CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-067

Medical Review(s)

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-067	TRADE NAME:	Asmanex® Twisthaler 220 mcg
APPLICANT/SPONSOR:	Schering Corporation	USAN NAME:	Mometasone furoate inhalation powder
MEDICAL OFFICER:	Tejashri S. Purohit-Sheth, M.D., FACAAI		
TEAM LEADER:	Lydia Gilbert-McClain, M.D., FCCP	CATEGORY:	Corticosteroid
REVIEW DATE:	1/20/05	ROUTE:	Inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
6/29/04	7/2/04	N-000-BZ,MR	Complete response to approvable letter from 5/17/04
11/05/04	11/12/04	N-000-C	Additional Safety Update Information

RELATED APPLICATIONS

Document Date	Application Type	Comments
11/30/1998	N-000	Original NDA application for Asmanex Twisthaler

REVIEW SUMMARY:

This review addresses Schering Corporation's safety update submitted with the complete response to the approvable letter dated 5/17/2004 for Asmanex® Twisthaler™ 220 mcg. Review of the two asthma studies, brief summaries of the two COPD trials, and line listings of Asmanex Spontaneous Adverse Events, does not raise any new concerns for Asmanex. The noted AEs are not unexpected, and review of this information does not warrant any further labeling changes. The application is still an approval from a clinical standpoint.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	___	SAFE TO PROCEED	___	CLINICAL HOLD	
NDA/SUPPLEMENTS:	___	FILEABLE	___	NOT FILEABLE	
	X	APPROVAL	___	APPROVABLE	___ NOT APPROVABLE
OTHER ACTION:	___		___		

1. INTRODUCTION

This review addresses Schering Corporation's safety update submitted with the complete response to the approvable letter dated 5/17/2004 for Asmanex® Twisthaler™ 220 mcg.

The sponsor originally submitted an NDA for Asmanex® Twisthaler™ 220 mcg (mometasone furoate powder inhaler) on 11/30/1998. This NDA was given an approvable action in October 1999 for mostly CMC deficiencies and some clinical as well. Review of the clinical section of the original submission supported the proposed doses of 400 mcg twice daily, 400 mcg once daily, and 200 mcg twice daily (ex-mouthpiece doses); however, the 200 mcg once daily (ex-mouthpiece dose) was not supported. The action letter stated that additional clinical trials would be required to support a once daily 200 mcg dose (ex-mouthpiece dose). Subsequently, the application underwent three additional review cycles, with the recommended action of approvable due to CMC deficiencies. The most recent complete response that contained new clinical data for review was submitted on 11/14/03. Based on review of the two presented clinical trials, a dose of 200 mcg once daily in the evening was supported; however, the complete response was given an approvable action mainly due to the manufacturing site not being ready for inspection. The sponsor subsequently submitted a complete response on 6/29/04; however, as the inspection site was not yet ready for inspection, the sponsor was told that this was not a complete response. Finally, a complete response was submitted on 9/29/04.

As there is no clinical data to review in the complete response, this review of the complete response to the most recent approvable letter focuses on the safety update submitted on 6/29/04 and also another update submitted on 11/5/04.

2. SAFETY UPDATE

The sponsor provided an extensive update on safety information with the complete response dated 11/14/03. The sponsor now provides updated safety information as of 9/01/03–the cut off point for the previous safety update.

This safety update consists of results of four clinical trials and review of 40 spontaneous adverse reports. The safety information from two of the four trials (Asthma trials: P02509 and P01199) are submitted individually since the designs are different and the results could not be pooled; the other two trials (P00345 and P00340) are COPD trials, whose safety information is combined. These trials are briefly summarized in the following table

Table 1. Summary Table of Studies

Study Number	Primary Objective	Design	MF DPI dose (mcg)	Total Evaluated for Safety (n receiving MF)
Asthma Studies				
P02509	Adherence	12-wk, MC, R, PG, OL Phase IV	• 400 mcg QD (2 puffs of 200 mcg) • 400 mcg QD (1 puff of 400 mcg)	1844

Study Number	Primary Objective	Design	MF DPI dose (mcg)	Total Evaluated for Safety (n receiving MF)
P01199	Safety/Efficacy	8-wk, MC, R, PG, OL Phase III	• 400 mcg QPM	88
COPD Studies				
P00340	Safety/Efficacy	12-week, R, DB,PC, DR, AC	• 800 mcg QD • 400 mcg BID	619
P00345	Safety/Efficacy	52-week, MC, R, DB, PC	• 200 BID • 400 QPM	318

Source: Safety Update, p. 38-47

2.1. Asthma Trials

The sponsor includes two open-label asthma trials in this safety update, which are briefly summarized below. As the designs are not similar, the trials were not pooled. Of note, the sponsor has not finalized the study report for study #P02509 as of yet; however, has looked at the safety data.

2.1.1. Protocol P02509: Asmanex Twisthaler® Subject Adherence Study

This was a European, 12-week, phase IV, multicenter, randomized, open-label, parallel group, study comparing the compliance of two treatment regimens: MF DPI 400 mcg QPM and MF DPI 200 mcg BID. A total of 1233 males and females, ages 12 years and older, with mild to moderate persistent asthma of at least 1 year's duration, previously using low or moderate doses of BDP (beclomethasone dipropionate) HFA (≤ 500 mcg/day) or CFC (≤ 1000 mcg/day) for at least 12 weeks were enrolled into the study.

The primary endpoint for the study was the evaluation of adherence to the assigned treatment group. Adherence was evaluated by drug count utilization as defined by the ration between the number of doses used (as indicated by the inhaler counter) and the scheduled number of doses over the subject's treatment period.

Reviewer's Comments: As the sponsor has yet to finalize a study report, no information on adherence data is available at this time for review; however, as the evaluation of safety information from this study is the primary aim of this review, this is not considered a problem.

2.1.1.1. Results

2.1.1.1.1. Disposition

A total of 1233 subjects were randomized from 148 centers to receive either MF DPI 400 mcg QPM (n=611) or MF 200 mcg BID (n=622). Of the 1233 subjects, 1037 (84%) completed the study, with 510 subjects (83%) in the MF 400 mcg QPM and 527 (85%) in the MF 200 mcg BID completing the study.

A total of 196 subjects (16%) discontinued from the study, 101 (17%) and 95 (15%) from the MF 400 mcg QPM and MF 200 mcg BID groups, respectively. The most common reasons for discontinuation were adverse events (4-5%), lost-to-follow up (4%), and

treatment failure (3-5%). Slightly more patients discontinued from the study due to treatment failure in the MF 400 mcg QPM group (5%) as compared to the MF 200 mcg BID group (3%). The other reasons for discontinuation were comparable between the two treatment groups. The results are summarized in the following table.

Protocol P02509: Disposition

	MF DPI 400 mcg QD PM (n=611)	MF DPI 200 mcg BID (n=622)
Number (%) Completed	510 (83)	527 (85)
Number (%) Discontinuing	101 (17)	95 (15)
Reason for Discontinuation		
Adverse event	23 (4)	32 (5)
Did not meet protocol	0	1 (<1)
Lost to follow-up	24 (4)	22 (4)
Noncompliance with protocol	6 (1)	0
Subject did not wish to continue (reasons unrelated)	18 (3)	19 (3)
Administrative	1 (<1)	0
Treatment failure	29 (5)	21 (3)

Source: safety update, p. 11

2.1.1.1.2. Demographic Data and Baseline Characteristics

The treatment groups were fairly similar at baseline with respect to age, sex, race, and weight, and duration of asthma. The mean age was 50.9 and 50.2 years for MF 400 mcg QPM and 50.2 for MF 200 mcg BID, respectively. The majority of subjects were in the 18 to < 65 years of age category (73% for MF 400 mcg QPM and 75% for MF 200 mcg BID). There were a greater percentage of females in both groups compared to males, 55-57% compared to 43-45%, respectively. The majority of subjects were Caucasian (99%). The mean duration of asthma was 16.4 years for the MF 400 mcg QPM and 16.2 years for MF 200 mcg BID. The results are summarized in the following table.

P02509: Summary of Demographic Data

		Number (%) of Subjects	
		MF DPI 400 mcg QPM n=611	MFDPI 200 mcg BID n=622
Age (Years)	Mean	50.9	50.2
	Median	53.0	52.0
	Range	12.0-87.0	12.0-86.0
Distribution of Subjects by Age Category			
	12 to <18 yr.	21 (3)	22 (4)
	18 to <65 yr.	444 (73)	465 (75)
	≥65 yr.	146 (24)	135 (22)
Sex	Female	338 (55)	357 (57)
	Male	273 (45)	265 (43)
Race	Caucasian	607 (99)	615 (99)
	Black	2 (<1)	2 (<1)
	Asian	2 (<1)	5 (1)
Duration of Asthma (yr)	Mean	16.4	16.2
	Median	11.0	11.0
	Range	0.5-75.0	0.2-70.0
Weight (kg)[a]		n=599	n=614
	Mean	77.3	76.7
	Median	76.0	74.9
	Range	35.0-141.0	32.0-146.0

Source: Safety Update, page 10

2.1.1.1.3. Extent of Exposure

The extent of exposure was fairly comparable between the two treatment groups, although, at any given time point, a greater percentage of subjects were exposed in the MF 200 mcg BID group compared to the MF 400 mcg QPM group. A total of 83% and 85% of subjects in the MF 400 mcg QPM and MF 200 mcg BID groups, respectively, received 71 days or greater (Week 10) of treatment and 72% and 77% of subjects, respectively, received 84 or greater days of treatment (12 Weeks). The results are summarized in the following table.

Reviewer's comments: the extent of exposure is less than ideal, especially for 12 weeks of treatment; however, the percentage of subjects receiving 10 weeks of treatment or greater is fairly reasonable.

Protocol P02509: Extent of Exposure

Duration of Exposure	Number (%) of Subjects	
	MF DPI 400 mcg QD PM[a] (n=611)	MF DPI 200 mcg BID (n=622)
≥1 day	593 (97)	606 (97)
≥15 days (Week 2)	568 (93)	584 (94)
≥29 days (Week 4)	540 (88)	575 (92)
≥43 days (Week 6)	526 (86)	560 (90)
≥57 days (Week 8)	515 (84)	545 (88)
≥71 days (Week 10)	510 (83)	529 (85)
≥84 days (Week 12)	441 (72)	480 (77)
Unknown	18 (3)	14 (2)
Randomized, not treated	0	2 (<1)

Source: SU, p. 11

2.1.1.1.4. Adverse Events

Adverse events (AE) were fairly common in this study, with 61% and 67% of subjects reporting AEs, in the MF 400 mcg QPM and MF 200 mcg BID groups, respectively. The most commonly reported AE was upper respiratory tract infection, reported in 16% of subjects in each group. Other commonly reported AEs were: headache (8% and 7% in MF 400 mcg QPM and MF 200 mcg BID, respectively), pharyngitis (7% and 8% in MF 400 mcg QPM and MF 200 mcg BID, respectively), and lower respiratory tract infection (6% in both groups). The incidence of AEs was comparable between treatment groups.

With respect to common AEs attributable to corticosteroids, oral candidiasis and dysphonia were reported more frequently. Oral candidiasis was reported in 2% and 3% of subjects in the MF 400 mcg QPM and MF 200 mcg BID groups, respectively. Dysphonia was reported in 1% and 2% of subjects in the MF 400 mcg QPM and MF 200 mcg BID groups, respectively.

The following table summarizes adverse events reported by at least two percent of subjects in any of the treatment groups.

Protocol P02509: Incidence of Adverse Events Reported by at Least Two Percent of Subjects in Any Treatment Group

Body System/Adverse Event	Number (%) of Subjects	
	MF DPI 400 mcg QD PM (n=611)	MF DPI 200 mcg BID (n=622)
Any Adverse Event	**374 (61)**	**414 (67)**
Body As A Whole - General Disorders	**90 (15)**	**92 (15)**
Dizziness	12 (2)	14 (2)
Edema legs	11 (2)	7 (1)
Headache	48 (8)	43 (7)
Central and Peripheral Nervous System Disorders	**21 (3)**	**33 (5)**
Dysphonia	4 (1)	13 (2)
Gastro-Intestinal System Disorders	**82 (13)**	**98 (16)**
Diarrhea	14 (2)	18 (3)
Mouth dry	15 (2)	18 (3)
Nausea	10 (2)	17 (3)
Vomiting	13 (2)	19 (3)
Infection and Infestations	**196 (32)**	**218 (35)**
Candidiasis, oral	15 (2)	19 (3)
Infection viral	10 (2)	5 (1)
Lower respiratory tract infection	39 (6)	40 (6)
Pharyngitis	45 (7)	50 (8)
Upper respiratory tract infection	96 (16)	101 (16)
Musculo-Skeletal System Disorders	**45 (7)**	**54 (9)**
Back pain	7 (1)	12 (2)
Musculo-skeletal pain	10 (2)	14 (2)
Respiratory System Disorders	**59 (10)**	**46 (7)**
Catarrh	8 (1)	10 (2)
Coughing	10 (2)	9 (1)
Nasal congestion	12 (2)	6 (1)
Throat dry	14 (2)	4 (1)
Skin and Subcutaneous Tissue Disorders	**34 (6)**	**51 (8)**
Rash	4 (1)	15 (<2)

Source: SU, p. 13

2.1.1.1.4.1. Adverse Events by Sex, Age and Race

Adverse events were reported more frequently by females compared to males in both treatment groups. A total of 158 males (58%) compared to 216 (64%) females reported AEs in the MF 400 mcg QPM group and 163 males (62%) compared to 251 females (70%) reported AEs in the MF 200 mcg BID group.

With respect to age, more subjects in the 18 to < 65 year age group reported AEs compared to the subjects 65 years of age and older. In the MF 400 mcg QPM group, 63% of subjects 18 <65 years of age compared with 55% of subjects 65 years or greater reported AEs. In the MF 200 mcg BID group, 68% of subjects 18 to <65 years of age compared to 64% of subjects ages 65 years of age or older reported AEs.

There were too few subjects in the 12 to <18 years of age group to make any meaningful analyses. Likewise, since 99% of subjects were Caucasian, a meaningful analysis by race could not be done.

2.1.1.1.5. Deaths, Pregnancies, and Serious Adverse Events

2.1.1.1.5.1. Deaths

Two deaths were reported in this study. One subject in the MF 400 mcg QPM group and 1 in the MF 200 mcg BID group died during the study or within 30 days of study completion. The death in the MF 400 mcg QPM group was due to cardiorespiratory arrest. A 44-year old male with history of alcohol abuse was admitted 12 days after receiving his last dose of MF 400 mcg QPM for detoxification. The subject was discharged in improved condition; however, the sponsor learned that the subject died 6.5 months later due to cardiopulmonary arrest. The sponsor also reports two additional deaths in this group; however, since these occurred greater than 30 days post last visit, these are not to be reported in the final report. Both individuals died of carcinoma.

In the MF 200 mcg BID group, a 58 year old woman was admitted to the hospital 4 days after receipt of her last dose of MF. She was diagnosed with metastatic adenocarcinoma of the lung, and died within 9 weeks of diagnosis.

It is unlikely that any of the reported deaths are due to treatment medication.

2.1.1.1.5.2. Pregnancies

One pregnancy was reported during the course of this study. A 24-year old female was discontinued from the study after 9 weeks of treatment when she had a positive pregnancy test. It was later discovered that the subject had lied about contraceptive use to be able to enter the study. No further information on the outcome of this subject is provided.

2.1.1.1.5.3. Serious Adverse Events

A total of 19 subjects reported serious adverse events (SAEs), 8 in the MF 400 mcg QPM and 11 in the MF 200 mcg BID group. Neither the type nor number of SAEs suggest a differential risk between treatment groups. Furthermore, this reviewer has perused the summaries of these SAEs and it appears unlikely that any of the SAEs are related to treatment. These SAEs are summarized in tabular format in the following table.

Protocol P02509: Serious Adverse Events Occurring in Subjects

Center/ Subject	Sex/Age[a]	Preferred Term	Day of Onset[b]	Severity	Action/Outcome
MF DPI 400 mcg QD					
4/000061	F/58	Angina Pectoris	63(1)	Sev	Rx, Hosp, Discon
25/000487	M/44	Alcohol Intoxication	45 (12)	Sev	Rx, Hosp
		Cardio-Respiratory Arrest		Sev	Death
		Alcoholic Liver Disease (NOS)		Sev	Death
38/000754	F/77	Fracture, Bone	54	Sev	Rx, Hosp
		Fall	54	Sev	Hosp
45/000900	F/66	Squamous Cell Carcinoma	75	Sev	Hosp, Interrupt
53/001047	F/46	Depression Psychotic	83	Sev	Hosp, Discon
80/001585	M/43	Rectal Bleeding	54	Mod	Hosp
		Diverticulitis	67	Mod	Rx, Hosp
115/002296	M/47	Fall	2	Mod	Hosp
128/002547	M/62	Aortic Stenosis	17 (1)	Lt	Hosp, Discon
MF DPI 200 mcg BID					
5/000086	F/40	Hysterectomy	74	Mod	Hosp
9/000162	F/72	Procedure	83	Mod	Hosp, Interrupt
19/000363	M/73	Myocardial Infarction	60	Lt	Rx, Hosp
56/001102	M/44	Diabetes Mellitus	9	Sev	Rx, Hosp
63/001245	F/49	Migraine	47	Mod	Hosp
		Photophobia	47	Mod	Hosp
		Gastroenteritis	47	Sev	Hosp
77/001523	F/58	Pulmonary Carcinoma	33 (4)	Lt	Hosp, Discon, Death
		Neoplasm, Brain	33 (4)	Lt	Hosp, Discon, Death
		Renal Carcinoma	33 (4)	Lt	Hosp, Discon, Death
88/001749	F/70	Cerebrovascular Accident (NOS)	66	Lt	Hosp, Discon
105/002091	F/24	Pregnancy Unintended	68	*	Discon
116/002301	F/53	Cholelithiasis	35	Mod	Rx, Hosp
116/002802	F/38	Lower Respiratory Tract Infection	73	Sev	Rx, Hosp, Discon
162/003245	F/38	Asthma Aggravated	77	Sev	Hosp

Source: SU, p. 16

2.1.1.1.6. Withdrawals Secondary to Adverse Events

A total of 55 subjects discontinued from the study due to AEs, 23 in the MF 400 mcg QPM (4%) and 32 in the MF 200 mcg BID (5%). Headache was the most commonly reported AE leading to discontinuation from the study, reported in three subjects (<1%) in the MF 400 mcg QPM and in six subjects (1%) in the MF 200 mcg BID group. In the MF 400 mcg QPM group, twos subjects each reported chest pain, leg edema, and insomnia. In the MF 200 mcg BID group, three subjects reported lower respiratory tract infection and two subjects each reported dizziness, dysphonia, nausea, vomiting, oral candidiasis, and pharyngitis. Other AEs were reported in one individual. Review of these SAEs does not raise any specific concern

2.1.1.1.7. Laboratory Evaluations

Clinical laboratory evaluations were not performed as part of this study

2.1.1.2. Safety Conclusions

Review of the safety data provided does not raise any specific safety concerns. The frequencies and nature of AEs is similar to what is included in the most recent Asmanex labeling, and do not warrant modification based on results of this study.

2.1.2. Protocol P01199: A Comparison of Mometasone Furoate DPI Vs. Budesonide DPI in Asthmatic Patients Previously Maintained on Budesonide DPI

This was a non-US, 8-week, multicenter, open-label, randomized, parallel-group comparison study in subjects with moderate asthma. A total of 236 males and females, ages 14 to 78 years of age were screened to receive MF 400 mcg QPM or Budesonide DPI (BUD-DPI) 400 mcg BID (total daily dose of 800 mcg). Subjects 12 years of age and older with an at least 6-month history of asthma, a baseline FEV_1 of $\geq$ 60% or $\leq$ 90% predicted, documented reversibility with bronchodilators, and having been on a stable regimen of BUD-DPI on a dose of 400-800 mcg daily for 30 days of greater, were eligible for study entry.

The primary efficacy endpoint was the change from baseline in FEV_1 to each post-visit timepoint. Secondary endpoints included the change from baseline in FVC, AM and PM PEFRs, nocturnal and daytime asthma scores, assessment of response to therapy, and rescue medicine use.

2.1.2.1. Results

2.1.2.1.1. Patient Disposition/Demographics

A total of 178 males and females, ages 14 to 78 years of age were randomized to receive MF DPI 400 mcg QPM (n=88) or Budesonide DPI (BUD) 400 mcg BID (n=90). The percent of subjects completing the study was comparable between both groups, 95% in MF DPI and 97% BUD-DPI.

The sponsor reports that nearly all subjects were Caucasian in the study and the mean age was similar between groups. Most subjects were in the 18 to 64 year range category.

Reviewer's comments: The sponsor does not provide any further information, neither in text or table format, on disposition or demographics. Since the majority of patients completed the study in both treatment groups, and most of the subjects were Caucasian and in the 18 to 64 year group, further information is not crucial to assess safety. It is unlikely that any safety subgroup analyses could be performed.

2.1.2.1.2. Extent of Exposure

The sponsor states that the proportion of subjects receiving treatment for 8 weeks (study duration) was 95% and 97% respectively for MF and BUD, respectively. Further information on extent of exposure in not provided; however, since the majority of subjects completed the study, the extent of exposure is more than adequate.

2.1.2.1.3. Adverse Events

Adverse events were reported in 41 subjects (47%) in the MF group and in 43 subjects (48%) in the BUD group. The most commonly reported AEs were: viral infection (MF 14%, BUD 21 %); headache (MF 13%, BUD 12%); overdose NOS (7% in each group); asthma

aggravated (MF 0, BUD 6%); dysphonia (MF 3%, BUD 2%); rhinitis (3% each); and coughing (MF 3%, BUD 2%). The incidence of AEs was fairly comparable between treatment groups, with a few exceptions. Aggravated asthma was reported in 6% of BUD subjects and none in the MF group and viral infection was reported in 21% of BUD subjects compared to 14% of MF subjects. The AEs are summarized in the following table.

Protocol P01199: Incidence of AEs Occurring in 2% of Subjects or Greater in Any Treatment Group

Body System Preferred Term	Number (%) of Subjects							
	MF-DPI (N = 88)				BUD-DPI (N = 90)			
	Mild	Moderate	Severe	Total Subjects	Mild	Moderate	Severe	Total Subjects
All Body Systems				41 (47)				43 (48)
Body as a Whole				15 (17)				13 (14)
Headache	8 (9)	3 (3)	0	11 (13)	10 (11)	1 (1)	0	11 (12)
Dizziness	0	0	0	0	0	2 (2)	0	2 (2)
Pain	1 (1)	1 (1)	0	2 (2)	0	0	0	0
Cardiovascular				0				1 (1)
Central and Peripheral Nervous System				4 (5)				4 (4)
Dysphonia	1 (1)	2 (2)	0	3 (3)	1 (1)	0	0 (1)	2 (2)
Disorders-Immune System				2 (2)				0
Allergy	2 (2)	0	0	2 (2)	0	0	0	0
Disorders-Reproductive				1 (1)				1 (1)
Endocrine Disorders				0				1 (1)
Gastrointestinal				6 (7)				5 (6)
Abdominal Pain	0	2 (2)	0	2 (2)	0	0	0	0
Diarrhea	0	2 (2)	0	2 (2)	0	0	0	0
Nausea	2 (2)	0	0	2 (2)	0	0	0	0
Infection and Infestations				18 (20)				24 (27)
Infection Viral	6 (7)	6 (7)	0	12 (14)	12 (13)	7 (8)	0	19 (21)
Infection	0	1 (1)	0	1 (1)	1 (1)	2 (2)	0	3 (3)
Sore Throat NOS	1 (1)	1 (1)	0	2 (2)	2 (2)	0	0	2 (2)
URTI	0	3 (3)	0	3 (3)	0	0	0	0
Injury and Poisoning				6 (7)				6 (7)
Overdose NOS	1 (1)	0	2(2)	6(7)	0	0	0	6(7)
Musculoskeletal				6 (7)				6 (7)
Arthralgia	1 (1)	0	0	1 (1)	1 (1)	1 (1)	0	2 (2)
Back Pain	0	1 (1)	0	1 (1)	0	2 (2)	0	2 (2)
Psychiatric				3 (3)				2 (2)
Insomnia	2 (2)	0	0	2 (2)	0	0	0	0
Renal and Urinary				0				1 (1)
Respiratory				8 (9)				11 (12)
Rhinitis	3 (3)	0	0	3 (3)	1 (1)	2 (2)	0	3 (3)
Asthma Aggravated	0	0	0	0	0	4 (4)	1 (1)	5 (6)
Coughing	2 (2)	1 (1)	0	3 (3)	1 (1)	1 (1)	0	2 (2)
Skin/Subcutaneous Tissue				3 (3)				1 (1)
Rash	0	2 (2)	0	2 (2)	0	0	0	0

Source: SU, p. 23-24

2.1.2.1.4. Deaths, Pregnancies, and SAEs

There were no deaths reported in this study and one unintentional pregnancy which is addressed in the SAE section.

Eleven SAEs were reported in this study, 9 of which were unintentional overdoses (the sponsor attributes these to the failure to understand and follow dosing instructions or the use of extra doses to relieve respiratory complications such as in the common cold). Six of these overdoses were reported in the MF group (7%) and three (3%) in the BUD group. Of the remaining two SAEs, one was an occurrence of bronchospasm in the MF DPI group, and the other was an unintended pregnancy in the BUD group.

The subject with bronchospasm in the MF group was a 20-year old female with a lifelong history of asthma. She experienced acute onset of bronchospasm of moderate intensity 5

days after starting therapy. She was seen in the hospital and given prednisone. She continued on study treatme nt until she told the investigator that she had bronchospasm and was treated. Her exacerbation abated the same day. Ten days after the bronchospasm, the subject notified the site of her exacerbation, and was discontinued from the study, although in these 10 days she continued on study drug. Information for this patient was obtained mainly from the Case Report Form.

The other non-overdose SAE occurred in a 25-year female with a 2-year history of asthma. At the final visit, it was determined that the subject was pregnant, and she chose to have an abortion.

2.1.2.1.5. Withdrawals Due to AEs

Four subjects withdrew from the study secondary to AEs, three (3%) in the MF group and 1 (1%) in the BUD group. In the MF group, the AEs leading to discontinuation were: hoarseness, exacerbation of asthma (described as an SAE above), and a rash (rash resolved 4 days after discontinuation of study treatment). In the BUD group, one subject discontinued due to dizziness, which resolved one day following discontinuation of study treatment.

2.1.2.1.6. Laboratory Evaluation

No laboratory evaluations were performed in this study.

2.1.2.2. Safety Conclusions

Review of safety data did not raise any concern. Adverse events noted are similar to known AEs noted in the pivotal studies. No labeling changes are warranted after review of this data.

2.2. COPD Trials

The sponsor conducted two trials in a COPD population, and these trials are [ ]. Safety information provided is not complete for these two trials; however, the dose is twice as high as for asthma trials summarized previously. The safety data is briefly summarized below, to the extent that information is provided in the safety update. [ ]

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2.2.1. Protocol P00340: Efficacy and Safety of Mometasone Furoate Dry Powder Inhaler in the Treatment of Patients with Chronic Pulmonary Disease

This was a 52-week, international, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 911 subjects, 40 years of age and older, with a clinical history of COPD. Key eligibility criteria included current or past history of smoking with at least a 10 pack-year history of smoking; absence of the use of inhaled, oral, or parenteral corticosteroids for 6 weeks prior to screening; $FEV_1 \leq 70\%$; and post-bronchodilator response in FEV_1 of $\leq 10\%$. Eligible subjects underwent a 2-3 week run-in period and a smoking cessation program phase of approximately 8 weeks prior to receiving randomized, double-blind treatment for 52 weeks. Eligible subjects were randomized to receive either MF DPI 800 mcg QD PM, MF 400 mcg BID, or placebo.

The primary efficacy variable was the change from Baseline in post-bronchodilator FEV_1. Alternative co-primary endpoints were: change from Baseline in total COPD symptom score and percentage of subjects with one or more COPD exacerbations. Secondary efficacy variables included change from Baseline in pre-bronchodilator FEV_1 , pre-and post-bronchodilatory FVC, and FEF 25-75%, AM and PM total symptom scores (as well as individual symptom scores), six-minute walk distance and Borg score, rescue medication use, response to therapy evaluations, and quality of life assessments.

Safety variables included standard safety assessments as well as assessments for systemic corticosteroid effects. Standard variables included adverse events, clinical laboratory tests, vital signs, physical and oropharyngeal examinations, and forearm bruising. Additional variables were percentage change from Baseline to the 12-month visit in bone mineral density in the lumbar spine/total femur region, the change from Baseline to the 12-month visit in 0-24 hour urine free cortisol, and the change from Baseline to the 12-month visit in 0-19 hour plasma cortisol.

Efficacy results were not provided, with the exception of a summary in the protocol synopsis, and the primary efficacy results, as reported by the sponsor, will be briefly summarized. The pooled MF DPI comparisons for all three primary efficacy endpoints were statistically significant compared to placebo ($p \leq 0.043$). The percentage of COPD exacerbations were not statistically significant between the individual MF DPI groups and placebo, the difference between the pooled MF DPI groups compared to placebo was significant ($p=0.043$). In terms of post-bronchodilator increase in FEV_1, subjects treated in both the MF 400 mcg BID and MF 800 mcg QPM had 50mL increases in FEV_1 compared to a decrease of 19 mL in placebo patients ($p<0.001$). The mean change from Baseline in total COPD symptoms scores over the 12-month treatment period were 0.34, 0.53, and 0.12 for the MF DPI 800 mcg QPM, 400 mcg BID, and placebo, respectively.

The sponsor reports that MF DPI was well tolerated with no unusual or unexpected adverse events. The percentages of subjects reporting AEs were 73%, 74%, and 69% for MF 800 mcg QPM, MF 400 mcg BID, and placebo, respectively. The most commonly reported AE was URI (27% in each of the MF treated groups; 24% in placebo treated group). Other commonly reported AEs for the MF 800 mcg QPM, MF 400 mcg BID, and placebo groups included: bruising (10%, 10%, 6%, respectively); oral candidiasis (11%, 10%, 3%, respectively); pharyngitis (8%, 9%, 8%, respectively). Other AEs reported in 5% of subjects in either MF DPI treatment group included: hypertension, diarrhea, sinusitis, bronchitis, and Musculo-skeletal pain.

Serious adverse events were reported by 142 subjects: 44 in the MF 800 mcg QPM group; 47 in the MF 400 mcg BID group; and 51 in the placebo group. The sponsor reports that review of these SAEs did not raise any safety concerns. There were 10 deaths in this study, and the sponsor reports that none of these deaths were considered treatment-related. Sixty-five subjects discontinued from the study due to AEs. Discontinuations due to AEs were reported to be similar among treatment groups. Adverse events reflecting possible systemic effects of corticosteroids, cataracts and glaucoma/increased intraocular pressure, were reported in less than 1% of subjects in each treatment group

With respect to evaluation of systemic adverse events relating to HPA-axis suppression, the sponsor reports results from the BMD endpoints and cortisol endpoints. For lumbar BMD at Endpoint, the differences between active treatments and placebo were reported to be small and not significant. For total femoral BMD, the sponsor reports a trend towards loss of BMD

in the MF 400 mcg BID group (p=0.150 reported), although a numerical increase of BMD in was noted in the MF 800 mcg QPM group. The sponsor reports that no significant differences were observed in the 24-hour urinary free-cortisol, but a statistically significant difference in the mean plasma cortisol concentrations was observed between MF 400 mcg BID and placebo and between MF 400 mcg BID and MF 800 mcg QPM. The sponsor concludes that the MF 800 mcg QPM had a favorable safety profile compared to MF 400 mcg BID.

Additionally, the sponsor reports that there were no observed clinically meaningful changes in laboratory parameters, vital signs, or physical examinations.

The sponsor concludes that this study supports a favorable risk/benefit ratio for MF 800 mcg QPM; however, based on more consistent efficacy on symptoms and quality of life, 400 mcg BID may be appropriate for some individuals.

Reviewer's comments: The sponsor has not provided any of the data, and only a study synopsis of results for the two COPD trials. Any conclusions regarding efficacy and safety are not corroborated by this reviewer by review of data, but are summarized as presented by the sponsor. Based on the summary of provided data, there appear to be no additional safety concerns that have arisen. Additionally, it should be noted that this current NDA is for the approval in an asthma population and not a COPD population, and the currently proposed dosing is a maximal dose of 400 mcg QPM in patients with asthma previously on inhaled steroids or bronchodilators alone. However, in patients on oral corticosteroids alone, a maximal dose of 800 mcg QD is proposed. The results of this COPD trial are consistent with HPA-axis suppression data in patients taking MF 400 mcg BID, summarized in the proposed label. Therefore, a change in the proposed label is not warranted based on this summary synopsis information.

2.2.2. Protocol P00345: International Placebo-Controlled Trial of Mometasone Furoate Dry Powder Inhaler in the Treatment of Subjects with Chronic Obstructive Pulmonary Disease

This was also a 52-week, international, multicenter, randomized, double-blind, placebo-controlled, parallel group study in 631 subjects, ages 40 years and older, with a clinical history of COPD. Subjects were randomized to receive either MF 800 mcg QPM (n=318) or placebo (n=313).

The design of this study, including eligibility criteria, efficacy endpoints, and safety assessments were similar to the previously summarized trial, with a few exceptions. This study only has two treatment arms, one of which MF 800 mcg QPM, and the other placebo. Additionally, the number of patients is different, with 631 subjects in this trial. Also, BMD and plasma/urine cortisol levels were not assessed. Otherwise, the design was fairly similar to the other study, and the methodology/assessments will not be reiterated.

The sponsor reports favorable efficacy results for the three co-primary endpoints. The sponsor reports a statistically significant difference in the post-bronchodilator FEV_1 from Baseline to Endpoint for MF 800 mcg QPM compared to placebo (p=0.017). Furthermore, a statistically significant (p<0.001) improvement in COPD symptom scores were reported for MF compared to placebo. However, a statistically significant difference in terms of COPD exacerbations was not noted between the two treatment groups (p=0.055), although there was a trend toward favoring active treatment.

In terms of safety, the sponsor reports that MF 800 mcg QPM was well tolerated with no unusual or unexpected AEs. Adverse events were reported by 72% and 64% of subjects in the MF 800 mcg QPM and placebo groups, respectively. Similar to the previous trial, the most commonly reported AE was upper respiratory tract infection (25% for MF, and 19% for placebo). Other commonly reported AEs in the MF group were : bruising (10%), headache (9%), pharyngitis (8%), and aggravation of COPD (8%). The sponsor does not provide a comparison of these AEs to placebo. Serious adverse events were reported in 66 subjects (21%) in the MF group and in 52 subjects (17%) of subjects in the placebo group. The sponsor states that review of these SAEs did not raise any safety concerns. Fifty one subjects discontinued from the trial due to AEs. The sponsor also states that withdrawals due to AEs were similar between treatment groups (numbers in each group not provided). Nineteen deaths were reported during the course of the study, and the sponsor states that none was considered related to study treatment. Furthermore, no clinically meaningful changes in laboratory parameters, vital signs, or physical examination were observed.

The sponsor concludes that this study demonstrated that MF 800 mcg QPM had superior efficacy compared to placebo, and that MF was well tolerated. The incidence and nature of AEs in the study did not raise any safety concerns for the sponsor.

Reviewer's comments: Compared to the two asthma studies summarized, the sponsor has provided very little data for these two COPD trials. Since the current application is for asthmatics, and the above summaries are in COPD patients, the lack of additional information is not vital for review of this safety update; it is reassuring to note that the summary data does not demonstrate any new or unexpected AEs with MF.

2.2.3. Integrated Safety Summary for COPD Trials

The sponsor has not provided an integrated summary of safety for the safety update, since the designs and study populations were different. The only available integrated data submitted is for commonly reported adverse events. These are summarized in the following table. The most commonly reported AEs in the combined COPD trials, were upper respiratory tract infection, bruise/bruising, headache, oral candidiasis, pharyngitis, back pain, aggravation of COPD, bronchitis, and sinusitis. The incidence of AEs occurring in 5% or more of subjects in any treatment regimen is presented in the following table.

Overall, the incidence of AEs was comparable between active treatment and placebo, with a few exceptions. Oral candidiasis, bruising, and pharyngitis was reported in a greater percentage of MF subjects compared to placebo. This is not unexpected of an inhaled corticosteroid with a relatively high dose.

Combined COPD Trials: Incidence of Adverse Events Occurring in 5% of Subjects or More for Any Treatment Regimen

Body System/Adverse Event	Number (%) of Subjects[a]							
	MF DPI 800 mcg QD PM n=626		MF DPI 400 mcg BID n=308		All MF DPI n=934		Placebo n=608	
Any Adverse Event	**453**	**(72)**	**228**	**(74)**	**681**	**(73)**	**403**	**(66)**
Body as a Whole - General Disorders	**133**	**(21)**	**69**	**(22)**	**202**	**(22)**	**135**	**(22)**
Headache	50	(8)	22	(7)	72	(8)	46	(8)
Infection and Infestations	**258**	**(41)**	**144**	**(47)**	**402**	**(43)**	**204**	**(34)**
Candidiasis, Oral	45	(7)	30	(10)	75	(8)	17	(3)
Pharyngitis	51	(8)	28	(9)	79	(8)	33	(5)
Sinusitis	24	(4)	17	(6)	41	(4)	29	(5)
Upper Respiratory Tract Infection	161	(26)	82	(27)	243	(26)	130	(21)
Musculo-Skeletal System Disorders	**132**	**(21)**	**73**	**(24)**	**205**	**(22)**	**105**	**(17)**
Back Pain	47	(8)	15	(5)	62	(7)	19	(3)
Musculo-Skeletal Pain	22	(4)	17	(6)	39	(4)	21	(3)
Platelet, Bleeding and Clotting Disorders	**77**	**(12)**	**44**	**(14)**	**118**	**(13)**	**160**	**(8)**
Bruise	44	(7)	32	(10)	76	(8)	28	(5)
Bruising	31	(5)	13	(4)	44	(5)	25	(4)
Respiratory System Disorders	**142**	**(23)**	**70**	**(23)**	**212**	**(23)**	**118**	**(19)**
Bronchitis	29	(5)	8	(3)	37	(4)	22	(4)
COPD Aggravated	36	(6)	12	(4)	48	(5)	34	(6)

2.3. Review of Asmanex Spontaneous Adverse Events

2.3.1. 02 September 2003 Through 01 June 2004

The sponsor provides line listings of Asmanex Spontaneous Adverse Events between September 2003 and June 2004. A total of 40 patients reported AEs during this time frame. The most commonly reported AE was drug ineffective (6 reports), followed by headache (5 reports), accidental overdose (4 reports), oral candidiasis (2 reports), throat pain/irritation (2 reports), and glossodynia/tongue coated (2 reports). Review of the line listings of these events does not reveal any unexpected adverse events, nor does raise any new safety concerns.

2.3.2. 02 June 2004 Through 01 October 2004

The sponsor provides line listings of additional Asmanex Spontaneous Adverse Events since the last safety update ending in June 2004. This one covers the time period of June 2004 through October 2004. During this time period, an additional 25 AEs were reported. The most commonly reported ones were: asthma (4 reports), drug ineffective (3), and headache (2). Review of the other line listings does not reveal any unexpected adverse events.

3. CONCLUSIONS

The sponsor provided a safety update for the most recent complete response to the Agency's most recent approvable letter. Review of the two asthma studies, brief summaries of the COPD trials, and line listings of Asmanex Spontaneous Adverse Events, does not raise any new concerns for Asmanex. The noted AEs are not unexpected, and review of this information does not warrant any further labeling changes. The application is still an approval from a clinical standpoint.

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/s/

Tejashri Purohit-Sheth
1/28/05 01:58:15 PM
MEDICAL OFFICER

Lydia McClain
1/31/05 12:49:27 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-067	TRADE NAME:	Asmanex® Twisthaler 220 mcg
APPLICANT/SPONSOR:	Schering Corporation	USAN NAME:	Mometasone furoate inhalation powder
MEDICAL OFFICER:	Tejashri S. Purohit-Sheth, M.D., FACAAI		
TEAM LEADER:	Lydia Gilbert-McClain, M.D., FCCP	CATEGORY:	Corticosteroid
DUE DATE:	5/16/04	ROUTE:	Inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
11/14/03	11/17/03	N-000-AZ	Complete response to approvable letter from 12/4/2000

RELATED APPLICATIONS

Document Date	Application Type	Comments
11/30/1998	NDA	Original NDA for Asmanex® Twisthaler 220 mcg

REVIEW SUMMARY:

This review addresses the clinical portion of the complete response from Schering Corporation to the approvable letter dated 12/4/2000 for Asmanex® Twisthaler™ 220 mcg.

The sponsor originally submitted an NDA for Asmanex® Twisthaler™ 220 mcg (mometasone furoate powder inhaler) on 11/30/1998. This NDA was given an approvable action in October 1999 for mostly CMC deficiencies and some clinical as well. The sponsor submitted a complete response again on February 17, 2002, to which an approvable letter was sent out on March 14, 2000, again mainly for CMC deficiencies. In response to the sponsor's complete response dated June 2, 2000 to the previous approvable letter, the Agency sent another approvable letter for CMC deficiencies as the rest of the clinical issues were adequately addressed in this submission. In response to another approvable letter dated 12/4/2000, the sponsor now submits a complete response.

In this response, the sponsor submits an updated response to the October 1, 1999 approvable letter to address the efficacy of once a day 200 mcg QPM dosing based on study reports of two recently completed studies: C98-475 and P01545. Review of the new study reports (C98-475 and P01545) supports the safety and efficacy for the once daily 200 mcg dose, and review of the safety update does not reveal any new safety concerns. From a clinical standpoint, the recommended action on this complete response is *approval.*

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	___	SAFE TO PROCEED	___	CLINICAL HOLD	
NDA/SUPPLEMENTS:	___	FILEABLE	___	NOT FILEABLE	
	X	APPROVAL	___	APPROVABLE	NOT APPROVABLE

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-067	TRADE NAME:	Asmanex® Twisthaler 220 mcg
APPLICANT/SPONSOR:	Schering Corporation	USAN NAME:	Mometasone furoate inhalation powder
MEDICAL OFFICER:	Tejashri S. Purohit-Sheth, M.D., FACAAI		
TEAM LEADER:	Lydia Gilbert-McClain, M.D., FCCP	CATEGORY:	Corticosteroid
DUE DATE:	5/16/04	ROUTE:	Inhalation
OTHER ACTION:			

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1. INTRODUCTION

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In this response, the sponsor submits an updated response to the October 1, 1999 approvable letter to address the efficacy of once a day 200 mcg QPM dosing based on study reports of two recently completed studies: C98-475 and P01545.

This review evaluates the new study reports (C98-475 and P01545) to determine if the sponsor has adequately provided safety and efficacy data for the once daily 200 mcg dose, evaluates the new safety update provided with this submission, including the new data with regard to Bone Mineral Density (BMD), and addresses the updated labeling.

2. SUMMARY OF DEVELOPMENT PROGRAM AND CLINICAL STUDIES ORIGINALLY SUBMITTED IN THE NDA

The development program for mometasone furoate DPI (MF DPI) was very extensive and consisted of eleven clinical studies in the original NDA submission. The efficacy studies evaluated three populations of asthmatic patients – those previously on bronchodilator therapy alone, those previously on inhaled corticosteroids, and those previously maintained on oral corticosteroid therapy.

Initially, the proposed dosing regimen was 400 mcg QD for patients previously on bronchodilators or inhaled corticosteroids alone, and 400 mcg BID for patients requiring oral corticosteroids. In the case of patients on the 400 mcg QD dose, the proposed dosing and administration section stated that *"a reduction to 200 mcg QD may be considered, increasing back to 400 mcg QD or 200 mcg BID if more control is needed."* The review has gone through 3 review cycles without an approval. In all three cycles, the application was given an approvable action. In the first review cycle there were outstanding clinical issues as well as significant CMC issues. The clinical issues were resolved in the sponsor's response to the first approvable letter and the Division indicated that the following doses were acceptable for approval from a clinical standpoint:

- MF 200 mcg BID administered as 200 mcg MF DPI 1 puff in the AM and PM
- MF 400 mcg Q AM administered as 200 mcg MF DPI x 2 puffs.

The studies submitted in the original NDA are summarized below. The studies considered pivotal and reviewed in detail in the original NDA medical officer review were:

- Studies in subjects on bronchodilators alone (placebo-controlled, double-blind, parallel group safety and efficacy: C96-136, C96-186).
- Studies in subjects previously on inhaled corticosteroids (placebo-controlled, double-blind, parallel group safety and efficacy: C96-196).
- Studies in subjects on oral corticosteroids (double-blind, parallel group safety and efficacy: C96-137)

2.1. Studies in Asthmatic Subjects Previously on Bronchodilator Therapy Alone

The sponsor conducted 4 studies–C96-136, C96-186, I96-401 and I96-402 in asthmatic subjects 12 years of age and older on bronchodilator therapy alone. Of these studies, I96-401 and I96-402 were single-center international crossover studies that evaluated the effects of MF DPI on AMP-induced bronchoconstriction and the early and late-phase asthmatic responses as the primary efficacy variables. These studies were mainly pharmacology studies and were of short duration and small size (n = 12 -15). Studies C96-136, C96-186 were studies with 12-week double-blind treatment periods that evaluated the efficacy and safety of MF DPI 200 mcg QD AM, and 400 mcg QD AM vs. placebo for 12 weeks. In addition, study C96-186 contained a 200 mcg BID arm. Study C96-136 had a 9-month open-label treatment period to assess long-term safety. The primary efficacy variable in these studies was the change in FEV_1 at Endpoint. Study C96-136 is discussed in the sponsor's proposed label and is described below.

2.1.1. Study C96-136: "Placebo –Controlled Efficacy and Safety Study with Long-Term Safety Evaluation of Mometasone Furoate Dry Powder in the Treatment of Asthma in Subjects Previously Maintained on Inhaled Beta-Agonists."

This was a study with a 12-week double-blind treatment period followed by an additional 9-month period in which all subjects received treatment with MF DPI. In the 12-week treatment period, subjects were randomized to one of the following treatment arms:

- MF DPI 200 mcg QAM,
- MF DPI 400 mcg QAM
- Placebo

Subjects who received ICS for asthma within 3 months prior to Screening, as well as subjects who were treated for more than 14 days with oral corticosteroids during the 6 months immediately prior to Screening were excluded.

A total of 236 subjects were randomized across 21 study centers in the U.S. The distribution in the treatment groups was as follows:

- MF DPI 200 mcg QD AM, 72 subjects
- MF DPI 400 mcg QD AM, 77 subjects
- Placebo, 87 subjects

The FEV_1 at baseline ranged from 2.57 L – 2.61 L and subjects were using an average of 4 puffs per day of Proventil at baseline (range 4.02 -4.18 puffs/day).

At Endpoint, the change from baseline in FEV_1 improved 14.8% and 14.2% in the MF 200 mcg and 400 mcg Q AM groups compared to 2.5% in the placebo groups. There was no difference between the 200 mcg Q AM and the 400 mcg Q AM dose except at Week 8 when the 200 mcg Q AM dose was numerically better. Subjects with $FEV_1 < 75\%$ at baseline (n =126) showed a slightly better response [change from baseline in FEV_1] with the 400 mcg Q AM dose than with the 200 mcg Q AM dose (18.6% vs. 16.9%). Whereas, for subjects with $FEV_1 > 75\%$ predicted the reverse was seen (11.5% with the 200 mcg Q AM dose vs. 8.5% with the 400 mcg Q AM dose).

The sponsor assessed symptoms as "AM wheezing" and "difficulty breathing and compared the change from Baseline to Endpoint in the score based on the following scale:

0 = None 1 = Noticeable
2 = Annoying 3 = Very uncomfortable

The mean Baseline asthma symptom scores ranged from 0.97 – 1.03 ("noticeable") with minimal changes at Endpoint that were difficult to qualify as clinically meaningful. [Medical Officer Review Sept 8, 1999, pgs 41 -42]

2.2. Studies in Asthmatic Subjects Previously Maintained on Inhaled Corticosteroids

The sponsor conducted six studies - C96-134, C96-168, C96-196, I96-111, I96-112, and I96-113 in asthmatic subjects who were maintained on inhaled corticosteroids. These studies were randomized, double-blind parallel group placebo and [in some studies] active controlled studies. Studies C96-134 and C96-168 used BDP 168 mcg BID as an active comparator and compared MF DPI 100 and 200 mcg BID (study C96-168) and MF DPI 100, 200 and 400 mcg BID (study C96-134) to placebo. Study I96-111 used fluticasone propionate powder 250 mcg BID and study I96-112 used budesonide powder 400 mcg BID as active comparators. The other two studies C96-196 (evaluating MF DPI 200 mcg QD AM, 200 mcg QD PM, 400 mcg QD AM and 200 mcg BID) and I96-113 (evaluating MF DPI 200 mcg, 400 mcg and 600 mcg BID) were only placebo-controlled and did not include active comparator arms.

The studies discussed in the sponsor's proposed label are described below.

2.2.2. Study C96-196 "Placebo –Controlled Efficacy and Safety Study of Mometasone Furoate Dry Powder Once Daily Vs. Twice Daily in Asthmatic Subjects Previously Maintained on Inhaled Corticosteroids."

In this randomized placebo-controlled study patients who were maintained on ICS [flunisolide 1000-2000 mcg/day, triamcinolone 600 – 1600 mcg/day, beclomethasone 252-840 mcg/day or fluticasone propionate 176 – 440 mcg/day] were treated with MF DPI 200 mcg (100 mcg x 2 actuations) Q PM or Q AM; 200 mcg (200 mcg x1)BID; 400 mcg (200 mcg x 2) QD AM or placebo for 12 weeks. Prior to randomization to MF DPI, patients

discontinued their prescribed ICS and were treated in an open-label fashion with MF DPI 200 mcg (100 mcg x 2 actuations) BID x 2 weeks.

The mean FEV_1 (L) at baseline ranged from 2.49 L – 2.75 L (mean 2.62 L). Of the 307 subjects enrolled in the study, 21 (7%) discontinued during the 2 week run-in period. Therefore, a total of 286 subjects were randomized to double-blind treatment. The pre-specified endpoint for the study was change in FEV_1 from Baseline to Endpoint. the sponsor also evaluated change from pre-Baseline (when all subjects were treated with MF DPI 200 BID) to Baseline and pre-Baseline to Endpoint.

For Baseline to Endpoint the 200 mcg QD PM, 200 mcg BID, and 400 mcg QD AM arms all had a statistically significant improvement in FEV_1 compared with placebo and 200 QD AM and no differences between the 200 QD PM, 200 BID or 400 QD AM arms were observed at Endpoint. The 200 QD AM arm was not statistically different from placebo. The FEV_1 decreased 9.8% in the placebo group and 8.4% in the 200 mcg Q AM group, whereas the FEV_1 was maintained in the other treatment groups with an improvement of 1.5% in the 200 mcg QD PM group, and a trivial inconsequential decrease of 1.4% in the 400 QD AM group and 0.6 % in the 200 BID group.

For Pre-Baseline to Endpoint, there was also a statistically significant improvement in FEV_1 for all the treatment groups except the 200 mcg QD AM group.

2.2.3. Study C-96-134

This was a randomized double-blind 12-week treatment study in which patients previously maintained on ICS [flunisolide 1000 -2000mcg; triamcinolone 600 -1600mcg; beclomethasone dipropionate 252 – 840 mcg; and fluticasone propionate 176 -440 mcg] were treated for 12-weeks with MF DPI following a 2-week Screening period where patients continued to take their usual dose of previously prescribed ICS. The doses of MF studied in this trial were MF 100 mcg BID, 200 mcg BID or 400 mcg BID compared to placebo, or BDP(MDI) 168 mcg BID. At baseline the mean FEV_1 percent predicted was similar to that seen in the other studies (mean range 2.49 – 2.61 L [average 2.6 L; 76% predicted normal]). Patients receiving MD 200 mcg BID had an improvement of 7.1% in FEV_1 at Endpoint over Baseline compared to a decrease of 6.6% in the placebo group. Subjects treated with 400 mcg BID had a 6.2% increase in FEV_1 while subjects treated with MF 100 mcg BID had a 4.8% increase. Subjects treated with BDP 168 mcg BID had a 3.0% increase in FEV_1 over Baseline at Endpoint.

With respect to rescue medication the Medical Officer review indicates that all the treatment groups used less Proventil than the placebo group. Specific data are not provided *(See Medical officer review Page 216).* For asthma worsenings (defined based on FEV_1, PEFR, rescue albuterol use) 54% (40/74) of patients in the placebo group had asthma worsenings compared to 13% (22/144) in the MF 200 BID and 400 BID treatment groups. Although this is a secondary endpoint which was not corrected for multiple comparisons, the magnitude of the difference (> 4-fold) can be considered significant.

2.3. Patients Maintained on Oral Corticosteroids

2.3.1. Study C96-137; " Placebo-Controlled Efficacy and Safety Study with Long-Term Safety Evaluation of Mometasone Furoate Dry Powder in Reducing Oral Steroid Requirements in Subjects with Severe Asthma."

This study was conducted in asthmatic patients who were previously maintained on oral corticosteroids and were treated for 12 weeks with MF 400 BID or 800 BID. The trial also had a long-term safety extension where patients were continued on MF 800 BID for 9 months in an open-label fashion. The average mean prednisone dose for patients enrolled in the study was 11.83 mg/day and ranged from 4.0-35 mg/day. Patients were also taking ICS (BDP 168- 840 mcg/day; budesonide 800 -1600 mcg/day; flunisolide 1000 – 2000 mcg/day; fluticasone 440 -1760 mcg/day or triamcinolone 400-2400 mcg/day). A total of 132 patients were randomized for the 3 month treatment phase. Subjects were diagnosed with severe asthma with an average mean FEV_1 of 1.81 L (59% predicted)

Both MF DPI treatment groups were significantly ($p<0.01$) more effective than placebo in reducing daily prednisone requirements at Endpoint. At Endpoint, the mean % reduction of prednisone use was 46.0% and 23.9% in the 400 and 800 BID groups respectively. For placebo-treated patients, mean prednisone requirements increased by 164.4%. FEV_1 (change from Baseline to Endpoint increased 14.0% in the 400 mcg BID group and 9.5% in the 800 BID group whereas, FEV_1 decreased by 12 % in the placebo group.

The secondary efficacy variables use of rescue medication and asthma worsenings showed favorable results for the MF treatment groups compared to placebo *(Note: Specific numbers (puffs/day) for rescue medication use were not stated in the primary MO review).* With respect to asthma worsening 35% (15/43) of subjects in the placebo group had asthma worsening compared to 4% (2/45) of subjects in the MF 400 BID group.

In the 3-month treatment period adverse events occurring at an incidence of 3% or greater in the MF 400 BID group and which occurred more frequently than the placebo group without regard to causality are shown in the table below

Table 1. Adverse Events Occurring at an Incidence of 3% or Greater in the MF 400 BID Group and Which Occurred More Frequently than the Placebo Group Without Regard to Causality

Adverse Event [n (%)]	MF 400 mcg BID (n = 46)	Placebo (n= 43)
Upper respiratory tract infection	7 (15)	6 (14)
Musculoskeletal pain	10 (22)	6 (14)
Candidiasis	10 (22)	4 (9)
Sinusitis	10 (22)	8 (19)
Fatigue	6 (13)	1 (2)

Adverse Event [n (%)]	MF 400 mcg BID (n = 46)	Placebo (n= 43)
Depression	5 (11)	0

2.4. Once Daily Dosing Studies

The sponsor initially sought a once daily dosing regimen in subjects previously on bronchodilators alone (200 mcg QD, or 400 mcg QD) or inhaled corticosteroids (400 mcg QD). The studies with once daily dosing regimens were:

- In asthmatics on bronchodilators alone:
  - C96-136 (MF 200 mcg and 400 mcg QD AM)
  - C96-186 (MF 200 mcg QD AM, 200 mcg BID, and 400 mcg QD AM)
- In asthmatics previously maintained on inhaled steroids:
  - study C96-196 (MF DPI 200 mcg QD AM, 200 mcg QD PM, 400 mcg QD AM and 200 mcg BID)

The data were inconclusive for the 200 mcg QD dosing regimen. Firstly, of the three studies that evaluated MF 200 mcg QD AM only one (C96-136) demonstrated statistical superiority to placebo. Secondly, in all the studies the 200 mcg QD dose was administered using the 100 mcg formulation which is not one of the to-be-marketed formulations. In study C96-196 MF 200 mcg QD PM was statistically superior compared to placebo but this efficacy finding was not replicated. It is important to note that in study C96-196 spirometry was essentially performed 12 hours after the dose was administered and not 24 and therefore does not represent end of dosing interval efficacy. However, PM PEFR evaluated as a secondary endpoint was superior to placebo.

For the 400 mcg (2 puffs x 200 mcg) QD AM dosing , efficacy was established compared to placebo in studies C96-136 and C96-186 [patients maintained on bronchodilators alone] and study C96-196 [subjects maintained on inhaled corticosteroids].

3. Updated Response to Comment 1 of the Approvable Letter Dated 10/1/1999

3.1. FDA Comment 1

The following was relayed to the sponsor as part of the approvable letter dated October 1, 1999 to the original NDA.

The efficacy of the 200 mcg QAM dose has not been sufficiently demonstrated as it failed to significantly improve FEV_1 in 2 out of 3 trials in which it was studied. The 200 mcg QPM dose appeared effective in a single trial, but was not replicated. In addition, none of these studies utilized the 200 mcg product. In order to support the efficacy of 200 mcg QAM and /or 200 mcg QPM dosing, additional efficacy trials with the to-be-marketed 200 mcg formulation are required.

3.1.2. Sponsor's Original Response to Comment 1

In response to the approvable letter dated October 1, 1999, the sponsor submitted a response to the clinical comments on December 1, 1999. The following was the sponsor's response to Comment 1 at that time.

We will remove the 200 mcg dose recommendation from the labeling at this time. We have recently completed an additional study of 200 mcg QPM using the 200 mcg product in patients previously maintained on β_2-agonists alone. Results of this study confirm a significant effect of this regimen relative to placebo. We intend to submit this information for incorporation into labeling post-approval.

3.1.3. Sponsor's Updated, Current Response to Comment 1

Since the initial response, the sponsor now states,

Two additional studies have been completed which we believe demonstrate that 200 mcg per day, dosed in the evening, provides effective asthma control for many patients. Since treatment guidelines and inhaled corticosteroid labeling support the desirability of titrating to the lowest effective dose, we believe it is important to revisit this lower daily dose in the context of the currently available data. The updated response contains an overview of the applicable data with 200 mcg QD PM dosing, and new clinical study reports C98-475 and P01545.

3.2. Financial Disclosures for Studies C98-475 and P01545 [N-000-BM/2/6/04]

For study C98-475, the Applicant was unable to obtain financial disclosure information from 35 out of 87 investigators. It is therefore difficult to make any assessments as to the impact of financial compensation on the results of the study. From the available financial disclosure data, three principle investigators had significant financial disclosures. Dr. [ ] and Dr. [ ] disclosed significant equity in Schering Plough (>$50,000). Dr. [ ] enrolled subjects — and Dr. [ ] enrolled — subjects — in this study. Dr. [ ] reported receipt of significant (>$25,000) payments from Schering-Plough as honoraria, grants, etc.; his site enrolled ~subjects —. There were no formal analyses by the Applicant to re-analyze the data excluding each of these centers. Since each site enrolled ~ of subjects in the study, it is doubtful that this would impact the final results to any significant degree. However, given that the financial disclosure information for 35 sub-investigators is unavailable for review, the impact of financial disclosures on the final results is unknown.

For study PO1545, 4 out of 51 principal investigators (197 total investigators include sub-investigators) had significant financial disclosures; however, it is doubtful that these would significantly impact the results of the study, although no formal analyses were performed. Dr. [ ] and Dr. [ ] disclosed significant equity in Schering-Plough (>$50,000) and enrolled ~ subjects — and ~ subjects —, respectively. Dr. [ ] and Dr. [ ] disclosed receipt of significant payments in terms of lectureships, grants, honorarias, etc. and enrolled ~ subjects ~ and ~ subjects ~ respectively. Although no formal analyses were performed to assess the effects of data from these sites on the final

results, it is doubtful that few numbers of subject enrolled at each of these sites would account for any significant change in the final analyses.

3.3. Study C98-475, Placebo-Controlled Efficacy and Safety Study of a Once-Daily, PM Regimen of Mometasone Furoate Dry Powder in Asthmatics Previously Maintained on Short-Acting Inhaled β_2-Agonists

Protocol #:	C98-475
Title:	Placebo-Controlled Efficacy and Safety Study of a Once-Daily, PM Regimen of Mometasone Furoate Dry Powder in Asthmatics Previously Maintained on Short-Acting Inhaled β_2-Agonists
Study Dates:	Initiated December 23, 1998. Completed June 29, 1999.
Sites:	18 sites in the United States
Investigators:	18 Principal Investigators
IRB:	The protocol, protocol amendments, and subject informed consent form were reviewed by an Institution Review Board for each center.
Ethical Considerations:	The investigators agreed to conduct this study according to the principles of Good Clinical Practices (GCP).

Source: Vol. 7, p. 2, 17

3.3.1. Study Design/Protocol

3.3.1.1. Objectives

The objective of this study was to evaluate the efficacy and safety of mometasone furoate dry powder inhaler (MF DPI) 200 mcg daily QD PM (once daily dosing in the evening) compared to placebo QD PM in subjects with asthma who were previously maintained on short-acting inhaled β_2-agonists alone. [Vol. 7, p. 19]

3.3.1.2. Description

This was a 12-week, multi-center randomized, double-blind, parallel-group, placebo-controlled study evaluating the efficacy and safety of mometasone furoate dry powder inhaler (MF DPI) 200 mcg daily QD PM (once daily dosing in the evening) compared to placebo QD PM in 195 males and females ages 12 to 66 years with asthma. The study was conducted in the United States from December 23, 1998 to June 29, 1999.

3.3.1.3. Population

The study was designed to recruit 8-16 adults and adolescents who were currently maintained on only short-acting β_2 agonists from 18 centers to ensure that at least 160 patients were eligible for evaluation of the primary efficacy endpoint. The inclusion and exclusion criteria used for study entry follow.

3.3.1.3.1. Inclusion Criteria

Patients were eligible for study entry if:

1. they were 12 years of age or older of either gender and of any race (with the exception of Center 13, where patients had to be aged 18 years or older)
2. they had a history of asthma of at least 6 months duration
3. they had a Baseline FEV_1 greater than or equal to 55% and less than or equal to 85% of predicted at the Screening and Baseline visits
4. they demonstrated evidence of an increase in absolute FEV1 of $\geq$12%, with an absolute volume increase of at least 200 mL, after reversibility testing at Screening or within the past 12 months
5. they had been using only short-acting inhaled β_2 agonists to control their asthma for the 2 weeks prior to Screening
6. they used Proventil® for acute relief of symptoms of bronchospasm on an average of at least three times per week during the run-in-period
7. their laboratory tests (CBC, chemistries, and urinalysis) within normal limits or clinically acceptable to the investigator
8. they were free of any clinically significant disease (other than asthma)
9. they (or parents/guardians where applicable) gave consent and were able to adhere to the protocol
10. they had informed their usual treating physician (if other than study investigator) of their participation in the study
11. they were non-pregnant women of childbearing potential who were using a medically acceptable, adequate form of birth control. This included: 1) hormonal contraceptive as prescribed by a physician (e.g. oral combined, hormonal implant, depot injectable) 2) medically prescribed IUD; 3) condom in combination with a spermicide; 4) monogamous relationship with a male partner who had a vasectomy

3.3.1.3.2. Exclusion Criteria [Vol. 7, p. 23-24]

Patients were excluded from the study if:

1. they were pregnant, lactating, or premenarcheal females
2. they were treated with inhaled corticosteroids for asthma within the 3 months prior to screening
3. they had been treated with methotrexate, cyclosporin, gold, or other cytotoxic agents, for the control of asthma or for a concurrent condition within the last 3 months
4. they had required daily or alternate-day oral corticosteroid treatment for more than a total of 14 days during the 6 months immediately prior to screening, and /or had required a burst of systemic steroids within the previous 3 months
5. they required the daily use of nebulized β_2-agonists or any use of long-acting inhaled β_2-agonists
6. they were unable to use the MF DPI device
7. they had used any investigational drug within the last 30 days or any investigational antibody for asthma or rhinitis within the past 3 months
8. they had received 6 or more months' treatment with fenfluramine or dexfenfluramine, alone or in combination with phentermine, prior to Screening

9. they were receiving escalating doses of immunotherapy, oral immunotherapy or short course (rush) immunotherapy
10. they had been taking any of the restricted medication prior to Screening (see section on prohibited medications)
11. they could not adhere to the concomitant medication prohibitions
12. they had participated in this same study at another investigational site or in any other investigational study at the same time
13. they had been randomized into the study more than once
14. they were a person or minor child of a person, directly associated wit the administration of the study
15. they had an allergy to corticosteroids or Beta-agonists
16. they had required inpatient hospitalization for asthma control within the previous three months
17. they had required ventilator support for respirator failure secondary to their asthma within the last 5 years
18. they had been treated in the ER (for a severe asthma exacerbation), or admitted to the hospital for management of airway obstruction on two or more occasions within the last 6 months
19. they had clinical evidence of emphysema, chronic bronchitis, bronchiectasis, or cystic fibrosis
20. they had 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, may interfere with the study , or required treatment which may interfere with the study (i.e. cancer within the last 10 years, insulin-dependent DM, hepatitis, history of glaucoma and/or posterior subcapsular cataracts)
21. they had an increase or decrease in FEV_1 of $\geq$20% between Screening and Baseline visits
22. they required the use of > 12 inhalations per day of Proventil® on any 2 consecutive days between screening and baseline
23. they had experienced an upper or lower respiratory tract infection (viral or bacterial within the previous 2 weeks prior to screening and baseline visits
24. they had any clinically relevant abnormalities in baseline vital signs, ECG (or within the past 30 days) or chest x-ray (or within the past year)
25. they had evidence on physical examination of clinically significant oropharyngeal candidiasis
26. they had obstructive sleep apnea
27. they were smokers or ex-smokers who had smoked in the previous 6 months
28. they were know to be HIV positive (HIV testing was not done at Screening)
29. they were know illicit drug abusers

3.3.1.4. Treatments

3.3.1.4.1. Study Treatments

At the baseline visit, all patients meeting the eligibility criteria were randomized to 12 weeks of treatment with one of the following:

- Mometasone furoate: 200 mcg/puff; 1 inhalation in the PM
- Placebo: 1 inhalation in the PM

3.3.1.4.2. 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 (6-hour withhold period prior to study visits was changed to a 4-hour washout period after study completion and prior to unblinding)
- Nebulized β_2 agonists
- Topical nasal or ocular decongestants, nasal or ocular cromolyn, nasal ipratropium bromide, nasal or ocular antihistamines
- Short-acting pseudoephedrine formulations (30mg), up to a total daily dose of 120 mcg/day; a 24 hour washout period prior to each study visit
- Oral antihistamines (except astemizole or terfenadine)
- Immunotherapy if they were on a stable maintenance schedule for at least one month prior to the screening visit
- Mild potency topical corticosteroids for dermatologic conditions
- Vaccines were allowed with a two-week washout period prior to study visit
- Otic mild-potency corticosteroids
- Antidepressant selective serotonin re-uptake inhibitors such as fluoxetine and sertraline
- Tricyclic antidepressants
- Sumatriptan
- Ritalin

3.3.1.4.3. Excluded Therapies

Patients were excluded from the study and instructed not to use any of the medications listed in the table below. In addition, no patients could receive any medications linked with clinically significant incidence of hepatotoxicity or which might cause significant liver

enzyme induction, oral or non-selective ophthalmic preparations of beta-blockers, oral or RUSH immunotherapy, or monoamine oxidase inhibitors after screening.

Table 2. Study C98-475, List of Excluded Medications

Excluded Medication	Washout Period
Methotrexate, cyclosporin, gold, and other cytotoxic agents	3 months
investigational antibodies for asthma or rhinitis	3 months
Any systemic bursts of oral or intravenous corticosteroids	3 months
Inhaled corticosteroids	3 months
Intramuscular or intra-articular corticosteroids	3 months
Astemizole	3 months
Investigational drugs	1 month
corticosteroids, high potency dermatological, plain or in combination	1 month
Fenfluramine, dexfenfluramine, phentermine	1 month
Beta-adrenergic bronchodilators: syrup, plain and sustained-release tablets, long-acting/inhaled	2 weeks
Theophylline	2 weeks
Inhaled cromolyn sodium or nedocromil	2 weeks
Ipratropium bromide, aerosol or nebulized or combination with albuterol	2 weeks
Nasal or Ocular Corticosteroids	2 weeks
Influenza or other vaccines	2 weeks
Long-acting oral decongestants	24 hours
Immunotherapy for rhinitis (only if on stable maintenance)	24 hours
Antihistamines (unless used daily, then is allowed without washout)	24 hours
β_2-agonists: short acting inhaled and nebulized	6 hours

Source: Vol. 7, p. 32

3.3.1.4.4. Withdrawal of Patients from Therapy or Assessment [vol. 7, p. 26]

Patients were withdrawn from the study if:

1. they experienced a clinically significant worsening of asthma defined as one of the following:
    a. twenty percent or greater decrease in FEV_1 (absolute value) from the baseline value (this was changed to 20% or greater during the conduct of the study)
    b. twenty-five percent of greater decrease in AM or PM peak flow from the mean AM baseline value on 2 consecutive days (this was changed to 25% or greater during the conduct of the study)
    c. clinically significant increase in use of bronchodilator (e.g. use of > 12 puffs of albuterol or > 2 nebulized treatments on any 2 consecutive days)
    d. clinical asthma exacerbation requiring emergency treatment, hospital admission (serious AE) or treatment with additional asthma medication (other than short-acting β_2-agonists)

2. they became pregnant
3. chose to withdraw at their discretion

3.3.1.4.5. Treatment Compliance

Compliance was evaluated at each visit by asking subjects and /or parent/guardian whether medication was taken as instructed and by reviewing diary cards for medication usage.

3.3.1.4.6. Use of Rescue Treatment

All patients were provided with Proventil® to be used on a prn basis for asthma symptoms. All inhalers were to be examined at each visit and the diary reviewed in addition to questioning the patients on the frequency of rescue medication use.

3.3.1.5. Conduct

This multicenter, randomized, double-blind, placebo-controlled, parallel group study consisted of a screening visit (Visit 1), Baseline visit (Visit 2, Day 1), follow-up visits (Visits 3-6 corresponding to Days 8, 15, 29 and 56, respectively), and a final visit (Visit 7).

Patients meeting eligibility criteria at screening were randomized equally to either mometasone furoate dry powder inhaler (MF DPI) 200 mcg once daily in the PM or to placebo once daily in the PM in a 1:1 ratio at Visit 2. Patients were instructed to take the medications once daily for 12 weeks. Complete histories, physical examinations, reversibility testing, vital signs, spirometry, EKG, chest x-ray, and laboratory analyses were performed at screening, and physical examination and laboratory testing were repeated at the final visit. Vital signs, pulmonary function testing, oropharyngeal exam, pulmonary auscultation, and adverse event review were performed at all treatment phase visits.

The following table summarizes the study sequence.

Table 3. Study A377-1001, Study flow chart

Phase	Screening	Treatment					
Visit	1	2 (Baseline)	3	4	5	6	7
Day	-14 to -7	1	8	15	29	57	85
Signed informed consent	✓						
Inclusion/exclusion criteria	✓	✓					
Medical History	✓						
Concomitant medication review	✓	✓	✓	✓	✓	✓	✓
Physical exam	✓					✓	
Vital signs	✓	✓	✓	✓	✓	✓	✓
Oropharyngeal exam	✓	✓	✓	✓	✓	✓	✓
Pulmonary auscultation	✓	✓	✓	✓	✓	✓	✓
Pulmonary function testing	✓						
Reversibility testing	✓						
Hematology, Chemistry, U/A,	✓	review					✓

Phase	Screening	Treatment					
Visit	1	2 (Baseline)	3	4	5	6	7
Day	-14 to -7	1	8	15	29	57	85
pregnancy test							
EKG	✓	review					
Chest X-ray	✓	review					
Dispense Peak Flow Meter	✓						
Dispense Diary	✓	✓	✓	✓	✓	✓	
Review Diary		✓	✓	✓	✓	✓	✓
Dispense/retrieve rescue medication	✓	✓	✓	✓	✓	✓	✓
Dispense study inhalers		✓					
Evaluation of response to therapy			✓	✓	✓	✓	✓
Adverse Events		✓	✓	✓	✓	✓	✓
Review compliance		✓	✓	✓	✓	✓	✓
Collect Study Inhalers							✓

Source: vol. 7, p. 21

3.3.1.6. Efficacy Assessments

Efficacy was assessed by the following measurements:

- Pulmonary Function Testing: spirometry was performed at all visits and three measurements were done. The sponsor does not specify the time of procedure with respect to dosing. The primary efficacy variable was FEV_1.

Reviewer's comments: the sponsor has not specified when the spirometry was done with respect to dosing. This is important to evaluate for end of dosing interval [EODI]. In lieu of this, the evening PEFR prior to dosing would be a useful objective parameter Additional support for EODI may come from the evaluation of PM asthma symptoms.

- Peak Expiratory Flow Rate (PEFR): each patient was given a diary card and a Peak flow Meter. PEFR were to be done twice a day and the best out of three was to be recorded in the diary. The evening PEFR was to be done approximately 12 hours after the morning PEFR and prior to taking medication.
- 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:
  - 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 or al o f normal daily activities/sleep
- Nocturnal Awakenings: patients recorded the number of times they were awakened at night from asthma symptoms, regardless of the need for Proventil® therapy

- Rescue Medication use: patients were also required to record the number of inhalations of Proventil® and or nebulized β_2-agonists used in each 24-hour period
- Assessment of Response to Therapy: the investigator or designee assess the patient's response to therapy using the following scale:
  - 1 = much improved
  - 2 = improved
  - 3 = no change
  - 4 = worse
  - 5 = much worse

3.3.1.7. Safety Assessments

Safety was assessed by history and physical examinations (including height and weight), blood and urine laboratory tests, and measurements of vital signs (BP, oral temperature, heart rate, respiratory rate). Screening laboratory tests included hemoglobin, hematocrit, white blood count with differential, urinalysis, serum pregnancy test (all females), and serum chemistries (and total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, AST, ALT, LDH and cholesterol). Additionally, the sponsor performed oropharyngeal examinations and pulmonary auscultations, spirometry and adverse event review at all visits. A screening EKG and chest X-ray was also performed.

