body as a Whole/General Disorders	**6**	**4**	**3**	**5**
Allergy aggravated	2	1	0	2
Chest Pain	1	2	0	2
Edema	0	1	0	0
Fever	2	0	2	0
Headache	0	1	3	1
Procedure	1	0	2	0
Central/Peripheral Nervous System Disorders	**0**	**0**	**1**	**0**
Dizziness	0	0	1	0
Hearing and Vestibular Disorders	**1**	**0**	**1**	**0**
Earache	0	0	1	0
Hearing Impairment	1	0	0	0
Gastrointestinal System Disorders	**0**	**2**	**1**	**1**
Abdominal pain	0	1	0	1
Diarrhea	0	0	1	0
Dyspepsia	0	1	0	0
Psychiatric Disorders	**0**	**0**	**0**	**1**
Insomnia	0	0	0	1
Musculo-skeletal System Disorders	**0**	**1**	**0**	**0**
Musculoskeletal Pain	0	1	0	0

Resistance Mechanism Disorders	**1**	**0**	**0**	**0**
Infection Viral	1	0	0	0
Respiratory System Disorders	**2**	**2**	**3**	**0**
Asthma Aggravated	1	0	0	0
Coughing	1	1	1	0
Epistaxis	0	0	1	0
Pharyngitis	0	2	1	0
Rhinorrhea	0	1	1	0
Upper Respiratory Tract Infection	0	0	1	0
Skin and Appendages Disorders	**2**	**0**	**1**	**0**
Dermatitis Contact	1	0	1	0
Insect Bite	0	0	1	0
Rash	1	0	0	0
Vision Disorders	**1**	**0**	**0**	**0**
Eye abnormality	1	0	0	0

Most adverse events were mild to moderate in severity and none were life threatening. Severe dizziness and severe headache were reported on Day 19 for one subject in the MF DPI 400 mcg BID treatment group. The subject did not have medication interrupted and did not discontinue from the study.

- Local Adverse Events

Pharyngitis was reported by 3 subjects overall; 1 in the MF DPI 100 mcg BID in the active treatment groups (PM, 9; BID 5) and 9% in the placebo group. All cases of pharyngitis were considered mild to moderate in severity. No cases of pharyngitis led to the discontinuation of a subject from the study.

- Deaths and Serious Adverse Events

There were no deaths reported during the study period or within 30 days of the last dose of the study drug. No serious adverse events were reported.

- Withdrawals Secondary to Adverse Events

None of the subjects discontinued from the study because of adverse events.

10.5.3 Conclusions

Study C96-361 was a 29-day, Phase 1, single center, randomized, placebo-controlled, double-blind, parallel group study of the effects of MF DPI on HPA-axis function in 50 children with mild asthma. Each subject was randomized to one of four treatment groups in a 1:1:1:1 ratio: MF DPI 100 mcg BID, 200 mcg BID, 400 mcg BID or placebo. The primary endpoint for this study was the Day-29 12-hour plasma cortisol AUC.

Based on ANCOVA results, the 100 mcg BID group was comparable to placebo. Although the 200 mcg and 400 mcg BID groups were not statistically significantly different when compared to placebo, there was a 24% and 27% reduction, respectively, in the 12 hour plasma cortisol AUC in both these treatment groups. As a result, a suppressive effect on the HPA axis cannot be ruled out with the data from this study, especially with total daily doses greater than 400 mcg.

Twenty-four urinary free cortisol testing did not reveal suppressive effect of MF DPI at any dose on the HPA axis. However, there were several problems with the analysis in this study. The data was not adjusted for highly variable baseline measurements between groups, and the individual data themselves were reported to be highly variable.

Because this study was primarily designed and powered to investigate safety and not to show differences between treatments in efficacy measurements, statistically significant differences across treatment groups in pulmonary function parameters (FEV1, % predicted FEV1, and PEFR) were not identified in response to 29 days of treatment.

All MF treatments were well tolerated; no unusual or unexpected adverse event was reported. The most frequently reported adverse events were headache, allergy aggravated, chest pain, fever, and pharyngitis. All adverse events were mild to moderate in severity with no apparent difference in distribution by treatment.

In conclusion, a suppressive effect of MF DPI on the HPA axis cannot be ruled out by the data available in this study.

Reviewer's Comment: The Biopharmaceutics Review and analysis of this study is pending as we await further data from the Sponsor. See the Biopharmaceutics review for this efficacy supplement by Dr. Wei Qiu for the values of plasma cortisol AUC and 24-hour urinary cortisol per the final analysis. These will be represented in the executive summary and in the main NDA template.

10.6 Study C97-385, One-Year, Open-Label Study of Mometasone Furoate Dry Powder Inhaler (MF DPI) And Beclomethasone Dipropionate (Vanceril® 84 mcg Double Strength) in Children with Asthma Previously Maintained on Inhaled Corticosteroids

Protocol #:	C97-385
Title:	One-Year, Open-Label Study of Mometasone Furoate Dry Powder Inhaler (MF DPI) And Beclomethasone Dipropionate (Vanceril® 84 mcg Double Strength) in Children with Asthma Previously Maintained on Inhaled Corticosteroids
Study Dates:	Initiated May 1998. Completed March 2000.
Sites:	22 centers in the United States (21 evaluable centers)
IRB:	The protocol, protocol amendments, and subject informed consent form were reviewed by an Institutional Review Board for each center.
Ethical Considerations:	The investigators conducted this study according to the principles of Good Clinical Practices (GCP).

