

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-067**

**Statistical Review(s)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/Serial Number:** 21-067

**Drug Name:** Asmanex Twisthaler 220 mcg (mometasone furoate) Inhalation powder

**Indication(s):** Treatment of asthma

**Applicant:** Schering Corporation

**Date(s):** Volumes dated November 14, 2003. Datafiles dated February 6, 2004.

**Review Priority:** Regular

**Biometrics Division:** Division Of Biometrics II (HFD-715)

**Statistical Reviewer:** James R. Gebert, Ph.D.

**Concurring Reviewers:** Stephen Wilson, Ph. D.

**Medical Division:** Division of Pulmonary and Allergy Drug Products (HFD-570)

**Clinical Team:** Tejashri Purohit-Sheth, M.D.

**Project Manager:** Ms Lori Garcia

**Keywords:** Clinical Studies, NDA Review

TABLE OF CONTENTS

**1 EXECUTIVE SUMMARY ..... 3**  
1.1 CONCLUSIONS AND RECOMMENDATIONS ..... 3  
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES ..... 3  
1.3 STATISTICAL ISSUES AND FINDINGS ..... 4

**2 INTRODUCTION ..... 4**  
2.1 OVERVIEW ..... 4  
2.1.1 Study C98-475 ..... 4  
2.1.2 Study P01545 ..... 5  
2.2 DATA SOURCES ..... 6

**3 STATISTICAL EVALUATION ..... 6**  
3.1 EVALUATION OF EFFICACY ..... 6  
3.1.1 Study C98-475 ..... 6  
3.1.2 Study P01545 ..... 8  
3.2 EVALUATION OF SAFETY ..... 10

**4 FINDINGS IN SPECIAL/ SUBGROUP POPULATIONS ..... 10**  
4.1 GENDER/AGE/RACE ..... 10  
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS ..... 11

**5 SUMMARY AND CONCLUSIONS ..... 11**  
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE ..... 11  
5.2 CONCLUSIONS AND RECOMMENDATIONS ..... 11

Appears This Way  
On Original

## 1 Executive Summary

This submission was a complete response to the December 4, 2000 Action Letter. The letter listed deficiencies to be addressed before approval of the MF DPI 400 mcg QD or 200 mcg BID doses. An approvable letter of October 1, 1999 stated that in order to support the efficacy of Mometasone Furoate (MF) 200 mcg QAM dosing and/or MF 200 mcg QPM dosing, additional efficacy trials with the to-be-marketed 200 mcg formulation were required. In a December 1, 1999 letter, the sponsor withdrew the 200 mcg per day dose from the application and agreed to revisit the issue at a later point of time. The sponsor in their complete response supplied study reports for two studies (C98-475 and P01545) to demonstrate that the MF DPI 200 mcg QD PM dosing was effective. This review will focus on those two studies. The sponsor wants to say in the label that MF DPI 200 mcg QD PM is the recommended dose for patients previously maintained on bronchodilators alone and may be considered for patients previously maintained on doses in the lower range of those recommended for their previous inhaled corticosteroid treatment. In preparing for the filing/planning meeting, it was discovered that the sponsor had not provided datafiles for these studies. These datafiles were requested and supplied by the sponsor in their February 6, 2004 submission. The sponsor also supplied programs that operated on these datasets and produced the analysis results given in the study reports.

### *1.1 Conclusions and Recommendations*

Studies C98-475 and P01545 demonstrate that Mometasone Furoate (MF) DPI 200 mcg QD PM was significantly more effective than placebo for changes from baseline at endpoint in FEV<sub>1</sub>. Other pulmonary function variables supported the efficacy seen in FEV<sub>1</sub>. Study P0145 showed efficacy in many of the non-pulmonary function parameters. These conclusions support labeling that MF DPI at a dose of 200 mcg QD PM is an effective dose for some mild patients. Whether these studies support the sponsor's labeling recommendations is left for clinical judgment. The results from Study P01545 for patients whose baseline FEV<sub>1</sub> was  $\geq 75\%$  of predicted normal is suggestive that higher doses (400 mcg QD PM or 200 mcg BID) might be more effective for these mild asthmatic patients. In Study C98-475, only slight efficacy for the 200 mcg QD PM dose of MF DPI was seen in change in FEV<sub>1</sub> at endpoint for patients with baseline FEV<sub>1</sub>  $> 80\%$  of predicted normal.

### *1.2 Brief Overview of Clinical Studies*

Study C98-475 was a randomized, placebo controlled, double-blind, multicenter study comparing MF DPI 200 mcg QD PM and placebo in subjects with asthma who were previously maintained on short-acting inhaled beta-agonists alone. Following a two week run-in period, patients were randomized to placebo or MF DPI 200 mcg QD PM for the 12 week treatment period.

Study P01545 was a randomized, placebo controlled, double-blind, multicenter study comparing MF DPI 200 mcg QD PM, MF DPI 400 mcg QD PM (one inhalation), MF DPI 400 mcg QD PM (two inhalations), MF DPI 200 mcg BID, and placebo in subjects

with asthma who were previously maintained on inhaled corticosteroids. There was a single blind placebo / ICS reduction period followed by a twelve week treatment period.

The primary efficacy variable for both studies was the change in FEV<sub>1</sub> from baseline at endpoint. Both studies used an ANOVA with treatments and centers as factors.

### ***1.3 Statistical Issues and Findings***

This reviewer was able to duplicate the primary efficacy analyses reported by the sponsor.

The only statistical issue was the failure of the sponsor to address the multiple comparison issue in Study P01545. Although the sponsor's study report specified a stepdown procedure, the protocol did not specify the use of that procedure. However, because of the significance seen in this study, the MF 200 mcg QD PM dose would be significantly different from placebo for changes from baseline in FEV<sub>1</sub> at endpoint using any of the commonly used multiple comparison procedures.

## **2 Introduction**

### ***2.1 Overview***

Mometasone Furoate is a synthetic corticosteroid. Mometasone Furoate aqueous nasal spray, Nasonex, is commercially available for the treatment of seasonal and perennial rhinitis.

The sponsor submitted an NDA for MF DPI on November 30, 1998 for the treatment of asthma in adults and adolescents. The studies for that submission were reviewed by this statistician in his statistical review dated September 14, 1999. An Approvable Letter for MF DPI 400 mcg QD or 200 mcg BID for the treatment of adults and adolescents with asthma was issued October 1, 1999. The Approvable Letter stated that in order to support the efficacy of Mometasone Furoate (MF) 200 mcg QAM dosing and/or MF 200 mcg QPM dosing, additional efficacy trials with the to-be-marketed 200 mcg formulation were required. The Action Letter dated December 4, 2000 listed deficiencies to be addressed before approval. The present submission is a complete response to the December 4, 2000 Action Letter. In addition to addressing CMC deficiencies, it also contained the results of two studies to demonstrate efficacy of MF DPI 200mcg QD PM dosing.

#### **2.1.1 Study C98-475**

Study C98-475 was a randomized, placebo controlled, double-blind, multicenter study comparing MF DPI 200 mcg QD PM and placebo in subjects with asthma who were previously maintained on short-acting inhaled beta-agonists alone. Following a two week run-in period, patients were randomized to placebo or MF DPI 200 mcg QD PM for the 12 week treatment period. During the run-in period subjects had to have been using

Proventil for acute relief of symptoms of bronchospasm on average at least three times per week. Subjects must have demonstrated evidence of an increase in absolute FEV<sub>1</sub> of  $\geq 12\%$ , with an absolute volume increase of at least 200 ml, after reversibility testing at screening or within the past three months. Their screening and baseline FEV<sub>1</sub> had to have been greater than or equal to 55% and less than or equal to 85% of predicted normal.

Study medication was taken once daily in the evening with no specific instruction about timing with respect to meals or other daily activities.

On-treatment clinic visits were at Weeks 1, 2, 4, 8 and 12. Efficacy was assessed by PFTs at each visit. The time of the visits were said to be standardized for each patient so that they were done about at the same time of day. They were not standardized across patients. This timing of clinic visits was not controlled with respect to time of dosing. In addition, subjects were to record peak expiratory flow (PEF) and symptom scores in the morning and evening, use of rescue medication, and number of nocturnal awakenings requiring Proventil use.

A centralized randomization list was created with a block size of four with 2 replicates of each treatment in a block. From the data supplied it appears that each of the 18 centers was first sent supplies for 8 patients (2 blocks) and then additional blocks (possibly 2 more) depending upon recruitment.

The primary efficacy variable was change in FEV<sub>1</sub> from baseline to endpoint. Analysis of variance was used to compare treatment means with factors for center and treatment.

### 2.1.2 Study P01545

Study P01545 was a randomized, placebo controlled, double-blind, multicenter study comparing MF DPI 200 mcg QD PM, MF DPI 400 mcg QD PM (one inhalation), MF DPI 400 mcg QD PM (two inhalations), MF DPI 200 mcg BID, and placebo in subjects with asthma who were previously maintained on inhaled corticosteroids. There was a single blind placebo / ICS reduction period followed by a twelve week treatment period. On-treatment clinic visits were scheduled at Weeks 1, 2, 4, 7, and 12. Efficacy was assessed by PFTs at each visit. In addition, subjects were to record peak expiratory flow (PEF) and symptom scores in the morning and evening. Use of rescue medication, number of nocturnal awakenings, time to asthma worsening, response to therapy, and quality of life were also to be assessed. At the first screening visit the patients had their daily ICS dose reduced 50%. If, after 1 week on the reduced dose, the subject did not meet randomization criteria, the ICS may have been discontinued or reduced further at the discretion of the investigator. After 4 weeks, subjects who failed to meet randomization criteria were ineligible for randomization. The randomization criteria were a decrease in FEV<sub>1</sub> of at least 10% from screening value and at least one of the following 4 symptoms below:

1. Use of 15 or more inhalations of rescue medications over the past 4 days. (No more than 12 inhalations per day.)

2. A total symptom score of 4 or greater on at least 1 day since the last center contact.
3. Twenty five percent or greater decrease in AM or PM peak flow (PEF) from the screening value on at least 12 days since the last contact with the study center.
4. At least one nighttime awakening due to asthma symptoms requiring the use of beta-agonists.