Adverse events were also assessed throughout the study and were defined as any untoward event that occurred during the study, regardless of the association with the test drug administration. The incidence and severity were recorded in the CRFs by the investigator. [vol. 7, p. 39-46]

3.3.1.8. Statistical Plan

The primary objective of this study was to evaluate the efficacy of MF DPI 200 mcg QD QPM compared to placebo. All treatment comparisons were to be made at the 0.05 (two-sided) level of significance without adjustment for multiple comparisons.

3.3.1.8.1. Primary analyses [vol. 7, p. 49-50]

The primary efficacy endpoint was the change from Baseline in FEV_1 to Endpoint (final visit). This was to be analyzed for all randomized patients using ANOVA at Endpoint and for each scheduled visit.

The efficacy of MF DPI 200 mcg was to be established by pairwise comparisons using least squares means (LS Means) of FEV_1 at the 5% significance level.

3.3.1.8.1.1. Changes to Evaluability Criteria

The sponsor has made some changes to the protocol in evaluability criteria. Prior to locking the database and insertion of treatment codes, the sponsor considered that certain minor deviations from the protocol would not be considered violations and would not affect the evaluability of the data. The range for baseline FEV_1 entry criteria was broadened from 55% to 85% inclusive to a slightly wider 50% to 90% inclusive. In addition, reversibility testing was determined to be significant if patients had an increase in FEV_1 of $\geq$10.5% when

the absolute change was ≥200 mL or an increase in FEV_1 of ≥12% when the absolute change was ≥ 180 mL.

Reviewer's comments: It is doubtful that the wider baseline FEV_1 entry criteria will interfere with the final efficacy analyses. In terms of the reversibility testing criteria, in general, it is recommended that patients have at least a 12% or greater change in FEV_1 following bronchodilator. However, since the sponsor has added that if the change is greater than 10.5% with an absolute change of 200 mL (a 200 mL change is also considered significant), this appears acceptable.. Since the change was made prior to breaking the blind, it is doubtful that this change in the protocol would affect the integrity of the data to any meaningful degree. However, it would be interesting to know the reason for this change. The final protocol and amendment section were reviewed in this submission, and an amendment specifically stating to change the entry criteria was not noted.

3.3.1.8.2. Secondary analyses

Secondary efficacy variables included [Vol. 7, p. 46-7]:

1. $FEF_{25-75\%}$
2. FVC
3. PEFR
4. Symptom scores
5. Rescue medication use
6. Nocturnal awakenings
7. Response to therapy
8. Time to worsening of asthma

3.3.1.8.3. Sample size considerations

The sample size was designed to enroll 160 patients (approximately 80 per treatment arm). This size was chosen to detect a 0.26 liter difference between the two treatment arms with 95% power at the 5% significance level, assuming a pooled standard deviation of 0.47 liters for FEV_1 change from Baseline (based on a previously completed study: C96-186).

3.3.1.8.4. Definition of study population

Three analysis populations were planned : intent-to treat (ITT), full analysis, and efficacy evaluable. The intent-to-treat subset was to include all randomized patients who received at least one dose of study medication. The full analysis subset was to include all randomized patients who received at least one dose of study medication and had follow-up efficacy data. The efficacy evaluable subset was to include al randomized patients who met key eligibility and evaluability criteria; confirmatory efficacy analyses were to be based on this subset.

3.3.1.8.5. Assessment of Comparability at Baseline

Comparability of the two treatment groups at Baseline was assessed by comparing the two treatment groups with respect to demographics (sex, age, and race) and disease characteristics (baseline FEV_1 and AM PEFR).

3.3.2. Results

3.3.2.1. Patient Disposition

A total of 196 patients were randomized to 18 centers and 195 received at least one dose of study medication. One patient of the 196 randomized patients was lost to follow-up after the baseline visit and the sponsor has no confirmation if this patient took any study medication. This patient has not been included in any efficacy analyses, and for all both the efficacy and safety evaluations the sponsor lists 195 patients as randomized.

Of the 195 treated patients, a total of 172 (88%) completed the study, with 89 (89%) and 83 (87%) in the MF DPI and placebo treatment groups, respectively. Treatment failure (3%) and lost to follow-up (3%) were the two most common reason for study discontinuation. A greater percentage of patients were lost to follow-up in the MF DPI treatment group (4%) as compared to placebo (1%). However, this will probably not affect the results since the numbers are so low. A greater percentage of patients discontinued secondary to adverse events from the placebo group (3%) as compared to MF DPI (1%). These results are summarized in the table below.

Table 4. Study C98-475, Patient disposition

Status	MF DPI n (%)	Placebo n (%)	Total n (%)
Number of patients randomized	100	95	195*
ITT for efficacy	100	95	352
Number of patients completing study	89 (89)	83 (87)	172 (88)
Number of patients discontinued	11 (11)	12 (13)	23 (12)
Adverse event	1 (1)	3 (3)	4 (2)
Treatment failure	3 (3)	2 (2)	5 (3)
Lost to follow-up	4 (4)	1 (1)	5 (3)
Did not meet entry criteria	1 (1)	3 (3)	4 (2)
Other	2(2)	3 (3)	5 (3)

*A total of 196 patients were randomized; however, one patient was lost to follow up following the baseline visit and the sponsor has no confirmation if this patient took any study medication. The group to which this patient was randomized is not provided.

Source: Vol. 7, p. 57-58

3.3.2.1.1. Protocol Deviations

Of the 195 patients who received treatment, 15 patients (7.7%) had protocol deviations, 5 patients (5.0%) in the MF DPI treatment group, and 10 patients (10.5%) in the placebo treated groups. The most common protocol deviation in either group was failure to discontinue patients who had asthma worsening. A total of 10 patients (5%) were listed with this protocol deviation, 3 patients (3%) in the MF DPI treatment group and 7 (7%) in the placebo treatment group; however, the patient was not invalidated from the study as a result. The other protocol deviations are listed in the following table.

Table 5. Study C98-475, Protocol Deviations

Protocol Deviation	MF DPI n=100	Placebo n=95
FEV_1 values that were not between 50-90% predicted at baseline	0	1 (1)
FEV_1 value exceeded variability criteria (> 20%)	0	1 (1)
No Proventil® use between screening and Baseline	0	1 (1)
Insufficient efficacy data (lost to follow-up)	2 (2)	0
Failure to discontinue patients with worsening asthma from the study	3 (3)	7 (7)
Source: Vol. 7, p. 59-60		

3.3.2.2. Demographics and Other Baseline Characteristics

Demographics

Treatment groups were fairly similar at baseline with respect to total number of subjects, race, height, weight, gender, and age. The study population was predominantly White; 79% of subjects in each treatment group were White. There was a greater representation of Blacks in the placebo group (14%) as compared to MF DPI group (7%). However, in the MF DPI group, there was a greater percentage of Hispanics (11%) as compared to placebo (4%). There was a slightly greater percentage of males as compared to females in both groups (53% vs. 47% in the MF DPI group and 51% vs. 49% in the placebo group). Patients ranged between 12-66 years of age with a mean age for the MF DPI group of 29.7 years and 28.6 years for the placebo group. The majority of the subjects were between the ages of 18-64 years in both treatment groups. Subjects in the 65 years or older category were poorly represented; there was only 1 subject in the MF DPI group and 3 in the placebo group. Twenty-three to twenty-six percent (23-26%) of subjects were under the age of 18 in each treatment group. [Vol. 7, page 63, page 106]

Subjects were fairly similar for baseline asthma characteristics for the most part. In both treatment groups, duration of asthma was similar, ranging form 15.4-15.9 years. The placebo group had a somewhat higher FEV_1 (2.55 liters) at baseline compared to MF DPI (2.64 liters); whereas, the MF DPI group had somewhat higher baseline AM PEFR (370 liters/min) compared to placebo (360 liters/min).

The demographics and baseline asthma characteristics are summarized in the following table.

Table 6. Study C98-475, Demographics and Other Baseline Characteristics

Demographic/Baseline Characteristic	MF DPI n = 100	Placebo n = 95
Age (years)		
Mean	29.7	28.6
Median	26.5	24.0
Range	12.0-65.0	12.0-66.0
Age Distribution		
12-17 years	23 (23%)	25 (26%)

18-64 years	76 (76%)	67 (71%)
≥ 65 years	1 (1%)	3 (3%)
Sex		
Male	53 (53%)	48 (51%)
Female	47 (47%)	47 (49%)
Race		
Caucasian	79 (79%)	75 (79%)
Black	7 (7%)	13 (14%)
Hispanic	11 (11%)	4 (4%)
Asian	2 (2%)	2 (2%)
Other	1 (1%)	1 (1%)
Weight (lbs)		
Mean	168.6	167.1
Median	164.5	160.0
Range	76.0-300.0	72.0-314.0
Height (in)		
Mean	66.3	66.3
Median	67.0	66.0
Range	55.0-74.0	58.0-74.0
Duration of Asthma Condition (years)		
Mean	15.4	15.9
Median	13.0	13.0
Range	1.0-47.0	1.0-57.0
Baseline FEV_1: LS Mean (liters)	2.55	2.64
Baseline AM PEFR: LS Mean (liters/min)	370.15	360.05

Source: Vol. 7, page 63

Reviewer's comments: Given the small percentage of other races studied, safety and efficacy of this drug may not be quite generalizable to the whole American population. There is a possibility that safety concerns pertaining to one race may become evident in post-marketing studies. Additionally, since the 65 years and greater age population was poorly represented, no conclusions may be drawn in this age group from this study.

Of note, the sponsor has not summarized baseline history/concomitant medications. This reviewer has perused the line listings for both and has not noted anything of concern. In general, both treatment groups were similar at baseline for medical history and concomitant medications. [Vol. 14, p. 1076-1133, 1136-1246]

3.3.2.3. Compliance

The patient symptom diary and was used to assess compliance in addition to questioning patients at each visit as to compliance. However, the sponsor did not provide specific criteria for compliance.

The sponsor states that all subjects with the exception of a few were compliant with the scheduled dosing. One subject, C98-475-09/187, was lost to follow up following the Baseline visit and the sponsor has no confirmation that the patient received any study medication. Another subject, C98-475-07/055 was randomized to the placebo group but received the placebo demonstration DPI rather than the double-blind medication and was discontinued from the stud on Day 13]. This subject was included in all safety and efficacy analyses, however. The final subject C98-475-13/150 inadvertently took 2 inhalations of study medication/day between Baseline and Visit 3 for a total of five extra doses. All other subjects were reported to have been compliant.

Reviewer's comments: As the sponsor has not specifically stated compliance criteria, it is difficult to assess what the patient calls compliance. It is difficult to imagine that even a few patients did not miss a few doses during any given week. The sponsor has not provided a summary table of compliance by week; however, this reviewer did peruse the line listings for compliance, and overall, it appears that the subjects were generally compliant.

3.3.2.4. Efficacy Outcomes

3.3.2.4.1. Primary Efficacy Analysis [Vol. 7, p. 65-67]

Efficacy analyses utilized the change between Baseline and Endpoint, and Endpoint was defined as the last assessment during the study. The primary efficacy endpoint was the change from Baseline to Endpoint in FEV_1 and the primary comparison was MF DPI 200 mcg QPM versus placebo. The primary efficacy analysis was performed on all treated subjects based on an ANOVA model with treatment and center effects. Pairwise comparisons were based on t-test from this ANOVA model.

The two treatment groups, MF DPI 200 mcg QPM and placebo, were similar at baseline with respect to FEV_1, although the Baseline FEV_1 LS Mean was slightly higher in placebo (2.55 L vs. 2.64 L for MF DPI and placebo, respectively).

Both treatment groups demonstrated some improvement in FEV_1 as the study progressed; however, the improvement was consistently greater in the MF DPI treatment group. Additionally, significant improvement in FEV_1 was noted at Week 1 which persisted throughout the study. At Endpoint, the LS Mean change from baseline for the MD DPI and placebo treatment groups was 0.43 L and 0.16 L, respectively. The mean % change from Baseline to Endpoint was 16.8% for MF DPI and 6.0% for placebo. The difference in improvement between MF DPI and placebo for LS Mean FEV_1 was statistically significant ($p = 0.0001$).

Although the sponsor used change from Baseline to Endpoint as the primary timepoint, analysis of the data comparing change from Baseline to Week 12 (end of study) also favored MF DPI. The change from Baseline to Week 12 for FEV_1 was 0.47 and 0.20 for MF DPI and placebo, respectively, corresponding to a % change in FEV_1 of 18.5% and 7.6%. This difference in improvement was also statistically significant ($p= 0.0001$).

The results for the primary efficacy variable are summarized in the following table.

Table 7. LS Mean FEV_1 at Baseline and LS Mean Change From Baseline in FEV_1 by Treatment Groups

FEV_1 (Liters)	MF DPI n = 100	Placebo n = 95	Outcomes Delta	Outcomes p-value
	LS mean (Mean% change)		MF DPI vs. Placebo	
Baseline	2.55	2.64		
Change from Baseline				
Week 1	0.29 (11.7)	0.10 (4.3)	0.19	<0.01
Week 4	0.38 (15.7)	0.15 (6.7)	0.23	<0.01
Week 8	0.47 (18.5)	0.20 (7.6)	0.27	0.0001
Week 12	0.47 (18.5)	0.20 (7.6)	0.27	0.0001
Endpoint	0.43 (16.8)	0.16 (6.0)	0.27	0.0001

Source: Vol. 7, p. 66, Vol. 10, p. 1376

Reviewer's comments: This study demonstrates that for the primary efficacy variable FEV_1, MF DPI 200 mcg QPM shows consistent efficacy over time in steroid-naïve patients which is noted at Week 1 and persists throughout the study period..

3.3.2.4.1.1. Subgroup Analysis for Primary Efficacy Variable by Sex, Age, and Race

The sponsor addressed subgroup analyses for the primary efficacy variable in relation to sex, age, and race. Results in males and females were similar to those described for the overall general population–changes in FEV_1 were significantly better in those subjects taking MF DPI as compared to placebo. No gender differences in efficacy were noted. In terms of age and race, the sponsor was unable to perform subgroup analyses since there were too few subjects aged 12 to 17 years (48 subjects), 65 years and older (4 subjects), and of a noncaucasian race (41) to permit meaningful comparisons. The sponsor does state that in general there is no indication to suggest that efficacy in these subsets was different from the overall results.

3.3.2.4.1.2. Response by Baseline Severity of Asthma

Response was evaluated in subjects whose Baseline FEV_1 was either greater than or equal to 80% predicted or less than 80% predicted. This analysis revealed that subjects who received MF DPI and had baseline FEV_1 <80%, demonstrated significant improvements in change from Baseline FEV_1 to Endpoint as compared to placebo. This, however, was not demonstrated in subjects whose Baseline FEV_1 was > 80%, suggesting that 200 mcg QPM should not be recommended for subjects with mild asthma.

3.3.2.4.2. Secondary Efficacy Analyses

As with the primary efficacy analyses, the secondary efficacy analyses evaluated the change from Baseline to Endpoint in all subjects who received treatment. The following parameters were evaluated as secondary variables:

- $FEF_{25-75\%}$

- FVC
- PEFR
- Symptom scores
- Response to therapy
- Rescue medication use
- Nocturnal awakenings
- Time to worsening of asthma

The other PFT variables $FEF_{25-75\%}$ and FVC supported the efficacy of MF DPI over placebo. Both variables were similar at baseline and the improvements seen in them were numerically greater in subjects in the MF DPI treatment group as compared to placebo.

Similarly, AM and PM PEFR analyses favored MF DPI over placebo. All subjects measured PEFR in the morning and again in the evening prior to dosing. Morning and evening PEFR were similar at baseline between both treatment groups. Although both treatment groups tended to show improvement in AM and PM PEFR, the improvements in AM and PM PEFR were numerically greater for MF DPI than placebo. For AM PEFR, the LS Mean changes from Baseline to Endpoint for MF DPI and placebo were 32.91 L/min (10%) and 10.41 L/min (3.2%), respectively. For PM PEFR, the results for MF DPI and placebo were 24.96 L/min (7.1%) and 8.67 L/min (3.7%), respectively. The PEFR results are summarized in the following table.

Table 8. Study C98-475, AM and PM PEFR (L/min) and Change from Baseline to Endpoint

	MF DPI 200 mcg Q PM			Placebo		
	Number of Subjects	AM PEFR (mean% change)	PM PEFR (mean% change)	Number of Subjects	AM PEFR (mean% change)	PM PEFR (mean% change)
Baseline	99	370.15			360.05	
Change from Baseline						
Week 1	99	15.70 (4.9)	9.15 (3.0)	94	5.92 (1.8)	3.87 (2.0)
Week 4	95	29.00 (8.4)	20.98 (6.5)	94	8.98 (2.4)	4.99 (2.8)
Week 8	91	37.66 (10.5)	28.66 (7.7)	87	12.93 (2.9)	13.16 (3.9)
Week 12	88	38.77 (11.2)	31.39 (8.4)	83	17.81 (4.8)	15.07 (5.0)
Endpoint	99	32.91 (10.0)	24.96 (7.1)	95	10.41 (3.2)	8.67 (3.7)

Source: Vol. 7; p. 71, 230

Reviewer's comments: For the primary efficacy variable, the sponsor did not specify the time of the PFT in relation to dosing. This reviewer assumes it was some time during the day, prior to evening dosing at home, when the office visits took place. Nonetheless, it is reassuring to note that the improvements from Baseline to Endpoint in PM PEFR (prior to evening dose) were better for MF DPI than placebo. This reviewer has focused on PM PEFR as this is the only objective assessment of end of dosing interval. As can be noted in the above table, the improvements in PM PEFR are numerically lower for both treatment groups compared to AM PEFR; this is not unexpected to some degree since PM PEFR

represent end of dosing interval results. This reviewer considers the differences in improvement between MF DPI and placebo in PM PEFR as additional support for once daily dosing.

Asthma symptoms were also assessed throughout the treatment. The symptoms of wheezing, difficulty breathing, and cough were rated on a scale from 0 (none) to 3 (very uncomfortable and interfered with most or all of normal daily activities/sleep). Morning, evening, and average daily symptoms scores were evaluated. For both treatments, the symptoms scores decreased with treatment; however, the decreases from Baseline to Endpoint were numerically larger in subjects receiving MF DPI as compared to placebo for all three of the symptoms. Again, this variable tended to favor MF DPI as well.

In addition to subjects rating their symptoms, the physician or designee also assessed the subject's response to therapy. In the physicians' opinion, 66% of subjects improved in the MF DPI treatment group as compared to 56% in the placebo.

In terms of rescue medication use and number of nocturnal awakenings, the results tended to favor MF DPI somewhat over placebo. Baseline mean puffs for Proventil® use were 3.26 puffs in the MF DPI treatment group and 3.18 in the placebo group. At endpoint, the mean change from baseline in the MF DPI treatment group was -1.34 puffs and in the placebo group was -1.11. Between Baseline and Endpoint, the use of rescue medication decreased by 44.2% in the MF DPI treatment group and 29.1% in the placebo group. Similarly, the number of nocturnal awakenings decreased by 0.17 in the MF DPI group as compared to 0.04 in the placebo group.

Reviewer's comments: For Proventil® use, this reviewer perused the line listings and it is apparent that most patients (60%) used rescue medication on a daily basis from 1 to 9 puffs per day in the MF DPI treatment group, compared to 66% in the placebo group. [Vol. 14, p. 1247-1397] Although the mean decrease from baseline in puffs used was greater in the MF DPI treatment group as compared to placebo, the findings in individual line listings was somewhat concerning. Patients on adequate controller therapy usually don't need to use rescue medication on a daily basis and these results would question the clinical utility of once a day MF DPI for treatment control. However, as there were definite improvements in FEV_1, and in some of the other secondary variables in patients taking MF DPI as compared to placebo, to some degree, these results may represent the severity of the population selected. When all the efficacy result are taken into accounts, this degree of rescue medication use becomes somewhat less concerning.

The time to worsening of asthma was evaluated by analyzing those subjects who discontinued the study at the time of their first worsening. The sponsor also included subjects who experienced an asthma worsening but did not discontinue from the study. A total of 20 subjects met this criteria, 9 in the MF DPI group and 11 in the placebo group. The sponsor states that log rank tests showed that the difference between treatment groups was comparable.

Clinical asthma exacerbations (CAE) were infrequent, and were defined as a deterioration of asthma that resulted in emergency treatment, hospitalization, or treatment with additional

asthma medications (other than short acting β_2 agonists). CAEs were reported in three subjects in the MF DPI treatment group and in five in the placebo group.

Analysis of efficacy demonstrates that MF DPI 200 mcg QPM was statistically superior to placebo for the primary efficacy endpoint, change from Baseline to Endpoint in FEV_1, and for the most part, secondary efficacy endpoints tended to favor MF DPI over placebo as well. Both treatment groups were similar at baseline with respect to FEV_1 and demonstrated some improvement in FEV_1 as the study progressed; however, the improvement was consistently greater in the MF DPI treatment group. At Endpoint, the LS Mean change from baseline for the MD DPI and placebo treatment groups was 0.43 L and 0.16 L, respectively. The mean % change from Baseline to Endpoint was 16.8% for MF DPI and 6.0% for placebo. The difference in improvement between MF DPI and placebo for LS Mean FEV_1 was statistically significant ($p = 0.0001$).

3.3.2.5. Safety Outcomes

3.3.2.5.1. Exposure

The sponsor has very briefly described extent of exposure by stating that most subjects in each treatment group completed the 12-week study period. However, the table below shows that most subjects in each treatment group (MF DPI: 91% and placebo: 92%) completed 8 weeks or more; however, only 68 % and 78% of subjects completed 12 weeks or more. Since the sponsor did not provide a more thorough breakdown of exposure, it is difficult to say exactly how many subjects had close to 12 weeks (11 weeks) and how many had more than 12 weeks.

Table 9. Study C98-475, Extent of Exposure

Length of Exposure	MF DPI 200 mcg QPM n=100 (%)	Placebo n=95 (%)
= 1 dose	100 (100)	95 (100)
= 4 days	99 (99)	95 (100)
= 1 week	99 (99)	95 (100)
= 2 weeks	95 (95)	93 (98)
= 4 weeks	94 (94)	89 (94)
= 8 weeks	91 (91)	87 (92)
= 12 weeks	68 (68)	69 (73)

Source: Vol. 7, p. 89

Reviewer's comments: The table provided does not adequately address extent of exposure between 8 and 12 weeks As summarized in the above table, extent of exposure of 68% is less than ideal to provide sufficient exposure to characterize safety. However, this may not be crucial to the safety evaluation, as the sponsor has already performed Phase III pivotal studies, including long-term safety studies that were adequate to support the safety of MF DPI 200 mcg bid.

3.3.2.5.2. Adverse Events

Of the 195 randomized patients, 150 (77%) reported adverse events (AEs). A total of 79 subjects (79%) and 71 subjects (75%) in the MF DPI and placebo treatment groups, respectively, reported adverse events. There were no deaths in this study and 2 serious adverse events, one each in each treatment group. A total of 3 subjects discontinued from the study secondary to AEs, 1 in the MF DPI group and 3 in the placebo group. Most of the AEs were reported to be mild to moderate in severity; however, a total of 13 patients (7%) reported severe/life threatening AEs, 6 (6%) and 7 (7%) in the MF DPI and placebo treatment groups, respectively. The following table summarizes these results.

Table 10. Study C98-475, Overall Adverse Event Summary

	MF DPI 200 mcg n (%)	Placebo n (%)
Randomized	100	95
Subjects with AEs	79 (79)	71 (75)
Subjects with Serious AEs	1 (1)	1 (1)
Subjects with Severe AEs	6 (6)	7 (7)
Subjects discontinued due to AEs	1 (1)	3 (3)
Subjects with dose reduced or temporary discontinuation due to AEs	1 (1)	1 (1)

Source: Vol. 7, p. 89-99

3.3.2.5.2.1. More Commonly Reported Adverse Events

The most frequently reported AEs were headache (28% in each treatment group), rhinitis (18 % in the MF DPI group and 14% in the placebo group), upper respiratory tract infection (14 % in MF DPI group and 13% in the placebo group), pharyngitis (13% in the MF DPI group and 6% in the placebo group), and sinusitis (7% in the MF DPI group and 8% in the placebo group).

Overall, the distribution of adverse events was similar between the two treatment groups, with a few exceptions. Allergy aggravated (MF DPI, 6%; Placebo, 3%) oral candidiasis (MF DPI, 5%; Placebo, 1%) and gastroenteritis (MF DPI, 5%; Placebo, 2%) were more commonly reported in patients taking MF DPI as compared to placebo; however, allergy (MF DPI, 5%; Placebo, 8%) and viral infection (MF DPI, 8%; Placebo, 13%) were more commonly reported in the placebo treated patients. The following table summarizes these results.

Table 11. Study C98-475, Adverse Events Occurring in Greater than or Equal to 3% of Subjects in Any Treatment Group

	MF DPI 200 mcg n=100 n (%)	Placebo n=95 n (%)
Total # of Subjects reporting AEs	79 (79)	71 (75)

	MF DPI 200 mcg n=100 n (%)	Placebo n=95 n (%)
Body as a Whole/General Disorders		
Allergy	5 (5)	8 (8)
Allergy aggravated	6 (6)	3 (3)
Back Pain	2 (2)	8 (8)
Headache	28 (28)	27 (28)
Gastrointestinal System Disorders		
Dyspepsia	4 (4)	5 (5)
Gastroenteritis	5 (5)	2 (2)
Toothache	3 (3)	0
Musculoskeletal Disorders		
Musculoskeletal pain	4 (4)	5 (5)
Myalgia	3 (3)	2 (2)
Reproductive System Disorders		
Dysmenorrhea	4 (8)	3 (6)
Resistance Mechanism Disorders		
Candidiasis	5 (5)	1 (1)
Infection, Viral	8 (8)	12 (13)
Respiratory System Disorders		
Bronchitis	4 (4)	6 (6)
Coughing	2 (2)	3 (3)
Epistaxis	0	4 (4)
Nasal congestion	4 (4)	5 (5)
Pharyngitis	13 (13)	6 (6)
Rhinitis	18 (18)	13 (14)
Sinus congestion	3 (3)	3 (3)
Sinusitis	7 (7)	8 (8)
Upper respiratory tract infection	14 (14)	12 (13)
Vision Disorders		
Conjunctivitis	2 (2)	3 (3)

Source: Vol. 8, p. 463-467

Reviewer's comments: In general, no clinically meaningful differences in adverse events between treatment groups were observed, with a couple of exceptions. Oral candidiasis and pharyngitis were reported more frequently in the active treated group and as MF DPI is an inhaled corticosteroid, it is highly likely that these events were treatment related, especially as many throat irritations and sore throats were coded as pharyngitis. As they are expected, and the overall numbers are low, this is not a cause for concern. However, it does underscore the importance of warning patients to rinse their mouths after use as a preventive measure.

3.3.2.5.2.2. Treatment-Related AEs

Treatment related adverse events as determined by the investigator, occurred in 12 subjects (6%)–7 subjects (7%) in the MF DPI treated group and 5 subjects (5%) in the placebo treated group. The most commonly reported AE was oral candidiasis (reported by 5 subjects in the MF DPI treatment group and 1 in the placebo group). Of interest, dysphonia, judged to be treatment related, was not reported in any patient in the MF DPI treatment group. Other AEs judged to be treatment related are summarized in the following table and were similar between treatment groups.

Table 12. Study C98-475, Incidence of Treatment-Related AEs as Judged by the Investigator

	MF DPI 200 mcg n=100 n (%)	Placebo n=95 n (%)
Total # of Subjects reporting AEs judged to be treatment related	7 (7)	5 (5)
Body as a Whole/General Disorders		
Edema	0	2 (2%)
Headache	0	1 (1%)
Central and Peripheral Nervous System Disorders		
Dysphonia	0	1 (1%)
Platelet, Bleeding, and Clotting Disorders		
Platelet count decreased	1 (1%)	0
Resistance Mechanism Disorders		
Candidiasis	4 (4)	1 (1)
Respiratory System Disorders		
Dry Throat	0	1 (1%)
Pharyngitis	2 (2%)	0

Source: Vol. 7, p. 93

Reviewer's comments: Although the above table relates those AEs judge by the investigator to be treatment related, this reviewer evaluated all of the listed AEs identifying AEs that could possibly be treatment related. In general, corticosteroid related adverse events were low, with the exception of oral candidiasis and pharyngitis (where throat irritation/sore throat were coded as pharyngitis). This reviewer perused the line listings for all of the adverse events, and was unable to find any events of cataracts, glaucoma, contusion/hematomas, DM, hypofunction of hypothalamic-pituitary-adrenal axis, or osteoporosis. There was one fracture; however, it occurred in the placebo treated group. In general, the incidence of more severe effects of systemic corticosteroids was low. [Vol. 12, p. 420-548]

3.3.2.5.2.3. Severe Adverse Events

Most subjects categorized reported adverse events as mild to moderate in severity; however, there were 13 subjects (MF DPI 6%, placebo 7%) who reported severe adverse events.

These AEs were anaphylactic reaction, headache, vertigo, dyspepsia, gastroenteritis, tooth disorder, ovarian cyst, pharyngitis, rhinitis, upper respiratory infection, insect bite and migraine. All but one of these AEs (headache, 2% of subjects in placebo) were reported at an incidence of 1% or less (1 subject) and there were no clinically meaningful differences between the two treatment groups.

3.3.2.5.2.4. Adverse Events by Sex, Age, and Race

The sponsor addressed subpopulation analyses in terms of adverse events by sex, age, and race. No clinically meaningful gender differences were noted for adverse events. The sponsor was unable to perform subpopulation analyses based on age and race as there were too few subjects between ages 12-17 and over 65 and too few noncaucasians to allow a meaningful analyses of adverse events. [Vol. 7, p. 92]

3.3.2.5.3. Deaths, Pregnancies, and Serious Adverse Events

There were no deaths reported for this study. There was one pregnancy, however, it was also listed as an SAE and will be summarized below.

Two patients reported SAEs during this study, one during the Screening period, prior to randomization, and one during the treatment phase in the placebo treatment group. These are summarized as follow:

- Subject C98-475-09/A04 was a 33 year old female (had a tubal ligation previously) who had a positive urine hCG during the screening laboratory testing. Subsequent quantitative analyses and pelvic ultrasound confirmed an intrauterine pregnancy; however, 10 days after positive hCG testing, the patient experienced spontaneous bleeding which resulted in a spontaneous abortion. This was not treatment related as the patient was not randomized into the study and as such had not received any medication.
- Subject C98-475-08/098 was a 14-year old female randomized to the placebo group who was hospitalized for ruptured ovarian cysts. Study medication was discontinued for one day in the hospital and restarted the following day. This event was also not treatment related, since the patient was receiving placebo.

3.3.2.5.4. Withdrawals Secondary to Adverse Events

Four subjects discontinued from the study secondary to an AE, 1 (1%) in the MF DPI treatment group and 3 (3%) in the placebo treatment group. All of these subjects reported AEs of upper respiratory tract infection. No safety signals arise from this information.

3.3.2.5.5. Laboratory, Vitals, PE

While there were some laboratory results outside the normal range, there were no laboratory results considered to be clinically important, and no laboratory adverse events. There were no clinically important abnormalities in physical examinations, vital signs, or ECGs.

3.3.3. Conclusions

Study C98-475 was a 12-week, multi-center, randomized, double-blind, placebo controlled trial in 195 males and females ages 4-11 evaluating the safety and efficacy of mometasone furoate 200 mc g QD compared to placebo. A total of 100 patients were randomized to MF DPI and 95 to placebo. At baseline, there were no clinically meaningful differences in demographic or disease characteristics between the two treatment groups.

Of the 195 treated patients, a total of 172 (88%) completed the study, with 89 (89%) and 83 (87%) in the MF DPI and placebo treatment groups, respectively. Treatment failure (3%) and lost to follow-up (3%) were the two most common reason for study discontinuation. A greater percentage of patients were lost to follow-up in the MF DPI treatment group (4%) as compared to placebo (1%). However, this will probably not affect the results since the numbers are so low. A greater percentage of patients discontinued secondary to adverse events from the placebo group (3%) as compared to MF DPI (1%).

In terms of efficacy, subjects taking MF DPI demonstrated statistically significant differences from Baseline to Endpoint in the primary efficacy variable, FEV_1 (p=0.0001). Similarly, secondary endpoints of FVC, $FEF_{25-75\%}$, and PEFR favored MF DPI as well. Other secondary endpoints of symptom scores, response to therapy, Proventil use, and nocturnal awakenings also demonstrated some, albeit smaller, numerical improvements from baseline to endpoint.

In terms of safety, MF DPI was well tolerated, although the extent of exposure may not have been optimal for safety assessment. Only 68% and 73%, respectively, completed treatment with MF DPI and placebo. Review of the safety data, does not raise any concerns. There were no clinically meaningful differences in the overall incidence or distribution of adverse events between the two treatment groups. The most commonly reported AEs were headache, rhinitis, and upper respiratory tract infection. With the exception of oral candidiasis and pharyngitis, the distribution of AEs in the two treatment groups did not raise any safety concerns. Oral candidiasis and pharyngitis were reported in 5% and 13% of subjects, respectively, in the MF DPI treatment group, as compared to 1% and 6%, respectively in the placebo treatment group. Since these are not unexpected in patients taking inhaled corticosteroids, they do not raise any special concerns. Systemic adverse events of corticosteroids were not seen in subjects taking MF DPI. There were no deaths in this study. There were only two serious adverse events, neither of which were related to study drug administration, since one SAE occurred prior to randomization and the other occurred in the placebo treatment group. No clinically meaningful differences were noted between treatment groups for vital signs, physical examinations, or EKGs.

Overall, this study supports the efficacy and safety of MF DPI 200 mcg QPM.

3.4. Study P01545. Placebo-Controlled Efficacy and Safety Study of Once-Daily PM and Twice Daily Regimens of Mometasone Furoate Administered Via Dry Powder Inhaler in Subjects with Asthma Who Were Previously Maintained on Inhaled Corticosteroids

Protocol #:	P01545
Title:	Placebo-Controlled Efficacy and Safety Study of Once-Daily PM and

	Twice Daily Regimens of Mometasone Furoate Administered Via Dry Powder Inhaler in Subjects with Asthma Who Were Previously Maintained on Inhaled Corticosteroids
Study Dates:	Initiated March 15, 2001. Completed April 9, 2002.
Sites:	45 study centers, 41 in the United States and 4 in Canada
IRB:	The protocol, protocol amendments, and subject informed consent form were reviewed by an Institution Review Board or Independent Ethics Committee for each center.

Sources: Vol. 18, p. 1-3, 17

3.4.1. Study Design/Protocol

3.4.1.1. Objectives

The primary objective of this study was to evaluate the efficacy and safety of MF DPI 400 mcg QD PM (as one inhalation of 400 mcg) compared to placebo. The secondary objective was to compare other dosing regimens with each other and to placebo.

3.4.1.2. Description

This was a 12-week, multi-center, randomized, parallel-group, study with a single-blind placebo/ICS reduction phase, followed by a double-blind treatment phase. This study evaluated the efficacy and safety of mometasone furoate dry powder inhaler (MF DPI) in 400 subjects ages 12 years and older with asthma of at least 12 months duration. The study was conducted mainly in the United States, with a few sites in Canada, from March 15, 2001 to April 9, 2002.

3.4.1.3. Population

The study was designed to enroll 420 subjects from approximately 45 centers to ensure that 400 subjects were eligible for evaluation of the primary efficacy endpoint. The inclusion and exclusion criteria used for the study follow.

3.4.1.3.1. Inclusion Criteria [Vol. 18, p. 24-25]

Patients were eligible for study entry if:

1. they were 12 years of age or older of either gender and of any race.
2. they had a history of asthma of at least 12 months duration.
3. they had a Baseline FEV_1 greater than or equal to 60% at the Screening visit, when all restricted medications were withheld for the specified intervals.
4. they demonstrated evidence of an increase in absolute FEV1 of ≥12%, with an absolute volume increase of at least 200 mL after reversibility testing at Screening or within the past 12 months.
5. they were using inhaled corticosteroids for at least 12 weeks prior to Screening. Two weeks prior to Screening, subjects must have been on a stable regimen of one of the following within the ranges specified below:

a. Beclomethasone dipropionate (HFA or CFC): 168-840 mcg/day
b. Beclomethasone dipropionate (QVAR): 40-320 mcg/day
c. Budesonide: 200-1600 mcg/day
d. Flunisolide: 500-2000 mcg/day
e. Fluticasone propionate: 88-660 mcg/day
f. Triamcinolone acetonide: 400-2000 mcg/day

6. 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 (or parents/guardians where applicable) gave consent and were able to adhere to the protocol.
9. they had informed their usual treating physician (if other than study investigator) of their participation in the study.
10. they were non-pregnant women of childbearing potential who were using a medically acceptable, adequate form of birth control. This included:

1) hormonal contraceptive as prescribed by a physician (e.g. oral combined, hormonal implant, depot injectable)
2) medically prescribed IUD
3) condom in combination with a spermicide
4) monogamous relationship with a male partner who had a vasectomy or was using a condom with spermicide.

3.4.1.3.2. Exclusion Criteria [Vol. 18, p.26-27]

Subjects were excluded from the study if:

1. they had been treated with methotrexate, cyclosporin, gold, or other cytotoxic agents, for the control of asthma or for a concurrent condition within the last 3 months
2. they were smokers or ex-smokers who had smoked within the previous 6 months or had a cumulative smoking history greater than 10/pack years.
3. they required daily use of nebulized β_2-agonists or long-acting inhaled β_2-agonists.
4. they had used any investigational drug within the previous 30 days or any investigational antibody for asthma or rhinitis within the previous 3 months.
5. they were receiving escalating doses of immunotherapy, oral immunotherapy or short course (rush) immunotherapy.
6. they were allergic to corticosteroids or β_2-agonists.
7. they required inpatient hospitalization for asthma control within the previous 3 months.
8. hey had required ventilator support for respiratory failure secondary to asthma within the last 10 years.

9. they had been treated in the emergency room for a severe asthma exacerbation or admitted to the hospital for management of airway obstruction on two or more occasions within the previous 6 months.
10. they had experience an upper or lower respiratory tract infection within two weeks prior to Screening.
11. they had required more than two courses of systemic corticosteroids for asthma control within the previous 6 months.
12. they had clinical evidence of emphysema, chronic bronchitis, bronchiectasis, or cystic fibrosis.
13. they had a significant history of renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, respiratory, gastrointestinal, cerebrovascular or other significant medical illnesses or disorders which, in the judgment of the investigator, may have interfered with the study, or required treatment which may have interfered with the study (i.e. glaucoma, cataracts, IDDM, cancer with in the last 10 years). Other conditions which were well-controlled and stable, and treated with appropriate medication were allowed upon consultation with the sponsor (i.e. HTN, arrhythmia, thyroid disorders).
14. they had any clinically relevant abnormal vital sign.
15. they had clinically significant abnormalities on chest x-ray at the Screening visit or within the previous 30 days.
16. they had evidence of clinically significant oropharyngeal candidiasis.
17. they were known to be HIV positive (HIV screening was not done at Screening).
18. they were known to be intravenous drug users.
19. they were pregnant, breast-feeding, or were premenarcheal.
20. they were unable to use the device.
21. they were taking any restricted medications.
22. they had participated in this study at another study site or another investigational study.
23. they (or the minor child of a person) were directly associated with the administration of the study

Overall, inclusion and exclusion criteria seem appropriate. It is interesting to note that the sponsor wished to exclude known HIV positive patients and known IV drug abusers; however, the sponsor did not conduct an HIV test or urine drug screen at Screening. It is anticipated that if any complications arose during the course of the study related to HIV or drug use, they would have been identified by the end of the study.

3.4.1.3.3. 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. Additionally, any subject who experienced a clinically significant worsening of his/her asthma or if any female subject

became pregnant during the study, they were to be discontinued from the study. [Vol. 18, p. 28-29]

3.4.1.4. Treatments

3.4.1.4.1. Study Treatments

At the Baseline visit, all subjects meeting the eligibility criteria above, were randomized to receive a treatment kit containing three inhalers, one was for use as one inhalation QAM and the other two were for one inhalation QPM, for one of the following regimens for 12 weeks:

- MF DPI 200 mcg/puff, 1 puff BID (with an additional placebo QPM)
- MF DPI 400 mcg/puff, 1 puff QPM (with additional placebo BID)
- MF DPI 200 mcg/puff, 1 puff from two different 200 mcg/puff canisters for a total dose of 400 mcg QPM (with an additional placebo in the morning)
- MF DPI 200 mcg QPM (with additional placebo BID)
- Placebo (taken as QAM and QPM from two different placebo inhalers)

3.4.1.4.2. Permitted Therapies [Vol. 18, p 34-35]

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 (6-hour withhold period prior to study visits was changed to a 4-hour washout period after study completion and prior to unblinding)
- Nebulized β_2 agonists (6-hour withhold period prior to study visits)
- Topical nasal or ocular decongestants, nasal or ocular cromolyn, nasal ipratropium bromide, nasal or ocular antihistamines
- Short-acting pseudoephedrine formulations (30mg), up to a total daily dose of 120 mcg/day; a 24 hour washout period prior to each study visit
- Oral antihistamines (except astemizole or terfenadine)
- Immunotherapy if there were on a stable maintenance schedule for at least one month prior to the screening visit
- Mild potency topical corticosteroids for dermatologic conditions
- Vaccines were allowed with a two-week washout period prior to a study visit
- Otic mild-potency corticosteroids

3.4.1.4.3. Excluded Therapies

The following table provides the prohibited medications and the exclusionary time period for each.

Table 13. Study P01545, Excluded Therapies

Excluded Medication	Washout Period
Methotrexate, cyclosporin, gold, and other cytotoxic agents	3 months
investigational antibodies for asthma or rhinitis	3 months
Any systemic bursts of oral or intravenous corticosteroids	3 months
Intramuscular or intra-articular corticosteroids	3 months
Astemizole	3 months
Investigational drugs	1 month
Corticosteroids, high potency dermatological, plain or in combination	1 month
Beta-adrenergic bronchodilators: long acting inhaled	2 weeks
Theophylline	2 weeks
Leukotriene modifiers	2 weeks
Inhaled cromolyn sodium or nedocromil	2 weeks
Nasal or Ocular Corticosteroids	2 weeks
Influenza or other vaccines	2 weeks
Long-acting oral decongestants	72 hours
Beta-adrenergic bronchodilators: sustained release tablets	48 hours
Immunotherapy for rhinitis (only if on stable maintenance)	24 hours
Ipratropium bromide, aerosol or nebulized or combination with albuterol	24 hours
Antihistamines (unless used daily, then is allowed without washout)	24 hours
Short-acting oral decongestants	24 hours
Beta-adrenergic bronchodilators: syrup and tablets	24 hours
β_2-agonists: short acting inhaled and nebulized	6 hours

Source: Vol. 18, p. 36

The sponsor also lists the following medications that are prohibited after screening and for the duration of the study:

- leukotriene modifiers
- oral immunotherapy or rush immunotherapy
- any medication linked with significant incidence of hepatotoxicity which may cause significant liver enzyme reduction
- β_2-blockers: oral or nonselective ophthalmic preparations
- Monoamine oxidase inhibitors
- Oral decongestants, except for short acting pseudoephedrine preparations
- Others as outlined above in the table

3.4.1.4.4. Compliance

Compliance was assessed by questioning the subject/parent or guardian, reviewing the patient diaries for times of medication usage, and recording the counter number from the DPI counter at each visit. [Vol. 18, p. 37]

3.4.1.5. Conduct

This Phase III, multi-center, randomized, double-blind, placebo-controlled, parallel group study consisted of an ICS reduction period of 2 days to 4 weeks, followed by a 12-week, double-blind treatment phase. Subjects who met eligibility criteria, were randomized at Baseline to either MF DPI 200 mcg QPM, MF DPI 400 mcg QPM (one inhalation of 400 mcg/puff formulation), MF DPI 200 mcg BID, MF DPI 400 mcg QPM (two inhalations of 200 mcg/puff formulation), or placebo.

Visits were scheduled at Weeks 1, 2, 4, 7, and at 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 the following table.

Table 14. Study P01545, Study Flow Chart

	ICS Reduction Phase				Treatment Phase					
	Screening Visit	Pre-Baseline	Pre-Baseline	Pre-Baseline	Baseline Visit	Study Visit	Study Visit	Study Visit	Study Visit	Study Visit
Visit #	1	1A	1B	1C	2	3	4	5	6	7
Day/Week	-28 to -2	-21 to -14	-14 to -7	-7 to -1	Day 1	Week 1	Week 2	Week 4	Week 7	Week 12
Informed Consent	√									
Review Entry Criteria	√	√	√	√	√					
Medical History	√									
Concomitant Meds Review	√	√	√	√	√	√	√	√	√	√
Dispense Placebo Inhaler	√									
Collect Placebo Inhaler					√					
Physical Examination	√									√
Height	√									
Weight	√									√
Vital Signs	√	√	√	√	√	√	√	√	√	√
PFTs	√	√	√	√	√	√	√	√	√	√
Reversibility Testing	√									
Laboratory Tests	√									√
Pregnancy Test	√									√
EKG	√									
Chest X-Ray	√									

	ICS Reduction Phase				Treatment Phase					
	Screening Visit	Pre-Baseline	Pre-Baseline	Pre-Baseline	Baseline Visit	Study Visit	Study Visit	Study Visit	Study Visit	Study Visit
Visit #	1	1A	1B	1C	2	3	4	5	6	7
Day/Week	-28 to -2	-21 to -14	-14 to -7	-7 to -1	Day 1	Week 1	Week 2	Week 4	Week 7	Week 12
Dispense PF meter	√									
Dispense Diary	√	√	√	√	√	√	√	√	√	
Retrieve/Review Diary		√	√	√	√	√	√	√	√	√
Dispense/Retrieve Rescue Medication	√	√	√	√	√	√	√	√	√	√
Dispense Treatment Inhaler					√				√	
DPI Training	√	√	√	√	√	√	√	√	√	√
Quality of Life Questionnaire		√	√	√	√				√	√
Pulmonary Auscultation	√	√	√	√	√	√	√	√	√	√
Evaluation of Response to Therapy						√	√	√	√	√
Adverse Event Evaluation		√	√	√	√	√	√	√	√	√
Review compliance		√	√	√	√	√	√	√	√	√
Collect Treatment Phase Inhaler									√	√

Source: Vol. 18, p. 22-23

3.4.1.6. Assessments

3.4.1.6.1. Efficacy Assessments

- Pulmonary Auscultation: will be done at all visits
- Pulmonary Function Testing: will be done at all visits
- Investigator Evaluation of Response to Therapy: will be done from Visit 3 to the final visit
    - A 5-point scale from 0-5, much improved to much worse will be used
- "Quality of Life Assessment": a self-reported health-related quality of life (HQOL) questionnaire the SF-36 will be done at all ICS reduction phase visits, Visit 2, Visit 6, and final visit
- Clinical Asthma Exacerbations: defined as a deterioration of asthma that resulted in emergency treatment, hospitalization or treatment with additional asthma medication (other than short-acting inhaled β_2-agonists
- PEFR as recorded in patient's diary

- Asthma symptoms, recorded in diary every morning and evening, rated on a scale from 0-3 (absent to severe)
- Number of nocturnal awakenings: defined as the number of times at night a subject awoke due to asthma symptoms which required Proventil® HFA

3.4.1.6.2. Safety Assessments

- Physical Examination: at Screening and at final visit
- Vital Signs: all visits
- Oropharyngeal Examination: all visits
- Laboratory Tests: Visit 1 and final visit
  - CBC
  - Chemistry: chem.-18, including liver function tests
  - Urinalysis with microscopic examination
  - Serum Pregnancy Test
- 12-Lead EKG: Screening
- Chest X-Ray: Screening
- Adverse Events

Reviewer's comments: the sponsor states that any asthma symptoms of wheezing, difficulty breathing, and cough were not considered adverse events, unless they showed a clear temporal relationship to study medication administration. The reason for this is understandable since these are the symptoms of the disease under study and it would be difficult to know if they are truly AEs or baseline symptoms; however, it would be useful to note the incidence of asthma symptoms in all treatment groups for comparison purposes.

3.4.1.7. Statistical Plan

3.4.1.7.1. 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 and evaluability criteria. The primary analysis sample was the ITT population.

3.4.1.7.2. Sample Size Determination

The sponsor planned to have 400 patients complete the study with 80 subjects per treatment arm. This sample size was chosen to detect a treatment difference of 0.25 liters or more between any pair of treatment groups with at least 90% power at the 5% significance level assuming a pooled standard deviation of 0.48 liters.

3.4.1.7.3. Definition of Baseline

The baseline period for diary data was defined as the interval of time which included the last four days of the Screening period up to and including the morning evaluation on the day of the Baseline Visit (the first day of randomized treatment).

3.4.1.7.4. Primary Efficacy Analyses [Vol. 18, p.58-59]

The primary efficacy endpoint was the change from Baseline in FEV_1 to Endpoint. Endpoint was defined as the last post-baseline non-missing observation. [Vol. 18, p. 64] The primary efficacy endpoint was evaluated using a two-way ANOVA accounting for treatment and center interactions. The primary comparison was the MF DPI 400 mcg QPM (one inhalation) versus placebo, which was analyzed using a pairwise comparison of the least squares means.

Although the primary comparison of interest was between MF DPI 400 mcg and placebo, the sponsor also evaluated the efficacy of the other active treatments. The sponsor accomplished this by sequential pair-wise comparisons between all active treatment groups and placebo in the following order:

1. MF DPI 400 mcg QD PM (one inhalation of 400 mcg/puff) vs. placebo (primary comparison)
2. MF DPI 200 mcg BID vs. placebo
3. MF DPI 400 mcg QPM (two inhalations of 200 mcg/puff)
4. MF DPI 200 mcg QPM vs. placebo

If the primary comparison was not statistically significant, then subsequent comparisons would not be considered statistically significant. To facilitate the interpretation of results, 95% confidence intervals for the differences between each of the pairs of treatments, including the primary comparison, were calculated.

Reviewer's comments: The sponsor's sequential analysis plan was discussed with the Statistical Reviewer, Dr. Jim Gebert, and this method of analysis is acceptable. Although the primary comparison of interest was the 400 mcg QPM versus placebo, the sponsor is seeking the MF DPI 200 mcg QPM dose. Although this is the final comparison in the step-wise analyses, if it is statistically significant, the results would be valid, since the preceding three comparisons must be statistically significant to proceed to this final comparison.

3.4.1.7.5. Secondary Efficacy Analyses

The secondary efficacy endpoints were as follows:

- % predicted FEV_1
- FVC and $FEV_{1\ 25\text{-}75\%}$
- AM and PM PEFR
- Asthma symptoms
- Response to therapy

- Proventil use during the study
- Number of nocturnal awakenings
- Time to first asthma worsening
- Clinical asthma exacerbations
- Asthma Recovery
- Quality of Life

All key secondary variables, except for asthma worsening, were to be analyzed at endpoint using the same two-way ANOVA noted above for the primary efficacy endpoint. Time to asthma worsening was summarized by treatment group using Kaplan-Meier estimates.

3.4.2. Results

3.4.2.1. Patient Disposition

A total of 400 subjects were randomized to 45 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 as follows:

MF DPI 200 mcg QPM, 78 subjects;

MF DPI 400 mcg QPM (one inhalation), 80 subjects;

MDPI 400 mcg QPM (2 inhalations), 78 subjects;

MF DPI 200 mcg BID, 81 subjects;

placebo, 83 subjects.

Discontinuations from the study were common in the placebo treatment group, and somewhat lower and variable in the active treatment groups. A total of 82 subjects (21%) discontinued from the study: 40 subjects (48%) in placebo, 13 subjects (17%) in MF DPI 200 mcg QPM, 12 subjects (15%) in the MF DPI 400 mcg QPM (one inhalation), 9 subjects (11%) in the MF DPI 200 mcg BID, and 8 subjects (10%) in the 400 mcg QPM (2 inhalations). The most common reason for discontinuation was treatment failure, reported by 52 subjects (13%). More patients in the placebo treatment group discontinued secondary to treatment failure (32 subjects, 38.6%) as compared to the MF active treatment groups.

A greater percentage of subjects discontinued from the study secondary to treatment failure in the MF 200 mcg QPM (8 subjects, 10.3%) and MF 400 mcg (400 mcg/puff) QPM (6 subjects, 7.5%) as compared to the MF 400 mcg (200 mcg/puff) QPM (3 subjects, 3.8%) and MF 200 mcg BID (3 subjects, 3.7%). Discontinuations secondary to adverse events were fairly comparable between treatment groups. Other less common reasons for study discontinuation were withdrawal of consent, lost to follow-up, and protocol violations. [Vol. 18, p.70-71; Vol. 23, p. 2-7] The patient disposition results are summarized in the following table.

Table 15. Study P01545, Patient disposition

Status	MF 200 mcg QPM n (%)	MF 400* mcg QPM (1 inh.) n (%)	MF 400** mcg QPM (2 inh.) n (%)	MF 200 mcg BID n (%)	Placebo n (%)
Number of patients randomized	**78**	**80**	**78**	**81**	**83**
Number of patients completing study	65 (83.3)	68 (85.0)	70 (89.7)	72 (88.9)	43 (51.8)
Number of patients discontinued	13 (16.7)	12 (15.0)	8 (10.3)	9 (11.1)	40 (48.2)
Adverse event	3 (3.8)	3 (3.8)	2 (2.6)	2 (2.5)	2 (2.4)
Treatment failure	8 (10.3)	6 (7.5)	3 (3.8)	3 (3.7)	32 (38.6)
Consent withdrawn	1 (1.3)	1 (1.3)	2 (2.6)	3 (3.7)	5 (6.0)
Lost to follow-up	0	0	1 (1.3)	1 (1.2)	0
Protocol violation	1 (1.3)	2 (2.5)	0	0	1 (1.2)

*This dose was administered as one puff of the 400 mcg/puff formulation
**This dose was administered as two puffs of the 200 mcg/puff formulation
Source: Vol. 18, p.71

3.4.2.1.1. Protocol Violations [Vol. 18, p. 71-72; Vol. 23, p. 8-11]

Major protocol violations were greater in placebo-treated subjects as compared to MF DPI treated subjects. A total of 28 subjects had 28 protocol violations. Five (5) subjects (6%) had 7 violations in the MF DPI 200 mcg QPM group, 4 subjects (5%) had 5 violations in the 400 mcg QPM (1 inh.) group, 3 subjects (4%) had 3 violations in the 400 mcg QPM (2 inh.) group, 4 subjects (5%) had 4 violations in the 200 mcg BID group, and 12 subjects (14%) had 14 violations in the placebo group.

The most common violation was no post-baseline data. A total of 12 subjects (9 in the placebo group, and 1 each in the MF DPI 200 mcg QPM, MF 400 mcg QPM (1inh.), and MF DPI 200 mcg BID) lacked post-baseline data. The high frequency of no post-baseline data in the placebo group is understandable given the high incidence of treatment failures noted in this group.

Other major violations were uncommon and no consistent trends were noted between the treatment groups. Other less common violations were: unacceptable concomitant medications/insufficient washout periods, Baseline FEV_1 values were not in the pre-specified range of less than 9% change in FEV_1 between Screening and Baseline, and poor compliance (defined as less than 75% of specified doses taken).

3.4.2.2. Demographics and Other Baseline Characteristics

3.4.2.2.1. Demographics

Generally, treatment groups were fairly similar at baseline with respect to age, age distribution, gender, race, height and weight, with a few exceptions. The mean age for the study population ranged from 35.9-40.3 years in a given treatment group, with a similar age range in all treatment groups. The greatest percentage of subjects were in the 18-64 year age group, ranging from 80-94%. The MF 400 mcg QPM (1 inh.) and placebo groups had the

greatest percentage of subjects in the 12-17 year range (15% and 14%, respectively) as compared to the MF 200 mcg QPM (9%), MF 200 mcg BID (8%) and MF 400 mcg (2 inh.) QPM (5%). Subjects aged 65 years and older were poorly represented, ranging from 1% (MF 400 mcg, 2inh.) to 8% (MF 200 mcg QPM). There were more females in the study as compared to males, ranging from 55-66% in a given treatment group. Similarly, the predominant race was Caucasian, represented by 84-91% of subjects. The sponsor did not further characterize the remaining represented races, other than by stating "non-Caucasian." The mean heights and weights were similar across treatment groups, ranging between 167.3-169.1 cm and 32.3-159 kg, respectively. These results are summarized in the table below.

Reviewer's comments: The sponsor did not provide a further breakdown of subjects of another race, other than Caucasian. Generally it would be useful to know this breakdown. However, since the number of subjects of other races is fairly low and therefore a subpopulation analysis based on race is unlikely to provide any clinically meaningful input, information on the breakdown of the other races is not crucial to this review, and will not be requested from the sponsor at this point.

Table 16. Study P01545, Demographics and Baseline Characteristics

	MF 200 mcg QPM	MF 400* mcg QPM (1 inh.)	MF 400** mcg QPM (2 inh.)	MF 200 mcg BID	Placebo
	n=78	n=80	n=78	n=81	n=83
Age (years)					
Mean	39.9	36.6	40.3	36.8	35.9
Range	12.0-71.0	12.0-77.0	12.0-76.0	12.0-67.0	12.0-78.0
Age Distribution [n (%)]					
12-17 years	7 (9%)	12 (15%)	4 (5%)	10 (8%)	12 (14%)
18-64 years	65 (83%)	64 (80)	73 (94%)	69 (85%)	68 (82%)
> 65 years	6 (8%)	4 (5%)	1 (1%)	2 (2%)	3 (4%)
Sex					
Female	47 (60%)	53 (66%)	45 (58%)	48 (59%)	46 (55%)
Male	31 (40%)	27 (34%)	33 (42%)	33 (41%)	37 (45%)
Race					
Caucasian	68 (87%)	73 (91%)	69 (88%)	68 (84%)	72 (87%)
Non-Caucasian	10 (13%)	7 (9%)	9 (12%)	13 (16%)	11 (13%)
Height (cm)					
Mean	168.4	167.3	169.1	168.7	167.5
Range	139.7-194.0	144.8-193.0	143.5-193.0	147.3-189.0	141.7-190.5
Weight (kg)					
Mean	78.4	77.9	80.6	79.4	79.2
Range	36.8-148.6	36.3-136.1	39.5-145.9	40.0-159.0	32.3-146.5

Source: Vol. 18, p. 75-76

3.4.2.2.2. Baseline Disease/Other Characteristics

The mean duration of asthma, baseline FEV_1 and FEV_1 %predicted, and mean reversibility were similar across treatment groups. The mean duration of asthma ranged between 17.2 to 20.8 years, with the widest range of 1-71 years in the MF 200 mcg QPM group. The mean FEV_1 at baseline was between 2.2 and 2.3 liters in all treatment groups. The mean baseline FEV_1 % predicted was between 65.1 and 69.1 % for all groups. The mean percent improvement post-bronchodilator ranged between 18.6 and 20.1%; however, the range was between 10.7 to 71.7 % in the study population. Most of the subjects were non-smokers (72-84%). These characteristics are summarized in the table below.

Reviewer's comments: Although 19-28% of the subjects in a given group were listed as smokers, it is anticipated that they had not smoked within the past 6 months and did not have a history greater than 10 pack/year history of smoking, as per the exclusion criteria. If these subjects did not meet these exclusion criteria then the presence of COPD in association with asthma in these patients would be in question.

Table 17. Study P01545, Baseline Disease/Other Characteristics

	MF 200 mcg QPM	MF 400* mcg QPM (1 inh.)	MF 400** mcg QPM (2 inh.)	MF 200 mcg BID	Placebo
	n=78	n=80	n=78	n=81	n=83
Duration of Disease (years)					
Mean	20.8	19.1	18.3	19.8	17.2
Range	1.0-71.0	2.0-65.0	1.0-60.0	1.0-56.0	1.0-54.0
Baseline FEV_1 (liters)					
Mean	2.2	2.3	2.3	2.3	2.2
Range	1.2-3.3	1.4-4.5	1.1-3.7	1.3-3.6	1.4-3.6
Baseline FEV_1 % predicted					
Mean	66.7	69.1	66.7	66.4	65.1
Range	48.9-85.2	49.8-87.2	50.4-93.9	49.6-82.8	50.5-93.9
Reversibility (% change)					
Mean	18.6	19.1	19.5	19.5	20.1
Range	11.2-50.0	11.7-71.7	11.2-43.0	10.7-48.0	10.8-50.4
Smoking Status					
Smoker	18 (23%)	22 (28%)	15 (19%)	22 (27%)	13 (16%)
Non-smoker	60 (77%)	58 (72%)	63 (81%	59 (73%)	70 (84%

Source: Vol. 18, p. 76-77

3.4.2.2.3. Baseline Concomitant Medications and Medical History

The sponsor has not provided any summaries on baseline concomitant medications or medical history. This reviewer has perused the line listings for concomitant medications and looked at the reasons for the medications to provide some information on baseline medical history. In general, the concomitant medications and baseline medical history appears comparable among the treatment groups. The most common baseline medications were

asthma related (steroids and β_2 agonists) and the most common concomitant diseases were asthma and allergic rhinitis. [Vol. 24, p. 670-738; Vol. 25, p. 739-907]

3.4.2.3. Compliance

Compliance was based on the number of doses documented on the diary cards. Non-compliance was defined as less than 75% or greater than 125% of protocol-specified doses. The sponsor stated that 6 subjects had less than 75% of the protocol-specified doses and none had more than 125%. The sponsor has not provided any further summary of the compliance data. [Vol. 18, p. 77]

Reviewer's comments: Based on the sponsor's definition of compliance, it appears that six subjects (1.5%) were non-compliant, two subjects (2.5%) in the MF 400 mcg QPM (1 inh.) group, one subject (1.2%) in the MF 200 mcg BID group, and three subjects (3.6%) in the placebo treatment group. Based on the sponsor's definition, overall compliance is greater than 95%, which is quite acceptable. However, using the sponsor's definition of compliance, it is difficult for this reviewer to truly assess compliance in terms of the exact distribution of missed doses. It is not clear how many doses most patients missed, except that they did not miss more than 75% of the defined doses (with the exception of the 1.5%).

3.4.2.4. Efficacy Outcomes

Efficacy analyses were based on pulmonary function testing, diary cards, investigator assessments, and global evaluations. The sponsor performed analyses on all randomized subjects (the ITT population) and all efficacy evaluable subjects. 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. A two-sided t-test was used for pairwise comparisons between the different treatment groups.

3.4.2.4.1. Primary Efficacy Analysis

The primary efficacy endpoint was the change in FEV_1 from baseline to Endpoint (the final visit) and the primary comparison was between MF 400 mcg QD (1 inh.) and 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.

Reviewer's comments: the Applicant states that MF 400 mcg QD (1 inh.) will be the primary comparison. However, as the formulation is different for this treatment group (440 mcg/puff), this reviewer will primarily focus on the other treatment group results as they represent the 220 mcg/puff formulation, the formulation for which the Applicant is currently seeking approval.

Screening and Baseline FEV_1 LS Means were fairly comparable between treatment groups. The Screening FEV_1 LS means ranged between 2.56 to 2.68 liters and Baseline FEV_1 LS Means ranged between 2.18 to 2.28 liters. As expected, the Screening FEV_1 LS Means were

higher than Baseline values, since the Baseline values represented pulmonary function at the end of the steroid-reduction run-in period.

The LS Mean and mean % changes in FEV_1 from Baseline to Endpoint were fairly similar across active treatment groups, but greater compared to placebo. In the active treatment groups, the LS Mean changes in FEV_1 ranged between 0.41 to 0.51 liters and the mean % change from Baseline ranged between 19.2 to 23.7%. The LS Mean change from Baseline to Endpoint for the placebo treatment group was 0.16 liters corresponding to a mean % change of 7.8%.

Although the change from Baseline to Endpoint was the primary timepoint of interest, results of at the other time points were also reviewed. The range of improvement in LS Mean FEV_1 from Baseline to any given time point ranged between 0.35 and 0.51 liters for all active treatments, compared to 0.15 to 0.3 liters for placebo. The mean % improvement in FEV_1 was between 17.9 and 23.7% for all active treatment groups, compared to between 7.3 and 13.8%. It is interesting to note that placebo patients at Week 12 (those that did not discontinue) had mean % change from Baseline of 13.8%. This is numerically lower than that noted for the active treatment groups; however, this change is not minimal. Since the 39% of subjects in the placebo group discontinued prematurely from the study, the Week 12 results only represent values for 41 out of 83 subjects. This may in part explain the fairly large change from baseline noted in FEV_1 LS Means. Subjects who tended to note some improvement in FEV_1 continued with the study, and the data from these subjects skew the results at the end of the trial. When the results from all subjects are included, the change from Baseline to Endpoint, is modest (7.8%). The following table summarizes the FEV_1 LS Mean and mean % changes from Baseline to Endpoint, Weeks 1, 7, and 12.

Table 18. Study P01545, Efficacy Measures Summary: Screening and Baseline LS Mean FEV_1 (liters) and Change from Baseline LS Mean FEV_1 (liters), in ITT Population

	MF 200 mcg QPM		MF 400 mcg QPM (1 inh.)		MF 400 mcg QPM (2 inh.)		MF 200 mcg BID		Placebo	
	LS Mean (Mean % change)	n	LS Mean (Mean % change)	n	LS Mean (Mean % change)	n	LS Mean (Mean % change)	n	LS Mean (Mean % change)	n
Screening	2.56	78	2.68	80	2.65	78	2.66	80	2.61	83
Baseline	2.18	78	2.28	80	2.24	78	2.26	80	2.19	83
Change from Baseline										
Week 1	0.37 (17.9)	77	0.35 (16.3)	78	0.40 (18.6)	77	0.36 (17.4)	76	0.15 (7.3)	78
Week 7	0.41 (19.6)	65	0.45 (20.3)	73	0.55 (24.4)	70	0.50 (23.7)	72	0.23 (10)	48
Week 12	0.50 (24.1)	62	0.46 (21.7)	65	0.48 (22.5)	67	0.52 (25.5)	69	0.30 (13.8)	41
Endpoint	0.41 (19.2)	78	0.41 (19.2)	80	0.49 (21.7)	78	0.51 (23.7)	80	0.16 (7.8)	83

Source: Vol. 18, p. 80

Reviewer's comments: In the original application, the pivotal studies supported MF 200 mcg BID. It is interesting to note that at Endpoint, the change from Baseline in LS Mean FEV_1 was numerically greater for the 200 mcg BID group (0.51liters) as compared to 200 mcg QPM (0.41liters). However, at the 12 week time point, the change was quite similar (200mcg BID, 0.52 liters; 200 mcg QPM, 0.50 liters). Overall, the differences between the treatment groups were not statistically significant, and the results were similar, supporting comparable efficacy between all of the active treatment groups.
Additionally, these results indicate, as in the previous study in steroid-naïve patients, that MF DPI treatment has superior efficacy compared to placebo in terms of the primary efficacy variable, FEV_1 , which is noted as early as Week 1. Results from both of the studies reviewed in this complete response indicate that in both steroid-naïve patients and patients previously on inhaled corticosteroids, MF DPI demonstrates significant improvements in FEV_1 compared to placebo as early as Week 1.

The analyses of change from baseline and the pairwise comparisons between active treatments and placebo revealed that all active treatments were statistically superior compared to placebo at Endpoint at the 5% significance level; however, no significant difference between the four active treatment groups was noted. The treatment difference in FEV_1 LS Mean change from baseline was 0.25 liters or greater for all active treatment comparisons vs. placebo. Although the sponsor did not adjust for multiple comparisons, a sequential step wise comparison process was involved. The primary comparison was between MF 400 mcg QPM (1 inh.) vs. placebo, and the last sequential comparison was between MF 200 mcg QPM vs. placebo. Since all comparisons prior to the final comparison were significant at $p < 0.001$, the final comparison between MF 200 mcg QPM vs. placebo is statistically significant as well.

Reviewer's comments: The sponsor has not adjusted for multiple comparisons. The protocol [Volume 20, page 928] *states 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. This was discussed with the Biometrics reviewer, Dr. Jim Gebert, and he agrees that 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 reports the unadjusted pairwise p-values given by the sponsor, as recommended by Dr. Jim Gebert.*

The following table summarizes the sequential efficacy analyses for the primary comparison through the final comparison, as the latter is the main comparison of interest since the results of this study may be used to potentially change the labeling to add the 200 mcg QPM dose.

Table 19. Study P01545, Primary Efficacy Analyses at Endpoint, ITT Population

Comparison	Treatment Difference in FEV_1 LS Mean Change from Baseline (Liters)	P-value
MF 400 mcg QPM (1 inh.) vs. Placebo*	0.25	<0.001

MF 200 mcg BID vs. Placebo	0.35	<0.001
MF 400 mcg QPM (2 inh.) vs. Placebo	0.33	<0.001
MF 200 mcg QPM vs. Placebo	0.25	<0.001

*Primary Comparison; the other comparisons are listed sequentially as analyzed

Source: Vol. 18, p. 80

3.4.2.4.1.1. Subgroup Analyses by Sex, Age, and Race

The sponsor analyzed FEV_1 with respect to sex, age, and race. Analysis of FEV_1 by sex demonstrated similar mean changes in FEV_1 over time for males and females. The sponsor was unable to perform meaningful subgroup analyses with respect to age 12 to 17 years (n = 45)or ages 65 years and older (n = 16) because of too few subjects. The sponsor noted similar efficacy with respect to LS Mean FEV_1 changes over time for the 18-64 year old age group. This is not surprising since the majority of the population was in this age group and the results would be skewed by this group towards the overall analyses. The sponsor was unable to provide any meaningful analyses of LS Mean changes in FEV_1 with respect to race, as the majority of the population was Caucasian (87%) and the other 13% were divided among four other races (the sponsor did not provide a breakdown with respect to the other races).

3.4.2.4.1.2. Response by Baseline Severity of Asthma

Response was evaluated in subjects whose Baseline FEV_1 was either greater than or equal to 75% predicted or less than 75% predicted. For subjects whose Baseline FEV_1 was <75% predicted (n = 309), the mean % change in FEV_1 from Baseline to Endpoint ranged between 20.9 to 25.5% for all active treatment groups, compared to 8.5% for placebo. For subjects whose Baseline FEV_1 was $\geq$ 75% (n = 91), the mean % change in FEV_1 from Baseline to Endpoint ranged from 11.3% to 20.2%, compared to 3.8% for placebo. Numerically, it appears that subjects with lower FEV_1 at Baseline, indicating a greater severity, tended to have greater improvements in FEV_1 . However, it should be noted that this comparison should be viewed as exploratory since the two subsets analyzed were disproportional in terms of number of subjects.

3.4.2.4.2. Secondary Efficacy Analyses

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

- Percent Predicted FEV_1
- FVC and FEF_{25-75}
- AM and PM PEFR
- Asthma Symptom Scores
- Response to Therapy
- Proventil Use During Study
- Number of Nocturnal Awakenings
- Time to First Worsening of Asthma
- Clinical Asthma Exacerbations

- Asthma Recovery
- Health Related Quality of Life

3.4.2.4.2.1. Percent Predicted FEV_1

The change from Baseline to Endpoint in FEV_1 % predicted favored the active treatments over placebo. The Baseline LS Mean FEV_1 % predicted ranged between 64.09 to 68.15% and was similar for all treatment groups. For all active treatment groups, the LS mean FEV_1 % change from Baseline to Endpoint ranged between 12.28 to 14.97% compared to 4.49% placebo. At 12 Weeks, the results also demonstrated numerically superior values for the active treatment groups as compared to placebo. The active treatment groups were similar in terms of results. [Vol. 18, p. 84-85]

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

The LS Mean FVC was similar between all treatment groups at Baseline, ranging from 3.28 to 3.33 liters. At Endpoint, the change from Baseline for all active treatment groups ranged from 0.37 to 0.48 liters (0.37 and 0.39 liters for MF 200 mcg QPM and MF 400 mcg QPM (1 inh.), respectively, and 0.48 and 0.45 liters for MF 400 mcg QPM (2 inh.) and 200 mcg BID, respectively). In comparison, the change from Baseline to Endpoint was 0.17 liters for placebo. All active treatment were numerically superior to placebo in terms of LS Mean change in FVC from Baseline to Endpoint. [Vol. 18, p. 86-88]

Similarly, for the secondary variable of $FEF_{25-75\%}$, all active treatment groups were favored over placebo. Also, greater numerical improvements were noted in MF 400 mcg QPM (2 inh.) and MF 200 mcg BID as compared to MF 200 mcg QPM and MF 400 mcg QPM (1 inh.)

3.4.2.4.2.3. AM and PM PEF

Subjects recorded measured PEF in the morning and evening in the subject diaries. At Baseline, the mean AM PEF ranged between 360.4 and 383.9 L/min. The change from Baseline to Endpoint in LS Mean AM PEF ranged between 23.62 to 41.48 L/min for the active treatment groups compared to -2.88 L/min for placebo. Similar to other efficacy endpoints, MF DPI 400 mcg QPM (2 inh.) and MF DPI 200 mcg BID demonstrated numerically superior changes in AM PEF as compared to MF 200 mcg QPM and MF 400 mcg QPM (1 inh.). Similar results were noted for PM PEFR. The improvement in LS Mean PM PEFR (L/min) from Baseline to Endpoint for MF 220 mcg QD PM was 15.65 L/min (4.1%), for MF 400 mcg (2 inh.) dose was 39.26 (10.7%) for MF 220 mcg BID dose was 36.70 L/min (10.8%), and placebo was 1.40 L/min (0.8%). [Vol. 18, p. 90, 235] These results are summarized in the following table.