10.6.1 Study Design/Protocol

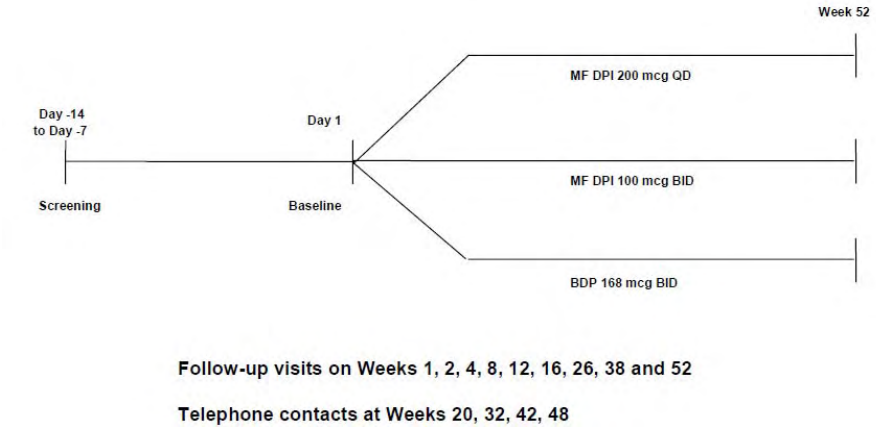
Objectives

The primary objective of this study was to characterize the long-term safety of two doses of MF DPI. The secondary objective was to compare the safety of the two doses of MF DPI to that of Vanceril 84 mcg Double Strength MDI, 168 mcg BID. The study was conducted in children 4 to 11 years of age with asthma previously maintained on inhaled corticosteroids.

Description

This was a Phase III, 52-week, multicenter, randomized, open-label, active-controlled, parallel group, 3-arm, long-term safety study of MF DPI at doses of 100 mcg BID and 200 mcg QD, and BDP 168 mcg BID, in 233 children with asthma who were previously maintained on inhaled corticosteroids. After a run-in period of approximately 1-2 weeks, subjects were randomized in a 1:1:1 ratio to receive study drug for 52 weeks (See Figure 18).

Figure 18 Study C97-385, Study Design Diagram



Population

The study was designed to recruit 240 subjects to have at least 100 subjects treated with both doses of MF DPI for 1 year. The inclusion and exclusion criteria used for the study follow:

- Inclusion Criteria
  Patients were eligible for study entry if:

1. they were 4 years of age through 11 years of age, of either gender, and of any race
2. they had a diagnosis of asthma of at least 6 months
3. they had a FEV1 at Screening (visit 1) and Baseline (visit 2) of at least 60% and no more than 85% of predicted normal when all restricted medications were withheld for the specified intervals; alternatively, for children 4-5 years of age, unable to perform spirometry, the subject's morning PEF must have been ≥ 60% of predicted normal at both Screening and Baseline visits in order to qualify.
4. they demonstrated evidence of an increase in absolute FEV1 of ≥ 12% after reversibility testing at Screening or within the past 12 months; alternatively for 4-5 year olds unable to perform reversibility testing, subjects may have qualified based on meeting the NHLBI criteria for the diagnosis and treatment of asthma for this age group
5. they were using inhaled corticosteroids for at least 30 days prior to Screening. For the two weeks prior to Screening, subjects must have been on a stable regimen of one of the following within the ranges specified below:
   h. Flunisolide: 500-1000 mcg/day
   i. Triamcinolone acetonide: 200-800 mcg/day
   j. Beclomethasone dipropionate: 84-336 mcg/day
   k. Budesonide: 200-800 mcg/day
   l. Fluticasone propionate: 88-220 mcg/day
   m. Flovent Rotadisk DPI: 100-250 mcg/day
6. if their clinical laboratory tests (CBC, chemistries, and urinalysis) were within normal limits or clinically acceptable to the sponsor/investigator.
7. they were free of any clinically significant disease (other than asthma) that would interfere with the study evaluations

8. they (and/or parents/guardians) gave consent and able to adhere to the protocol
9. they had informed their usual treating physician (if other than the study investigator) of their participation in the study
10. they were premenarchal girls. If a girl began menstruating during the study, a serum pregnancy test was to be done at the next study visit. In order to continue in the study, the subject and parent/guardian must have consented to the subject using a double-barrier method of contraception should she become sexually active during the remainder of the study.
11. the subject must have had morning screening plasma cortisol level of at least 5 mcg/dL (at approximately 10 evaluable pre-selected centers)

- Exclusion Criteria

Patients were excluded from the study if:

1. their clinical condition required daily use of nebulized beta agonists, or any use of long-acting beta agonists
2. they required in-patient hospitalization for asthma control within the previous 3 months
3. they had required ventilator support for respiratory failure secondary to their asthma within the last 5 years
4. they had used more than 15 days of systemic corticosteroids in the 6 months prior to Screening
5. they had been admitted to the hospital for management of airway obstruction on 2 or more occasions within the last 6 months
6. they had demonstrated an increase or decrease in FEV1 of 20% or more between the Screening and Baseline visits
7. they had required the use of >12 inhalations per day of rescue medication (or three nebulizer treatments) on any two consecutive days between the Screening and Baseline visits
8. they had experienced an upper or lower respiratory tract infection (viral or bacterial) within the previous 2 weeks prior to either the Screening or Baseline Visits.
9. they were receiving escalating doses of immunotherapy, oral immunotherapy, or short course (rush) immunotherapy for treatment of rhinitis.
10. they were allergic to corticosteroids or beta agonists.
11. they had clinical evidence of bronchiectasis or cystic fibrosis
12. they had a significant history of renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, respiratory, gastrointestinal, cerebrovascular, psychiatric, immunologic, or other significant medical illness or disorder which, in the judgment of the investigator, could have interfered with the study, or required treatment that might have interfered with the study (i.e. glaucoma, cataracts, IDDM, cancer, active hepatitis). Other conditions which were well-controlled and stable, and on appropriate medications may have been allowed upon consultation with the sponsor.
13. they had clinically significant abnormal vital signs at Baseline
14. they had clinically significant abnormal ECG at Screening or within previous 30 days.
15. they had clinically significant abnormalities on chest x-ray at Screening or within the previous year
16. they had evidence of clinically significant oropharyngeal candidiasis

17. they had been taking any of the restricted medications prior to the Screening Visit
18. they could not adhere to the concomitant medication prohibitions (see below)
19. they were unable to use the DPI device
20. they were unable to effectively use a peak flow meter

- Withdrawal Criteria

Any subject whose health or well-being would have been threatened by study continuation was to be withdrawn from the study by the investigator. Subjects who experienced a clinically significant worsening of their asthma during the study were to be discontinued. The criteria for significant worsening of asthma that required a subject to be discontinued were any one of the following:

1. Oral steroid treatment for more than a total of 15 days during the study (for IV or short-acting IM preparations each day's administration was considered equivalent to one day's treatment with oral steroids). There must have been an interval of at least 4 weeks between the last dose of systemic steroid and 8 AM plasma cortisol and 12 hour urinary cortisol testing.
2. Hospitalization for asthma on more than two occasions during the study
3. Ventilator support required.
4. Chronic treatment with additional inhaled corticosteroids.