The visit at which the subject met criteria for randomization became the Baseline Visit.

Each subject was to take one inhalation from the AM DPI every morning, and one inhalation each from the PM "1" DPI and the PM "2" DPI in the early evening preferably prior to dinner. The two PM DPIs were needed to double-blind the treatments.

The primary efficacy variable was change in FEV<sub>1</sub> from baseline to endpoint. Analysis of variance was used to compare treatment means with factors for center and treatment. The primary comparison was MF DPI 400 mcg QD PM (one inhalation) vs. placebo. The sponsor in the study report specified the following sequential stepwise testing to control the error rate (NDA 20-167 Volume 18, page 59). The first was MF DPI 400 mcg QD PM (one inhalation) vs. Placebo. The second was MF DPI 200 mcg BID vs. Placebo. The third was MF DPI 400 mcg QD PM (two inhalations) vs. Placebo. The fourth and last was MF DPI 200 mcg QD PM vs. Placebo. [The protocol, however, states (NDA 21-067 Volume 20, page 928) that if the primary comparison of 400 mcg vs. Placebo is significant, all other pairwise comparisons will be made at the nominal alpha=0.05 level with no adjustments.) With the number of treatments included in this study, this does not adequately control the per comparison error rate. However, because of the levels of significance seen in this study, the 200 mcg QD PM vs. Placebo comparison would be significant with all the reasonable multiple comparison procedures that do adjust the significance levels for multiple testing. This reviewer will report the unadjusted pairwise p-values given in the sponsor's study report.]

A centralized randomization list was created with a block size of five with each treatment in a block. From the data supplied it appears that each of the 45 centers was sent supplies in blocks.

## **2.2 Data sources**

Data for Studies C98-475 and P01545 were included in the Sponsor's February 6, 2004 submission.

## **3 Statistical Evaluation**

### **3.1 Evaluation of Efficacy**

#### **3.1.1 Study C98-475**

There were 196 subjects randomized at 18 centers. One subject was lost to follow-up following the baseline visit and the sponsor had no confirmation that the patient took any

medication. Of the 195 treated subjects (100 MF 200 mcg QD PM, 95 placebo), 23 (11 MF 200 mcg QD PM and 12 placebo) withdrew prior to scheduled completion with no major differences for reason for withdrawal. The treatment groups were comparable in demographic and baseline pulmonary function. There were 101 females and 94 males treated. The average age was 29 years. The baseline LS FEV<sub>1</sub> means for the MF 200 mcg QD PM and placebo groups were 2.55 and 2.64 Liters, respectively.

The primary efficacy variable was change from baseline in FEV<sub>1</sub> at Endpoint. It was analyzed with an analysis of variance with treatment and centers as factors. Treatment by investigator interaction was investigated in a supplementary analysis. For this supplementary analysis centers with six or fewer subjects were combined to form one large center. The p-value of treatment-by-center interaction was 0.56. The table below contains the results for the analysis of changes from baseline in FEV<sub>1</sub> at each visit and Endpoint.

	MF DPI 200mcg QD PM			Placebo			P.SD <sup>c</sup>	P-value <sup>b</sup>	
	N	Mean <sup>a</sup>	(Mean % Change)	N	Mean	(Mean % Change)		Treat	Center
Baseline	100	2.55		95	2.64				
Change From Baseline									
Week 1	97	0.29	(11.7%)	92	0.10	(4.3%)	0.35	<0.01	0.33
Week 2	93	0.34	(14.2%)	94	0.14	(6.1%)	0.40	<0.01	0.28
Week 4	93	0.38	(15.7%)	92	0.15	(6.7%)	0.38	<0.01	0.07
Week 8	89	0.42	(16.9%)	84	0.13	(6.5%)	0.42	<0.01	0.42
Week 12	86	0.47	(18.5%)	80	0.20	(7.6%)	0.43	<0.01	0.41
Endpoint <sup>d</sup>	100	0.43	(16.8%)	95	0.16	(6.0%)	0.44	<0.01	0.29

<sup>a</sup>Means of percent changes are raw means. All the other means presented in this table were LS means which were based on an ANOVA model with treatment and center effects.

<sup>b</sup>Based on an ANOVA model with treatment and center effects.

<sup>c</sup>P.SD =Pooled Standard Deviation

<sup>d</sup>Endpoint=last available data for each subject.

The primary efficacy variable, change in FEV<sub>1</sub> from baseline at endpoint, was significant as was the analysis at each week. The sponsor analyses for the subsets (FEV<sub>1</sub> <80% of Predicted Value at baseline, FEV<sub>1</sub> ≥ 80% of Predicted Value at Baseline) showed almost no effect in subjects ≥ 80% of predicted FEV<sub>1</sub>. The choice of 80% FEV<sub>1</sub> for dichotomizing seems to have been made *post hoc*. The difference in mean changes from baseline at endpoint between MF DPI (n=30, mean change 0.27) and Placebo (n=31, mean change 0.22) for subset with FEV<sub>1</sub> ≥ 80 % was only 0.05 Liters. The difference in mean changes from baseline at endpoint between MF DPI (n=70, mean change 0.48) and placebo (n=64, mean change 0.12) for subset with FEV<sub>1</sub> < 80 % was 0.36 Liters.

Efficacy at endpoint in changes from baseline was also seen for the 200 mcg QD PM dose compared to placebo for other pulmonary function parameters ( FVC, FEF25-75%, AM and PM PEFr). Only sporadic significant results were seen in non-pulmonary

function variables (except for AM Wheezing Scores which showed consistent efficacy up to week 10), although the trends were in the direction of demonstrating efficacy.

### 3.1.2 Study P01545

A total of 400 subjects were randomized {78 to MF DPI 200 mcg QD PM, 80 to MF DPI 400 mcg QD PM (one inhalation), 78 to MF DPI 400 mcg QD PM (two inhalations), 81 to MF DPI 200 mcg BID, and 83 to placebo} at 45 centers. A total of 82 subjects {13 on MF DPI 200 mcg QD PM, 12 on MF DPI 400 mcg QD PM (one inhalation), 8 on MF DPI 400 mcg QD PM (two inhalations), 9 on MF DPI 200 mcg BID, and 40 on placebo} discontinued from the study prior to scheduled completion. [The large drop-out rate for placebo is not unexpected in light of the placebo/ICS reduction run-in period.] Treatment failure was the most frequent reason for discontinuation (32 placebo, 8 MF DPI 200 mcg QD PM, 6 MF DPI 400 mcg QD PM one inhalation, 3 MF DPI 400 mcg QD PM two inhalations, 9 MF DPI 200 mcg BID). The treatment groups were comparable in demographic and baseline pulmonary function. There were 239 females (59.7%) and 161 males (40.3%).

The table below contains the results for the analysis of changes from baseline in FEV<sub>1</sub> at each visit and Endpoint.

Appears This Way  
On Original

Table FEV1 (Liters)- Change from Baseline (All Randomized Subjects)															
	MF 200mcg QD PM			MF 400 mcg QD PM (one inhalation)			MF 400 mcg QD PM (two inhalations)			MF 200 mcg BID			Placebo		
	(A)			(B)			(C)			(D)			(E)		
	N	LS Mean	(Mean % Change)	N	LS Mean	(Mean % Change)	N	LS Mean	(Mean % Change)	N	LS Mean	(Mean % Change)	N	LS Mean	(Mean % Change)
Screening	78	2.56		80	2.68		78	2.65		80	2.66		83	2.61	
Baseline	78	2.18		80	2.28		78	2.24		80	2.26		83	2.19	
Change from Baseline															
Week 1	77	0.37	(17.9%)	78	0.35	(16.3%)	77	0.40	(18.6%)	76	0.36	(17.4%)	78	0.15	(7.3%)
Week 2	73	0.36	(17.5%)	77	0.38	(18.3%)	75	0.45	(21.2%)	76	0.42	(20.5%)	67	0.25	(13.4%)
Week 4	69	0.42	(20.5%)	77	0.40	(19.0%)	74	0.48	(22.7%)	76	0.48	(23.2%)	58	0.22	(11.1%)
Week 7	65	0.41	(19.6%)	73	0.45	(20.3%)	70	0.55	(24.4%)	72	0.50	(23.7%)	48	0.23	(10.0%)
Week 12	62	0.50	(24.1%)	65	0.46	(21.7%)	67	0.48	(22.5%)	69	0.52	(25.5%)	41	0.30	(13.8%)
Endpoint	78	0.41	(19.2%)	80	0.41	(19.2%)	78	0.49	(21.7%)	80	0.51	(23.7%)	83	0.16	(7.8%)

Analysis Results (Change from Baseline)													
P-values			Pairwise Comparisons (P-values)										
Time	Pooled SD	Treat	Site	A-B	A-C	A-D	A-E	B-C	B-D	B-E	C-D	C-E	D-E
Week 1	0.30	<0.001	0.020	0.053	0.583	0.813	<0.001	0.271	0.755	<0.001	0.433	<0.001	<0.001
Week 2	0.30	0.004	0.002	0.695	0.090	0.238	0.045	0.185	0.423	0.017	0.596	<0.001	0.002
Week 4	0.32	<0.001	0.278	0.797	0.280	0.247	0.001	0.172	0.145	0.002	0.942	<0.001	<0.001
Week 7	0.32	<0.001	0.003	0.512	0.018	0.100	0.005	0.076	0.304	<0.001	0.442	<0.001	<0.001
Week 12	0.32	0.013	0.051	0.524	0.822	0.637	0.004	0.675	0.259	0.017	0.478	0.006	<0.001
Endpoint	0.38	<0.001	0.175	0.948	0.200	0.116	<0.001	0.221	0.128	<0.001	0.780	<0.001	<0.001

The primary efficacy variable, changes in FEV<sub>1</sub> from baseline at endpoint, was significant as was the analysis at each week for each MF dose compared to placebo. The sponsor analyses for the subsets (FEV<sub>1</sub> <75% of Predicted Value at baseline, FEV<sub>1</sub> ≥ 75% of Predicted Value at Baseline) showed less effect in subjects ≥ 75% of predicted FEV<sub>1</sub> for the 200 mcg QD dose. The choice of 75% FEV<sub>1</sub> for dichotomizing seems to have been made *post hoc*. The mean changes from baseline at endpoint for the subset with FEV<sub>1</sub> < 75 % was 0.44 for MF DPI 200 mcg QD PM (n=64), 0.46 for MF DPI 400 mcg QD PM [one inhalation] (n=55), 0.47 for MF DPI 400 mcg QD PM [two inhalations] (n=62), 0.53 for MF DPI 200 mcg BID (n=57), and 0.18 for placebo (n=70). The mean changes from baseline at endpoint for the subset with FEV<sub>1</sub> ≥ 75 % was 0.27 for MF DPI 200 mcg QD PM (n=14), 0.35 for MF DPI 400 mcg QD PM [one inhalation] (n=25), 0.54 for MF DPI 400 mcg QD PM [two inhalations] (n=16), 0.51 for MF DPI mcg BID (n=23), and 0.13 for placebo (n=13). Less efficacy as measured by FEV<sub>1</sub> was seen for MF DPI 200 mcg QD PM for the less severe patients than for the more severe patients. MF DPI 200 mcg BID and MF DPI 400 mcg QD PM [two inhalations] did not show this difference.