Table 20. Baseline AM and PM PEFR (L/min) and Change from Baseline in AM and PM PEFR (L/min) by Treatment Group

	MF 200 mcg QPM		MF 400 mcg QPM (2 inh.)		MF 200 mcg BID		Placebo	
	n	LS Mean (Mean % change)	n	LS Mean (Mean % change)	n	LS Mean (Mean % change)	n	LS Mean (Mean % change)
AM PEFR L/min								
Baseline	78	360.04	78	383.9	80	373.3	83	365.3
Change from Baseline								
Week 1	78	11.85 (3.5)	78	15.95 (5.3)	80	16.97 (5.7)	83	-0.79 (-0.3%)
Week 7	66	29.53 (8.6)	73	38.94 (11.4)	74	37.85 (11.5)	50	6.58 (2.6)
Week 12	62	28.88 (8.4)	67	(39.09 (12.0)	72	43.00 (13.0)	41	9.31 (2.7)
Endpoint	78	23.62 (6.2)	78	41.48 (11.8)	80	40.23 (11.7)	83	-2.88 (-1.0)
PM PEFR L/min								
Baseline	78	378.9	78	401.6	81	387.7	83	381.7
Change from Baseline								
Week 1	78	5.81 (1.6)	78	11.91 (3.6)	81	11.53 (4.0)	83	0.08 (0.5)
Week 7	66	19.4 (5.8)	73	35.93 (10.1)	74	34.09 (10.2)	50	13.36 (4.0)
Week 12	61	20.25 (5.9)	67	39.42 (11.1)	72	38.06 (11.0)	40	13.40 (3.5)
Endpoint	78	15.65 (4.1)	78	39.26 (10.7)	81	36.70 (10.8)	83	1.40 (0.8)

Source: Vol. 7, p. 231, 235

Reviewer's comments: These results show that MF DPI is numerically superior to placebo treatment in terms of both AM and PM PEFR. The PM PEFR results are of interest since these are the only objective assessments of end of dosing interval for MF DPI. For the most part, AM and PM PEFR were similar, and MF DPI 400 mcg (2 inh.) and 200 mcg BID were numerically greater than MF 200 mcg QPM for both AM and PM PEFR. As these are secondary endpoints, statistical significance is not commonly reported as adjustments for multiplicity are not done. The Statistical Reviewer, Dr. Jim Gebert, stated that since PM PEFR is the only assessment for EODI, adjustment for multiplicity is not necessary, and stating P-values for this secondary endpoint under these circumstances may be legitimate. As such, for PM PEFR at Endpoint, the difference between all MD DPI treatments and placebo, were associated with p-values less than 0.05, which supports once daily treatment, keeping in mind the limitations of such a post hoc analysis.

3.4.2.4.2.4. Asthma Symptoms

Subjects recorded AM and PM symptom scores for wheezing, cough, and shortness of breath, each rated on a scale from 0-3. For wheezing, the AM LS Mean change from Baseline to Endpoint ranged between -0.46 to -0.53 for all active treatment groups compared to -0.16 for placebo. For cough, the AM LS Mean change from Baseline to Endpoint ranged between -0.32 to -0.44 for the active treatments as compared to 0.13 for placebo. For shortness of breath, the AM LS Mean change from Baseline to Endpoint ranged from -0.45

to -0. 77 for the active treatments as compared to -0.18 for placebo. These changes were numerically greater for both MF 400 mcg QPM groups (-0.77 and -0.70 for 1 inh. and 2 inh, respectively), compared to MF 200 mcg QPM (-0.45) and MF DPI 200 mcg BID (-0.57). Results were similar for PM symptom scores as well. Thus, there is a trend towards improvement in asthma scores for the active treatment groups as compared to placebo, the improvements are numerically small. [Vol. 18, p. 92-95]

3.4.2.4.2.5. Response to Therapy

The investigator or designee assessed the subjects' 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*, 47.4 to 56.3% for the active treatment groups compared to 33.7% for placebo. The percentages of patients that were categorized as *much improved* were greater in the active treatment groups as compared to placebo (19.2-30.0% for active treatment groups and 6% for placebo). Also, 1.3 to 3.8% of subjects were categorized as *much worse* in the active treatment groups as compared to 15.7% in placebo. Overall, it appears that the subjects in the active treatment groups had more favorable responses to therapy as compared to placebo. [Vol. 18, p. 96-97]

3.4.2.4.2.6. Proventil Use During Study

Subjects recorded the number of inhalations of Proventil used per day throughout the study period. At Baseline, the mean number of inhalations ranged from 3.19 to 3.93 for the active treatment groups as compared to 3.01 for placebo. For the active treatment groups, the change from Baseline to Endpoint in LS Mean number of Proventil puffs/day, ranged from -1.36 (-1.36 for MF 200 mcg QPM and -1.70 for MF 200 mcg BID) to -1.84 (MF 400 mcg QPM, 2 inh.), compared to 0.52 for placebo. Mean change at Endpoint in number of Puffs/day). For all active treatment groups, the LS Mean number of puffs of Proventil used decreased from Baseline to Endpoint as compared to placebo, although the numerical values were small. [Vol. 18, p. 97-99]

3.4.2.4.2.7. Number of Nocturnal Awakenings

Subjects recorded the number of times during the night that they were awakened by asthma symptoms requiring Proventil. The number of nocturnal awakenings was low at Baseline, and ranged from 0.31 to 0.41 for all treatment groups. The change from Baseline to Endpoint in LS Mean number of nocturnal awakenings ranged from -0.17 to -0.28 for all active treatment groups, compared to 0.09 for placebo. The smallest change from Baseline to Endpoint in any active treatment group was noted for MF 200 mcg QPM, -0.17. Although, these results also favor the active treatment groups as compared to placebo, the numerical values are low. [Vol. 18, p. 99-100]

3.4.2.4.2.8. Time to First Asthma Worsening

The sponsor states that since less than 50% of subjects in any treatment group did not meet the criteria for asthma worsening, the median time to asthma worsening could not be estimated. Kaplan-Meier Survival curves of time to first asthma worsening demonstrate that

all active treatment were better than placebo with a distinct separation between the active treatment groups and placebo. [Vol. 18, p. 101-102]

3.4.2.4.2.9. Clinical Asthma Exacerbations

The sponsor defined clinical asthma exacerbation (CAE) as a worsening of asthma that resulted in emergency treatment, hospitalization, or treatment with additional asthma medications (other than short acting β_2 agonists). Overall, 37 subjects experienced protocol defined CAEs: MF 200 mcg QPM, 7 subjects; MF 400 mcg QPM (1 inh.), 7 subjects; MF 400 mcg (2 inh.), 3 subjects; MF 200 mcg BID, 5 subjects; Placebo, 15 subjects. These results demonstrate that CAEs in general were low, and occurred in more placebo treated subjects than active treated subjects.

3.4.2.4.2.10. Asthma Recovery

The sponsor assessed asthma recovery to determine if treatment with MF could help subjects return to their condition prior to ICS reduction (Screening). Criteria for asthma recovery included a > 10% increase in FEV_1 as well as a return to Screening values for any one of the following four criteria: PEF, Proventil use, asthma symptoms, and nighttime awakenings. Review of these results demonstrated that the number of subjects experiencing asthma recovery ranged from 41 to 56 corresponding to 53 to 69% for all active treatment groups, compared to 25 subjects (30%) in the placebo treatment group. Although more patients in the active treatment groups had asthma recovery as compared to placebo, the MF 200 mcg QPM had numerically lower numbers as compared to the other active treatment groups. Reviewing these results using the protocol defined criteria, is somewhat disturbing. It would be expected that a greater percentage of subjects would return to Screening values after treatment with MF. However, it is somewhat assuring to look at the percentage of subjects whose FEV_1 returned to Screening values. This ranged between 78 to 88 percent for all active treatments compared to 49% for placebo.

Reviewer's comments: this secondary endpoint is somewhat arbitrary as defined by the sponsor, and this reviewer does not put much emphasis on this variable.

3.4.2.4.2.11. Health Related "Quality of Life" (HQOL)

The HQOL questionnaire (SF-36) was administered to 376 of 400 randomized subjects (English speaking only) at Baseline, Week 7, Week 12, and Endpoint. The domains evaluated were physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. At Baseline, all treatment groups were comparable with a mild-moderate effect of asthma on HQOL. At Endpoint, all MF active treatment groups generally reported better HQOL than placebo. [Vol. 18, p. 110-112]

3.4.2.5. Safety Outcomes

3.4.2.5.1. Exposure

The extent of exposure in the active treatments was better than placebo. The majority (85 to 94%) of subjects in the active treatment groups received at least 12 weeks of treatment [Vol. 18, p. 116], compared to 57% in the placebo treatment group. However, it should be noted that

the extent of exposure was somewhat lower in the MF 200 mcg QPM group (85%) as compared to the other active treatment groups (91-94%). Nonetheless, the extent of exposure was satisfactory to allow for safety assessments. This information is summarized in the following table.

Table 21. Study P01545, Extent of Exposure

Length of Exposure	MF 200 mcg QPM n = 78	MF 400 mcg QPM (1 inh.) n = 80	MF 400 mcg QPM (2 inh.) n = 78	MF 200 mcg BID n = 81	Placebo n = 83
1-7 days	78 (100)	80 (100)	78 (100)	81 (100)	83 (100)
8-14 days	75 (96.2)	78 (97.5)	78 (100)	80 (98.8)	74 (89.2)
15-28 days	70 (89.7)	78 (97.5)	75 (96.2)	78 (96.3)	62 (74.7)
29-49 days	68 (87.2)	76 (95.0)	73 (93.6)	77 (95.1)	56 (67.5)
50-84 days	66 (84.6)	73 (91.3)	73 (93.6)	75 (92.6)	47 (56.6)
≥ 85 days	33 (42.3)	39 (48.8)	41 (52.6)	48 (59.3)	21 (25.3)

Source: Vol. 18, p. 117

Reviewer's comments: although from the table it is difficult to see how many subjects had 50 days of exposure or 84 days of exposure within this category; however, the sponsor has stated in the text that approximately 84 to 94 % of active treated subjects received at least 12 weeks of therapy. The sponsor has not provided any further data to verify the accuracy of this statement. This reviewer believes the statement and will not request further information regarding the breakdown of length of exposure in the 50-84 day category.

3.4.2.5.2. Adverse Events

3.4.2.5.2.1. Most Commonly Reported Adverse Events

In general, adverse events were more common and of similar incidences in the active treatment groups as compared to placebo. Adverse events were reported in 48 to 52 subjects (61.5-64.2%) in the active treatment groups as compared to 37 subjects (44.6%) in the placebo treatment group. A total of 48 subjects (61.5%) in the MF 200 mcg QPM, 50 subjects (62.5%) in the MF 400 mcg QPM (1 inh.), 48 subjects (61.5%) in the MF 400 mcg QPM (2 inh.), 52 subjects (64.2%) in the MF 200 mcg BID, and 37 subjects (44.6%) in the placebo group reported adverse events.

Upper respiratory tract infection, headache, pharyngitis, oral candidiasis, and sinusitis were the most commonly reported adverse events. Upper respiratory tract infection was reported in 20.5-26.3% of subjects in the active treatment groups as compared to 14.5% in the placebo treated groups. Headache occurred in 7.7-11.1% of active treated subjects and in 7.2% of placebo treated subjects. Pharyngitis occurred in 6.4-11.1% of active treated subjects and in 6% of placebo treated subjects. Oral candidiasis was reported more frequently in the active treated subjects (6.3-7.4%) as compared to placebo (2.4%). Sinusitis was reported in 0-5% of active treated subjects and in 2.4% of placebo treated subjects. Adverse events occurring at an incidence of 2% or higher in any treatment group are summarized in the following table.

Table 22. Study P01545, Incidence of Adverse Events Reported in at Least 2% of Subjects

	MF 200 mcg QPM n = 78 n (%)	MF 400 mcg QPM (1 inh.) n = 80 n (%)	MF 400 mcg QPM (2 inh.) n = 78 n (%)	MF 200 mcg BID n = 81 n (%)	Placebo n = 83 n (%)
Subjects Reporting any Adverse Event	**48 (61.5)**	**50 (62.5)**	**48 (61.5)**	**52 (64.2)**	**37 (44.6)**
Body as a Whole/General Disorders					
Dizziness	1 (1.3)	0	3 (3.8)	0	0
Headache	6 (7.7)	7 (8.8)	6 (7.7)	9 (11.1)	6 (7.2)
Influenza-like symptoms	0	0	0	3 (3.7)	0
Central and Peripheral Nervous System Disorders					
Dysphonia	0	2 (2.5)	0	0	1 (1.2)
Disorders of Ear/Labyrinth System					
Earache	1 (1.3)	1 (1.3)	2 (2.6)	1 (1.2)	0
Disorders of the Reproductive System and Breast					
Balanoposthitis	1 (3.2)	0	0	0	0
Dysmenorrhea	1 (2.1)	1 (1.9)	1 (2.2)	1 (2.1)	0
Endometriosis	0	0	0	0	1 (2.2)
Leukorrhea	0	0	0	1 (2.1)	0
Pregnancy Unintended	0	0	1 (2.2)	0	0
Prostatitis	0	0	1 (3.0)	0	0
Vaginitis	1 (2.1)	0	1 (2.2)	1 (2.1)	0
Gastrointestinal System Disorders					
Abdominal pain	2 (2.6)	3 (3.8)	2 (2.6)	1 (1.2)	3 (3.6)
Diarrhea	3 (3.8)	1 (1.3)	0	2 (2.5)	3 (3.6)
Dyspepsia	0	2 (2.5)	1 (1.3)	0	1 (1.2)
Gastroenteritis	0	0	2 (2.6)	1 (1.2)	1 (1.2)
Nausea	5 (6.4)	3 (3.8)	0	3 (3.7)	4 (4.8)
Vomiting	0	0	1 (1.3)	2 (2.5)	3 (3.6)
Infections and Infestations					
Candidiasis (oral)	5 (6.4)	5 (6.3)	6 (6.4)	6 (7.4)	2 (2.4)
Infection, viral	1 (1.3)	0	1 (1.3)	2 (2.5)	2 (2.4)
Lower respiratory tract infection	0	0	2 (2.6)	0	1 (1.2)
Pharyngitis	5 (6.4)	6 (7.5)	8 (10.3)	9 (11.1)	5 (6.0)
Sinusitis	0	4 (5.0)	2 (2.6)	4 (4.9)	2 (2.4)
Upper Respiratory Tract Infection	16 (20.5)	21 (26.3)	18 (23.1)	17 (21.0)	12 (14.5)
Urinary Tract Infection	0	0	2 (2.6)	2 (2.5)	0
Injury and Poisoning					
Insect bite	2 (2.6)	0	0	0	0

	MF 200 mcg QPM n = 78 n (%)	MF 400 mcg QPM (1 inh.) n = 80 n (%)	MF 400 mcg QPM (2 inh.) n = 78 n (%)	MF 200 mcg BID n = 81 n (%)	Placebo n = 83 n (%)
Subjects Reporting any Adverse Event	**48 (61.5)**	**50 (62.5)**	**48 (61.5)**	**52 (64.2)**	**37 (44.6)**
Joint Sprain	0	2 (2.5)	2 (2.6)	1 (1.2)	2 (2.4)
Musculo-Skeletal System Disorders					
Arthralgia	1 (1.3)	1 (1.3)	4 (5.1)	2 (2.5)	1 (1.2)
Back Pain	3 (3.8)	0	1 (1.3)	3 (3.7)	1 (1.2)
Musculo-skeletal pain NOS	2 (2.6)	2 (2.5)	3 (3.8)	3 (3.7)	0
Myalgia	1 (1.3)	1 (1.3)	2 (2.6)	0	0
Neck Stiffness	0	2 (2.5)	0	0	0
Psychiatric Disorders					
Anxiety	2 (2.6)	0	0	1 (1.2)	1 (1.2)
Insomnia	1 (1.3)	1 (1.3)	0	2 (2.5)	0
Respiratory System Disorders					
Allergy aggravated	0	2 (2.5)	1 (1.3)	2 (2.5)	3 (3.6)
Bronchitis	1 (1.3)	3 (3.8)	2 (2.6)	1 (1.2)	2 (2.4)
Coughing	0	1 (1.3)	0	1 (1.2)	2 (2.4)
Nasal Congestion	0	0	0	2 (2.5)	0
Rhinorrhea	0	0	1 (1.3)	2 (2.5)	0
Sinus Congestion	0	0	2 (2.6)	0	0

Source: Vol. 18, p. 119-120

Reviewer's comments: The incidence of adverse events was greater in the active treatment group as compared to placebo. However, it should be noted that approximately 40% of subjects in the placebo treated group discontinued from the study prematurely. If more subjects would have remained in the study, it is reasonable, although not necessarily true, to anticipate that the incidence of adverse events would have been somewhat higher.

3.4.2.5.2.2. Local Adverse Events

Corticosteroids are commonly implicated as causes of local adverse events such as pharyngitis, oral candidiasis, and hoarseness/dysphonia. The incidence of these events was greater in the active treatment groups for pharyngitis and oral candidiasis and comparable for dysphonia to the placebo treatment group. Pharyngitis was reported in 6.4-11.1% of active treated subjects compared to 6.0% of placebo treated subjects. Oral candiasis was reported in 6.3-7.4% of active treated subjects as compared to 2.4% of placebo treated subjects. Dysphonia was reported in only the MF 400 mcg QPM (1 inh.) group (2 subjects, 2.5%) and placebo (1 subject, 1.2%).

Reviewer's comments: Oral candidiasis is a well known local adverse event of corticosteroids and is expected to occur in the active treated subjects. Overall the incidence and types of local adverse events noted are similar to those noted with other corticosteroids, and do not raise any specific new safety concerns.

3.4.2.5.2.3. Treatment-Related Adverse Events

Most of the reported adverse events were not considered to be treatment-related by the investigators. In the active treatment groups, 11.5-17.5% of subjects had AEs that were judged to be treatment related by the investigator as compared to 6% of subjects in the placebo treatment group. Of these, the most commonly reported was oral candiasis reported in 6.3-7.4% of active treated subjects compared to 2.4% of placebo treated subjects. The other AEs judged to be treatment related are summarized in the following table, and no consistent trends or safety concerns were noted. Of note, local adverse events considered to be treatment related by this reviewer were discussed in the previous section.

Table 23. Study P01545, Incidence of Adverse Events Considered to be Treatment-Related by the Investigators

	MF 200 mcg QPM n = 78 n (%)	MF 400 mcg QPM (1 inh.) n = 80 n (%)	MF 400 mcg QPM (2 inh.) n = 78 n (%)	MF 200 mcg BID n = 81 n (%)	Placebo n = 83 n (%)
Subjects Reporting any Adverse Event	**9 (11.5)**	**14 (17.5)**	**13 (16.7)**	**13 (16.0)**	**5 (6.0)**
Body as a Whole/General Disorders					
Dizziness	0	0	1 (1.3)	0	0
Fever	0	0	1 (1.3)	0	0
Headache	0	0	1 (1.3)	1 (1.2)	0
Central and Peripheral Nervous System Disorders					
Dysphonia	0	2 (2.5)	0	0	1 (1.2)
Migraine	0	1 (1.3)	0	0	0
Gastrointestinal Disorders					
Dry Mouth	1 (1.3)	1 (1.3)	0	0	0
Tongue Ulceration	0	1 (1.3)	0	0	0
Infections and Infestations					
Candidiasis (oral)	5 (6.4)	5 (6.3)	5 (6.4)	6 (7.4)	2 (2.4)
Folliculitis	0	0	1 (1.3)	0	0
Pharyngitis	3 (3.8)	0	1 (1.3)	1 (1.2)	1 (1.2)
Upper Respiratory Tract Infection	0	0	1 (1.3)	1 (1.2)	0
Urinary Tract Infection					
Liver and Biliary System Disorders					
Bilirubinemia	0	1 (1.3)	0	0	0
Hepatic Enzymes Increased	0	1 (1.3)	0	1 (1.2)	0
Musculo-Skeletal System Disorders					
Arthralgia	0	0	1 (1.3)	0	0
Arthritis aggravated	0	1 (1.3)	0	0	0
Musculo-skeletal pain NOS	0	0	1 (1.3)	0	0
Neck Stiffness	0	1 (1.3)	0	0	0

	MF 200 mcg QPM n = 78 n (%)	MF 400 mcg QPM (1 inh.) n = 80 n (%)	MF 400 mcg QPM (2 inh.) n = 78 n (%)	MF 200 mcg BID n = 81 n (%)	Placebo n = 83 n (%)
Subjects Reporting any Adverse Event	**9 (11.5)**	**14 (17.5)**	**13 (16.7)**	**13 (16.0)**	**5 (6.0)**
Respiratory System Disorders					
Bronchitis	0	0	0	1 (1.2)	1 (1.2)
Coughing	0	1 (1.3)	0	0	1 (1.2)
Respiratory disorder NOS	0	0	1 (1.3)	0	0
Throat Dry	0	0	1 (1.3)	0	0
Miscellaneous					
Bruising	0	1 (1.3)	0	0	0
Erythema	0	0	0	1 (1.2)	0
Taste Perversion	0	0	1 (1.3)	0	0

Source: Vol. 18, p. 123-124

3.4.2.5.2.4. Subgroup Analyses of Adverse Events

The sponsor attempted to address any differentials in adverse events noted in different genders, races, or age. Ninety men (56%) and 145 women (61%) reported adverse events. In general, the incidence was similar between the two genders and no indication of a differential response to treatment for males and females was noted. The sponsor states that there were too few subjects in the 12-17 year age group and 65 years and older age group that a subgroup analyses by age was not possible. Similarly, there were too few subjects of other non-Caucasian races to allow for any clinically meaningful interpretation of subgroup analysis by race. [Vol. 18, p. 121]

3.4.2.5.3. Deaths, Serious Adverse Events, and Pregnancies

There were no deaths reported in during the study period or within 30 days of last dose of study treatment. [Vol. 18, p. 128]

Serious adverse events were reported in six subjects, one in each of the MF 400 mcg QPM (1 inh.), MF 400 mcg QPM (2 inh.), and MF 200 mcg BID active treatment groups, and two in the placebo treatment group. One additional patient had an SAE within 30 days of Screening, prior to randomization. No patients in the MF 200 mcg QPM were reported to have SAEs. A brief summary of these SAEs follows. [Vol. 18, p.130-133]

- Subject P01545-01/163, was a 30-year old female, who was admitted to the hospital on Day 83 of treatment (placebo) for severe right lower quadrant pain, nausea and vomiting. The subject was diagnosed with endometriosis and underwent a right salpingo-oophorectomy. The procedure was complicated by atrial fibrillation which responded well to Digoxin, and the hospital course was complicated by pulmonary embolism and seizure. The sponsor states that these events are unlikely related to treatment, and this reviewer agrees with this assessment.

- Subject P01545-10/S00902 was a 16-year old male who received blinded screening medication (placebo) and one month later he was discontinued as a screen failure prior to randomization. Four days later, he experienced an accident involving injury to his face and right hand, with multiple fractures, proptosis and persistent CSF rhinorrhea. This event is unlikely to be related to treatment.
- Subject P01545-25/363 was a 30-year old female, who was admitted to the hospital with right lower quadrant pain on Day 6 of treatment with placebo. The study medication was discontinued and the patient subsequently underwent a laparoscopic appendectomy for appendicitis. This event is also unlikely related to treatment.
- Subject P01545-01/164 was a 34-year old female who underwent an elective total vaginal hysterectomy with bladder tuck for symptoms of stress incontinence and dysmenorrhea on Day 5 of treatment with MF DPI 400 mcg QPM (1 inh.). This event is unlikely to be related to treatment.
- Subject P01545-21/262 was a 35-year old female who received MF DPI 200 mcg BID. On Day 42 of treatment, she reported an increase in severity of depression with suicidal ideation. The subject discontinued therapy 22 days later and withdrew from the study. This event does not appear likely to be related to treatment.
- Subject P01545-23/229 was a 61-year old female who was evaluated in the ER for chest pain on Day 60 of treatment with MF 400 mcg QPM. The patient was observed for 23 hours and the chest pain was reported as unknown etiology. This event is unlikely to be related to active treatment.

The sponsor has reported one unintended pregnancy in the most commonly reported adverse events table. The sponsor has not provided any further information regarding this pregnancy or its outcome. [Vol. 18, p. 110]

3.4.2.5.4. Withdrawals Secondary to Adverse Events [Vol. 18, p.133-134]

Twelve subjects (3%) withdrew from the study secondary to adverse events, three subjects (4%) in the MF 200 mcg QPM group, three (4%) in the MF DPI 400 mcg (1 inh.) group, two (3%) in the MF DPI 400 mcg QPM (2 inh.) group, two (2%) in the MF DPI 200 mcg BID group, and two (2%) in the placebo treatment group. The most commonly reported AEs leading to study discontinuation were bronchitis, upper respiratory infection, and sinusitis, each reported in two patients.

In the MF 200 mcg QPM group, the three subjects that withdrew from the study were reported as having bronchitis (Day 6), upper respiratory infection (Day 27), and sinus infection (Day – 4). In the MF DPI 400 mcg group (1 inh.), the three discontinuations were for migraine headache (Day 51), acute sinusitis (Day 60), and upper respiratory infection (Day 75). In the MF 400 mcg group (2 inh.), the two discontinuations were for prostatitis (Day 66) and dizziness (Day1). In the MF 200 mcg BID group, the two discontinuations were for suicidal ideation (Day 53) and asthmatic bronchitis (Day 1). The two in the placebo group were for appendicitis (Day 7) and bronchitis (Day 45).

Reviewer's comments: With the exception of dizziness, and bronchitis, none of the other AEs are likely to be treatment related. In terms of dizziness and bronchitis, the possibility of

association is present; however, the relatively 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.

3.4.2.5.5. Laboratory Evaluation

Laboratory evaluation did not reveal any clinically meaningful results. [Vol. 23 -24, p. 130-437]

3.4.2.5.6. Vital Signs

No clinically meaningful changes in vital signs [Vol. 24, p. 438-520] were noted after review of the line listings.

3.4.3. Conclusions

This was a 12-week, multi-center, randomized, parallel-group, study with a single-blind placebo/ICS reduction phase, followed by a double-blind treatment phase. This study evaluated the efficacy and safety of mometasone furoate dry powder inhaler (MF DPI) in 400 subjects ages 12 years and older with asthma of at least 12 months duration.

A total of 400 subjects were randomized to 45 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. Discontinuations from the study were common in the placebo treatment group, and somewhat lower and variable in the active treatment groups. A total of 82 subjects (21%) discontinued from the study: 40 subjects (48%) in placebo, 13 subjects (17%) in MF DPI 200 mcg QPM, 12 subjects (15%) in the MF DPI 400 mcg QPM (one inhalation), 9 subjects (11%) in the MF DPI 200 mcg BID, and 8 subjects (10%) in the 400 mcg QPM (2 inhalations). The most common reason for discontinuation was treatment failure, reported by 52 subjects (13%). More patients in the placebo treatment group discontinued secondary to treatment failure (32 subjects, 38.6%) as compared to the MF active treatment groups. In the active treatment groups more patients in the MF DPI 200 mcg QD treatment group (10.3%) discontinued due to treatment failure compared to only 3.7% in the MF DPI 200 mcg BID treatment group. Discontinuations secondary to adverse events were fairly comparable between treatment groups.

The mean duration of asthma, baseline FEV_1 and FEV_1 %predicted, and mean reversibility were similar across treatment groups. The mean duration of asthma ranged between 17.2 to 20.8 years, with the widest range of 1-71 years in the MF 200 mcg QPM group. The mean FEV_1 at baseline was between 2.2 and 2.3 liters in all treatment groups. The mean baseline FEV_1 % predicted was between 65.1 and 69.1 % for all groups.

The primary efficacy endpoint was the change in FEV_1 from baseline to Endpoint (the final visit) and the primary comparison was between MF 400 mcg QD (1 inh.) and placebo. The sponsor in the study report specified the following sequential stepwise testing to control the error rate. 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.

Screening and Baseline FEV_1 LS Means were fairly comparable between treatment groups. The Screening FEV_1 LS means ranged between 2.56 to 2.68 liters and Baseline FEV_1 LS Means ranged between 2.18 to 2.28 liters. As expected, the Screening FEV_1 LS Means were higher than Baseline values, since the Baseline values represented pulmonary function at the end of the steroid-reduction run-in period.

The LS Mean and mean % changes in FEV_1 from Baseline to Endpoint were fairly similar across active treatment groups, but greater compared to placebo. In the active treatment groups, the LS Mean changes in FEV_1 ranged between 0.41 to 0.51 liters and the mean % change from Baseline ranged between 19.2 to 23.7%. The LS Mean change from Baseline to Endpoint for the placebo treatment group was 0.16 liters corresponding to a mean % change of 7.8%.

The analyses of change from baseline and the pairwise comparisons between active treatments and placebo revealed that all active treatments were statistically superior compared to placebo at Endpoint at the 5% significance level ($p < 0.001$); however, no significant difference between the four active treatment groups was noted. The treatment difference in FEV_1 LS Mean change from baseline was 0.25 liters or greater for all active treatment comparisons vs. placebo. Although the sponsor did not adjust for multiple comparisons, a sequential step wise comparison process was involved. The primary comparison was between MF 400 mcg QPM (1 inh.) vs. placebo, and the last sequential comparison was between MF 200 mcg QPM vs. placebo. Since all comparisons prior to the final comparison were significant at $p < 0.001$, the final comparison between MF 200 mcg QPM vs. placebo is considered statistically significant as well. Secondary endpoints, for the most part, trended towards favoring the active treatments as well.

The extent of exposure for the active treatment group was better than for the placebo group. The majority (85 to 94%) of subjects in the active treatment groups received at least 12 weeks of treatment, compared to 57% in the placebo treatment group. The extent of exposure was satisfactory to allow for safety assessments.

In general, adverse events were more common and of similar incidences in the active treatment groups as compared to placebo. Adverse events were reported in 48 to 52 subjects (61.5-64.2%) in the active treatment groups as compared to 37 subjects (44.6%) in the placebo treatment group. A total of 48 subjects (61.5%) in the MF 200 mcg QPM, 50 subjects (62.5%) in the MF 400 mcg QPM (1 inh.), 48 subjects (61.5%) in the MF 400 mcg QPM (2 inh.), 52 subjects (64.2%) in the MF 200 mcg BID, and 37 subjects (44.6%) in the placebo group reported adverse events. Upper respiratory tract infection, headache, pharyngitis, oral candidiasis, and sinusitis were the most commonly reported adverse events. Local adverse events previously suspected of being secondary to corticosteroids, were pharyngitis, oral candiasis and dysphonia. No specific 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 unusual for corticosteroids.

There were no deaths reported during the study period or within 30 days of last dose of study treatment. Serious adverse events were reported in six subjects, one in each of the MF 400 mcg QPM (1 inh.), MF 400 mcg QPM (2 inh.), and MF 200 mcg BID active treatment groups, and two in the placebo treatment group. One additional patient had an SAE within

30 days of Screening, prior to randomization. No patients in the MF 200 mcg QPM were reported to have SAEs. 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 200 mcg QPM dosing.

4. SAFETY UPDATE

Since the original NDA was filed on 11/30/1998, the sponsor is providing a safety update including pooled safety data for finalized studies for MF DPI, MF MDI, and MFNS (nasal spray). This reviewer will mainly focus on the studies relevant to MF DPI. The pooled data bases will be reviewed, as well as brief reviews of relevant safety from supporting studies that could not be pooled secondary to differences in designs.

4.1. Safety Update of Finalized Studies with MF DPI with the Original NDA Safety Pools

The original NDA consisted of two safety populations: the placebo-controlled pool and the grand safety pool. The placebo-controlled pool and the grand safety pool comprised five and eight completed, 3-month studies, respectively in adolescents/adults with asthma. Since submission of the original NDA, the sponsor has completed five additional trials (C98-475, P98-598, P98-601, P01545, and P01978). These studies provide an additional 808 subjects for the MF DPI treated pool. To integrate these studies with the original NDA, the sponsor has combined the data with the original NDA studies in adolescents/adults with asthma, to now have an updated safety pool. The studies in the updated grand safety pool are summarized below.

Table 24. Summary Table of Studies included in the Updated Grand Safety Pool

Study Number	Primary Objective	Design	MF DPI dose (mcg)	Total Evaluated for Safety (n receiving MF)
Phase III Studies in Bronchodilator-Dependent Adolescents/Adults with Asthma				
C96-136	Safety/Efficacy	12-week, R, DB, PC	200, 400 mcg QAM	236 (149)
C96-136 Extension		9-month extension	200, 400 mcg BID 9-month extension)	166 (166)
C96-186	Safety/Efficacy	12-week, R, DB, PC	200, 400 QAM 200 BID	306 (232)
C98-475	Safety/Efficacy	12-week, R, DB, PC	200 QPM	195 (100)
Phase III Studies in Corticosteroid-Dependent Adolescents/Adults with Asthma				
C96-134	Safety/Efficacy	12-week, R, DB,PC, DR, AC	100, 200, 400 BID	365 (220)
C96-168	Safety/Efficacy	12-week, R,DB, PC, AC	100, 200 BID	227 (113)
C96-196	Safety/Efficacy	12-week, R,DB,	200, 400 QAM	286 (228)

		PC	200 QPM 200 mcg BID	[307 in the 2-week open label run-in period]
I96-111	Safety/Efficacy	12-week, R,DB, AC	100, 200, 400 BID	732 (548)
I96-112	Safety/Efficacy	12-week, R,DB, AC	100, 200, 400 BID	730 (549)
I96-113	Safety/Efficacy	12-week, R,DB, AC	200, 400, 600 BID	507 (507)
P01545	Safety/Efficacy	12-week, R,DB, PC	200 BID 400 QPM (1 inh.) 400 QPM (2 inh.) 200 QPM	400 (317)
P01978	Safety/Efficacy	12-week, R, DB, PC	200 BID 400 QPM	268 (181)
P98-598	Safety/Efficacy	2-month, R, DB, AC, PC	400 QAM	264 (106)
P98-601	Safety/Efficacy	2-month, R, DB, AC, PC	400 QAM	262 (104)

Source: Vol. 4, p. 22-25, 35

4.1.4. Study Designs and Conduct

The updated grand-safety pool is comprised of 13 studies;10 placebo-controlled [of which 2 included active comparators], and 3 active-controlled studies. The 10 placebo-controlled studies include eight 3-month studies and two 2-month studies of MF DPI in adolescent and adult asthmatics who were maintained on either β_2-agonists alone or inhaled corticosteroids. The 10 studies were multi-center, randomized, double-blind, placebo-controlled, parallel-group studies in which a total of 2809 patients were treated with the mometasone DPI product, placebo, or an active comparator. The three non-placebo controlled studies include three 3-month, multi-center, randomized, double-blind, active- controlled studies conducted in Europe with similar entry criteria to the placebo-controlled studies. [Vol. 4, p. 30-31]

4.1.5. Safety Endpoints

The safety population comprised all randomized subjects who received at least one dose of study medications. Safety assessments included monitoring for adverse events, serious adverse events, vital signs, physical examinations, routine laboratory testing, pregnancy testing, EKGs, and chest X-rays. [Vol. 4, p. 32-33]

4.1.6. Extent of Exposure

The extent of exposure to MF DPI was reasonably adequate. Eighty-seven percent (87%) or greater of subjects in all MF DPI dose groups received at least 8 weeks of therapy. For most dose groups, 71% or greater received at least 12 weeks of therapy. For the, 200 mcg BID and 200 mcg QPM doses 76% and 71 % of subjects received at least 12 weeks of therapy, respectively. The extent of exposure in general was lower for the placebo group, with only

67% and 47% of subjects receiving 8 weeks and 12 weeks of treatment, respectively. This is not unexpected, since this most likely represents discontinuation from the trial for lack of efficacy. The following table displays the extent of exposure for all of the dose groups receiving MF DPI in the grand safety pool, in addition to those subjects receiving budesonide, beclomethasone, and fluticasone in the active comparator trials.

Table 25. Updated Grand Safety Pool, Extent of Exposure

	Number of Subjects (%)						
	MF DPI BID				MF DPI QD		
Duration of Exposure	100 mcg n=500	200 mcg n=959	400 mcg n=612	600 mcg n=173	200 mcg QAM n=209	200 mcg QPM n=232	400 mcg QAM n=419
≥1 Dose	495 (99)	956 (99)	608 (99)	173 (100)	205 (98)	231 (99)	419 (100)
>4 Days	491 (98)	951 (99)	605 (99)	172 (99)	205 (98)	230 (99)	418 (100)
≥1 Week	488 (98)	947 (99)	601 (98)	171 (99)	200 (96)	221 (95)	408 (97)
≥2 Weeks	471 (94)	924 (96)	589 (96)	171 (99)	200 (96)	221 (95)	408 (97)
≥4 Weeks	452 (90)	902 (94)	569 (93)	161 (93)	197 (94)	215 (93)	393 (94)
≥ 8 Weeks	434 (87)	873 (91)	543 (89)	156 (90)	187 (89)	205 (88)	347 (83)
≥12 Weeks	372 (74)	732 (76)	475 (78)	126 (73)	160 (77)	164 (71)	160 (38)
≥14 Weeks	6 (1)	63 (7)	11 (2)	7 (4)	42 (20)	41 (18)	44 (11)
Unknown	5 (1)	3 (<1)	4 (1)	0	4 (2)	1 (<1)	0
Mean Days	77	80	79	80	79	80	66
Median Days	85	85	85	85	85	84	59
Max Days	106	108	126	108	106	113	102
	MF DPI QM		BUD* QAM	BUD BID	BDP* BID	FP* BID	Placebo
Duration of Exposure	400 mcg (1 inh.) n=172	400 mcg (2 inh) n=78	400 mcg n=211	400 mcg n=181	168 mcg n=128	250 mcg n=184	n=720
≥1 Dose	172 (100)	78 (100)	210 (100)	178 (98)	126 (98)	184 (100)	715 (99)
>4 Days	171 (99)	78 (100)	209 (99)	178 (98)	126 (98)	184 (100)	707 (98)
≥1 Week	169 (98)	78 (100)	209 (99)	177 (98)	121 (95)	183 (99)	685 (95)
≥2 Weeks	167 (97)	77 (99)	202 (96)	174 (96)	117 (91)	180 (98)	623 (87)
≥4 Weeks	165 (96)	74 (95)	187 (89)	168 (93)	113 (88)	177 (96)	558 (78)
≥ 8 Weeks	158 (92)	71 (91)	154 (73)	163 (90)	104 (81)	171 (93)	482 (67)
≥12 Weeks	118 (69)	51 (65)	1 (<1)	143 (79)	88 (69)	150 (82)	339 (47)
≥14 Weeks	0	0	0	7 (4)	2 (2)	6 (3)	30 (4)
Unknown	0	0	1 (<1)	3 (2)	2 (2)	0	5 (1)
Mean Days	79	79	53	81	74	81	62
Median Days	84	85	57	85	84	85	83
Max Days	96	91	89	128	99	118	120

*BUD=budesonide; BDP=beclomethasone; FP=fluticasone

Source Vol. 4, p. 38

4.1.7. Demographics, Updated Grand Safety Pool

Overall, the treatment groups were fairly comparable with respect to gender, race, mean age, mean height and weight. A greater percentage of subjects were female in all treatment groups, ranging from 56-68%, compared to 32-44% for males. The majority of subjects were Caucasian, ranging from 76-88%. The mean age for all subjects ranged from 34-45 years. The majority of subjects were in the 18-<65 year age category (83-94%), compared to 1-15% in the 12 to <18 year age category and 1 to 9% in the 65 year and older category. The mean height for all subjects ranged from 168-169 cm and the mean weight ranged from 71-81 kg. The results for the Grand Safety Pool are presented in the following table. [Vol. 4, p. 42-43]. In the 10 placebo-controlled studies, there were 1669 (59%) females and 1140 (41%) males.

Table 26. Updated Grand Safety Pool, Summary of Demographics

	Number of Subjects (%)						
	MF DPI BID				MF DPI QD		
Characteristic	100 mcg n=500	200 mcg n=959	400 mcg n=612	600 mcg n=173	200 mcg QAM n=209	200 mcg QPM n=232	400 mcg QAM n=419
Sex [n (%)]							
Female	279 (56)	557 (58)	358 (59)	97 (56)	119 (57)	134 (58)	251 (60)
Male	221 (44)	402 (42)	254 (42)	76 (44)	90 (43)	98 (42)	168 (40)
Race [n (%)]							
Caucasian	393 (79)	774 (81)	487 (80)	153 (88)	171 (82)	192 (83)	351 (84)
Non-Caucasian	107 (21)	185 (19)	125 (20)	20 (12)	38 (18)	40 (17)	68 (16)
Age [n (%)]							
12 to <18	30 (6)	59 (6)	36 (6)	1 (1)	23 (11)	34 (15)	64 (15)
18 to <65	448 (90)	837 (87)	520 (85)	160 (93)	182 (87)	189 (82)	350 (84)
≥65	21 (4)	63 (7)	56 (9)	12 (7)	4 (2)	9 (4)	5 (1)
Mean	40 (15)	41 (15)	42 (16)	45 (14)	34 (13)	35 (15)	34 (14)
Range	12-75	12-79	12-75	13-81	12-74	12-71	12-78
Mean Height [cm (SD)]	167 (11)	168 (11)	166 (11)	168 (10)	169 (10)	168 (9)	168 (10)
Mean Weight [kg (SD)]	73 (17)	75 (18)	72 (17)	77 (17)	78 (19)	78 (23)	77 (19)
	MF DPI QPM		BUD* QAM	BUD BID	BDP* BID	FP* BID	Placebo
Characteristic	400 mcg (1 inh.) n=172	400 mcg (2 inh) n=78	400 mcg n=211	400 mcg n=181	168 mcg n=128	250 mcg n=184	n=720
Sex [n (%)]							
Female	108 (63)	45 (58)	120 (57)	103 (57)	87 (68)	113 (61)	419 (58)
Male	64 (37)	33 (42)	91 (43)	78 (43)	41 (32)	71 (39)	302 (42)
Race [n (%)]							
Caucasian	149 (87)	69 (88)	180 (85)	139 (77)	106 (83)	139 (76)	613 (85)

Non-Caucasian	23 (13)	9 (12)	31 (15)	42 (23)	22 (17)	45 (24)	107 (15)
Age [n (%)]							
12 to <18	25 (15)	4 (5)	23 (11)	5 (3)	10 (8)	5 (3)	93 (13)
18 to <65	141 (82)	73 (94)	175 (83)	162 (90)	116 (91)	168 (91)	611 (85)
≥65	6 (4)	1 (1)	13 (6)	14 (8)	2 (2)	10 (5)	16 (2)
Mean (SD)	37 (15)	40 (13)	39 (16)	42 (16)	38 (13)	40 (16)	36 (15)
Range	12-77	12-76	12-83	12-76	12-75	12-79	12-78
Mean Height [cm (SD)]	167 (9)	169 (11)	169 (11)	166 (10)	168 (9)	166 (10)	168 (10)
Mean Weight [kg (SD)]	76 (20)	81 (19)	81 (24)	73 (15)	76 (16)	71 (16)	78 (21)

*BUD=budesonide; BDP=beclomethasone; FP=fluticasone

Source Vol. 4, p. 42-43

4.1.8. Adverse Events

Reviewer's comments: In this review adverse events are described for the updated Grand Safety Pool which includes safety information from the 3 European active-controlled studies and the 10 placebo-controlled studies. The proposed label only describes adverse events from the 10 placebo-controlled studies. While it is acceptable to focus on the placebo-controlled studies in the label, there are inaccuracies in the table of adverse events that the Applicant needs to correct. Historically, AE tables in the label have reported AEs with an incidence of = 3% however, in the proposed label the sponsor reported AEs with an incidence of = 5%. The Applicant will be advised to revise the AE table.

4.1.8.1. Commonly Reported Adverse Events/Corticosteroid Adverse Events

Adverse events were fairly common in all treatment groups, and generally comparable. In the MF DPI treatment groups, 60-77% of all subjects reported adverse events, compared to 49-82% of subjects in other active treatment groups, and 65% of subjects in the placebo group. The most commonly reported adverse events were headache (6-32%), upper respiratory infection (1-24%), viral infection NOS (0-23%), pharyngitis (6-15%), allergy aggravated (0-16%), sinusitis (1-13%), and oral candidiasis (1-12%). With the exception of oral candidiasis, these were fairly comparable between the active treatments and placebo. Other respiratory adverse events, bronchitis (<1-5%), coughing (0-7%), dry throat (0-7%), nasal congestion (0-10%), and rhinitis (0-8%), were fairly similar between treatment groups and placebo, and did not raise any safety concerns.

The incidence of adverse events that could potentially be corticosteroid-related, was low and fairly similar between active treatment groups and placebo, with few exceptions. Pharyngitis as summarized above was reported with a similar frequency among treatment groups. Cataracts were reported in one patient (<1%) in the MF DPI 400 mcg QAM group and in one patient (<1%) in the placebo group. Glaucoma was not reported in any subject. Osteoporosis was not reported in any MF DPI treated subject; however, was reported in one patient each in the FP and placebo treatment groups (<1%). The incidence of factures and

bruising was <1% and comparable to placebo. In general, oral candidiasis and dysphonia were reported in a greater percentage of active-treated subjects compared to placebo (1-12% vs. 2% in placebo and 0-8% vs. 1% in placebo respectively).Oral candidiasis and dysphonia are commonly seen in patients using inhaled corticosteroids, and are not unexpected.

Adverse events reported in 5% or subjects or greater in any treatment group are summarized in the following table.

Reviewer's comments: Although the following table lists AEs occurring at an incidence of 5% or greater, this reviewer examined the line listings of all of the AEs, and did not note data that raised safety concerns. [Vol. 5, p. 348-404] *Additionally, the Applicant stated that the most commonly reported AEs judged to be treatment related by the investigator, were oral candidiasis (≤ 15% per group), pharyngitis (≤8% per group), and headache (<6% per group It is reasonable to conclude that oral candidiasis and pharyngitis are drug-related. Without an actual review of the case reports it is difficult to make a case for headache being a drug-related AE.*

Table 27. Updated Grand Safety Pool, Summary of Adverse Events Occurring ≥5% of Subjects in any Treatment Group

	Number (%) of Subjects													
	MF DPI BID				MF DPI QD					BUD QAM	BUD BID	BDP BID	FP BID	PBO
	100 mcg (n=500)	200 mcg (n=959)	400 mcg (n=612)	600 mcg (n=173)	200 mcg AM (n=209)	200 mcg PM (n=232)	400 mcg AM (n=419)	400 mcg (1 inh) PM (n=172)	400 mcg (2 Inh.) PM (n=78)	400 mcg (n=211)	400 mcg (n=181)	168 mcg (n=128)	250 mcg (n=184)	(n=720)
Any AE	341 (68)	639 (67)	397 (65)	125 (72)	161 (77)	171 (74)	259 (62)	104 (60)	48 (62)	103 (49)	110 (61)	105 (82)	121 (66)	465 (65)
Body As a Whole														
Allergy	14 (3)	17 (2)	18 (3)	9 (5)	0	5 (2)	0	2 (1)	0	1 (<1)	4 (2)	2 (2)	1 (1)	11 (2)
Allergy Aggravated	29 (6)	64 (7)	12 (2)	0	41 (20)	17 (7)	49 (12)	4 (2)	1 (1)	2 (1)	1 (1)	21 (16)	1 (1)	78 (11)
Fatigue	15 (3)	17 (2)	17 (3)	9 (5)	3 (1)	1 (<1)	7 (2)	0	0	2 (1)	3 (2)	0	1 (1)	3 (<1)
Fever	17 (3)	20 (2)	19 (3)	6 (3)	9 (4)	2 (1)	4 (1)	1 (1)	1 (1)	1 (<1)	6 (3)	1 (1)	9 (5)	12 (2)
Headache	115 (23)	194 (20)	126 (21)	39 (23)	65 (31)	46 (20)	81 (19)	20 (12)	5 (6)	23 (11)	32 (18)	41 (32)	33 (18)	146 (20)
Central/Peripheral Nervous System Disorders														
Dysphonia	15 (3)	24 (3)	31 (5)	14 (8)	1 (<1)	0	8 (2)	5 (3)	0	2 (1)	5 (3)	2 (2)	13 (7)	6 (1)
Gastrointestinal System Disorders														
Abdominal Pain	17 (3)	25 (3)	12 (2)	2 (1)	13 (6)	7 (3)	7 (2)	5 (3)	2 (3)	0	2 (1)	7 (5)	8 (4)	15 (2)
Dyspepsia	18 (4)	35 (4)	14 (2)	8 (5)	13 (6)	6 (3)	13 (3)	4 (2)	1 (1)	4 (2)	7 (4)	5 (4)	3 (2)	24 (3)
Nausea	10 (2)	27 (3)	13 (2)	10 (6)	5 (2)	7 (3)	6 (1)	5 (3)	0	5 (2)	0	4 (3)	7 (4)	16 (2)
Infections/Infestations														
Candidiasis/Oral	11 (2)	53 (6)	42 (7)	20 (12)	4 (2)	10 (4)	14 (3)	8 (5)	5 (6)	1 (<1)	3 (2)	5 (4)	18 (10)	12 (2)
Infection/Viral	76 (15)	121 (13)	111 (18)	32 (18)	24 (11)	13 (6)	30 (7)	0	1 (1)	7 (3)	30 (17)	13 (10)	43 (23)	62 (9)
Pharyngitis	67 (13)	97 (10)	66 (11)	12 (7)	16 (8)	29 (13)	31 (7)	11 (6)	8 (10)	17 (8)	18 (10)	17 (13)	28 (15)	51 (7)
Sinusitis	24 (5)	43 (4)	22 (4)	7 (4)	11 (5)	12 (5)	27 (6)	8 (5)	2 (3)	5 (2)	2 (1)	17 (13)	3 (2)	37 (5)
URI	22 (4)	60 (6)	30 (5)	2 (1)	11 (5)	35 (15)	21 (5)	42 (24)	18 (23)	5 (2)	4 (2)	8 (6)	7 (4)	53 (7)
Musculoskeletal System Disorders														

	Number (%) of Subjects													
	MF DPI BID				MF DPI QD					BUD QAM	BUD BID	BDP BID	FP BID	PBO
	100 mcg (n=500)	200 mcg (n=959)	400 mcg (n=612)	600 mcg (n=173)	200 mcg AM (n=209)	200 mcg PM (n=232)	400 mcg AM (n=419)	400 mcg (1 inh) PM (n=172)	400 mcg (2 inh.) PM (n=78)	400 mcg (n=211)	400 mcg (n=181)	168 mcg (n=128)	250 mcg (n=184)	(n=720)
Any AE	**341 (68)**	**639 (67)**	**397 (65)**	**125 (72)**	**161 (77)**	**171 (74)**	**259 (62)**	**104 (60)**	**48 (62)**	**103 (49)**	**110 (61)**	**105 (82)**	**121 (66)**	**465 (65)**
Arthralgia	0	7 (1)	0	0	0	3 (1)	0	5 (3)	4 (5)	0	0	0	0	8 (1)
Back Pain	17 (3)	52 (5)	26 (4)	8 (5)	10 (5)	8 (3)	17 (4)	3 (2)	0	4 (2)	6 (3)	14 (11)	6 (3)	31 (4)
Musculoskeletal Pain	21 (4)	47 (5)	24 (4)	0	10 (5)	9 (4)	15 (4)	7 (4)	3 (4)	0	8 (4)	17 (13)	5 (3)	36 (5)
Myalgia	16 (3)	28 (3)	25 (4)	3 (2)	11 (5)	8 (3)	8 (2)	4 (2)	2 (3)	8 (4)	6 (3)	1 (1)	1 (1)	16 (2)
Reproductive System Disorders														
Dysmenorrhea	13 (5)	35 (6)	12 (3)	2 (2)	10 (8)	6 (4)	10 (4)	4 (4)	1 (2)	2 (2)	2 (2)	5 (6)	8 (7)	18 (4)
Menstrual Disorder	3 (1)	6 (1)	8 (2)	5 (5)	0	0	1 (<1)	0	0	0	2 (2)	0	0	2 (<1)
Respiratory System Disorders														
Bronchitis	15 (3)	23 (2)	29 (5)	9 (5)	2 (1)	5 (2)	2 (<1)	4 (2)	2 (3)	3 (1)	5 (3)	4 (3)	7 (4)	22 (3)
Coughing	23 (5)	30 (3)	39 (6)	7 (4)	7 (3)	4 (2)	12 (3)	3 (2)	0	6 (3)	10 (6)	5 (4)	12 (7)	27 (4)
Dry Throat	3 (1)	17 (2)	23 (4)	12 (7)	1 (<1)	2 (1)	4 (1)	0	1 (1)	1 (<1)	2 (1)	0	3 (2)	9 (1)
Nasal Congestion	23 (5)	50 (5)	29 (5)	7 (4)	21 (10)	10 (4)	11 (3)	2 (1)	0	1 (<1)	3 (2)	11 (9)	12 (7)	38 (5)
Rhinitis	43 (9)	47 (5)	44 (7)	13 (8)	0	18 (8)	5 (1)	1 (1)	0	6 (3)	10 (6)	5 (4)	12 (7)	27 (4)
Rhinorrhea	12 (2)	14 (1)	10 (2)	3 (2)	2 (1)	4 (2)	8 (2)	1 (1)	1 (1)	0	1 (1)	6 (5)	6 (3)	13 (2)

Source: Vol. 4, p. 50-52

4.1.8.2. Subpopulation Analysis of Adverse Events with Respect to Gender, Age, and Race

Although the incidence of AEs was somewhat greater in females (58-82%) compared to males (37-83%), in general, males and females had similar adverse event profiles. No specific gender effects were noted.

The sponsor did not perform any formal subpopulation analyses of AEs by age or race, since non-Caucasians and subjects less than 18 years of age or 65 years of age and older were not well represented. [Vol. 4, p.62-63]

4.1.9. Deaths

No deaths have been reported in any of the studies in the Updated Grand Safety Pool. [Vol. 4, p. 67]

4.1.10. Serious Adverse Events

A total of 56 subjects reported serious adverse events in the Updated Grand Safety Pool, ranging from 0 to 2% of subjects in any treatment group. The most commonly reported SAE was asthma exacerbation, reported by 10 subjects (5 in the MF DPI treatment groups, 3 in the placebo group, 1 in the BDP group, and 1 in the BUD group). Of the MF DPI-treated subjects, two subjects reported asthma exacerbation in the 400 mcg BID group, and one subject reported asthma exacerbation in each of the following groups: MF DPI 100 mcg BID, 200 mcg BID, 600 mcg BID. The other SAEs were varied and the incidence and the types of SAEs were fairly similar between treatment groups and placebo. [Vol. 4, p. 70, 206-209]

Table 28. Updated Grand Safety Pool, Incidence of Overall SAEs and the SAE of Asthma Exacerbation

	Number of Subjects (%)						
	MF DPI BID				MF DPI QD		
	100 mcg n=500	200 mcg n=959	400 mcg n=612	600 mcg n=173	200 mcg QAM n=209	200 mcg QPM n=232	400 mcg QAM n=419
Any SAE	5 (1)	11 (1)	7 (1)	4 (2)	1 (<1)	1 (1)	5 (1)
Asthma Exacerbation	1 (<1)	1 (<1)	2 (<1)	1 (<1)	0	0	0
	MF DPI QPM		BUD* QAM	BUD BID	BDP* BID	FP* BID	Placebo
	400 mcg (1 inh.) n=172	400 mcg (2 inh) n=78	400 mcg n=211	400 mcg n=181	168 mcg n=128	250 mcg n=184	n=720
Any SAE	3 (2)	1 (1)	0	3 (2)	2 (2)	3 (2)	10 (1)
Asthma Exacerbation	0	0	0	1 (<1)	1 <1)	0	3 (<1)

*BUD=budesonide; BDP=beclomethasone; FP=fluticasone

Source Vol. 4, p. 70, 206-209

4.1.11. Pregnancies

A total of seven unintended pregnancies were reported for the updated grand safety pool (all new studies in addition to the original NDA studies). Of the seven pregnancies, two resulted in a normal pregnancy with healthy newborns, two in spontaneous abortions, one elective termination of pregnancy, and two were lost-to-follow up. Of the two spontaneous abortions, one occurred in a subject taking MF DPI 600 mcg BID and one occurred in a subject during screening, prior to receipt of any medication. The two healthy pregnancies with normal outcomes were noted in the MF DPI 400 mcg QAM group.

Reviewer's comments: the number of unintended pregnancies was low, and although one subject on active treatment reported a spontaneous abortion, this finding is insufficient to draw conclusions on a possible association between mometasone and miscarriage.

4.1.12. Withdrawals Secondary to Adverse Events

Withdrawals secondary to adverse events were uncommon, and fairly comparable between all MF DPI treatment groups, BUD BID, BDP BID, FP BID, and placebo groups. A total of 3-6% of subjects in the MF DPI-treated groups withdrew secondary to adverse events compared to 6% of placebo-treated subjects. The most common reasons for discontinuation were asthma exacerbation/asthma aggravation (25 subjects total, 0.5% total study population), upper respiratory tract infection/flu like symptoms (23 subjects, 0.5%), bronchitis (23 subjects, 0.4%), and sinusitis (13 subjects, 0.3%). The percentage of subjects discontinuing for any given reason were comparable between all treatment groups.

Reviewer's comments: the reasons for discontinuation are not unexpected given the disease under study and the incidences are quite low. These data do not present any new safety concerns.

The following table summarizes the number (%) of subjects discontinuing from the studies secondary to adverse events occurring in =2 subjects in any active treatment group in the Updated Grand Safety Pool.

Table 29. Updated Grand Safety Pool, Number (%) of Subjects Discontinuing From Study Secondary to Adverse Events Occurring in 2 Subjects or More in any Active Treatment Group

	Number of Subjects (%)						
	MF DPI BID				MF DPI QD		
	100 mcg n=500	200 mcg n=959	400 mcg n=612	600 mcg n=173	200 mcg QAM n=209	200 mcg QPM n=232	400 mcg QAM n=419
Discontinued for any AE	20 (4)	26 (3)	19 (3)	8 (5)	13 (6)	5 (2)	17 (4)
Asthma Exacerbation	4 (<1)	2 (<1)	1 (<1)	1 (<1)	4 (2)	0	2
Bronchitis	2 (<1)	1 (<1)	2 (<1)	0	0	1 (<1)	2
Dysphonia	0	3 (<1)	3 (<1)	0	1 (<1)	0	2 (<1)
Headache	2 (<1)	1 (<1)	0	0	1 (<1)	0	1 (<1)

	Number of Subjects (%)						
	MF DPI BID				MF DPI QD		
	100 mcg n=500	200 mcg n=959	400 mcg n=612	600 mcg n=173	200 mcg QAM n=209	200 mcg QPM n=232	400 mcg QAM n=419
Discontinued for any AE	20 (4)	26 (3)	19 (3)	8 (5)	13 (6)	5 (2)	17 (4)
Nasal/Sinus Congestion	2 (<1)	2 (<1)	0	0	0	0	0
Nausea/Vomiting	2 (<1)	0	0	0	2 (1)	0	0
Pharyngitis	2 (<1)	2 (<1)	0	0	0	0	0
Sinusitis	2 (<1)	0	0	0	0	1 (<1)	5 (1)
URI/Flu Like Sxs	0	6 (<1)	1 (<1)	0	2 (1)	2 (1)	2 (<1)
Viral Infection	1 (<1)	0	1 (<1)	0	0	0	0
	MF DPI QPM		BUD* QAM	BUD BID	BDP* BID	FP* BID	Placebo
	400 mcg (1 inh.) n=172	400 mcg (2 inh) n=78	400 mcg n=211	400 mcg n=181	168 mcg n=128	250 mcg n=184	n=720
Discontinued for Any AE	5 (3)	2 (3)	1 (<1)	7 (4)	7 (5)	8 (4)	42 (6)
Asthma Exacerbation	0	0	0	1 (<1)	0	1 (<1)	9 (1)
Bronchitis	1 (<1)	0	0	1 (<1)	2 (2)	0	8 (1)
Dysphonia	0	0	0	0	0	1 (<1)	0
Headache	1 (<1)	0	0	0	0	0	0
Nasal/Sinus Congestion	0	0	0	0	0	0	1 (<1)
Nausea/Vomiting	0	0	0	0	0	0	1 (<1)
Pharyngitis	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Sinusitis	1 (<1)	0	0	0	1 (<1)	0	3 (<1)
URI/Flu Like Sxs	1 (<1)	0	0	0	1 (<1)	0	9 (1)
Viral Infection	0	0	0	3 (2)	0	1 (<1)	2 (<1)

*BUD=budesonide; BDP=beclomethasone; FP=fluticasone

Source Vol. 4, p. 67, 210-216; Note: this table was not provided by the sponsor; it was created by this reviewer from Line Listings

4.1.13. Laboratory Testing and Vital Signs

No clinically meaningful or consistent abnormalities were noted in laboratory testing or vital signs. The inclusion of the additional completed studies in the updated Safety Data Pool did not change this safety finding. [Vol. 4, p. 73-75]

4.1.14. Summary

Since the original NDA submission, the sponsor completed five additional studies, for an updated grand safety pool. The updated grand-safety pool is comprised of 13 studies, 10 placebo-controlled, and 3 non-placebo controlled.

Review of these additional studies pooled with the original NDA studies does not raise any new safety concerns. Overall, the incidence and types of AEs, SAEs, laboratory abnormalities, and vital sign changes were similar between treatment groups. A greater percentage of subjects in the MF DPI group had an increased incidence of oral candidiasis, pharyngitis, and dysphonia compared to placebo as would be expected for an inhaled corticosteroid. In summary review of the Updated Grand Safety Pool does not change the safety conclusion from the initial NDA review that mometasone furoate DPI is reasonably safe and well tolerated in the adolescent/adult asthmatic population..

4.2. Other Studies of MF DPI in Adolescent/Adults with Asthma Not Included in the Updated Grand Safety Pool

This section will briefly review other studies pertinent to safety that could not be pooled secondary to different study designs. Two 2-year bone densitometry studies, two 1-month HPA-axis function studies, two 2-month studies, one 8-week study comparing MF DPI to fluticasone, and one 14-day HPA-Axis function study will be briefly summarized.

4.2.15. Safety from two 2-Year Bone Densitometry Studies

Two 2-year studies C97-210 and C98-302 were conducted in asthmatics to evaluate the effect of mometasone on bone mineral density.

4.2.15.1. C97-210

This was a Phase 3, double-blind, parallel-group, 2-year safety study of MF 400 mcg BID vs. placebo in 87 adults 18 to 50 years of age with asthma (of at least 6 months duration and an FEV_1 at least 65% predicted) maintained on inhaled β_2 agonists alone or in combination with non-steroidal anti-inflammatory medications. Subjects were randomized 2:1 to MF DPI or placebo and were seen in the office at Screening, Baseline, and Weeks 1, 4, 12, 26, 39, 52, 65, 78, 91, and 104.

The primary safety endpoint was percent change in lumbar spine bone mineral density (BMD) from baseline to the end of 2 years. Secondary endpoints were total femoral and femoral neck BMD, markers of bone metabolism (serum osteocalcin and N-telopeptide), and adrenal axis function (urinary free cortisol and Cortrosyn®-stimulation test). Other safety variables included adverse events, vital signs, physical examination (to include specific eye examinations), and laboratory testing.

A total of 87 subjects were randomized; however, 42 subjects (48%) discontinued from the study. All randomized subjects received at least one dose of treatment. Of the subjects randomized to MF DPI 400 mcg BID, 32/51 (63%) completed the full 104 weeks of treatment compared to 13/30 (43%) of placebo-treated subjects. Nine subjects discontinued form the study secondary to AEs and two subjects discontinued for treatment failure. Of the discontinuations secondary to AEs, four subjects in the MF DPI treatment group and one in

the placebo treatment group discontinued for a bone disorder (at least a 6% loss of BMD in the lumbar spine or total femur). Other AEs leading to discontinuation in the MF group included pleurisy, pregnancy, subcapsular cataract, arthralgia and anxiety.

The sponsor states that both treatment groups were similar at baseline with respect to sex, race, age, and baseline disease status. Most subjects were Caucasian (94%) with fairly equal representation of males and females. The mean age for the study population ranged from 30 to 32 years, the mean duration of asthma from 16 to18 years, and mean FEV_1 % predicted at baseline from 82 to 83%.

The primary safety endpoint was change from baseline in LS lumbar spine BMD. The baseline LS mean lumbar spine BMDs were similar at baseline in both treatment groups (1.104 g/cm^2 for MF DPI and 1.110 g/cm^2 for placebo). There was no statistically significant difference between the two treatment groups with respect to change from Baseline in LS mean lumbar spine BMD at endpoint. However, there was a numerical trend for a greater decrease in BMD in the MF DPI treatment group compared to placebo. At endpoint, the LS mean change from Baseline in the MF DPI and placebo treatment groups was -0.018 and -0.006, respectively. The LS% mean change from Baseline to Endpoint was -1.57% for the MF DPI group and -0.46% for the placebo group. At Week 104, the LS mean change was -0.014 and 0.002, respectively. These results are summarized in the following table.

Table 30. Study C97-210, Baseline and Change from Baseline in Lumbar Spine BMD (g/cm^2) by Visit and Treatment Group

	MF DPI 400 mcg BID			Placebo				
	n	LS Mean	LS % mean	n	LS Mean	LS % mean	Pooled SD	P-value
Baseline	51	1.104	–	27	1.110	–	0.137	0.849
Change from Baseline at								
Week 26	45	-0.007	-0.541	24	0.002	0.273	2.598	0.228
Week 52	41	-0.016	-1.392	18	-0.003	-0.114	3.403	0.198
Week 104	33	-0.014	-1.245	11	0.002	0.082	3.128	0.256
Endpoint	45	-0.018	-1.574	24	-0.006	-0.426	3.500	0.207

Source: Vol.4, p. 83

Similarly, there were no statistically significant differences between MF DPI and placebo for change from Baseline to Endpoint in Total Femoral BMD. At Baseline, the femoral neck BMDs were similar for both treatment groups, 1.017 g/cm^2 for the MF DPI group and 1.026 g/cm^2 for the placebo group. The LS mean change from Baseline at Endpoint was -0.015 g/cm^2 for MF DPI and 0 g/cm^2 for placebo. The LS% mean change from baseline to Endpoint was -1.4% for MF DPI, compared to 0.12% for placebo. Although the differences between the two treatment groups did not reach statistical significance at Endpoint, there was a numerical trend towards BMD loss in the MF DPI treatment group compared to placebo. These results are summarized in the following table.

Table 31. Study C97-210, Baseline and Change from Baseline in Total Femoral Neck BMD (g/cm^2) by Visit and Treatment Group

	MF DPI 400 mcg BID			Placebo				
	n	LS Mean	LS % mean	n	LS Mean	LS % mean	Pooled SD	P-value
Baseline	50	1.017	–	30	1.026	–	0.135	0.765
Change from Baseline at								
Week 26	44	-0.007	-0.659	25	0.006	0.612	2.065	0.019
Week 52	40	-0.014	-1.313	19	0.002	0.275	2.456	0.027
Week 104	32	-0.015	-1.333	13	0.001	0.237	3.072	1.040
Endpoint	44	-0.15	-1.415	25	0	0.12	2.885	0.057

Source: Vol.4, p. 83

Serum osteocalcin, urinary N-telopeptide, Cortrosyn-stimulation tests were also performed as secondary safety endpoints. Markers of bone metabolism - serum osteocalcin and urinary N-telopeptide were decreased in the mometasone group compared to placebo at Week 104. The clinical interpretation of these findings in the setting of a clinical study is unclear. Additionally, the consistent elevation of urinary N-telopeptide at all time points in the placebo group make these data even less interpretable.

Evaluation of HPA-axis suppression using the Cortrosyn-stimulation testing showed similar results for the mean change in post minus pre-stimulation values for the MF DPI and the placebo groups. However, six individuals had an abnormal response to Cortrosyn-stimulation at Endpoint. At Endpoint, Six out of 48 individuals in the MF DPI group had pre-Cortrosyn plasma cortisol levels less than 5 mcg/dL (low) and post-Cortrosyn plasma cortisol levels less than 18 mcg/dL (low) compared to none in the placebo treatment group. This finding is clinically relevant as it demonstrates that although there was not a population mean suppressive effect on adrenal function, there were individual subjects with increased sensitivity and possible adrenal suppression.

A total of 98% DPI-treated subjects (n=51) reported AEs compared to 90% of placebo-treated subjects (n=30). The most frequently reported AEs were headache (MF DPI: 55%; placebo: 43%), upper respiratory tract infections (MF DPI: 53%; placebo 40%), rhinitis (MF DPI: 51%; placebo 33%), and viral infection (MF DPI: 41%; placebo 20%). As expected, pharyngitis and oral candidiasis were reported in a greater percentage of subjects in the MF DPI group (29% and 18% respective) compared to placebo (20% and 3%). Four SAEs were reported in this study, three in the MF DPI group (spinal disorder, cholelithiasis, and spontaneous abortion) and one in the placebo group (salivary gland calculus). No clinically relevant changes in vital signs, laboratory testing, or physical examination were observed in this study.

Reviewer's comments: In general, a greater percentage of MF DPI treated subjects reported AEs than placebo treated subjects. This may be related to the 2:1 randomization used in this study to some degree and the small study size as well. As the incidences and types of

AEs were similar between active treatment and placebo in the pooled study results, the results of this study are not that concerning.

4.2.15.2. C98-302

This was a Phase III, double-blind, placebo controlled, 2-year safety study of MF DPI 200 mcg BID compared to placebo in adult males and females ages 18 to 50 years of age with asthma previously maintained on inhaled β_2-agonists alone or in combination with non-steroidal anti-inflammatory medications. The study population and design was similar to the previously described study, with the exception of doses studied and that HPA-axis suppression was assessed by urinary free cortisol and 8-am plasma cortisol concentrations.

One hundred and three (103) subjects were randomized to receive either MF DPI 200 mcg BID (n=52) or placebo (n=51). A total 31 subjects (60%) and 25 subjects (51%) completed the study in the MF DPI and placebo groups, respectively. Six subjects in the MF DPI group and four subjects in the placebo group discontinued secondary to AEs and three subjects (all in the placebo group) discontinued secondary to lack of efficacy. Four subjects in the MF DPI group and none in the placebo-treated group discontinued from the study for a BMD loss of $\geq$6%.

There were no appreciable differences between the treatment groups with respect to sex, race, age, baseline disease status, or duration of asthma. Most subjects were Caucasian (81%) and there was an equal representation of males and females in the MF DPI group (25 and 27, respectively) and a slightly greater representation of females than males in the placebo group (30 and 21 respectively). Baseline FEV_1 % predicted ranged from 85 to 88%.

The primary safety endpoint was the change in lumbar spine BMD from Baseline to the 2-year time point; the change in femoral neck BMD was a secondary endpoint. The two treatment groups were fairly comparable at Baseline for LS BMD, 1.150 g/cm^2 for MF DPI and 1.165 g/cm^2 for placebo. The mean change from Baseline to Endpoint in the LS BMD was -0.015 (-1.43%) for the MF DPI group and 0.002 (0.25%) for the placebo group. The difference between MF DPI and placebo was statistically significant at Endpoint ($p = 0.016$) and at Week 104 ($p = 0.025$). In contrast, no statistically significant differences were noted between the treatment groups for change from Baseline to Endpoint or Week 104 in total femoral BMD or femoral neck BMD. The MF DPI had a slightly lower mean Baseline BMD (1.064 g/cm^2) compared to placebo (1.082 g/cm^2) and the mean change from Baseline to Endpoint was -0.003 (-0.36%) for the MF DPI group and 0.003 (0.29%) for the placebo group.

Serum osteocalcin and urinary telopeptide measurements did not reveal any clinically meaningful differences between the two treatment groups. The population mean 8-AM cortisol values showed a similar trend for both the active and the placebo treatment groups except for Week 52 where the mean 8-AM cortisol values were lower in the MF DPI group compared to the placebo group. This could be attributable to the fact that at Week 52 2/38 subjects had 8-AM cortisol values below the lower limit of normal compared to 0/34 in the placebo group which may have skewed the data. Additionally 5/52 subjects in the MF group compared to 3/51 in the placebo group had an 8-AM cortisol below the lower limit of

normal at any visit. The Applicant reported that 12-hour urine cortisol data was highly variable and as such would be disregarded.

Adverse events were reported by 46 subjects (89%) and 46 subjects (90%) in the MF DPI and placebo groups, respectively. The most commonly reported AEs were upper respiratory tract infection (MF DPI: 58%; placebo: 41%), headache (MF DPI:39%; placebo: 33%), back pain (MF DPI: 25%; placebo 6%), sinusitis (MF DPI: 21%; placebo: 6%), pharyngitis (MF DPI: 15%; placebo: 12%), allergy aggravate (MF DPI: 14%; placebo: 8%), and oral candidiasis (MF DPI: 14%; placebo: 4%). Three SAEs were reported in the study, two in the MF DPI group (proctitis/gastroenteritis and ovarian disorder) and one in the placebo treatment group (maternal drug exposure).

4.2.15.3. Summary of BMD Studies

In Study C97-210, at the end of two years, no statistically significant differences between active treatment (MF DPI 400 mcg BID) and placebo treatment in either LS or total femoral BMD were noted, although there was a trend towards a greater decrease in BMD in the MF DPI treatment group compared to placebo. However, in Study C98-302, where lower daily doses of MF DPI (200 mcg BID) were compared to placebo, statistically significant differences in the change from Baseline to Endpoint in LS BMD were seen between active treatment and placebo. No significant changes were noted for total femoral or femoral neck BMD in this second study. The small sample size, unequal randomization in study C97-210, and the large percentage of discontinuations (48% in study C97-210) probably account for the different results in the two studies. Generally, a 2:1 randomization as done in C97-210 should not have a significant impact on demonstrating differences between treatments; however, with the small sample size and the large percentage of drop outs, only 32 patients in the MF-treated group compared to 13 in the placebo group completed the study and had Week 104 (end of study treatment) data. Despite the differing results, we can conclude that MF DPI at doses of 200 mcg BID or greater may decrease BMD with prolonged use. These findings are clinically important given that the population studied comprised pre-menopausal females and male asthmatic patients with a mean age of 31 years who unlike COPD patients do not have inherent risk factors for decrease BMD.

4.2.16. Safety from two 1-Month, HPA-Axis Function Studies: P00682 and P00683

Studies P00682 and P0063 were similar in design and were single-center, randomized, third-party blind, placebo-controlled 30-day safety studies whose objective was to evaluate the potential systemic activity of MF DPI 400 mcg QD compared to FP DPI (250 and 500 mcg BID), BUD DPI (400 and 800 mcg BID), prednisone 10 mg QD, and placebo on 24-hour integrated serum cortisol concentrations ($AUC_{0\text{-}24}$). Secondary objectives included cosyntropin-stimulation testing, and routine standard safety assessments.

Adults 18 years and older with asthma (FEV_1 at least 60% predicted and not greater than 90% predicted) maintained on inhaled corticosteroids for at least 30 days with serum cortisol between 8 and 25 mcg/dL were enrolled into the study. A total of 80 subjects were randomized in each study, of which 80 and 79 subjects completed the studies in P00682 and P00683, respectively. Mean exposure was 29 to 30 days for both studies with compliance 90 to 107% in P00682 and 63 to 110% in P00683. Subjects were similar at Baseline for

demographics in all treatment groups for both studies. The majority of subjects were females in both studies (74-84%) and the mean ages ranged from 31 to 40 years. The mean FEV_1 % predicted at Baseline ranged from 78 to 82%.