Other criteria which may have contributed to the physician's decision to discontinue a subject included:

1. A 20% or greater decrease in FEV1 (absolute value) from the value at the Baseline Visit
2. A 25% or greater decrease in AM or PM peak flow from the mean AM Baseline value (obtained between Screening and Baseline) on any 2 consecutive days
3. Clinically significant increase in use of bronchodilator (e.g., use of >12 inhalation or > 3 nebulizer treatments of Proventil-HFA® per day for 2 consecutive days).
4. A clinical asthma exacerbation (CAE) which was defined as a deterioration of asthma that resulted in: hospitalization, treatment with asthma medications prohibited by the protocol, or any other emergency treatment.
    a. Since the primary purpose of this study was to obtain data on long-term treatment with MF DPI, it was not required that subjects be discontinued for an asthma exacerbation provided that they did not meet any of the mandatory criteria for discontinuation above.

If a premenarchal girl began menstruating during the study, a serum pregnancy test was to be performed at the next study visit. A positive pregnancy test would also be criteria for study withdrawal.

Treatments

- Study Treatments

Run-in phase (Between Screening and Baseline Visits)

All subjects were to continue to take their prescribed inhaled corticosteroid between Screening and Baseline visits. The last dose of prescribed inhaled corticosteroid was to be taken prior to the Baseline visit. A primed Proventil MDI was provided at the Screening visit as rescue mediation.

Open-Label Treatment Phase

At the Baseline visit (Visit 2), subjects who met the eligibility criteria were randomized to 52 weeks treatment with one of the following open label treatments (See Table 73):

Table 73 Study C97-385, Treatment Groups

Treatment Group	AM Dose	PM Dose	Total MF (mcg/day)
MF DPI 100 mcg BID	100 mcg MF DPI	100 mcg MF DPI	MF 200 mcg
MF DPI 200 mcg QD AM	200 mcg MF DPI	---	MF 200 mcg
BDP 168 mcg BID	BDP 84 mcg x 2	BDP 84 mcg x 2	BDP 336 mcg

Each treatment kit contained 2 DPI devices, one AM device and one PM device. Proventil HFA or another albuterol inhaler was provided for rescue medication use.

- Permitted Therapies

The following medications were permitted during the study:

- Theophylline, stable dose 2 weeks prior to screening
- Proventil-HFA metered dose inhaler (MDI; with at least a 6 hour withhold period prior to any study visit).
- Nebulized beta-agonists (with at least a 6-hour withhold prior to any study visit). For the purposes of this study, one nebulized treatment was regarded as equivalent to four inhalations of Proventil HFA MDI.
- Oral steroid bursts up to 15 days per year
- Intravenous or short-acting intramuscular corticosteroid preparation
- Oral antihistamines (except astemizole and terfenadine)
- Guaifenesin
- Topical nasal or ocular decongestants, nasal or ocular cromolyn, nasal or ocular antihistamines, intranasal anticholinergics; nasal dexamethasone was not permitted
- Mild potency topical corticosteroids for dermatologic conditions
- Otic mild-potency corticosteroids
- Over the counter pain relief medications
- Antibiotics , systemic or topical
- OTC pain relief medications
- Ritalin® (methylphenidate hydrochloride)

- Excluded Therapies

Table 74 provides the prohibited medications and the exclusionary time period prior to Screening for each. In addition, no patients could receive any medications linked with clinically significant incidence of hepatotoxicity or which might cause significant liver enzyme induction.

Table 74 Study C97-385, Excluded Therapies

Excluded Medication	Washout Period
Methotrexate, cyclosporine, gold and other cytotoxic agents	3 months
Investigational drugs	1 month
Investigational antibodies for asthma or rhinitis	1 months
Beta-adrenergic bronchodilators (syrups, tablets)	1 day
Beta-adrenergic bronchodilators, sustained-release tablets	1 week
Bronchodilators, short-acting inhaled	6 hours
Beta-adrenergic bronchodilators, nebulized	6 hours
Beta-adrenergic bronchodilators, long-acting	1 week
Cromolyn sodium, nedocromil, inhaled	2 weeks
Ipratropium bromide, aerosol or nebulized or combination with albuterol	6 hours
Leukotriene modifiers	2 weeks
Any systemic bursts of oral, iv, or short-acting intramuscular corticosteroids (not more than 15 days in the 6 months prior to the Screening Visit)	1 month
Corticosteroids, nasal or ocular	2 weeks
Corticosteroids, intramuscular or long acting depot	3 months
Corticosteroids, mid-strength, potent, or superpotent dermatologicals, plain and/or combination	1 month
Astemizole	3 months
Terfenadine	48 hours
Oral decongestants (long-acting)	3 days
Oral decongestants (short-acting)	1 day
Influenza Vaccine	2 weeks
Antidepressants (tricyclic and serotonin uptake inhibitors)	3 months

At pre-selected centers collecting MF samples, any dermatologic or nasal preparation of mometasone furoate was prohibited within 1 month of screening.

The following medications were prohibited after the Screening visit and for the duration of the study:

- Beta-adrenergic bronchodilators, inhaled long acting
- Medications linked with a clinically significant incidence of hepatotoxicity or which may cause significant liver enzyme induction
- Beta blockers (oral or non-selective ophthalmic preparations)
- Inhaled, nasal, ocular, oral, intramuscular, intra-articular, intravenous corticosteroids
- Any dermatological corticosteroids other than the mild category
- Any dermatologic or nasal preparations of mometasone furoate (for the pre-selected centers collecting MF samples only).
- Inhaled ipratropium bromide alone or in combination with albuterol
- Astemizole or terfenadine
- Inhaled cromolyn sodium, nedocromil
- Leukotriene modifiers
- Other investigational drugs
- Monoamine oxidase inhibitors
- Antidepressants (TCAs and SSRIs)

- Compliance

Compliance was evaluated throughout the study by asking subjects and/or parent/guardian whether all medications had been taken as instructed Further, patient diaries were reviewed at each visit (per line listings).