Homogeneity of results across centers could not be assessed due to the small number of subjects enrolled at each center. The centers that were of reasonable size (9 or more patients) were evaluated and the treatment-by-center interaction p-value was 0.78.

Efficacy at endpoint in changes from baseline was also seen for the 200 mcg QD PM dose compared to placebo for other pulmonary function parameters ( FVC, FEF<sub>25-75%</sub>, AM and PM PEF<sub>R</sub>) and non-pulmonary parameters (AM Wheezing Score, AM Difficulty Breathing Score, AM Coughing Score, Inhalations of Proventil Used Per Day, and Number of Nocturnal Awakenings).

### **3.2 Evaluation of safety**

The original medical officer of the November 30, 1998 submission found MF DPI 400 mcg QD and MF 200 mcg QD BID to be safe and effective. Since a dose of 200 mcg QD PM is a smaller dose, the safety data from these two studies only provide a small amount of additional safety information in the overall evaluation of safety for MF DPI. No safety problem was seen in these studies.

## **4 Findings in special/ subgroup populations**

### **4.1 Gender/age/race**

The sponsor provided treatment means for the changes from baseline in FEV<sub>1</sub> for subgroup categories for each of the two studies in the present submission. The subgroups categories for age were 12 to 17 years, 18 to 64 years, and ≥ 65 years. The race categories were Caucasians, and Non-Caucasians. Some of the subgroup categories were extremely small. There was no indication that MF DPI 200 mcg QD PM was not effective in the various age, race or gender categories.

#### ***4.2 Other special/subgroup populations***

Each of the studies was conducted in a special subgroup. Both study populations were mild asthmatics with the population of Study C98-475 the mildest. In Study C98-475, the sponsor did an analysis of patients with baseline FEV<sub>1</sub> ≥ 80% of predicted normal and for baseline FEV<sub>1</sub> < 80 % of predicted normal. For the subset with baseline FEV<sub>1</sub> ≥ 80% of predicted normal, there was only a minor suggestion of efficacy for the 200 mcg PM QD dose. In Study P01545, the sponsor did an analysis of patients with baseline FEV<sub>1</sub> ≥ 75% of predicted normal and for baseline FEV<sub>1</sub> < 75 % of predicted normal. For the subset with baseline FEV<sub>1</sub> ≥ 75% of predicted normal, there was much less efficacy for the 200 mcg PM QD dose. The results for this subset is suggestive that higher doses (400 mcg QD PM or 200 mcg BID) might be more effective for these mildest patients.

### **5 Summary and Conclusions**

#### ***5.1 Statistical Issues and Collective Evidence***

The only statistical issue was the failure of the sponsor to address the multiple comparison issue in Study P01545. Although the sponsor's study report specified a stepdown procedure, the protocol did not specify the use of that procedure. Because of the significance seen in this study, the MF 200 mcg QD PM dose would be significantly different from placebo for changes from baseline in FEV<sub>1</sub> at endpoint using any of the commonly used multiple comparison procedures.

#### ***5.2 Conclusions and Recommendations***

Studies C98-475 and P01545 demonstrate that Mometasone Furoate (MF) 200 DPI mcg QD PM was significantly more effective than placebo for changes from baseline at endpoint in FEV<sub>1</sub>. Other efficacy variables supported the efficacy seen in FEV<sub>1</sub>. These conclusions support labeling that MF DPI at a dose of 200 mcg QD PM is an effective dose for some mild patients. Whether these studies support the sponsor's labeling recommendations is left for clinical judgment. The results from Study P01545 for patients whose baseline FEV<sub>1</sub> was ≥75% of predicted normal is suggestive that higher doses (400 mcg QD PM or 200 mcg BID) might be more effective for these mildest patients.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
James Gebert  
4/26/04 09:14:07 AM  
BIOMETRICS

Steve Wilson  
4/26/04 10:53:51 AM  
BIOMETRICS

**STATISTICAL REVIEW AND EVALUATION  
STABILITY STUDY**

---

**NDA Number:** 21-067  
**Applicant:** Schering-Plough Research Institute  
**Name of Drug:** ASMANEX® TWISTHALER™ 200µg (mometasone furoate inhalation powder)  
**Document Reviewed:** Stability data reports – Dated 10/17/00  
**Statistical Reviewer:** Feng Zhou, M.S., HFD-715  
**Chemistry Reviewer:** Prasad Peri, Ph.D., HFD-570

## 1. Introduction

The sponsor submitted a stability report with the stability data for the Kenilworth stability batches of the drug product Mometasone Furoate Inhalation Powder (NDA 21-067) on October 17, 2000. The electronic stability data was submitted on January 26, 2001. The purpose of the report is to support the sponsor's proposed shelf life with data up to 18 months in storage at 25°C/60% R.H. according to the ICH Guideline "Stability testing of new drug substances and drug products" and FDA guidance "Stability testing of drug substances and drug products".

On December 10, 2003, the sponsor submitted a stability report with new specification limits. This stability review is to evaluate the stability batches based on the sponsor new specification limits to support its proposed 18 month shelf life under 25°C/60% R.H. storage condition.

## 2. Sponsor's Stability Analysis

The sponsor submitted the stability data up to [ ] of the two batches of the drug product Mometasone Furoate Dry Powder Inhaler 200mcg (8-GEN-876 and 8-GEN-880 manufactured at Kenilworth, NJ facilities) on October 17, 2000. (See Table 1 for detail) The sponsor performed statistical analyses with the old specification limits showed in Table 2 and the analysis results concluded as following: (p1038, Volume 3)

*"In general, the statistical analyses of the data fro the Kenilworth stability batches support a proposed 18-month shelf life. There are a few instances in the analysis of the [ ] data for the middle and end doses where the projected shelf life falls short of 18 months by a few months. The analysis for the middle and end doses is mitigated by the lack of the initial data for these doses. However, for both batches, the data are within specifications at all timepoints."*

**Table 1. Summary of Stability Data Points Submitted by the Sponsor**

Parameters	Batch No.	Storage Conditions	Testing Frequency and Storage period (mon.)
Emitted Dose Uniformity (at 60L/minute)	8-GEN-876	25°C / 60% r.h.	[
	8-GEN-880	25°C / 60% r.h.	
(at 60 L/minute) All Groups	8-GEN-876	25°C / 60% r.h.	]
	8-GEN-880	25°C / 60% r.h.	

### 3. Reviewer's Stability Analysis

This reviewer analyzed the data in accordance with FDA guidance<sup>1</sup> using stability data of batches (8-GEN-876 and 8-GEN-880 manufactured at Kenilworth, NJ facilities) which were submitted on October 17, 2000 and the new specification limits listed in Table 2.

**Table 2. List of Old and New Specification Limits Used to Establish Its Shelf Lives**

Test Parameter	Old Acceptance Criteria	New Acceptance Criteria
Emitted Dose Uniformity (at 60 L/minute)	For the Initial, Middle, and End Unit Dose [	
	(at 60 L/minute)	
Group I	For the Initial, Middle, and End Unit Dose	
Group II	For the Initial, Middle, and End Unit Dose	
Group III	For the Initial, Middle, and End Unit Dose	
Group IV	For the Initial, Middle, and End Unit Dose	
Total	For the Initial, Middle, and End Unit Dose	]

It is noted that, FDA guidance recommends that at least three batches be tested for each manufacturing site and package size combination. The sponsor's study failed to meet the FDA minimum requirement of three batches. The results of this reviewer's analysis are presented in Table 3.

For [ ] groups 1 and 4, the minimum estimated expiration date was [ ] based on the batch 8-GEN-876. Figure 1 shows the expiry date analysis for [ ] in group 1 for the end unit dose. The 95% two-sided confidence interval for the population regression line is outside of upper specification limit. Figure 2 and Figure 3 shows the expiry date analysis for [ ] in group 4 for the middle dose and the end dose. The 95% two-sided confidence intervals for the population regression lines are outside of lower specification limit.

<sup>1</sup> Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics, FDA.