The primary endpoint was the percent change in serum cortisol from Baseline to Day 15 and Day 29. The Applicant presented the results of these 2 studies together. At day 15 the mean % change in the 24-hour cortisol AUC showed a decrease of 20.7% for the placebo group, and 16 % for the prednisone group and on Day 29 showed a decrease of 2.2% for the placebo group and an increase of 6.45% for the prednisone group. The results of the prednisone and the placebo group raise serious questions about the design and conduct of the study. The MF 400 mcg QD group showed essentially no difference on Days 15 and 29 compared to notable differences for the FP 500 BID group (16% and 28% decrease at Day's 15 and 29 respectively) however, no conclusions can be drawn from these results given the findings in the placebo and the prednisone group.

In general, AEs were not commonly reported in either study (0-13% incidence in both studies). The types and incidences of AEs was comparable between treatment groups and the most commonly reported AE was headache (6-19%). No SAEs or clinically relevant changes in vital signs or physical examinations were reported.

4.2.17. Safety from Two 2-Month Studies: P98-602 and P98-603

Studies P98-602 and P98-603 were randomized, double-blind, double-dummy, placebo-controlled, 8-week safety and efficacy studies comparing MF DPI 400 mcg QAM to FP 250 mcg BID and placebo. Subjects with asthma (FEV_1 between 50% and 85% predicted) who were previously maintained on inhaled corticosteroids were enrolled into the study. The primary efficacy endpoint was the percent change in FEV_1 from Baseline to Endpoint. Safety variables included AEs, vitals, physical examination, and laboratory testing.

A total of 227 subjects were enrolled in Study P98-602 (MF DPI, 78; FP DPI, 76; placebo, 73) and 233 subjects in Study P98-603 (MF DPI, 75; FP DPI, 79; placebo, 79). Seventy-one percent (71%) to 89% of subjects in Study P98-602 and 67% to 92% in Study P98-603 completed the studies. Four and eight subjects, respectively, discontinued from Study P98-602 and P98-603 due to AEs.

Subjects were similar at Baseline for demographic and baseline disease characteristics in both studies. The majority of subjects in both studies were Caucasian (87%-91%) and female (59%-62%). The mean ages for both studies ranged from 36-41 years. The Baseline FEV_1 percent predicted ranged from 71%-73%.

Adverse events were reported in 47%-70% of subjects in Study P98-602 and in 49%-65% of subjects in Study P98-603. The most commonly reported AEs were headache (11-19%), pharyngitis (4-10%), and back pain (4-6%) in study P98-602 and pharyngitis (9-15%), URIs (6-9%), and headache (5-14%) in Study P98-603. The incidence of these AEs in general was comparable to placebo and lower than or comparable to FP. Oral candidiasis was reported only in Study P98-603, in one subject each (1%) in the MF DPI and placebo treatment groups and in seven subjects (9%) in the FP treatment group. Dysphonia was reported in only Study P98-602, and only in four subjects (5%) in the FP treatment group (none in the other groups). Three SAEs were reported in these studies, two in the FP group

(anaphylactic reaction to peanuts and hysterectomy for fibroid) and one in the placebo group (umbilicus cyst). No clinically relevant changes in vital signs or laboratory testing were reported.

In conclusion, MF DPI 400 mcg QAM was well tolerated with the incidence and types of AEs comparable to the Updated Grand Safety Pool.

4.2.18. Safety from 8-Week Study Vs. Fluticasone, P01198

This was a Phase III, open-label, randomized, active-controlled, 8-week safety and efficacy study comparing MF DPI 400 mcg QPM to FP MDI 250 mcg BID in subjects 12 years of age and older with asthma (FEV_1 % predicted between 60% and 90% inclusive). Routine safety assessments were performed.

A total of 167 subjects were randomized, 82 to MF DPI and 85 to FP MDI. The majority of subjects completed the study in each treatment group (93.9% and 97.6% for MF DPI and FP MDI, respectively). Two subjects withdrew from the study in the FP MDI group secondary to AEs, and none in the MF DPI group. Subjects were comparable at Baseline for demographics and baseline disease characteristics. The mean age was 42.8 and 43.3 years for the MF DPI and FP MDI groups, respectively. Most subject were Caucasian (98-99%) and female (63-64%).

Adverse events were reported in 65.9% of MF DPI treated subjects and in 62.4% of FP MDI treated subjects. In general, the types and incidences of AEs were comparable between treatment groups, and the most commonly reported AE was headache (17-25.6%). Four SAEs were reported in the study, including one death. The sponsor does not elaborate further on the SAEs, except to state that the death occurred prior to randomization before any treatment was received.

This study shows that the safety profiles for MF DPI and FP MDI were similar, and the types and incidences of AEs noted were similar to the overall Updated Grand Safety Pool.

4.2.19. Safety from 14-Day HPA-Axis Function Study, P01372

This was a Phase IV, randomized, third-party blind, parallel-group, active-controlled single-center study comparing the effects of 14-days of treatment with MF DPI 400 mcg QAM to beclomethasone dipropionate (BDP) 200 mcg BID and BDP 400 mcg BID on HPA-axis suppression in mild asthmatics (FEV_1 % predicted $\geq$80%) 18 to 65 years of age. The primary endpoint was the mean change in serum cortisol $AUC_{0\text{-}24}$ from Baseline to Day 14 and secondary endpoints included 24-hour urinary free cortisol and standard safety assessments (except routine laboratory testing was not reported as being done).

Fifty-three subjects were randomized to the study, 18 to the MF DPI group, 18 to the BDP 200 mcg BID group, and 17 to the BDP 400 mcg BID group. Ninety-two percent (92%, 49 subjects) completed the study, with one subject each in the MF DPI and BDP 200 mcg BID groups and two subjects in the BDP 400 mcg BID group discontinuing from the study for protocol deviations. No notable differences in Baseline demographics or disease characteristics were reported. The majority of subjects were male (88-100%/group) and Caucasian (94-100%/group). The mean age was 27.3 to 29.4 years and the baseline mean FEV_1 % predicted was 87%-91%.

At Day 14, all three treatment groups had decreases in mean serum cortisol AUC_{0-24} and 24-hour urinary cortisol. The mean % decrease in serum cortisol AUC_{0-24}, was lowest for the MF 200 mcg BID group (6.5%) compared to the BDP 200 mcg BID and 400 mcg BID groups, (32.5%, and 30.5% respectively). Similarly all treatment groups showed decreases in mean urinary 24-hour cortisol levels from Baseline, with the MF DPI showing lesser mean% decreases (9.6%) compared to BDP 200 mcg BID (34.3%) and BDP 400 mcg BID (33.4%).

Of note this study had no placebo arm and these results should be interpreted with caution. This study is not adequately designed to make comparative claims of MF over BDP.. Adverse events were reported in 11 subjects (61%) in the MF DPI-treated group, in 8 subjects (44%) in the BDP 200 mcg BID-treated group, and in 11 subjects (65%) in the BDP 400 mcg-treated group. The most commonly reported AEs in the MF DPI group were headache (33%), and dry throat (16.7%) compared to headache (16.7%) and dyspepsia (11%) in the BDP 200 mcg BID group and headache (29%) and sore throat (18%) in the BDP 400 mcg BID group. There were no SAEs or discontinuations secondary to AEs in this study. No clinically relevant changes in vital signs or physical examination were reported.

In conclusion, this study shows that MF DPI does demonstrate some HPA-axis suppression, however, to a lesser degree compared to BDP 200 mcg BID or BDP 400 mcg BID.

4.3. Relevant Studies of MF DPI in Children (Aged 4-11 Years, Inclusive) With Asthma

The Applicant is completing their pediatric development for children ages 4-11 years., All of the studies briefly summarized in this safety update will be submitted as full clinical study reports in a subsequent NDA or supplemental NDA and as such these safety summaries will not be reviewed here, with the exception of a 1-year growth study.. This reviewer has looked at the safety summaries from the other studies, and in general the safety profile appear to be similar to what was seen in adults. Study C98-384

This was a Phase III, multi-center, randomized, double-blind, placebo-controlled 52-week intermediate-growth study in children ages 4-9 years with asthma (FEV_1 or PEFR $\geq$75% predicted), whose skeletal age was within 2 years of chronological age, baseline cortisol was $\geq$5 mg/dL, and sexual maturity was no greater than Tanner Stage 1. The primary objective was to compare the effects of MF DPI 100 mcg BID,100 mcg QAM, 200 mcg QAM on growth velocity to placebo and to each other. The primary safety endpoint was the change from Baseline in growth velocity as measured by stadiometry during the 1-year treatment period. Other safety variables included 8-AM plasma cortisol, 12-hour urinary free cortisol, absolute change in standing height, AEs, laboratory testing, vital signs, and physical examination.

A total of 187 subjects were randomized to the study: MF DPI 100 mcg BID, 44; MF DPI 100 mcg QAM, 48; MF DPI 200 mcg QAM, 50; and placebo, 45. A total of 67-75% of subjects completed the study (MF DPI 100 mcg BID, 75%; MF DPI 100 mcg QAM, 79%; MF DPI 200 mcg QAM, 68%; and placebo, 67%). Seventy percent of subjects received at least 50 weeks of treatment. Of a 187 subjects, 122 entered the 3-month follow-up period, and greater than 80% of subjects completed the Follow-up Phase.

The primary safety variable was growth velocity over the 1-year study period and showed a statistically significant overall treatment effect (p=0.046). The mean growth velocities during the 1-year treatment period were 5.88 cm/yr for MF DPI 100 mcg BID, 6.42 cm/yr for MF DPI 100 mcg QAM, 5.82 cm/yr for MF DPI 200 mcg QAM, and 6.52 cm/yr for placebo. The difference between MF DPI 200 mcg QAM and placebo was statistically significant (p=0.02). Although MF DPI 100 mcg BID or 100 mcg QAM has no statistically significant effect on growth velocity compared to placebo, the 100 mcg BID approached statistical significance (p=0.10).

Other measures of bone maturity and bone formation were similar between the active treatment groups and placebo. The mean change from Baseline in skeletal age for all MF DPI groups was compared to placebo, and no meaningful changes were noted. Similarly, no meaningful changes were noted in serum osteocalcin.

MF DPI treatment had no effect on HPA-axis as assessed by plasma cortisol and 12-hour urinary cortisol.

Review of adverse events indicated that MF DPI was well tolerated. The incidence and types of AEs observed were similar to those observed with other adult studies. Five SAEs were reported in this study: one in the MF DPI 100 mcg BID (pneumonia/viral infection/aggravated asthma), two subjects in the MF DPI 200 mcg QAM (both with aggravated asthma, and two subjects in the placebo treatment group (both with aggravated asthma).

In conclusion, MF DPI was well tolerated; however, MF DPI 200 mcg daily for one year decreased linear growth velocity , with MF DPI 200 mcg QAM having a statistically significantly difference compared to placebo., and MF DPI 100 mcg BID approaching a statistical significance difference compared to placebo.

4.4. Conclusions from Safety Update

The safety update provided safety summaries from an additional five randomized, double-blind 12-weeks studies, which were pooled with the original NDA studies, and the updated grand safety pool was reviewed for safety purposes. Additionally, the safety update provided information on other studies that were not able to be pooled with the original NDA, two 2-year studies assessing BMD, three studies assessing HPA-axis suppression, and one study assessing pediatric growth velocity.

Review of these additional studies pooled with the original NDA studies does not raise any new safety concerns. Overall, the incidence and types of AEs, SAEs, laboratory abnormalities, and vital sign changes were similar between treatment groups. A greater percentage of subjects in the MF DPI group had an increased incidence of oral candidiasis, pharyngitis, and dysphonia compared to placebo, but this is not unexpected for corticosteroids. Mometasone furoate DPI appears to safe and well tolerated based on review of the Updated Grand Safety Pool, and the other additional studies.

The two BMD studies support the conclusion that MF DPI may decrease BMD in some individuals. Although the two HPA-axis suppression studies did not demonstrate HPA-axis suppression, they may not have been adequately designed to do so. Growth velocity was assessed in children 4-9 years of age, and MF DPI was shown to have a significant effect on

growth velocity compared to placebo with MF DPI 200 mcg QAM shown to be statistically significantly different compared to placebo, and MF DPI 100 BID shown to be approaching a statistically significant difference compared to placebo.

In conclusion, MF DPI was well tolerated and the types and incidences of AEs and SAEs reported were similar to those noted in the original NDA. The data taken together support the conclusion that MF DPI has effects on BMD, the HPA-axis, and growth velocity (in children).

5. LABELING

See annotated label for labeling comments and changes.

6. RECOMMENDATION

From a clinical standpoint, MF 200 mcg QPM can be approved.

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

/s/

Tejashri Purohit-Sheth
5/4/04 01:49:43 PM
MEDICAL OFFICER

Lydia McClain
5/5/04 07:45:10 AM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY DRUG PRODUCTS (HFD-570)

APPLICATION #:	21-067	APPLICATION TYPE:	NDA/ Proposed labeling
SPONSOR:	Schering Plough	PROPRIETARY NAME:	ASMANEX® Twisthaler ™
CATEGORY OF DRUG:		USAN / Established Name:	Mometasone Furoate Inhalation powder
		ROUTE:	Oral inhalation
MEDICAL REVIEWER:	Lydia I. Gilbert-McClain, M.D.	REVIEW DATE:	11/16/00

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
June 2, 2000	June 5, 2000	Complete Response to March 14, 2000 approvable letter	Response to clincal comments previously reviewed. This review is labeling only

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
Nov 30, 1998	Original NDA	Approvable
Dec 1, 1999	Response to Oct 1, 1999 approvable letter	Approvable

Outstanding Issues:
CMC, labeling

Recommended Regulatory Action:

NDAs:

xxx Approvable _____ Not Approvable

Signed: Medical Reviewer: _____ Date:

Medical Team Leader: _____ Date: _____

Labeling Comments (Clinical Section)

These are general labeling comments and are not all-inclusive. Specific wording can be addressed when the indicated sections and subsections have been appropriately revised.

1. **In the** CLINICAL PHARMACOLOGY **Section,** Clinical Trials **Subsection, paragraph 2, first sentence. Delete** [ ] **These parameters are not measurements of lung function.**

2. In the **CLINICAL PHARMACOLOGY** Section, **Clinical Trials** Subsection, paragraph 2, second sentence. Delete [ ] This statement implies an onset of action claim, and the data do not support an onset of action within 24 hours of the start of treatment.

3. In the **CLINICAL PHARMACOLOGY** Section, **Clinical Trials** Subsection, under the heading "Patients Not Receiving Corticosteroid Therapy," second sentence. Delete [ ] Statements regarding reduction in beta-2 agonists rescue medication are only acceptable without the statement that this is a measure of significant improvement in asthma control.

4. In the **CLINICAL PHARMACOLOGY** Section, **Clinical Trials** Subsection, under the heading "Patients Previously Maintained on Inhaled Corticosteroids," third sentence. Delete [ ] Reasons stated in preceding bullet point.

5. In the **WARNINGS** Section, [ ].

6. In the **PRECAUTIONS** Section, **General** Subsection, include class labeling for orally inhaled corticosteroids with regard to growth suppression in children: **General:** Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. (see **PRECAUTIONS, Pediatric Use** section).

7. In the **PRECAUTIONS** Section, **Pediatric Use** Subsection, include class labeling for orally inhaled corticosteroids with regard to growth suppression in children: **Pediatric Use**: Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one cm per year (range 0.3 to 1.8 cm per year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory

evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The growth of children and adolescents receiving orally inhaled corticosteroids, including *(insert product name)*, should be monitored routinely (e.g. via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including *(insert product name)*, each patient should be titrated to his/her lowest effective dose.

8. In the **PRECAUTIONS** Section, **Pediatric Use** Subsection, in accordance with 21 CFR 201.57 (f)(9)(i-viii), provide any additional information regarding the safe and effective pediatric use of this drug, or provide reasons for the omission of such information.

9. In the **PRECAUTIONS** Section, **Geriatric Use** Subsection, in accordance with 21 CFR 201.57 (f)(10)(i-vi), provide information regarding the safe and effective geriatric use of this drug, or provide reasons for the omission of such information. Include the number of geriatric patients (age 65 years and older) who were also age 75 years or older.

10. In the **ADVERSE REACTIONS** Section, if applicable to your drug product, include class labeling for orally inhaled corticosteroids with regard to growth suppression in children: **ADVERSE REACTIONS:** Cases of growth suppression have been reported for orally inhaled corticosteroids *[(including (insert product name, if appropriate)]*. (see **PRECAUTIONS, Pediatric Use** section).

11. In the **DOSAGE AND ADMINISTRATION** Section, third sentence, delete [and fourth sentence, delete [See above for rationale (second bullet point).

12. Provide a copy of the **PPI** or **Patient Package Insert** in MSWord 97 format. Note that the **Information for Patients** Subsection of the **PI** should be consistent with the **PPI**, and should be revised accordingly.

CC: Original NDA 21-067
HFD-570/Division File
HFD-570/Gilbert-McClain
HFD-570/Purucker
HFD-570/Hilfiker

/s/

Lydia McClain
11/16/00 01:44:18 PM
MEDICAL OFFICER

Mary please sign off on the labeling review. Thanks

Mary Purucker
11/16/00 03:05:24 PM
MEDICAL OFFICER

Hilfiker

SEP - 5 2000

MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY DRUG PRODUCTS (HFD-570)

APPLICATION #:	**N21067**	**APPLICATION TYPE:**	**NDA Complete response**
SPONSOR:	**Schering Corporation**	**PROPRIETARY NAME:**	**Asmanex ® Twisthaler™**
CATEGORY OF DRUG:	**Corticosteroid**	**USAN / Established Name:**	**Mometasone furoate**
		ROUTE:	**Oral Inhalation**
MEDICAL REVIEWER:	**Lydia I. Gilbert-McClain, M.D.**	**REVIEW DATE:**	**8/25/00**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
June 2, 2000	June 5, 2000	Response to AE letter	Complete response

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
Nov 30, 1998	Original NDA	

Overview of Application: This is the medical review of volume 3 of the sponsor's complete response to the Division's approvable letter dated March 14, 2000. There were 3 clinical issues to be addressed. The sponsor has addressed these issues satisfactorily and there are no outstanding issues from the clinical standpoint.

Outstanding Issues:
There are several CMC issues that still need to be resolved before the drug can be approved.

Recommended Regulatory Action:

NDA's: ___xxx_ __**Approvable** _____ **Not Approvable**

Signed: **Medical Reviewer:** [signature] **Date:** 8/30/00

Medical Team Leader: [signature] **Date:** 5 Sept 2000

cc: ORIG NDA 21-067
HFD-570/Div File, Gilbert-McClain, Parucker, Meyer, Hilfiker

Lydia I Gilbert-McClain, MD
Medical Reviewer

MEDICAL OFFICER REVIEW

NDA 21067

Type of submission: Complete response to approvable letter
Product: Mometasone furoate Inhalation Powder (Asmanex® Twisthaler™)
Sponsor: Schering Corporation
Date of Submission: June 2, 2000
CDER stamp date: June 5, 2000
PUDUFA due date: December 5, 2000
Date reviewed: August 25, 2000
Date revised: August 30, 2000

INTRODUCTION

This is the medical review of volume 3 of the sponsor's complete response to the Division's approvable letter dated March 14, 2000.

On November 30, 1998, Schering submitted an original NDA 21-067 for Monetasone Furoate inhalation Powder (Asmanex ® Twisthaler ™) which provides 220 μg and 430 μg per actuation (200 μg and 400 μg from the mouthpiece respectively). The drug is to be indicated for the prophylactic treatment of asthma in adults and children 12 years of age and older. The drug demonstrated efficacy with the 400 μg Q AM and 200 μg BID dosing schedule. The drug was not approved because of several chemistry and manufacturing issues as well as some clinical issues. Schering's NDA 20-762 for Nasonex (Mometasone Furoate Nasal Spray) 50 μg/actuations has been approved by the Agency on 10/01/97 for the treatment of seasonal and perennial allergic rhinitis in adults and children 12 years of age and older.

The Agency sent an AE action letter on October 1, 1999 outlining the issues that needed to be addressed in NDA 21-067. The sponsor submitted a complete response to the AE letter on December 1, 1999. Upon review of the Sponsor's submission many CMC issues remained outstanding as well as 3 clinical issues. Therefore, the Agency sent another AE action letter dated March 14, 2000. This submission dated June 2, 2000 is a complete response to the March 14, 2000 action letter.

The Division's comments from the action letter of March 14, 2000 are in bold type followed by the reviewer's comments to the sponsor's response.

COMMENT 45
Submit the case report form for patient C97-222-23/571. In addition, clarify why the patient's liver function test results, as reported on CD-ROM included in your December 1999 submission, appear normal, yet the patient is listed as having hepatitis.

REVIEWER COMMENT
The sponsor's response to comment 45 is acceptable.

The sponsor's response included a letter from the investigator dated April 7, 2000 explaining the circumstances surrounding this patient. In this letter the investigator Dr. Allen K. Lieberman, MD stated that the patient in May 1998, during his participation in the trial, attempted to donate blood. The patient was found to be positive for hepatitis C during the routine blood screening done prior to the acceptance of blood. The patient notified the coordinator, [ ] about these findings and was terminated from the study on June 5, 1998. The sponsor submitted the CRF for this patient. Liver function tests (ALT, AST, and blilirubin) done [ ] were all normal. Other laboratory studies done on these dates [CBC, routine chemistry and urinalysis were also normal.

COMMENT 46
Submit additional information to the mometasone furoate MDI IND concerning the GCP violations that occurred at center number 8 in study C97-222.

REVIEWER COMMENT
The sponsor's response to comment 46 is acceptable.

The sponsor submitted a letter jointly to IND 46,216 (Mometasone Furoate dry Powder Inhaler, Serial No. 105) and IND 52,214 (Mometasone Furoate Metered Dose Inhaler, Serial No. 043) on June 9, 1999 providing information concerning the GCP violations that occurred at center number 8. The sponsor clarified that the identified GCP violations were not specific to that center's data for study C97-222. The Letter dated June 9, 1999 cited the following GCP violations:

1. The auditors had questions about four subject's chest x-ray reports because the header information appeared different from other reports received from the same radiology laboratory (subjects A16/276- — , A15/277- — A10/279- — and A09/280- —).
2. Subject A13/274- — was enrolled in a clinical study with another pharmaceutical company while concurrently enrolled in the SPRI C97-380 study. Use of the drug involved in the other clinical study was an exclusion criterion for the C97-380 study. Also, at two visits this subject's blood samples were taken for both studies.

3. The auditors observed an IRB advertisement approval which stipulated that the patient compensation dollar amount be deleted from the advertisement. However, the advertisement that ran in the [ ] newspaper included the compensation dollar amount.

The sponsor indicated in that letter that data from all trials involving that site including C97-222 would be excluded. The investigator Dr. Gary Cohen, MD was terminated from participation in these studies. Study C97-222 was a long-term safety study in asthmatic patients on inhaled corticosteroids. The treatment duration was to be 52 weeks. Even with the exclusion of data from this study the sponsor had adequate studies to support the long term safety of Mometasone Furoate Inhalation Powder i.e. study C96-136 and study C96-137 with a total enrollment of over 200 patients for 1 year.

COMMENT 47

In your response to comment 12.b. of our October 1, 1999 letter, you mentioned that RIA data in trial C97-049 for the cortrosyn stimulation testing is available at both screening and day 29. Submit a statistical analysis of the comparison between the post-cosyntropin values at Screening and the post-cosyntropin values at Day 29 for mometasone furoate DPI given 400 μg BID and 800 μg BID versus placebo.

REVIEWER COMMENT

The sponsor's response to comment 47 is acceptable.

Study C97-049-01 was a four-week randomized, placebo controlled safety study of 400 μg and 800 μg BID of Mometasone Furoate Inhalation Powder (MF). This was a phase 1 study conducted at one center with 16 subjects per treatment arm. The objective of this study was to evaluate the potential for systemic exposure of MF DPI at doses of 400 μg or 800 μg BID for 29 days compared with prednisone 10 mg p.o. QD in the AM and with placebo. In our October 1 1999 letter, the Division asked the sponsor to submit a statistical analysis of the comparison between the post-cosyntropin values at baseline and the post-cosyntropin values at Day 29 for each active treatment versus placebo. The Sponsor responded that for study C97-049, Cosyntropin stimulation testing, using HPLC to measure cortisol levels, was performed at Day 29 only, therefore changes from baseline are not applicable. The sponsor also stated that Cosyntropin stimulation testing, using a RIA method to assess cortisol levels was performed at screening and Day 29. The sponsor also mentioned that RIA crossreacts with prednisone, and its usefulness in assessing differences between treatment groups in this study is limited. The sponsor was then asked to submit the statistical analysis for subjects treated with either of the MF treatment groups or placebo. These results are depicted in the table below.

Results of RIA assay of Cosyntropin stimulation test for study C97-049

Treatment Arm	Baseline mean ±SD (n= 16)	Day 29 mean ±SD (n= 16)	Mean change ±SD	p-value MF compared with placebo
MF 400 µg	23.31 ± 3.49	23.56 ± 3.40	0.25 ± 4.32	p ≤ 0.046*
MF 800 µg	24.25 ± 3.78	21.437 ±2.27	-2.81 ± 3.763	p=0.734
Placebo	26.81 ± 3.01	24.437 ± 3.36	-2.37 ± 2.52	-
*MF 400 µg also compared with MF 800 µg				

The increase of 0.25 points for the MF 400 µg BID treatment was statistically significantly higher that the other two treatment groups which showed a decrease (Placebo = –2.38 and MF 800 µg BID = -2.81). The placebo and MF 800 µg BID treatment groups were not significantly different from each other. Additional comments on this statistical analysis may be given by Dr. Jim Gebert, biometrics reviewer.

CONCLUSION

The sponsor's response to the three clinical comments # 45, 46, and 47 in the Division's action letter dated March 4, 2000 are complete and acceptable. There are no further clinical comments to be forwarded to the sponsor.

Hilfiker

FEB 28 2000

MEDICAL OFFICER REVIEW

Division Of Pulmonary Drug Products (HFD-570)

APPLICATION #:	21-067	**APPLICATION TYPE:**	Response to October 1, 1999 Approval Letter
SPONSOR:	Schering Plough	**PROPRIETARY NAME:**	Asmanex
CATEGORY:	Inhaled Corticosteroid	**USAN NAME:**	Mometasone DPI
		ROUTE:	Oral Inhaled
MEDICAL OFFICER:	Daniel J. O'Heam, M.D.	**REVIEW DATE:**	February 2, 2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
December 1, 1999	December 2, 1999	Original Amendment	

RELATED APPLICATIONS (if applicable)

Document Date	Application Type	Comments
November 30, 1998	December 1, 1998	Original NDA

REVIEW SUMMARY: This represents a review of the clinical comments of the response to the approvable letter. The sponsor had adequately addressed the majority of the comments conveyed in the approvable letter.

OUTSTANDING ISSUES: If the plan of the sponsor is to promote a 400 mcg strength product, then pharmacokinetic and pharmacodynamic study utilizing the same nominal doses from the two inhalation strengths of 200 mcg and 400 mcg will be required. The sponsor will also be asked to submit a statistical analysis of RIA data from the cortrosyn testing in C97-049.

RECOMMENDED REGULATORY ACTION

New Clinical Studies:	____	**HOLD**	____	**MAY PROCEED**
NDA/Efficacy/Label Supplements:	X	**APPROVABLE**	____	**NOT APPROVABLE**

SIGNATURES

Reviewer: Daniel J O'Heam MD **Date:** 2/19/00

Team Leader: m Hammer **Date:** 2/28/00

The sponsor received a letter dated October 1, 1999 designating NDA 21-067 as approvable. This clinical response to the approvable letter is reviewed in this document. Comments 1-14 refer to clinical issues specifically and are discussed here.

FDA Comment 1

The efficacy of the 200 mcg QAM dose has not been sufficiently demonstrated as it failed to significantly improve FEV_1 in 2 out of 3 trials in which it was studied. The 200 mcg QPM dose appeared effective in a single trial, but was not replicated. In addition, none of these studies utilized the 200 mcg product. In order to support the efficacy of the 200 mcg dosing and/or 200 mcg QPM dosing, additional efficacy trials with the to-be marketed formulation are required.

Sponsor's Response - "We will remove the 200 mcg dose recommendation from the labeling at this time. We have recently completed an additional study of 200 mcg QPM using the 200 mcg product in patients previously maintained on beta-agonists alone. Results of this study confirm a significant effect of this regimen relative to placebo. We intend to submit this information for incorporation into labeling post-approval."

FDA Response - This response adequately addresses Comment 1. The Division will review the additional study of 200 mcg QPM using the 200 mcg product when it is submitted and will make comments at the appropriate time.

FDA Comment 2

The to-be-marketed strength of 400 mcg per inhalation was not utilized in the clinical trials to provide the 400 mcg QAM dose nor the 400 mcg BID dose in oral steroid dependent asthmatic patients. Therefore, there is a lack of effectiveness using this product. In addition, there is no clinical or biopharmaceutics information regarding the comparability of the 200 mcg and 400 mcg products at the same nominal dose, though in vitro data suggest some disparity in dose proportionality. Perform a pharmacokinetic and pharmacodynamic study utilizing the same nominal doses from the two to-be-marketed inhalation strengths (200 mcg and 400 mcg).

Include evaluation of dose response to demonstrate sensitivity of the trial. We encourage you to contact the Division to discuss the trial design prior to initiating the trial.

Sponsor's Response/ **Part 1** - "At this time, we request that the 200 mcg strength to be considered for approval while we work toward a mutually acceptable approach for later approval of the 400 mcg strength."

FDA Response – In the original Asmanex labeling, the recommended starting dose for most patients, whether previously maintained on either bronchodilators alone or inhaled

corticosteroids, is 400 mcg once daily. Dose reduction to 200 mcg once daily may be considered, increasing to 400 mcg once daily or 200 mcg twice daily if more control is needed.

The 200 mcg inhalational strength was utilized for MF 400 mcg QAM in C96-136, C96-186, and C96-196 and was found to be efficacious with the primary endpoint as well as most other endpoints. C96-136 and C96-186 were performed in subjects previously maintained on beta-agonists while C96-196 was performed in subjects previously maintained on inhaled corticosteroids. Thus, 400 mcg QAM administered as 200 mcg MF DPI x 2 puffs is acceptable.

The 200 mcg inhalational strength was utilized for MF 200 mcg BID in C96-134 and C96-168 and was efficacious with the primary endpoint as well as most other endpoints in subjects previously maintained on inhaled corticosteroids. Thus, MF 200 mcg BID administered as 200 mcg MF DPI x 1 puff in the AM and PM is acceptable.

C96-136

	AM Dose	Total mcg/Day
Group 1	100 mcg x 2	MF 200 mcg (AM)
Group 2	200 mcg x 2	MF 400 mcg (AM)
Group 3	Placebo x 2	0

C96-186

Treatment Group	AM	PM	TOTAL (mcg/day)
Group 1	100 mcg MF DPI x 2 puffs	Placebo x 2 puffs	MF DPI 200 mcg QD
Group 2	200 mcg MF DPI x 2 puffs	Placebo x 2 puffs	MF DPI 400 mcg QD
Group 3	100 mcg MF DPI x 2 puffs	100 mcg MF DPI x 2 puffs	MF DPI 400 mcg (BID dosing)
Group 4	Placebo x 2 puffs	Placebo x 2 puffs	Placebo

C96-196

	Regimen	AM	PM	Total mcg/day
Group 1	200 mcg BID	100 mcg x 2	100 mcg x 2	MF 400 mcg
Group 2	400 mcg QAM	200 mcg x 2	Placebo x 2	MF 400 mcg
Group 3	200 mcg QAM	100 mcg x 2	Placebo x 2	MF 200 mcg
Group 4	200 mcg QPM	Placebo x 2	100 mcg x 2	MF 200 mcg
Group 5	Placebo	Placebo x 2	Placebo x 2	0

C96-134

	AM		PM		
Treatment Group	MF DPI	BDP MDI	MF DPI	BDP MDI	Total (mcg/day)
Group 1	100 mcg x 1	Placebo x 4 puffs	100 mcg x 1	Placebo x 4 puffs	MF 200 mcg
Group 2	200 mcg x 1	Placebo x 4 puffs	200 mcg x 1	Placebo x 4 puffs	MF 400 mcg
Group 3	400 mcg x 1	Placebo x 4 puffs	400 mcg x 1	Placebo x 4 puffs	MF 800 mcg
Group 4	Placebo x 1	42 mcg x 4 puffs	Placebo x 1	42 mcg x 4 puffs	BDP 336 mcg

Group 5	Placebo x 1	Placebo x 4 puffs	Placebo x 1	Placebo x 4 puffs	Placebo 0 mcg

C96-168

	AM		PM		
Treatment Group	MF DPI	BDP MDI	MF DPI	BDP MDI	Total mcg/Day
Group 1	100 mcg x 1 puff	Placebo x 4 puffs	100 mcg x 1 puff	Placebo x 4 puffs	MF 200 mcg
Group 2	200 mcg x 1 puff	Placebo x 4 puffs	200 mcg x 1 puff	Placebo x 4 puffs	MF 400 mcg
Group 3	Placebo x 1 puff	42 mcg x 4 puffs	Placebo x 1 puff	42 mcg x 4 puffs	BDP 336 mcg
Group 4	Placebo x 1 puff	Placebo x 4 puffs	Placebo x 1 puff	Placebo x 4 puffs	Placebo (0)

C96-137

	AM	PM	
	MF DPI	MF DPI	Total mcg/day
Group 1	200 mcg x 2	200 mcg x 2	MF 800 mcg
Group 2	400 mcg x 2	400 mcg x 2	MF 1600 mcg
Group 3	Placebo x 2	Placebo x 2	Placebo (0)

If the plan of the sponsor is to promote a 400 mcg strength product, then the pharmacokinetic and pharmacodynamic study utilizing the same nominal doses from the two inhalation strengths of 200 mcg and 400 mcg will be required. There was one study that utilized the 400 mcg strength product successfully, but C96-137 also showed that this dosage strength administered as 800 mcg BID did not offer any superior effect to that of 400 mcg BID, which utilized the 200 mcg strength. Thus, it appears that there is little available evidence on the clinical efficacy of the 400 mcg strength.

Sponsor's Response/ **Part 2** - "We note that the C97-049 study showed that the 2 X 400 BID (400 mcg device: total daily dose 1600) resulted in an approximate doubling of Cmax and AUC versus 2 X 200 BID (200 mcg device; total daily dose 800 mcg). There was slightly greater suppression of cortisol with the high dose. There was considerable inter subject variability, and variability associated with the fact that several subjects administered 2X200 BID had plasma SCH 32088 concentrations below the limit of quantitation. Nevertheless, these data suggest that equal minimal doses would result in comparable systemic concentrations.

We are concerned about the feasibility of trials designed to demonstrate small differences in dose delivery of this compound, even at the highest labeled dose. We will contact the Division with a proposal regarding qualification of the 400 mcg strength."

FDA Response – C97-049 give some sense that there is pharmacokinetic linearity in the dosing of MF DPI but it is not sufficient to address the concerns in Comment 2 and the lack of pharmacodynamic data and pharmacokinetic data comparing the dosage strengths. It is noted that there is an approximate doubling of the Cmax and AUC between 400 BID and 800 BID. These doses, however, are not the typical doses to be utilized for patients previously on beta agonists alone or on inhaled corticosteroids previously. In this study, there were low concentrations and/or non-quantifiable levels in the mean SCH 32088 concentrations with the 400 mcg dose as well as high variability. While the sponsor seems concerned that there will potentially be difficulty in demonstrating small differences in dose delivery, it does not obviate the need for accurate biopharmaceutic information comparing the 200 mcg strength and the potentially marketable 400 mcg strength.

The Division awaits this more definitive proposal regarding qualification of the 400 mcg strength.

FDA Comment 3

Part a – The graph for AM PEFR in Figure 3 does not reflect the same data for AM PEFR that are presented in Table 13. Clarify this discrepancy.

Sponsor's Response to Part a– "The graph for AM PEFR in Figure 3 of the C96-196 study report is incorrect. The correct graph is given below and does reflect the data presented in Table 13 of the report."

FDA Response to Part a– This graph (not shown in this review) was compared with the data for AM PEFR and does seem to correlate.

Part b – Explain why there are so few patients included for the FEV_1 on Day 4 for the MF DPI 200 QD AM and MF DPI 200 BID treatment groups for those subjects with $FEV_1 < 75\%$ predicted and for the MF DPI 200 QD PM and MF DPI 400 QD AM treatment groups for those subjects with $FEV_1 > 75\%$.

Sponsor's Response to Part b– "Subjects were to return to the clinic on Day 4, and Weeks 1,2, 4, 8 and 12 relative to the start of the randomized treatment. As described in Section 9.9.2. of CSR C96-196, for the purposes of analysis, mutually exclusive relative day windows were defined prior to data base closure for each protocol-specified visit. These windows were considered to be the most appropriate way to examine the effect of treatment after a given protocol-specified duration of exposure. Any data that were collected outside the relative day window of a protocol-specified visit were not included in any analyses or summaries of the visit. The Endpoint, the primary evaluation time point, included all treated subjects, regardless of the duration of treatment. Because subjects could discontinue at any time during the study, Endpoint visits could fall outside the relative day windows. Additional analyses of FEV_1 for the Day 4

visit data (for all treated subjects combined) without regard to the prespecified visit windows, resulted in identical inferences as those based on the visit window approach (Table 3b.1).

The relative day window for the protocol specified, Day 4 visit was from Day 3 through Day 5. Twenty-eight percent (28%; 79/286) of subjects had this visit either earlier than Day 3 (1/79) or later than Day 5 (78/79) and were, therefore, not included in the Day 4 visit summaries and analyses. An additional 6% (18/286) of the subjects did not return to the clinic for this visit. Table 3b.2. summarizes subjects according to their Baseline percent of predicted FEV_1 and Day 4 visit status. The number of subjects observing the protocol specified visit within the prespecified Day 4 visit window as presented in CSR C96-196 by Baseline percent of the predicted FEV_1 are correct. The imbalance in numbers between the two subgroups as presented in CSR C96-196 occurred at random."

FDA Response to Part b– This explanation adequately addresses the concerns presented in Comment 3b. Let it also be added that when those subjects that did not meet the protocol specified Day 4 criteria were added back into Table 3b.1 (which included all subjects in a treatment group together, regardless of the baseline FEV_1), that it did not appreciably change the data for Day FEV_1 originally presented in CSR C96-196.

FDA Comment 4

For Trial C96-136, Table 50 contains a footnote indicating that the severe adverse events listed are related or possibly related to treatment. The next paragraph in the report indicates only one subjects had an adverse event that was considered treatment related and severe during the 9 month phase. Clarify this discrepancy.

Sponsor's Response – "The table in question, Table 50, contains an error in the footnotes. This was likely carried over from the previous table, Table 49, Incidence for All Treatment-related Treatment-Emergent Adverse Events Reported by Subjects During the 9-Month phase, by Body System/Organ Class (All treated subjects), which would have been used to create the shell for Table 50. The statement in the text, "Only one subject had an adverse event that was considered treatment related and severe during the 9-month phase, and no treatment-related adverse event was considered life threatening" is incorrect. Table 50 data reflect all severe adverse events regardless of relationship to treatment."

FDA Response – This error adequately explains the discrepancy. If indeed, the statement, "Only one subject had an adverse event that was considered treatment related and severe during the 9-month phase, and no treatment-related adverse event was considered life threatening" is incorrect, the CSR does not appear to report what is the correct number for severe adverse events considered treatment related during the 9 month phase. Nonetheless, whether or not a severe adverse event was considered treatment related by the sponsor is of limited value.

FDA Comment 5

Part a - (Regarding Trial C96-137) - Subjects were allowed to take other medications for their asthma (i.e. Serevent, Atrovent, and Cromolyn-like drugs) during the treatment period with appropriate washout periods. Provide these data in a summary table over the course of the treatment period.

Sponsor's Response to Part a – " Protocol-allowed, supplemental asthma medications include nebulized or oral beta agonists, salmeterol, cromolyn, nedocromil, or anticholinergics. Per protocol, the subject was to attempt to withhold the medication for an appropriate interval before each visit as follows (FDA reviewer – these times were previously listed in the CSR for C96-137 and will not be repeated here.)

The use of protocol-allowed, supplemental asthma medications as recorded at each visit is summarized in Table 5a.2. and 5a.3. Information is also provided regarding washouts observed prior to spirometry."

The following sponsor's response section is highlighted for brevity sake.

	MF DPI 400 BID (n=46)	MF DPI 800 BID (n=43)	Placebo (n=43)
Salmeterol	27 (59)	20 (47)	23 (53)
Cromolyn/Nedocromil	4 (9)	9 (21)	7 (16)
Nebulized Ipratropium	2 (4)	1 (2)	1 (2)
Ipratropium MDI	10 (22)	7 (16)	10 (23)

The extent of use of salmeterol or Serevent was reported to be 59%, 47%, and 53% in the MF DPI 400 BID, MF DPI 800 BID and placebo groups, respectively. All subjects using salmeterol did so for the duration of the study. The numbers of subjects observing a minimum 12 hour washout of salmeterol is shown in Table 5a.2.Additionally, it should be noted that for those subjects not observing a 12 hour washout, the majority had a washout of at least 8 hours.

Relatively few subjects in each treatment group required use of supplemental medications other than salmeterol (presented in tables.) Overall, 9%, 21%, and 16% of subjects treated with MF DPI 400 BID, MF DPI 800 BID, and placebo respectively were using cromolyn or nedocromil, while 26%, 19%, and 26%, respectively, were using inhaled or nebulized ipratropium bromide.

Changes in prednisone dosing were summarized for the subset of subjects using salmeterol at any time during treatment and for the subset of subjects who did not use salmeterol. 65-96% of subjects treated with MF DPI were able to decrease their prednisone use, regardless of MF DPI dose or salmeterol use. No more than 26% of those treated with placebo decreased prednisone use, regardless of concomitant salmeterol. It is concluded that the use of supplemental

medications did not impact significantly on the benefit of MF DPI over placebo for reduction of oral prednisone use.

FDA Response to Part a– In examining the number of subjects using these protocol allowed supplemental medications, it appears that they were generally distributed evenly among the treatment groups (table above). When the washout period for salmeterol were examined, it generally appeared in this data presentation that there were more subjects in the MF DPI 400 BID treatment groups that were withholding salmeterol for any washout period. When specifically the washout period was less than 12 hours, the numbers between 400 BID and placebo were very similar. For Cromolyn/Nedocromil and both dosage forms of ipratropium, there was little discrepancy in their use or in their washout periods (for ipratropium) between treatment groups.

There was a somewhat higher percentage of subjects able to decrease their prednisone use among those on salmeterol (25/26 subjects) as compared to those who were not in the MF DPI 400 BID treatment group (11/17) but these differences were not noted in the other treatment groups and is probably not a significant finding.

Part b- Supply the case report forms (CRF) for the five instances of fetal disorders observed in the nine month phase. Indicate the location of adverse events within the CRF.

Sponsor's Response to Part b– "In a 27-Aug-99 response to Dr. O'Hearn's request for clarifications, it was reported that the adverse events of artery malformation and ear malformation classified under the body system/organ class of fetal disorder in the 9 month, open label phase of study C96-137 were not, in fact, adverse events of fetal disorder, but rather, represented encoding errors of adverse events of leg pain (joint pain), which was miscoded as artery malformation, and pedal edema, which was miscoded as ear malformation.

As per FDA's request, the relevant CRFs are included in this response (archival copy only)."

FDA Response to Part b – Because of the severity of these adverse events and because of the connotation regarding fetal development, this mislabeling was taken very seriously and the CRFs were requested to assure that these malformations really did not occur and that the corrected adverse events did occur. The CRF for C96-137-18/016 was briefly reviewed for "artery malformation"and this 55 year old subject had leg (joint) pain and there was no apparent evidence of artery malformation in the CRF. The CRFs for C96-137-13/114 (60 year old male), C96-137-07-101 (64 year old female), C96-137-01-088 (66 year old male), and C96-137-01-86 (50 year old female) were also briefly reviewed and the adverse event was listed as pedal edema on the pages of the CRF as indicated by the sponsor. Furthermore, it is unlikely that these subjects listed would potentially be associated with a fetal malformation.

Part c – An adverse event of idiopathic thrombocytopenic purpura was noted at the last visit in Subject 213. Provide follow-up on this patient.

Sponsor's Response to Part c – "This refers to subject 213 of Trial C96-136-09 (not C96-137). The final laboratory visit for this subject (on 11-Mar-98) showed a platelet count of 30,000 cells/µl. A retest on 13-Mar-98 revealed a platelet count of 31,000 cells/µl. The adverse event reported at the Final visit was "decreased platelet count," and the subject will be referred to a hematologist, as noted on the comments page of the CRF. The diagnosis of idiopathic thrombocytopenic purpura was later provided by the hematologist. The subject's condition was unchanged as of 01-July-98, the date of last contact. The investigator considered the event unrelated to study medication.

FDA Response to Part c – The sponsor has provided very little additional information on this patient. This 38 year old female patient was found to have the low platelet count during the last visit at the end of the 9 month phase. This patient is listed as having taken Augmentin 875 mg po BID from Day 208 to Day 218 as well as Tylenol from Day 206-208 as well as Proventil MDI. It appears that she was only on Proventil as well as MF DPI 4000 QPM at the end of the 9 month phase. Overall, it does not seem likely that the ITP is drug related. Although acute ITP is rare in adults, women aged 20 to 40 are afflicted most commonly with chronic ITP and outnumber men 3:1. They may present with an abrupt fall in platelet counts similar to acute ITP although they more often have a prior history of easy bruising or menometrorrhagia.

FDA Comment 6

For trial C96-186, there were baseline differences among the treatment groups in the AM and PM PEFR. Perform an analysis factoring in these baseline differences, for example, by using them as a covariate in the analysis.

Sponsor's Response - "Analysis of Baseline AM and PM PEFR data in study C96-186 did not reveal statistically significant overall treatment differences, although numerical differences were evident.

Analyses of covariance (ANCOVA) using the Baseline value as a covariate for both of these variables has been performed at all timepoints following Baseline. Results of these analyses are provided in Tables 6.1 and 6.2. Note that the covariate was not significant at all timepoints in each analysis and the slopes of the covariate by response for the treatment groups were statistically different at many timepoints (see Table 6.3). These violations of the assumptions inherent in the analysis of covariance may call into question the validity of the treatment effect inferences. Despite this, the inferences based on the results of the ANCOVA are identical to those presented in the study report, which were based on the ANOVA which did not include the covariate in the analysis model. Specifically, both the MF DPI 200 mcg BID and MF DPI 400 mcg QD groups demonstrated significant improvements in both AM and PM PEFR compared to placebo at Endpoint, as well as for most of the time points evaluated. Additionally, MF DPI 200 mcg BID and MF DPI 400 mcg QD were not significantly different from each other. As was the case with the original ANOVA, results of the ANCOVA indicated that MF DPI 200 mcg BID

was not significantly different from placebo, but was numerically superior to placebo at most timepoints for both AM and PM PEFR.

FDA Response – While it is not clearly labeled, this reviewer is assuming that the ANCOVA for AM PEFR utilized baseline AM PEFR as the adjusted covariable and the ANCOVA for PM PEFR utilized baseline PM PEFR as the adjusted covariable.

	P values	
	Baseline	Baseline and Treatment
AM PEFR		
Week 1	0.12	0.44
Week 2	0.10	0.30
Week 3	0.18	0.11
Week 4	0.11	0.04
Week 5	0.10	0.07
Week 6	0.05	0.02
Week 7	0.02	<0.01
Week 8	0.03	<0.01
Week 9	0.04	0.02
Week 10	0.02	0.03
Week 11	0.04	0.04
Week 12	0.03	0.08
Endpoint	0.08	0.02
PM PEFR		
Week 1	0.03	0.46
Week 2	0.33	0.41
Week 3	0.13	0.31
Week 4	0.08	0.08
Week 5	0.17	0.43
Week 6	0.16	0.23
Week 7	0.13	0.09
Week 8	0.07	0.07
Week 9	0.06	0.06
Week 10	0.04	0.16
Week 11	0.17	0.32
Week 12	0.12	0.20
Endpoint	0.23	0.12

Looking at AM PEFR, it appears that baseline AM PEFR did not have the same effect on the different treatment groups in the same manner. It also appears that baseline AM PEFR has an important effect on AM PEFR at most timepoints. Comparing, however, the original ANOVA table in the CSR with the ANCOVA table submitted in the response, the change from baseline AM PEFR has changed very little and the p values for the pairwise comparisons between

treatment groups has changed very little. Thus, it appears overall that adjusting for baseline AM PEFR has had ultimately little impact on the interpretation of the data.

For PM PEFR, there was little to no discernible effect when adjustment for baseline PM PEFR was performed.

FDA Comment 7

Part a – Clarify whether baseline use of salbutamol was covariate in the analysis.

Sponsor's Response to Part a – "Baseline use of salbutamol was not used as a covariate in any of the analyses of efficacy data in Study I96-111. No statistically significant differences among treatment groups in Baseline salbutamol use were noted, although some marginally significant ($p \leq 0.10$) differences were noted.

Additional analyses of the primary efficacy parameter, FEV_1, and of salbutamol use using Baseline salbutamol use as a covariate were performed. Results of these analyses are provided in Tables 7a.1. and 7a.2., respectively. Note that the covariate was not significant at all time points in each analysis and the slopes of the covariate by response for the treatment groups were statistically different at many time points. These violations of the assumptions inherent in the ANCOVA may call into question the validity of the treatment effect inferences. Despite this, the inferences based on the results of the ANCOVA are identical to those presented in the study report, which were based on the ANOVA which did not include the covariate in the analysis model. Specifically, MF DPI 400 mcg BID demonstrated significantly greater improvements at most of the individual time points evaluated. Similarly, as was the case with the results from the original ANOVA, results from the ANCOVA indicated that the MF DPI 400 mcg BID group demonstrated numerically greater decreases in salbutamol use compared to the MF DPI 100 mcg BID group throughout the study and at Endpoint, although statistical significance between these groups was not achieved at any time point.

FDA Response to Part a – This ANCOVA was asked for by the FDA because it appeared there were differences in use of salbutamol at Baseline but the sponsor said the differences were not significant.

	MF DPI 100 BID		MF DPI 200 BID		MF DPI 400 BID		FP	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	170	333.07	173	355.57	167	303.17	174	278.07
Change From Baseline								
Week 1	170	-69.91	169	-94.93	163	-75.63	170	-53.08
Week 2	163	-69.26	163	-89.81	165	-55.30	166	-33.41
Week 4	155	-90.42	158	-118.94	156	-81.80	160	-75.65
Week 6	149	-93.34	160	-121.21	149	-93.85	153	-63.14
Week 8	147	-92.58	156	-137.63	149	-92.73	154	-62.18

Week 10	142	-80.22	152	-143.51	145	-109.48	145	-62.60
Week 12	135	-51.71	150	-149.10	138	-109.61	144	-73.85
Endpoint	170	-13.23	173	-94.84	167	-38.10	174	-52.06

While the baseline mean for MF DPI 200 BID was the highest, it also had the greatest numerical decrease in the absolute mean (as seen above in the original CSR). Statistically significant differences in salbutamol use were noted at Endpoint only between MF DPI 100 BID (-13.23 mcg/day) and MF DPI 200 BID (-94.84 mcg/day). It was not clear at the time of the original review whether the baseline differences were a covariate in this analysis.

As requested, the sponsor has provided an ANCOVA for the primary variable, FEV_1, as well as salbutamol use adjusting for baseline salbutamol use.

	P values	
	Baseline	Baseline and Treatment
FEV1		
Week 1	0.24	0.22
Week 2	0.09	0.02
Week 4	0.79	0.51
Week 8	0.26	0.12
Week 12	0.03	0.21
Endpoint	0.27	0.04
Salbutamol Use		
Week 1	<0.01	0.4
Week 2	<0.01	0.88
Week 3	<0.01	0.39
Week 4	<0.01	0.25
Week 5	<0.01	0.25
Week 6	<0.01	0.13
Week 7	<0.01	0.01
Week 8	<0.01	<0.01
Week 9	<0.01	<0.01
Week 10	<0.01	<0.01
Week 11	<0.01	0.05
Week 12	<0.01	<0.01
Endpoint	<0.01	<0.01

The first column of the FEV_1 data tells us whether baseline salbutamol use has a significant effect on FEV_1 at that particular timepoint. In general, it can be seen that it does not. The second column in the FEV_1 data tests whether baseline salbutamol use has affected all treatment groups the same. While it appears that at Endpoint there has been an important effect of salbutamol, it is borderline, represents a post-hoc analysis as well as multiple comparisons that may be unjustified. For these reasons and the fact that the p value at Endpoint stands apart from the p values for the other time points makes it unlikely that baseline salbutamol use had a

significant effect on this primary variable. Furthermore, when the Change in Baseline FEV_1 table is examined (not shown here in this review), there are not important changes.

While the sponsor says that "the covariate was not significant at all timepoints," this does not appear to be so when one examines the ANCOVA data above considering the variable salbutamol use. From the first column above, it does appear that baseline salbutamol use retains a significant effect on salbutamol use at each of the timepoints examined. This is logical. Furthermore, baseline salbutamol use does not appear to have the same effect on all of the treatment groups the same from Week 7 onwards. Adjusting for baseline salbutamol use appears to have decreased the change from baseline for the MF DPI 100 BID and 200 BID treatment groups and increased it for the MF DPI 400 BID and FP treatment groups. While the difference between MF DPI 100 BID and 200 BID remains significant, there also appears to be a new significant difference between MF DPI 100 BID and FP. Overall, this is not a particularly important revelation, particularly considering the fact that MF DPI 100 BID is not planned for marketing at this time.

In summary, the sponsor has performed the ANCOVA adjustment for baseline salbutamol use as requested and no important changes have been noted.

Part b – Section 11.4.1.7 indicates that clinical asthma exacerbations were reported at some time during the study by 13 subjects in the MF DPI 100 µg BID group, 11 subjects in the MF DPI 200 µg BID group, 9 subjects in the MF DPI 400 µg BID group, and 9 subjects in the Fluticasone Propionate group. It is not clear why these numbers do not match the numbers for clinical asthma exacerbations in the Time to Worsening table in Section 11.4.1.7. Clarify this discrepancy.

Sponsor's Response to Part b – " Subjects indicated in the Time to Worsening table (Section 11.4.1.6) as having experienced a clinical asthma exacerbation include only those subjects who experienced a clinical asthma exacerbation at the time of their FIRST asthma worsening. Note that subjects may have experienced a clinical asthma exacerbation alone or in conjunction with one or more of the other criteria for asthma worsening. Because subjects may have continued in the study following their first worsening, some subjects may have met a criterion for worsening other than clinical asthma exacerbation (i.e., decrease in FEV_1, decrease in PEFR, overuse of salbutamol, etc.) at the time of their first worsening and then experienced a clinical asthma exacerbation at the time of a subsequent worsening. Such a subject would be represented in the Time to Worsening table only under the criteria met at the time of their first worsening.

Section 11.4.1.7., on the other hand, addresses all clinical asthma exacerbations experienced by subjects in the study regardless of when the exacerbation occurred, hence the wording "clinical asthma exacerbations were reported at some time during the study. . ." Thus, all clinical asthma exacerbations, not only those representing first asthma worsenings, are included here. Therefore, the table in Section 11.4.1.6. and the text in Section 11.4.1.7. may not necessarily match as the table in Section 11.4.1.6. represents only a subset of the clinical asthma exacerbations presented in the text in Section 11.4.1.7.

In the case of CSR I96-111, 33 subjects were reported as having experienced a clinical exacerbation at the time of their first worsening as follows: MF DPI 100 μg BID, 8 subjects; MF DPI 200 μg BID, 11 subjects; MF DPI 400 μg BID, 8 subjects and FP 6 subjects, and 42 subjects were reported as having experienced a clinical asthma exacerbation at some time during the study as follows: MF DPI 100 μg BID, 13 subjects; MF DPI 200 μg BID, 11 subjects; MF DPI 400 μg BID, 9 subjects and FP 9 subjects. Review of this data indicates that while 33 subjects did experience a clinical asthma exacerbation at the time of their first worsening, only 40 (not 42) experienced a clinical asthma exacerbation at some time during the study as follows: MF DPI 100 μg BID, 11 subjects; MF DPI 200 μg BID, 11 subjects; MF DPI 400 μg BID, 9 subjects and FP 9 subjects. These subjects are summarized in Table 7b.1.

FDA Response to Part b – Table 7b.1. shows that there were 2 less subjects in the MF DPI 100 μg BID group than was reported in the CSR. Overall, this is an acceptable explanation for the apparent discrepancy.

Part c – (Pertains to I96-111) The range of weights listed as 45-665 kg and 44-835 kg, at Week 12 and endpoint for females in the MF DPI 200 mcg BID and FP group, respectively. Clarify these values, as well as the weight ranges for Caucasians in these same treatment groups.

Sponsor's Response to Part c– (paraphrased by this reviewer) The three subjects whose recorded weights were incorrect were one with 83.5 kg (was 835 kg), 65 kg (was 665 kg), and 66 kg (was 655 kg). The correct ranges for the MF DPI 200 mcg BID and FP groups were also presented.

FDA Response to Part c– This is an acceptable clarification.

FDA Comment 8

For Trial I96-112, the glucose values for Site 12 (C. Bisbal, M.D.) both at screening and at Week 12 appear to be out of the normal range of 3.9-6.4 mmole/L listed for the site. The creatinine data at Week 12 also appear to be well out of the range of 62-124 mcmol/L. Submit a clarification of the glucose and creatinine data at this site.

Sponsor's Response – "Some normal ranges for the laboratory used to analyze samples from site I96-112-12 changed during the course of the study. Therefore, the normal ranges reflected in the data base are incorrect for some of the values recorded in the data base. Review of the CRFs indicates that all affected laboratory values are within the normal range when correct normal ranges are applied. Thus, it is concluded that this issue is one of data presentation, not of source data.

With regards to glucose values, a normal range of 70-110 mg/dl, which replaced an earlier range of 3.9-6.4 mcmol/L, is not reflected in the data base. A similar situation exists in the case of creatinine values. In this case, normal ranges of 0.5-1.2 mg/dl for females and 0.7-1.4 mg/dl for

males, which replace earlier ranges in units of micromoles/L, are not reflected in the data base. Review of the CRFs indicates that the correct glucose values are all within normal range when the appropriate normal range is applied. All creatinine values, as reflected in the data base, are correct."

FDA Response – This is an acceptable clarification.

FDA Comment 9

For Trial I96-113, it appears that the increase in the listed weight of women on 600 mcg BID is erroneous. Clarify the data.

Sponsor's Response – "Subject I96-113-11/014 is recorded in the data base as weighing 675 kg at her Final Visit. The correct weight for this subject at the Final Visit is 68 kg. Her weight at Baseline was 66 kg." (Reviewer's note – The correct ranges for the weight at the Final Visit were also supplied.)

FDA Response – This is an acceptable clarification.

FDA Comment 10

For Trials I96-113 and C96-136, "menstrual disorder" was one of the adverse events listed. Clarify the definition of pain and menstrual disorder.

Sponsor's Response – Menstrual Disorder – Literal terms in this category reported for Trial I96-113 include:

- Menses occurred twice within one month
- Irregular periods
- Menstruation too early
- Extended length of menses
- Irregular period
- Menses 2 weeks late
- Menstrual clotting
- Early menses
- Menses occurred for third time in one month
- Metrorrhagia

Literal terms in this category reported for Trial C96-136 include:

- Irregular menses

Menstrual Pain – Literal terms suggestive of menstrual pain were coded to the preferred term "Dysmenorrhea." Literal terms in this category reported for Trial I96-113 include:

- Dysmenorrhea
- Menstrual pain
- Menstrual cramps
- Abdominal pain-menstruation

Literal terms in this category reported for Trial C96-136 include:

- Dysmenorrhea
- Menstrual pain
- Menstrual cramps
- Premenstrual syndrome

FDA Response – This clarification was largely requested because it was not made clear what was meant by the term "menstrual disorder." The data excerpt from I96-113 is below.

	200 mcg BID (n=168)	400 mcg BID (n=166)	600 mcg BID (n=173)
pain	2 (1)	7 (4)	11 (6)
dysmenorrhea	2 (2)	3 (4)	2 (2)
menstrual disorder	1 (1)	3 (4)	5 (5)

In the comment and information request, the Division wanted to know more about the terms "pain" and "menstrual disorder" and not specifically "menstrual pain" which appeared to have been adequately covered by the term "dysmennorhea." Of the ten terms supplied by the sponsor for "menstrual disorder" there appeared to have been nine adverse events for this trial under this term. The reason for this discrepancy is not clear but is not probably that important. We appear to have the term "menstrual disorder" adequately described.

Going back to the original submission for I96-113, the sponsor says that the general term "pain" encompasses 57 different literal terms (e.g., ache in neck, arm pain, cervical pain, hand ache, knee pain, pain in leg, sciatica pain, sore jaw, thoracic pain.) This explanation of the possible causes of pain should suffice and no further information will be requested at this time.

The term "menstrual disorder" has also been adequately clarified for C96-136.

FDA Comment 11

In the package labeling under Clinical Trials, a reference is made to C96-136 indicates that the subjects entered into this study [ ]
Clarify what is meant by [ ] and justify why these subjects met that criterion.

Sponsor's Response – "This will be amended to state "previously maintained on inhaled beta-agonists" per the protocol title."

FDA Response – The sponsor offers really no explanation of why these subjects were to be considered [ ]. It is acceptable, however, that the term "previously maintained on inhaled beta-agonists" is utilized, instead. The sponsor has not yet submitted the revised package labeling.

FDA Comment 12

The following comments pertain to the evaluation of the effect of mometasone furoate on the HPA axis.

Part a – For Trials C95-135 and C97-049, the post-cosyntropin stimulation mean serum cortisol concentration data could not be located in a table format. Supply this information as well as outlier data (subjects whose prestimulation concentration of plasma cortisol was <5 μg/dl, whose poststimulation concentration was <18 μg/dl, or whose response to stimulation was not an increase of at least 7 μg/dl) in a summary table.

Sponsor's Response to Part a – (Reviewer's note – The sponsor has provided the mean serum cortisol concentration data for Trials C95-135 and C97-049 as well as the outlier data for C9 97-049. The sponsor says that no subject in study C95-135 had an abnormal response to the cosyntropin stimulation test.) "In study C97-049, similar numbers of subjects across all treatment groups demonstrated abnormal cortisol levels pre- and poststimulation, with the exception of the prednisone group. Similar numbers of subjects across all treatment groups, including the prednisone group, demonstrated abnormal responses to stimulation testing (poststimulation minus prestimulation cortisol levels)."

FDA Response to Part a - C95-135 evaluated MF DPI 400, 800, and 1200 mcg QAM and 200 mcg BID versus placebo for 28 days in subjects with a history of moderate asthma. In the original NDA submission, the data on cortisol was submitted, but not in tabulated form and only as individual data points.

DAY 29 C95-135	MF DPI 400 QD			MF DPI 200 BID			MF DPI 800 QD			MF DPI 1200 QD			Placebo		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Pre	12	16.08	3.06	12	18.08	3.26	12	16.25	3.31	12	15.92	2.5	12	14.83	4.11
Post	12	26.67	3.87	12	28	3.07	12	28.92	5.78	12	26.83	2.79	12	27.75	5.63
Change	12	10.58	3.87	12	9.92	2.68	12	12.67	4.42	12	10.92	2.78	12	12.92	5.37

It does not appear that there was an abnormal mean response to the cosyntropin stimulation test in C95-135. The sponsor also provided a summary of the ANOVA with p values from LS means pairwise comparisons and none of the comparisons between treatment groups

were significant. While the tabulation of outliers was not provided by the sponsor for C95-135, it is noted from this reviewer's previous review that at 30 minutes post-cosyntropin, cortisol was increased by at least 7 µg/dl to values >18 µg/dl and at pre-ACTH, all subjects had cortisol levels of at least 10 µg/dl except for a 9 µg/dl in a placebo subject.

C97-049 evaluated 400 mcg twice-daily or 800 mcg twice-daily for 29 consecutive days compared with prednisone administered orally at a dose of 10 mg once-daily in the morning and with placebo DPI in patients with mild to moderate asthma.

Endpoint C97-049	MF DPI 400 BID			MF DPI 800 BID			Prednisone			Placebo		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Pre	16	12.96	3.76	16	11.99	2.92	16	4.85	2.94	16	12.85	4.47
Post	16	23.24	5.59	16	20.81	4.3	16	14.53	4.16	16	25.03	5.56
Change	16	10.28	3.72	16	8.83	4.53	16	9.68	5.52	16	11.75	3.61

The mean pre-cosyntropin cortisol was quite low in the prednisone group and the mean was not able to increase above 18. There were numerical differences between the data for MF DPI 400 BID and placebo as compared to MF DPI 800 BID. The sponsor provided a summary of the ANOVA with p values from LS means pairwise comparisons and none of the comparisons between the MF DPI 400 BID treatment group and placebo were significant. The p value for the difference between the mean post-cosyntropin cortisol for MF DPI 800 BID and placebo was 0.019 and for the post-pre cosyntropin levels it was very nearly significant at 0.071. Thus, it appears that there is a signal that MF DPI 800 BID has HPA axis suppression.

Outliers in C97-049	Pre < 5	Post < 18	Response < 7
800 mcg	0	2	4
1600 mcg	0	5	4
Prednisone	11	15	5
Placebo (one subject had no pre or response data)	1	1	2

While the sponsor contends that similar numbers of subjects across all treatment groups, including the prednisone group, demonstrated abnormal responses to stimulation testing, this is not this reviewer's conclusion. It is clear that there were many more outliers among the prednisone group. Furthermore, at least for the post-cosyntropin value <18, there was also an

over representation of the MF DPI 800 BID treatment group. There also seems to be an overrepresentation of the MF DPI 400 BID treatment group, as well as the MF DPI 800 BID treatment group, in the "Response <7" column with 4 subjects in each of these two groups which is double that seen in the placebo group.

In conclusion of Part a, the sponsor appears to have provided the requested data. It also appears that MF DPI 800 BID produces HPA axis suppression as well as MF DPI 400 BID.

Part b – For Trial C97-049, submit a statistical analysis of the comparison between the post-cosyntropin values at baseline and the post-cosyntropin values at Day 29 for each active treatment versus placebo.

Sponsor's Response to Part b – "For Study C97-049, cosyntropin stimulation testing, using HPLC to measure cortisol levels, was performed at Day 29 only. Therefore, changes from baseline are not applicable.

Cosyntropin stimulation testing, using an RIA method to measure cortisol levels, was performed at Screening and Day 29. Because results from RIA are available soon after the procedure is completed, this method of testing was used primarily as a safety assessment to determine whether subjects could be enrolled in the study and whether they could be safely discharged. However, because the RIA crossreacts with prednisone, its usefulness in assessing differences between treatment groups in this study is limited. HPLC is a more specific assay for endogenous cortisol levels and does not cross react with prednisone. Therefore, only results based on HPLC were presented in this study report.

FDA Response to Part b- It appears that RIA testing is available from the sponsor at both Screening and Day 29. There would be potentially useful RIA data available for MF DPI 400 BID and 800 BID and placebo. The sponsor should be requested to submit an analysis for the treatment arms, other, than prednisone, with the RIA data available.

Part c – Using mean cortisol $AUC_{(0\text{-}24)}$ (g-hr/dl) data, submit an analysis comparing the change in cortisol AUC from baseline for each particular treatment arm with the change from baseline for placebo for Trials C97-049 and C95-135.

Sponsor's Response to Part c – "For both studies, changes from baseline in serum cortisol AUC across the treatment period were analyzed using an analysis of variance model.

In Study C97-049, significant differences were found at Day 7 for all groups when compared to placebo (MF DPI 400 mcg BID, MF DPI 800 mcg BID, and prednisone 10 mg versus placebo: $p \leq 0.01$). No further significant differences from placebo were found for either MF DPI group at Days 14, 21, or 28. The prednisone group continued to show significant differences from placebo at Days 14, 21 and 28. Prednisone produced the expected physiologic change in plasma cortisol levels, which were persistent throughout the study. Changes produced by MF DPI, however, were no different from placebo after Day 7.

In Study C95-135, significant differences from placebo were found for only one group, MF DPI 1200 mcg, at two time points, Days 7 and 14. Changes from baseline for this group were not significantly different from placebo at Days 21 and 28, and no other significant differences from placebo were found for any other MF DPI group.

FDA Response to Part c- As the sponsor mentions, there were significant differences found at Day 7 for all groups when compared to placebo (as seen below in the p values from LS means pairwise comparisons). The significant differences in the "change from baseline" compared to placebo were no longer seen after Day 7 for either MF DPI group, however, there were significant differences when the means of the actual values were compared with placebo at all timepoints for MF DPI 800 BID and for Days 14 and 21 for MF DPI 400 BID. It is unclear why there is a discrepancy between the actual value and the change from baseline values. It could be related to the fact that the Baseline AUC was numerically higher than the Baseline for the other treatment groups. In fact, it was significantly higher than that for the MF DPI 800 BID group. In any case, there appears to be a signal here for HPA axis suppression again, as was discussed in Part a above.

C97-049 Cortisol 11pm-11pm	A-B	A-C	A-D	B-C	B-D	C-D
Day 0	0.147	0.215	0.565	0.829	0.045	0.72
Day 7, Actual	0.029	<0.001	<0.001	<0.001	<0.001	<0.001
Day 7, Change from Baseline	0.862	<0.001	0.011	<0.001	0.007	<0.001
Day 14, Actual	0.369	<0.001	0.034	<0.001	0.003	<0.001
Day 14, Change from Baseline	0.505	0.008	0.313	<0.001	0.73	<0.001
Day 21, Actual	0.451	<0.001	0.025	<0.001	0.003	<0.001
Day 21, Change from Baseline	0.462	0.003	0.29	<0.001	0.745	<0.001
Day 28, Actual	0.266	<0.001	0.293	<0.001	0.033	<0.001
Day 28, Change from Baseline	0.724	0.004	0.759	<0.001	0.964	<0.001

A= MF DPI 400 BID; B= MF DPI 800 BID; C= Prednisone 10 mg QAM; D= Placebo DPI.

As for C95-135, the sponsor mentions that significant differences from placebo were found for MF DPI 1200 mcg, at two time points, Days 7 and 14 and that changes from baseline for this group were not significantly different from placebo at Days 21 and 28, and no other significant differences from placebo were found for any other MF DPI group. There were clear numerical differences for the treatment groups from placebo at most timepoints. The difference between

the actual values for MF DPI 400 QD and placebo was significant at Day 28. There is not clear statistical evidence, however, for suppression based on this evidence from C95-135.

Part d – There is considerable difference in the 24 hour cortisol AUC results between Trials C97-049 and C95-135. Provide an explanation for the difference. Discuss, based on pharmacokinetic data, what to-be-marketed doses and formulations would be supported by the data available in trial C95-135.

Sponsor' Response to Part d – The difference between cortisol AUCs for studies C97-049 and C95-135 likely stems from the fact that different methodologies were used to determine cortisol levels in the two studies. Because prednisone was used as an active comparator in study C97-049, an HPLC method was used to determine cortisol levels in this study. Study C95-135, on the otherhand, used an RIA method for the determination of cortisol levels. The specific details of each assay are contained in the response to Comment 15. In addition, the following may have contributed to the differences in results: (1) the studies were conducted at two different centers; and (3) the studies were conducted years apart.

Study C95-135 was performed using a 100 mcg/inhalation device and, therefore, does not directly support the 200 mcg/inhalation device, which will be marketed at this time. However, two of the doses tested in C95-135, MF DPI 200 BID and MF DPI 400 QD are in the proposed labeling for the to-be-marketed 200 mcg/inhalation device. Mean maximal concentrations of MF were below the LOQ with the MF DPI 200 BID dose and were slightly above the LOQ with the MF DPI 400 QD dose. These data reflect the low-level systemic exposure of MF when given at total doses of 400 mcg.

FDA Response to Part d – The first part of this comment is based on the data that seemed to show that there was more suppression of the cortisol AUC in C97-049 as compared to C95-135. The sponsor's explanation for the difference is acknowledged. It is not known whether this explanation for the differences between the results of the studies is correct.

The sponsor makes the important point that C95-135 was conducted with the 100 mcg inhalation device and not the 200 mcg inhalation device. Their explanation as to what doses will be supported by C95-135 does not seem to justify the to-be-marketed doses supplied as 200 mcg per inhalation. Looking at the table that was supplied with this explanation (below), there does not appear to be any proportionality between doses. This may be explained in part by the problems in quantification because the doses, especially 200 BID, fell below the LOQ. We therefore do not really know what the pharmacokinetic exposure to the patient was that correlated with the essential lack of MF DPI effect on the cortisol AUC by these doses. It is not believed that this study, therefore, rules out an HPA axis effect by the to-be-marketed doses.

	C_{MAX} (pg/ml) on Day			
Treatment	7	14	21	28
200 BID	16.6	19.3	8.5	15.5

400 QAM	55.2	55.6	75	65.6

Part e – For Trial C96-196, while Cortrosyn stimulation testing was performed at screening, the data was made available only as individual line listings. Provide tabulated data with statistical analysis comparing the mean values at screening with those at baseline and endpoint.

Sponsor's Response to Part e – "As reported, results of analyses performed on the poststimulation cortisol values and on the response to stimulation (poststimulation minus prestimulation cortisol values) show differences ($p \leq 0.06$) between the placebo group and the MF DPI 400 mcg QD and MF DPI 200 mcg BID groups. This was true for both the Screening and Endpoint visits. Results of analyses of changes from Screening to Baseline and Screening to Endpoint show no significant differences among the treatment groups."