Conduct

This Phase III, 52-week, multi-center, open-label, active-controlled, randomized, parallel group study consisted of a run-in period of 1-2 weeks, during which subjects remained on their prescribed ICS. The run-in period was followed by a 52 week double-blind treatment phase. Subjects who met eligibility criteria were randomized at Baseline in a 1:1:1 ratio to one of three parallel treatment arms: MF DPI 100 mcg BID, 200 mcg QD AM, or BDP 168 mcg BID. The population was stratified according to age (4-5 years and 6-11 years). There were eleven scheduled visits: Screening, Baseline, Weeks 1, 2, 4, 8, 12, 16, 26, 38, and 52. The study schedule appears in Table 75.

Table 75 Study C97-385, Study Flow Chart

Protocol No. C97-385

Study Procedure	Screening Visit 1 -14 to -7	Treatment Period[e] Baseline Visit 2 1	Visit 3 Week 1 ±2 days	Visit 4 Week 2 ±2 days	Visit 5 Week 4 ±3 days	Visit 6 Week 8 ±1 week	Visit 7 Week 12 ±1 week	Visit 8 Week 16 ±1 week	Visit 9 Week 26 ±1 week	Visit 10 Week 38 ±1 week	Visit 11 Week 52 ±1 week
Obtain Informed Consent[a]	X										
Review Inclusion/Exclusion Criteria	X	X									
Medical/Disease History	X										
Concomitant Medications Review	X	X	X	X	X	X	X	X	X	X	X
Physical Examination, Weight	X								X		X
Height	X										
Vital Signs (temperature, blood pressure, pulse, respiratory rate)	X	X	X	X	X	X	X	X	X	X	X
Oropharyngeal Exam	X	X	X	X	X	X	X	X	X	X	X
Pulmonary Auscultation	X	X	X	X	X	X	X	X	X	X	X
Pulmonary Function Tests	X	X	X	X	X	X	X	X	X	X	X
Reversibility Test	X										
Ophthalmic Examination	X										X
Hematology, Blood Chemistry plus 8 AM cortisol[b], Urinalysis	X	Review							X		X
12-Hour Urine Collection[b]		X							X		X
Mometasone Furoate Plasma Concentration[b]									X		X
Electrocardiogram[c]	X										
Chest X-ray[d]	X										
Dispense Diary	X	X	X	X	X	X	X	X	X	X	
Retrieve/Review Diary		X	X	X	X	X	X	X	X	X	X
Dispense Peak Flow Meter	X										
Dispense/Retrieve Rescue Medication (as needed)	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Medication		X					X		X	X	
Administration of First Dose in Office		X									

Protocol No. C97-385

Study Procedure	Screening Visit 1 -14 to -7	Treatment Period[e] Baseline Visit 2 1	Visit 3 Week 1 ±2 days	Visit 4 Week 2 ±2 days	Visit 5 Week 4 ±3 days	Visit 6 Week 8 ±1 week	Visit 7 Week 12 ±1 week	Visit 8 Week 16 ±1 week	Visit 9 Week 26 ±1 week	Visit 10 Week 38 ±1 week	Visit 11 Week 52 ±1 week
Evaluation of Response to Therapy			X	X	X	X	X	X	X	X	X
Adverse Events/Intercurrent Illness Evaluation		X	X	X	X	X	X	X	X	X	X
Review Compliance		X	X	X	X	X	X	X	X	X	X
Collect Study Inhalers							X		X	X	X

a: Earlier than Day -14 if longer medication washouts are required. Informed consent must be signed prior to any study-related procedures, including required washout of medications.
b: Preselected centers only.
c: If not done within previous 30 days.
d: If not done within previous year.
e: Telephone Contact: Weeks 20, 32, 42 and 48.

Efficacy Assessments

Because this study was primarily designed to evaluate the long-term safety of MF DPI, efficacy variables pertaining to pulmonary function, nighttime awakenings, Proventil MDI and nebulizer use, and response to therapy were considered supplementary variables to confirm that asthma did not worsen. The study was not designed to show differences between treatment groups.

Safety Assessments

- Medical History: Visit 1
- Physical Examination: Visit 1, Visit 9, and Final Visit
- Vital signs: All visits
- Concomitant Medication Review: All visits
- Oropharyngeal examination: All visits
- Ophthalmic Examination: Visit 1 and Final Visit
- Laboratory Tests: Visit 1, Visit 9, and Final Visit
    - CBC
    - Blood Chemistry : sodium, potassium, chloride, BUN, creatinine, liver enzymes, total protein, albumin, calcium, inorganic phosphorous, LDH
    - Serum pregnancy tests on all females who became menarchal while on study
    - Complete urinalysis
    - 12 hour urinary free cortisol (at 10 pre-selected centers)
    - Blood samples for MF (at 10 pre-selected centers) – Weeks 26 and 52
- 12-Lead ECG: Visit 1
- Chest X-ray: Visit 1
- Telephone Contacts: Weeks 20, 32, 42, 48
- Adverse Events: All visits
- Clinical Asthma Exacerbatiosn

> *Reviewer's Comment: The sponsor states that any asthma symptoms of wheezing, difficulty breathing, cough, and chest tightness or congestion were not considered adverse events, unless they showed a clear temporal relationship to study drug administration or resulted in hospitalization. This is atypical. These events are usually reported as adverse events as inhalers can have paradoxical effects, such as bronchospasm which may mimic asthma symptoms.*

Statistical Plan

- Data Sets Analyzed

The sponsor analyzed one data set: all randomized subjects. All summaries of safety data were to be based on this data set (intent-to-treat principle).

- Sample Size Determination

In this study, the total target population as 240 subjects to have at least 100 subjects treated with both doses of MF DPI for one year. With 80 subjects per treatment group (assuming a 20% drop out rate at the end of one year) the probability that one or more subjects reported a given adverse event is 98% for any given adverse event with an underlying incidence rate of 5%. Similarly, if the incidence rate was at least 2%, the probability of observing the event in the study was 80%. *Reviewer's comment: These calculations are per the sponsor.*

- Primary Safety Analyses

Frequency tables were provided for the incidence of all adverse events. Time to common (≥5%) adverse events were also tabulated. At the Screening/Baseline, Week 26, and Week 52 visits, the

following values were summarized (pooled data from 10 evaluable pre-selected centers): 8 AM plasma cortisol levels and 12-hour urinary cortisol concentrations.