**Table 3. Summary of Statistical Analyses for the Stability Batches of ASMANEX® TWISTHALER™ 200mcg Stored Under 25°C/60%RH Condition (Kenilworth, NJ)**

Test	Specification	Minimum Expiration Date	Model Selection	Fitted Line	Batch
Emitted Dose Uniformity (at 60 L/min) Active Ingredient					
For the Initial Unit Dose	┌	┌	Model 2	┌	8-GEN-876
					8-GEN-880
For the Middle Unit Dose	┌		Model 2		8-GEN-876
					8-GEN-880
For the End Unit Dose	┌		Model 3		8-GEN-876
					8-GEN-880
( ) (at 60 L/min) - Group I					
For the Initial Unit Dose	┌		Model 3		8-GEN-876
					8-GEN-880
For the Middle Unit Dose	┌		Model 3		8-GEN-876
					8-GEN-880
For the End Unit Dose	┌		Model 2		8-GEN-876
					8-GEN-880
( ) (at 60 L/min) - Group II					
For the Initial Unit Dose	┌		Model 3		8-GEN-876
					8-GEN-880
For the Middle Unit Dose	┌		Model 1		POOLED
For the End Unit Dose	┌		Model 1		POOLED
( ) (at 60 L/min) - Group III					
For the Initial Unit Dose	┌		Model 3		8-GEN-876
					8-GEN-880
For the Middle Unit Dose	┌		Model 3		8-GEN-876
					8-GEN-880
For the End Unit Dose	┌		Model 2		8-GEN-876
					8-GEN-880
( ) (at 60 L/min) - Group IV					
For the Initial Unit Dose	┌		Model 1		POOLED
For the Middle Unit Dose	┌		Model 3		8-GEN-876
					8-GEN-880
For the End Unit Dose	┌		Model 2		8-GEN-876
					8-GEN-880
( ) (at 60 L/min) - Total					
For the Initial Unit Dose	┌		Model 1		POOLED
For the Middle Unit Dose	┌		Model 1		POOLED
For the End Unit Dose	┌		Model 1		POOLED

KEY: Model 1 – common slope and common intercepts  
 Model 2 – common slope and separate intercepts  
 Model 3 – separate slopes and separate intercepts

Figure 1. [ J - Group I for the End Unit Dose of Batch 8-GEN-876 for ASMANEX® TWISTHALER™ 200mcg Stored Under 25°C/60%RH Condition (Kenilworth, NJ)

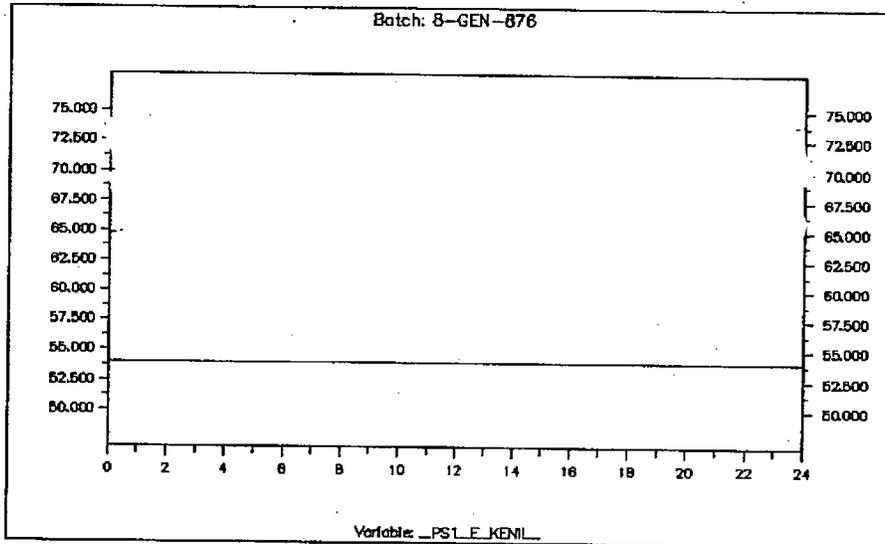
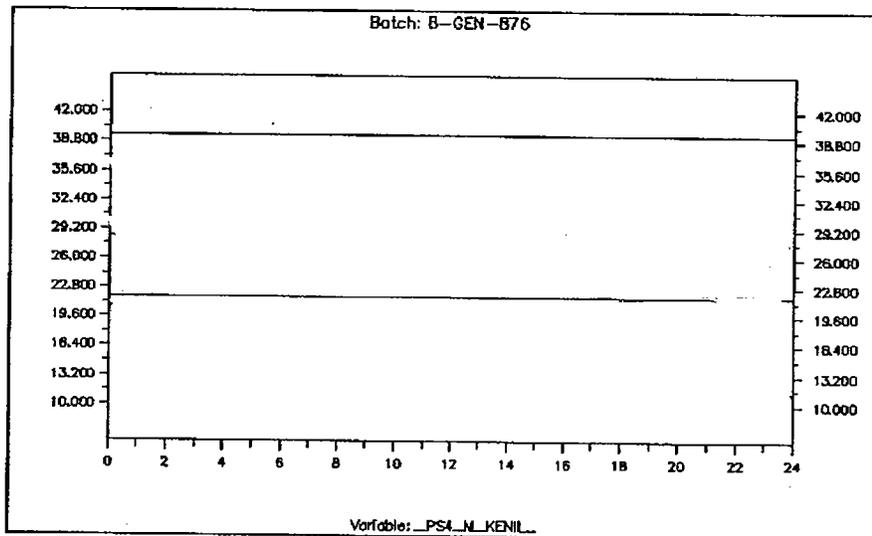
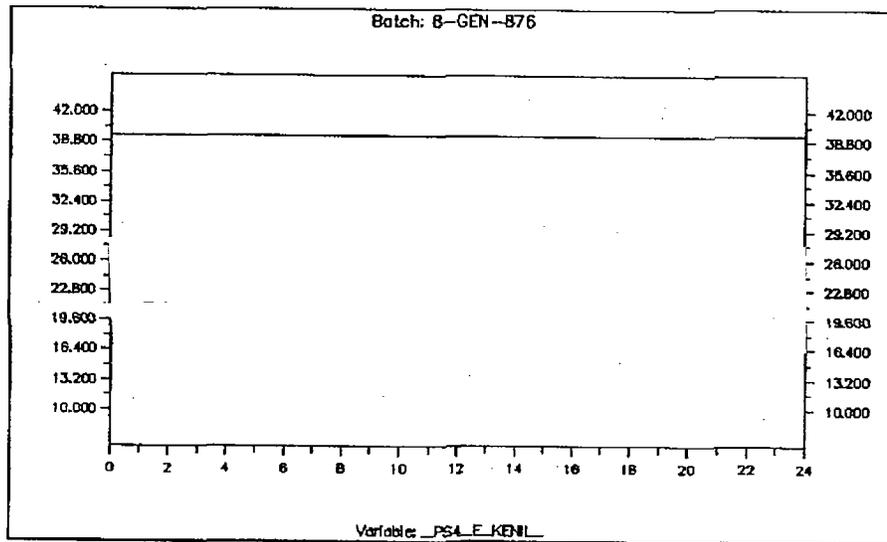


Figure 2. ( ) - Group IV for the Middle Unit Dose of Batch 8-GEN-876 for ASMANEX® TWISTHALER™ 200mcg Stored Under 25°C/60%RH Condition (Kenilworth, NJ)



**Figure 3.** Group IV for the End Unit Dose of Batch 8-GEN-876 for ASMANEX® TWISTHALER™ 200mcg Stored Under 25°C/60%RH Condition (Kenilworth, NJ)



#### 4. Conclusion

The results of this reviewer's analysis using the data of two batches (8-GEN-876 and 8-GEN-880) of the drug product Mometasone Furoate Inhalation Powder (NDA 21-067) under 25°C/60%RH storage condition show that the sponsor's stability data did not support an 18-month expiration date. Moreover, the sponsor's stability study failed to meet the FDA requirement of testing at least three batches for each manufacturing site and package size combination.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Feng Zhou  
3/30/04 08:53:58 AM  
BIOMETRICS

Karl Lin  
3/30/04 08:57:55 AM  
BIOMETRICS  
Concur with review

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 12/4/00

FROM: Director, Division of Biometrics II (HFD-715)

SUBJECT: Stability consult request from Dr. Bertha dated 10/17/00

TO: IND 46,216/ NDA 21,067 – Asmanex Twisthaler (Mometasone Furoate Inhalation Powder)

Ref. stability consult request dated 10/17/00 and attached e-mail message from Dr. Bertha, the statistical review for this product will be postponed until the stability limits have been reassessed by the reviewing chemist.

  
Stephen E. Wilson, Dr.P.H..

cc:

Orig NDA 21-067  
HFD-570/CBertha  
HFD-570/DHilfiker  
HFD-570/SBarnes

**ATTACHMENT**

**ELECTRONIC MAIL MESSAGE**

**Sensitivity: COMPANY CONFIDENTIAL**

**Date: 29-Nov-2000 12:04pm EST**  
**From: Craig Bertha**  
**BERTHAC**  
**Dept: HFD-570 PKLN 10B45**  
**Tel No: 301-827-1050 FAX 301-827-1271**

**TO: Steve Wilson (WILSONS)**  
**CC: James Gebert (GEBERT)**  
**CC: Feng Zhou (ZHOUF)**  
**CC: Guiragos Poochikian (POOCHIKIAN)**

**Subject: Biometrics Consult for N21067**

Steve,

Hopefully this is not too much of a problem but I would ask that you have your reviewer (Feng?) hold off on the analysis of the expiration dating period [ ] specifications for the Asmanex DPI (mometasone furoate inhalation powder). Because of new discrepancies between the data between the two manuf. sites we are going to ask them to tighten the limits for this parameter in the next action letter. If you could still perform the rest of the analysis it would be worthwhile for the time being. As soon as we come to an agreement [ ] I'll submit an updated consult to you.

Sorry for the confusion.

Craig

56

SB for KJM 11/9/00

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	<b>REQUEST FOR CONSULTATION</b>
---	---------------------------------

TO: (Division/Office) Steve Wilson, Biometrics, HFD-715	FROM: Craig M. Bertha, HFD-820
--	-----------------------------------

RECEIVED 11/8/00	IND NO. 146,216	NDA NO. 21-067	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT 10/17/00
NAME OF DRUG ASMANEX TWISTHALER (Mometasone Furoate Inhalation Powder)		PRIORITY CONSIDERATION 3	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE CDER Goal date 12/1/00

NAME OF FIRM  
 Schering Corporation CB  
11/8/00

**REASON FOR REQUEST**

- I. GENERAL**
- |  |  |   |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER    |
| <input checked="" type="checkbox"/> PROGRESS REPORT    | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING           |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE      |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW               |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (Specify below) |
| <input type="checkbox"/> MEETING PLANNED BY _____      |  |   |

**II. BIOMETRICS**

- |  |  |
|--|--|
| STATISTICAL EVALUATION BRANCH  | STATISTICAL APPLICATION BRANCH   |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER | <input type="checkbox"/> CHEMISTRY<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER |

**III. BIOPHARMACEUTICS**

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

**IV. DRUG EXPERIENCE**

- |  |   |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

**V. SCIENTIFIC INVESTIGATIONS**

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: See attached sheet for details.

cc: Orig NDA 21-067  
 HFD-570/Div File  
 HFD-570/CBertha  
 HFD-570/DHilfiker  
 HFD-570/SBarnes

SIGNATURE OF REQUESTER 	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
----------------------------	--

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
-----------------------	------------------------

Statistical Review and Evaluation  
Clinical

NDA #: 21-067

SEP 14 1999

Applicant: Schering

Name of Drug: Mometasone Furoate Inhalation Powder  
220,

Indication: Treatment of Asthma in Adults and  
adolescents

Documents Reviewed: Volumes 1.333-1.562 dated November 30, 1998  
and an unnumbered volume dated May 24, 1999.  
A CANDAs was supplied with the November 30,  
1999 submission.