Mean AM Plasma Cortisol Levels (mcg/dl) (ANOVA from the Original NDA submission)

	MF DPI 200 QD AM (A)		MF DPI 200QD PM (B)		MF DPI 400 QD AM (C)		MF DPI 200 BID (D)		PLACEBO (E)	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Baseline										
Pre-cortrosyn	27	14.28	22	15.14	26	13.82	26	13.12	26	15.75
Post-cortrosyn	27	26.82	22	28.16	26	26.07	26	25.86	26	29.54
Diff. Between Post- and Pre-cortrosyn	27	12.53	22	13.02	26	12.26	26	12.73	26	13.79
Endpoint										
Pre-cortrosyn	24	14.53	22	15.94	25	14.04	24	15.13	20	16.73
Post-cortrosyn	24	26.68	22	28.16	25	25.31	24	27.71	20	31.21
Diff. Between Post- and Pre-cortrosyn	24	12.15	22	12.21	25	11.27	24	12.58	20	14.48
Change From Baseline to Endpoint in the Difference Between Post- and Pre-cortrosyn	**24**	**-0.55**	**22**	**-0.82**	**25**	**-0.70**	**24**	**-0.24**	**20**	**0.28**

Analysis Results

		P-value		Pairwise Comparisons (P Value)									
	P.SD	Treat	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
Baseline													
Pre-cortrosyn	7.35	0.73	0.93	0.69	0.82	0.57	0.47	0.54	0.35	0.77	0.73	0.35	0.20
Post-cortrosyn	7.65	0.39	0.43	0.54	0.72	0.65	0.20	0.35	0.30	0.54	0.92	0.11	0.09
Diff. Between Post- and Pre-cortrosyn	4.25	0.74	0.02	0.69	0.81	0.86	0.29	0.54	0.81	0.54	0.69	0.20	0.37
Endpoint													
Pre-cortrosyn	7.48	0.77	0.98	0.52	0.82	0.78	0.34	0.39	0.71	0.74	0.61	0.24	0.48
Post-cortrosyn	7.27	0.11	0.23	0.49	0.51	0.63	**0.04**	0.18	0.84	0.18	0.25	**<0.01**	0.12
Diff. Between Post- and Pre-cortrosyn	4.13	0.15	<0.01	0.96	0.46	0.72	0.07	0.44	0.76	0.08	0.27	**0.01**	0.13
Change From Baseline to Endpoint in the Difference Between Post- and Pre-cortrosyn	**4.55**	**0.94**	**0.15**	**0.84**	**0.90**	**0.82**	**0.55**	**0.93**	**0.67**	**0.44**	**0.72**	**0.47**	**0.70**

FDA Response to Part e - Shown above is the original ANOVA from the NDA that looked at changes from Baseline to Endpoint. The sponsor seems to be referring to the ANCOVA from the original NDA that corrected for differences at Baseline in their current discussion. While the new table from this response showing the Screening to Baseline and Screening to Endpoint data was not yet available electronically, it does not seem that there were appreciable differences when this new data was made available as compared to the original Baseline to Endpoint analyses. There remain no significant differences among the treatment groups in the change from Baseline to Endpoint in the difference between post- and pre-cortrosyn.

FDA Comment 13

It is stated in the Integrated Summary of Safety that ECGs were performed at Week 12 in C96-134 (Section 8.2.6.1), however, the protocol did not require Week 12 ECGs. Clarify this discrepancy.

Sponsor's Response – "The sentence in question reads: "No ECG abnormalities reported at Screening (or at Week 12 in Studies C96-134 and C96-136) were considered to be clinically significant." A review of the protocols indicates that this is in error and should read: "No ECG abnormalities reported at Screening (or at Week 12 in Studies C96-137 and C96-136) were considered to be clinically significant." A review of the listings confirmed that no Week 12 ECGs were collected as part of Trial C96-134 and that Week 12 ECGs were collected as part of Trials C96-136 and C96-137."

FDA Response – This is an acceptable clarification.

FDA Comment 14

Based on concerns raised to the Division by the Division of Scientific Investigators (DSI), supply a re-analysis of the data for Trials C96-137 and C96-136 without Dr. Jay Grossman's subjects. Specifically, provide re-analysis of the prednisone data and FEV_1 data for Trial C96-137 and FEV_1 data and peak-flow data for Trial C96-196.

Sponsor's Response – (Reviewer's Note – The sponsor has provided this data in tabulated form.) Dr. Grossman's site contributed six subjects in each treatment group to the all-treated-subjects subset of Study C96-196 and two subjects in each treatment group to the all-treated-subjects subset of Study C96-137 (these six subjects participated in both the double-blind and the 9-month phases of the study.) For both studies, the inferences drawn from the results of the analyses excluding data from Dr. Grossman's site are identical to those drawn from the results of the analyses in the CSRs, which included these data.

FDA Response – Regarding The Percent Change in Prednisone Dose, there is a small numerical decline in the decrease in prednisone use in the MF DPI groups as well as a decrease in the

increase in prednisone use in the placebo groups during the 3 month phase but this has not resulted in any significant change in the ultimate results which show that both MF DPI 400 and 800 mcg BID resulted in statistically significant decrease in prednisone as compared to placebo throughout most of the trial and at Endpoint. Results during the 9 month phase for this variable were also essentially unaffected. The results and conclusion based on the FEV_1 data for both the 3-month and 9-month phases are also not affected by the exclusion of Dr. Grossman's data.

Dr. Grossman had a fairly large representation in C96-196 with a total of 24 subjects. There were 6 in each treatment group. The sponsor has provided statistical analysis with the change from Prebaseline in Table 14.5 and the change from Baseline in Table 14.6. The primary efficacy variable as stated in the protocol is the change from Baseline. It does not appear that there has been an important change in the mean changes at Endpoint from either Prebaseline or Baseline. The only somewhat appreciable change has been that instead of MF DPI 400 mcg QAM having a p value < 0.05 for the comparison with placebo for Weeks 2, 4,8,12 and Endpoint, this difference is now only significant at Week 12 and at Endpoint. Because the primary endpoint was the change from Baseline to Endpoint, the conclusion has not changed from that of the original review.

When the AM PEFR data from C96-196 is re-examined, MF DPI 200 QPM, 400 QAM and 200 BID remain statistically different from placebo at most timepoints including the Endpoint and MF DPI 200 QAM is different from placebo at Endpoint and Week 4 only as compared to Endpoint and Weeks 4, 10, and 12 previously with Dr. Grossman's data.

In conclusion, the removal of Dr. Grossman's subjects has not appreciably changed the conclusion of either C96-137 or C96-196.

Remarks to be conveyed to the Sponsor

1) If the plan of the sponsor is to promote a 400 mcg strength product, then pharmacokinetic and pharmacodynamic study utilizing the same nominal doses from the two inhalation strengths of 200 mcg and 400 mcg will be required.

2) Regarding Comment 12b and Trial C97-049, you mention that RIA data for the cortrosyn stimulation testing is available at both Screening and Day 29. Submit a statistical analysis of the comparison between the post-cosyntropin values at Screening and the post-cosyntropin values at Day 29 for MF DPI 400 mcg BID and 800 mcg BID versus placebo.

CC – Archival File for NDA 21-067
Divisional File for NDA 21-067
Himmel, M. / Clinical
Gilbert-McClain, L./ Clinical
Hilfiker, D./ Project Management

MEDICAL OFFICER REVIEW

Division Of Pulmonary Drug Products (HFD-570)

APPLICATION #:	21-067	**APPLICATION TYPE:**	NDA
SPONSOR:	Schering Plough Corp.	**PROPRIETARY NAME:**	Asmanex
CATEGORY:	Inhaled corticosteroid	**USAN NAME:**	Mometasone DPI
		ROUTE:	Inhaled
MEDICAL OFFICER:	Daniel J. O'Hearn, M.D.	**REVIEW DATE:**	September 8, 1999

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
November 30, 1998	December 1, 1998	NDA	
March 31, 1999	April 2, 1999	Supplement	4-month safety update
May 20, 1999		New Correspondence	Corrected safety update for C96-136
July 14, 1999	July 15, 1999	Original Amendment	Requested Vital Sign and Weight Data
August 27, 1999	August 30, 1999	Original Amendment	Request for Clarifications

REVIEW SUMMARY: The purpose of this NDA is to obtain approval for the use of Mometasone DPI (MF DPI) in patients 12 years of age and older in the maintenance treatment of asthma as a prophylactic therapy and as a treatment in asthma patients who require systemic corticosteroid administration where adding MF DPI may reduce or eliminate the need for systemic therapy. Analysis of the primary endpoint, change in FEV_1 from baseline, has demonstrated efficacy with the 400 mcg QAM and 200 mcg BID doses of MF DPI in subjects previously maintained on B-agonists alone as well as in subjects previously maintained on inhaled corticosteroids. In the one steroid-sparing trial, the efficacy of MF DPI 400 mcg BID has been demonstrated in its ability to allow for the successful reduction of oral corticosteroid therapy. In clinical trials, the most common adverse event was headache, which was no more common with MF DPI than with placebo. Oral candidiasis was clearly more common with MF DPI than with placebo. A lack of HPA axis effect of MF DPI has not been convincingly demonstrated in this clinical program.

OUTSTANDING ISSUES: Mometasone furoate has not received approval at this time because of several outstanding chemistry and manufacturing issues as well as some clinical issues. The sponsor has been previously made aware of these CMC deficiencies. The clinical issues are to be outlined in the Action Letter.

RECOMMENDED REGULATORY ACTION

New Drug Application: ___X___ **APPROVABLE** _____ **NOT APPROVABLE**

SIGNATURES

Reviewer: Daniel J. O'Hearn, MD **Date:** SEPT. 16, 1999.

Team Leader: see secondary Review memo **Date:** 9/16/99

A. Introduction/Overview to the NDA

NDA 21-067 seeks to obtain approval for the use of Mometasone DPI (MF DPI) in patients 12 years of age and older in the maintenance treatment of asthma as a prophylactic therapy and as a treatment in asthma patients who require systemic corticosteroid administration where adding MF DPI may reduce or eliminate the need for systemic therapy. Each actuation of the to-be-marketed dry powder inhaler is to provide a measured dose of 220 mcg or 430 mcg mometasone furoate which is to result in a delivery of 200 or 400 mcg from the mouth piece, respectively. These inhalation strengths were infrequently utilized in the pivotal clinical studies.

There were six large domestic placebo-controlled clinical trials, one large domestic non-placebo-controlled trial, three large international non-placebo controlled trials, as well as a few other smaller studies, including some that utilized the pure MF formulation. The placebo-controlled trials differed in the populations examined: asthmatics previously treated with B-agonists alone, asthmatics previously on inhaled corticosteroids, and asthmatics dependent on oral corticosteroid therapy. The primary endpoint for all but one of the large placebo-controlled studies was the change in FEV_1 between Baseline and Endpoint. The one study that examined asthmatics dependent on oral corticosteroid therapy had a primary endpoint was the percent change from Baseline at Endpoint in daily prednisone requirement. A table highlighting the large placebo-controlled trials and their efficacy endpoints can be located near the beginning of the Integrated Summary of Efficacy.

B. Review Process

The primary medical review was largely done independently of the other primary reviewers but there were multiple discussions with the primary Biometrics reviewer throughout the review process. The review was compiled trial by trial and the secondary reviewer reviewed the primary reviewer's reports as they were composed.

The six large placebo-controlled trails as well as the one large domestic non-placebo-controlled trial (C96-135) were reviewed in full detail. The review of the three large international non-placebo trials was reviewed in a more cursory manner but special attention was given to laboratory abnormalities in all of the large trials. Studies C97-049 and C95-135, which examined pharmacokinetic and HPA axis testing, were reviewed in full detail. Any other study, including I96-401 and 402, were reviewed in a most cursory manner.

The sponsor, Schering Corporation, supplied the NDA both in paper volume form as well as electronically in PDF format. At the request of the agency, clinical reports were also supplied electronically in Word format, which greatly facilitated the creation of tables for this NDA review. As previously agreed to by the Agency, a 4 month safety update which included 9 month open label extension safety data on three of the large placebo-controlled trials was also supplied in paper and electronic form. The Integrated Summary of Efficacy and that of Safety as prepared by the sponsor did not include data from the 9 month open label extensions.

C. NDA Demographics

Demographic Data: Pooled Data for Large Domestic Placebo-Controlled Studies (not including C97-137)

	MF DPI, BID			MF DPI, QD			BDP 168 mcg	
	100 mcg (n=133)	200 mcg (n=263)	400 mcg (n=74)	200 mcg (AM) (n=209)	200 mcg (PM) (n=54)	400 mcg (AM) (n=209)	BID (n=128)	Placebo (n=350)
Gender, No. subjects (%)								
Female	74 (56)	155 (59)	47 (64)	119 (57)	34 (63)	106 (51)	87 (68)	201 (57)
Male	59 (44)	108 (41)	27 (37)	90 (43)	20 (37)	103 (49)	41 (32)	149 (43)
Race, No. subjects (%)								
Asian	3 (2)	8 (3)	--	4 (2)	--	2 (1)	2 (2)	3 (1)
Black	10 (8)	17 (7)	7 (10)	24 (12)	4 (7)	22 (11)	9 (7)	19 (5)
Caucasian	112 (84)	220 (84)	61 (82)	171 (82)	45 (83)	168 (80)	106 (83)	306 (87)
Hispanic	6 (5)	15 (6)	6 (8)	10 (5)	5 (9)	16 (8)	10 (8)	16 (5)
Other	2 (2)	3 (1)	--	--	--	1 (1)	1 (1)	6 (2)
Age, No. subjects (%)								
12-17	11 (8)	29 (11)	8 (11)	23 (11)	4 (7)	34 (16)	10 (8)	37 (11)
18-64	116 (87)	229 (87)	64 (87)	182 (87)	48 (89)	174 (83)	116 (91)	306 (87)
≥65	6 (5)	5 (2)	2 (3)	4 (2)	2 (4)	1 (1)	2 (2)	7 (2)
Age, years								
Mean (sd)	39 (14)	37 (14)	37 (15)	34 (13)	37 (14)	31 (13)	38 (13)	37 (14)
Median	39	37	39	33	36	30	39	37
Min-Max	12-74	12-77	12-68	12-74	13-71	12-76	12-75	12-76
Height (cm)								
Mean (sd)	170 (10)	170 (10)	165 (11)	169 (10)	167 (10)	169 (10)	168 (9)	169 (10)
Median	170	168	164	168	165	168	168	168
Min-Max	142-196	150-196	132-191	147-198	150-191	142-196	150-191	145-193
Weight (kg)								
Mean (sd)	80 (20)	78 (20)	71 (20)	78 (19)	82 (25)	76 (18)	76 (16)	78 (20)
Median	80	75	71	76	77	74	73	76
Min-Max	43-144	41-156	31-142	38-133	40-159	36-127	46-118	36-166

The demographic profiles of the 5 large placebo-controlled trial (not including the steroid-sparing C97-137) for the MF DPI (BID), MF DPI (QD), BDP (BID), and placebo treatment groups were generally similar. Most subjects were within the 18—64 years of age category (>85% of all subjects), with approximately 10% of subjects in the 12—17 years of age range, and the remainder were ≥65 years of age. There were consistently more females than males in all treatment groups (approximately 60% females). The subjects were predominantly Caucasian (approximately 80% across all treatment groups).

D. C96-136 (Vol.101-117)

"Placebo-Controlled Efficacy And Safety Study With Long-Term Safety Evaluation Of Mometasone Furoate Dry Powder In The Treatment Of Asthma In Subjects Previously Maintained On Inhaled Beta-Agonists"

1. Investigators and Investigational Centers

There were 21 centers in the United States involved.

2. Objectives/Rationale

a) Primary:

The primary objective was to characterize the efficacy of the mometasone furoate dry powder inhaler (MF DPI) at two dose levels (200 and 400 mcg QD) compared with placebo, as evaluated by the change in FEV_1 between Baseline and Endpoint. The primary efficacy variable for the 3-month phase was change from Baseline to Endpoint (last available observation) in FEV_1.

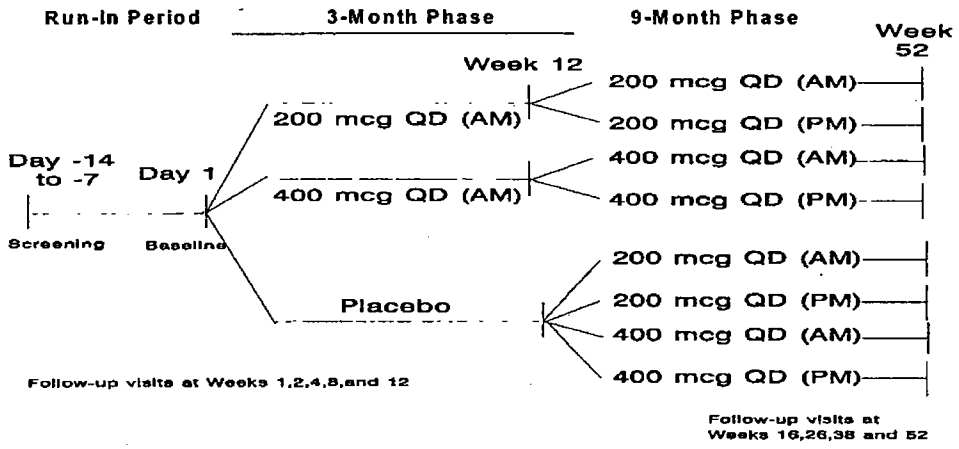
b) Secondary:

Among the secondary evaluations were $FEF_{25\%-75\%}$, FVC, daily peak flow, asthma symptom scores, physician assessment of wheezing, Proventil use, nighttime awakenings, physician assessment of response to therapy, Quality of Life, and bronchial reactivity to methacholine in subjects treated with MF DPI and placebo. Safety evaluations included the monitoring of adverse events, laboratory tests, ECGs, vital signs, and physical examinations.

3. Study design

This was a Phase III, multicenter, randomized, double-blind, parallel group study of the MF DPI in the treatment of asthma in subjects previously maintained on inhaled beta-agonists alone. Following a run-in period of 1 to 2 weeks, a 3-month placebo-controlled double blind phase was initiated. The 3-month phase was followed by an additional 9-month phase in which all subjects received treatment with MF DPI. It was originally anticipated that most subjects would receive a total of 12 months of treatment. The 3-month phase of the study compared the efficacy and safety of MF DPI (200 QAM and 400 QAM) with placebo. Subjects who completed this phase were encouraged to continue into a 9-month phase, which compared AM and PM dosing of MF DPI at 200 QD and 400 QD. In a previous dose-ranging study in subjects with moderate asthma treated with a MF pure powder DPI formulation, MF administered at 200 mcg BID and 400 mcg BID was safe and effective. Thus, the doses chosen for this study, 200 QD and 400 QD, were considered appropriate for subjects with mild to moderate asthma.

4. Summary of Study Protocol



a) Study population

C96-136 selected adult and adolescent subjects who had been maintained on short-acting inhaled beta-agonists alone and had not been treated with inhaled corticosteroids within the three months prior to entering the study. The study was designed to enroll approximately 12 (range 9-24) subjects at each of 21 (range 21-25) study centers for a total of approximately 220 enrolled subjects, to ensure 210 subjects (70 per treatment group) in the 3-month phase of the study who would meet the criteria for the evaluation of the primary endpoint.

(1) Inclusion Criteria

- Subjects must have been 12 years of age or older, of either sex and of any race.
- Subjects must have had a diagnosis of asthma for at least 6 months.
- The subject's Baseline FEV_1 must have been greater than or equal to 55% and less than or equal to 85% of predicted at the Screening and Baseline Visits when all restricted medications had been withheld for the specified intervals.
- Subjects must have demonstrated evidence of an increase in absolute FEV_1 of ≥12%, with an absolute volume increase of at least 200 ml, after reversibility testing, at Screening or within the prior 12 months.
- Subjects must have been using only short-acting inhaled beta-agonists to control their asthma for the 2 weeks prior to Screening.
- Subjects must have been using Proventil for acute relief of symptoms of bronchospasm on average at least three times per week during the Run-in period.
- Clinical laboratory tests (must have been within normal limits or clinically acceptable to the investigator.
- Subjects were to be free of any clinically significant disease (other than asthma), that would interfere with the study evaluations.
- Subjects (and/or parent/guardian) must have been willing to give written informed consent and able to adhere to dose and visit schedules.
- Women of childbearing potential were required to use an acceptable method of birth control during the study

(2) Exclusion Criteria

- Female subjects who were pregnant, breast-feeding, or were premenarcheal.
- Subjects who had received treatment with inhaled corticosteroids for asthma within three months prior to Screening
- Subjects who were on immunotherapy, unless on a stable maintenance schedule. Subjects should not have received immunotherapy within the 24 hours prior to any visit.
- Subjects who required daily or alternate day oral corticosteroid treatment for more than a total of 14 days during the 6 months immediately prior to the Screening visit, and/or subjects who required a burst of systemic steroids within the previous 3 months.
- Subjects who had been treated with methotrexate, cyclosporin, gold, or treatments of a similar nature, for the control of asthma, or for a concurrent condition within the prior 3 months.
- Subjects whose clinical condition required daily use of nebulized beta-agonists.
- Subjects who used any investigational drug in the 30 days prior to study entry.
- Subjects who were allergic to corticosteroids or beta-agonists or who were allergic to more than two classes of medications.
- Subjects who required ventilator support for respiratory failure secondary to their asthma within the previous 5 years.
- Subjects who had been treated in the emergency room for a severe asthma exacerbation or admitted to the hospital for management of airway obstruction on two or more occasions within the prior 6 months.
- Subjects who had required inpatient hospitalization for asthma control within the previous 3 months.
- Subjects who had clinical evidence of chronic obstructive pulmonary disease (COPD), e.g., bronchiectasis, emphysema, cystic fibrosis.
- Subjects who demonstrated an increase or decrease in FEV_1 of ≥20% between Screening and Baseline visits.
- Subjects who required the use of >12 puffs per day of Proventil on any 2 consecutive days between Screening and Baseline.
- Subjects who had a history of glaucoma and/or posterior subcapsular cataracts.
- Subjects who had evidence of clinically significant oropharyngeal candidiasis.
- Smokers or ex-smokers who had smoked within the previous 6 months.
- Subjects who had experienced an upper or lower respiratory tract infection (viral or bacterial) within the previous 2 weeks prior to Screening and Baseline visits.
- Subjects who had any clinically relevant abnormal baseline vital signs.
- Subjects who had clinically significant ECG abnormalities.
- Subjects who had clinically significant abnormalities on chest x-ray.
- Subjects who were known to be HIV positive.
- Subjects who were known illicit drug abusers.

(3) Removal of Subjects from Treatment

Subjects who became pregnant from either the 3 or 9-month phase were discontinued. In the 3-month phase only, subjects who had a clinically significant worsening of their asthma during the study were to be discontinued. The criteria included any one of the following:

- 20% or greater decrease in FEV_1 (absolute value) from the Baseline value.
- 25% or greater decrease in AM or PM peak flow from the mean AM Baseline value on 2 consecutive days.
- Clinically significant increase in use of bronchodilator (e.g., use of >12 puffs of Proventil or >2 treatments with nebulized beta-agonists on any 2 consecutive days).
- Clinical asthma exacerbation requiring emergency treatment, hospital admission or treatment with additional asthma medication (other than short-acting inhaled beta-agonists).

During the 9-month phase, however, discontinuation of subjects for asthma exacerbation was left to the discretion of the investigator except for those subjects that required hospitalization or therapy with additional ICS.

b) Treatments administered

(1) Run-in period

A Proventil inhaler was provided at the Screening visit (Visit 1). Subjects were instructed not to take Proventil regularly or in anticipation of asthma symptoms, unless it was being used prior to exercise. The use of the inhaler was withheld for 6 hours before the Baseline visit. If the subject required the use of a Proventil within 6 hours prior to a visit, he/she was instructed to take the Proventil and to reschedule the visit. Nebulized beta-agonists were permitted during the study. One nebulization treatment was regarded as equivalent to 6 puffs of Proventil MDI. All other asthma medications, including beta-agonists, theophylline, cromolyn and nedocromil, were prohibited during the Run-in period and for the 3-month phase of the study.

(2) 3-month Phase

	AM Dose	Total mcg/Day
Group 1	100 mcg x 2	MF 200 mcg (AM)
Group 2	200 mcg x 2	MF 400 mcg (AM)
Group 3	Placebo x 2	0

(3) 9-month Phase

Subjects who received MF DPI 200 mcg QD AM in the first 3 months continued on the same 200 mcg dose; however, in the 9-month phase, half of these subjects took study medication in the AM and half took medication in the PM. Similarly, subjects who previously received the MF DPI 400 mcg QD AM continued with that dose, but half of the subjects took the dose in the AM and half in the PM. Subjects who were in the placebo treatment group in the first 3 months received treatment with MF either 200 mcg/day AM or PM, or 400 mcg/day AM or

PM. Subjects and investigators were blinded to the dose of MF (200 or 400 mcg) but not to the dosing regimen (AM or PM).

	AM	PM	Total mcg/Day
Group 1	100 mcg x 2		MF 200 mcg (AM)
Group 2		100 mcg x 2	MF 200 mcg (PM)
Group 3	200 mcg x 2		MF 400 mcg (AM)
Group 4		200 mcg x 2	MF 400 mcg (PM)

(4)Concomitant/Restricted Medications

The following concomitant medications were permitted:

- OTC pain relief medications.
- Antibiotics (Note: subjects requiring antibiotics for the treatment of lower respiratory tract infections during the 3-month phase were required to be discontinued from this phase.)
- Topical antimicrobials.
- Proventil (with 6 hour withhold prior to study visits).
- Nebulized beta-agonists (with 6 hour withhold prior to study visits). One nebulization treatment was regarded as equivalent to 6 puffs of Proventil® MDI.
- In the 9-month safety phase, additional asthma medications such as theophylline, cromolyn, nedocromil, salmeterol, oral beta-agonists or anticholinergics were permitted as needed for the treatment of asthma. Subjects taking oral beta-agonists or salmeterol were required to withhold the dose prior to pulmonary function tests. For example, if the visit was scheduled before 12 noon, the morning dose was to be withheld; if the visit was after 12 noon, the evening dose should have been withheld until pulmonary function testing was completed. Ipratropium bromide administered via MDI or nebulizer were required to be withheld for 12 hours prior to visits. There was no requirement to withhold theophylline or cromolyn or nedocromil before visits.
- Oral steroid bursts – 9-month phase only. Up to 21 days of treatment in 9 months.
- Intravenous steroids – 9-month phase only. Each administration was equivalent to one day's treatment with oral steroids.
- Nasal or ocular decongestants, nasal cromolyn, nasal ipratropium bromide, topical antihistamines
- Oral antihistamines such as terfenadine, loratadine or chlorpheniramine were permitted for subjects who experienced allergy symptoms while on-study. If any of these medications were used in a PRN manner, it was preferred that the subject observe an appropriate washout period prior to any study visit in the 3-month phase. If subjects used either medication on a daily basis, prior to Screening, they were told

to continue this dosing regimen; no washout was necessary. Subjects were required to refrain from using astemizole while on-study.

- Nasal corticosteroids – 9-month safety phase only. Up to 2 seasons of treatment up to 6 weeks each or 12 weeks in 9 months. Nasal dexamethasone was not permitted.
- Oral decongestants were permitted in the 9-month phase only.
- Subjects were allowed to 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 permitted within 24 hours prior to a study visit. Subjects were allowed to receive their immunotherapy dose while in the office for a study visit, after all protocol-specified procedures were completed. Oral immunotherapy was prohibited.
- Mild potency topical corticosteroids for dermatological use only, for use in controlling eczema, hives, etc., were allowed.

The following medications were restricted prior to Screening:

Prohibited Medication	Washout Time Prior to Screening Visit
Beta-adrenergic bronchodilators, syrups and tablets	2 weeks
Beta-adrenergic bronchodilators, sustained-release tablets	2 weeks
Bronchodilators, inhaled	6 hours
Bronchodilators, nebulized	6 hours
Theophylline	2 weeks
Salmeterol	2 weeks
Cromolyn sodium, nedocromil, inhaled	2 weeks
Ipratropium bromide aerosol or nebulized	2 weeks
Any systemic bursts of (oral or intravenous) corticosteroids	3 months
Corticosteroids - inhaled	3 months
Corticosteroids -- nasal or ocular	2 weeks
Corticosteroids -- intramuscular or intra-articular	3 months
High potency topical corticoids for dermatological use	1 month
Astemizole	3 months
Hydroxyzine	5 days
Long-acting antihistamines -- e.g., loratadine, terfenadine, sustained-	72 hours

release chlorpheniramine	
Short-acting antihistamines (e.g., 4 mg chlopheniramine)	24 hours
Oral decongestants (long-acting)	72 hours
Oral decongestants (short-acting)	24 hours
Immunotherapy	24 hours
Zafirlukast (Accolate)	2 weeks

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

- No subject in the study could concurrently receive any medication linked with a clinically significant incidence of hepatotoxicity (e.g., methotrexate, 17-alkylsteroids) or which could cause significant liver enzyme induction (e.g., barbiturates).
- Beta blockers - oral or non-selective ophthalmic preparations
- Ocular, intramuscular, intra-articular, and inhaled corticosteroids.
- High potency topical corticoids
- Astemizole

The medications listed below were prohibited in the 3-month phase, but permitted in the 9-month phase:

- Theophylline.
- Oral beta-agonists (withheld prior to pulmonary function tests).
- Salmeterol (withheld prior to pulmonary function tests).
- Ipratropium bromide MDI or nebulized (withheld 12 hours prior to visits).
- Oral steroid burst (up to 21 days of treatment in 9 months).
- Intravenous steroids (each administration equivalent to one day's treatment with oral steroids).
- Cromolyn sodium or nedocromil (inhaled; no withholding was necessary before visits).
- Nasal corticosteroids, (up to two seasons of six weeks each, or 12 weeks in nine months; nasal dexamethasone was prohibited).
- Oral decongestants
- Zafirlukast

c) Randomization

After completing the one to two week Run-in period, qualified subjects were randomized at Baseline (Visit 2) to one of eight treatment arms in a 2:2:2:2:1:1:1:1 ratio. This randomization code resulted in three treatment regimens during the 3-month phase (MF DPI 200 mcg QD AM, MF DPI 400 mcg QD AM, and placebo), and four treatment regimens during the 9-month phase

(MF DPI 200 mcg QD AM, MF DPI 200 mcg QD PM, MF DPI 400 mcg QD AM, and MF DPI 400 mcg QD PM).

Treatment	3-Month Phase	9-Month Phase	No. per Block
A	MF DPI 200 mcg QD AM	MF DPI 200 mcg QD AM	2
B	MF DPI 200 mcg QD AM	MF DPI 200 mcg QD PM	2
C	MF DPI 400 mcg QD AM	MF DPI 400 mcg QD AM	2
D	MF DPI 400 mcg QD AM	MF DPI 400 mcg QD PM	2
E	Placebo	MF DPI 200 mcg QD AM	1
F	Placebo	MF DPI 200 mcg QD PM	1
G	Placebo	MF DPI 400 mcg QD AM	1
H	Placebo	MF DPI 400 mcg QD PM	1

Subject numbers were assigned sequentially as subjects qualified for entry into the study. A computer generated the randomization schedule with codes in blocks of twelve via SAS function UNIFORM with a seed based on clock time.

d) Assessments/Study Procedures

Baseline Period was defined as the interval of time that began 7 to 14 days prior to the Baseline visit (the first day of treatment) and ended on the day of the Baseline visit (before the first dose of treatment was given).

Treatment Period During the 3-month Phase was the interval of time that began on the first day of treatment (Baseline visit, after the first dose of treatment) and ended on the last study visit in the 3-month phase.

Schedule of Study Procedures and Evaluations											
		12-month Treatment Period									
		3-month Phase						9-month Phase			
	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Treatment Days/Weeks:	-14 to-7	1	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 26	Week 38	Week 52
Obtain Informed Consent	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										
Hematology, Blood Chemistry, Urinalysis	X						X		X	X	X
Pregnancy Test	X						X		X	X	X
Electrocardiogram	X						X				X
Chest X-ray (if none in previous year)	X										
Methacholine challenge (Selected Centers)		X					X		X		X
Quality of Life Assessment		X					X				
Dispense Diary	X	X			X	X	X	X	X	X	
Review Diary		X	X	X	X	X	X	X	X	X	X
Dispense Peak Flow Meter	X										
Dispense Study Medication		X					X		X	X	
Response to Therapy Assessment			X	X	X	X	X	X	X	X	X
Adverse Events Evaluation		X	X	X	X	X	X	X	X	X	X
Compliance Check/Collect Medication			X	X	X	X	X	X	X	X	X

Telephone Contact: Weeks 20, 32, 42 and 48

Note: PIFR was measured at Center 22.

Physician's evaluations were recorded during subject visits to the clinic which were scheduled for Days 1, 8, 15, 29, 57, and 85 of treatment during the 3-month phase. Treatment days were numbered relative to the start of treatment, which was designated as Day 1.

Nominal (Scheduled) Visit Day	Relative Day Range	Derived Visit
Day 1	Day -1 to 1	Baseline
Day 8	Day 6-11	Week 1
Day 15	Day 12-21	Week 2
Day 29	Day 22-36	Week 4
Day 57	Day 50-64	Week 8
Day 85	Day 78-92	Week 12

- Review Inclusion/Exclusion Criteria: Visit 1 (Screening) and Visit 2 (Baseline)

- Pulmonary Function Tests: All Visits

Spirometry was performed to measure FVC, FEV_1, and $FEF_{25\%-75\%}$. Every attempt was made to use one spirometer consistently on each subject. Spirometry could be performed with the subject either standing or sitting; the position was to be consistent throughout the study.

Three measurements were done. The spirometry effort with the highest FEV_1 was recorded as the best effort. If two spirometry efforts had identical FEV_1, the effort with the highest FVC was recorded. The FEV_1 at both Screening and Baseline visits must have been $\geq$55% and $\leq$85% of the predicted normal value for the subject to qualify. If the FEV_1 recorded at the Baseline visit showed an increase or decrease of $\geq$20% from the FEV_1 recorded at the Screening visit, the subject was not eligible for the study.

If the subject was African-American, appropriate adjustments were made for this race by programming the spirometer or by hand calculation, using the formula: FEV_1 predicted x 0.88 = FEV_1 predicted adjusted for race

- Reversibility Test: Visit 1 (Screening)

Subjects received. Spirometry was repeated several times within 30 minutes after administration of 2 puffs of Proventil from a primed MDI. Reversibility, which was defined as an increase in absolute FEV_1 of $\geq$12% over the Baseline value, with an absolute volume increase of at least 200 ml, must have been demonstrated within 30 minutes of bronchodilator administration.

- Pulmonary Auscultation: All Visits

Wheezing was assessed at all visits during the 3-month phase and the 9-month phase of this study. Wheezing was evaluated by the investigator or designee based on pulmonary auscultation grading the severity as:

0 = No wheezing,

1 = Wheezing on forced expiration,

2 = Wheezing during tidal volume on expiration only,

3 = Wheezing during tidal volume on expiration and inspiration.

- Methacholine Testing: 3-month Phase - Visit 2 (Baseline) and Visit 7 (Week 12); 9-month Phase - Visit 9 (Week 26) and Visit 11 (Week 52); Centers 03, 09, 10, 11, 14, 15, 17, 18, and 21 only

Selected centers measured PD_{20} FEV_1, defined as the dose of methacholine required to produce a 20% decrease in FEV_1, relative to Baseline.

Following Baseline pre-challenge spirometry, five inhalations of saline were given, followed by repeat spirometry testing. The post-saline FEV_1 must have been within 15% of the Baseline FEV_1 for the challenge to proceed. The challenge was performed by giving the subject ascending serial concentrations of methacholine according to the manufacturer's recommendations. At each concentration, five breaths were administered by a nebulizer that permitted a fixed delivery time of 0.6 seconds. Spirometry was performed within 2-5 minutes after dose delivery. The challenge test was terminated when either 1) there was a 20% reduction in FEV_1 compared with the post-saline value, or 2) the maximum concentration had been administered. The subject was allowed to recover spontaneously or was given Proventil® to restore lung function to Baseline values.

- Assessment of Response to Therapy: 3-month phase - Visits 3-8 (Weeks 1, 2, 4, 8, and 12); 9-month Phase - Visits 9-11 (Weeks 16, 26, 38, and 52)

The response to therapy was evaluated at Visits 3-8 of the 3-month phase and Visits 9-11 of the 9-month phase. The investigator assessed the subject's response to therapy by comparing the subject's current level of symptoms with those noted at the Baseline visit with the following scale:

1 = much improved
2 = improved
3 = no change
4 = worse
5 = much worse

Reviewer's Note – This is a commonly used symptom questionnaire but to the best of this reviewer's knowledge, it has not been validated. This symptom score represents only a secondary endpoint.

- Quality of Life Assessments: Visit 2 (Baseline) and Visit 7 (Week 12)

A self-administered health-related quality of life (HQOL) questionnaire was comprised of the validated acute form of the Short-Form Health Survey (SF-36) and a validated asthma specific HQOL module (which evaluated breathlessness, mood, social impact, asthma concerns, psychological impact, and physical symptoms) and was administered at Baseline and at Visit 7 (or at subject's last visit if discontinued early).

- HQOL data from this study was collected separately from adverse event data and no reconciliation of HQOL data and adverse event data occurred.
- Final Visit Activities: 3-month phase - Visit 7 (Week 12); 9-month Phase - Visit 11 (Week 52); or Last Visit for Subject

Subjects who discontinued either phase prior to completion had Visit 7 or Visit 11 evaluations and procedures completed as appropriate. At the Final visit in the 3-month phase of the study, all scheduled procedures and evaluations were performed. The subjects who

completed the 3-month phase were encouraged to enter the subsequent 9-month phase of the study. For subjects who elected not to continue into the 9-month phase, the subjects were directed by the physician to resume appropriate therapy for their asthma. Any abnormalities or adverse events present at the final visit in the 3-month phase of the study were followed or treated until satisfactory resolution occurred.

- Diary Data

Each subject was given a diary card at Screening, Baseline, and Visits 5-7 of the 3-month phase, and at Visits 8-10 in the 9-month phase. 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 awakenings due to asthma requiring Proventil use, adverse events, and use of study drug and concomitant medications. Asthma symptoms were not recorded after the first 4 weeks in the 9-month phase (Visit 8, Week 16).

- Peak Expiratory Flow Rate Measurements

At the Screening visit, subjects were given a [ ] Peak Flow Meter and were instructed in its proper use. Subjects were instructed to perform triplicate peak expiratory flow rate (PEFR) measurements in the morning and the evening before taking their asthma medication and/or Proventil if needed at that time. In the 3-month phase, subjects were dosed with study medication once daily in the morning; they were instructed to measure their PEFR in the morning before dosing and again in the evening, approximately 12 hours after the morning dose. In the 9-month phase, subjects who were assigned to once daily dosing in the evening were instructed to measure their PEFR in the morning and again in the evening, before the evening dose. PEFR measurements were separated by approximately 12 hours. The highest of the three values was recorded in the diary.

- Asthma Symptoms: Up to Visit 8 (Week 16) Only

Every morning and evening, prior to dosing, the subject evaluated the following asthma symptoms as they were experienced during the time period since the last evaluation: wheezing, difficulty breathing, and cough using the following 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 or all of my normal daily activities/sleep.

- Number of Nocturnal Awakenings

The subject recorded the number of times during the night that he/she was awakened due to asthma symptoms that required Proventil. The subject also recorded the number of Proventil puffs used and the time taken.

- Daily Medication Record

From the Baseline visit onward, the subject recorded the number of inhalations and time of dosing of study medication. In addition, the total number of puffs of Proventil used in each 24-hour period an any other medications taken was recorded.

- Full Medical History: Visit 1 (Screening)

- Oropharyngeal Examination: All Visits

If oropharyngeal candidiasis was present at the Screening or Baseline visits, it was treated and the subject rescheduled when the candidiasis resolved. During the treatment period, if there was clinical evidence of infection, a culture was taken and sent to the central laboratory, and appropriate therapy was initiated. Subjects with culture-positive infection could continue in the study on appropriate treatment with the approval of the investigator.

- Physical Examination: 3-month Phase - Visit 1 (Screening) and Visit 7 (Week 12); 9-month Phase - Visit 11 (Week 52)

- Vital Signs: All Visits

Systolic and diastolic blood pressure (mm Hg), oral temperature (°F), pulse (beats/minute), and respiratory rate (breaths/minute) were recorded at all visits, just prior to spirometry, with the subject in the sitting position.

- Concomitant Medication Review: All Visits

- Laboratory Procedures (analyzed at a central laboratory, [ ], later re-named [ ] 3-month Phase - Visit 1 (Screening) and Visit 7 (Week 12); 9-month Phase – Visit 9 (Week 26), Visit 10 (Week 38), and Visit 11 (Week 52)

Complete Blood Count - including WBC, differential, and platelet count.

Blood Chemistry- Total protein, Albumin, Calcium, Inorganic phosphorus, Blood urea nitrogen (BUN), Total bilirubin, Alkaline phosphatase, AST (SGOT), ALT (SGPT), LDH, Creatinine, Glucose, Potassium, Sodium, Chloride, Bicarbonate, Serum pregnancy test (beta hCG) - all female subjects, Cholesterol

Complete Urinalysis including pH, specific gravity, protein, glucose, ketones, blood, and microscopic examination.

- Electrocardiogram: 3-month Phase - Visit 1 (Screening) and Visit 7 (Week 12); 9-month Phase - Visit 11 (Week 52) (The ECG at Screening was required to be without clinically significant abnormalities.)

- Chest X-Ray: Visit 1 (Screening)

- Recording of Adverse Events

The subject was instructed to record any adverse event in the diary, whether or not it was thought to be related to the study treatment. He/she was also instructed to record any

incident of intercurrent illness. At each visit, subjects were questioned regarding the occurrence and severity of any adverse events. Asthma symptoms of wheezing, difficulty breathing and cough were not considered adverse events, except if they showed a clear temporal relationship to study drug administration or resulted in hospitalization. The following definitions were used for grading adverse events:

Mild:	awareness of sign, symptom or event, but easily tolerated,
Moderate:	discomfort enough to cause interference with usual activity and may warrant intervention,
Severe:	incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention,
Life-threatening:	immediate risk of death.

The investigator assessed the relationship of any adverse event to the use of study drug using the following guidelines:

0 = Not related - no temporal association, or the cause of the event has been identified, or the drug cannot be implicated based on available information.
1 = Possibly related - temporal association, but other etiologies are likely the cause. However, involvement of the drug cannot be excluded.
2 = Probably related - temporal association, other etiologies are possible but unlikely.
3 = Related - established temporal association (e.g. rechallenge), or event not reasonably explained by the subject's known clinical state or any other factor.

- Serious Adverse Events

All serious adverse events, whether or not they were deemed drug-related or expected, were to be reported by the investigator to the sponsor immediately or within 24 hours (one working day) by telephone. A written report, which included a full description of the event and any sequelae, followed as soon as possible. This included serious adverse events that occurred anytime while enrolled in the study or within 30 days after a subject completed the study. A serious adverse event, according to the sponsor's policy, was defined as one that:

- was fatal
- was life-threatening
- was significantly/permanently disabling
- required in-patient hospitalization, or prolonged an existing hospitalization
- was cancer
- was an overdose, either intentional or inadvertent
- was a congenital anomaly

In addition, end-organ toxicity, including hematological, renal, cardiovascular, hepatic, gastrointestinal, and central nervous system adverse events, may be considered serious. This includes abnormal laboratory value(s) changes, unless otherwise specified in this section of the protocol.

End organ toxicity includes adverse events that are medically important that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent the development of a life-threatening situation, hospitalization, disability, or incapacity. These should usually be considered serious.

- Clinical Asthma Exacerbation

A clinical asthma exacerbation was defined as a worsening of asthma that resulted in emergency treatment, hospitalization or treatment with additional asthma medication (other than short-acting inhaled beta-agonists). In the first 3-month phase of the study, a subject experiencing an exacerbation was required to be discontinued from the study. In the 9-month phase, subjects having exacerbations were permitted to remain in the study, provided that they did not require hospitalization or treatment with additional inhaled beta-agonists.

- Telephone Contacts (Weeks 20, 32, 42, and 48) and unscheduled visits were permitted at any time at the discretion of the investigator.

e) Statistical and Analytic Plans

(1) Study population

The analyses were to be based on the following subsets of subjects:

Randomized Subjects (intent-to-treat principle): This subset was to include all randomized subjects.

Efficacy Evaluable Subjects: This data set was defined as randomized subjects who met key eligibility and evaluability criteria. Confirmatory efficacy analyses were to be based on this subject subset.

(2) Efficacy analysis

- Comparability of the treatment groups at Baseline was to be assessed by comparing the three treatment groups with respect to demographic (sex, age, and race) and disease characteristics (Baseline FEV_1, and PEFR).

- Assessment of Consistency of Results Across Centers- to be based on an examination of the center-specific results and on the significance of the treatment by center interaction for the primary efficacy variable (from a two-way analysis of variance [ANOVA] model extracting sources of variation due to treatment, center and their interaction).

- Analysis of the Primary Efficacy Variable

In this study, change in FEV_1 from Baseline to Endpoint, where Endpoint is defined as the last observation obtained for a given subject during the treatment period, was chosen as the primary efficacy variable to account for the expected discontinuance of subjects because of treatment failure, especially in the placebo group.

The primary efficacy variable at Endpoint was to be analyzed for all randomized subjects (pooled across all centers) using an ANOVA model which extracted sources of variation due to treatment and center and treatment by center interaction. The primary efficacy analysis for demonstrating the activity of MF DPI was to be based on a pairwise comparison of least square

means between MF DPI 400 mcg QD and placebo (from the ANOVA) using a 0.05 level of significance. If this comparison was significant, then the other two pairwise comparisons were made at the 0.05 (two-sided) level of significance, without adjustment for multiple comparisons.

In addition to the analysis at Endpoint, all three pairwise comparisons among the three treatment groups were to be made with respect to the change from Baseline in FEV_1 for each scheduled visit, using the same two-way ANOVA described above.

- Analysis of Secondary Efficacy Variables

All other continuous efficacy variables were to be analyzed at each time point also using the two-way ANOVA. These included FVC, $FEF_{25\%-75\%}$ and the physician's evaluations of response to therapy at the scheduled visits, and physicians evaluation of wheezing, as well as subject evaluations recorded on the diary (averaged over each 7-day interval) -- PEFR, asthma symptoms, nocturnal awakenings, and the number of Proventil inhalations. For time to discontinuation because of asthma worsening, Kaplan-Meier survival time estimates were to be calculated and treatment groups were to be compared using the log-rank test.

Methacholine challenge testing was to be performed at Baseline and Week 12 (final visits of 3-month phase) at centers 03, 09, 10, 11, 14, 15, 17, 18, 19 and 21. Results were tabulated by treatment group; no formal analyses were planned. Inspiratory flow rate data collected at Center 22 was summarized and tabulated.

- Summary of Safety Data

Summaries of clinical adverse events, laboratory test values, and vital signs were to be based on all subjects who received at least one dose of study medication.

- Quality of Life Data

The quality of life data in this study was measured using the widely used and validated general health questionnaire (SF-36) and an asthma-specific module. that evaluated breathlessness, mood, social impact, asthma concerns, psychosocial impact, and physical symptoms.

(3) Sample Size

The study was designed to enroll 210 subjects or 70 subjects per treatment group for the 3-month phase. The sample size was chosen to detect (with 90% power and 5% significance level) a clinically meaningful pairwise difference in the FEV_1 mean change from Baseline (the primary efficacy variable) between any active treatment group and placebo. With 70 subjects per treatment group, assuming a pooled standard deviation of 0.45 units for FEV_1 change from Baseline, mean treatment differences of approximately 0.25 units (approximately 10% of Baseline) or more would be detectable with power greater than 90%.

f) Protocol Deviations

Before the database was locked and treatment assignments for the 3-month phase were unblinded, the sponsor decided that certain variations from the letter of the protocol during enrollment of subjects would not significantly affect the evaluability of the data.

- The range of the allowable proportion of actual FEV_1 values relative to predicted values at the Screening and Baseline visits was broadened from 55% to 85% to a slightly wider 50% to 90%.

- Reversibility testing had to demonstrate an increase in FEV_1 of ≥10.5%, rather than ≥12%, with an absolute volume increase of at least 200 ml.

- The minimum acceptable Proventil washout time prior to PFTs was changed from 6 to 4 hours for determination of evaluability of the Endpoint visit only.

- The definition of the dataset that formed the basis of the ITT analyses was changed, and specific criteria for the Efficacy Evaluable subset were developed. The "All treated subjects" data set included all subjects randomized who received at least one dose of study medication (intent-to-treat principle). All analyses of efficacy and summaries of safety were based on all treated subjects.

- Subjects with major protocol deviations were excluded from the Efficacy Evaluable dataset.

- The protocol described the primary method of analysis as a two-way ANOVA extracting sources of variation due to treatment, center and their interaction. Because of the low center enrollment in this study, the analysis model was being modified to a reduced, main-effects, two-way ANOVA for the primary efficacy analysis.

The sponsor says that regulatory authorities, IRBs, and investigators, were notified by letter, prior to the unblinding of any of the MF DPI study data, of the above protocol change.

A full two-way ANOVA model including the interaction term was still performed in order to conduct a preliminary assessment of consistency of results per the protocol. Centers with six or fewer Efficacy Evaluable subjects were combined for the preliminary analysis. These composite centers were used for the preliminary assessment of consistency of results across centers and the ANOVA model used for this analysis included the treatment-by-center interaction term. An ANOVA model with main effects for treatment and center was used for the analyses of the primary and secondary efficacy variables, and there was no need to combine any center for these analyses.

- The planned analysis of "time to discontinuation due to asthma worsening" was changed to an analysis of "time to asthma worsening," which is the first treatment day on which a subject met any criterion for worsening.

5. Results

a) Study Population Characteristics

There were 236 subjects randomized at 21 study centers. (One additional center, #13, did not enroll any subjects.) All randomized subjects received at least one dose of study medication. The numbers of subjects randomized and treated in the three groups of the 3-month phase were as follows: 72 in the MF DPI 200 QD group; 77 in the MF DPI 400 QD group; and 87 in the placebo treatment group. The apparent imbalance between the placebo treatment group (87 subjects) and MF treatment groups (MF DPI 200 QD, 72 subjects, and MF

DPI 400 QD, 77 subjects) was due to the randomization block size of 12 (which included allocation to all eight treatment arms for the entire 12-month period of the study) coupled with enrollment of fewer than a complete randomization block at most centers.

Summary of Demographic and Baseline Characteristics

	MF DPI 200 mcg QD (n=72)	MF DPI 400 mcg QD (n=77)	Placebo (n=87)
Age (years)			
Mean	33	31	35
Min-Max	14-65	12-62	12-72
Distribution of Subjects in Age Categories			
12 to 17 years	8	10	8
18 to 64 years	63	67	78
≥65 years	1	0	1
Sex			
Female	38	42	46
Male	34	35	41
Race			
White	62	65	76
Black	6	8	7
Hispanic	1	4	4
Asian	3	0	0
Weight (lb.)			
Mean	174	167	176
Min-Max	108-284	90-273	80-300
Smoking History			
Never Smoked	56	64	70
Has Not Smoked in 6 Months	16	13	17
Duration of Asthma Condition (years)			
Mean	17	15	15
Min-Max	1-40	1-40	1-48
FEV_1 % Predicted at Baseline (%)			
Mean	72	72	73
Min-Max	54-95	46-91	53-90
FEV_1 at Baseline (liters)			
L.S. Mean	2.60	2.57	2.61
Puffs Proventil at Baseline (per day)			
L.S. Mean	4.02	4.18	4.09

The groups appear similar with regard to demographic characteristics and baseline spirometry.

Distribution of Subjects in Datasets Analyzed

	200 mcg QD	400 mcg QD	Placebo
Efficacy	64	70	80
Safety	72	77	87
Total Enrolled	72	77	87

A total of 44 subjects (19%) discontinued from the 3-month phase of the study prior to scheduled completion. Discontinuations were less common in the MF DPI 200 mcg QD treatment group (7 subjects, 10%) and the MF DPI 400 mcg QD treatment group (15 subjects, 19%) than in the placebo treatment group (22 subjects, 25%). Adverse events were the most common reason for discontinuation (24 subjects, 10%). The incidence of discontinuation due to

adverse events was similar (8 to 12%) among the treatment groups. The incidence of discontinuation for treatment failure was notably higher in the placebo treatment group (8%) than in the MF DPI treatment groups (1%, both groups).

Final Disposition

	Treatment Groups			
	MF DPI 200 mcg QD (n=72)	MF DPI 400 mcg QD (n=77)	Placebo (n=87)	Total (n=236)
Number (%) Completed	65 (90)	62 (81)	65 (75)	192 (81)
Reason for Discontinuation				
Adverse Event	6 (8)	9 (12)	9 (10)	24 (10)
Treatment Failure	1 (1)	1 (1)	7 (8)	9 (4)
Lost to Follow-Up	0 (0)	2 (3)	2 (2)	4 (2)
Did Not Continue for Reasons Unrelated to Treatment	0 (0)	2 (3)	2 (2)	4 (2)
Non-Compliance	0 (0)	1 (1)	1 (1)	2 (1)
Did Not Meet Entry Criteria	0 (0)	0 (0)	1 (1)	1(<1)
TOTAL NUMBER (%) DISCONTINUING	7 (10)	15 (19)	22 (25)	44 (19)

Subject Evaluability Criteria: Because some of the reasons for failure to meet entry criteria were considered unlikely to affect the evaluation of efficacy significantly, only those subjects who had major deviations were regarded as non-evaluable (classification into major and minor deviations was performed prior to unblinding the study). Subjects were classified as non-evaluable if one or more of the following major deviations was present:

- Screening or Baseline FEV_1 was <50% or >90% of the predicted value.
- Variability in FEV_1 between the Screening and Baseline visits was ≥20%.
- Subject failed the reversibility test; that is, did not demonstrate evidence of an increase in absolute FEV_1 of 10.5%, with an absolute volume increase of at least 200 ml, or an increase in absolute FEV_1 of 12%, with increase of at least 180 ml.
- Corticosteroids used within 87 days of medication start date.
- Use of asthma medications that are listed for washout or study prohibition in protocol.
- Subjects who did not use Proventil on at least 3 occasions during the Run-in.
- Study medication non-compliance (<75% or >125% over the entire study period).

Distribution of Subjects by Analysis Subset and Treatment Group

	Number of Subjects			
	MF DPI 200 mcg QD	MF DPI 400 mcg QD	Placebo	Total
All Treated Subjects	72	77	87	236
All Treated Subjects with Follow-up Data	72	76	86	234
Subjects Lost to Follow Up After Baseline	0	1	1	2
Efficacy Evaluable Subset	64	70	80	214
Excluded From Efficacy Evaluable	8	7	7	22

Reviewer's Note – One subject in the 400 mcg and placebo group did not have any post-baseline data.

Twenty-two subjects were excluded from the Efficacy Evaluable subset. Most were excluded because they were not eligible according to the requirements of the inclusion or exclusion criteria and two (one in 400 mcg QD MF DPI Treatment group and one in Placebo group) were excluded because they had no efficacy data recorded or because they received insufficient treatment.

Reviewer's Note: These patients' data in Section 16.2.3 were reviewed electronically and appear to corroborate with the text. Most were excluded because of spirometry exclusion criteria. There did not appear to be an over representation of subjects at any one site.

Number of Subjects in the Analysis of the Primary Efficacy Endpoint – FEV_1

	Baseline			Week 1			Week 2			Week 4			Week 8			Week 12			Endpoint		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
RANDOMIZED	72	77	87	72	77	87	72	77	87	72	77	87	72	77	87	72	77	87	72	77	87
Missing Data	0	0	0	7	8	6	6	8	11	4	5	9	9	15	21	11	21	30	0	1	0
No post Baseline	NA	NA	NA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Missing Evaluation	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Missing Visit	0	0	0	7	8	6	6	8	11	4	4	9	9	13	21	11	21	30	0	0	0
ITT Subset	72	77	87	65	69	81	66	69	76	68	72	78	63	62	66	61	56	57	72	76	86
Excluded from Evaluable Set	8	7	7	6	5	6	7	6	6	7	7	9	6	8	9	8	9	9	8	6	6
Noncompliance With Protocol	7	6	6	4	5	5	7	5	5	7	5	7	6	6	7	6	6	8	7	6	6
Insufficient Data	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Hrs since last dose Unaccept.	0	0	0	2	0	1	0	1	1	0	2	2	0	2	2	2	3	1	0	0	0
Evaluable Set	64	70	80	59	64	75	59	63	70	61	65	69	57	54	57	53	47	48	64	7	80

b) Protocol Deviations

Twenty two subjects (eight in the MF DPI 200 mcg QD group, seven in the MF DPI 400 mcg QD group, and seven in the placebo group) had one or more major protocol deviations and were excluded from the Efficacy Evaluable data set.

	MF DPI 200 mcg QD	MF DPI 400 mcg QD	Placebo
FEV_1 value exceeded criteria for variability (>20%) between Screening & Baseline	5	2	3
FEV_1 values that were not between 50% and 90% of predicted values at Baseline	1	2	0
Poor compliance (<75% of specified doses taken)	1	2	1
Reversibility <10.5% at Screening	1	0	0
Lost to follow-up following Baseline Visit	0	1	1
Use of Proventil <3 times during Run-in phase	0	1	1
Insufficient washout of prohibited medications	0	0	2

There were also 48 subjects who met one or more criteria for worsening of asthma. (All 48 subjects should have been removed from the study at the time of the first worsening per protocol. Twenty-five subjects were removed as planned, but 23 were not. Most of these subjects had experienced a ≥25% decrease in AM or PM PEFR on two or more consecutive days. Many of these asthma worsenings resolved with Proventil use and the investigator made the decision to continue the subject in the study. It should be noted that two subjects with worsening of asthma were excluded from the Efficacy Evaluable analysis for other protocol deviations.

Number Of Subjects with Worsening Of Asthma who Continued in the study

Reasons for First Occurrence of Asthma Worsening	MF DPI 200 mcg QD (n =72)	MF DPI 400 mcg QD (n =77)	Placebo (n =87)	Total Asthma Worsening
Decrease in FEV_1	3	1	5	9
Clinical Asthma Exacerbation	0	0	2	2
Decrease in PEFR	6	2	3	11
Overuse of PROVENTIL	0	1	0	1
TOTAL	**9**	**4**	**10**	**23**

- Compliance of <75% or >125% constituted a protocol deviation. Four subjects who completed the 3-month phase were found to have taken fewer than 75% of the doses specified. No subject took >125% of the doses specified.

6. Analysis of Efficacy

The sponsor makes an important point (p. 77, Vol.1-101) that it should be noted that subjects with favorable treatment effects were more likely to contribute data to the later weekly assessments than subjects with poor treatment effects. Dropouts for treatment failure over time were more common in the placebo treatment group than in the MF DPI treatment groups. This

difference between active and placebo treatment groups was particularly noticeable in evaluations after Week 4. Thus, differential dropout rate in subjects with and without favorable treatment effects influences the size and the composition of the treatment groups at post-Baseline weekly assessments. For these reasons, results of changes between Baseline and individual time points must be interpreted with care.

(1) FEV_1

(a) 3 month phase

Evaluation of Endpoint results, which allow comparison among treatment groups in the presence of dropouts, reveal a significant ($p<0.01$) difference in response in the MF DPI 400 mcg QD treatment group (14.2%) and the placebo treatment group (2.5%). A significant difference ($p<0.01$) also was observed between the MF DPI 200 mcg QD treatment group (14.8%) and the placebo treatment group (2.5%) at Endpoint. There was no statistically significant ($p=1.00$) or clinically meaningful difference in response between the MF DPI 400 mcg QD and MF DPI 200 mcg QD treatment groups at Endpoint.

FEV_1 (liters) - Change from Baseline by Treatment Group (All Treated Subjects)

	MF DPI 200 mcg QD (A)			MF DPI 400 mcg QD (B)			Placebo (C)		
	N	Mean[a]	(Mean % Change)[a]	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[b]	**72**	**0.35**	**(14.8%)**	**76**	**0.35**	**(14.2%)**	**86**	**0.06**	**(2.5%)**

Analysis Results (Change From Baseline)[c]

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

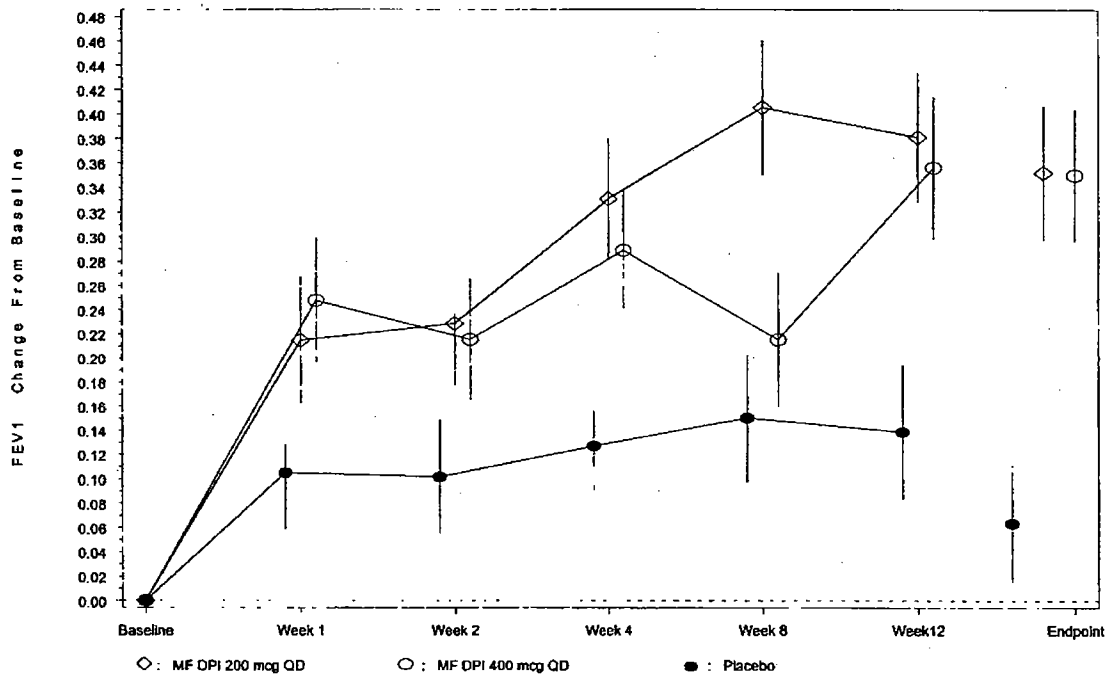
c: Based on an ANOVA model with treatment and center effects. Pairwise treatment comparisons were based on t-test from the ANOVA model. Note: two subjects, one each in the 400 mcg QD and placebo groups, lost to follow-up after the Baseline visit had no post Baseline data and were, therefore, excluded from this analysis.

Reviewer's Note- Remember that Endpoint is only the last visit for each subject and not necessarily Week 12's FEV_1. Note that there is no difference between 200 and 400 mcg except at Week 8. The FEV_1 for 400 mcg at Week 8 is particularly low compared with the rest of the dose's spirometry and does not beat placebo at this time point or at Week 2. In fact, the mean FEV_1 change appears to jump up from an earlier high of 0.29 liters before Week 12 to 0.36 liters at Week 12. This may be indicative of a drop out of poor responders. It is true, however, that continued improvement in FEV_1 may have been occurring.

200 mcg appears to beat placebo at all time points after Week 2.

Nearly one-third of the original randomized subjects had data points for Week 12 and this seems like a particularly high dropout rate.

The mean FEV_1 for placebo appears to be unusually low at Endpoint compared to the rest of the time points. This may be resultant of the fact that Endpoint data includes those who left the Protocol earlier in the study.



Reviewer's Note: This graph seems to highlight the fact that there is not a dose effect in this study. If there is a difference, 200 mcg is better, at least at Week 8.

The sponsor submitted the data on mean change in FEV_1 by age, sex and Caucasian vs. non-Caucasian but did not submit any statistical analysis.

At baseline, 88% of the subjects were in the age group 18-64 years. There were only 2 subjects 65 or over and 1 did not complete three months of therapy. Reviewing the Table submitted in Section 14.2.1.1.2, There did not appear to be an overt difference in response for those ages 18-64 years between the 200 mcg and 400 mcg. Both doses appear to do better than placebo in this age group. There do not appear to be enough individuals in the other age groups and statistical analysis on our part is not needed.

There were 110 males and 124 females at Baseline. Females appeared to have a higher rate of completion of the three months of therapy with 94 out of 110 completing Week 12 while only 80 out of 124 males completed Week 12. There did not appear to be an overt difference in the % mean increase in

FEV_1 between the sexes. Females appeared to have a much more meager placebo increase in FEV_1 with placebo.

16% of the baseline subjects were considered Non-Caucasian. There did not appear to be an overt difference in the response between the race categories. The study did not have enough representation of Non-Caucasians, in any case, to draw any conclusions.

Response was evaluated in subjects whose Baseline FEV_1 was <75% of the predicted value versus those whose Baseline FEV_1 was ≥75% of the predicted value.

Subjects with FEV_1 <75% Predicted and FEV_1 ≥75% Predicted

	MF DPI 200 mcg QD (A)			MF DPI 400 mcg QD (B)			Placebo (C)		
	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
FEV_1 <75% Predicted Value at Baseline									
Baseline	43	2.29		42	2.36		41	2.42	
Change From Baseline									
Week 1	39	0.30	(12.9%)	37	0.34	(14.7%)	39	0.13	(5.6%)
Week 2	40	0.29	(13.1%)	36	0.36	(15.5%)	36	0.18	(7.4%)
Week 4	42	0.40	(16.9%)	42	0.42	(17.6%)	35	0.22	(9.4%)
Week 8	37	0.48	(20.3%)	35	0.32	(14.7%)	29	0.24	(9.6%)
Week 12	38	0.43	(19.8%)	31	0.44	(19.6%)	24	0.30	(10.9%)
Endpoint	**43**	**0.37**	**(16.9%)**	**42**	**0.43**	**(18.6%)**	**41**	**0.14**	**(5.1%)**
FEV_1 ≥75% Predicted Value at Baseline									
Baseline	29	3.11		34	2.86		45	2.82	
Change From Baseline									
Week 1	26	0.20	(5.9%)	32	0.19	(7.1%)	42	0.11	(3.4%)
Week 2	26	0.24	(7.1%)	33	0.13	(4.9%)	40	0.07	(2.5%)
Week 4	26	0.28	(8.7%)	30	0.14	(5.2%)	43	0.06	(1.9%)
Week 8	26	0.31	(10.1%)	27	0.09	(3.7%)	37	0.10	(3.0%)
Week 12	23	0.34	(11.1%)	25	0.25	(8.3%)	33	0.01	(0.2%)
Endpoint	**29**	**0.36**	**(11.5%)**	**34**	**0.26**	**(8.5%)**	**45**	**0.01**	**(0.1%)**

Reviewer's Note - There appears to be a marked difference in the improvement of subjects with an FEV_1 <75% Predicted versus those with an FEV_1 ≥75% Predicted in the steroid treatment groups. Both treatments appeared to beat placebo except again at Week 8 for 400 mcg.

It must be noted that the Adobe electronic submission of data in Section 14 was essentially illegible and required printing before it could be read.

Analysis was done on the Efficacy Evaluable data set (Section 14.2.1.1.5). There were no significant differences ($p>0.05$) between groups in FEV_1 at baseline in the Efficacy Evaluable data set. At Endpoint and at Week 12, there were significant differences between each of the two mometasone treatments and placebo.

Reviewer's Note – In general, there were typically 5-9 subjects less in each group at each time point. 200 mcg was better than placebo at each timepoint while 400 mcg was, again, not significantly better than placebo at Week 2 and Week 8.

(b) FEV_1 through the 9 month phase

Subjects who were treated with MF DPI in the 3-month treatment phase were divided into AM and PM dosing groups in the 9-month phase; subjects who were treated with placebo in the 3-month phase were distributed among the 4 resulting MF DPI dose groups in the 9-month phase.

FEV_1 - Change from Baseline by Treatment Group in the 9-Month Phase (All Treated Subjects)

	Placebo + MF DPI 200 mcg QD AM			Placebo + MF DPI 200 mcg QD PM			Placebo + MF DPI 400 mcg QD AM			Placebo + MF DPI 400 mcg QD PM		
Visit	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline 1	15	2.67	—	12	2.62	—	14	2.74	—	16	2.60	—
Change From Baseline 1												
Endpoint 1	15	0.15	(5.5%)	12	0.02	(0.0%)	14	0.07	(2.2%)	16	0.32	(10.7%)
Endpoint 2	15	0.32	(13.1%)	12	0.23	(8.0%)	14	0.20	(7.9%)	16	0.52	(18.9%)
Baseline 2	**15**	**2.82**	—	**12**	**2.64**	—	**14**	**2.81**	—	**16**	**2.92**	—
Change From Baseline 2												
Week 4	14	0.10	(4.5%)	10	0.14	(6.3%)	10	0.29	(12.2%)	13	0.17	(6.5%)
Week 14	10	0.19	(8.0%)	8	0.24	(11.0%)	10	0.01	(0.8%)	11	0.39	(15.0%)
Week 26	10	0.09	(3.9%)	7	0.19	(10.0%)	10	0.31	(12.7%)	10	0.33	(12.8%)
Week 40	8	0.16	(7.4%)	7	0.36	(16.5%)	9	0.20	(8.9%)	8	0.26	(10.6%)
Endpoint 2	**15**	**0.17**	**(7.6%)**	**12**	**0.20**	**(9.2%)**	**14**	**0.13**	**(6.3%)**	**16**	**0.20**	**(8.1%)**
95% Confidence Intervals												
Endpoint 2		**(-0.01, 0.36)**			**(0.00, 0.40)**			**(-0.05, 0.31)**			**(0.03, 0.37)**	

	MF DPI 200 mcg QD AM + QD AM			MF DPI 200 mcg QD AM + QD PM			MF DPI 400 mcg QD AM + QD AM			MF DPI 400 mcg QD AM + QD PM		
	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline 1	26	2.56	—	28	2.69	—	30	2.69	—	25	2.48	—
Change From Baseline 1												
Endpoint 1	26	0.36	(15.4%)	28	0.53	(20.4%)	30	0.41	(15.4%)	25	0.35	(14.7%)
Endpoint 2	26	0.37	(15.7%)	28	0.62	(24.6%)	30	0.32	(12.9%)	25	0.41	(17.4%)
Baseline 2	**26**	**2.92**	—	**28**	**3.22**	—	**30**	**3.01**	—	**25**	**2.84**	—
Change From Baseline 2												
Week 4	24	-0.02	(-1.7%)	24	0.08	(3.6%)	28	-0.02	(0.0%)	23	0.02	(1.3%)
Week 14	22	0.02	(0.2%)	19	0.06	(3.6%)	21	0.20	(6.0%)	20	0.08	(3.2%)
Week 26	18	0.03	(0.9%)	19	0.08	(3.1%)	17	-0.07	(-1.7%)	17	-0.09	(-3.6%)
Week 40	15	0.05	(2.2%)	17	0.10	(4.5%)	15	-0.02	(0.1%)	15	0.01	(0.8%)
Endpoint 2	**26**	**0.00**	**(0.2%)**	**28**	**0.09**	**(3.8%)**	**30**	**-0.09**	**(-1.8%)**	**25**	**0.05**	**(2.6%)**
95% Confidence Intervals												
Endpoint 2		**(-0.12, 0.12)**			**(-0.07, 0.25)**			**(-0.20, 0.02)**			**(-0.07, 0.17)**	

Reviewer's Note – The Endpoint of the three-month phase is Endpoint 1. The Endpoint of the nine-month phase is Endpoint 2.

It is apparent from this table that the subjects previously on mometasone during the 3 month treatment phase were able to maintain their increase in FEV_1 during the subsequent 9 months. There did not appear to be an overt difference between the doses during the nine month phase. When subjects were switched over from placebo, increases were noted in the FEV_1 once the subjects were on glucocorticoids. The numbers in each group were small so it is difficult to make any conclusions. There seemed to be a trend, however, for the evening dosing to cause more of a % increase in FEV_1 than the am dosing suggesting that qd dosing may not be optimal. This finding could be because the pm dosing had PFTs done 12 hours post-dose versus 24 hours.

(2) FVC and FEF25-75

FVC (liters) - Change from Baseline by Treatment Group (All Treated Subjects)

	MF DPI 200 mcg QD (A)			MF DPI 400 mcg QD (B)			Placebo (C)		
	N	Mean	(Mean % Change)[a]	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	72	3.56		76	3.40		86	3.55	
Change From Baseline									
Week 1	65	0.14	(5.6%)	69	0.32	(13.3%)	81	0.09	(3.5%)
Week 2	66	0.15	(6.2%)	69	0.27	(12.3%)	76	0.11	(4.7%)
Week 4	68	0.29	(8.9%)	72	0.29	(11.6%)	78	0.11	(4.0%)
Week 8	63	0.32	(10.2%)	62	0.27	(12.6%)	66	0.11	(4.2%)
Week 12	61	0.29	(9.7%)	56	0.39	(15.7%)	57	0.11	(3.5%)
Endpoint	**72**	**0.23**	**(7.6%)**	**76**	**0.38**	**(13.8%)**	**86**	**0.02**	**(1.7%)**

Analysis Results (Change From Baseline)[b]

		p-value		Pairwise Comparisons (p-value)		
Time point	Pooled SD	Treatment	Center	A Vs B	A Vs C	B Vs C
Week 1	0.55	0.03	0.09	0.05	0.64	0.01
Week 2	0.57	0.20	0.07	0.23	0.61	0.08
Week 4	0.54	0.06	0.89	0.99	0.04	0.04
Week 8	0.59	0.11	0.35	0.62	0.05	0.13
Week 12	0.48	<0.01	<0.01	0.27	0.05	<0.01
Endpoint	**0.64**	**<0.01**	**0.28**	**0.14**	**0.05**	**<0.01**

Reviewer's Note – There were no important differences at baseline. There were no significant differences after Week 1 between the mometasone treatments. Both treatments were better than placebo except for 400 mcg on Week 8.