At Weeks 26 and 52 of the study, mometasone furoate levels were to be listed and summarized for these 10 centers as well. Results of other safety measures (adverse events, change from Baseline in vital sings and laboratory tests, physical, oropharyngeal, and ophthalmic examination results) were to be summarized and evaluated as appropriate.

- Protocol Amendments

The original protocol was finalized March10, 1998. The protocol was subsequently amended on September 23, 1998 to reflect revisions to the pediatric DPI program. The major changes reflected in C97-38, Amendment No. 1, include:

- Modification of the inclusion criteria to include Vanceril 84 mcg Double Strength, and Flovent Rotadisk DPI, as permitted inhaled corticosteroids prior to screening
- Daytime and nighttime symptoms cores were removed as a secondary endpoint, as their inclusion in the protocol was an error.
- All reference to Cortosyn testing were deleted and replaced with 8 AM plasma cortisol and 12-hour urinary cortisol testing at 11, not 12 centers
- Six-month interim analysis was removed

A second amendment was finalized on January 20, 1999. The major change reflected in Amendment No. 2 was the modification of inclusion criteria to include children 4 or 5 years of age. In addition, there was one center specific amendment (Center 03), Amendment S1, finalized on May 11, 1998. This amendment specified that at this center, females who experienced the onset of menses at any time during the study were to be immediately discontinued from the study.

10.6.2 Results

Patient Disposition

The data from Center 04 has been excluded from all efficacy and pooled safety analyses as significant departures from Good Clinical Practice were observed. With the exclusion of this center, there were 233 subjects randomized at 21 study centers. All randomized subjects received at least one dose of study medication. The number of subjects randomized to each of the treatment groups is as follows:

- MF DPI 200 mcg QD AM: 78 subjects
- MF DPI 100 mcg BID: 74 subjects;
- BDP 168 mcg BID: 81 subjects.

Of the 233 enrolled subjects, 190(82%) completed the study. Discontinuation occurred in 43 subjects. No treatment was associated with a greater frequency of discontinuation, as the rates

for discontinuation were 18-19% in all groups. Non-compliance with the protocol and treatment failure were reported as the most common reasons for discontinuation. Discontinuation secondary to adverse events occurred most often in subjects in the MF DPI 200 mcg QD AM treatment group (5%), compared to 1% in the other groups. The patient disposition results are summarized in Table 76:

Table 76 Study C97-385, Patient disposition

	Protocol No. C97-385		
	Number (%) of Subjects		
	MF DPI 200 mcg QD AM (n=78)	MF DPI 100 mcg BID (n=74)	BDP 168 mcg BID (n=81)
Completed	64 (82)	60 (81)	66 (81)
Discontinued	14 (18)	14 (19)	15 (19)
Reasons for Discontinuation			
Adverse Event	4 (5)	1 (1)	1(1)
Treatment Failure	4 (5)	4 (5)	3 (4)
Lost to Follow-up	0	3 (4)	0
Did Not Continue For Reasons Unrelated To Treatment	2 (3)	1 (1)	4 (5)
Noncompliant With Protocol	4 (5)	4 (5)	5 (6)
Did Not Meet Entry Criteria	0	1(1)	2 (2)

Reviewer's comment: Discontinuations were common in the 200 mcg QD AM dosing group.

- Protocol Violations

Protocol violations were not formally defined because there was no Efficacy Evaluable data set. However, there were 2 subjects who were on higher doses of inhaled corticosteroids (fluticasone QD) than was defined by the inclusion criteria, and one subject had a borderline low FEV1. Four subjects were continued in the study despite experiencing a worsening of their asthma. Although these variations were not approved prior to subject enrollment, and were considered to be protocol violations, these variations were not considered to be significant and the subjects were included in all analyses.

Demographics and Other Baseline Characteristics

- Demographics

Demographic data for the study population are presented in Table 77. The randomized treatment groups were generally similar with regard to age, sex, race, and weight. There was a higher proportion of males than females in each treatment group and the majority of subjects were 6 to 11 years of age and Caucasian. Of the Non-Caucasians (n= 42, 18%), approximately 65-70% of the patients were Black, 25-30% were Hispanic. There were two patients who were characterized as "Asian" and "Other".
Reviewer's Comment: The demographic information of breakdown of the non-caucasian category was tabulated by this reviewer from the line listings in Section 14.1.1 of the study report.

Table 77 Study C97-385, Demographics and Baseline Characteristics

	MF DPI 200 mcg QD AM	MF DPI 100 mcg BID	BDP 168 mcg BID
	n = 78	**n=74**	**n=81**
Age (years)			
Mean	8.4	8.1	8.0
Range	4 – 11	4-11	4-11
Age Distribution [n (%)]			
4-5 years	9 (11.5%)	10 (13.5%)	17(21%)
6-11 years	69 (88.5%)	64 (86.5%)	64(79%)
Sex			
Female	35 (44.8%)	26 (35.1%)	32 (39.5%)
Male	43 (55.2 %)	48 (64.9 %)	49 (60.5 %)
Race			
Caucasian	66 (84.6%)	61 (82.4%)	64 (79%)
Non-Caucasian	12 (15.4%)	13 (17.6%)	17 (21%)
Black	8 (10%)	9(12%)	11 (13.6%)
Hispanic	3 (3.8%)	4 (5.4%)	5 (6.2%)
Asian	1 (1.3%)	---	---
Other	----	---	1 (1.2%)
Weight (kg)			
Mean	34.1	33.2	32.3
Range	16.0-86.0	17.0-71.0	17.0-74.0

- Baseline Disease/Other Characteristics

The mean duration of asthma and baseline FEV1 % predicted were similar across all groups. The mean duration of asthma ranged from 4.8 to 5.3 years, with the range being 0.5 to 11 years. The mean % predicted FEV1 at baseline was between 85-87% in all treatment groups. Notable differences between the groups included greater number of subjects (30 subjects) randomized to the BDP 168 mcg BID group using fluticasone at Baseline than subjects in either of the other groups (MF DPI 200 mcg QAM, 13 subjects, and MF DPI 100 mcg BID, 14subjects). These characteristics are summarized in Table 78.