The Medical Officer for this review is D. O'Hearn, M. D. (HFD-570) with whom this review was discussed.

This review pertains to 2 studies in patients previously maintained on inhaled corticosteroids, 2 studies in patients previously maintained on beta-agonists, and one oral-prednisone-sparing study.

I. Background

Mometasone Furoate DPI will be denoted by MF throughout this review.

The proposed label states that the recommended starting dose is 400 mcg QD for most patients, whether previously maintained on either bronchodilators alone or inhaled corticosteroids. Dose reduction to 200 mcg once daily may be considered, increasing back to 400 mcg once daily or 200 mcg BID, if more control is needed. The recommended starting dosage for patients requiring oral corticosteroids is 400 mcg BID. Once reduction of oral steroid is complete, the label states that MF should be titrated down to the lowest effective dose.

This review will primarily focus on the primary efficacy assessment, change in FEV<sub>1</sub> at endpoint. The results from some secondary efficacy assessments at endpoint will be provided to justify the efficacy of the doses recommended after dose reduction. The oral-steroid sparing study will discuss the percentage reduction in oral-steroids, which is its primary

efficacy parameter. The secondary variables (AM symptom assessments, AM PEFr) at endpoint will be discussed because they are important in the decision about whether MF should be given QD or BID.

This reviewer noticed that an analysis of covariance for the primary efficacy variable referenced in the submission was not supplied in the submission. The results of that analysis were requested in a telecon with the sponsor on May 18, 1999. The analysis of covariance results was supplied in their May 24, 1999 submission.

## II. Studies in Patients Controlled on Corticosteroids

### A. Study C96-134

#### 1. Description of Study and Method of Analysis

This was a parallel group, double-blind, double-dummy study comparing MF 100mcg BID, MF 200mcg BID, MF 400mcg BID, Beclomethasone Dipropionate (BDP) MDI 168 mcg BID, and placebo in adults and adolescents with asthma who were currently on inhaled corticosteroids. There was a two-week run-in period followed by a 12-week treatment period. During the two-week run-in period, the patients continued on the corticosteroid that they were currently taking at study entry.

Clinic visits were scheduled at Days 1,4,8,15,29,57, and 85 of treatment. The Day 1 assessment, taken before treatment assignment, was the baseline assessment of PFTs. At clinic visits triplicate PFTs were taken and the highest FEV<sub>1</sub> was used as the assessment value. The time of assessment of the PFTs with respect to dosing was not mentioned in the protocol. Because the patients did not always return on the scheduled day of visit, the sponsor formed relative visit day windows to assign patients to visits.

The primary efficacy variable was change from baseline in FEV<sub>1</sub> at endpoint. The primary population was not specified in the protocol but the intent-to-treat population was used in the study report. The sponsor used an analysis of variance with treatments and center in the model. The treatment-by-center interaction was tested in a supplementary analysis and was not significant for the primary efficacy variable.

The sponsor stated in the protocol that a test for non-decreasing response with increasing MF doses using a linear contrast would be performed, and, if significant, pairwise comparisons of

treatment means would be performed, without adjusting further for multiple comparisons. In the study report, the sponsor performed a linear trend test. However, in a Documentation of Statistical Methods section, the sponsor provided the results of the Jonckheere-Terpstra test on the changes from baseline. This test is appropriate for testing the above protocol-specified hypothesis.

During the run-in period and treatment period the patient kept a daily diary in which he/she recorded AM and PM PEF (highest of 3 assessments), number of nighttime awakenings, the total number of puffs of proventil used in each 24 hours, morning and evening symptom assessments for the symptoms wheezing, difficulty breathing, and cough. The three symptom assessments used a 4-point scale (0=none, 1=noticeable but did not bother me or interfere with my normal daily activities/sleep, 2=annoying and may have interfered with my normal daily activities/sleep, 3=very uncomfortable and interfered with most of all of my normal daily activities/sleep.) The diary data was analyzed weekly as changes from baseline. The baseline was the last 7 days (PM assessments) or 8 days (AM assessments) before randomized treatment. Endpoint was the last of these weekly assessments.

## **2. Results**

There were 365 patients (76 for MF 100 mcg BID, 70 for MF 200 mcg BID, 74 for MF 400 mcg BID, 71 for BDP 168 mcg BID, and 74 for placebo) randomized at 20 centers. A total of 87 patients (12 on MF 100 mcg BID, 9 on MF 200mcg BID, 12 on MF 400mcg BID, 15 on BDP, and 39 on placebo) discontinued the study prior to scheduled completion. Whereas approximately 7% of patients treated with any dose of MF or BDP discontinued because of treatment failure, 38% of placebo patients discontinued for this reason. The treatment groups were similar at baseline with regard to demographic variables, disease characteristics, and previous asthma therapies.

The sponsor pooled centers 16,19 and 20 for their analysis to test whether results were consistent across centers for the analysis of the primary efficacy variable. The treatment-by-center p-value was 0.78, which shows relative consistency. The standardized value of the Jonckheere-Terpstra test statistic was 3.941 ( $P=0.001$ ).

Table 1 provides adjusted treatment means and p-values from the analysis of changes from baseline FEV<sub>1</sub> at clinic visits and

endpoint. At endpoint all MF treatment groups were significantly different from placebo. Significant differences from placebo were seen for the MF 200 mcg and 400 mcg BID groups as early as Week 1. The results for the MF 100 mcg BID group were only significantly different from placebo, sporadically. The results for other efficacy parameters (PEFR, asthma symptom assessments, puffs of proventil used per day, number of nocturnal awakenings, etc) showed similar efficacy for the MF treatments.

The efficacy results (all variables considered) tended to show better efficacy for MF 200 mcg BID than for MF 100 mcg BID with no added benefit for 400 mcg BID.

### **3. Reviewer's Comments**

The multiple comparison procedure used (an overall Jonckheere-Terpstra test and then all pairwise comparisons) is not a closed procedure and hence does not adequately control experiment-wise error rate. The procedure used is similar to a protected LSD procedure. The MF doses would be significantly different ( $P < 0.05$ ) from placebo using any of the commonly used multiple comparison procedures, because the pairwise p-values comparing MF dose with placebo were all less than 0.01.

This study showed that MF 200 and 400 mcg BID were effective doses. For the primary efficacy variable there was no added benefit for the MF 400 mcg BID dosing.

### **B. Study C96-196**

#### **1. Study Description and Method of Analysis**

This study was similar to study C96-134 with the following exceptions. The doses studied were MF 200 mcg QD given in the morning, MF 200 mcg QD given in the evening, MF 400 mcg QD given in the morning, MF 200 mcg BID, and placebo. During the run-in period patients were on MF 200 mcg BID rather than their normal corticosteroid dosage.

#### **2. Results**

There were 307 patients who enrolled at 16 study centers. 21 patients discontinued during the 2-week run-in period while on MF 200 mcg BID. There were 5 of these patients who discontinued for treatment failure. Thus a total of 286 patients (58 on MF 200 mcg QD AM, 54 on MF 200 mcg QD PM, 58 on MF 400mcg QD AM, 58 on MF 200mcg BID, and 58 on placebo) were randomized into the study.

Of these 286 patients, 67 (16 on MF 200 mcg QD AM, 7 on MF 200 mcg QD PM, 13 on MF 400 mcg QD AM, 7 on MF 200 mcg BID, and 24 on placebo) discontinued prior to scheduled completion of the study. Of these 67 discontinuations, 41 were for treatment failure (10 on MF 200 mcg AM, 2 on MF 200 mcg QD PM, 10 on MF 400 mcg QD AM, 0 on MF 200mcg BID, and 19 on placebo).

The treatment groups were generally similar in demographic variables but were different in baseline FEV<sub>1</sub>. The sponsor provided the results of the analysis of covariance in their May 24, 1999 submission.

The sponsor pooled centers 6,7,8 and 16 for their analysis to test whether results were consistent across centers for the analysis of the primary efficacy variable. The treatment-by-center p-value was 0.34, which shows relative consistency.

Table 2 provides the adjusted treatment means and p-values for the analysis of changes from baseline FEV<sub>1</sub> at clinic visits and endpoint. At endpoint all MF treatment groups except 200 mcg QD AM were significantly different from placebo. Significant differences from placebo were seen for all MF groups except 200 mcg QD AM after Week 1 (the results for MF 200 mcg BID at week 12 were only nearly significant, P=0.07). The results of the covariance analysis adjusting also for baseline FEV<sub>1</sub> gave similar results.

Table 3 provides the adjusted treatment means for changes from baseline for AM measurements at endpoint. All MF treatments were significantly different from placebo for all of these AM assessments except for AM cough for the MF 200 mcg QD PM group. Numerically, with sporadic differences reaching statistical significance, the 200 mcg BID dose of MF was the best of the MF treatments.

### 3. Reviewer's Comments

This study showed that MF 400 mcg QD given in the morning and MF 200 mcg BID were effective doses. The MF 200 mcg QD dose was also effective if given in the evening. Numerically, BID dosing was more effective than QD dosing for the AM assessments of PEF and symptoms. The significant difference between MF 200 mcg QD AM and 200 mcg QD PM indicate that 200 mcg QD might not be enough to maintain patients at a steady state. The times of assessment of the PFTs, unspecified in the protocol, favored the PM dosing.

### III. Studies Where Patients Were Only on Beta-agonists

#### A. Study C96-186

##### 1. Study Design and Methods of Analysis

This study was similar to Study C96-134 with the following exceptions: The doses studied were MF 200 mcg QD given in the AM, MF 400 mcg QD given in the AM, MF 200 mcg BID, and placebo. Patients were only on beta-agonists at study entry.