$FEF_{25\%-75\%}$ (liters/second) - Change from Baseline by Treatment Group (All Treated Subjects)

	MF DPI 200 mcg QD (A)			MF DPI 400 mcg QD (B)			Placebo (C)		
	N	Mean	(Mean % Change)[a]	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	72	2.09		76	2.23		86	2.18	
Change From Baseline									
Week 1	65	0.38	(28.8%)	69	0.23	(18.4%)	81	0.12	(8.8%)
Week 2	66	0.41	(28.2%)	69	0.19	(14.9%)	76	0.05	(9.2%)

Week 4	68	0.48	(33.9%)	72	0.28	(21.7%)	78	0.15	(13.0%)
Week 8	63	0.67	(39.1%)	62	0.17	(14.1%)	66	0.23	(13.9%)
Week 12	61	0.66	(40.8%)	56	0.36	(22.3%)	57	0.13	(10.3%)
Endpoint	**72**	**0.65**	**(38.8%)**	**76**	**0.37**	**(23.7%)**	**86**	**0.08**	**(10.4%)**

Analysis Results (Change From Baseline)[c]

		p-value		Pairwise Comparisons (p-value)		
Time point	Pooled SD	Treatment	Center	A Vs B	A Vs C	B Vs C
Week 1	0.64	0.05	0.18	0.17	0.01	0.28
Week 2	0.65	<0.01	0.49	0.05	<0.01	0.21
Week 4	0.66	0.01	0.56	0.07	<0.01	0.25
Week 8	0.66	<0.01	0.48	<0.01	<0.01	0.64
Week 12	0.73	<0.01	0.74	0.03	<0.01	0.11
Endpoint	**0.73**	**<0.01**	**0.88**	**0.02**	**<0.01**	**0.01**

Reviewer's Note – It is interesting to note that 400 mcg produces a significantly smaller effect than 200 mcg and is not significantly better than placebo. This variable is not particularly important for regulatory purposes.

Data was also submitted for FVC and FEF25-75 for the 9 month phase. Increases in FVC and FEF were preserved during the 9 month phase. In patients switched over from placebo, the increases in FVC did not appear as impressive for the 400 mcg dose and the 200 mcg q am dose as that seen during the 3 month phase. This may be explained in part by the higher baseline FVC at Baseline 2.

(3) PEFR

Subjects measured PEFR before dosing and prior to the use of Proventil (in those subjects that required treatment with this therapy) in the morning and evening each day. Based on AM and PM PEFR, treatment with MF DPI at 400 mcg QD, was superior to placebo. There were no statistically significant differences in response based on AM or PM PEFR between the MF DPI 200 mcg QD and placebo treatment groups.

AM PEFR (liters/minute) - Change from Baseline by Treatment Group –3 month data

	MF DPI 200 mcg QD (A)			MF DPI 400 mcg QD (B)			Placebo (C)		
	N	Mean	(Mean % Change)[a]	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	72	372.77		76	369.67		86	376.79	
Change From Baseline									
Week 1	72	4.57	(1.9%)	76	16.29	(5.2%)	86	2.47	(1.2%)
Week 2	71	16.98	(6.8%)	76	29.94	(9.0%)	83	8.50	(3.7%)
Week 4	70	20.76	(8.4%)	72	36.90	(11.5%)	75	11.19	(4.3%)
Week 6	70	24.20	(9.0%)	69	45.08	(13.1%)	71	9.53	(3.8%)
Week 8	69	24.67	(8.5%)	65	44.78	(13.2%)	68	15.32	(5.5%)
Week 10	68	31.02	(11.3%)	63	42.56	(12.0%)	65	18.75	(6.6%)
Week 12	66	22.91	(9.5%)	60	46.54	(14.2%)	64	18.28	(6.5%)
Endpoint	**72**	**15.80**	**(7.5%)**	**76**	**41.29**	**(13.1%)**	**86**	**7.95**	**(3.0%)**

Analysis Results (Change From Baseline)

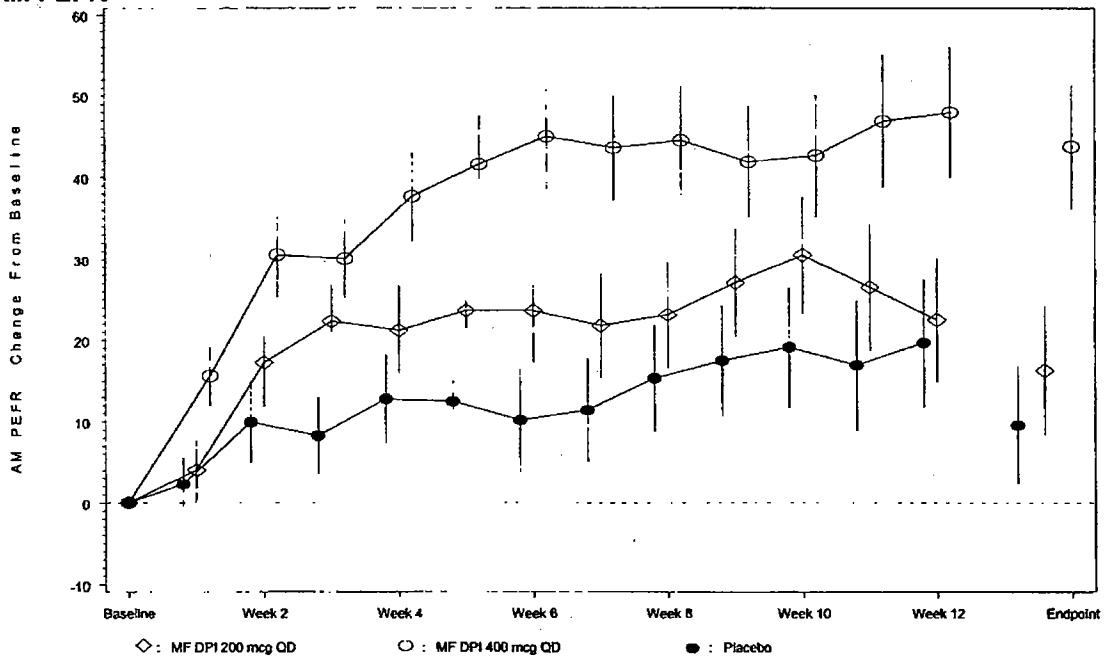
p-value Pairwise Comparisons (p-value)

Time point	Pooled SD	Treatment	Center	A Vs B	A Vs C	B Vs C
Week 1	32.39	0.02	0.80	0.03	0.69	<0.01
Week 2	45.78	0.02	0.59	0.09	0.26	<0.01
Week 4	46.70	<0.01	0.36	0.04	0.22	<0.01
Week 6	54.66	<0.01	0.54	0.03	0.12	<0.01
Week 8	53.83	<0.01	0.77	0.03	0.32	<0.01
Week 10	60.06	0.09	0.95	0.28	0.25	0.03
Week 12	61.43	0.03	0.75	0.03	0.67	0.01
Endpoint	**66.51**	**<0.01**	**0.42**	**0.02**	**0.46**	**<0.01**

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.

Reviewer's Note – With the variable PEFR, 400 mcg is significantly better than both 200 mcg and placebo. 200 mcg only tends to be better numerically than placebo. It appears with PEFR that there is some dose ranging.

AM PEFR



Reviewer's Note - The data for the efficacy seen with p.m. PEFR was not as impressive as the a.m. PEFR. While the mean baseline PEFR tended to be higher p.m. compared with a.m., 400 mcg was not significantly better than placebo at Weeks 10 and 12 while it was at other timepoints including the Endpoint. 200 mcg was not significantly better than placebo at any timepoint while it was numerically better.

Data on PEFR am and pm was also presented for the 9 month phase. Unlike the other physiologic variables, it seems that the am PEFR continued to increase in the patients continued on mometasone during the nine month phase. For the subjects switched over from placebo, the increases were not as impressive as those subjects originally treated with MM DPI during the first three months. The data (p.

493 – Vol. 40 supp.) for the pm PEFR was also reviewed. There continued to be improvement in the 9 month phase in those previously on MM DPI in the 3 month phase. The mean increases in pm PEFR for those switched over from placebo tended to be less that the % increases in the am PEFR.

(4) Asthma Symptoms

Every morning and evening prior to dosing throughout the treatment, the subject rated wheezing, difficulty breathing, and cough on a scale of 0 (none) to 3 (very uncomfortable and interfered with most or all of normal daily activities/sleep).

There were no significant differences ($p>0.05$) in AM or PM wheezing, difficulty breathing, or cough between groups at Baseline.

AM Wheezing Scores - Change from Baseline by Treatment Group (All Treated Subjects)

	MF DPI 200 mcg QD (A)		MF DPI 400 mcg QD (B)		Placebo (C)	
	N	Mean	N	Mean	N	Mean
Baseline	72	1.03	76	0.97	86	0.98
Change From Baseline						
Week 1	72	-0.21	76	-0.27	86	-0.04
Week 2	71	-0.25	76	-0.33	83	-0.16
Week 4	70	-0.41	73	-0.34	75	-0.18
Week 6	70	-0.47	69	-0.43	71	-0.20
Week 8	69	-0.48	65	-0.40	68	-0.29
Week 10	68	-0.44	64	-0.37	65	-0.20
Week 12	66	-0.44	60	-0.46	64	-0.25
Endpoint	**72**	**-0.40**	**76**	**-0.39**	**86**	**-0.14**

Analysis Results (Change From Baseline)

		p-value		Pairwise Comparisons (p-value)		
Time point	Pooled SD	Treatment	Center	A Vs B	A Vs C	B Vs C
Week 1	0.49	0.01	0.38	0.48	0.03	<0.01
Week 2	0.54	0.15	0.50	0.40	0.29	0.05
Week 4	0.55	0.03	0.35	0.44	0.01	0.07
Week 6	0.63	0.03	0.46	0.68	0.01	0.04
Week 8	0.65	0.24	0.59	0.50	0.09	0.33
Week 10	0.67	0.12	0.24	0.55	0.04	0.16
Week 12	0.67	0.16	0.10	0.83	0.12	0.08
Endpoint	**0.72**	**0.03**	**0.12**	**0.88**	**0.02**	**0.03**

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

Reviewer's Note – While the differences for this variable are statistically significant at Endpoint, the baseline asthma score is essentially quite low with the mean just at "noticeable." It is not apparent to this reviewer what a clinically significant change in this am wheezing score is. The data on this variable cannot be considered very important in supporting the efficacy of either dose. The same goes for the variable "Difficulty Breathing." Data was also submitted on am cough with the subjects having a mean of 0.58-0.65 with "noticeable" being 1.0. The change in this score with active therapy was quite meager and not statistically significant.

(5) Investigator Graded Response to Therapy

At all visits from Week 1 through Week 12, the investigator assessed the subject's response to therapy by comparing the current level of symptoms with those noted at Baseline on a scale from 1 (much improved) to 5 (much worse).

Physician's Evaluation of Response to Therapy - Change from Baseline by Treatment Group During the 3-Month Phase

	MF DPI 200 mcg QD (A)		MF DPI 400 mcg QD (B)		Placebo (C)	
	N	Mean	N	Mean	N	Mean
Summary of Scores						
Week 1	65	2.52	69	2.34	81	2.74
Week 2	66	2.35	69	2.27	76	2.68
Week 4	68	2.27	72	2.05	77	2.49
Week 8	62	2.15	63	2.27	66	2.43
Week 12	61	2.26	56	2.06	57	2.35
Endpoint	**72**	**2.28**	**76**	**2.17**	**86**	**2.60**

		Analysis Results				
		p-value		Pairwise Comparisons (p-value)		
Time point	Pooled SD	Treatment	Center	A Vs B	A Vs C	B Vs C
Week 1	0.66	<0.01	<0.01	0.11	0.05	<0.01
Week 2	0.73	<0.01	0.04	0.56	<0.01	<0.01
Week 4	0.78	<0.01	0.04	0.10	0.10	<0.01
Week 8	0.80	0.15	0.06	0.41	0.05	0.27
Week 12	0.75	0.12	<0.01	0.16	0.55	0.05
Endpoint	**0.83**	**<0.01**	**<0.01**	**0.42**	**0.02**	**<0.01**

Reviewer's Note – While the sponsor submitted data indicating a significant difference between either dose and placebo at Endpoint, it is not apparent how much of a change is clinically significant. For example, the mean score for 200 mcg was 2.28 while for 400 mcg it was 2.17 and for placebo 2.60. This data does not appear to be particularly helpful.

The 9 month phase data was complicated by the fact that the subgroups previously on placebo appeared to differ at baseline so no conclusions should be drawn. Overall, however, those who received MF DPI initially had a better baseline response score before the 9 month phase than those previously on placebo.

(6) B-agonist Use during Study

Throughout the study, subjects recorded the number of puffs of Proventil used each day. There were no significant differences ($p>0.05$) in puffs of Proventil used between groups at Baseline.

Puffs of Proventil Used per Day - Change from Baseline by Treatment Group (All Treated Subjects)

	MF DPI 200 mcg QD (A)		MF DPI 400 mcg QD (B)		Placebo (C)	
	N	Mean	N	Mean	N	Mean
Baseline	72	4.02	76	4.18	86	4.09
Change from Baseline						
Week 1	72	-0.91	76	-1.27	86	-0.39

Week 2	70	-1.30	76	-1.57	81	-0.53
Week 4	70	-1.41	73	-2.05	73	-0.70
Week 6	70	-1.53	69	-2.23	70	-0.70
Week 8	69	-1.46	65	-2.36	68	-0.86
Week 10	68	-1.63	64	-1.97	64	-0.69
Week 12	66	-1.48	60	-2.37	63	-0.79
Endpoint	72	-1.58	76	-2.23	86	-0.47

		Analysis Results (Change From Baseline)				
		p-value		Pairwise Comparisons (p Value)		
Time point	Pooled SD	Treatment	Center	A vs. B	A vs. C	B vs. C
Week 1	1.79	<0.01	0.51	0.23	0.07	<0.01
Week 2	2.08	<0.01	0.84	0.43	0.03	<0.01
Week 4	2.06	<0.01	0.44	0.07	0.04	<0.01
Week 6	2.09	<0.01	0.36	0.05	0.02	<0.01
Week 8	2.20	<0.01	0.85	0.02	0.12	<0.01
Week 10	2.19	<0.01	0.50	0.39	0.02	<0.01
Week 12	2.30	<0.01	0.62	0.03	0.10	<0.01
Endpoint	**2.36**	**<0.01**	**0.30**	**0.10**	**<0.01**	**<0.01**

Thus, there is a significant decrease in the # puffs of Proventil between MF DPI and placebo.

Reviewer's Note – There is a consistent difference between 400 mcg and placebo at all time points after baseline and at most time points for 200 mcg. It appears here that there is a suggestion of a dose response for the product, although 400 mcg was not significantly different from 200 mcg at most time points.

The use of nebulizer medication was also tracked and the line listings were reviewed. There were 4 subjects in the placebo group (one subject required 8, 8, and 14 treatments on consecutive days), 2 in the 400 mcg group, and 4 in the 200 mcg group (one was treated with 20 nebulizations on Day 37). Data on Proventil use was reviewed from the 9 month phase. At Baseline of the 9-month phase, subjects previously treated with placebo in the initial 3-month phase used an average of 2.3 to 3.3 puffs of Proventil per day; groups treated with mometasone throughout both phases used an average of 1.4 to 2.7 (but generally 1.4 –1.6) puffs per day. At Endpoint, this usage decreased by 0.9 to 0.6 puffs per day in groups previously treated with placebo, and decreased by 0.7 puffs per day remained the same. No correlations were apparent with dose or timing in the 9-month phase.

(7) Nocturnal Awakenings

Subjects recorded the number of times during the night that they were awakened due to asthma symptoms severe enough to require treatment with Proventil. It should be noted that the number of nocturnal awakenings/night was generally low at Baseline (<0.50 awakenings per night) in all treatment groups.

Number of Nocturnal Awakenings - Change from Baseline by Treatment Group (All Treated Subjects)

	MF DPI 200 mcg QD (A)		MF DPI 400 mcg QD (B)		Placebo (C)	
	N	Mean	N	Mean	N	Mean
Baseline	72	0.41	76	0.45	86	0.41
Change from Baseline						
Week 1	72	-0.05	76	-0.06	86	0.06
Week 2	71	-0.09	76	-0.18	83	-0.04

Week 4	70	-0.22	73	-0.26	74	-0.10
Week 6	70	-0.18	69	-0.28	70	-0.10
Week 8	69	-0.18	65	-0.30	68	-0.06
Week 10	68	-0.25	64	-0.13	65	-0.04
Week 12	66	-0.25	60	-0.28	64	-0.10
Endpoint	**72**	**-0.16**	**76**	**-0.22**	**86**	**-0.04**

		Analysis Results (Change From Baseline)				
		p-value		Pairwise Comparisons (p Value)		
Time point	Pooled SD	Treatment	Center	A vs. B	A vs. C	B vs. C
Week 1	0.63	0.40	0.67	0.90	0.28	0.22
Week 2	0.52	0.22	0.67	0.27	0.56	0.08
Week 4	0.42	0.05	0.48	0.52	0.09	0.02
Week 6	0.45	0.07	0.56	0.21	0.29	0.02
Week 8	0.46	0.01	0.63	0.17	0.12	<0.01
Week 10	0.60	0.17	0.78	0.29	0.06	0.40
Week 12	0.46	0.06	0.84	0.72	0.06	0.03
Endpoint	**0.60**	**0.16**	**0.22**	**0.57**	**0.20**	**0.06**

Reviewer's Note – No consistent differences in nocturnal awakenings can be identified except for Weeks 4, 6, and 12 for 400 mcg vs. placebo. Again, we are dealing with very small numbers and no real conclusions should be drawn.

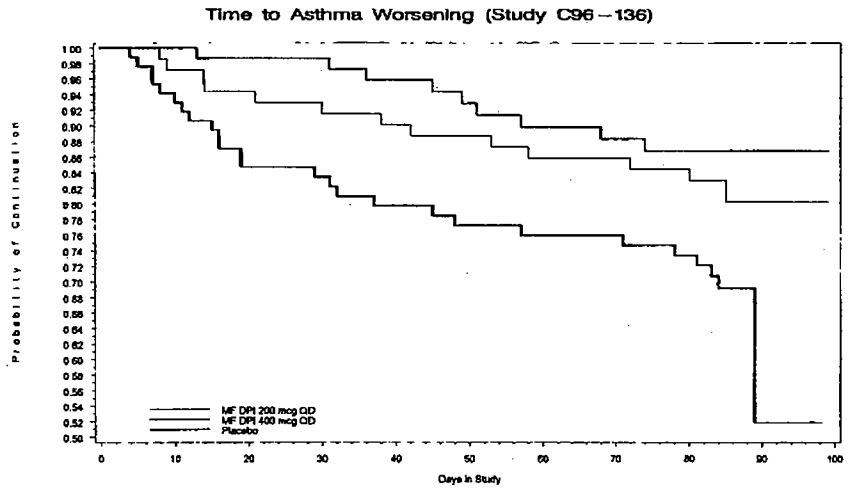
The sponsor also provided a table summarizing an exploration of treatment effect on the variables but most of this data has already been presented.

Data was also presented on methacholine challenge testing which was performed on 35 subjects at selected centers. At baseline, there was a difference in the PD20 between groups with 0.03 in the 200 mcg, 0.29 in the 400 mcg, and 0.99 in the placebo groups. Data for only the Endpoint was presented. The Endpoint must have differed for these patients as it did for others. The Endpoint PD20 for the respective groups was 0.34 for 200 mcg, 0.49 for 400 mcg, and 0.91 for placebo. No real conclusions should be drawn from this data.

(8)Time to Worsening of Asthma

Results of log-rank tests show a significant difference among the treatment groups ($p<.01$) in survival curves of time to worsening of asthma (time to first occurrence). The two active treatments were clearly better than placebo, which had a median time to worsening of approximately 54 days. Because more than 80% of subjects in each of the active treatment groups had not met the criteria for worsening by the time of their last visit in the 3-month phase, median time to worsening could not be determined.

Time to Worsening of Asthma



Forty-eight subjects met one or more criteria for worsening of asthma. Worsening asthma was more common in the placebo treatment group (26 subjects) than in the MF DPI 400 mcg QD treatment group (9 subjects) or the MF DPI 200 mcg QD treatment group (13 subjects). Of these 48 subjects, 25 were discontinued at the time of their first worsening as specified by the protocol and 23 were not.

Reviewer's Note – The sponsor later points out in the Integrated Summary of Efficacy that because the scheduled treatment duration was 3 months (84 days), small numbers of subjects remained in the study after Day 80. Therefore, larger decrements are noted at timepoints after Day 80 than before in the calculated probabilities of continuing in the trial without asthma worsening.

Subjects Who Had Worsening of Asthma

Reason for First Worsening	MF DPI 200 mcg QD (n=72)	MF DPI 400 mcg QD (n=77)	Placebo (n=87)
Decrease in FEV_1	3	1	12
Decrease in PEFR	8	3	6
Exacerbation of Asthma	0	1	7
Decrease in FEV_1 & Exacerbation of Asthma	1	0	1
Decrease in PEFR& Exacerbation of Asthma	1	0	0
Overuse of Proventil	0	1	0
Decrease in FEV_1 & Exacerbation of Asthma & Overuse of Proventil	0	1	0
Other	0	2	0
Total	**13**	**9**	**26**

Reviewer's Note – A brief section also presents data on asthma exacerbations among the groups. Seventeen subjects had a clinical asthma exacerbation during the study. They were reported more often in the placebo group (11 subjects) than in either the MF DPI 200 mcg QD (3 subjects) or MF DPI 400 mcg QD (3 subjects) groups.

(9) Quality of Life

A quality-of-life instrument (the SF-36 questionnaire and an asthma-specific module) was used to determine whether the MF DPI-treated subjects showed better improvement in quality of life compared with placebo-treated subjects at the 3-month Endpoint. While no minimally important difference between groups was specified in the protocol, it did specify that improvement was expected to be seen in the asthma-specific module domains and as well as the physical functioning, role physical and bodily pain domains of the SF-36 questionnaire.

There were 236 subjects enrolled in the study. Of the 236 subjects enrolled into the study, 221 (94%) completed the quality of life questionnaires (SF-36 questionnaire) at both baseline and post-treatment. Eighty-nine percent of the subjects (196/221) completed these forms after at least 9 weeks of treatment, with approximately 15% (94%, 131/140) more of the MF DPI-treated subjects completing the forms after 9 weeks than placebo-treated subjects (80%, 65/81).

These scales are scored from 0 to 10, with a higher score indicating greater symptoms.

Mean Baseline Scores (Asthma Specific Scale) : All Treatment Groups Combined – 3 month phase

Asthma Specific Scale	Mean	Std
Breathlessness	3.1	1.7
Mood	2.1	1.7
Social Impact	2.0	1.9
Asthma Concerns	2.2	1.8
Total (of above)	2.4	1.5
Physical Symptoms	2.9	1.7
Psychosocial Impact	1.5	1.8

N=221; N for a few of the domains vary slightly.

Total is the total score for all the individual questions associated with the four domains (breathlessness, mood, social impact, and asthma concerns).

The baseline mean scores of approximately 2 for mood, social impact, and asthma concerns indicate that the subjects described the effect of their asthma as mild during the past week. (The raw rating choices for each question within each of these domains were 0=not at all, 1=mild, 2=moderate, 3=severe and 4=very severe. The average raw score of each domain was multiplied by 2.5 to transform it to a domain scale of 0 to 10.) For physical symptoms and psychosocial impact, the mean baseline scores of approximately 2-3 indicate that limitations due to asthma only occur once or twice or a few times over the course of a week. The rating scores for these domain questions were 0=never, 1=once or twice, 2=a few times, 3=fairly often and 4=very often (transformed as above to 0-10). In summary, the quality of life scores at Baseline of the subjects studied in this trial indicate that the quality of life is mildly impacted, on average by the disease.

Summary Statistics (SF-36) and the Probability Levels Asso. with Comparing Treatment Groups

	Summary Statistics (LS mean i.e.-Model Adjusted Means)				Probabilities	
	N	Baseline	End of treatment	Change from baseline	MF DPI 200 mcg QD vs. placebo	MF DPI 400 mcg QD vs. placebo
Physical Functioning						
MF DPI 200 mcg	70	72.5	79.8	7.3	.17	.24
MF DPI 400 mcg	70	74.0	80.7	6.6		

Placebo	81	72.0	75.1	3.1		
Role Physical						
MF DPI 200 mcg	70	79.1	84.0	4.8	.21	.26
MF DPI 400 mcg	70	75.8	79.8	4.0		
Placebo	81	76.6	73.6	-3.0		
General Health						
MF DPI 200 mcg	69	68.5	69.6	.75	.40	.71
MF DPI 400 mcg	70	65.0	64.7	-.30		
Placebo	81	68.5	67.4	-1.11		

The asthma specific scale in C96-136 also showed the greatest improvement in the MF DPI treatment groups and in a dose-ordered pattern; the only difference for MF DPI with a p value ≤ 0.05, however, was for physical symptoms (and the probability levels were not adjusted for the large number of multiple comparisons made.)

Greater improvement from baseline in the SF-36 domains as well as the asthma-specific domains was observed in the two MF DPI groups, but no statistically significant differences were observed. It must be noted that the subjects generally had a mild disease burden at baseline. Caution should be used when interpreting these results, as these probability levels were not adjusted for the large number of comparisons made.

Subjects also evaluated their combined asthma symptoms. (Rating choices were 1=none, 2=trivial or doubtful, 3=mild; clearly present, but causing little or no discomfort, 4= moderately severe, causing marked discomfort, 5=severe; some interference with sleep or activities, but not incapacitating, 6=incapaciting.)

Number (%) of Subjects by Changes In Their Evaluation of Overall Asthma Symptoms

	MF DPI 200 mcg QD (n=70)	MF DPI 400 mcg QD (n=70)	Placebo (n=81)
Combined Asthma Symptoms:			
Improved	31(44%)	32 (46%)	22 (28 %)
Did not change	31 (44%)	29 (42%)	40 (51%)
Got worse	8 (11%)	8 (12%)	17 (22%)
Missing	0 (0%)	1 (1%)	2 (2%)
Total Completing Both Questionnaires	70	69	79

Note, percentages are based on the total number completing both questionnaires.

More subjects showed improvement in combined asthma symptoms in both of the MF DPI groups over placebo.

(10) Methacholine Challenge Testing

Methacholine challenge testing was performed on 35 subjects at 9 centers during the 3 and 9 month phases. At Baseline, the dose of methacholine (PD_{20}) required to provoke a 20% decrease in FEV_1 varied among the treatment groups (MF DPI 200 QD, 0.03 mcg; MF DPI 400 QD, 0.29 mcg; placebo, 0.99 mcg). At Endpoint, the dose of methacholine required to cause bronchoconstriction increased in the MF DPI 200 QD group (0.31 mcg) and the MF DPI 400 QD group (0.19 mcg) but decreased in the placebo treatment group (-0.07 mcg). At Endpoint, however, the mean PD_{20} were 0.34, 0.49 and 0.91 for 200 QD, 400 QD and placebo, respectively, so placebo still had a higher PD_{20}. While there was some improvement in the PD_{20}, this data is of minor importance for this trial. The sponsor says that insufficient data on

methacholine testing was collected during the 9 month phase to allow "relevant summarization."

(11) Peak Inspiratory Flow Rates

At Center #22, inspiratory flow rates through a functional model of the dry powder inhaler were recorded for six subjects during the 3-month phase. These subjects all had flow rates higher than 30 l/min and rise times of less than 300 msec and thus were believed to have achieved flow rates that were adequate for functional drug delivery using the DPI.

Subject	Treatment Group	Time of Measurement	Peak Flow Rate (l/min)	Rise Time (msec)	Baseline FEV_1 (l)	Endpoint FEV_1 (l)
277	Placebo	Visit 5	68.63	50	2.91	--
		Endpoint Visit	65.62	33	--	2.55
278	MF DPI	Visit 5	68.1	48	2.63	--
	200 mcg QD	Endpoint Visit	76.1	50	--	3.04
279	MF DPI	Visit 5	53.07	40	1.99	--
	200 mcg QD	Endpoint Visit	67.65	40	--	2.14
280	Placebo	Baseline	74.25	18	3.18	3.36
281	MF DPI	Visit 4	76.08	18	3.12	--
	400 mcg QD	Endpoint Visit	72.35	40	--	2.64
282	MF DPI	Visit 4	63.33	45	2.51	--
	200 mcg QD	Endpoint Visit	71.25	70	--	2.54

(12) Efficacy Conclusions

The primary efficacy endpoint for regulatory purposes for this study is the FEV_1. Subjects on either mometasone treatment had significant improvement in their FEV_1 compared with placebo except for Week 8 and 400 mcg. There were no notable differences between the doses. At baseline, 88% of the subjects were in the age group 18-64 years so there were too few subjects to draw any conclusions in other age groups. There did not appear to be an overt difference in the % mean increase in FEV_1 between the sexes. There were not enough Non-Caucasians to draw any conclusions. There appears to be a marked difference in the improvement of subjects with an FEV_1 <75% Predicted versus those with an FEV_1 ≥75% Predicted in the steroid treatment groups. Both treatments appeared to beat placebo except again at Week 8 for 400 mcg.

Data on the FEV_1 was also available for the 9 month phase which was submitted with the 4 month safety update. Increases in FEV_1 gotten during the first 3 months of MF DPI therapy appeared to be sustained for the subsequent 9 months. Interestingly, there did not appear to be further improvements over these 9 months. In those subjects were switched over from placebo, increases were noted in the FEV1 once the subjects were on glucocorticoids. The numbers in each group were small so it is difficult to make any conclusions. There seemed to be a trend, however, for the evening dosing to cause more of a % increase in FEV_1 than the am dosing suggesting that qd dosing may not be optimal but this study is not conclusive on this point.

For FVC, both treatments were better than placebo except for 400 mcg on Week 8. For FEF_{25-75}, 400 mcg produced a significantly smaller effect than 200 mcg and was not significantly better than placebo. FEF_{25-75} is not particularly important for regulatory purposes. With the variable PEFR, 400 mcg is significantly better than both 200 mcg and placebo. 200 mcg only tends to be better numerically than placebo. It appears with PEFR that there is some dose ranging. The data for the efficacy seen with p.m. PEFR was not as impressive as the a.m. PEFR.

The data presented on "Asthma Symptoms" and "Investigator Graded Response to Therapy" involved essentially low baseline scores and overall did not appear to be useful for regulatory purposes. Considering supplemental use of B-agonist therapy, there is a consistent difference between 400 mcg and placebo at all time points after baseline and at most time points for 200 mcg. It appears here that there is a suggestion of a dose response for the product, although 400 mcg was not significantly different from 200 mcg at most time points. No real conclusions should be drawn from the data on nocturnal awakenings and methacholine challenge.

Worsening asthma was more common in the placebo treatment group (26 subjects) than in the MF DPI 400 mcg QD treatment group (9 subjects) or the MF DPI 200 mcg QD treatment group (13 subjects). There did appear to be a dose response with this variable. In the Quality of Life data, greater improvement from baseline in the SF-36 domains as well as the asthma-specific domains was observed in the two MF DPI groups, but no statistically significant differences were observed.

7. Safety

a) Adverse Events – 3 month phase

Treatment-emergent adverse events were reported by 82 to 83% of subjects across treatment groups. The most common adverse events (those reported by ≥10% of subjects in any treatment group) included headache, pharyngitis, viral infection, allergy aggravated, sinusitis, nasal congestion, musculo-skeletal pain, and dysmenorrhea.

Incidence of Adverse Events Reported by ≥10% in Any Treatment Group (All Treated Subjects)

	Number (%) of Subjects		
	MF DPI 200 mcg QD (n=72)	MF DPI 400 mcg QD (n=77)	Placebo (n=87)
Headache	21 (29)	18 (23)	21 (24)
Infection, viral	17 (24)	13 (17)	16 (18)
Allergy aggravated	13 (18)	16 (21)	21 (24)
Pharyngitis	6 (8)	14 (18)	11 (13)
Musculo-skeletal pain	6 (8)	11 (14)	7 (8)
Sinusitis	4 (6)	10 (13)	9 (10)
Nasal congestion	8 (11)	6 (8)	14 (16)
Dysmenorrhea (%females)	1 (3)	5 (12)	2 (4)

Pharyngitis was more common in the 400 mcg treatment group (18%) than in either the 200 mcg (8%) or placebo (13%) treatment groups. Musculo-skeletal pain and dysmenorrhea

also were both more common in the 400 mcg group than in other treatment groups. It is interesting to note that nasal congestion was also more prominent in the placebo group.

The following list has been edited to include those adverse events that appear over-represented in one treatment group or which are otherwise notable in other clinical trials.

Incidence of Any Other Adverse Events Reported by ≥1% of Subjects – 3 month phase

	MF 200 mcg QD (n=72)	MF 400 mcg QD (n=77)	Placebo (n=87)
Any Adverse Event	**60 (83%)**	**63 (82%)**	**71 (82%)**
back pain	4 (6)	4 (5)	3 (3)
fatigue	1 (1)	4 (5)	0 (0)
influenza – like symptoms	5 (7)	4 (5)	3 (3)
dysphonia	1 (1)	2 (3)	2 (2)
tremor	0 (0)	3 (4)	0 (0)
abdominal pain	2 (3)	2 (3)	3 (3)
dyspepsia	2 (3)	3 (4)	4 (5)
ear disorder NOS	0 (0)	2 (3)	0 (0)
earache	0 (0)	4 (5)	0 (0)
hepatic function abnormal	0 (0)	0 (0)	2 (2)
hepatitis	0 (0)	1 (1)	0 (0)
weight increase	0 (0)	2 (3)	0 (0)
myalgia	5 (7)	3 (4)	4 (5)
menstrual disorder	0 (0)	1 (2)	0 (0)
candidiasis, oral	2 (3)	3 (4)	3 (3)
asthma aggravated	2(3)	2 (3)	6 (7)
bronchitis	1 (1)	1 (1)	4 (5)
coughing	3 (4)	2 (3)	7 (8)
rhinorrhea	1 (1)	5 (6)	3 (3)
sinus congestion	3 (4)	1 (1)	0 (0)
sneezing	4 (6)	1 (1)	0 (0)
rash	1 (1)	1 (1)	0 (0)
arthritis	4(6)	0(0)	2(2)
conjunctivitis	1 (1)	4 (5)	2 (2)
lymphadenopathy	2 (3)	0 (0)	0 (0)

It appears that fatigue, tremor, ear disorder NOS, earache, rhinorrhea, sneezing, weight increase, and conjunctivitis were reported out of proportion for 400 mcg relative to 200 mcg and placebo. Back pain and influenza-like symptoms were slightly more common with MF DPI. The reports of arthritis and lymphadenopathy were reported out of proportion for 200 mcg but the significance of this is doubtful. Aggravation of asthma, bronchitis, migraine, and coughing were common in the placebo group. Myalgia, dyspepsia, dysphonia and abdominal pain did not appear to be any more common with MF DPI than with placebo. There was only one case of "menstrual disorder" and it was in the 400 QD group. (This term was not defined more specifically and a clarification will be requested of the sponsor.) There were a total of two cases of rash in the MF DPI groups. The case of hepatitis in the 400 mcg group will again be presented in the section on severe adverse events and discontinuation because of AEs.

While the incidence of oral candidiasis was low and essentially no different than placebo in this trial, it must be noted that subjects were advised to rinse their mouth with water or a suitable mouthwash after study drug administration. Therefore, the apparent low incidence of oral candidiasis with MF DPI may be more reflective of the post-dose rinsing rather than an intrinsic quality of the drug. The fact that rinsing was specified in the protocol may be an important issue to be highlighted in the package labeling.

Section 14.3.1.5-7 was reviewed to discern if there appeared to be an overexpression of particular adverse events based on sex, age or race. There appeared to be too few Non-Caucasians or subjects not in the 18-64 age range to discern any trends if such were present. Females appeared to be over-represented with influenza-like symptoms with 4, 3 and 0 for 200, 400 and placebo respectively while there was only one incident in the 200 and 400 mcg group each for males. There were 3 incidences of earache in the 400 mcg female group compared with 1 for males. These and other AE's in which there appeared to be somewhat of an imbalance between the sexes are in the following table:

AE	Gender	200 mcg	400 mcg	Placebo
Influenza-like symptoms	Female	4	3	0
	Male	1	1	0
Earache	Female	0	3	0
	Male	0	1	0
Musculo-Skeletal Pain	Female	3	9	5
	Male	3	2	2
Pharyngitis	Female	2	11	6
	Male	4	3	5
Conjunctivitis	Female	1	0	1
	Male	0	4	1

It is hard to discern which AE's are related to medication but perhaps influenza-like symptoms and pharyngitis could be more common in females on mometasone and conjunctivitis more common in males. Such a pattern should be looked for in other studies in this NDA.

The sponsor also submitted data on what were thought to be in investigator attributed/treatment-related adverse events. The most common treatment related events were headache, pharyngitis and oral candidiasis. Only oral candidiasis with 2 reports with 200 mcg, 3 in 400 mcg and 1 in placebo appeared to have any suggestion of a dose response.

b) Severe Adverse Events – 3 month phase

Severe/life-threatening (Grade 3 and Grade 4) adverse events were reported by 27 subjects. The percentages of subjects with one or more severe/life-threatening adverse event were similar in the MF DPI treatment groups (11%-12%) and the placebo treatment group (11%). Three subjects had events that were categorized as Grade 4 (life-threatening) which included one subject in the MF DPI 400 mcg QD treatment group with hepatitis C, one subject in the placebo treatment group with an asthma exacerbation (classified as life-threatening) and one subject in the placebo treatment group with abnormal hepatic function. None of these

Grade 4 events was considered related to treatment. The most common severe adverse event was headache, reported by one subject in the 200 mcg group and two subjects in the 400 mcg group.

Severe/Life-threatening Adverse Events

	MF 200 mcg QD (n=72)	MF 400 mcg QD (n=77)	Placebo (n=87)
Any Severe/life-threatening Adverse Event	**8 (11)**	**9 (12)**	**10 (11)**
allergic reaction	0 (0)	1 (1)	1 (1)
headache	1 (1)	2 (3)	0 (0)
convulsions	0 (0)	1 (1)	0 (0)
dysphonia	1 (1)	0 (0)	0 (0)
abdominal pain	1 (1)	0 (0)	0 (0)
intestinal disorder	0 (0)	1 (1)	0 (0)
nausea	1 (1)	0 (0)	0 (0)
toothache	0 (0)	1 (1)	0 (0)
hepatic function abnormal	0 (0)	0 (0)	1 (1)
hepatitis	0 (0)	1 (1)	0 (0)
weight increase	0 (0)	1 (1)	0 (0)
arthritis	0 (0)	0 (0)	1 (1)
myalgia	0 (0)	0 (0)	1 (1)
osteoporosis	0 (0)	0 (0)	1 (1)
cold sores non-herpetic	0 (0)	0 (0)	1 (1)
asthma aggravated	1 (1)	0 (0)	2 (2)
bronchitis	1 (1)	0 (0)	0 (0)
coughing	1 (1)	0 (0)	1 (1)
nasal congestion	1 (1)	0 (0)	0 (0)
sinusitis	0 (0)	1 (1)	0 (0)
sneezing	1 (1)	0 (0)	0 (0)
upper respiratory. tract infection	0 (0)	0 (0)	1 (1)
dental procedure	1 (1)	0 (0)	0 (0)
migraine	0 (0)	0 (0)	1 (1)
lymphadenopathy	1 (1)	0 (0)	0 (0)

None of these severe AE's appears to have a particular over-representation among the treatment groups with the possible exception of asthma exacerbation in the placebo group. It is also interesting that a severe AE noted as weight increase was seen in the 400 mcg group. This subject (#79), a 49-year-old female, was discontinued from the study at Day 72 due to weight increase which was considered to be possibly related to study medication. Her weight at screening was 204 pounds and at the final visit it was 212 pounds. No other comments regarding this weight increase were provided by the investigator. It is important to note that weight was poorly tabulated in the 3 month phase of the study overall.

The line listings for the severe AE's subjects were reviewed from Section 16.2.7.2. The following cases are noted. Subject 183 is a 49 year old female on 200 mcg who experienced a severe paroxysm of cough and dysphonia on Day 84. Both were considered treatment related and the subject discontinued the study. Subject 151 was a 23 year old female on 400 mcg who had a petit mal seizure on Day 29 after which the study medication was discontinued. She was treated in the Emergency Room and released the same day. The investigator noted that the subject had not informed him that she had a history of seizures 5 years ago. The event was considered unrelated to the study. Subject 52 was a 39 year old female on 400 mcg who was noted to have an elevated SGPT at baseline and reported also on Days 8, 15, 29, and 37 after

which the study medication was discontinued. At Screening, the subject had a high value for both SGPT (100 U/L) and SGOT (84 U/L). The investigator did not, however, consider these values to be clinically significant, and the subject was randomized to treatment. Liver enzymes were re-evaluated during the study and again found to be above normal values. The subject was then discontinued at the request of the sponsor. It was noted that the subject had been using acetaminophen and ibuprofen for headaches. The subject agreed to washout these medications prior to final-visit laboratory tests. The SGPT had decreased to 36 U/L after the washout for headache medications. The event was considered unrelated. Subject 157 is a 37 year old female on placebo who had an asthma exacerbation considered severe on Day 78 - although it was considered unrelated, the study medication was discontinued.

Subject 266 in the 400 mcg group had elevated SGOT (AST) and SGPT (ALT) values at Screening. These values were SGOT 61 U/L and SGPT 105 U/L. Values were also high at re-test one week later (85 and 51 U/L, respectively). The subject was randomized before the results of the re-test were known. At a subsequent evaluation approximately 2 weeks later, liver enzymes were still elevated, and a hepatitis profile drawn on this date was positive for hepatitis C. The subject was discontinued.

No deaths were reported during the 3-month phase, or within 30 days of the last dose of study medication of this phase of the study.

c) Discontinuance Because of Adverse Events – 3 month phase

A total of 24 subjects discontinued from the study because of adverse events. These included six subjects (8%) in the 200 mcg group, nine subjects (12%) in the 400 mcg group and nine subjects (10%) in the placebo group. The most frequent adverse events leading to discontinuation were events in the respiratory system such as aggravated asthma and bronchitis.

List of Subjects Who Discontinued Treatment Because of Adverse Events – 3 month phase

Center/Subject	Sex/ Age/ Race	Day of Onset	Adverse Event(s)	Severity	Relation-ship
			MF DPI 200 mcg QD		
C96-136-07/270	F/31/C	69	Musculo-skeletal pain	Moderate	Possible
C96-136-09/212	M/31/C	42	Upper Resp Tract Infection	Moderate	Unrelated
C96-136-14/032	M/14/C	1	Headache	Moderate	Probable
		1	Nausea	Severe	Probable
C96-136-15/086	M/33/C	84	Asthma aggravated	Moderate	Unrelated
C96-136-17/183	F/49/C	68	Coughing	Severe	Related
		68	Dysphonia	Severe	Related
C96-136-21/089	M/19/C	72	Asthma aggravated	Severe	Unrelated
			MF DPI 400 mcg QD		
C96-136-02/151	F/23/C	18	Convulsions	Severe	Unrelated
C96-136-07/266	M/36/NC	9	Hepatitis	Life threat (Serious)	Unrelated
C96-136-07/271	M/14/C	37	Tremor	Moderate	Probable
C96-136-10/045	M/12/C	61	Sinusitis	Moderate	Unrelated
		61	Bronchitis	Moderate	Unrelated

List of Subjects Who Discontinued Treatment Because of Adverse Events – 3 month phase

Center/Subject	Sex/ Age/ Race	Day of Onset	Adverse Event(s)	Severity	Relation-ship
		61	Asthma aggravated	Moderate	Unrelated
C96-136-11/305	F/24/C	7	Respiratory disorder	Mild	Unrelated
C96-136-15/079	F/44/C	22	Weight increase	Severe	Possible
C96-136-17/191	M/21/C	25	Dysphonia	Moderate	Possible
C96-136-18/052	F/39/C	-7	SGPT increased	Severe (Serious)	Unrelated
C96-136-21/253	M/18/C	39	Sinusitis	Severe	Unrelated
			Placebo		
C96-136-03/229	F/26/C	47	Bronchitis	Moderate	Possible
C96-136-05/176	M/27/C	9	Vomiting	Mild	Possible
C96-136-06/161	M/36/C	11	Coughing	Moderate	Unrelated
C96-136-14/036	F/27/C	15	Asthma aggravated	Life threat (Serious)	Unrelated
C96-136-19/116	F/39/C	16	Pharyngitis	Mild	Possible
C96-136-19/245	M/28/NC	85	Hepatic function abnormal	Life threat (Serious)	Unrelated
C96-136-21/088	F/30/C	31	Bronchitis	Moderate	Unrelated
C96-136-21/090	F/18/C	10	Upper resp tract infection	Severe	Unrelated
C96-136-07/195	F/29/C	4	Asthma aggravated	Severe	Unrelated

The line listings for these 24 subjects were reviewed in Section 14.3.2.3. Some cases had previously been mentioned in the section on Severe AE's, however, some other cases were notable. Subject 271 was a 14 year old male on 400 mcg who discontinued after 42 days on study medication because of a "shakes" which developed after taking the study medication. Subject 191 was a 21 year old male on 200 mcg which stopped medication after 44 days because of dysphonia/hoarse voice.

Subject 245 on placebo had a life threatening increase of LFTs and discontinued the medication on Day 85. The increased hepatic enzymes were noted on a regularly scheduled laboratory test on Day 85: SGPT of 240 U/L. Other hematology and biochemistry values were unremarkable. The subject had values within normal range at Screening: SGOT 44 U/L and SGPT 32 U/L. The subject had been drinking heavily (up to 20 ounces of alcohol per day). The subject was discontinued from the study. A hepatitis screen was negative. The investigator considered the event unlikely to be related to study medication, and instead related to alcohol consumption. Subjects 86 and 89 on 200 mcg discontinued on Days 80 and 72, respectively, because of asthma exacerbation.

d) Adverse Event Data - 9-month phase

The most obvious difference between the 3-month phase and 9-month phase was in "allergy aggravated," which doubled in incidence in all treatment groups in the longer phase. The sponsor attributed this to the fact that subjects had the opportunity to experience additional allergy seasons during long-term treatment.

Incidence of AE's Reported by ≥10% of Subjects During the 9-Month Phase

	MF DPI 200 mcg QD (AM) (n = 41)	MF DPI 200 mcg QD (PM) (n = 40)	MF DPI 400 mcg QD (AM) (n = 44)	MF DPI 400 mcg QD (PM) (n = 41)
allergy aggravated	20 (49)	20 (50)	16 (36)	16 (39)
headache	14 (34)	13 (33)	12 (27)	20 (49)
infection, viral	10 (24)	8 (20)	9 (20)	12 (29)
sinusitis	10 (24)	9 (23)	4 (9)	8 (20)
upper resp tract infection	7 (17)	8 (20)	5 (11)	5 (12)
pharyngitis	8 (20)	2 (5)	5 (11)	8 (20)
nasal congestion	8 (20)	3 (8)	7 (16)	3 (7)
musculoskeletal pain	4 (10)	6 (15)	5 (11)	5 (12)
dyspepsia	1 (2)	3 (8)	6 (14)	5 (12)
influenza-like symptoms	5 (12)	0	3 (7)	5 (12)
back pain	3 (7)	3 (8)	2 (5)	5 (12)
myalgia	5 (12)	1 (3)	3 (7)	3 (7)
bronchitis	1 (2)	2 (5)	2 (5)	5 (12)
coughing	2 (5)	2 (5)	1 (2)	4 (10)
candidiasis, oral	0	4 (10)	1 (2)	2 (5)
dysmenorrhea	2 (8)	3 (16)	1 (5)	3 (13)

Note that this data is not placebo-controlled. It is also difficult to discern the meaning of difference in the incidence of a given adverse event between similar doses given at different times of the day. There appears to be a distinct difference in the incidence of dyspepsia between the 400 mcg dosing and the 200 mcg dosing. There appears to be a higher incidence of nasal congestion with either dose when it is given in the morning compared with the evening. The clinical significance of this is not clear. Aside from these two AE's, there is not a clear discrepancy among the groups. Furthermore, with the lack of a placebo group it is difficult to discern what is attributable to medication and what is not. The rather high incidence of allergy aggravated is most likely due to the high rate of atopy among asthmatics and probably has nothing to do with the medication.

The following list has been edited to include those adverse events which are more common in particular treatment groups or which are otherwise notable in other trials. Abnormal LFT results were edited from this list because they will be discussed in more detail in other sections.

Incidence of Any Adverse Events During 9-Month Phase

	MF DPI 200 mcg QAM (n = 41)	MF DPI 200 mcg QPM (n = 40)	MF DPI 400 mcg QAM (n = 44)	MF DPI 400 mcg QPM (n = 41)
Any Adverse Event	**37 (90)**	**34 (85)**	**38 (86)**	**37 (90)**
back pain	3 (7)	3 (8)	2 (5)	5 (12)
fatigue	2 (5)	1 (3)	3 (7)	2 (5)
dysphonia	1 (2)	0	3 (7)	1 (2)
abdominal pain	1 (2)	1 (3)	2 (5)	1 (2)
dyspepsia	1 (2)	3 (8)	6 (14)	5 (12)
nausea	3 (7)	0	4 (9)	0
ear abnormality	1 (2)	0	0	1 (2)
ear disorder NOS	0	0	3 (7)	0
earache	0	1 (3)	2 (5)	2 (5)
arthritis	1 (2)	0	0	1 (2)
musculoskeletal pain	4 (10)	6 (15)	5 (11)	5 (12)
myalgia	5 (12)	1 (3)	3 (7)	3 (7)
dysmenorrhea	2 (8)	3 (16)	1 (5)	3 (13)
menstrual disorder	1 (4)	0	0	1 (4)
candidiasis, oral	0	5 (12.5)	1 (2)	2 (5)
infection viral	10 (24)	8 (20)	9 (20)	12 (29)
bronchitis	1 (2)	2 (5)	2 (5)	5 (12)
coughing	2 (5)	2 (5)	1 (2)	4 (10)
nasal congestion	8 (20)	3 (8)	7 (16)	3 (7)
pharyngitis	8 (20)	2 (5)	5 (11)	8 (20)
rhinorrhea	2 (5)	1 (3)	3 (7)	3 (7)
sinus congestion	2 (5)	3 (8)	0	0
sinusitis	10 (24)	9 (23)	4 (9)	8 (20)
sneezing	2 (5)	0	0	0
upper respiratory tract infection	7 (17)	8 (20)	5 (11)	5 (12)
taste loss	1 (2)	0	0	0
migraine	0	2 (5)	3 (7)	0
conjunctivitis	2 (5)	0	4 (9)	0
lymphadenopathy	0	2 (5)	1 (2)	0

Dysphonia and dyspepsia (although also common in the general public, there may be a dose response here) appear to be more common with the 4oo mcg doses. Interestingly, it seems that candidiasis was more common during the p.m. dosing. The incidence of pharyngitis was similar to that seen during the 3 month phase (when placebo actually had the highest incidence.) Notably, tremor is not seen on this 9-month list which had been seen in 2 subjects in the 400 mcg group during the 3-month phase.

Four subjects had adverse events that were coded as abnormal hepatic function, increase in values on laboratory tests of liver function, or hepatitis. Subject 084, who received placebo previously, was found to have hepatitis A after approximately 3 months of follow-up treatment with 400 mcg QD PM; this was considered serious but unrelated to treatment.

The investigator at Site19 noted that Subject 245, who admitted to "drinking heavily", had "elevated LFTs" at the end of the 3-month phase (placebo treatment) that carried over to the 9-month phase and resulted in discontinuation after approximately 10 days of treatment with 200 mcg qd p.m. SGPT was 240 U/L at the end of the 3-month phase, increased from 32 U/L at Baseline. This event was considered to be serious but unrelated to treatment.

Subject 170 had "abnormal hepatic function" listed as an adverse event because of increases in values of SGOT and SGPT, which were considered possibly related to treatment by the investigator. Values for this subject were slightly above the normal range at Screening for the study (SGOT 37 U/L; SGPT 35 U/L), and were moderately elevated at Week 12 (SGOT 71 U/L; SGPT 53 U/L), after 3 months of treatment with placebo. These elevations continued throughout the 9-month phase, during treatment with 400 mcg QD p.m., and for the 2 months that the subject was followed after completing the study (SGOT 49-70 U/L, SGPT 43-56 U/L). Values for alkaline phosphatase and total bilirubin were unaffected. The investigator noted that the subject had reported drinking alcohol more than usual.

Subject 047, who had received 200 mcg during the 3-month phase, had increases in values of alkaline phosphatase, SGOT, and SGPT at the end of the 9-month phase (200 mcg QD a.m.) recorded as adverse events possibly related to treatment. Values for SGOT were 24 to 27 U/L, for SGPT were 46 to 51 U/L, and for alkaline phosphatase were 67 U/L in previous weeks; the values increased to 129, 156, and 132 U/L, respectively at the final study visit. The subject denied drinking heavily prior to the visit. Two weeks after completing the study, the subject's values had returned to or near values recorded in the previous weeks: 32, 68, and 77 U/L, respectively. Values for total bilirubin were unaffected, and a screen for hepatitis yielded negative results. In this subject, it seems that the transaminases returned to the patient's "baseline" elevation after the medication was stopped. It does not appear that an explanation for the liver enzyme abnormality was identified.

e) Severe Adverse Events – 9 month phase

Appears This Way
On Original

Severe/Life-threatening Adverse Events During the 9-Month Phase (Treatment-related?)*

Adverse Event	MF DPI (AM) 200 mcg QD n = 41	MF DPI (PM) 200 mcg QD n = 40	MF DPI (AM) 400 mcg QD n = 44	MF DPI (PM) 400 mcg QD n = 41
Any Severe/life-threatening Event	**3 (7)**	**6 (15)**	**7 (16)**	**9 (21)**
allergy aggravated	0	1 (3)	2 (5)	1 (2)
back pain	0	1 (3)	0	0
headache	2 (5)	0	1 (2)	2 (5)
influenza-like symptoms	0	0	1 (2)	1 (2)
LFTs increased (Life threatening)	0	1 (3)	0	0
vertigo	0	0	0	1 (2)
diarrhea	0	1 (3)	0	0
dyspepsia	0	0	0	1 (2)
irritable bowel syndrome	0	0	1 (2)	0
tooth disorder	1 (2)	0	0	0
hepatitis	0	0	0	1 (2)
angina pectoris	0	1 (3)	0	0
aortic stenosis	0	0	0	1 (2)
platelet count decreased	0	0	0	1 (2)
cellulitis	0	0	0	1 (2)
infection viral	0	0	1 (2)	0
coughing	0	1 (3)	0	0
nasal congestion	1 (2)	0	0	0
pharyngitis	1 (2)	0	0	0
acne	0	1 (3)	0	0
laceration, skin	1 (2)	0	0	0
dental procedure	0	0	0	1 (2)
urinary tract infection	0	0	0	1 (2)
migraine	0	0	1 (2)	0

* Reviewer's Note: The sponsor has labeled this list as related or possibly related to treatment. In the next paragraph in the report, the sponsor then goes on to say that only one subject had an adverse event that was considered treatment related and severe during the 9 month phase. It is believed that the labeling of the above list in a footnote as treatment-related was in error and the sponsor will be asked for clarification.

In general, these severe adverse events are not easily attributable to medication. The one mentioned as life threatening is the individual (#245) who had liver enzyme elevation previously described which actually occurred near the end of the 3 month phase.

f) Combined 3 and 9 month phase data

The sponsor submitted a combination of the data for any individual who received either 200 mcg or 400 mcg during either phase. This medical officer reviewed this table. Allergy aggravated, headache, viral infection, upper respiratory tract infection, and sinusitis were reported most often for both treatments. The incidence of AE's seems to be fairly comparable between the doses with some possible exceptions. Dysphonia was reported by 5 subjects in the 400 mcg group compared with 2 in the 200 mcg. Dyspepsia seemed to be more common with 400 mcg – 6 versus 12. Earache also seemed to be more common with 400 mcg – 6 versus 1. Musculoskeletal was more common with 400 mcg – 20 versus 13. Pharyngitis was more common with 400 mcg – 24 versus 14. Rhinorrhea was more common with 400 - 9

versus 4. Conjunctivitis was more common with 400 mcg – 7 versus 3. Only perhaps lymphadenopathy seemed to be more common with 200 mcg - 4 versus 1.

The data was also presented by the sponsor in groupings of adverse events by length of time of treatment. It appeared that allergy aggravated, headache, influenza-like symptoms, nausea, earache, musculoskeletal pain, myalgia, dysmenorrhea, viral infection, nasal congestion, pharyngitis, rhinorrhea, sinusitis and URI were more common in the subjects treated for longer periods. The sponsor attributes this to the increased duration of observation.

g) Discontinuation Because of Adverse Events – 9 month phase

Seven of the 166 subjects who participated in the 9-month phase had treatment discontinued early because of adverse events.

List of Subjects Who Discontinued Treatment During the 9-Month Phase Because of Adverse Events

Center/Subject	Sex/Age/ Race	Day of Onset	Adverse Event(s)	Severity	Relation-ship
MF DPI 200 mcg QD AM (previously placebo)					
C96-136-12 / 128	F/56/C	104	Asthma aggravated	Moderate	Unrelated
MF DPI 200 mcg QD PM (previously placebo)					
C96-136-19 / 245[a]	M/28/NC	1	Increased liver function test results	Life threat. (Serious)	Unrelated
MF DPI 400 mcg QD AM (previously 400 mcg QD)					
C96-136-19 / 112	F/48/C	85	Musculoskeletal pain (coccyx pain)	Moderate	Unrelated
MF DPI 400 mcg QD AM (previously placebo)					
C96-136-17 / 182	M/35/C	280	Irritable bowel syndrome	Severe	Unrelated
MF DPI 400 mcg QD PM (previously 400 mcg QD)					
C96-136-05 / 173	M/29/C	84	Mitral stenosis[b]	Severe	Unrelated
MF DPI 400 mcg QD PM (previously placebo)					
C96-136-11 / 058	F/47/C	197	Musculoskeletal pain (pain and inflammation in right shoulder	Moderate	Unrelated
C96-136-15 / 084	F/43/NC	84	Hepatitis A	Severe	Unrelated

a: This subject was also mistakenly recorded as discontinuing at the end of the 3-month phase.

b: The investigator discontinued the subject's treatment because of limited improvement in FEV_1; the investigator wished to optimize the subject's asthma therapy prior to mitral valve surgery, planned within the next 2 to 3 years.

h) Serious Adverse events – 3 and 9 month phase

Serious adverse events were reported for ten subjects, one of who had a serious adverse event in both the 3-month phase and 9-month phase (Subject 129); thus, there were five reports in the 3-month phase and six in the 9-month phase.

Serious Adverse Events During the 3-Month Phase

Center/Subject	Sex/Age/Race	Adverse Event(s)	Relationship	Status
		MF DPI 200 mcg QD		
No subject				
		MF DPI 400 mcg QD		
07/266	M/36/NC	Hepatitis C	Unrelated	Additional Therapy, Discontinued
12/129	F/34/C	Intestinal Disorder	Unrelated	Hospitalized
18/052	F/39/C	Elevated SGPT	Unrelated	Additional Therapy
		Placebo		
14/036	F/27/C	Asthma aggravated Acute respiratory distress	Unrelated	Hospitalized, Additional Therapy, Discontinued
19/245	M/28/NC	Elevated LFT	Unrelated	Discontinued

Subjects 136, 052 and 245 are discussed in the section on 3 month severe adverse data. Subject 136 in the 400 mcg group first reported an intestinal disorder (intermittent lower right quadrant pain) approximately 1 month after randomization. The subject subsequently was hospitalized for a laparoscopic appendectomy and drainage of an ovarian cyst. Subject 036 in the placebo group reported acute respiratory distress and asthma aggravated. Two weeks after randomization, the subject was exposed to paint fumes at work. Previous exposures to paint products had resulted in an increase in asthma symptoms, but not nearly as severe as this episode. The evening after exposure, the subject reported increased chest tightness and shortness of breath and was taken to the emergency room by ambulance in respiratory distress. Arterial blood gases and evaluations of peak flow rates confirmed respiratory compromise. She was treated aggressively (IV aminophylline, IV solumedrol, oxygen and nebulized Proventil; intubation was discussed). The event abated 4 days later. The subject was discontinued from the study. The cause of the event was suspected to be exposure to paint fumes and was considered the event unlikely to be related to study medication.

List of Subjects Who Had Serious Adverse Events During the 9-Month Phase

Center/Subject	Sex/Age/ Race	Adverse Event(s)	Relationship	Status
MF DPI 200 mcg QD AM and 200 mcg QD PM				
No subject				
MF DPI 400 mcg QD AM (previously 400 mcg QD)				
C96-136-21/092[a]	M/40/NC	Back pain	Unrelated	Hospitalized, Additional Therapy
MF DPI 400 mcg QD AM (previously placebo)				
C96-136-17/182	M/35/C	Irritable bowel syndrome	Unrelated	Hospitalized, Additional Therapy, Discontinued
MF DPI 400 mcg QD PM (previously 400 mcg QD)				
C96-136-09/213	F/38/C	ITP	Unrelated	Additional Therapy
C96-136-12/129[b]	F/34/C	Pelvic pain	Unrelated	Hospitalized, Additional Therapy
C96-136-17/181	F/52/C	Cellulitis	Unrelated	Hospitalized, Additional Therapy
MF DPI 400 mcg QD PM (previously placebo)				
C96-136-15/084	F/43/NC	Hepatitis (hepatitis A)	Unrelated	Additional Therapy, Discontinuation

a: This adverse event was inadvertently not included in the study data base.

b: Subject also had a serious adverse event in the previous 3-month phase (appendectomy, ovarian cyst).

Subject 182 at Site C96-136-17 was hospitalized and discontinued treatment at the end of the 9-month phase following 2 weeks of weight loss and diarrhea presumed to be secondary to inflammation of the pancreas. CT of the abdomen and pelvic region revealed no remarkable finding. The subject improved after concomitant therapy for the abdominal discomfort and was discharged from the hospital after 10 days with a diagnosis of irritable bowel syndrome. Subject 092 was involved in an automobile accident, which aggravated an old back injury, resulting in hospitalization for back pain and thereafter stopped taking drug and was lost to follow-up. Subject 213 had a platelet count of 30,000/μl at her last study visit at the end of the 9-month phase. Previous counts had been normal and she had no evidence of bleeding. A hematologist rendered a final diagnosis of idiopathic thrombocytopenic purpura. Subject 129, who had a history of ovarian cysts and uterine fibroid tumors, was hospitalized after approximately 2 weeks in the 9-month phase for total abdominal hysterectomy with bilateral salpingo-oophorectomy following a week of pain and fever and she was later discontinued from the study because of non-compliance.

After approximately 2.5 months of treatment in the 9-month phase, Subject 084 began to experience abdominal cramping and diarrhea following meals. This progressed to nausea, vomiting, and influenza-like symptoms, along with increased values for tests of liver function. Positive results on a panel for hepatitis A provided final evidence for the diagnosis, and the subject was withdrawn from the study. Her condition improved after 2 weeks. Subject 181 was hospitalized for 3 days for treatment of cellulitis on her right heel, which had worsened during prior self-treatment with a topical antifungal agent. The cellulitis resolved following administration of intravenous antibiotics, and the subject completed the 9-month phase.

i) Laboratory Values – 3 month phase

Typically, labs were done for this phase at Screening and at Week 12. Clinically significant abnormalities were defined for all blood chemistry parameters as ≥ 2.6 times the upper limit of normal. Other abnormal values were: hemoglobin concentration ≤ 9.4g/dl, platelet count ≤ 74,000/μl, or white blood cell count ≤ 2,900/μl.

Reviewer's Note – The subjects fitting this description had previously been discussed. There was Subject 52 (400 mcg) who had a SGPT of 100 on one screening date and 136 on another. Subject 245 (placebo) had a SGOT of 144 and a SGPT of 240 at Week 12.

The line listings for subjects with any type of abnormal lab values were reviewed (Volumes 102 and 103). The following abnormalities were notable.

Subject 206	200 mcg	Week 12	K 5.6	Day 86 (Vol.54 sup., p. 5423)
Subject 183	200 mcg	Week 12	Hgb 11.2	Day 84
Subject 163	400 mcg	Week 12	plts 0	Day 84 (Vol. 55 sup., p.5556)
Subject 004	400 mcg	Week 12	WBC 3.57	Day 85
Subject 092	400 mcg	Week 12	K 3.1	Day 85
Subject 044 (Site 10)	Placebo	Week 4	Glu 159 Na 151, CO_2-18.3 Chol 312 (269 on Screening) (Vol. 55 sup., p.5760)	Day 20 (Glucose - 117 on screening)
Subject 134	Placebo	Week 12	WBC 3.22	Day 85
Subject 096	Placebo	Week 1	Alk phos 421	Day 11 (Alk phos - 388 on screening)

Subject 206 (Site 9) is a 55 year old Caucasian female who had a Screening K of 4.8. No further data on this subject is available and it does not appear that the subject participated in the 9 month phase. As for Subject 163, many lab values appear to be missing for this Day 84 but platelets are listed as 0 – it appears that the patient was called back for Week 12 labs for Day 91 and these are normal. No further data is available on Subject 044 and it appears that Day 20 were the final labs. No further investigation is required noting this patient is on placebo. Subject 134 (Site 12) had a WBC of 4.59 at Screening that is low normal.

The other laboratory abnormalities were predominately related to transaminases. Subjects which had an elevated SGPT (all generally below 90) or SGPT/SGOT during drug treatment also tended to have an elevated SGPT at screening. Subjects in the 200 mcg group: 185, 189, 047; 400 mcg group: 163, 266 (SGPT was 105 at screening), 015, 052 (previously discussed); placebo group: 153, 071, 170, 176, 021, 042, and 131. Some subjects were listed as only having an elevated transaminase at screening: 136 (400 mcg), 085 (400 mcg), 119 (400 mcg), 155 (placebo), 230 (placebo), 164 (placebo), 138 (placebo) and 116 (placebo). Some subjects had an isolated listing of SGOT being elevated: 209 (placebo, 66 at screening, 40 on Day 85), and 002 (placebo, 41 at Screening, 52 on Day 85).

Subject 047 (Site 18, Vol.54 sup., p.5488) is notable for its variability as the SGPT was 87 at Screening, 47 at Week 12, 46 at Week 26, 51 at Week 38, then was 156 at day 368 with 68 at repeat on Day 383 (p. 5974.)

Some subjects had elevated transaminases noted during the trial and are not listed at Screening as having an elevation during the trial: 130 (400 mcg, SGOT – 35, SGPT – 38, day 83 – discussed further in 9 month phase), 061 (400 mcg, SGOT – 40, Day 31 – stopped drug Day 21, SGOT at Screening was 35 – not appreciably different, Vol. 55 Sup, p. 5600), 192 (400 mcg, SGOT – 57, Day 95 – SGPT was 24 on Day 95, SGOT was 22 at Screening and 21 on Day 127, Vol. 55 Sup., p.5640), 038 (placebo, SGOT – 41, SGPT – 36, on Day 89 –SGOT was 32 at Screening - not appreciably different, Vol. 55 sup. P.5760), 245 (placebo, SGOT – 144, Day 85, previously discussed in section on severe AE's), and 170 (placebo, 35 at Screening to 53 on trial).

The medians of each lab parameter for each treatment were reviewed (Volume 103). The groups appeared to compare well at baseline and there did not appear to be any appreciable change in the median for any of the lab parameters. The only possible change noted was in cholesterol where the

median value increased from 176.5 to 181 for the 200 mcg group, 169.5 to 178.5 for the 400 mcg group and decreased 183.5 to 183 for the placebo group. When the data was grouped by sex, there did not appear to be any overt dose-response difference in lab parameter change between the sexes. Because of the small number of Non-Caucasians and subjects not in the 18-64 age group, the data based on these subgroups was not reviewed.

The data on shifting of parameter data between baseline and endpoint was reviewed. No particular notable differences between shifts among the groups was discerned.

j) Laboratory Values - 9 month phase

Laboratory tests were performed at Visits 9, 10 and 11 on weeks 26, 38, and 52 respectively. The following lab abnormalities were notable from Section 14.3.4.2.1.

	#	parameter	Visit	Value
200 mcg qd	189	SGPT	Week 26	122
	047	SGOT	Final	129
		SGPT	Final	156
400 mcg qd	170	Glucose	Final	445
	213	Platelets	Final	30
	130	SGPT	Final	96
	131	SGPT	Week 38	117

Subject 189 had a value of 122 U/L for SGPT at Week 26 (normal range 6-43 U/L). Treatment was continued and the value decreased steadily to 45 U/L at the end of the study. The value for SGOT was also slightly elevated at Week 26, 48 U/L, and decreased to 26 U/L at the end of the study. Other indicators of liver function were unaffected.
Reviewer's Note - Note that this subject had elevated SGPT at screening (47) and also at Week 12 (63). It is not clear why this subject has such elevations of ALT but it was apparent at screening.

Subject 047 had an increase in SGPT and SGOT at the final visit that returned to normal at follow-up. The subject completed the study.
Reviewer's Note - Notably, this subject had an elevated SGPT at Screening (87) and at Weeks 12 (47), 26 (46) and 38 (51). It was not normal at follow-up as the sponsor says but it was lower at 68. The bilirubin was not elevated. Whatever the cause, it is probably not related to drug noting the elevation at screening.

Subject 170 (placebo to 400 q p.m.) had values for blood glucose of ≈150 to 200 mg/dl (normal range 70-115 mg/dl [fasting]) during the 9-month extension, which the subject completed. Approximately 4 weeks after the end of the study, a value of 455 mg/dl was recorded; the value was 235 and 267 mg/dl at follow-up visits approximately 5 and 9 weeks, respectively, after the end of the study. The subject also had moderately elevated values for SGOT and SGPT during and after the 9-month extension (SGOT 49-70 U/L, SGPT 43-56 U/L).
Reviewer's Note – This subject, a 300 lb woman, had elevations of glucose during the placebo phase of 138-193 (p. 5719, Vol. 55 suppl). Her SGPT was elevated at Screening at 53. It appears that the subject was a baseline diabetic –is it possible that the medication could have worsened her glucose tolerance?

Subject 213 had repeat platelet counts of 30,000/μL and 31,000/μL associated with her last visit in the study; the investigator subsequently diagnosed a serious adverse event of idiopathic

thrombocytopenic purpura unrelated to study medication, which was reported as an SAE. The subject completed the study.

Subject 130 (400 mcg q a.m. to 400 q a.m.) had a value of 96 for SGPT at the end of the study (normal range 6-34 U/L). The value for SGOT was also slightly elevated at 53 U/L. Other indicators of liver function were unaffected.
Reviewer's note – (p.6230 – Vol. 57 Sup) At screening, the SGPT was 24. She had elevation of SGPT at Weeks 12 (38), 26 (52) but it was normal (21) at Week 38. The sponsor supplies no explanation for this elevation during treatment.

Subject 131(placebo to 400 q pm) had moderately elevated values for SGOT and SGPT of ≈60 to 80 U/L throughout the 9-month extension, except for a single value for SGPT of 117 U/L at Week 38. Other indicators of liver function were unaffected. The subject completed the study.
Reviewer's note – (vol. 55(p5776) and 57 (p6382)) This subject's ALT was elevated at screening on two occasions (63 and 69). The final value was 76. Elevation does not appear treatment related.

There were some data submission problems in the original safety update. The median laboratory data was well out of range in much of 14.3.4.2.2. The sponsor was contacted and corrected safety update tables were submitted in a new correspondence dated May 20, 1999. The median laboratory data between double-blind baseline and 6, 9 and 12 months were reviewed and there did not appear to be any important differences between MF 200 QD and 400 QD. The data between gender, race and age was not reviewed.

k) Vital signs – 3 month phase

The data for mean vital sign change between the groups was reviewed. There did not appear to be any particular change in vital signs (BP, pulse, respiratory rate, and temperature) among the treatment groups. It must be noted that data on weight was only available for 5 subjects in this trial in the original NDA submission. When the data for vital signs was grouped by sex, the only difference appeared to be that the mean heart rate increased for males from 71.8 to 75.6 in the 200 mcg group, 69.9 to 72.1 in the 400 mcg group, and remained the same or nearly the same for the placebo group and all female treatment groups. The clinical significance of this change is doubtful; there does not appear to be a dose response.

The sponsor was requested to supply the correct data on weight, that is, for all patients at Endpoint. In this information request, no important changes in the mean weight were noted between Screening and Endpoint.

l) Vital Signs - 9 month phase

The means of the vital signs at each visit for each group were reviewed. There is no appreciable change in the vital signs over the treatment period. This time, as opposed to the 3 month phase, the sponsor reports more data on weight. There is an increase in the mean of 1.3 lbs. in the 200 mcg group and 1.9 lbs. in the 400 mcg group

m) EKG Results

An ECG was performed at Screening, Week 12 and at Week 52. The sponsor submitted descriptions of the ECG but did not supply a listing of the intervals (Vol. 61 –sup.). None of the ECG changes that were seen were believed to be clinically significant. Subject 197 (200 mcg) is listed as having a non-specific T wave abnormality and long QT interval at Week

12 which was considered not clinically significant. No further ECGs were available for this subject. Subject 094 is listed with a non-specific T-wave abnormality (considered not clinically significant) at Week 12 after a normal Screening ECG. No further ECGs were available for this subject. Subject 063 is listed with poor R wave progression in V2-4 at Day 288 abnormality (considered not clinically significant) whereas it had been normal at Screening and borderline poor R wave progression at Week 12. Subject 215 is listed with nonspecific inferior T wave abnormalities (considered not clinically significant) at Day 56 (End of study for subject) – subject had LVH at Screening which was no longer present at Week 12's study. Subject 111 is listed with a possible infarction and ST abnormality at Day 114 into open label phase. Notably, the subject had been off study medication for 47 days at this point. The subject is listed with a ST abnormality and possible Digitalis effect at Week 12.

n) Safety conclusions for C96-136

The mometasone DPI was generally well-tolerated with the doses and duration utilized in this study. The most common adverse events included headache, pharyngitis, viral infection, allergy aggravated, sinusitis, nasal congestion, musculo-skeletal pain, and dysmenorrhea. Musculo-skeletal pain, dysmenorrhea, and perhaps pharyngitis were more common in the 400 mcg group than in other treatment groups. Although less common than the aforementioned events, it appears that tremor, ear disorder NOS, earache, and weight increase were reported out of proportion for 400 mcg relative to 200 mcg and placebo. Aggravation of asthma, bronchitis, migraine, nasal congestion, and coughing were common in the placebo group. While the incidence of oral candidiasis was low, it must be noted that subjects were advised to rinse their mouth with water or a suitable mouthwash after study drug administration. The low incidence of oral candidiasis with MF DPI may be more reflective of the post-dose rinsing rather than an intrinsic quality of the drug.

The percentages of subjects with one or more severe/life-threatening adverse event were similar in the MF DPI treatment groups (11%-12%) and the placebo treatment group (11%). None of these severe AE's appears to have a particular over-representation among the treatment groups with the possible exception of asthma exacerbation in the placebo group. The one severe AE that seemed to be treatment related was a 49 year old female on 200 mcg who experienced a severe paroxysm of cough and dysphonia on Day 84.