Table 78 Study C97-385, Baseline Disease Characteristic and Inhaled Corticosteroid Use (All Randomized Subjects)

	MF DPI 200 mcg QD AM	MF DPI 100 mcg BID	BDP 168 mcg BID
	N = 78	N = 74	N = 81
Duration of disease (years)			
Mean	5.3	4.8	5.1
Range	0.83-10.0	0.50-11.0	0.58-11
Baseline FEV1 % predicted			
Mean	85.2	86.1	87.4
Baseline AM PEF (l/min)			
Mean	232.7	252.6	223.9
BDP			
no. of subjects	41	45	34
Mean mcg/day	234	239	213
Range	84-336	84-336	84-336
Budesonide			
no. of subjects	5	2	6
Mean mcg/day	400	300	367
Range	400-400	200-400	200-400
Flunisolide			
no. of subjects	1	3	0
Mean mcg/day	500	833	--
Range	500-500	500-1000	--

	MF DPI 200 mcg QD AM	MF DPI 100 mcg BID	BDP 168 mcg BID
Fluticasone Propionate			
no. of subjects	13	14	30
Mean mcg/day	184	189	196
Range	88-440	88-220	110-440
Triamcinolone Acetonide			
no. of subjects	18	10	11
Mean mcg/day	506	500	436
Range	200-800	200-600	200-800
Theophylline Use			
Yes	1	2	0
No	77	72	81

- Baseline Concomitant Medications

The sponsor did not summarize baseline concomitant medications or medical history. This reviewer reviewed the line listings for concomitant medications. The concomitant medications were divided into asthma/allergy related and unrelated medications. Among the concomitant medications used to treat asthma/allergy were short acting b2-agonists, antihistamines, inhaled/nasal corticosteroids, cromolyn, ipratropium, oral corticosteroids, and decongestants. Of the asthma/allergy unrelated concomitant medications, the most common drugs were acetaminophen, ibuprofen, and antibiotics.

Compliance

Reviewer's Comment: At the time of the completion of this review, an information request to the sponsor is pending asking them to provide a more detailed tabular summary of the compliance data for this study. This is not critical to the completion of the review, as the sponsor has also provided PK data to confirm compliance.

Efficacy Outcomes

Because this study was primarily a safety study, efficacy evaluations were considered secondary. The study was not designed nor powered to detect differences between treatment groups. This reviewer summarized the results of comparisons of FEV1(L) and % predicted FEV1 Table 79 s a means to confirm compliance. Treatment groups were comparable at Baseline in terms of FEV1 and percent predicted FEV1.

Table 79 Study C97-385, Efficacy Outcomes Summary: FEV1 and %Predicted FEV1, Change from Baseline to Endpoint (all randomized subjects)

	MF DPI 200 mcg QAM N=78		**MF DPI 100 mcg BID N=74**		**BDP 168 mcg BID N=81**	
	LS Mean		**LS Mean**		**LS Mean**	
	% predicted FEV	**FEV1 (L)**	**% predicted FEV**	**FEV1 (L)**	**% predicted FEV**	**FEV1 (L)**
Baseline	85.90	1.61	87.08	1.57	88.36	1.58
Change from Baseline At Endpoint	**9.74**	**0.18**	**12.93**	**0.23**	**9.47**	**0.16**

At Endpoint, change from Baseline in % predicted FEV1 was similar between the MF DPI 200 mcg QD AM and BDP 168 mcg BID groups, and numerically greater in the MF DPI 100 mcg BID group. All groups showed a response to therapy, but the significance of this response is unclear as there is no placebo group with which to compare. Additionally, there were no statistically significant differences between groups. t Endpoint, change from Baseline in FEV1 (L) was comparable in all three groups, but greatest in the 100 mcg BID group, correlating to the data obtained with % predicted FEV1.

Limited efficacy conclusions can be drawn from this study. Minimally, all groups appeared to show some response to therapy, but the magnitude of this response cannot be assessed due to the design of the study.

Reviewer's Comment: From the above efficacy data, it is likely that compliance is comparable between groups, but we will await the data from the sponsor. An information request regarding tabular presentation of compliance data was sent to the Sponsor on November 7, 2007.

Safety Outcomes

- Exposure

Of the 233 subjects enrolled in the study, 154 subjects (66%) received treatment for at least 12 months (MF DPI 200 mcg QD AM, 64%; MF DPI 100 mcg BID, 69%; BDP 168 mcg BID, 65%). The extent of exposure was satisfactory to allow for safety assessments. There was no notable difference in the extent of exposure among the treatment groups. This information is summarized in Table 80.

Table 80 Study C97-385, Extent of Exposure

Number (%) Subjects			
Length of Exposure	**MF 200 mcg QD AM (n = 78)**	**MF 100 mcg BID (n = 74)**	**BDP 168 mcg BID (n = 81)**
> 1 dose	78	73	81
> 1 week	77	72	81
> 2 weeks	76	72	79
> 4 weeks	75	71	78
> 8 weeks	75	70	77
> 12 weeks	75	70	77
> 16 weeks	73	67	77
> 26 weeks	71	65	74
> 32 weeks	70	64	72
> 38 weeks	67	62	70
> 42 weeks	64	62	68
> 52 weeks	50	51	53

(Source Data: Study Report Section 14.5)

- Adverse Events

Overall, the number of subjects reporting adverse events was similar among the three treatment groups (MF DPI 200 mcg QD AM: 96% , MF DPI 100 mcg BID: 97%, BDP 168 mcg BID: 96%). The data is summarized in Table 81.

Table 81 Study C97-385, Number (%) of Subjects Reporting Adverse Events

	MF DPI 200 mcg QD AM	MF DPI 100 mcg BID	BDP 168 mcg BID
No. Subjects	78	74	81
Adverse Events	75 (96)	72 (97)	78 (96)
Related Adverse Events	16 (21)	15 (20)	8 (10)
Severe Adverse Events	13 (17)	8 (11)	10 (12)
Severe-Related Adverse Events	3 (4)	0	0

The most frequently reported adverse event in this study was upper respiratory tract infection, reported by 47%-51% of subjects. Other frequently reported adverse events included are listed in Table 82.