##### 2. Results

There were 306 patients (79 MF 200 mcg QD, 74 MF 400 mcg QD, 79 MF 200 mcg BID, and 74 placebo) randomized at 22 centers. A total of 43 patients (12 MF 200mcg QD, 6 MF 400 mcg QD, 7 MF 200 mcg BID, and 18 placebo) withdrew before scheduled completion. Adverse events and treatment failures causing failure to complete the study were more common in the placebo group than in the MF groups.

The treatment groups were comparable at baseline in demographic characteristics (age, sex, race, and weight), and baseline disease characteristics.

The sponsor pooled centers 4 and 18 for their analysis to test whether results were consistent across centers for the analysis of the primary efficacy variable. The treatment-by-center p-value was 0.46, which shows relative consistency.

Table 4 provides the adjusted treatment means and p-values for the analysis of changes from baseline FEV<sub>1</sub> at clinic visits and endpoint. At endpoint all MF treatment groups except 200 mcg QD AM were significantly different from placebo. Significant differences from placebo were seen for all MF groups except 200 mcg QD AM on all clinic visits.

Table 5 provides the adjusted treatment means for changes from baseline for AM measurements at endpoint. Both MF 400 mcg QD AM and MF 200 mcg BID were significantly different from placebo for all of these AM assessments. Numerically the BID dose of MF was the best MF treatment.

### 3. Reviewer's Comments

This study showed that MF 400 mcg QD given in the morning and MF 200mcg BID were effective doses. This study did not show MF 200 mcg given in the morning to be an effective dose.

### B. Study C96-136

#### 1. Study Design and Methods of Analysis

This study was similar to Study C96-134 with the following exceptions: The doses studied were MF 200 mcg QD given in the AM, MF 400 mcg QD given in the AM, and placebo. Patients were only on beta-agonists at entry.

#### 2. Results

There were 236 patients (72 MF 200 mcg QD, 77 MF 400 mcg QD, and 87 placebo) randomized at 21 centers. A total of 44 patients (7 MF 200 mcg QD, 15 MF 400 mcg QD, and 22 placebo) withdrew before scheduled completion. There were 7 withdrawals for treatment failure in the placebo group and only 1 each in the two MF groups.

The treatment groups were comparable at baseline in demographic characteristics (age, sex, race, and weight), and baseline disease characteristics.

The sponsor pooled centers 1 and 3, 5 and 6, 20 and 22 for their analysis to test whether results were consistent across centers for the analysis of the primary efficacy variable. The treatment-by-center p-value was 0.39, which shows relative consistency.

Table 6 provides the adjusted treatment means and p-values for the analysis of changes from baseline FEV<sub>1</sub> at clinic visits and endpoint. At endpoint both MF treatment groups were significantly different from placebo. Significant differences from placebo were seen for all MF groups (except 400 mcg QD AM at Week 8) on all clinic visits after week 2.

Table 7 provides the adjusted treatment means for changes from baseline for AM measurements at Endpoint. Both MF 400 mcg QD AM and MF 200 mcg QD AM were significantly different from placebo for AM Difficulty breathing and AM wheezing assessments. MF 400 mcg QD was also significantly better than placebo for AM PEFR.

### 3. Reviewer's Comments

This study showed that MF 200 mcg and 400 mcg QD were effective doses.

## IV. Oral-Prednisone-Sparing Study (C96-137)

### 1. Study Design and Methods of Analysis

This was a randomized, placebo controlled, parallel group study with a three-month double blind phase and a nine-month open label phase in adults and adolescents. During the double-blind period, MF 400mcg BID, MF 800mcg BID and placebo were compared. During the open label period all patients were on MF 800mcg BID at the start but could be titrated down to MF 400mcg BID. At baseline patients were on the level of their own inhaled corticosteroids and the minimum dose of oral prednisone that controlled their asthma. This prednisone dose was either 5-30mg daily or 10-60 mg every other day.

To enter the study patients had to have an FEV<sub>1</sub> of between 40% to 85% of predicted normal and demonstrated an increase in FEV<sub>1</sub> of 12%, with an absolute increase of at least 200ml, after reversibility testing (with beta agonist or corticosteroids) at screening or within the 12 months before entering the trial.

Dosage adjustment criteria were reviewed at each visit. Unless reduction was considered inappropriate by the investigator, the oral prednisone dose was to be reduced if the subject met the following criteria.

- 1) FEV<sub>1</sub> had not decreased by 20% or more from the baseline value (provided Proventil had been withheld for at least 6 hours)
- 2) FEV<sub>1</sub> was  $\geq 40\%$  of predicted (provided Proventil had been withheld for at least 6 hours)
- 3) In the last 7 days, any morning peak flow rate (PEFR) had not decreased by 20% or more from the mean baseline AM PEFR value established in the 7 days preceding the baseline visit
- 4) Subject had taken no more than 4 puffs of Proventil above the mean baseline daily Proventil use for 2 consecutive days, and had taken no more than 12 puffs on 2 consecutive days in the last 7 days

- 5) In the last 7 days, subject had no more than 2 nocturnal awakenings per week above baseline
- 6) A prednisone burst had not been used in last 7 days
- 7) Two prednisone bursts had not been used since last visit

Subjects meeting these criteria were to receive prednisone at the reduced dose until the next visit, when adjustment criteria were again reviewed. If these criteria were met and the investigator did not consider reduction appropriate, a comment was to be provided. Prednisone dose reductions were to be made in the following manner:

<u>Daily Prednisone</u>	<u>Alternate Day Prednisone</u>
30 mg QD Reduce in $\leq 5$ mg QD steps	60 mg QOD Reduce in $\leq 10$ mg QOD steps
10 mg QD Reduce in $\leq 2.5$ mg QD steps	20 mg QOD Reduce in $\leq 5$ mg QOD steps
5 mg QD Reduce in 1.0- 2.5 mg QD steps	10 mg QOD Reduce in $\leq 2.5$ mg QOD steps
0 mg	0 mg

If the subject did not meet the above criteria, the prednisone dose could either be held stable or increased by increments of up to 10 mg for subjects on a daily regimen or increments of up to 20 mg for subjects on an alternate-day regimen. For clinical exacerbation, subjects could be rescued with a prednisone burst of up to 60 mg/day, tapered down within 2 weeks to a dosage of 2.5 mg above the preburst daily prednisone dosage.

During the 3-month phase of the study, subjects requiring a second burst of prednisone were to be maintained on a fixed dose of prednisone for the remainder of this phase. Subjects requiring more than two prednisone bursts in this phase were to

be discontinued from this study phase but could be eligible to enter the 9-month phase. Subjects completing the 3-month phase were also eligible to enter the 9-month phase. Prednisone dosage was adjusted according to the same criteria as above. Bursts of prednisone could be given as necessary to control the subject's asthma; it was not mandated that the subject be discontinued.

Randomization was stratified by baseline oral prednisone level into 2 strata: <12.5 mg/day ( or <25 on alternate days) and  $\geq$ 12.5mg/day ( or  $\geq$ 15mg on alternate days).

Percent changes from baseline in prednisone dosage were analyzed using an analysis of variance with factors treatment and center. The endpoint analysis was considered to be the primary efficacy variable. The sponsor used a step-down procedure to control per-experiment-wise error rate.

## 2. Results

There were 132 subjects (46 for MF 400mcg BID, 43 for MF 800mcg BID, and 43 for placebo BID) randomized at 21 centers. One subject who received MF 400mcg BID was lost to follow-up on Day 1 and was excluded from the efficacy analyses. Ninety-five patients (39 MF 400mcg BID, 36 MF 800mcg BID and 20 placebo) completed the 3-month double-blind phase. Thirty-one of the 37 non-completers withdrew for treatment failure.

The treatment groups were comparable at baseline except for inhaled corticosteroid usage. Eleven MF 800mcg BID patients did not use inhaled corticosteroids compared to 4 and 2 for MF 400mcg BID and placebo, respectively.

Table 8 presents the results of the analysis of mean percent changes in oral prednisone at the various visits and endpoint. The treatment groups were comparable in mean oral prednisone usage at baseline. The MF groups were significantly different from placebo from week 4 onwards. Using the sponsor step-down multiple comparison procedure the results at week 2 and 3 would not be significant for MF 400mcg versus placebo. Both MF treatments were significantly different at endpoint, which was the primary efficacy assessment time.

Both MF treatment groups had a mean increase in FEV<sub>1</sub> whereas the placebo group showed a decrease in FEV<sub>1</sub>. Similarly, the MF groups decreased their use of proventil and had a decrease in their mean asthma symptom scores, whereas the placebo group increased their use of proventil and showed a mean increase in

their asthma symptom scores. Therefore, the decreased use of oral prednisone in the MF groups compared to placebo did not lead to a worsening of asthma compared to the placebo group.

### 3. Reviewer's Comments

This study showed that MF 400 mcg BID and 800 mcg BID were oral corticosteroid sparing with no added benefit in the primary efficacy analysis for the higher dose.

### V. Overall Comments

Mometasone Furoate Inhalation powder 400 mcg QD given in the AM was shown to be effective for changes from baseline in FEV<sub>1</sub> in patients maintained on inhaled corticosteroids in Study C96-196, and on patients maintained on only beta agonists in Studies C96-189 and C96-136. In these studies AM assessments of PEF and symptoms at the end of the dosing interval confirmed efficacy as a QD dosing regimen. Efficacy was also seen for MF 200 mcg QD and MF 200 mcg BID. This supports the dose recommended after dose reduction and the recommended doses if more control is needed. The favoring of MF 200 mcg QD PM over MF 200 mcg QD AM in Study C96-196 for Changes from Baseline in FEV<sub>1</sub> is suggestive that a 200 mcg QD dose might not have attained steady state in patients maintained on corticosteroids. This dose might not be adequate for such patients.

Mometasone Furoate Inhalation powder at 400mcg and 800mcg BID were shown to be oral-prednisone sparing in Study C96-137 with 400mcg BID the preferred dose.