A total of 24 subjects discontinued from the study during the 3 month phase because of adverse events. These included six subjects (8%) in the 200 mcg group, nine subjects (12%) in the 400 mcg group and nine subjects (10%) in the placebo group. The most frequent adverse events leading to discontinuation were events in the respiratory system such as aggravated asthma and bronchitis.

"Allergy aggravated" doubled in incidence between the 3 and 9 month phase. The sponsor attributed this to the fact that subjects were able to experience additional allergy seasons during the longer term. Headache, viral infection, sinusitis and URI also appeared to be relatively common in the 9 month phase. There appeared to be a difference in the incidence of dyspepsia between the 400 mcg dosing and the 200 mcg dosing. There appears to be a higher incidence of nasal congestion with either dose when it is given in the morning compared with the evening. The clinical significance of this is not clear. Aside from these two AE's, there was not a clear discrepancy among the groups.

There was a long list of AE's for the less common events reported during the 9 month phase. The AE's generally did not appear to be related to the study medication with the possible exceptions of dysphonia, dyspepsia (with a possible dose response), dysmennorhea, pharyngitis, and oral candidiasis. It seems that candidiasis was more common during the p.m. dosing.

The data for both 3 and 9 month phases were pooled. Allergy aggravated, headache, viral infection, upper respiratory tract infection, and sinusitis were reported most often for both treatments, 200 and 400 mcg per day. The incidence of AE's seems to be fairly comparable between the doses with some possible exceptions: dysphonia, dyspepsia, earache, musculoskeletal pain, pharyngitis, tremor, rhinorrhea, and conjunctivitis that appeared to be more common with the 400 mcg dosing. Only perhaps lymphadenopathy seemed to be more common with 200 mcg. To determine whether or not these AE's are more common with 400 mcg will have to be determined after review of other trials.

The data was also presented by the sponsor in groupings of adverse events by length of time of treatment. It appeared that allergy aggravated, headache, influenza-like symptoms, nausea, earache, musculoskeletal pain, myalgia, dysmenorrhea, viral infection, nasal congestion, pharyngitis, rhinorrhea, sinusitis and URI were more common in the subjects treated for longer periods. The sponsor attributes this to the increased duration of observation.

Laboratory tests were done for the 3 month phase at Screening and at Week 12. Laboratory tests were performed at Visits 9, 10 and 11 on weeks 26, 38, and 52, respectively, for the 9 month phase. Minor increases in SGPT were seen sporadically but were either: 1) associated with an elevated Screening value, 2) accounted for by viral hepatitis or ethanol use. Subject 130 (400 mcg q a.m. to 400 q a.m.) had a value of 96 for SGPT at the end of the study but at Screening, the SGPT was 24. She had elevation of SGPT at Weeks 12 (38), 26 (52) but it was normal (21) at Week 38. The sponsor supplies no explanation for this elevation during treatment. No explanation is available either for the SGOT of 57 on Day 95 in Subject 192 (400 mcg) with a normal SGPT. The SGOT was 22 at Screening and 21 on Day 127. Subject 213 was diagnosed with ITP during the 9 month phase. No further data is available on Subject 206 who was noted to have a serum potassium of 5.6 on Week 12.

Neither the median in the laboratory values or vital signs among the treatment groups appreciably changed during the trial. Weight was not documented well in the 3 month phase.

E. C96-186 (Vol. 151-167)

"Placebo-controlled, efficacy and safety study of Mometasone Furoate dry powder in the treatment of asthma in subjects previously maintained on inhaled beta-agonists"

1. Investigators and Investigational Centers

There were 306 subjects randomized at 22 centers.

2. Objectives/Rationale

The objectives of this randomized, multicenter, double-blind, placebo-controlled, parallel-group, Phase III study were to compare the efficacy and safety of MF DPI 200 mcg QD, MF DPI 400 mcg QD and MF DPI 200 mcg BID to placebo.

a) **Primary**

The primary efficacy endpoint was the change in forced expiratory volume (L) in one second (FEV_1) from Baseline to Endpoint.

b) **Secondary**

The secondary efficacy endpoints included the change in the following variables between Baseline and Endpoint : FVC, $FEF_{25-75\%}$, PEFR AM and PM, Asthma symptoms, (wheezing, difficulty breathing and cough), # nocturnal awakenings secondary to asthma which required Proventil, number of Proventil inhalations, and the physician's evaluations of response to therapy.

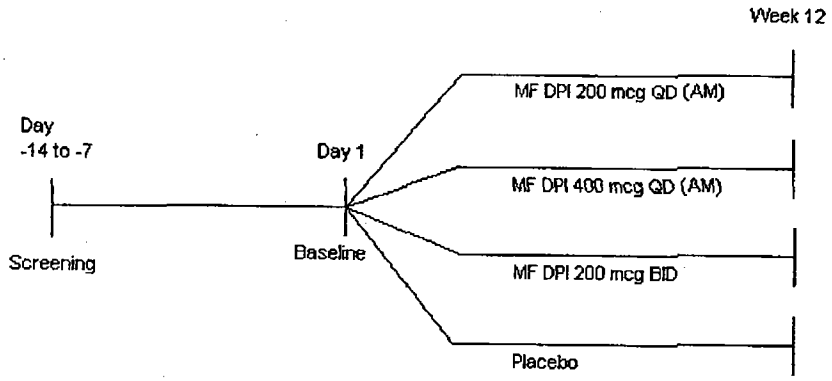
c) **Safety Data**

Frequency tabulations and summary statistics were to be provided for the following safety parameters: a) Incidence of treatment-emergent adverse events, b) Discontinuations due to adverse events, c) Changes from Baseline in vital signs, d) Changes from Baseline in laboratory tests. Physical and oropharyngeal examinations were to be summarized and tabulated.

3. Study Design

This was a Phase III, multicenter, randomized, double-blind, parallel-group study of MF DPI in the treatment of asthma in subjects previously maintained on inhaled beta-agonists alone. Subjects must not have been treated with inhaled corticosteroids within 3 months prior to the study. After informed consent and satisfying the inclusion and exclusion criteria for the study, eligible subjects were randomized at Baseline (Visit 2) to receive one of the following: MF DPI 200 mcg QD, MF DPI 400 mcg QD, MF DPI 200 mcg BID, or placebo in a 1:1:1:1 ratio according to a computer-generated code.

4. Summary of Study Protocol



Follow-up visits on Day 4, Weeks 1, 2, 4, 8 and 12.

a) Study Population

This study selected adults and adolescents who were currently maintained on short-acting inhaled beta-agonists alone. They must not have been treated with inhaled corticosteroids within the 3 months prior to entering the study. The study was designed to recruit 12-32 subjects at approximately 22 centers to ensure 280 subjects who met the criteria for the evaluation of the primary Endpoint.

(1) Inclusion Criteria

Same as C96-136.

(2) Exclusion Criteria

Same as C96-136.

(3) Removal of Subjects from Therapy

Same as C96-136, except that a subject could be removed from this study at any point because of a clinically significant worsening of asthma as previously defined in C96-136.

b) Treatments Administered

A Run-in period existed between the Screening and Baseline Visits. At the Baseline Visit, subjects meeting eligibility criteria were randomized to 12 weeks of the following:

Rx	AM	PM	TOTAL (mcg/day)
Group 1	100 mcg MF DPI x 2 puffs	Placebo x 2 puffs	MF DPI 200 mcg QD

Group 2	200 mcg MF DPI x 2 puffs	Placebo x 2 puffs	MF DPI 400 mcg QD
Group 3	100 mcg MF DPI x 2 puffs	100 mcg MF DPI x 2 puffs	MF DPI 400 mcg (BID dosing)
Group 4	Placebo x 2 puffs	Placebo x 2 puffs	Placebo

Each subject was instructed to take two inhalations from the dry powder inhaler labeled "MF DPI AM" in the morning and two inhalations from the dry powder inhaler labeled "MF DPI PM" in the evening, approximately 12 hours after the morning dose. Treatments were double blinded and the two dosage strengths (100 and 200 mcg) were indistinguishable from each other and placebo.

Subjects were advised to rinse their mouth with water or a suitable mouthwash after study drug administration.

(1) Concomitant/Restricted Medications

The list of permitted medications resembles that seen for the 3 month phase in C96-136. The list of restricted medications and their time of restriction prior to Screening is the same as C96-136 with the addition of Zileuton (2 weeks).

c) Assessments/Study Procedures

Schedule of Study Procedures and Evaluations for Study C96-186

		Treatment Period						
	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
TREATMENT DAYS (Weeks)	-14 to-7	1	4	8 (Wk 1)	15 (Wk 2)	29 (Wk 4)	57 (Wk 8)	85 (Wk 12)
Obtain Informed Consent	X							
Review Inclusion/Exclusion Criteria	X	X						
Medical/Disease History	X							
Concomitant Medications Review	X	X	X	X	X	X	X	X
Physical Examination, Weight	X							X
Height	X							
Vital Signs (temperature, blood pressure, pulse, respiratory rate)	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							X
Pregnancy Test	X							X

Electrocardiogram	X							
Chest X-ray	X							
Dispense/Collect Diary	X	X	X	X	X	X	X	X
Review Diary		X	X	X	X	X	X	X
Dispense Peak Flow Meter	X							
Dispense Study Medication		X						
Response to Therapy Assessment			X	X	X	X	X	X
Adverse Events Evaluation		X	X	X	X	X	X	X
Compliance Check / Collect Medication			X	X	X	X	X	X

Further specific details on the Visit procedures include:

- Pulmonary Function Tests

Three measurements were done. The spirometry effort with the highest FEV_1 was recorded as the best effort. If two or three spirometry efforts had identical FEV_1, the effort with the highest FVC was recorded. During the study, if the subject demonstrated a 20% or greater decrease in FEV_1 from the Baseline value, the subject was to have been discontinued from the study. If the subject was African-American, adjustments were made for race by programming the spirometer or by hand calculation, using the formula: FEV_1 predicted x 0.88 = FEV_1 predicted adjusted for race.

- Wheezing was assessed as absent or present (not graded as in C96-136).

- Reversibility Test (at Screening) - Reversibility, which was defined in the protocol as an increase in absolute FEV_1 of ≥12% over the Baseline value, with an absolute volume increase of at least 200 ml, must have been demonstrated within 30 minutes of 2 puffs of Proventil. If an increase in FEV_1 of ≥12% with absolute volume increase of at least 200 ml was documented in the subject record as a result of reversibility testing within the previous year, then this value could have been used to qualify the subject.

- Assessment of Response to Therapy: The investigator assessed the subject's response to therapy by comparing their current level of symptoms with those noted at the Baseline visit. The following scale was used to rate response to therapy: 1 = much improved, 2 = improved, 3 = no change, 4 = worse, 5 = much worse.

- Diary Data - Each subject was given a diary card at Screening for the Run-in period and the study treatment period. The following information was recorded daily on the diary: morning and evening peak expiratory flow (PEFR) (before study meds or any Proventil), total number of Proventil inhalations per day, symptoms of asthma, number of nocturnal awakenings due to asthma requiring Proventil use, adverse events, and use of study drug and concomitant medications.

- Asthma Symptoms - Every morning and evening, prior to dosing, the subject evaluated the following asthma symptoms as they were experienced during the time period since the last evaluation: wheezing, difficulty breathing, and cough using the following 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 or all of my normal daily activities/sleep

- Safety Evaluations – A medical history, EKG, and Chest X-ray were taken only at Screening. Physical exams and laboratory procedures were done at Screening and Week 12. Oropharyngeal exam, vital signs, medication review was done each visit.

- At each visit, subjects were questioned regarding the occurrence and severity of any adverse events. A clinical asthma exacerbation was defined as a worsening of asthma that resulted in emergency treatment, hospitalization, or treatment with additional asthma medication (other than short-acting inhaled beta-agonists). During the study, a subject experiencing an exacerbation was required to be discontinued from the study.

d) Statistical and Analytic Plans

The objective of the study was to evaluate the efficacy of three different dose regimens of MF DPI. In order to control the overall Type I error, the primary comparison for demonstrating the activity of MF DPI was to be made between MF DPI 400 mcg QD and placebo at the 0.05 (two-sided) level of significance. If this treatment comparison was significant then each of the remaining two MF DPI regimens were to be compared to placebo. Finally, all pairwise comparisons among the three MF DPI regimens were to be provided in order to estimate their relative effectiveness. All treatment comparisons were to be made at the 0.05 (two-sided) level of significance without adjustment for multiple comparisons.

No interim analyses were planned or performed. There was no data monitoring committee for this study.

(1) Study populations

Randomized Subjects: This subset was to include all randomized subjects. All summaries of safety data and efficacy analyses were to be based on all randomized subjects (intent-to-treat principle).

Efficacy Evaluable Subjects: Defined as randomized subjects who met key eligibility and evaluability criteria. Confirmatory efficacy analyses were to be based on this subject subset.

(2) Efficacy Analyses

Comparability of the treatment groups at Baseline was to be assessed by comparing the four treatment groups with respect to demographic (gender, age, and race) and disease characteristics (Baseline FEV_1 and PEFR).

The primary efficacy variable (change from Baseline in FEV_1 at Endpoint as compared to Baseline) was to be analyzed for all randomized subjects using a two-way ANOVA which extracted sources of variation due to treatment and center and treatment by center interaction. The primary efficacy analysis for demonstrating the activity of MF DPI was to be based on a pairwise comparison of least square means between MF DPI 400 mcg QD and placebo using a 5% significance level. If this comparison was significant, then the other two pairwise comparisons were to be made at the 0.05 (two-sided) level of significance, without adjustment of multiple comparisons.

In addition to the analysis at Endpoint, all six pairwise comparisons among the four treatment groups were to be made with respect to the change from Baseline in FEV_1 for each scheduled visit, using the same two-way ANOVA described above.

All other continuous efficacy variables were to be analyzed at each time point using the same two-way ANOVA and included FVC, $FEF_{25\%-75\%}$ and the physician's evaluations of response to therapy, as well as subject evaluations recorded on the diary (averaged over 7-day intervals) - PEFR, asthma symptoms, nocturnal awakenings, and the number of Proventil inhalations. For time to discontinuation because of asthma worsening, Kaplan-Meier survival time estimates were to be calculated.

(3) Summary of Safety Data

Physical and oropharyngeal examinations were to be summarized and tabulated. Frequency tabulations and summary statistics were to be provided for the following safety parameters:

a. Incidence of treatment-emergent adverse events

b. Discontinuations due to adverse events

c. Changes from Baseline in vital signs

d. Changes from Baseline in laboratory tests

(4) Sample Size

The sample size was chosen to detect (with 90% power and 5% significance level) a clinically meaningful pairwise difference in the mean change from Baseline (the primary efficacy variable) between an active treatment group and placebo. With 70 subjects per treatment group, assuming a pooled standard deviation of 0.45 units for FEV_1 change from Baseline (Reference - Study No. C94-127), mean treatment differences of approximately 0.25 units (approximately 10% of Baseline) or more would be detectable with power greater than 90%.

(5) Changes in Study Conduct or Planned Analyses

Before the database was locked and treatment assignments were unblinded, the following was changed:

- The range of the allowable proportion of actual FEV_1 values relative to predicted values at the Screening and Baseline visits was broadened from 55% to 85% to a wider 50% to 90%.
- Reversibility testing had to demonstrate an increase in FEV_1 of ≥10.5%, rather than ≥12%, with an absolute volume increase of at least 200 ml, or an increase in absolute FEV_1 of 12% with an increase of at least 180 ml.
- The definition of the data set that formed the basis of the intent-to-treat analyses was changed slightly (from all randomized subjects to all randomized subjects who received study medication and who had a post-treatment evaluation), and criteria for defining the Efficacy Evaluable data set were developed.
- The original protocol described the primary method of analysis as a two-way ANOVA extracting sources of variation due to treatment, center and their interaction. Because of the low center enrollment in this study, however, regulatory authorities, IRBs, and investigators, as appropriate, were notified by letter prior to the unblinding of any of the MF DPI study data, that the analysis model was being modified to a reduced, main-effects, two-way ANOVA for the primary efficacy analysis.
- Because some subjects may have met one or more of the criteria for asthma worsening but did not discontinue treatment as specified in the protocol, for purposes of analysis, subjects meeting any one criterion were considered to have worsening of asthma. Therefore, the planned analysis of "time to discontinuation due to asthma worsening" was changed to an analysis of "time to asthma worsening," which was defined as the first treatment day on which a subject met any criterion for worsening. Subjects who did not meet any criterion during the study were to be considered "censored" for purposes of the Kaplan-Meier estimate.
- A post-hoc analysis by day for the first 2 weeks of the study of the difference between each MF DPI group and placebo was provided for AM PEFR, asthma symptoms (coughing, difficulty breathing, and wheezing), number of nocturnal awakenings and Proventil® inhalations. The purpose of this analysis was to explore the first time point at which significant differences from placebo were consistently observed.

5. Results

There were 306 subjects randomized at 22 centers. An additional center (Center 01) was not initiated and did not enroll any subjects. All randomized subjects received at least one dose of study medication. The numbers of subjects randomized and treated in the four groups were as follows: MF DPI 200 mcg QD, 79 subjects; MF DPI 400 mcg QD, 74 subjects; MF DPI 200 mcg BID, 79 subjects; and placebo, 74 subjects.

A total of 43 subjects (MF DPI 200 mcg QD, 12 subjects; MF DPI 400 mcg QD, 6 subjects; MF DPI 200 mcg BID, 7 subjects; and placebo, 18 subjects) discontinued prior to scheduled completion. The two main reasons for discontinuation were adverse events (6% of subjects) and treatment failure (4% of subjects). Discontinuations for adverse events and treatment failure appeared to be more common in the placebo treatment group than in MF DPI treatment groups.

Randomized Subjects Who Completed the Entire Treatment Period, Subjects Who Discontinued the Study and Reasons for Discontinuance

	NUMBER (%) OF SUBJECTS				
	MF DPI 200 mcg QD (n=79)	MF DPI 400 mcg QD (n=74)	MF DPI 200 mcg BID (n=79)	Placebo (n=74)	Total (n=306)
Subjects Who Completed	67 (85%)	68 (92%)	72 (91%)	56 (76%)	263 (86%)
Reason for Discontinuation					
Adverse Event	5 (6%)*	3 (4%)	2 (3%)	7 (9%)	17 (6%)
Treatment Failure	1 (1%)*	1 (1%)	3 (4%)	7 (9%)	12 (4%)
Lost to Follow-up	4 (5%)	0	1 (1%)	1 (1%)	6 (2%)
Did Not Continue for Reasons Unrelated to Treatment	1 (1%)	0	0	2 (3%)	3 (1%)
Non-Compliance	1 (1%)	2 (2%)	0	0	3 (1%)
Did Not Meet Entry Criteria	0	0	1 (1%)	1 (1%)	2 (1%)
Subjects Overall Who Discontinued	12 (15%)	6 (8%)	7 (9%)	18 (24%)	43 (14%)

*Subjects C96-186-08-027 and C96-186-15-166 (MF DPI 200 mcg QD) appear in Sections 14.4.3. and 16.2.1. as having discontinued for treatment failure. These subjects actually experienced "asthma aggravated", an adverse event, and discontinued for this reason. Therefore, C96-186-027 and C96-186-15-166 appear here under Adverse Event rather than under Treatment Failure. Only one subject in this treatment group, Subject C96-186-23-230, discontinued for treatment failure.

15 subjects with protocol deviations were excluded from the **Efficacy Evaluable** data. Protocol deviations were reported by 4 in the 200 mcg QD group, 5 in the 400 mcg QD group, 2 in the 200 mcg BID treatment group and 4 in the placebo group. These protocol deviations included poor compliance (defined as compliance of <75%) (6 subjects), missing follow-up data (3 subjects total; 2 subjects with no postbaseline efficacy data and 1 subject with insufficient efficacy data), change of ≥20% in FEV_1 between Screening and Baseline (8 subjects) and FEV_1 values that were not between 50% and 90% of predicted at Baseline (2 subjects).

Number of Subjects by Analysis Subset and Treatment Group

	MF DPI 200 mcg QD	MF DPI 400 mcg QD	MF DPI 200 mcg BID	Placebo	Total
Randomized	79	74	79	74	306
All Treated Subjects Data Set	77	74	79	74	304
Excluded from All Treated Subjects Data Set for No Post-baseline Data	2	0	0	0	2
Efficacy Evaluable Data Set	75	69	77	70	291
Excluded From Efficacy Evaluable Data Set for No Post-baseline Data or Other Protocol Deviations	4	5	2	4	15

Demographic Data (All Treated Subjects)

	MF DPI 200 mcg QD (n=79)	MF DPI 400 mcg QD (n=74)	MF DPI 200 mcg BID (N = 79)	Placebo (n=74)
Age (years)				
Mean	30	29	32	32
Min-Max	12-63	13-53	12-66	12-70
Distribution of Subjects in Age Categories				
12 to 17 years	9	14	17	17
18 to 64 years	70	60	61	56
≥64 years	0	0	1	1
Sex				
Female	45	34	44	31
Male	34	40	35	43
Race				
Caucasian	65	57	63	63
Black	8	10	6	3
Hispanic	5	5	4	3
Asian	1	1	5	2
Other	0	1	1	3
Weight (lbs.)				
Mean	164	170	165	166
Min-Max	84-279	80-280	91-344	81-327
Smoking History				
Never Smoked	66	65	62	62
Not Smoked in 6 Mos.	13	9	17	12
Duration of Asthma Condition (years)				
Mean	16	17	17	16
Min-Max	1-49	2-47	1-49	1-50
FEV_1 % Predicted at Baseline				
Mean	73	72	72	71
Min-Max	55-87	55-90	55-91	45-85
Absolute FEV_1 at Baseline (liters)				
n	77	74	79	74
Mean	2.58	2.64	2.56	2.55
AM PEFR at Baseline (liters/minute)				
n	78	74	79	74
Mean	377.0	397.5	362.2	369.9

6. Analysis of Efficacy

a) FEV_1

Spirometry was generally performed in the morning with many exceptions. Sometimes the spirometry was not performed on the same time of day for the series of measurements on a

single patient. In the protocol as stated in Section 9.5.1.1, there is no mention of the specific hourly timing required for spirometry although efforts were made to use the same spirometer for each patient and maintain the same body position. The timing of spirometry was reviewed in Section 16.2.6.1 (Vol. 1-156). The following sites for 200 mcg BID and 400 mcg QD, for example, had at least one patient whose values were measured after 1300. All dose values are not listed here for the sake of time and effort.

Dose	Spirometry with more than one value after 1300	Variability (> 2 hours)
200 mcg BID	3 (2), 6(1),7(2), 8(1),9(2), 10(1), 12(1), 13(3), 14(3),15(4), 16(4),17(1), 23(2)	2 (1), 6(2), 9(2), 10(1), 12(1), 13(3),14(3),15(4), 16(2), 17(1)
400 mcg QD	2(1), 3(1), 4(1),5(3),6(3),8(2), 9(2),10(1),12(1),14(2).15(1), 16(3),17(2), 22(1),23(2)	2(1),3(1),4(1),5(1),6(2), 8(1),9(2),10(1),11(2),12(1),13(2),14(2),15(4),16(2),17(1),

This general pattern was noted for all doses so this effect should affect all QAM doses generally the same. The late timing of the doses may have served to improve the perceived efficacy of the AM and BID doses. Such variance in the daily timing of spirometry may potentially detract from the ability of a study to accurately test whether QD dosing is efficacious. Few sites had early morning values within 45 minutes of each other.

For All Treated Subjects, the increase in the primary efficacy outcome, change in FEV_1 between Baseline and Endpoint, was significantly greater ($p<0.01$, both comparisons) in the 400 mcg QD and 200 mcg BID groups than in the placebo group. While the response in the 200 mcg QD group was larger than the response in the placebo treatment group, the difference between the groups was not statistically significant ($p=0.09$). FEV_1 increased between Baseline and Endpoint in all MF DPI treatment groups (200 mcg QD, 10.4%; 400 mcg QD, 16.0%; 200 mcg BID, 16.1%) as well as in the placebo group (5.5%). Increases observed in the MF DPI groups were at least twice as large as those observed in the placebo group at Day 4 and were consistently larger at time points thereafter.

The differences between MF DPI treatment groups at Endpoint were not statistically significant. Please note that 400 mcg QD is better than 200 mcg QD at Week 8 and 12.

FEV_1 (liters) - Change from Baseline by Treatment Group (All Treated Subjects)

	MF DPI 200 mcg QD (A)			MF DPI 400 mcg QD (B)			MF DPI 200 mcg BID (C)			Placebo (D)		
	N	Mean [a]	(Mean % Change) [a]	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	77[b]	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	(10.0%)	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	**77**	**0.27**	**(10.4%)**	**74**	**0.41**	**(16.0%)**	**79**	**0.40**	**(16.1%)**	**74**	**0.14**	**(5.5%)**

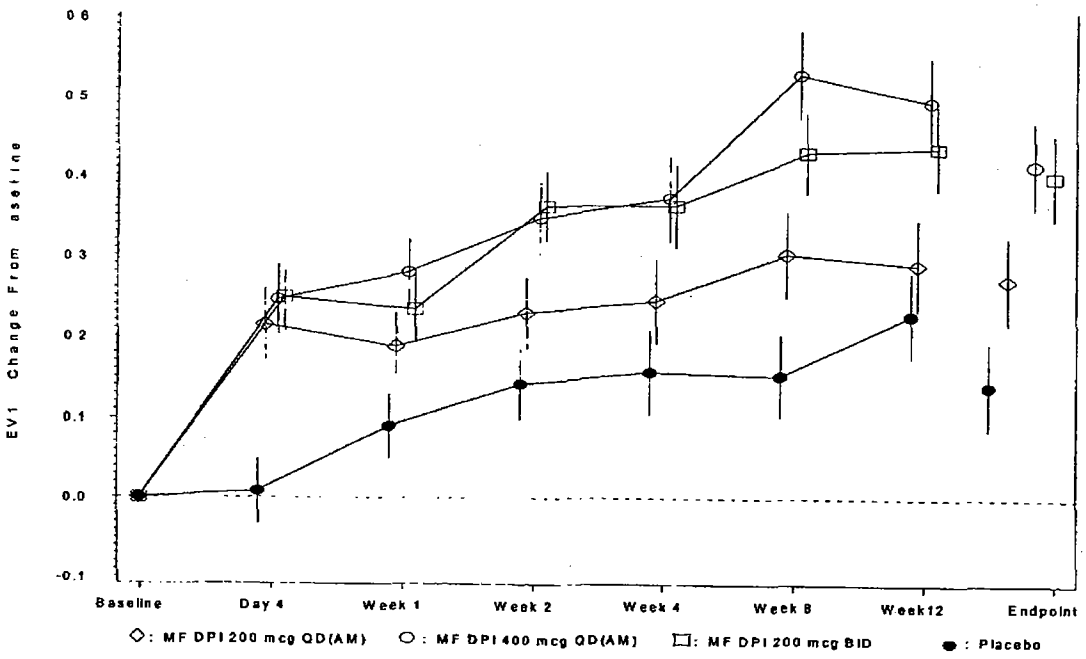
Analysis Results (Change From Baseline)[c]

		P-value		Pairwise Comparisons (P Value)					
Time point	Pooled SD	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: Two subjects had no post-baseline FEV_1 value.

d: Pairwise treatment comparisons were based on t-test from the ANOVA model.



Results in male and female subjects were similar to those described for the population overall, i.e., increases in FEV_1 were greater in MF DPI treatment groups than in the placebo treatment group in both subsets of subjects. There were too few subjects who were aged 12 to 17 years or ≥ 65 years and too few Non-caucasian subjects to permit meaningful comparisons among age or race groups.

Response was evaluated in subjects whose Baseline FEV_1 was <75% of the predicted value versus those whose Baseline FEV_1 was ≥75%. In subjects with Baseline FEV_1 of <75% of the predicted value, the change in FEV_1 between Baseline and Endpoint was: 200 QD, 12.3%; 400 QD, 20.8%; and 200 BID, 20.3%, compared to 6.8% in the placebo treatment group. The difference between each MF DPI treatment group (200 mcg QD group, 7.6%; 400 mcg QD group, 8.4%; 200 BID, 9.7%) and the placebo group (3.0%) was also apparent in the subset consisting of subjects with Baseline FEV_1 of ≥75%.

FEV_1 (liters) - Change from Baseline by Treatment Group (All Treated Subjects, and FEV_1 <75% or ≥ 75% Predicted Value at Baseline)

	MF DPI 200 mcg QD (A)			MF DPI 400 mcg QD (B)			MF DPI 200 mcg BID (C)			Placebo (D)		
Baseline	46	2.43		45	2.49		48	2.33		48	2.38	
Change From Baseline												
Day 4	31	0.22	(9.5%)	36	0.30	(13.0%)	37	0.32	(14.6%)	37	-0.01	(0.1%)
Week 1	43	0.23	(9.3%)	44	0.35	(14.7%)	47	0.28	(12.6%)	44	0.13	(4.5%)
Week 2	45	0.29	(12.0%)	45	0.43	(18.1%)	47	0.44	(18.9%)	44	0.19	(7.8%)
Week 4	42	0.32	(13.1%)	44	0.47	(19.9%)	47	0.45	(19.7%)	41	0.24	(9.4%)
Week 8	38	0.36	(14.9%)	41	0.68	(28.1%)	46	0.52	(22.0%)	38	0.22	(9.2%)
Week 12	36	0.34	(14.0%)	40	0.59	(23.2%)	44	0.45	(19.7%)	35	0.26	(10.7%)
Endpoint	**46**	**0.30**	**(12.3%)**	**45**	**0.51**	**(20.8%)**	**48**	**0.46**	**(20.3%)**	**48**	**0.15**	**(6.8%)**

FEV_1 ≥75%	MF DPI 200 mcg QD (A)			MF DPI 400 mcg QD (B)			MF DPI 200 mcg BID (C)			Placebo (D)		
	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	31	2.84		29	2.90		31	2.95		26	2.93	
Change From Baseline												
Day 4	23	0.17	(5.9%)	22	0.11	(4.6%)	26	0.15	(5.6%)	24	0.01	(0.4%)
Week 1	31	0.12	(4.5%)	28	0.16	(5.6%)	28	0.15	(5.6%)	24	0.03	(1.1%)
Week 2	31	0.12	(4.5%)	27	0.19	(7.2%)	29	0.23	(7.6%)	25	0.07	(2.6%)
Week 4	31	0.15	(6.0%)	26	0.22	(7.6%)	29	0.25	(8.5%)	24	0.07	(2.5%)
Week 8	30	0.22	(8.1%)	23	0.24	(8.7%)	29	0.27	(9.1%)	22	0.04	(2.0%)
Week 12	28	0.20	(7.6%)	23	0.28	(10.3%)	27	0.38	(13.0%)	19	0.15	(4.6%)
Endpoint	**31**	**0.20**	**(7.6%)**	**29**	**0.24**	**(8.4%)**	**31**	**0.27**	**(9.7%)**	**26**	**0.09**	**(3.0%)**

As in the All Treated Subjects data set, review of the Efficacy Evaluable data set, showed that subjects in the 400 mcg QD and 200 mcg BID DPI groups had significantly better responses than subjects in the placebo group. Differences between the 200 mcg group and the placebo group were not statistically significant.

The sponsor reports that there was no significant treatment-by-center interaction (p=0.458) at Endpoint for FEV_1. There was no indication that any one large center biased the conclusions on the population as a whole. Of the 22 centers in this study, nine had four or more subjects per treatment group.

b) FVC and FEF_{25-75}

For the FVC, only the difference between the 200 mcg BID group and the placebo group was statistically significant (p=0.05). Other comparisons between MF DPI groups and the placebo group were not statistically significant.

FVC (liters) - Change from Baseline by Treatment Group (All Treated Subjects)

	MF DPI 200 mcg QD (A)			MF DPI 400 mcg QD (B)			MF DPI 200 mcg BID (C)			Placebo (D)		
	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	77	3.49		74	3.62		79	3.55		74	3.48	
Change From Baseline												
Day 4	54	0.20	(5.2%)	58	0.23	(6.1%)	63	0.20	(7.0%)	61	0.01	(0.8%)
Week 1	74	0.17	(4.8%)	72	0.24	(6.7%)	75	0.19	(6.0%)	68	0.12	(3.3%)
Week 2	76	0.21	(6.3%)	72	0.27	(7.8%)	76	0.31	(9.2%)	69	0.18	(5.6%)
Week 4	73	0.20	(5.9%)	70	0.30	(8.6%)	76	0.31	(9.4%)	65	0.19	(6.2%)
Week 8	68	0.30	(9.1%)	64	0.43	(12.0%)	75	0.38	(11.0%)	60	0.22	(6.7%)
Week 12	64	0.26	(7.7%)	63	0.38	(10.5%)	71	0.35	(10.7%)	54	0.27	(8.0%)
Endpoint	**77**	**0.24**	**(7.3%)**	**74**	**0.30**	**(8.9%)**	**79**	**0.33**	**(10.0%)**	**74**	**0.17**	**(5.1%)**

Analysis Results (Change From Baseline)

		P-value		Pairwise Comparisons (P Value)					
Time point	Pooled SD	Treatment	Center	A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D
Day 4	0.34	<0.01	0.02	0.67	0.92	<0.01	0.74	**<0.01**	**<0.01**
Week 1	0.37	0.31	0.03	0.24	0.65	0.48	0.47	0.07	0.25
Week 2	0.39	0.18	0.20	0.39	0.13	0.58	0.53	0.17	0.04
Week 4	0.45	0.24	0.06	0.17	0.14	0.94	0.93	0.16	0.13
Week 8	0.41	0.03	<0.01	0.09	0.26	0.26	0.51	**<0.01**	**0.03**
Week 12	0.43	0.32	<0.01	0.12	0.21	0.89	0.74	0.19	0.29
Endpoint	0.49	0.19	**0.02**	0.45	0.29	0.34	0.77	0.09	**0.05**

Between Baseline and Endpoint, increases in $FEF_{25\%-75\%}$ observed in the MF DPI treatment groups (MF DPI 200 mcg QD, 22.7%; MF DPI 400 mcg QD, 31.6%; MF DPI 200 mcg BID, 31.0%) were significantly larger (p<0.01, all comparisons) than the increase observed in the placebo treatment group (7.3%). There were no statistically significant differences between any two MF DPI groups.

$FEF_{25-75\%}$ (liters/second) - Change from Baseline by Treatment Group (All Treated Subjects)

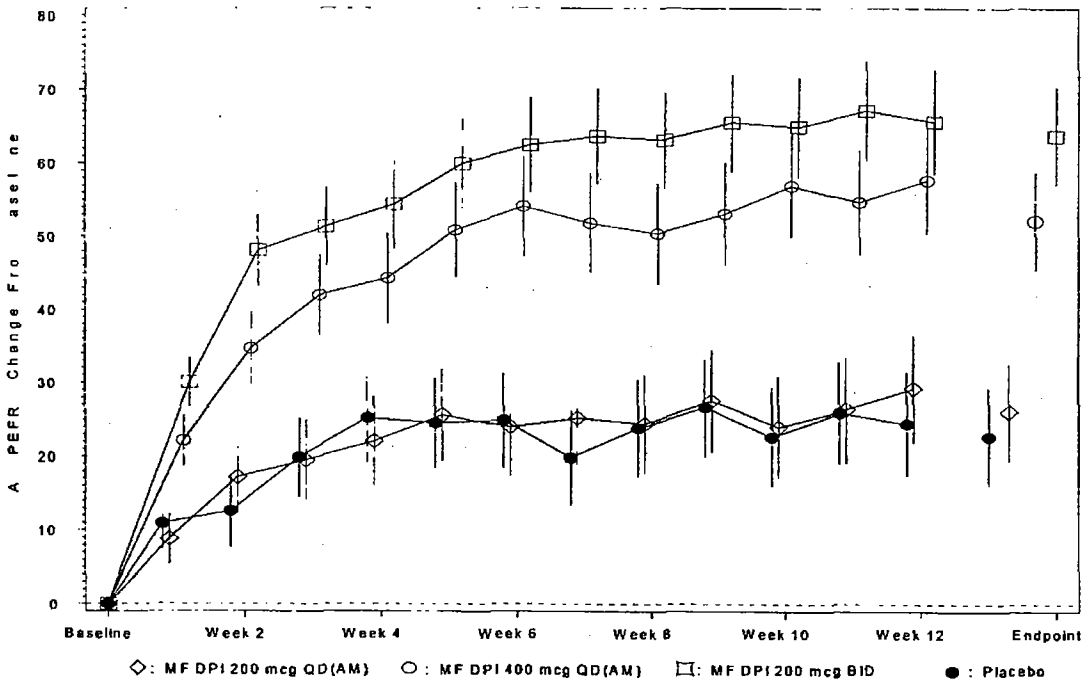
	MF DPI 200 mcg QD (A)			MF DPI 400 mcg QD (B)			MF DPI 200 mcg BID (C)			Placebo (D)		
	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	77	2.17		74	2.18		79	2.03		74	2.11	
Change From Baseline												

Day 4	54	0.28	(16.4%)	58	0.30	(21.4%)	63	0.33	(21.3%)	61	-0.01	(1.3%)
Week 1	74	0.25	(15.7%)	72	0.35	(21.0%)	75	0.31	(21.1%)	68	0.06	(5.3%)
Week 2	76	0.29	(16.9%)	72	0.47	(28.5%)	76	0.49	(28.2%)	69	0.13	(8.7%)
Week 4	73	0.38	(23.0%)	70	0.52	(32.9%)	76	0.52	(32.5%)	65	0.11	(9.7%)
Week 8	68	0.34	(20.5%)	64	0.70	(44.0%)	75	0.51	(31.8%)	60	0.05	(6.5%)
Week 12	64	0.42	(24.2%)	63	0.62	(34.2%)	71	0.55	(33.0%)	54	0.17	(10.7%)
Endpoint	**77**	**0.40**	**(22.7%)**	**74**	**0.55**	**(31.6%)**	**79**	**0.50**	**(31.0%)**	**74**	**0.09**	**(7.3%)**

Analysis Results (Change From Baseline)

		P-value		Pairwise Comparisons (P Value)					
Time point	Pooled SD	Treatment	Center	A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D
Day 4	0.57	<0.01	0.89	0.83	0.60	**<0.01**	0.76	**<0.01**	**<0.01**
Week 1	0.57	0.02	0.37	0.31	0.54	**0.05**	0.68	**<0.01**	**<0.01**
Week 2	0.61	<0.01	0.43	0.07	**0.04**	0.11	0.85	**<0.01**	**<0.01**
Week 4	0.71	<0.01	0.29	0.22	0.23	**0.03**	0.95	**<0.01**	**<0.01**
Week 8	0.69	<0.01	0.12	**<0.01**	0.13	**0.02**	0.11	**<0.01**	**<0.01**
Week 12	0.69	<0.01	0.45	0.12	0.29	**0.05**	0.58	**<0.01**	**<0.01**
Endpoint	**0.70**	**<0.01**	**0.14**	0.18	0.38	**<0.01**	0.64	**<0.01**	**<0.01**

c) **PEFR**



AM PEFR (liters/minute) - Change from Baseline (All Treated Subjects)

	200 mcg QD (A)			400 mcg QD (B)			200 mcg BID (C)			Placebo (D)		
	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	78	377.01		74	397.49		79	362.16		74	369.86	

Change From Baseline												
Week 1	78	8.79	(2.5%)	74	22.10	(6.1%)	79	30.01	(8.6%)	74	10.86	(3.2%
Week 2	77	17.16	(5.1%)	74	34.69	(10%)	77	48.12	(14.3%)	70	12.57	(3.3%
Week 4	73	22.00	(6.3%)	72	44.28	(12.8%)	76	54.35	(16.7%)	65	25.20	(6.6%
Week 6	70	23.99	(7.2%)	69	54.10	(15.7%)	76	62.43	(19.5%)	63	24.90	(6.4%
Week 8	70	24.42	(7.0%)	68	50.39	(14.7%)	74	63.13	(20.0%)	62	23.84	(6.0%
Week 10	69	23.99	(7.1%)	68	56.87	(16.4%)	72	64.82	(20.2%)	58	22.60	(5.7%
Week 12	66	29.23	(8.5%)	67	57.65	(16.3%)	70	65.55	(20.8%)	57	24.48	(6.2%
Endpoint	**78**	**26.13**	**(7.4%)**	**74**	**52.10**	**(15.0%)**	**79**	**63.58**	**(19.6%)**	**74**	**22.73**	**(5.8%**

Analysis Results (Change From Baseline)

		P-value		Pairwise Comparisons (P Value)					
Time point	Pooled SD	Treatment	Center	A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D
Week 1	30.77	<0.01	0.32	**<0.01**	**<0.01**	0.68	0.11	**0.03**	**<0.01**
Week 2	43.11	<0.01	0.14	**0.01**	**<0.01**	0.52	0.06	**<0.01**	**<0.01**
Week 4	52.76	<0.01	0.53	**0.01**	**<0.01**	0.72	0.25	**0.04**	**<0.01**
Week 6	56.58	<0.01	0.53	**<0.01**	**<0.01**	0.93	0.38	**<0.01**	**<0.01**
Week 8	55.70	<0.01	0.43	**<0.01**	**<0.01**	0.95	0.18	**<0.01**	**<0.01**
Week 10	56.81	<0.01	0.41	**<0.01**	**<0.01**	0.89	0.41	**<0.01**	**<0.01**
Week 12	58.59	<0.01	0.33	**<0.01**	**<0.01**	0.66	0.43	**<0.01**	**<0.01**
Endpoint	**58.13**	**<0.01**	0.28	**<0.01**	**<0.01**	0.72	0.22	**<0.01**	**<0.01**

It should be noted that the Baseline PEFR values in the MF DPI 400 mcg QD group (mean 397.5) were greater than those of the MF DPI 200 mcg BID (mean 362.2) (p=0.02) and placebo (mean 370) (p=0.07) groups. The differences between these groups may have unduly influenced the analyses and the sponsor's analysis did not factor these baseline analyses into an ANCOVA that would have considered the baseline differences as a covariate.

At Endpoint for AM PEFR, there was a significant difference between the placebo group (5.8%) and the 400 mcg QD (15.0%) and 200 mcg BID (19.6%) groups (p<0.01, both comparisons). The difference between the 200 mcg QD group (7.4%) and the placebo group (5.8%) was not statistically significant (p=0.72). Further, the response in both the 400 mcg QD and 200 mcg BID groups was significantly greater than the response in the 200 mcg QD group (p<0.01, both comparisons). While 200 mcg bid was never significantly better than 400 mcg, it was consistently numerically greater which seems to suggest that the evening dosing of MF DPI has a favorable effect on morning peak flows.

The data for the PM PEFR (p.324, Vol.1-151) was reviewed and a similar pattern was seen among the groups. 200 mcg QD was only modestly numerically different from placebo throughout the weeks and at Endpoint. 200 mcg BID and 400 mcg QD were better than placebo at very week and at Endpoint. Again 200 mcg bid was consistently numerically better than 400 mcg QD, but because this is PM PEFR, it seems to go against the idea that the improved effect in PEFR is simply because of the temporal relationship of PEFR to the dosing of QD in the morning. Both AM and PM PEFR are numerically better with 200 mcg bid compared with 400 mcg QD throughout the study and at Endpoint.

During an exploration of treatment effect analysis, the sponsor identified significant differences ($p<0.05$) between the changes from Baseline in PEFR in the 200 mcg BID group and those in the placebo group were evident as early as Days 1 (PM) or 2 (AM). Significant differences in AM PEFR were noted consistently from Day 4 through Day 14 and in PM PEFR on Days 2, 4 through 8, and 11 through 13. Only sporadic differences of statistical significance were noted between the changes from Baseline in PEFR (AM or PM) in the 400 mcg QD group and those in the placebo group. It should be noted, however, that the mean values following treatment with 400 mcg QD were greater than those for the 200 mcg BID group, and, therefore, these results should be interpreted with caution, particularly in view of the significantly higher Baseline for 400 mcg QD. Significant differences from placebo were not seen in changes in PEFR (AM or PM) from Baseline for the 200 mcg QD group.

	Daily AM PEFR MF DPI mcg			Daily PM PEFR MF DPI mcg		
	200 QD	400 QD	200 BID	200 QD	400 QD	200 BID
Baseline	377.01	397.49	362.16	392.37	422.68	385.65
(N)	(78)	(74)	(79)	(78)	(74)	(79)
Difference Between Changes from Baseline[a]						
Day 1	N/A	N/A	N/A	-7.1	-14.9	0.5
Day 2	0.0	13.3	19.8 *	-7.0	9.3	14.7 *
Day 3	-5.0	7.3	12.4	-3.0	7.2	18.2 *
Day 4	-3.1	11.5	19.7 *	-5.1	-2.6	2.9
Day 5	-3.9	10.6	15.4 *	4.4	14.6	17.8 *
Day 6	-7.8	15.8 *	26.7 *	-0.9	7.5	16.7 *
Day 7	5.3	11.7	24.0 *	-4.4	5.5	23.4 *
Day 8	-3.6	23.4 *	40.4 *	5.7	18.8 *	21.0 *
Day 9	1.7	16.0	23.8 *	-1.9	8.1	17.0
Day 10	3.5	19.1 *	30.9 *	-2.4	12.3	16.7
Day 11	6.3	27.7 *	34.4 *	7.5	15.9	20.1 *
Day 12	14.7	28.5 *	44.8 *	10.5	24.2 *	27.2 *
Day 13	5.1	18.3	41.3 *	1.9	7.8	24.3 *
Day 14	6.0	28.4 *	36.6 *	N/A	N/A	N/A

[a] Difference between mean changes of treated and placebo

* $p < 0.05$.

d) Asthma Symptoms

It should be noted that symptom scores were generally low (generally <1) at Baseline so the results should be interpreted with care. It is also not clear how much of a difference should be considered clinically important.

AM Wheezing Scores - Change from Baseline by Treatment Group (All Treated Subjects)

	MF DPI 200 mcg QD (A)		MF DPI 400 mcg QD (B)		MF DPI 200 mcg BID (C)		Placebo (D)	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	78 [b]	0.85	74	0.79	79	0.92	74	1.06
Change From Baseline								
Week 1	78	-0.15	74	-0.22	79	-0.40	74	-0.18

Week 2	77	-0.19	74	-0.33	77	-0.47	70	-0.20
Week 4	73	-0.27	72	-0.36	76	-0.47	65	-0.27
Week 6	70	-0.32	69	-0.43	76	-0.56	63	-0.25
Week 8	70	-0.30	68	-0.39	74	-0.56	62	-0.26
Week 10	69	-0.33	68	-0.48	72	-0.59	58	-0.24
Week 12	66	-0.38	67	-0.48	70	-0.64	57	-0.24
Endpoint	**78**	**-0.31**	**74**	**-0.44**	**79**	**-0.60**	**74**	**-0.23**

Analysis Results (Change From Baseline)

		P-value		Pairwise Comparisons (P Value)					
Time point	Pooled SD	Treatment	Center	A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D
Week 1	0.40	<0.01	0.38	0.28	**<0.01**	0.71	<0.01	0.48	**<0.01**
Week 2	0.49	<0.01	0.80	0.09	**<0.01**	0.96	0.08	0.11	**<0.01**
Week 4	0.52	0.05	0.06	0.29	**0.02**	0.99	0.18	0.31	**0.02**
Week 6	0.51	<0.01	0.42	0.21	**<0.01**	0.39	0.13	**0.04**	**<0.01**
Week 8	0.54	<0.01	0.49	0.33	**<0.01**	0.67	**0.05**	0.17	**<0.01**
Week 10	0.53	<0.01	0.68	0.10	**<0.01**	0.33	0.23	**0.01**	**<0.01**
Week 12	0.57	<0.01	0.91	0.29	**<0.01**	0.19	0.12	**0.02**	**<0.01**
Endpoint	0.61	<0.01	0.89	0.19	**<0.01**	0.47	**0.11**	**0.05**	**<0.01**

200 mcg QD is not significantly different from placebo. It is interesting to note that, while both 200 mcg BID and 400 mcg QD produce a significant decrease in AM Wheezing scores, 200 mcg BID appears to do it more consistently throughout the course of the study. Also, while 200 mcg BID is consistently better than 200 mcg QD, 400 mcg QD is not better than 200 mcg QD at any time point. As for the PM Wheezing Scores (p. 357, Vol. 1-152), the scores appear to be remarkably similar, as is the general pattern. Thus, 200 mcg BID appears to be somewhat more efficacious in this variable of Wheezing than 400 mcg QD.

AM Difficulty Breathing - Change from Baseline by Treatment Group (All Treated Subjects)

	MF DPI 200 mcg QD (A)		MF DPI 400 mcg QD (B)		MF DPI 200 mcg BID (C)		Placebo (D)	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	78[b]	0.98	74	1.04	79	1.10	74	1.14
Change From Baseline								
Week 1	78	-0.15	74	-0.26	79	-0.40	74	-0.22
Week 2	77	-0.23	74	-0.35	77	-0.46	70	-0.18
Week 4	73	-0.32	72	-0.36	76	-0.55	65	-0.26
Week 6	70	-0.31	69	-0.44	76	-0.60	63	-0.30
Week 8	70	-0.34	68	-0.43	74	-0.63	62	-0.33
Week 10	69	-0.38	68	-0.55	72	-0.66	58	-0.27
Week 12	66	-0.36	67	-0.56	70	-0.68	57	-0.28
Endpoint	**78**	**-0.34**	**74**	**-0.49**	**79**	**-0.64**	**74**	**-0.26**

Analysis Results (Change From Baseline)

		P-value		Pairwise Comparisons (P Value)					
Time point	Pooled SD	Treatment	Center	A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D

Week 1	0.43	<0.01	0.65	0.12	**<0.01**	0.30	0.04	0.59	**<0.01**
Week 2	0.53	<0.01	0.97	0.17	**<0.01**	0.61	0.20	0.06	**<0.01**
Week 4	0.56	0.02	0.62	0.72	**0.02**	0.50	0.04	0.31	**<0.01**
Week 6	0.58	<0.01	0.46	0.19	**<0.01**	0.94	0.09	0.17	**<0.01**
Week 8	0.58	<0.01	0.70	0.36	**<0.01**	0.95	**0.04**	0.34	**<0.01**
Week 10	0.59	<0.01	0.62	0.11	**<0.01**	0.29	0.24	**<0.01**	**<0.01**
Week 12	0.61	<0.01	0.77	0.06	**<0.01**	0.50	0.25	**0.01**	**<0.01**
Endpoint	0.63	<0.01	0.32	0.13	**<0.01**	0.41	0.15	**0.02**	**<0.01**

The pattern with the AM Difficulty Breathing is very similar to that of Wheezing. 200 mcg QD is not significantly better than placebo and only slightly numerically better. While both 400 mcg QD and 200 mcg BID are better than placebo, the 400 mcg QD dose only becomes better by Week 10. 200 mcg BID is consistently better than 400 mcg QD while it is at only two time points where the difference is significant. The 400 mcg QD fares better against placebo when the PM Difficulty Breathing data is examined. 200 mcg BID is still consistently better with this variable.

The table for AM or PM Cough is not shown in this NDA review but was examined. For AM Cough, no MF DPI group produced a statistically significant decrease compared with placebo although the changes were generally numerically greater. For PM Cough (p. 453, Vol. 1-152), 200 mcg BID and 400 mcg QD were better than placebo at Endpoint.

e) B-agonist Use During the Study

. Based on the number of puffs of Proventil used per day, treatment with 400 mcg QD, 200 mcg QD, and 200 mcg BID was significantly better than treatment with placebo but 200 mcg QD was only better than placebo at Endpoint and no other timepoints. While there was no significant difference between 200 mcg BID and 400 mcg QD, the latter dose was consistently numerically greater.

Puffs of Proventil Used per Day - Change from Baseline by Treatment Group (All Treated Subjects)

	MF DPI 200 mcg QD (A)		MF DPI 400 mcg QD (B)		MF DPI 200 mcg BID (C)		Placebo (D)	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	78	3.70	74	3.84	79	3.66	74	4.50
Change From Baseline								
Week 1	78	-1.25	74	-1.57	79	-1.19	74	-0.89
Week 2	77	-1.42	74	-1.75	77	-1.57	69	-1.02
Week 4	73	-1.66	71	-1.94	76	-1.83	65	-1.18
Week 6	70	-1.70	69	-2.10	76	-1.93	62	-1.23
Week 8	70	-1.61	68	-2.27	74	-1.94	62	-1.06
Week 10	68	-1.64	67	-2.38	72	-2.15	58	-1.31
Week 12	66	-1.81	66	-2.36	70	-2.16	57	-1.21
Endpoint	**78**	**-1.84**	**74**	**-2.22**	**79**	**-1.99**	**74**	**-1.08**

Analysis Results (Change From Baseline)

Time point	Pooled SD	P-value Treatment	P-value Center	Pairwise Comparisons (P Value) A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D
Week 1	1.45	0.05	0.01	0.18	0.81	0.13	0.11	**<0.01**	0.20
Week 2	1.87	0.12	0.01	0.28	0.61	0.20	0.57	**0.02**	0.07
Week 4	2.08	0.17	<0.01	0.43	0.62	0.18	0.76	**0.04**	0.07
Week 6	2.12	0.11	0.01	0.27	0.51	0.21	0.63	**0.02**	0.06
Week 8	2.18	0.01	0.02	0.08	0.38	0.15	0.37	**<0.01**	**0.02**
Week 10	2.16	0.03	<0.01	**0.05**	0.17	0.40	0.52	**<0.01**	**0.03**
Week 12	2.19	0.03	0.04	0.15	0.35	0.14	0.61	**<0.01**	**0.02**
Endpoint	2.24	0.01	0.11	0.30	0.68	**0.04**	0.53	**<0.01**	**0.01**

An analysis was performed (p.99, vol.1-151) by the sponsor examining when the difference between active treatment and placebo from Baseline became statistically evident. Significant differences from placebo were observed for daily Proventil puffs in the 400 mcg QD group at Days 3 through 6, 8, 10-13 and in the MF DPI 200 mcg BID group at Days 3 and 8. Significant differences between change from Baseline in the 200 mcg QD and placebo groups were not observed during the first two weeks of the study except for Day 3.

f) Nocturnal Awakenings with Asthma Symptoms requiring Proventil

Number of Nocturnal Awakenings -Change from Baseline (All Treated Subjects)

	MF DPI 200 mcg QD (A)		MF DPI 400 mcg QD (B)		MF DPI 200 mcg BID (C)		Placebo (D)	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	78	0.35	73	0.38	79	0.29	74	0.48
Change From Baseline								
Week 1	78	-0.17	73	-0.17	78	-0.13	74	-0.14
Week 2	77	-0.19	73	-0.24	77	-0.18	70	-0.17
Week 4	73	-0.23	70	-0.21	76	-0.19	65	-0.13
Week 6	70	-0.24	67	-0.25	75	-0.20	63	-0.18
Week 8	70	-0.25	66	-0.24	74	-0.22	62	-0.23
Week 10	69	-0.22	66	-0.27	72	-0.24	58	-0.21
Week 12	66	-0.26	65	-0.26	70	-0.23	57	-0.15
Endpoint	**78[c]**	**-0.22**	**73**	**-0.25**	**79**	**-0.20**	**74**	**-0.12**

Analysis Results (Change From Baseline)

Time point	Pooled SD	P-value Treatment	P-value Center	Pairwise Comparisons (P Value) A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D
Week 1	0.36	0.86	0.87	0.99	0.48	0.65	0.48	0.65	0.81
Week 2	0.43	0.77	0.84	0.49	0.89	0.75	0.41	0.32	0.85
Week 4	0.48	0.67	0.34	0.78	0.65	0.23	0.87	0.36	0.43
Week 6	0.45	0.75	0.45	0.90	0.53	0.44	0.45	0.37	0.86
Week 8	0.46	0.98	0.49	0.90	0.67	0.81	0.77	0.91	0.87
Week 10	0.47	0.89	0.92	0.55	0.77	0.89	0.76	0.48	0.67

Week 12	0.49	0.58	0.98	0.99	0.72	0.22	0.73	0.22	0.36
Endpoint	0.48	0.43	0.96	0.70	0.77	0.22	0.50	0.11	0.35

As can be noted in the table above, the number of awakenings at Baseline was low. While no treatment appeared to produce a statistically significant decrease compared with placebo, it should be noted that there was typically double the degree of decrease in nocturnal awakenings for any dose of MF DPI than for placebo.

g) Time to Worsening of Asthma

Thirty-seven subjects met one or more criteria for worsening of asthma.

Number of Subjects Who Had Worsening of Asthma and Criteria

Reason for First Worsening	200 mcg QD	400 mcg QD	200 mcg BID	Placebo
Discontinued as protocol required				
Clinical Asthma Exacerbation (CAE)	1	2	1	6
Decrease in FEV_1	2	3	0	9
Decrease in PEFR	3	3	1	3
CAE + Decrease in FEV_1	0	0	1	1
CAE + Decrease in PEFR	1	0	0	0
Total	**7**	**8**	**3**	**19**

While this represents only a tabulation, all MF DPI groups did better than placebo. 200 mcg BID appears to do better than the other two MF DPI groups. Furthermore, MF DPI treatment also appears to significantly delay the time to any worsening of asthma (see p. 94 of Vol. 1-151 for Figure). In this figure also, 200 mcg BID appears to stand apart from the other two MF DPI doses.

A clinical asthma exacerbation was distinct from a "worsening of asthma." 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 inhaled beta-agonists). CAEs were reported more often for placebo subjects than for those treated with MF DPI. CAEs were reported at some time during the study by three subjects in the 200 mcg QD group, two subjects in the 400 mcg QD group, two subjects in the 200 mcg BID group, and seven subjects in the placebo group.

h) Response to Therapy

Physician Assessment of Response to Therapy at Endpoint (All Treated Subjects)

	Number (%)							
	MF DPI 200 mcg QD (AM) (n=77)		MF DPI 400 mcg QD (AM) (n=74)		MF DPI 200 mcg BID (n=79)		Placebo (n=74)	
	n	(%)	n	(%)	n	(%)	n	(%)
Much Improved	16	(20.8)	24	(32.4)	29	(36.7)	6	(8.1)

Improved	32	(41.6)	30	(40.5)	34	(43.0)	27	(36.5)
No change	24	(31.2)	16	(21.6)	14	(17.7)	29	(39.2)
Worse	3	(3.9)	2	(2.7)	1	(1.3)	10	(13.5)
Much Worse	2	(2.6)	2	(2.7)	1	(1.3)	2	(2.7)

It is quite clear that blinded physicians interpreted an improved clinical response in those subjects on MF DPI. An inferential analysis (not shown) was presented by the sponsor which had assigned a score to each of the responses. In this analysis, only 200 mcg BID and 400 mcg QD were significantly better than placebo. In fact, at nearly every time point, 200 mcg BID did significantly better than 200 mcg QD.

i) Peak Inspiratory Flow Rates

Peak inspiratory flow rates (PIFR) were tested with a functional model of the DPI at Center 05 with 16 subjects. The sponsor says that PIFR was used to obtain preliminary data on the ability of subjects to produce inspiratory rates adequate to generate DPI particles of respirable size, [redacted]

[redacted] Based on previous *in vitro* data, it was determined that subjects needed to generate an inspiratory flow rate of approximately 30 L/min or more, with a "rise time" (the time between flow rates of 10 L/min and 30 L/min) of 300 msec or less.

15 of 16 subjects had flow rates higher than 30 L/min (all were >50) and rise times of less than 300 msec (generally 20-68 msec). So it was thought that most subjects achieved flow rates that were adequate for functional drug delivery using the DPI. The subject that did not meet these criteria was one who discontinued the study for treatment failure.

j) Efficacy Summary for C96-186

This study compared three doses of MF DPI with placebo in a blinded fashion over 12 weeks. With the primary efficacy endpoint of change in FEV_1 from Baseline to Endpoint, both 200 mcg BID and 400 mcg QD were significantly and consistently better than placebo while 200 mcg QD was only numerically better. There was no significant difference between the two 400 mcg daily doses. 200 mcg QD appeared to have an effect midway between the 2 400 mcg daily doses and placebo. It should be noted that 71 subjects (90%) completed 12 weeks of 200 mcg BID therapy while 83%, 85% and 72% of subjects completed 12 weeks of 200 mcg QD, 400 mcg QD and placebo, respectively. The data at Endpoint did not appear to appreciably differ from the data seen at earlier timepoints. All three doses and placebo had a much greater effect in subjects with an FEV_1<75% predicted. Only 48 subjects were not in the age 18-64 bracket (and only two >65 years), so no real conclusions should be made about specific responses in age groups. If there was a suggestion of any difference, 400 mcg QD and 200 mcg BID appeared to have a greater response in subjects ages 12-17 years.

No comparative statistical analysis was performed for data between the genders. No persuasive differences in response were noted between the genders. Approximately 15-22% of subjects in the study was Non-Caucasian. It appeared that MF DPI seemed to produce a greater mean % change in FEV_1 in Caucasians. Because the study was not designed to detect a differential response based on race, no real conclusions should be drawn from this data and a hypothesis-driven statistical analysis was not performed.

No appreciable differences in the change in FVC were noted among MF DPI treatment groups although the response was numerically greater than placebo. All three MF DPI groups did better than placebo with the variable, FEF_{25-75}, and, while the two 400 mcg daily doses were numerically greater than 200 mcg QD, the difference was not significant. For AM and PM PEFR, the response in both the 400 mcg QD and 200 mcg BID groups was significantly greater than the response in the 200 mcg QD group ($p<0.01$, both comparisons) and placebo. While 200 mcg bid was never significantly better than 400 mcg, it was numerically greater.

Subject's evaluations of symptoms were evaluated. As for the AM and PM Wheezing and Difficulty Breathing Scores, 200 mcg BID appears to be somewhat more efficacious than 400 mcg QD and both doses outperform placebo statistically. 200 mcg QD is not significantly better than placebo for either variable. MF DPI, while it did not produce a statistical difference in Cough scores, did generally produce numerical improvements compared with placebo.

Based on, treatment with 400 mcg QD, 200 mcg QD, and 200 mcg BID was significantly reduced the number of puffs of Proventil used per day more than placebo but 200 mcg QD was only better than placebo at Endpoint. While there was no significant difference between 200 mcg BID and 400 mcg QD, 400 mcg QD was numerically greater. While MF DPI did not significantly decrease nocturnal awakenings, the degree of decrease for MF DPI doubled any decrease seen with placebo. All doses of MF DPI appear to significantly delay the time to any worsening of asthma compared with placebo. An inferential analysis of the physician's evaluation of response to therapy indicated only 200 mcg BID and 400 mcg QD were significantly better than placebo.

The study C96-186 appears to support the efficacy of 200 mcg BID and 400 mcg QD. While beneficial effects with 200 mcg QD were often identified numerically, the effect of 200 mcg QD was statistically significant compared with placebo only with the variables FEF_{25-75} and # puffs Proventil used (only at Endpoint), and time to worsening of asthma.

7. Safety C96-186

a) Adverse Events

The most common adverse events reported in this study included headache, allergy aggravated, pharyngitis, musculo-skeletal pain, dyspepsia, and dysmenorrhea.

Adverse Events Reported by ≥10% of Subjects in Any Group

	Number (%) of Subjects			
	200 mcg QD (n=79)	400 mcg QD (n=74)	200 mcg BID (n=79)	Placebo (n=74)
Headache	29 (37)	27 (36)	26 (33)	26 (35)
Allergy aggravated	16 (20)	19 (26)	18 (23)	16 (22)
Pharyngitis	7 (9)	7 (9)	10 (13)	6 (8)
Musc.-skeletal pain	3 (4)	2 (3)	8 (10)	4 (5)
Dyspepsia	8 (10)	2 (3)	7 (9)	4 (5)
Dysmenorrhea	6 (13)	3 (9)	6 (14)	2 (6)

Headache and allergy aggravated were equally represented in the treatment groups. Pharyngitis appeared to be more common in the 200 mcg BID group (13%) than in other MF DPI or placebo treatment groups (8-9%). Similarly, musculo-skeletal pain was more common in the

200 mcg BID treatment group (10%) than in other treatment groups (3-5%). Dysmenorrhea was more common in all MF DPI groups (9-14%) than in the placebo group (6%). Dyspepsia was more common in the 200 mcg QD group (10%) and 200 mcg BID (9%) groups than in the 400 mcg QD (3%) or placebo (5%) groups.

General Summary of Notable Treatment-Emergent Adverse Events (All Treated Subjects)

	Number (%) of Subjects			
	200 mcg QD (n=79)	400 mcg QD (n=74)	200 mcg BID (n=79)	Placebo (n=74)
Any Adverse Event	**58 (73)**	**54 (73)**	**59 (75)**	**52 (70)**
asthenia	0 (0)	3 (4)	1 (1)	0 (0)
dysphonia	0 (0)	4 (5)	1 (1)	0 (0)
anorexia	0 (0)	0 (0)	2 (3)	0 (0)
nausea	1 (1)	3 (4)	1 (1)	0 (0)
candidiasis, oral	1 (1)	4 (5)	2 (3)	1 (1)
infection	2 (3)	4 (5)	2 (3)	0 (0)
asthma, aggravated	2 (3)	1 (1)	0 (0)	2 (3)
nasal congestion	6 (8)	2 (3)	7 (9)	0 (0)
taste perversion	0 (0)	1 (1)	1 (1)	0 (0)

Although the sponsor made a much longer list of adverse events available, these adverse events were selected by this reviewer because of their particular expression with MF DPI compared with placebo. Asthenia and dysphonia appears to have a higher incidence with 400 mcg QD than any other dose. Why asthenia is more common is not apparent. Nausea, infection, and nasal congestion are suspicious because they are listed only for MF DPI and no cases were seen for placebo. Asthma aggravated is left on this list only to point out that its incidence appears to be higher for 200 mcg QD and placebo. Oral candidiasis still appears to be more common with MF DPI despite the required rinsing after study drug administration. This incidence of candidiasis will not reflect the natural incidence after inhaled corticosteroids without the protocol rinsing although one should not assume adherence to rinsing was 100%. Taste perversion was uncommon but interestingly was seen only with the 400 mcg total daily dosing thus suggesting a drug implication and potential dose response.

No subject in an active treatment group reported an AE that coded to the liver and biliary system. Increased hepatic enzymes were reported for two subjects in the placebo group. (Subjects 206 and 121).

The reporting of AE's by gender was reviewed (pp.566-580, Vol. 1-152). Pharyngitis was more common in females with 18% (200 BID), 9%(200 QD), 15% (400 QD), 10% (Placebo) versus 6% (200 BID), 9%(200 QD) 5% (400 QD) 7% (Placebo) for males. Reports of abdominal pain also appeared to be more common with females but because of a lack of a dose response seen with this AE it is unlikely that it is related to drug. The numbers of Non-Caucasians or subjects outside of age range 18-64 years did not allow for a useful analysis of a differential in the expression of AE's with treatment.

b) Severe/Life-Threatening Adverse Events

Thirty subjects reported severe or life-threatening (severe, 29 subjects; life-threatening, 1 subject) adverse events. The most common event in this category was headache, reported by nine subjects.

Incidence of Subjects Reporting Severe/Life-threatening Adverse Events

	Number (%) of Subjects			
	MF DPI 200 mcg QD (n=79)	MF DPI 400 mcg QD (n=74)	MF DPI 200 mcg BID (n=79)	Placebo (n=74)
Any Severe/Life-threatening Adverse Event	**8 (10)**	**13 (18)**	**6 (8)**	**3 (4)**
Allergy, aggravated	0 (0)	3 (4)	1 (1)	0 (0)
Asthenia	0 (0)	1 (1)	0 (0)	0 (0)
Back pain	2 (3)	0 (0)	0 (0)	0 (0)
Fever	0 (0)	1 (1)	0 (0)	0 (0)
Headache	3 (4)	3 (4)	2 (3)	1 (1)
Influenza-like symptoms	1 (1)	0 (0)	0 (0)	0 (0)
Post-procedure pain	0 (0)	0 (0)	1 (1)	0 (0)
Procedure (no adverse event)	0 (0)	0 (0)	1 (1)	0 (0)
Gastroesophageal reflux	1 (1)	0 (0)	0 (0)	0 (0)
Arthritis	0 (0)	1 (1)	0 (0)	0 (0)
Fracture, bone	0 (0)	0 (0)	1 (1)	0 (0)
Musculo-skeletal pain	0 (0)	0 (0)	2 (3)	1 (1)
Dysmenorrhea	0 (0)	0 (0)	1 (2)	0 (0)
Oral candidiasis	0 (0)	1 (1)	0 (0)	0 (0)
Asthma aggravated	2 (3)	1 (1)	0 (0)	0 (0)
Dyspnea	0 (0)	1 (1)	0 (0)	0 (0)
Sinusitis	0 (0)	0 (0)	0 (0)	2 (3)
Urticaria	0 (0)	0 (0)	1 (1)	0 (0)
Kidney infection	0 (0)	1 (1)	0 (0)	0 (0)
Phlebitis	0 (0)	1 (1)	0 (0)	0 (0)

Among these severe AE's, it is difficult to discern any dose response except for perhaps allergy aggravated and headache. The incidence of these AE's was not found to be higher for MF DPI when total AE's were evaluated so it is not possible to attribute a relationship to active treatment. Only one patient was reported to have a life threatening adverse event (Subject-166, 200 mcg QD, asthma aggravated). This event also met the criteria for a serious adverse event.

c) Serious Adverse Events

Serious adverse events were reported in six subjects, two prior to randomization and four after randomization. No deaths occurred during the study.

Subject 166 was a 17 year old female at Site 15 with a hospitalization for status asthmaticus. She was randomized 5/31/97 to 200 mcg QD and presented to the ER on [redacted] and was discharged the following day. She had not admitted to two previous intubations at Screening and was discontinued from the study on 7/1/97.

Subject 220 at Site 23 was a 25 year old female on 400 mcg QD who had pelvic pain and pelvic inflammatory disease. The event was not considered to be related to study medication.

Subject 331 at Site 21 was a 48 year old female on 200 mcg BID who was hospitalized for a painful uterine fibroid and bleeding. The event was not considered to be related to study medication.

The fourth patient with a serious AE after randomization was on placebo.

These serious adverse events are not thought to be drug related by this reviewer although it must be noted that Subject 166 still had status asthmaticus while on 200 mcg QD.

d) Discontinuation Because of Adverse Events

Center/Subject	Sex/ Age/ Race	Day of Onset	Adverse Event(s)	Severity	Relationship
MF DPI 200 mcg QD					
C96-186-06-175	F/32/C	29	abdominal pain, nausea	moderate	possible
C96-186-11-328	F/27C	2	vaginitis	moderate	possible
C96-186-08-027	F/23/C	10	asthma aggravated	severe	possible
C96-186-20-083	F/29/C	30	rash	moderate	unrelated
C96-186-15-166	F/17/NC	29	asthma aggravated	life threatening	unrelated
MF DPI 400 mcg QD					
C96-186-03-105	M/29/NC	28	asthma aggravated	severe	unrelated
			upper respiratory infection	moderate	unrelated
C96-186-10-143	F/36/C	11	dysphonia	moderate	probable
C96-186-14-345	F/24/NC	8	dyspnea	severe	probable
MF DPI 200 mcg BID					
C96-186-10-146	M/44/C	43	dysphonia	moderate	related
C96-186-02-298	F/27/C	74	uterine bleeding	moderate	possible
Placebo					
C96-186-04-236	F/70/C	45	bronchitis	moderate	possible
C96-186-13-066	F/58/C	79	bronchitis	moderate	unrelated
C96-186-14-350	M/44/C	7	lab test abnormality (hyperglycemia, glucosuria)	mild	unrelated
C96-186-20-088	F/21/C	3	asthma aggravated	moderate	unrelated
C96-186-20-091	M/21/C	13	allergy aggravated, URI	moderate	unrelated
C96-186-22-203	M/30/C	5	asthma aggravated	moderate	unrelated
C96-186-22-206	M/20/C	not recorded	hepatic enzymes increased	moderate	unrelated

Dysphonia appears to be a drug-attributable reason for discontinuation. Asthma aggravated is seen twice with 200 mcg QD and placebo. The asthma aggravated event for Subject 105 in the 400 mcg QD group is also listed with upper respiratory infection that may have been the cause. Subject 345 is a 25 year old female at Site 14 with dyspnea and respiratory distress listed as the cause of discontinuation from the 400 mcg group.

e) Laboratory Values

The listing of abnormal laboratory values (Section 14.3.4.1 – Vol. 1-152) were reviewed. Higher than normal % eosinophils in the blood (>6.8%) were often seen, both at Screening and at the Endpoint. Such elevations are not uncommon in asthmatics. Another frequent abnormality was alterations in urine specific gravity, both high and low, and is unlikely attributable to drug treatment.

It is also highly unlikely that urine RBC's identified could be attributable to drug. This abnormality was seen at Screening and/or after drug treatment in some subjects. Subject 116 (200 BID) had 3+ RBC (with microscopic confirmation)in the urinalysis, Subject 346 (200 BID) had 3+ RBC, Subject 036 (200 BID) had 2+ RBC, Subject 178 (200 QD) had 2+ RBC, Subject 181 (200 QD) had 2+ RBC, Subject 036 (200 QD) had 3+ RBC, Subject 207 (400 QD) had 3+ RBC, Subject 121 (Placebo) had 3+ RBC at Endpoint.

Occasional abnormalities were identified in the transaminases. Cases in which abnormalities were seen at Screening and did not rise further during drug treatment were seen and will not be discussed. The following elevations were identified at Endpoint:

- #235 200 BID ALT 46 to 64 (AST 42 at Endpoint)
- #293 200 BID ALT 48 (nl 6-43), AST 39 (nl 11-36) at Endpoint
- #036 200 BID AST 80 at Endpoint (29 at Scr – Vol.160. p.3172)
- #141 200 QD ALT 65 at Endpoint (27 at Scr – Vol.160. p. 3254)
- #049 200 QD ALT 39 (nl 6-34) at Endpoint 26 at Scr – Vol.160. p. 3278)
- #251 200 QD ALT 75, AST 38 at Endpoint (26, 19 at Scr – p.3282)
- #234 400 QD ALT 47 to 77, AST 40 to 50
- #158 Placebo ALT 54 at Endpoint
- #121 Placebo ALT 147 to 267, AST 128 to 291
- #339 Placebo ALT 48 at Endpoint

Other smaller elevations (generally < 5 U/L above upper limit of normal) were not mentioned here. It is not possible to discern any pattern based on drug treatment or dose response. It is not likely that these elevations are due to MF DPI.