Table 82 Study C97-385, Adverse Events Occurring in ≥ 20% of subjects in any treatment group

	MF DPI 200 mcg QD AM	MF DPI 100 mcg BID	BDP 168 mcg BID
Allergy	28%	15%	25%
Fever	23%	27%	32%
Headache	42%	36%	31%
Viral Infection	35%	35%	36%
Nasal congestion	9%	23%	14%
Pharyngitis	33%	34%	31%
Rhinitis	37%	27%	27%
Sinusitis	19%	20%	14%
Upper Respiratory Tract Infection	49%	47%	51%

Local Adverse Events

Local adverse events included pharyngitis and oral candidiasis. Pharyngitis was reported by 76 (33%) of the subjects overall; 33% in MF DPI 200 mcg QD AM, 34% in MF DPI 100 mcg BID, and 31% in BDP 168 mcg BID. All but two cases were considered to be mild to moderate in severity. No subject discontinued or interrupted treatment due to pharyngitis.

Oral candidiasis was reported by 9 subjects (4%) overall. Oral candidiasis was reported by 4% of subjects in each treatment group. No subject discontinued or interrupted treatment due to oral candidiasis. The majority of cases were mild in severity and required additional therapy. Seven of the nine patients had a positive mouth or throat culture for yeast (Section 16.2.9.3.2).

Subgroup Analysis of Adverse Events

Per the Sponsor, there were no indications of a differential response to treatment between males and females. There were too few subjects aged 4 to 5 years to provide a meaningful analysis by age (36 subjects, 15%). Similarly, there were too few non-Caucasian subjects (42, 18%) to allow a meaningful analysis of adverse events by race.

Severe/Life Threatening Adverse Events

Most adverse events in this study were categorized as mild to moderate in severity. Overall, severe adverse events were reported in 30 subjects and a life-threatening adverse event was reported in 1 subject. No single severe adverse event was reported by more than two subjects. Of note, severe/life threatening respiratory system disorders as a whole were most frequent in the MF DPI 200 mcg QD AM group (10%), and in fact were twice more frequent than in the 100 mcg BID group (5%). The data is presented in Table 83.

Reviewer's Comment: The 200 mcg QD AM dose appears to be associated with more severe AEs. However, the clinical implications of this are unclear, as some of the severe events include rhinitis and nasal congestion.. The significance of this finding is unclear, as the dose under review (100 mcg QD PM) is not included in this study, but it does raise the question regarding the overall safety of once daily dosing.

Table 83 Study C97-385, Summary of Severe/Life Threatening Adverse Events

	Number[a] (%) of Subjects		
	MFDPI 200 mcg QD AM (n=78)	MFDPI 100 mcg BID (n=74)	BDP 168 mcg BID (n=81)
Respiratory System Disorders	8 (10)	4 (5)	5 (6)
asthma aggravated	1 (1)	0	1 (1)
coughing	2 (3)	0	0
nasal congestion	1 (1)	2 (3)	0
pharyngitis	1 (1)	1 (1)	0
rhinitis aggravated	2 (3)	1 (1)	1 (1)
sinusitis	1 (1)	0	0
tonsillitis	0	0	1 (1)
upper resp tract infection	2 (3)	0	2 (2)
Skin And Appendages Disorders	0	0	3 (4)
eczema aggravated	0	0	3 (4)
Urinary System Disorders	0	0	1 (1)
kidney infection nos	0	0	1 (1)
Vascular (extracardiac) Disorders	0	0	1 (1)
migraine	0	0	1 (1)

a: Number of subjects reporting severe/life-threatening treatment-emergent adverse events at least once during the study, without regard to relationship to treatment. Some subjects may have reported more than one adverse event.

Clinical Asthma Exacerbations

A clinical asthma exacerbation (CAE) was defined as a worsening of asthma that resulted in emergency treatment, hospitalization, or treatment with additional asthma medication (other than short-acting beta agonists). Of the 233 randomized subjects, 27% experienced a protocol defined CAE. CAEs were reported most often in the MF DPI 200 mcg QD AM (27 subjects, 35%) treatment group. The number of subjects reporting CAEs in the MF DPI 100 mcg BID (17 subjects, 23%) and BDP 168 mcg BID (18 subjects, 22%) was similar, and lower than in the 200 mcg QD AM group.

Reviewer's Comment: Again, 200 mcg QD AM dosing was associated with more CAEs. This raises the question of the efficacy and safety of the 200 mcg QD AM dose.

- Deaths, Serious Adverse Events, and Pregnancies

There were no deaths. Serious adverse events were reported in six patients:

- MF DPI 200 mcg QD AM: 3 subjects
- MF DPI 100 mcg BID: 1 subject
- BDP 168 mcg BID: 1 subject

One additional patient had an SAE during the Screening period, prior to randomization. Two subjects discontinued the study and one subject interrupted study treatment as a result of the SAE. A brief summary of these SAEs follows in Table 84:

Table 84 Study C97-385, Serious Adverse Events

	MF DPI 200 mcg QD AM			**MF DPI 100 mcg BID**	**BDP 168 mcg BID**
Center/Subject	01/118	05/404	22/164	12/244	14/360
Sex/Age/Race	M/7/C	F/11/C	F/7/NC	F/5/NC	F/9/C
SAE	• Anaphylactic Reaction • Asthma aggravated	Status Asthmaticus	Asthma Aggravated	Gastroenteritis	Asthma Aggravated
Outcome	Hospitalized	Hospitalized	Hospitalized	Hospitalized	Hospitalized
Narrative	Occurred three months into treatment 5 minutes after immunotherapy treatment Status asthmaticus and anaphylaxis were diagnosed	Occurred 5 months into treatment	Occurred 9 months into therapy Increased asthma symptoms, along with sore throat, and URI sx Admitted for 6 days to treat asthma exacerbation	Occurred 6 months into therapy After travel to Mexico: Stomach cramps, vomiting, diarrhea	51 weeks into therapy Increased asthma sx Hospitalized x 1 day Discontinued from the study

Reviewer's Comment: Asthma aggravated was reported in 3/3 subjects in the MF DPI 200 mcg QD AM group vs. 0/1 and 1/1 in the other two groups.