James R. Gebert, Ph.D.  
Mathematical Statistician

Concur: Dr. Nevius *SEN 9-14-99*

Dr. Wilson *WA 9/13/99*

This review contains 12 pages of text and 8 pages of tables.

cc:

Archival NDA 21-067

HFD-570

HFD-570/Dr. O'Hearn

HFD-570/Mr. ~~Foyet~~ *Dunn*

HFD-715/Div. File, Chron  
HFD-715/Dr. Gebert  
HFD-715/Dr. Wilson

Table 1 FEV<sub>1</sub> (liters) — Change from Baseline by Treatment Group (All Treated Patients)

	MF DPI 100 mcg BID (A)		MF DPI 200 mcg BID (B)		MF DPI 400 mcg BID (C)		BDP MDI 168 mcg BID (D)		Placebo (E)	
	N	Mean <sup>a</sup> (Mean % Change) <sup>a</sup>	N	Mean (Mean % Change)	N	Mean (Mean % Change)	N	Mean (Mean % Change)	N	Mean (Mean % Change)
Baseline	76	2.61	70	2.67	73	2.49	71	2.62	74	2.48
Change From Baseline										
Day 4	68	0.13 (5.5%)	66	0.15 (6.3%)	69	0.11 (4.2%)	69	0.08 (2.9%)	67	0.01 (0.9%)
Week 1	73	0.09 (4.4%)	65	0.20 (8.2%)	71	0.13 (5.7%)	67	0.07 (2.8%)	69	-0.02 (-0.6%)
Week 2	71	0.21 (8.6%)	68	0.20 (8.1%)	72	0.16 (6.4%)	68	0.10 (4.1%)	63	-0.00 (0.2%)
Week 4	74	0.16 (5.7%)	67	0.25 (9.9%)	70	0.19 (7.4%)	65	0.16 (6.4%)	53	0.04 (0.8%)
Week 8	64	0.17 (5.9%)	66	0.26 (9.7%)	65	0.23 (8.2%)	59	0.17 (6.4%)	40	0.08 (2.5%)
Week 12	63	0.20 (6.0%)	63	0.27 (10.2%)	61	0.24 (9.1%)	56	0.17 (6.3%)	36	0.08 (2.5%)
Endpoint <sup>b</sup>	76	0.14 (4.8%)	70	0.18 (7.1%)	73	0.15 (6.2%)	71	0.09 (3.0%)	74	-0.16 (-6.6%)

Analysis Results (Change From Baseline)<sup>c</sup>

Timepoint	P,SD	P-value		Pairwise Comparisons (P Value)										
		L-Trend	Treatment	Center	A vs B	A vs C	A vs D	A vs E	B vs C	B vs D	B vs E	C vs D	C vs E	D vs E
Day 4	0.33	0.10	0.14	0.66	0.81	0.65	0.36	0.03	0.48	0.25	0.02	0.64	0.09	0.23
Week 1	0.38	<0.01	0.01	0.80	0.09	0.51	0.71	0.08	0.29	0.04	<0.01	0.31	0.02	0.19
Week 2	0.37	0.02	<0.01	0.12	0.81	0.37	0.06	<0.01	0.52	0.11	<0.01	0.32	0.01	0.12
Week 4	0.40	0.02	0.08	0.46	0.17	0.60	0.90	0.11	0.39	0.22	<0.01	0.71	0.04	0.10
Week 8	0.38	0.03	0.19	<0.01	0.21	0.39	0.99	0.25	0.71	0.22	0.02	0.39	0.05	0.26
Week 12	0.42	0.04	0.24	0.25	0.34	0.54	0.73	0.19	0.74	0.20	0.03	0.35	0.07	0.32
Endpoint	0.48	<0.01	<0.01	0.67	0.60	0.85	0.59	<0.01	0.74	0.30	<0.01	0.47	<0.01	<0.01

a: Means of percent changes were raw means. All the other means presented in this table were adjusted for treatment and center effects.  
 b: Endpoint = last visit for each patient.  
 c: Based on an ANOVA model with treatment and center effects. Trend tests were based on linear contrasts of the treatment means, pairwise treatment comparisons were based on t-test from the ANOVA model.

Table 2 FEV<sub>1</sub> (liters) — Change from Baseline by Treatment Group (All Treated Patients)

(Study No. C96-196)

	MF DPI 200 mcg QD AM (A)		MF DPI 200 mcg QD PM (B)		MF DPI 400 mcg QD AM (C)		MF DPI 200 mcg BID (D)		Placebo (E)	
	N	Mean <sup>a</sup> (Mean % Change)	N	Mean (Mean % Change)	N	Mean (Mean % Change)	N	Mean (Mean % Change)	N	Mean (Mean % Change)
Baseline	58	2.57	54	2.49	58	2.64	58	2.75	58	2.68
Change From Baseline										
Day 4	38	-0.06 (-1.4%)	33	0.08 (4.1%)	40	-0.08 (-2.8%)	41	0.04 (1.8%)	37	-0.09 (-0.4%)
Week 1	55	-0.08 (-2.5%)	53	0.04 (3.0%)	58	0.01 (1.6%)	58	0.03 (2.3%)	56	-0.07 (0.2%)
Week 2	54	-0.09 (-3.0%)	54	0.07 (3.3%)	55	-0.02 (-0.8%)	56	0.05 (2.2%)	52	-0.15 (-3.5%)
Week 4	53	-0.10 (-3.2%)	52	0.09 (3.5%)	55	0.03 (1.2%)	56	0.03 (1.2%)	46	-0.16 (-3.2%)
Week 8	49	-0.09 (-3.3%)	50	0.10 (3.4%)	50	0.00 (0.1%)	52	0.00 (0.7%)	35	-0.17 (-5.7%)
Week 12	41	-0.11 (-4.5%)	43	0.07 (1.7%)	44	0.06 (1.2%)	50	-0.02 (-0.2%)	30	-0.16 (-6.6%)
Endpoint <sup>b</sup>	58	-0.22 (-8.4%)	54	0.03 (1.5%)	58	-0.01 (-1.4%)	58	-0.03 (-0.6%)	58	-0.30 (-9.8%)

Analysis Results (Change From Baseline)<sup>c</sup>

Timepoint	P,SD	P-value		Pairwise Comparisons (P Value)									
		Treatment	Center	A vs B	A vs C	A vs D	A vs E	B vs C	B vs D	B vs E	C vs D	C vs E	D vs E
Day 4	0.24	<0.01	0.25	0.01	0.76	0.07	0.57	<0.01	0.44	<0.01	0.03	0.79	0.02
Week 1	0.29	0.07	0.40	0.03	0.10	0.04	0.88	0.60	0.87	0.05	0.71	0.13	0.06
Week 2	0.30	<0.01	0.81	<0.01	0.30	0.02	0.31	0.10	0.72	<0.01	0.19	0.04	<0.01
Week 4	0.33	<0.01	0.53	<0.01	0.05	0.05	0.35	0.38	0.35	<0.01	0.96	<0.01	<0.01
Week 8	0.35	<0.01	0.76	<0.01	0.18	0.17	0.32	0.18	0.18	<0.01	0.99	0.03	0.03
Week 12	0.34	0.01	0.74	0.02	0.02	0.19	0.56	0.91	0.22	<0.01	0.26	<0.01	0.07
Endpoint	0.40	<0.01	0.74	<0.01	<0.01	0.01	0.23	0.54	0.42	<0.01	0.84	<0.01	<0.01

a: Means of percent changes were raw means. All the other means presented in this table were adjusted for treatment and center effects.

b: Endpoint = last visit for each patient.

c: Based on an ANOVA model with treatment and center effects. Trend tests were based on linear contrasts of the treatment means, pairwise treatment comparisons were based on t-test from the ANOVA model.

Table 3 — Change from Baseline at Endpoint<sup>b</sup> by Treatment Group (All Treated Patients)

(Study No. C96-196)

	MF DPI 200 mcg QD AM (A)		MF DPI 200 mcg QD PM (B)		MF DPI 400 mcg QD AM (C)		MF DPI 200 mcg BID (D)		Placebo (E)	
	N	Mean <sup>a</sup>	N	Mean	N	Mean	N	Mean	N	Mean
AM PEFR	58	-8.93	54	4.30	58	-6.03	58	6.85	58	-36.90
AM Cough	58	0.05	54	0.17	58	0.06	58	-0.09	58	0.38
AM Breathing Difficulty	58	0.14	54	0.17	58	0.12	58	-0.11	58	0.53
AM Wheezing	58	0.15	54	0.22	58	0.12	58	-0.02	58	0.61

Analysis Results (Change From Baseline)<sup>c</sup>

Pairwise Comparisons (P Value)

	A vs B	A vs C	A vs D	A vs E	B vs C	B vs D	B vs E	C vs D	C vs E	D vs E
AM PEFR	0.16	0.76	0.09	<0.01	0.28	0.79	<0.01	0.17	<0.01	<0.01
AM Cough	0.31	0.98	0.20	<0.01	0.32	0.02	0.07	0.19	<0.01	<0.01
AM Breathing Difficulty	0.81	0.93	0.04	<0.01	0.74	0.03	<0.01	0.05	<0.01	<0.01
AM Wheezing	0.57	0.78	0.15	<0.01	0.40	0.05	<0.01	0.24	<0.01	<0.01

a: Means presented in this table were adjusted for treatment and center effects.

b: Endpoint = last week for each patient.

c: Based on an ANOVA model with treatment and center effects. Pairwise treatment comparisons were based on t-test from the ANOVA model. Asthma Symptom Scores: 0=None, 1=Noticeable, 2=Annoying, 3= Very uncomfortable

Table 4 FEV1 (liters) — Change from Baseline by Treatment Group (All Treated Subjects)

(Study No. C96-186)

	MF DPI 200 mcg QD (AM) (A)			MF DPI 400 mcg QD (AM) (B)			MF DPI 200 mcg BID (C)			Placebo (D)		
	N	Mean <sup>a</sup>	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	77	2.58		74	2.64		79	2.56		74	2.55	
Change From Baseline												
Day 4	54	0.21	(8.0%)	58	0.25	(9.8%)	63	0.25	(10.9%)	61	0.01	(0.2%)
Week 1	74	0.19	(7.3%)	72	0.28	(11.2%)	75	0.23	(10%)	68	0.09	(3.3%)
Week 2	76	0.23	(8.9%)	72	0.35	(14.0%)	76	0.36	(14.6%)	69	0.14	(5.9%)
Week 4	73	0.24	(10.1%)	70	0.37	(15.3%)	76	0.36	(15.4%)	65	0.16	(6.9%)
Week 8	68	0.30	(11.9%)	64	0.53	(21.1%)	75	0.43	(17.1%)	60	0.15	(6.6%)
Week 12	64	0.29	(11.2%)	63	0.49	(18.5%)	71	0.44	(17.1%)	54	0.23	(8.5%)
Endpoint <sup>b</sup>	77	0.27	(10.4%)	74	0.41	(16.0%)	79	0.40	(16.1%)	74	0.14	(5.5%)