- Withdrawals Secondary to Adverse Events

Six subjects (3%) withdrew from the study because of adverse events. This included four subjects (5%) in the MF DPI 200 mcg QD AM group, one subject (1%) in the MF DPI 100 mcg BID group, and one subject (1%) in the BDP treatment group. Three of the four subjects in the MF DPI 200 mcg QD AM group reported coughing (1 subject) and asthma aggravated (2) as reasons for discontinuation. Bronchitis and sinusitis were reported as the reasons for the withdrawal of 2 subjects in the MF DPI 100 mcg BID group. One subject in the BDP group withdrew secondary to asthma aggravated as well.

Two subjects interrupted treatment because of adverse events, both treated with 200 mcg QD AM. One subject had treatment interrupted at Day 117 due to an anaphylactic reaction of moderate severity and severe aggravated asthma. The other subject interrupted treatment on day 106 due to bronchitis of moderate severity.

Reviewer's Comment: 4 subjects in the MF DPI 200 mcg QD AM group withdrew secondary to adverse events. 3 of the 4 subjects had a respiratory system reason for discontinuation (coughing, 1 subject or asthma aggravated, 2 subjects). Again, along with severe AEs, SAEs, and CAEs, it appears that the 200 mcg QD AM dose is associated with more respiratory adverse events.

- Laboratory Evaluation

Laboratory evaluation did not reveal any clinically meaningful abnormal results.

- Vital Signs

No clinically meaningful abnormal changes in vital signs were noted after review of the line listings.

- Ophthalmic Examinations

Ophthalmic examinations were performed at Screening and at the Final Visit. One case of posterior subcapsular cataract at Week 26 was reported in the MF 100mcg BID treatment group. This subject had not cataract present at Screening and a 52 week evaluation was not reported. No cases of increased intraocular pressure were reported.

10.6.3 Conclusions

This was a Phase III, 52-week, multicenter, randomized, open-label, active-controlled, parallel group, 3-arm, long-term safety study of MF DPI at does of 100 mcg BID and 200 mcg QD, and BDP 168 mcg BID, in 233 children 4 to 11 years of age with asthma who were previously maintained on inhaled corticosteroids. After a run-in period of approximately 1-2 weeks, subjects were randomized in a 1:1:1 ratio to receive study drug for 52 weeks.

A total of 233 patients were randomized from 21 evaluable centers, and all randomized subjects received at least one dose of study medications. The number of subjects randomized to each of the treatment groups was comparable. . Discontinuation occurred in 43 subjects. No treatment was associated with a greater frequency of discontinuation, as the rates for discontinuation were

18-19% in all groups. Non-compliance with the protocol and treatment failure were reported as the most common reasons for discontinuation. Discontinuation secondary to adverse events occurred most often in subjects in the MF DPI 200 mcg QD AM treatment group (5%), compared to 1% in the other groups. Baseline demographic (age, sex, gender, race) and disease characteristics (duration of disease, FEV1, PEFR, ICS use) were generally similar across all groups.

The primary objective of this study was to characterize the long-term safety of two doses of MF DPI. The secondary objective was to compare the safety of the two doses of MF DPI to that of Vanceril 84 mcg Double Strength MDI, 168 mcg BID. Efficacy outcomes were considered supplementary as the study was not designed nor powered to detect differences in pulmonary function between treatment groups. All groups appeared to show some response to therapy from baseline to endpoint. Safety assessments evaluated included adverse events, vital signs, laboratory values, and ophthalmic examination.

Of the 233 subjects enrolled in the study, 154 subjects (66%) received treatment for at least 12 months (MF DPI 200 mcg Qd AM, 64%; MF DPI 100 mcg BID, 69%; BDP 168 mcg BID, 65%). The extent of exposure was satisfactory to allow for safety assessments. There was no notable difference in the extent of exposure among the treatment groups.

Local adverse events included pharyngitis and oral candidiasis. Pharyngitis was reported by 76 (33%) of the subjects overall; 33% in MF DPI 200 mcg QD AM, 34% in MF DPI 100 mcg BID, and 31% in BDP 168 mcg BID. All but two cases were considered to be mild to moderate in severity. No subject discontinued or interrupted treatment due to pharyngitis.

Oral candidiasis was reported by 9 subjects (4%) overall. Oral candidiasis was reported by 4% of subjects in each treatment group. No subject discontinued or interrupted treatment due to oral candidiasis. The majority of cases were mild in severity and required additional therapy. Seven of the nine patients had a positive mouth or throat culture for yeast (Section 16.2.9.3.2).

Overall, the number of subjects reporting adverse events was similar among the three treatment groups (MF DPI 200 mcg QD AM: 96%, MF DPI 100 mcg BID: 97%, BDP 168 mcg BID: 96%). The most frequently reported adverse event in this study was upper respiratory tract infection, reported by 47%-51% of subjects. Other frequently reported adverse events included allergy, fever, headache, viral infection, nasal congestion, pharyngitis, rhinitis, sinusitis, and upper respiratory tract infection. Of note, “asthma aggravated” occurred in 5% of the MF DPI 200 mcg QD AM treatment group, vs. in 0 and 1% of the MF DPI 100 mcg BID and BDP groups, respectively.

The majority of adverse events were mild to moderate in severity. Severe adverse events were reported in 30 subjects and a life-threatening adverse event was reported in 1 subject. No single severe adverse event was reported by more than two subjects. Of note, severe/life threatening respiratory system disorders as a whole were most frequent in the MF DPI 200 mcg QD AM group (10%), were twice more frequent than in the 100 mcg BID group (5%).

There were no deaths reported in this study. SAEs were reported in 5 treated patients, 3 in the MF DPI 200 mcg QD AM group, and 1 each in the other groups. For the 3 patients in the MF DPI 200 mcg QD AM group, the reported SAE was asthma aggravated, resulting in hospitalization.

From this 52 week long term safety study, it appears that same total daily dose (200 mcg) given once daily in the AM versus divided BID may have more associated severe respiratory-related adverse events, though not an increase in the overall rate of respiratory-related adverse events.

It is unclear how to relate these findings to the proposed dose under review (100mcg MF QPM) as it was not included in this study. After review of the 3 safety and efficacy studies, two of which included the MF 200mcg QD dosing regimen, there was no safety signal in either of these two studies.

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/s/

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I concur. See my CDTL memo.