Analysis Results (Change From Baseline)<sup>c</sup>

Time point	Pooled SD	P-value		Pairwise Comparisons (P Value)					
		Treatment	Center	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
Day 4	0.33	<0.01	0.44	0.61	0.58	<0.01	0.96	<0.01	<0.01
Week 1	0.35	0.01	0.31	0.12	0.43	0.10	0.44	<0.01	0.02
Week 2	0.39	<0.01	0.63	0.07	0.04	0.17	0.82	<0.01	<0.01
Week 4	0.45	0.02	0.34	0.09	0.11	0.26	0.90	<0.01	<0.01
Week 8	0.44	<0.01	0.13	<0.01	0.09	0.06	0.19	<0.01	<0.01
Week 12	0.44	<0.01	0.20	0.01	0.06	0.45	0.45	<0.01	0.01
Endpoint	0.47	<0.01	0.07	0.06	0.09	0.09	0.85	<0.01	<0.01

a: Baseline means and mean changes from baseline are LS means (adjusted means) which were obtained from an ANOVA model with treatment and center effects. Means of percent changes were raw means.

b: Endpoint = last visit for each patient.

c: Based on an ANOVA model with treatment and center effects. Pairwise treatment comparisons were based on t-test from the ANOVA model.

Table 5 — Change from Baseline at Endpoint<sup>b</sup> by Treatment Group (All Treated Patients)  
(Study No. C96-186)

	MF DPI 200 mcg QD AM (A)		MF DPI 400 mcg QD AM (B)		MF DPI 200 mcg QD BID (C)		Placebo (D)	
	Mean <sup>a</sup>		Mean		Mean		Mean	
	N	Mean	N	Mean	N	Mean	N	Mean
AM PEFR	78	26.13	74	52.10	79	63.58	74	22.73
AM Cough	78	-0.24	74	-0.32	79	-0.33	74	-0.12
AM Breathing Difficulty	78	-0.34	74	-0.49	79	-0.64	74	-0.26
AM Wheezing	78	-0.31	74	-0.44	79	-0.60	74	-0.23

Analysis Results (Change From Baseline)<sup>c</sup>

Pairwise Comparisons (P Value)

	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
AM PEFR	<0.01	<0.01	0.72	0.22	<0.01	<0.01
AM Cough	0.41	0.36	0.20	0.95	0.04	0.03
AM Breathing Difficulty	0.13	<0.01	0.41	0.15	0.02	<0.01
AM Wheezing	0.19	<0.01	0.47	0.11	0.05	<0.01

a: Means presented in this table were adjusted for treatment and center effects.

b: Endpoint = last week for each patient.

c: Based on an ANOVA model with treatment and center effects. Pairwise treatment comparisons were based on t-test from the ANOVA model.

Asthma Symptom Scores: 0=None, 1=Noticeable, 2=Annoying, 3= Very uncomfortable

Table 6 FEV<sub>1</sub> (liters) — Change from Baseline by Treatment Group (All Treated Subjects)

(Study No. C96-136)

	MF DPI 200 mcg QD (A)			MF DPI 400 mcg QD (B)			Placebo (C)		
	N	Mean <sup>a</sup>	(Mean % Change) <sup>a</sup>	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	72	2.60		76	2.57		86	2.61	
Change From Baseline									
Week 1	65	0.21	(10.1%)	69	0.25	(11.2%)	81	0.10	(4.5%)
Week 2	66	0.23	(10.7%)	69	0.22	(10.5%)	76	0.10	(4.8%)
Week 4	68	0.33	(13.7%)	72	0.29	(12.4%)	78	0.13	(5.2%)
Week 8	63	0.41	(16.1%)	62	0.22	(9.9%)	66	0.15	(5.9%)
Week 12	61	0.38	(16.5%)	56	0.36	(14.5%)	57	0.14	(4.7%)
Endpoint <sup>b</sup>	72	0.35	(14.8%)	76	0.35	(14.2%)	86	0.06	(2.5%)

Analysis Results (Change From Baseline)<sup>c</sup>

Time point	Pooled SD	P-value		Pairwise Comparisons (P Value)	
		Treatment	Center	A vs B	A vs C
Week 1	0.42	0.10	0.04	0.65	0.12
Week 2	0.40	0.12	0.03	0.85	0.06
Week 4	0.40	<0.01	0.46	0.54	<0.01
Week 8	0.42	<0.01	0.09	0.01	<0.01
Week 12	0.40	<0.01	<0.01	0.75	<0.01
Endpoint	0.45	<0.01	0.31	1.00	<0.01

c: Baseline means and mean changes from baseline are LS means (adjusted means) which were obtained from an ANOVA model with treatment and center effects. Means of percent changes were raw means.

b: Endpoint = last visit for each patient.

a: Based on an ANOVA model with treatment and center effects. Pairwise treatment comparisons were based on t-test from the ANOVA model.

Table 7 — Change from Baseline at Endpoint<sup>b</sup> by Treatment Group (All Treated Patients)  
(Study No. C96-136)

	MF DPI 200 mcg QD (A)		MF DPI 400 mcg QD (B)		Placebo (C)	
	N	Mean <sup>a</sup>	N	Mean	N	Mean
AM PEFR	72	15.80	76	41.29	86	7.95
AM Cough	71	-0.06	76	-0.20	86	-0.05
AM Breathing						
Difficulty	71	-0.44	76	-0.48	86	-0.20
AM Wheezing	72	-0.40	76	-0.39	86	-0.14

Analysis Results (Change From Baseline)<sup>c</sup>

Pairwise Comparisons (P Value)

	A vs B	A vs C	B vs C
AM PEFR	0.02	0.46	<0.01
AM Cough	0.25	0.92	0.19
AM Breathing			
Difficulty	0.73	0.05	0.02
AM Wheezing	0.88	0.02	0.03

a: Means presented in this table were adjusted for treatment and center effects.

b: Endpoint = last week for each patient.

c: Based on an ANOVA model with treatment and center effects. Pairwise treatment comparisons were based on t-test from the ANOVA model.  
Asthma Symptom Scores: 0=None, 1=Noticeable, 2=Annoying, 3= Very uncomfortable

**Table 8** Prednisone Dose (mg/day) — Percent Change from Baseline by Treatment Group (All Treated Subjects)

(Study No. C96-137)

	MF DPI 400 mcg BID (A)			MF DPI 800 mcg BID (B)			Placebo (C)		
	N	Mean % Change <sup>a</sup>	Mean <sup>a</sup>	N	Mean % Change	Mean	N	Mean % Change	Mean
Baseline	45		11.93	43		12.02	43		11.56
Percent Change From Baseline									
Week 1	45	2.7%	-0.44	43	0.9%	-0.14	43	33.1%	2.04
Week 2	44	-4.4%	-1.47	43	12.4%	0.81	42	42.9%	3.07
Week 3	43	-16.5%	-1.18	43	40.6%	6.53	39	98.3%	7.68
Week 4	42	-14.0%	-2.47	40	-37.1%	-3.18	37	115.1%	7.45
Week 5	40	-39.9%	-4.79	39	-33.4%	-3.65	35	108.6%	7.58
Week 6	40	-71.6%	-7.23	39	-34.1%	-4.18	32	111.9%	8.31
Week 7	40	-96.3%	-8.83	38	-52.1%	-4.71	26	138.4%	7.98
Week 8	40	-60.0%	-6.42	38	-27.5%	-3.03	25	32.4%	2.24
Week 9	40	-75.1%	-7.70	37	-35.4%	-4.74	23	62.5%	3.95
Week 10	40	-53.4%	-6.02	36	-57.5%	-6.91	21	59.9%	4.46
Week 11	40	-49.9%	-5.62	36	-63.9%	-7.29	19	56.0%	5.03
Week 12	39	-51.1%	-6.40	36	-72.9%	-8.59	19	55.7%	4.75
<b>Endpoint<sup>b</sup></b>	<b>45</b>	<b>-46.0%</b>	<b>-6.33</b>	<b>43</b>	<b>-23.9%</b>	<b>-3.19</b>	<b>43</b>	<b>164.4%</b>	<b>11.81</b>

Analysis Results (Percent Change From Baseline)<sup>c</sup>

Time point	Pooled SD	P-value		Pairwise Comparisons (p-value)		
		Treatment	Center	A vs B	A vs C	B vs C
Week 1	92.90	0.21	0.46	0.93	0.14	0.12
Week 2	101.16	0.10	<0.01	0.45	0.04	0.18
Week 3	199.96	0.05	0.42	0.20	0.01	0.21
Week 4	151.13	<0.01	0.58	0.50	<0.01	<0.01
Week 5	104.86	<0.01	0.02	0.79	<0.01	<0.01
Week 6	123.27	<0.01	0.13	0.19	<0.01	<0.01
Week 7	252.35	<0.01	0.95	0.46	<0.01	<0.01
Week 8	72.21	<0.01	0.15	0.06	<0.01	<0.01
Week 9	105.36	<0.01	0.25	0.12	<0.01	<0.01
Week 10	103.16	<0.01	0.20	0.87	<0.01	<0.01
Week 11	104.26	<0.01	0.63	0.58	<0.01	<0.01
Week 12	93.88	<0.01	0.76	0.34	<0.01	<0.01
<b>Endpoint</b>	<b>228.28</b>	<b>&lt;0.01</b>	<b>0.84</b>	<b>0.66</b>	<b>&lt;0.01</b>	<b>&lt;0.01</b>

a: All the means presented in this table were LS means, which were based on an ANOVA model with treatment and center effects.

b: Endpoint = last dose of prednisone for each subject.

c: Based on an ANOVA model with treatment and center effects. Pairwise treatment comparisons were based on t-test from the ANOVA model.