Other lab abnormalities seen include:

- #173 200 BID Cholesterol 328 at Endpoint (271 at Scr.–Vol.160. p. 3162)
- #181 200 QD Glucose 152 at Endpoint *(A discrepancy exists in the reporting of the data for this individual from Site 06in the original NDA Submission. In Vol. 153, p.716, the glucose at Visit 8F is listed as 152 but in Vol. 160, p. 3243, the value is listed for Visit 8F as 89. An explanation for this discrepancy provided by the sponsor. The normal repeated value was provided in Volume 160, Section 16.2.8.2 but the original abnormal value was provided in Volume 153, Section 14.3.4.1)*
- # 091 Placebo Glucose 152 at Endpoint

For the overall results of the laboratory studies, the medians, minimums, maximums, change, and % change between Screening and Endpoint were tabulated by the sponsor. The medians were highlighted in this review and not important changes in the median of any laboratory value for any treatment was distinguished. The one possible exception was a decrease in the % eosinophils: there was a decrease in the median of 20% for 200 BID, 12.5% for 200 QD, 21.4% for 400 QD and 7% for placebo. The results for gender were also reviewed and no important differences were noted except for possibly % eosinophils.

Two subjects in the 400 mcg QD group (Subjects 220 and 198) had positive pregnancy tests at their final visit. The sponsor maintains that both subjects experienced normal pregnancies and delivered healthy babies at term. Subject 198 was said to have been using a protocol-acceptable form of birth control at the time of Screening.

The most common adverse events in this study were headache, pharyngitis, viral infection, allergy aggravated and nasal congestion. At least a 10% incidence in any treatment group was noted for sinusitis, back pain, oral candidiasis, dysmenorrhea, and pain. Headache and allergy aggravated were similar in all treatment groups including placebo. Pharyngitis was most common with 200 QD PM, viral infection with 200 BID, and nasal congestion with 200 QD AM and PM. Sinusitis was seen only in MF DPI treatment groups but no dose response was noted. Back pain, oral candidiasis and dysmenorrhea were reported by ≥ 10% of the subjects in the 200 BID group only. It was difficult to clearly implicate a type of adverse event with treatment in this study. Dyspepsia, dysmennorhea, coughing, influenza-like symptoms, dysphonia, and epistaxis appeared to be more common in the MF DPI but a dose response was difficult to implicate.

Under the heading of severe adverse events, headache and dysmennorhea were more common in C96-196 with treatment with MF DPI. Although other severe adverse events occurred only in MF DPI treatment groups, these cases were seemingly sporadic with at most 2 cases in any MF DPI treatment group. No deaths were reported in this study. Of the serious adverse events, one was particularly notable with elevations of transaminases and LDH at the final study visit; the total bilirubin also rose from 0.2 to 0.5. An explanation for this rise in this subject in the 200 QD PM treatment group on was not identified. The subject experienced a flu-like illness with headache but a hepatitis panel was negative and the subject denied any history of drug or alcohol abuse. This case is worrisome. There were other incidences of elevation in transaminases during study treatment which were identified in this study and further details are given in the laboratory section of this trial's review. It must be noted that transaminase elevation was also identified in the placebo group.

Cortrosyn testing was performed in 127 subjects in the study. The sponsor states that the results of this cortrosyn testing "indicate that none of the MF DPI treatments had any effect on the HPA axis." Subjects had already been on 2 weeks of MF DPI 200 mcg BID at Baseline so a comparison at Endpoint cannot tell us the true steroid effect of MF DPI. A difference between Screening and Baseline is suggested by the fact that there were somewhat more individuals that did not meet protocol-specified criteria for cortrosyn testing at Baseline compared with Screening. While it is true that no real differences were identified among the treatment groups after study drug treatment after adjusting for differences at Baseline (the p value for the difference between 400 mcg QAM and placebo was reduced from <0.01 and 0.01 to 0.05 and 0.05 for post-cortrosyn and difference between post- and pre-cortrosyn, respectively) the testing was performed with the 250 μg dose of ACTH which is not sensitive enough to make the statement that there was no effect on the HPA axis.

Vital sign testing was mentioned as part of the protocol for every visit yet, for unclear reasons, data was submitted on only approximately 6 patients for every treatment group. It was also mentioned in the protocol that weight would be measured at Visit 9, as at Screening, but no weight data was made readily available by the sponsor.

G. C96-137 (Update Vol. 76-120)

"Placebo-Controlled Efficacy And Safety Study With Long-Term Safety Evaluation Of Mometasone Furoate Dry Powder In Reducing Oral Steroid Requirements In Subjects With Severe Asthma"

f) Vital Signs

Vital signs were performed at every visit. The means, minimums and maximums were presented by visit. The only value that appeared to stand out was the maximum value for heart rate was 140 at Week 4 for the 400 mcg QD dose whereas it whereas it was 96 at Baseline. There was no change in the mean for this variable. There was no important change in the means based on gender, age grouping, or race.

g) EKG Results

During the study, EKGs were performed at only Screening Visit 1 and only if one was not done within the last 30 days. Vol. 1-163 contained brief reports of these screening EKGs but because they did reflect any drug treatment effect they were not closely reviewed. Any abnormality listed was designated by the investigator as "not clinically significant."

h) Safety Conclusions for C96-186

Overall, this study did not elucidate any unexpected safety findings. The most common adverse events reported were headache, allergy aggravated, pharyngitis, musculo-skeletal pain, dyspepsia, and dysmenorrhea. Dysmennorhea, dyspepsia and musculo-skeletal pain appeared to be more common in the MF DPI treatment groups. Other adverse events were also noted but were less common. Asthenia and dysphonia appeared to have a higher incidence with 400 mcg QD than any other dose. Nausea, infection, and nasal congestion are were listed only for MF DPI and no cases were seen for placebo. Asthma aggravated was more common in the placebo group. Oral candidiasis appeared to be more common with MF DPI despite the required rinsing after study drug administration. Taste perversion was uncommon but interestingly was seen only with the 400 mcg total daily dosing thus suggesting a drug implication and potential dose response.

Adverse events as a cause for discontinuation of the study were examined. Dysphonia appears to be a drug-attributable reason for discontinuation. Asthma aggravated is seen twice with 200 mcg QD and placebo.

Among these AE's listed as severe, allergy aggravated and headache appeared to have a somewhat of a dose response. Because a higher incidence of these symptoms was not noted when all level of AE's were considered, no drug causality is implicated. No serious adverse events were thought to be drug related by this reviewer but it must be noted that one subject still had status asthmaticus while on 200 mcg QD.

Three subjects in the 200 BID, 200 QD and placebo treatment groups and one subject in the 400 mcg QD treatment group were noted to have minor elevations in a transaminase. One of the placebo subjects is more accurately stated to have had a large increase in the ALT and AST from 147 to 267 and from 128 to 291, respectively.

F. C96-196 (Vol. 168-184)

"Placebo-controlled efficacy and safety study of Mometasone Furoate (SCH 32088) dry powder, once daily vs. twice daily, in asthmatic subjects previously maintained on inhaled corticosteroids."

1. Investigators and Investigational Centers

There were 16 centers involved – all within the United States.

2. Objectives/Rationale

The objectives of this randomized, multicenter, double-blind, parallel group study was to compare the efficacy and safety of MF DPI 200 mcg QD AM, 200 mcg QD PM, 400 mcg QD AM, and 200 mcg BID, to placebo after a 2-week open-label period on standard dose (MF DPI 200 mcg BID).

a) Primary

The primary efficacy variable was change in FEV_1 from Baseline to Endpoint (last available observation in the 3-month placebo-controlled, double-blind phase).

b) Secondary

Secondary efficacy variables included FVC, $FEF_{25\%-75\%}$, AM and PM PEFR, asthma symptom scores, Proventil use, nocturnal awakenings due to asthma which required the use of Proventil, physician assessment of response to therapy, and time to worsening of asthma.

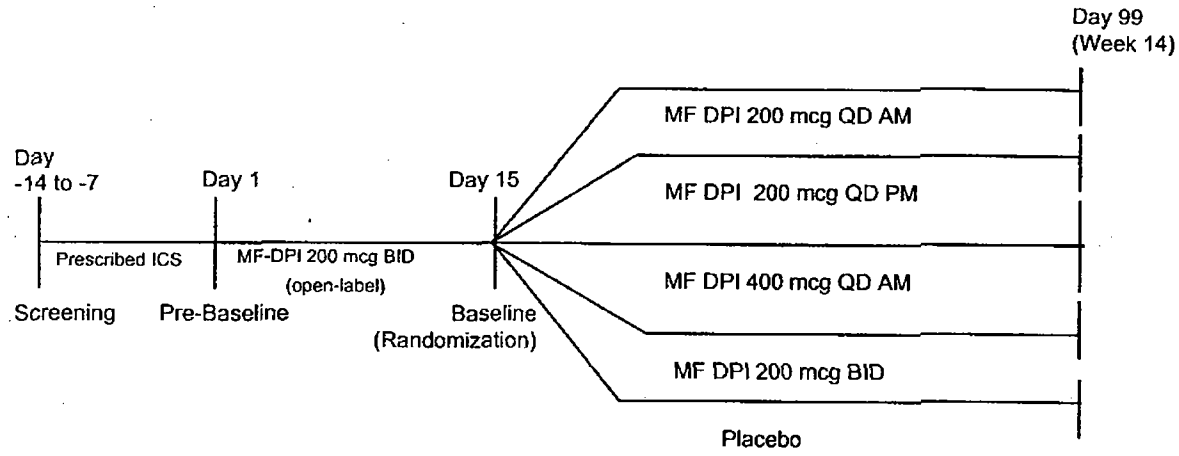
c) Safety

Safety variables included adverse events, physical examination including oropharyngeal examination, vital signs, laboratory tests and chest x-rays.

3. Study Design

This was a Phase III, multicenter, randomized, double-blind, parallel group study of MF DPI in the treatment of subjects previously maintained on inhaled corticosteroids. After an initial run-in Screening period of 1-2 weeks, during which time subjects continued on their normal inhaled steroid, subjects were then treated with study medication for 14 weeks. The 14-week period was comprised of an initial 2-week open-label period during which all subjects transferred to a standard 200 mcg BID dose of MF DPI, followed by double-blind randomization to one of 5 treatment arms for an additional 12 weeks of therapy. Subjects were randomized at the Baseline Visit (Visit 3) in a 1:1:1:1:1 ratio according to a computer-generated schedule.

4. Summary of Study Protocol



Follow-up visits on Days 19, 22, 29, 43, 71 and 99

a) Study Population

Adolescent and adult subjects with a diagnosis of asthma who had been using daily inhaled corticosteroids for at least 30 days prior to entering the study were selected for the study. The study was designed to enroll approximately 20 (range 15-30) subjects at each of approximately 16 (range 16-20) study centers for a total of approximately 260 enrolled subjects, to ensure 250 subjects who would meet the criteria for evaluation of the primary Endpoint.

(1) Inclusion Criteria

The criteria were similar to those of C96-136 and 186 with the following exceptions:

- The subject's FEV_1 must have been greater than or equal to 60% (was 55% in C96-186) and less than or equal to 90% (was 85%in C96-186) of predicted at both the Screening (Visit 1) and Pre-Baseline (Visit 2) visits, when all restricted medications have been withheld for the specified intervals. (later broadened to 55% and 95%, respectively, before the database was locked.)
- Subjects must have been using daily 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 (no change in dose) of inhaled corticosteroid within the limits outlined below:

Drug	Minimum Dose	Maximum Dose	mcg/day
Flunisolide (Aerobid)	4 puffs/day	8 puffs/day	1000-2000
Triamcinolone acetonide (Azmacort)	6 puffs/day	16 puffs/day	600-1600
Beclomethasone dipropionate (Vanceril or Vanceril DS, or Beclovent)	252 mcg/day 88 mcg BID	840 mcg/day 220 mcg BID	252-840 176-440
Fluticasone propionate (Flovent)			

- At seven preselected sites, the subject must have had an unstimulated Screening (8 AM ± 1 hour) plasma cortisol level of ≥5 mcg/dl, and a stimulated cortisol value of ≥18 mcg/dl, 30 minutes after Cortrosyn stimulation.

(2) Exclusion Criteria

The criteria were similar to those of C96-136 and 186 with the following exceptions related to Cortrosyn testing:

- Subjects who were allergic to Cortrosyn (Cortrosyn sites only), corticosteroids or beta agonists, or who were allergic to more than two different classes of medications.

- Subjects whose normal sleep/wake cycle was inverted (e.g., night shift workers); applicable only to sites conducting Cortrosyn testing.

(3) Removal of Subjects from Therapy

Same as C96-186.

b) Treatments Administered.

Initially, all subjects were to continue to take their prescribed inhaled corticosteroid for a one-to-two week period between the Screening and Pre-Baseline visits. Any use of a Proventil inhaler (which was not to be used regularly) was to be withheld for 6 hours before the Pre-Baseline and Baseline visits or call the office to reschedule the visit. Nebulized beta-agonists were permitted during the study. One nebulization treatment was regarded as equivalent to six puffs of Proventil MDI. All other bronchodilators (except for theophylline, which could be continued on a constant dose only to be changed when a dose adjustment was necessary for safety purposes) were to be discontinued during the first run-in period and for the duration of the study. All other asthma medications including cromolyn, nedocromil, anticholinergics, oral or inhaled bronchodilators, zafirlukast, zileuton, and oral, intravenous and intramuscular corticosteroids were prohibited during the run-in periods and for the duration of the study.

Subjects were advised to rinse their mouth with water or a suitable mouthwash after study drug administration.

Following the initial one-to-two week run-in period, all eligible subjects were to return for the Pre-Baseline visit (Visit 2), at which time they discontinued their prescribed inhaled corticosteroid and were transferred to an open-label, 200 mcg BID dose of MF DPI for two weeks of treatment. Subjects received one open-label MF DPI device (100 mcg/inhalation) to be used each morning and evening for two weeks.

At the Baseline visit (Visit 3), subjects were assigned to follow one of five double-blind treatments for 12 weeks:

	Regimen	AM	PM	Total mcg/day
Group 1	200 mcg BID	100 mcg x 2	100 mcg x 2	MF 400 mcg

Group 2	400 mcg QD AM	200 mcg x 2	Placebo x 2	MF 400 mcg
Group 3	200 mcg QD AM	100 mcg x 2	Placebo x 2	MF 200 mcg
Group 4	200 mcg QD PM	Placebo x 2	100 mcg x 2	MF 200 mcg
Group 5	Placebo	Placebo x 2	Placebo x 2	0

The sponsor notes that the two dosage strengths of MF DPI (100 mcg and 200 mcg/inhalation) were indistinguishable from each other and from the placebo DPI device. Each subject received two sets of DPI inhalers. Each set contained one inhaler designated "AM" and one inhaler designated "PM". Subjects were instructed to use the first set of inhalers for 7 weeks, and the second set for the remaining period of the study.

(1)Concomitant/Restricted Medications

The list of concomitant and restricted medications were similar to that of Study C96-186 except that theophylline was allowed in this study and the washout times were generally longer for many medications in C96-186. The following differences were noted:

Prohibited Medication	Washout Time Prior to Screening
Beta-adrenergic bronchodilators, syrups and tablets	24 hours (2 weeks)
Beta-adrenergic bronchodilators, sustained-release tablets	48 hours (2 weeks)
Salmeterol	1 week (2 weeks)
Ipratropium bromide aerosol/nebulized	12 hours (2 weeks)
Any bursts of oral or intravenous corticosteroids	1 month (3 months)
Corticosteroids – intra-articular	1 month (3 months)

c) Assessments/Study Procedures

Schedule of Study Procedures and Evaluations

Treatment Days	Screening Visit 1	Treatment Period							
		Pre-Baseline Visit 2	Baseline Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Day-14 to-7	Day 1	Day 15 (±2 days)	Day 19 (±1 day)	Day 22 (±2 days)	Day 29 (±2 days)	Day 43 (±2 days)	Day 71 (±3 days)	Day 99 (±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	X
Physical Examination, Weight	X								X
Height	X								
Vital Signs (temperature, blood pressure, pulse, respiratory rate)	X	X	X	X	X	X	X	X	X
Oropharyngeal exam	X	X	X	X	X	X	X	X	X
Pulmonary auscultation	X	X	X	X	X	X	X	X	X
Pulmonary function tests	X	X	X	X	X	X	X	X	X
Reversibility test	X								
Hematology, Blood Chemistry, Urinalysis	X								X
Cortrosyn Test (at 7 selected sites)	X		X						X
Pregnancy Test	X								X
Electrocardiogram	X								
Chest X-ray	X								
Dispense Diary	X	X	X				X	X	
Retrieve/Review Diary		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
Dispense Study Medication		X	X						
Response to Therapy Assessment				X	X	X	X	X	X
Adverse Events Evaluation		X	X	X	X	X	X	X	X
Compliance Check		X	X	X	X	X	X	X	X
Collect Study Medication			X						X

Further specific details on the Visit Procedures (not previously stated in reviews of C96-136 and 186) include:

- Three measurements of spirometry were done at each visit and the effort with the highest FEV_1 was used as the best effort.

- Cortrosyn Testing: Visits 1, 3, and Visit 9 (sites 01, 02, 04, 08, 11, 12 and 13)

At selected sites, an 8 AM (±1 hour) blood sample for plasma cortisol was drawn. The plasma cortisol level must have been ≥5 mcg/dl for the subject to qualify at the Screening visit for continued Cortrosyn testing.

After the 8 AM (±1 hour) baseline sample was drawn, an intravenous injection of Cortrosyn was administered at a dose of 0.25 mg. Another blood sample was taken 30 minutes after the injection for the measurement of plasma cortisol. At the Screening visit, the stimulated value must have been ≥18 mcg/dl for the subject to qualify as a Cortrosyn subject. If the results of Cortrosyn testing were abnormal, the investigator could repeat the test as medically indicated. Cortrosyn testing was to be repeated at visits 3 (Baseline visit) and 9 for subjects successfully screened at Visit 1.

- Safety Evaluations – A medical history, EKG, and Chest X-ray were taken only at Screening. Physical exams and laboratory procedures were done at Screening and Visit 9. Oropharyngeal exam, vital signs, medication review was done each visit.

d) Statistical and Analytic Plans

The primary objective of the study was to evaluate the efficacy and safety of the four different dose regimens of MF DPI compared with placebo. In order to control the overall Type I error, the primary comparison for demonstrating the activity of MF DPI was to be made between MF DPI 200 mcg BID and placebo at the 0.05 (two-sided) level of significance. If this treatment comparison was significant, then each of the remaining three MF DPI regimens were to be compared to placebo. Finally, all pairwise comparisons among the four MF DPI regimens were to be provided in order to estimate their relative effectiveness. All treatment comparisons were to be made at the 0.05 (two-sided) level of significance without adjustment for multiple comparisons.

(1) Subject Data Sets

Intent-to-Treat Data Set: All randomized subjects. All summaries of safety data and efficacy analyses were to be based on this data set.

Efficacy Data Set: This data set was defined as randomized subjects who met key eligibility and evaluability criteria. Efficacy analyses of this data set were for confirmatory purposes.

(2) Efficacy Analyses

Comparability of the treatment groups at Baseline was to be assessed by comparing the five treatment groups with respect to demographic (sex, age, race, and weight) and disease characteristics (duration of disease condition, Baseline FEV_1 and PEFR).

The primary efficacy variable was the change from Baseline in FEV_1 and the primary time point was the Endpoint visit. The primary objective of the study was to evaluate the

efficacy of the four doses of MF DPI compared to placebo. The comparison of MF DPI 200 mcg BID and placebo was identified in the protocol as the primary comparison.

The primary efficacy variable at Endpoint was to be analyzed for all randomized subjects using a two-way analysis of variance (ANOVA) which extracted sources of variation due to treatment and center and treatment-by-center interaction. The primary efficacy analysis for demonstrating the activity of MF DPI was to be based on pairwise comparisons of the least squares means of the MF DPI doses and placebo using a 5% significance level. Since all pairwise comparisons addressed independent questions, and the comparison between 200 mcg BID and placebo was identified as the primary efficacy analysis, if the test for no difference between 200 mcg BID and placebo was significant, then each comparison was to be performed at the 0.05 (two-sided) level of significance, with no adjustment for multiple comparisons.

In addition to the analysis at Endpoint, all ten pairwise comparisons between the five treatment groups were to be made with respect to the change from Baseline in FEV_1 for each scheduled visit, using the same two-way ANOVA.

All other continuous efficacy variables (FVC, $FEF_{25\%-75\%}$ and the physician's evaluations of response to therapy at the scheduled visits, as well as subject evaluations recorded on the diary (averaged over 7-day intervals) -- PEFR, asthma symptoms, nocturnal awakenings, and the number of Proventil inhalations) were to be analyzed at each time point using the same two-way ANOVA. For time to discontinuation because of asthma worsening, Kaplan-Meier survival time estimates were to be analyzed using the log-rank test.

The following plasma cortisol values were to be by the same two-way ANOVA for the Screening, Baseline and Week-12 visits: Pre-Cortrosyn Value, Post-Cortrosyn Value, difference between Post- and Pre-Cortrosyn values (Post-Pre), and change from Baseline to Week 12 in the Difference between Post and Pre values (Week 12 Difference - Baseline Difference).

(3) Sample Size

The study was designed to enroll 250 subjects or 50 subjects per treatment group. The sample size was chosen to detect (with 90% power and 5% significance level) a clinically meaningful pairwise difference in the FEV_1 mean change from Baseline between an active treatment group and placebo. With 50 subjects per treatment group, assuming a pooled standard deviation of 0.45 liters for FEV_1 change from Baseline (based on the standard deviation from Study No. C94-127), mean treatment differences of approximately 0.29 liters (approximately 12% of Baseline) or more would be detectable with power greater than 90%.

(4) Changes in Study Conduct or Planned Analyses

- FEV_1 criteria – eligibility was again broadened from 60-90% to 55-85% predicted.
- Reversibility testing was demonstrated with an increase in FEV_1 of ≥10.5% when the absolute change was ≥200 ml, or an increase in FEV_1 of >12% when the absolute change was ≥180 ml (rather than 12% for all as mentioned in the protocol.)

- The definition for the ITT data set was changed slightly (from all randomized subjects to all randomized subjects who received study medication and had at least one post-treatment evaluation), and specific criteria for the efficacy data set were developed.

- The analysis model was being modified to a reduced, main-effects, two-way ANOVA for the primary efficacy analysis rather than a two-way ANOVA extracting sources of variation due to treatment, center, and treatment-by-center interaction. The analysis model was changed, according to the sponsor, because of low enrollment at many centers. A full two-way ANOVA model including the interaction term was still performed in order to do a preliminary assessment of consistency of results per the protocol. Centers in which ten or fewer subjects were enrolled, however, were combined to form one large center in the analysis, which included the treatment-by-center interaction term in the ANOVA model.

- The planned analysis of "time to discontinuation due to asthma worsening" was changed to an analysis of "time to asthma worsening", which is the first treatment day on which a subject met any criterion for worsening. These criteria for asthma worsening were the same as those for the other trials, for example C96-136.

5. Results

There were 307 subjects enrolled at 16 study centers. Of the 307 subjects enrolled in the study, 21 (7%) discontinued the study during the 2 week run-in period of 200 mcg BID prior to randomization; thus, a total of 286 subjects were randomized to double-blind treatment. The major reasons for discontinuing the study prior to randomization included treatment failure (5 subjects, 2%), lack of protocol eligibility (5 subjects, 2%) and non-compliance with the protocol (4 subjects, 1%). The numbers of subjects randomized and treated in the five groups: 58 in the 200 mcg QD AM treatment group; 54 in the 200 mcg QD PM treatment group, 58 in the 400 mcg QD AM treatment group, 58 in the 200 mcg BID treatment group; and 58 in the placebo group.

A total of 67 of the 286 subjects who were randomized to double-blind treatment (23%) discontinued from the 3-month phase of the study prior to scheduled completion. Overall, discontinuations were less common in the 200 mcg QD AM group (16 subjects, 28%), the 200 mcg QD PM group (7 subjects, 13%), the 400 mcg QD AM group (13 subjects, 22%), and the 200 mcg BID (7 subjects, 12%) than in the placebo group (24 subjects, 41%). The incidence of discontinuation due to treatment failure was notably higher in the placebo group (33%) than in the MF DPI groups [17%, 4%, 17%, and 0, respectively in the 200 mcg QD AM, the 200 mcg QD PM, the 400 mcg QD AM, and the 200 mcg BID treatment groups].

Number (%) of Subjects Who Completed the Open-label Phase and the 3-month Phase of the Study and Number (%) Who Discontinued each Phase and Reasons for Discontinuance

	Open Label	Double-blind Treatment (3-month Phase)					
	MF DPI 200 mcg BID (n=307)	MF DPI 200 mcg QD AM (n=58)	MF DPI 200 mcg QD PM (n=54)	MF DPI 400 mcg QD AM (n=58)	MF DPI 200 mcg BID (n=58)	Placebo (n=58)	Total (n=286)
Number (%) Completed	286 (93)	42(72)	47(87)	45(78)	51 (88)	34(59)	219(77)

Reason for Discontinuation							
Adverse Event	0	2(3)	1(2)	0	1(2)	1(2)	5(2)
Treatment Failure	5(2)	10(17)	2(4)	10(17)	0	19(33)	41(14)
Lost to follow-up	2(1)	0	2(4)	0	1(2)	2(3)	5(2)
Did Not Continue for Reasons Unrelated to Treatment	3(1)	3(5)	2(4)	3(5)	4(7)	1(2)	13(5)
Non-Compliance With Protocol	4(1)	1(2)	0	0	1(2)	1(2)	3(2)
Did Not Meet Entry Criteria	5(2)	0	0	0	0	0	0
Administrative	2(1)	0	0	0	0	0	0
TOTAL NUMBER (%) DISCONTINUING	21(7)	16(28)	7(13)	13(22)	7(12)	24(41)	67(23)

There is a marked difference in the % of completers between the placebo and treatment groups. Treatment failure appears to account for most of this difference.

There were 16 subjects who met criteria for worsening of asthma but did not discontinue as per protocol. There was 2-4 per treatment group including placebo. In addition, of the 286 subjects who were randomized to double-blind treatment, 12 subjects (one each in the 200 mcg QD AM and PM groups, three each in the 400 mcg QD AM and 200 mcg BID groups, and four in the placebo group) had one or more major protocol deviations and were, therefore, excluded from the Efficacy Evaluable data set. These deviations are not worth mentioning for review purposes.

Distribution of Subjects by Analysis Subset and Treatment Group

	Number of Subjects						
	MF DPI 200 mcg BID Open Label Only	MF DPI 200mcg QD AM	MF DPI 200 mcg QD PM	MF DPI 400 mcg QD AM	MF DPI 200 mcg BID	Placebo	Total
All Enrolled Subjects[a]	21	58	54	58	58	58	307
All Treated Subjects[b]	0	58	54	58	58	58	286
Efficacy Evaluable Subset	NA[c]	57	53	55	55	54	274
Excluded From Efficacy Evaluable	NA[c]	1	1	3	3	4	12

a: All 307 subjects received at least one dose of open-label study medication.

b: All 286 subjects were randomized to double-blind treatment and received at least one dose of double-blind study medication.

c: Not applicable. These subjects received open-label study medication only and were discontinued prior to randomization to double-blind study medication. These subjects were not evaluated for efficacy.

Summary of Baseline Characteristics

	MF DPI 200 mcg QD (AM) (n=58)	MF DPI 200 mcg QD (PM) (n=54)	MF DPI 400 mcg QD (AM) (n=58)	MF DPI 200 mcg BID (n=58)	Placebo (n=58)
Age (years)					
Mean	40	38	36	42	41
Min-Max	13-74	13-71	13-76	13-77	20-76
12-17 years	6	4	10	4	0
18-64 years	49	48	47	52	56
≥ 65 years	3	2	1	2	2
Sex					
Female	36	34	30	32	40
Male	22	20	28	26	18
Race					
Asian	0	0	1	2	0
Black	10	4	4	2	2
Caucasian	44	45	46	48	49
Hispanic	4	5	7	6	6
Other	0	0	0	0	1
Weight (lb.)					
Mean	178	181	168	178	172
Min-Max	105-293	88-350	91-259	115-310	95-240
Duration/Asthma Condition (years)					
Mean	18	20	17	21	20
Min-Max	1-61	1-53	1-62	2-72	1-61
FEV_1 %Predicted at Baseline					
Mean	78	76	79	79	81
Min-Max	63-100	57-96	56-109	54-105	57-108
FEV_1 Mean Actual at BSL (L)	2.57	2.49	2.64	2.75	2.68
Mean AM PEFR at Baseline(L/min)	393.72	391.49	387.32	383.53	396.95

Of the subjects entering the open label portion of the study, 100 had been on BDP (mean 338 mcg/d), 35 on Flunisolide (mean 1149 mcg/d), 78 on Fluticasone (mean 377 mcg/d), and Triamcinolone (mean 791 mcg/d).

6. Analysis of Efficacy

a) FEV_1

The sponsor presents three types of spirometry data: 1) change from Pre-Baseline to Baseline (when all subjects were treated with MF DPI 200 BID), 2) Baseline to Endpoint, and 3) pre- Baseline to Endpoint. The data for the change in FEV_1 from Baseline to Endpoint was the pre-ordained primary efficacy endpoint as per protocol.

It must be noted that FEV_1 improved for all groups, including placebo from Pre-Baseline to Baseline. Only the change for 200 QD PM was less than that for placebo. The difference between in the change Pre-Baseline and Baseline was statistically significant only for the comparison between 200 QD PM and 200 BID.

For Baseline to Endpoint: 200 QD PM, 200 BID, and 400 QD AM all had a statistically significant improvement of effect on the FEV_1 compared with placebo and 200 QD AM. 200 QD AM was not statistically different from placebo. No differences between 200 QD PM, 200 BID and 400 QD AM were observed at Endpoint.

For Pre-Baseline to Endpoint: One explanation for the improvement in Baseline to Endpoint of all MF DPI doses relative to 200 QD AM could be the marked improvement seen between Pre-Baseline and Endpoint. For this reason, it is important to look at the change from Pre-Baseline to Endpoint. The differences remain between 200 QD AM and the rest of the MF DPI doses but now a nearly significant difference between 200 QD AM and placebo is seen (0.06). Nonetheless, the other MF DPI show a much better maintenance of FEV_1 than 200 QD AM and placebo.

The fact that 200 QD PM outperformed QD AM could theoretically be attributed to the timing of spirometry relative to dosing. A review of the timing of spirometry shows that at least 75% of the measures were performed in the morning. The fact that such a difference was found between PM and AM dosing does not support the idea that MF DPI is best dosed as a QD drug.

The sponsor also presented the change in FEV_1 from Baseline for Day 4 and Weeks 1,2,4,8, and 12. The difference between AM and PM 200 mcg QD dosing was apparent consistently beginning at Day4. Indeed, at Baseline, the difference already had a p value of 0.10.

FEV_1 (liters) — Change from Pre-baseline / Baseline by Treatment Group (All Treated Subjects)

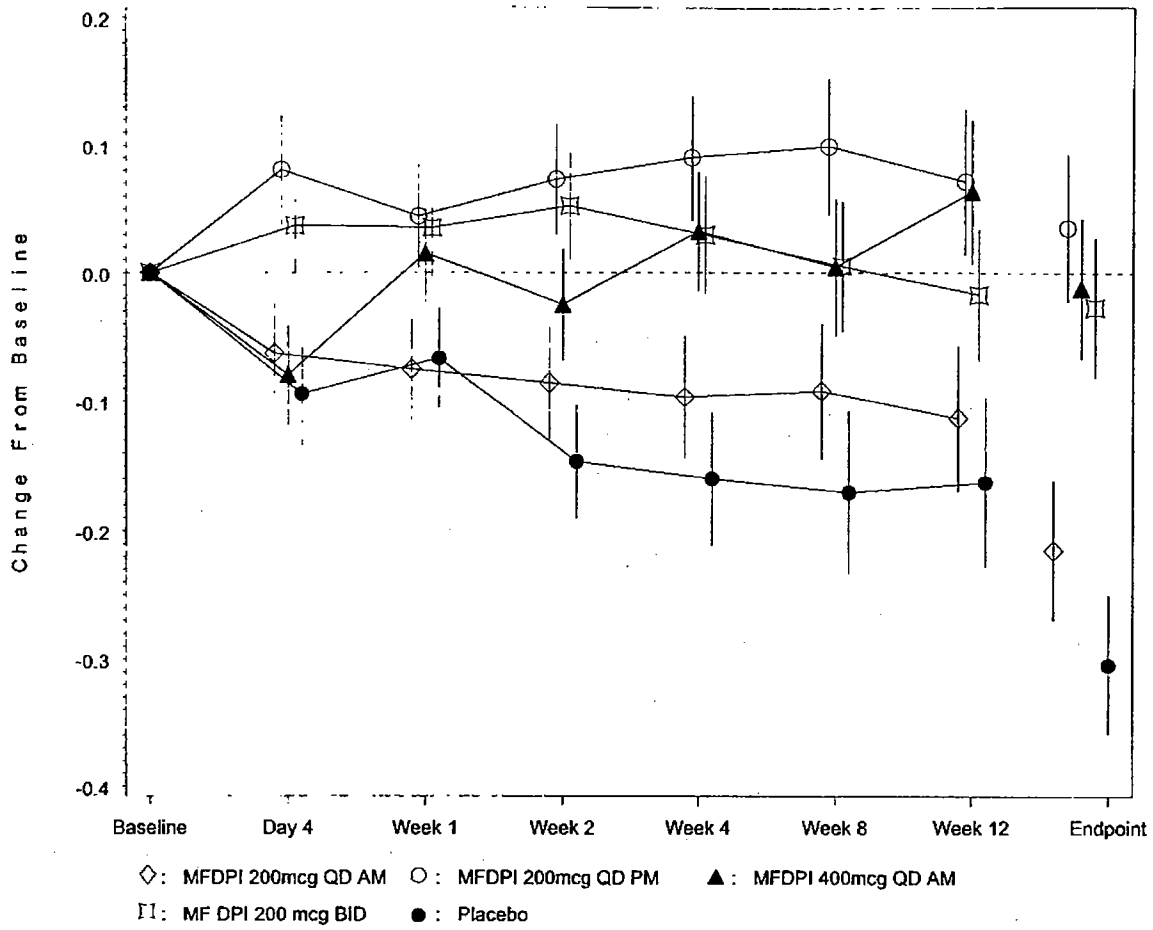
	MF DPI 200 mcg QD AM (A)			MF DPI 200 mcg QD PM (B)			MF DPI 400 mcg QD AM (C)			MF DPI 200 mcg BID (D)			Placebo (E)		
	N	Mean[a]	(Mean % Change)[a]	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Pre-baseline	58	2.41		54	2.42		58	2.52		58	2.54		58	2.57	
Baseline	58	2.57		54	2.49		58	2.64		58	2.75		58	2.68	
Change From Pre-baseline															
Baseline	**58**	**0.16**	**(6.4%)**	**54**	**0.07**	**(2.8%)**	**58**	**0.12**	**(5.5%)**	**58**	**0.20**	**(7.8%)**	**58**	**0.10**	**(3.4%)**
Endpoint	**58**	**-0.06**	**(-3.0%)**	**54**	**0.11**	**(4.2%)**	**58**	**0.11**	**(3.5%)**	**58**	**0.18**	**(6.7%)**	**58**	**-0.20**	**(-7.9%)**
Change From Baseline															
Endpoint	**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)[b]

		P-value		Pairwise Comparisons (P Value)									
Time Point	P.SD	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
Change From Pre-baseline													
Baseline	**0.28**	**0.11**	**0.30**	**0.10**	**0.48**	**0.38**	**0.28**	**0.33**	**0.01**	**0.54**	**0.12**	**0.71**	**0.05**
Endpoint	**0.41**	**<0.01**	**0.67**	**0.04**	**0.03**	**<0.01**	**0.06**	**0.96**	**0.36**	**<0.01**	**0.38**	**<0.01**	**<0.01**
Change From Baseline													
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 LS means, which were based on an ANOVA model with treatment and center effects.

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



When the data is looked at graphically, it is apparent that 200 mcg QD AM does not track with the other doses of MF DPI.

FEV_1 responses were also available from the sponsor for groupings by sex, age and race (Section 14.2.1.1). There appeared to be similar results for men and women (Vol.1-168, p.301). No real conclusion should be drawn from the differentiation of the data based on race or age because of the small numbers of Non-Caucasians and those not in the 18-64 age group.

Data was also provided for subjects whose Baseline FEV_1 was <75% of the predicted value versus those whose Baseline FEV_1 was ≥75% of the predicted value (see table on next page of this review). Subjects whose Baseline FEV_1 was <75% again appear to have a better improvement with MF DPI relative to those with a Baseline FEV_1 was ≥75%. This has been also seen in Studies C96-136 and 186. Another interesting point from this table is how well preserved the FEV_1 was for those subjects whose Baseline FEV_1 was <75% when they were on 12 weeks of placebo.

The sponsor also supplied an analysis for the Efficacy Evaluable data set (Vol.1-168, p. 305). All MF DPI doses were significantly better than placebo with this data set. It must be noted, however, that 200 mcg QD AM was only significantly better at the Endpoint and at no

other timepoint. In fact, the p values for the other timepoint were quite high for this comparison. This finding of a significant difference at Endpoint between 200 QD AM and placebo may be attributable to the relatively high dropout rate for this MF DPI treatment group (66.6%) relative to the others (74.5-82%). Thus, this finding of significance in the Efficacy Evaluable group is not very convincing.

b) FVC and FEF_{25-75}

In looking at the FVC at Endpoint, there was a significantly ($p<0.01$) better response (that is, a maintenance of effect) in the 200 QD PM, the 400 QD AM and the 200 BID groups than in the placebo group. Similar to FEV_1, the response in the 200 QD PM group was also significantly ($p=0.02$) better than that observed in the 200 QD AM group but this difference was present only at Endpoint and at no other timepoint. No statistically significant differences in response at Endpoint were observed between the 200 QD PM, the 400 QD AM, and the 200 BID groups.

For the FEF_{25-75}, similar results were generally noted. Again, 200 QD PM, 400 QD AM, and 200 BID were better than placebo for most timepoints and the Endpoint. While no significant differences were noted between these doses and 200 QD AM, there were numeric differences and 200 QD AM was found only to be numerically different from placebo.

c) PEFR

Based on AM and PM PEFR (measured before any Proventil used), all treatments with MF DPI were superior to placebo. There were no statistically significant differences in response based on AM or PM PEFR between any of the MF DPI treatment groups, although the MF DPI 200 mcg QD AM treatment group was numerically the least effective. No significant differences between any of the treatment groups were observed ($p \geq 0.09$). (Please see the page following the next for the AM PEFR table.)

FEV_1 (liters) — Data based on Baseline Predicted FEV_1 (All Treated Subjects)

	MF DPI 200 mcg QD AM			MF DPI 200 mcg QD PM			MF DPI 400 mcg QD AM			MF DPI 200 mcg BID			Placebo		
	N	Mean	(Mean % Change)[a]	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
FEV_1 < 75% Predicted Value at Baseline															
Baseline	22	2.10		29	2.32		24	2.41		21	2.12		13	2.20	
Change From Baseline															
Day 4	14	0.03	(1.2%)	22	0.07	(4.1%)	20	0.00	(0.3%)	15	0.14	(5.7%)	11	-0.06	(-3.3%)
Week 1	21	-0.07	(-3.3%)	29	0.10	(4.4%)	24	0.16	(6.7%)	21	0.12	(5.2%)	11	0.11	(4.4%)
Week 2	21	-0.06	(-2.4%)	29	0.11	(4.8%)	22	0.12	(4.8%)	21	0.14	(5.3%)	10	0.04	(1.0%)
Week 4	19	-0.07	(-3.0%)	27	0.10	(3.6%)	23	0.12	(4.7%)	20	0.12	(4.6%)	10	0.11	(5.6%)
Week 8	17	-0.07	(-2.8%)	27	0.11	(4.0%)	21	0.11	(4.1%)	17	0.22	(8.4%)	9	-0.09	(-4.0%)
Week 12	14	-0.04	(-2.7%)	20	0.12	(4.6%)	16	0.12	(4.2%)	16	0.20	(7.9%)	8	-0.02	(-2.0%)
Endpoint	**22**	**-0.15**	**(-7.6%)**	**29**	**0.08**	**(3.4%)**	**24**	**0.09**	**(3.0%)**	**21**	**0.14**	**(5.3%)**	**13**	**-0.03**	**(-1.9%)**
FEV_1 ≥ 75% Predicted Value at Baseline															
Baseline	36	2.89		25	2.74		34	2.83		37	3.13		45	2.84	
Change From Baseline															
Day 4	24	-0.09	(-2.9%)	11	0.13	(4.3%)	20	-0.16	(-5.9%)	26	-0.02	(-0.5%)	26	-0.09	(0.9%)
Week 1	34	-0.05	(-2.0%)	24	0.04	(1.4%)	34	-0.06	(-2.1%)	37	0.02	(0.7%)	45	-0.09	(-0.8%)
Week 2	33	-0.10	(-3.4%)	25	0.05	(1.5%)	33	-0.11	(-4.6%)	35	0.01	(0.3%)	42	-0.18	(-4.6%)
Week 4	34	-0.11	(-3.4%)	25	0.10	(3.4%)	32	-0.03	(-1.3%)	36	-0.01	(-0.6%)	36	-0.22	(-5.7%)
Week 8	32	-0.10	(-3.6%)	23	0.09	(2.7%)	29	-0.07	(-2.7%)	35	-0.09	(-3.1%)	26	-0.19	(-6.3%)
Week 12	27	-0.16	(-5.4%)	23	-0.01	(-0.8%)	28	0.01	(-0.5%)	34	-0.13	(-4.1%)	22	-0.23	(-8.3%)
Endpoint	**36**	**-0.27**	**(-9.0%)**	**25**	**-0.02**	**(-0.8%)**	**34**	**-0.09**	**(-4.4%)**	**37**	**-0.13**	**(-3.9%)**	**45**	**-0.39**	**(-12.1%)**

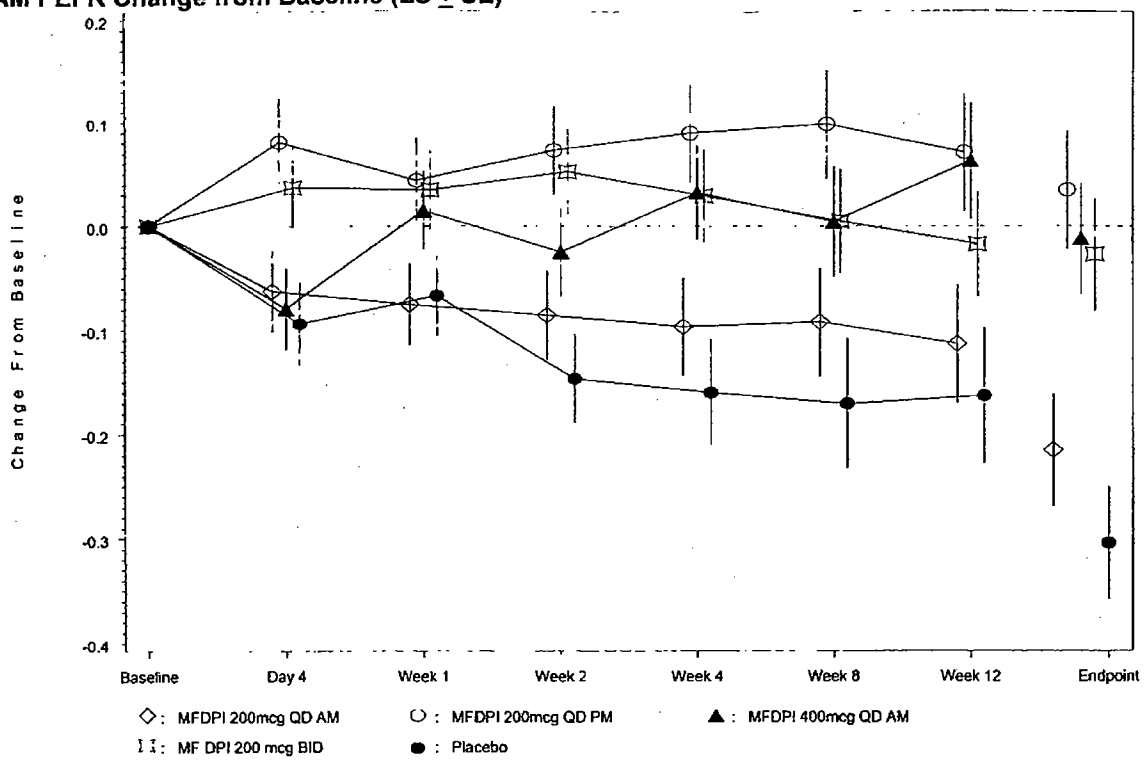
AM PEFR (liters/minute) — Change from Baseline by Treatment Group (All Treated Subjects)

	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	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	58	393.72		54	391.49		58	387.32		58	383.53		58	396.95	
Change From Baseline															
Week 1	58	-4.32	(-0.6%)	54	0.54	(1.2%)	58	-5.42	(-1.2%)	58	7.38	(2.8%)	57	-7.29	(-1.0%)
Week 2	57	-8.95	(-1.8%)	54	1.57	(1.0%)	58	-6.91	(-1.8%)	57	6.17	(2.2%)	56	-17.51	(-3.5%)
Week 4	53	-4.36	(-0.2%)	53	4.46	(2.6%)	55	-1.34	(0.3%)	56	9.62	(3.9%)	46	-25.41	(-5.0%)
Week 6	51	-7.20	(-1.1%)	51	10.51	(3.9%)	53	1.10	(1.2%)	54	9.33	(4.1%)	40	-21.82	(-4.1%)
Week 8	49	-3.59	(-0.3%)	50	6.12	(2.7%)	52	3.54	(1.6%)	52	11.24	(4.3%)	39	-17.46	(-2.8%)
Week 10	46	6.87	(1.8%)	47	10.32	(3.5%)	48	6.58	(1.7%)	51	10.39	(3.2%)	33	-15.29	(-2.7%)
Week 12	44	6.94	(1.8%)	46	9.57	(2.9%)	46	2.12	(0.7%)	51	9.32	(2.8%)	32	-18.19	(-3.5%)
Endpoint	**58**	**-8.93**	**(-1.8%)**	**54**	**4.30**	**(1.8%)**	**58**	**-6.03**	**(-1.6%)**	**58**	**6.85**	**(2.2%)**	**58**	**-36.90**	**(-8.1%)**

Analysis Results (Change From Baseline)

		P-value		Pairwise Comparisons (P Value)									
Time Point	P.SD	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
Week 1	25.88	0.02	0.03	0.32	0.82	0.02	0.54	0.23	0.16	0.11	<0.01	0.70	<0.01
Week 2	32.53	<0.01	0.65	0.09	0.74	0.01	0.16	0.17	0.46	<0.01	0.03	0.08	<0.01
Week 4	35.95	<0.01	0.10	0.21	0.66	0.04	<0.01	0.40	0.46	<0.01	0.11	<0.01	<0.01
Week 6	37.83	<0.01	0.50	0.02	0.27	0.03	0.07	0.21	0.87	<0.01	0.27	<0.01	<0.01
Week 8	41.81	0.02	0.61	0.25	0.39	0.08	0.13	0.76	0.54	<0.01	0.35	0.02	<0.01
Week 10	43.02	0.07	0.72	0.70	0.97	0.69	0.03	0.67	0.99	0.01	0.66	0.03	<0.01
Week 12	43.96	0.05	0.44	0.78	0.61	0.80	0.02	0.42	0.98	<0.01	0.43	0.05	<0.01
Endpoint	**49.98**	**<0.01**	**0.89**	**0.16**	**0.76**	**0.09**	**<0.01**	**0.28**	**0.79**	**<0.01**	**0.17**	**<0.01**	**<0.01**

AM PEFR Change from Baseline (LS ± SE)



A very similar grouping of data to that of the FEV_1 is seen but in the case of the PEFR, the pairwise comparison between 200 QD AM and placebo was significant. When graphed, however, it appears as though there are differences between the 200 QD AM dose and the other MF DPI doses.

The PM PEFR data was also examined (Vol. 1-169, p. 365). In general, the patterns of effect were similar. 200 BID appeared to be numerically the most effective but was not statistically different from any other MF DPI dose. 200 QD AM was only better than placebo at Endpoint and in general was numerically less than 200 QD PM although the difference was not very large. The difference between these doses was clearly less than that seen in the AM PEFR data. The fact, however, that 200 QD AM was not better than 200 QD PM with PM PEFR seems to suggest that the PM dosing may be intrinsically better and not wholly an artifact of when the testing is performed.

d) Asthma Symptoms

To reiterate, every morning and evening prior to dosing, the subject rated wheezing, difficulty breathing, and cough on a scale of 0 (none) to 3 (very uncomfortable and interfered with most or all of normal daily activities/sleep). This scale has been presented previously in this review. Symptom scores were generally low (<1.0) at Baseline.

Based on changes from Baseline in AM Wheezing, treatment with all four MF DPI doses were statistically superior to treatment with placebo ($p<0.01$) at the Endpoint. 200 BID appeared to be the most effective numerically and interestingly, 200 QD AM appeared to fare better numerically than 200 QD PM despite the apparent disadvantage in the timing of the dose. 200 BID also did best when PM Wheezing was examined and, again, 200 QD AM was numerically better than 200 QD PM. When the averages of the AM and PM Wheezing scores

were examined (p. 462), these patterns were maintained. In conclusion, all four MF DPI doses performed better than placebo at Endpoint but the small effect should be considered.

For AM difficulty breathing, 200 BID again appeared to fare the best. Statistically significant differences between the 200 BID group and the 200 QD AM (only at Endpoint) and 200 QD PM groups ($p \leq 0.04$) at at least the Endpoint were observed. The p value for the difference between 200 BID and 400 QD AM was only 0.05. In general, all doses were significantly different from placebo at Endpoint for AM Difficulty Breathing. For PM Difficulty Breathing, 200 BID also did best and a similar pattern to AM Difficulty Breathing was noted.

For AM or PM coughing scores at Endpoint, significant differences between the 200 QD AM, the 400 QD AM, or the 200 BID group and the placebo group were demonstrated. These differences were noted at other timepoints. There was only a numerical difference between 200 QD PM and placebo throughout the study. Evaluation of PM coughing scores at Endpoint for the MF DPI 200 mcg QD PM treatment group showed a significant difference over placebo.

e) Response to Therapy

At all visits from Day 4 to Week 12, the physician assessed the subject's response to therapy by comparing the current level of symptoms with those noted at Baseline on a scale from 1 (much improved) to 5 (much worse). At Endpoint, the % of subjects evaluated as much improved or improved was similar for all four MF DPI groups (41%, 54%, 50%, and 57%, respectively, in the 200 QD AM, the 200 QD PM, the 400 QD AM, and the 200 BID groups) and lower in the placebo group (28%). The % reported as worse or much worse was lower in the MF DPI groups (10-22%) compared with placebo (53%). Thus, it appears that all MF DPI

Physician's Eval. at Endpoint (compared with Baseline)

Rating	Number (%) of Subjects				
	MF DPI 200 mcg QD AM (n=58)	MF DPI 200 mcg QD PM (n=54)	MF DPI 400 mcg QD AM (n=58)	MF DPI 200 mcg BID (n=58)	Placebo (n=58)
Much Improved	6(10)	10(19)	12 (21)	11 (19)	5 (9)
Improved	18(31)	19(35)	17 (29)	22 (38)	11 (19)
No Change	21(36)	18(33)	20 (34)	19 (33)	11 (19)
Worse	10(17)	6(11)	5(9)	5(9)	21 (36)
Much Worse	3(5)	1(2)	4(7)	1(2)	10 (17)

groups did better than placebo. There is a hint that 200 QD AM did not fare quite as well with a lower % of "much improved." Statistical analysis of the scores was provided by the sponsor with pairwise treatment comparisons. All MF DPI groups were better than placebo at Endpoint and for most other timepoints but 200 QD AM was statistically better than placebo only at Endpoint. In fact, 200 BID was nearly better than 200 QD AM with a p value of 0.05.

f) B-agonist Use During the Study

Although numerical differences did exist, there were no significant differences ($p>0.05$) between treatment groups in Proventil use at Baseline. At Endpoint, the 200 QD AM, the 400 QD AM, and the 200 BID groups were significantly better than placebo. Although the difference between the 200 QD PM group and placebo was marginally significant at Endpoint

(p=0.07), the mean change from Baseline was numerically less (0.73 puffs/day) in the 200 QD PM group than in the placebo group (1.53 puffs/day). It is noteworthy that 200 QD AM seems to outperform 200 QD PM in this variable - this is most likely due to the timing of the dosing. Again, 200 BID appears to be the most effective dose.

The list of subjects who received nebulizations was reviewed and there appeared to be no appreciable differences among the groups as the number who utilized this therapy was small.

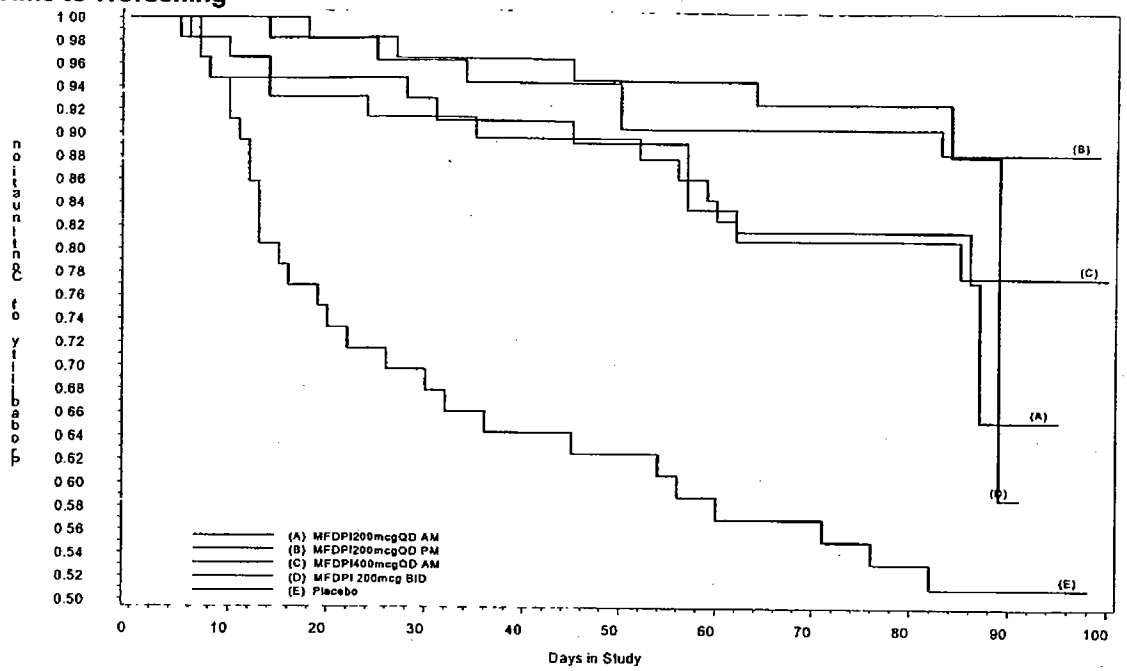
g) Number of Nocturnal Awakenings

Subjects recorded the number of times during the night that they were awakened due to asthma symptoms severe enough to require treatment with Proventil. The change from Baseline in the number of nocturnal awakenings was significantly less at Endpoint in the 200 QD AM, the 400 QD AM and 200 BID groups, in comparison to the placebo group. While the change from Baseline in the number of nocturnal awakenings was numerically lower in the 200 QD PM group than in the placebo group at Endpoint, this difference was not statistically significant. It is interesting to note that 200 QD AM appeared to do numerically better than 200 QD PM - the opposite effect would seem to have otherwise been more probable. 200 BID again fared the best. It must be noted, however, that the # of awakenings was small, in general, so it is problematic to make any solid conclusion from this data.

h) Time to Worsening of Asthma

The definition of "worsening of asthma" has been previously discussed. Because > 83% of subjects (average of % censored for each group) in each of the MF DPI groups had not met the criteria for worsening by the time of their last visit, median time to worsening could not be determined for these groups over the treatment period; however all the active treatments were superior than placebo. The sponsor's analysis indicated that after 30 days of study drug, the probability of a subject continuing in the study (not discontinuing for asthma worsening) was 91% to 95% for the MF DPI groups compared to only 68% for placebo. No further analysis is discussed for later time points. It is interesting to note in the survival analysis table below that around Day 85, there is a drop-off among all treatment groups. Previous to this drop-off, however, it seems that the two QAM doses have a worse probability of continuing in the study relative to the PM and BID doses. It must be noted that this analysis did not take into consideration those subjects who discontinued the study with asthma worsening during the open label phase of the study.

Time to Worsening



Reviewer's Note – The sponsor later points out in the Integrated Summary of Efficacy that because the scheduled treatment duration was 3 months (84 days), small numbers of subjects remained in the study after Day 80. Therefore, larger decrements are noted at timepoints after Day 80 than before in the calculated probabilities of continuing in the trial without asthma worsening.

i) Efficacy Summary for C96-196

The primary efficacy analysis was the comparison of placebo to 200 BID for change from Baseline to Endpoint in FEV_1. The null hypothesis of no difference between the groups was tested against the alternative that 200 BID was more effective than placebo. Since the result was significant ($p<0.05$), then all pairwise comparisons were made without penalty for multiple comparisons, at a 5% level of significance. 200 BID, 200 QD PM, and 400 QD AM all had a statistically significant improvement of effect on the FEV_1 compared with placebo and 200 QD AM. 200 QD AM was not statistically different from placebo. No differences between 200 QD PM, 200 BID and 400 QD were observed at Endpoint. Subjects whose Baseline FEV_1 was <75% appeared to have a better improvement with MF DPI relative to those with a Baseline FEV_1 was ≥75%.

There was a significantly better response with the FVC and FEF_{25-75} in the 200 QD PM, the 400 QD AM and the 200 BID groups than in the placebo group. Changes in the 200 QD AM group were only numerically better than that seen in placebo.

There were no statistically significant differences in response based on AM or PM PEFR between any of the MF DPI treatment groups, although the MF DPI 200 QD AM treatment group was numerically the least effective. No significant differences between any of the treatment groups were observed.

Asthma scores between Baseline and Endpoint were examined. Treatment with all four MF DPI doses were statistically superior to treatment with placebo at the Endpoint for AM and PM Wheezing. 200 BID was the most effective numerically and 200 QD AM did better numerically than 200 QD PM.

For AM and PM difficulty breathing, 200 BID performed the best but all doses of MF DPI were significantly different from placebo at Endpoint for AM Difficulty Breathing. For AM or PM coughing scores at Endpoint, significant differences were noted between the 200 QD AM, the 400 QD AM, or the 200 BID group and placebo. The 200 QD PM dose was only numerically better than placebo. Evaluation of PM coughing scores at Endpoint for the MF DPI 200 QD PM treatment group showed a significant difference over placebo.

Pairwise treatment comparisons were performed between treatments and placebo for the physician's evaluation of response. All MF DPI groups were better than placebo at Endpoint and for most other timepoints but 200 QD AM was statistically better than placebo only at Endpoint. The p value for the difference between 200 BID and 200 QD AM was 0.05.

For the number of Proventil puffs used per day as well as the number of nocturnal awakenings requiring the use of a puffer, the 200 QD AM, the 400 QD AM, and the 200 BID groups were significantly better than placebo. While the nocturnal awakenings or # of puffs used in the 200 QD PM group was less than that of placebo, the difference was not found to be statistically significant. 200 QD AM did better numerically than 200 QD PM with either variable. Again, 200 BID appeared to be the most effective dose.

Overall, it appears that there is clear data to support the efficacy of MF DPI 200 BID and 400 QD AM in the treatment of asthma. For the primary efficacy endpoint of FEV_1 as well as FVC, FEF_{25-75}, AM/PM PEFR, AM and PM Wheezing, AM Difficulty Breathing, PM Coughing and the evaluation of response, 200 QD PM was significantly better than placebo. 200 QD AM did better than placebo only with AM/PM PEFR, self-reported asthma scores, # puffs of Proventil utilized and # of nocturnal awakenings. While the efficacy of 200 QD AM may have its basis in the variable of PEFR, its data tended to group away from the data for the other MF DPI doses.

7. Safety Data for C96-196

a) Adverse Events

The most common adverse events (those reported by ≥10% of subjects in any treatment group) included headache, pharyngitis, viral infection, allergy aggravated, nasal congestion, sinusitis, back pain, oral candidiasis, dysmenorrhea, and pain. During the open-label phase of the study, no adverse event was reported by ≥10% of the subjects in any treatment group.

Incidence of Adverse Events Reported by ≥10% of Subjects (All Enrolled Subjects)

	Number (%) of Subjects					
	200 BID Open Label (n=307)	200 QD AM (n=58)	200 QD PM (n=54)	400 QD AM (n=58)	200 BID (n=58)	Placebo (n=58)

Headache	25(8)	15(26)	14 (26)	10 (17)	13 (22)	10 (17)
Pharyngitis	8(3)	3(5)	11 (20)	2(3)	6(10)	6 (10)
Infection, viral	4(1)	5(9)	4(7)	6(10)	11(19)	10 (17)
Allergy aggravated	17(6)	12 (21)	11(20)	14 (24)	14(24)	10(17)
Nasal congestion	4(1)	7 (12)	6 (11)	2(3)	2(3)	4(7)
Sinusitis	3(1)	6(10)	5(9)	2(3)	3(5)	0(0)
Back Pain	1(<1)	2(3)	3(6)	2(3)	8(14)	4(7)
Oral Candidiasis	4(1)	1(2)	1(2)	2(3)	7(12)	2(3)
Dysmenorrhea	7(4)	3(8)	1(3)	0	4(13)	1(3)
Pain[a]	0	2(3)	2(4)	1(2)	4(7)	6 (10)

a: The following literal terms were all coded as "pain": neck pain and neck ache, sore leg, carpal tunnel syndrome, painful leg, leg pain, arm pain, knee pain, finger pain, and hand pain.

Pharyngitis was more common in the MF DPI treatments dosed at night with 200 QD PM (20%) and 200 BID (10%) as well as placebo (10%). Nasal congestion was more common in the 200 QD AM (12%) and the 200 QD PM (11%) groups than in the remaining MF DPI treatment groups (3% each in the 400 QD AM and 200 BID groups) and the placebo (7%) group. Sinusitis was more common in the 200 QD AM (10%) and the 200 QD PM (9%) groups than in the remaining groups (3% in the 400 QD AM group, 5% in the 200 BID group, and none in the placebo group). Sinusitis, therefore, was only seen with active treatment but was less common with the higher daily doses. Dysmennorhea was more common with active treatment as was seen in C96-136 and 186. There was a notable increase of oral candidiasis in the 200 BID group relative to all other groups. Oral candidiasis was till a problem even though subjects had been advised to rinse their mouth after study drug administration.

The sponsor submitted a list of adverse events. The following represents a list of adverse events with particularly increased expression among the MF DPI groups or has been mentioned as increased among the MF DPI groups in previous trials.

Incidence of Any Treatment-Emergent Adverse Events Reported (All Enrolled Subjects)(Without regard to relationship to treatment.)

	Number (%) of Subjects					
	200 mcg BID Open Label (n=307)	200 mcg QD AM (n=58)	200 mcg QD PM (n=54)	400 mcg QD AM (n=58)	200 mcg BID (n=58)	Placebo (n=58)
Any Adverse Event	**92 (30)**	**43 (74)**	**44 (81)**	**35 (60)**	**43 (74)**	**45 (78)**
influenza – like symptoms	0	1 (2)	2 (4)	4 (7)	1(2)	0
dysphonia	0	0	0	1 (2)	1(2)	0
dyspepsia	5 (2)	3 (5)	2 (4)	0	2(3)	1 (2)
nausea	2 (1)	1 (2)	1 (2)	1 (2)	2 (3)	0
musculo-skeletal pain	1 (<1)	1 (2)	3 (6)	2 (3)	3(5)	4 (7)
myalgia	2 (1)	0	4 (7)	1 (2)	2(3)	1 (2)
menstrual disorder	2 (1)	0	0	0	2(6)	0
candidiasis, oral	4(1)	1 (2)	1 (2)	2 (3)	7 (12)	2 (3)
coughing	3 (1)	3 (5)	2 (4)	3 (5)	2(3)	0
epistaxis	0	1 (2)	0	1 (2)	2(3)	0
nasal congestion	4 (1)	7 (12)	6 (11)	2 (3)	2(3)	4 (7)
nasal irritation	3 (1)	0	0	0	2(3)	0
taste perversion	0	1 (2)	0	0	0	1 (2)

Influenza-like symptoms appears to have an increased expression in the MF DPI groups except for the 200 BID open-label portion – perhaps with the longer 3 month phase this AE had greater opportunity for expression. This AE was not noted in C96-186 and had only a slightly greater expression with MF DPI in C96-136. Dysphonia is mentioned here because it was a notable AE from C96-186. The data for dysphonia is not impressive in this trial nor was it in C96-136. Dyspepsia appears to be overexpressed among the MF DPI groups but it interestingly was not seen in the 400 QD AM group. In other C96-136 and 186, the data on dyspepsia appear equivocal. Musculoskeletal pain, more common with MF DPI in C96-186 and136, is not more common with active treatment in this trial. Myalgia here is most common with 200 QD PM for unclear reasons. The menstrual disorder listing may require more investigation. Both in this trial as in C96-136 and 186, dysmennorhea is more often seen with MF DPI compared with placebo. All cases of oral candidiasis were considered mild or moderate in severity, and none led to the discontinuation of any subject from treatment Coughing was clearly more common with active treatment in this trial. Coughing was actually less common in C96-136 and 186 was equivocal. Epistaxis was seen here in some active treatment groups and rarely in C96-186. Nasal congestion was least common in the 400 QD groups and most common in the 200 QD groups so it is difficult to implicate a drug effect. Nasal irritation was seen only in the 200 BID groups, the significance of which is unclear. Taste perversion was not an important issue here or in C96-136 but was been rarely seen with active treatment in 186 (2 patients only).

The differential expression of adverse events between the sexes was examined. In general, there were no indications of a differential response to treatment among men or women, with the exception of a clearly greater incidence of headache in women but headache was not overtly more prevalent with active drug treatment. Review of the incidence of AE's within age or racial groups was not helpful, especially noting the small number involved who were not 18-64 years of age or were Non-Caucasian.

b) Severe/Life-Threatening Adverse Events

Severe/life-threatening (Grade 3 and Grade 4) adverse events were reported by 37 subjects. No subject had events that were categorized as Grade 4 (life-threatening). During the blinded phase of the study, the percentages of subjects with one or more severe/life-threatening adverse events that were categorized as Grade 3 were similar in the 200 QD PM, the 400 QD AM, the 200 BID and the placebo groups (15%, 10%, and 14%, and 12% respectively) and was lower in the 200 QD AM group (5%).

Incidence of Severe/Life-threatening Treatment-Emergent Adverse Events (All Enrolled Subjects).

Adverse Event Type	MF 200 mcg BID Open Label (n=307)	MF DPI 200 mcg QD AM (n=58)	MF DPI 200 mcg QD PM (n=54)	MF DPI 400 mcg QD AM (n=58)	MF DPI 200 mcg BID (n=58)	Placebo (n=58)
Any Severe/life-threatening Adverse Event	**5 (2)**	**3 (5)**	**8 (15)**	**6 (10)**	**8 (14)**	**7 (12)**
allergic reaction	0	0	0	0	1 (2)	0
allergy aggravated	1 (<1)	1 (2)	0	1 (2)	2 (3)	1 (2)
back pain	0	0	0	1 (2)	1 (2)	1 (2)

Incidence of Severe/Life-threatening Treatment-Emergent Adverse Events (All Enrolled Subjects).

Adverse Event Type	MF 200 mcg BID Open Label (n=307)	MF DPI 200 mcg QD AM (n=58)	MF DPI 200 mcg QD PM (n=54)	MF DPI 400 mcg QD AM (n=58)	MF DPI 200 mcg BID (n=58)	Placebo (n=58)
headache	2 (1)	1 (2)	2 (4)	2 (3)	3 (5)	0
influenza-like symptoms	0	0	1 (2)	0	0	0
injury accidental	0	0	0	1 (2)	0	0
pain	0	1 (2)	0	0	1 (2)	0
procedure (no adverse event)	0	0	0	0	0	1 (2)
hypertension	0	0	0	0	0	1 (2)
hypertonia	0	0	0	1 (2)	0	0
gastro-intestinal disorders NOS	0	0	0	0	0	1 (2)
hiccup	0	0	0	1 (2)	0	0
tongue disorder	0	0	0	0	0	1 (2)
ear disorder NOS	0	1 (2)	0	0	0	0
arthritis	0	0	1 (2)	0	0	0
musculo-skeletal pain	0	0	0	0	1 (2)	0
myalgia	0	0	0	0	1 (2)	0
synovitis	1 (<1)	0	0	0	0	0
insomnia	1 (<1)	0	0	0	0	0
dysmenorrhea	1 (1)	0	0	0	2 (6)	0
menstrual disorder	1 (1)	0	0	0	1 (3)	0
infection bacterial	0	0	1 (2)	0	0	1 (2)
asthma aggravated	0	0	0	0	0	2 (3)
coughing	0	0	0	1 (2)	0	0
nasal congestion	0	0	0	0	1 (2)	0
sinus congestion	0	0	0	0	1 (2)	0
sinusitis	1 (<1)	0	1 (2)	0	1 (2)	0
dermatitis	0	0	1 (2)	0	0	0
rash	0	0	0	0	1 (2)	0
migraine	0	0	1 (2)	0	1 (2)	0
eye abnormality	0	0	0	0	1 (2)	0

No further insights come from this list as to the relative contribution of the drug treatment to their occurrence. Severe headache and dysmennorhea are more common with treatment with MF DPI. Because of the apparent lack of increase of headache with MF DPI when all levels of severity are considered, it is difficult to implicate active treatment. Dysmennorhea, however, was seen more commonly with active treatment.

c) Serious Adverse Events

Serious adverse events were reported by two subjects (one in the 200 QD PM group and one in the placebo group) during the study. One of these events was considered possibly related to treatment by the investigator while the other was considered unrelated to treatment.

- One 34-year old female, non-Caucasian subject (C96-196-06/281) in the placebo group was hospitalized for exacerbation of asthma symptoms after 16 days of study drug. The subject

was treated with IV Solumedrol and oral prednisone, recovered and was discharged from the hospital 5 days later. Subsequently, the subject was discontinued from the study 11 days later due to this adverse event. The investigator considered this event unlikely related to study drug treatment because of the subject's underlying disease.

- One 23-year old female, non-Caucasian subject (C96-196-12/258) in the 200 QD PM group who completed the study had elevated SGPT (244 U/L; normal range 6-34 U/L), SGOT (435 U/L; normal range 9-34 U/L) and LDH (794 U/L; normal range 53-234 U/L) values at the final study visit. The bilirubin level was 0.5 mg/dl at the time these other enzymes were elevated (It was 0.2 at Screening.) Screening Values for this subject were 14 U/L for SGPT and 13 U/L for SGOT and 131 U/L for LDH, respectively. Repeat lab values 1 week later showed decreases in SGPT to 112 U/L, and in SGOT to 43 U/L. LDH values had decreased to within the normal range. Values were retested within another week, and all returned to normal range. Hepatitis testing 1 week after the final visit (at the final retest) and a repeat hepatitis panel on [ ] were both negative. With the exception of five days of moderate flu-like symptoms and severe headache, for which she took ibuprofen, Theraflu, and Contac Severe Cold and Flu Formula, the subject could not recall any event which could be associated with elevated laboratory values and denied any history of drug or alcohol abuse. All other lab values measured were within normal range. This event was considered by the investigator to be possibly related to treatment with study medication.

It should be noted that such decreases in the transaminases, although good for the individual patient, does not rule out drug effect.

d) Discontinuation Because of Adverse Events

Eight subjects did not complete the study because of adverse events.

List of Subjects Who Discontinued the Study Because of Adverse Events

Center/Subject	Sex/ Age/ Race	Day of Onset	Adverse Event(s)	Severity	Relationship
			200 BID Open Label		
C96-196-02/505	F/54/C	7	Viral Cold Causing Asthma Exacerbation	Moderate	Unrelated
			200 QD AM		
C96-196-10/263	F/19/NC	27	Upper Resp Tract Infection	Moderate	Possible
C96-196-12/256	M/73/C	32	Allergic Rhinitis	Moderate	Unrelated
		33	Heavy Phlegm Production	Moderate	Unrelated
			200 QD PM		
C96-196-06/282	F/44/C	33	Worsened Contact Dermatitis	Severe	Unrelated
			400 QD AM		
no subjects					
			200 BID		
C96-196-10/269	F/53/C	57	Upper Resp Tract Infection	Moderate	Unrelated
			Placebo		

List of Subjects Who Discontinued the Study Because of Adverse Events

Center/Subject	Sex/ Age/ Race	Day of Onset	Adverse Event(s)	Severity	Relationship
C96-196-06/281	F/34/C	29	Asthma Aggravated	Severe	Unrelated
C96-196-06/286	F/30/C	23	Worsening Asthma Symptoms	Moderate	Possible
C96-196-10/348	M/22/NC	29	Sinus Congestion	Mild	Unrelated

This number of discontinuations is small and they do not appear to be convincingly related to drug treatment.

Median laboratory changes from Baseline to Endpoint were reviewed. No important differences were discerned before or after treatment. The results if median lab changes were also reviewed by sex. The only potentially discernable median change was the 3 point decrease in hematocrit for females from 42 to 39 for 400 QD AM and 2 points for 200 BID. There was a 0.5 point change for placebo. The corresponding decreases for males were 1 point in each group. Because there was a 2 point decrease in the placebo group for males and because this would seem to be a highly implausible change for an inhaled corticosteroid product, it is unlikely that the changes reflect drug treatment but any change in hematocrit should be specially noted in other trials.

Individual lab abnormalities during the trial were reviewed (Vol. 1-170.) The following abnormalities represent: (1) those seen at Visit 9 or the last visit which were not seen at Screening, (2) notable abnormalities.

Subject #	Treatment	Abnormality
330	200 BID	2+ Blood UA
22		Glucose 104 to 149 (p.3286, Vol. 1-176)
156		ALT 44 to 67 (AST 30 to 36, nl. Bili)(p.3292)
43		Glucose 111 to 170 (HCT 50 to 58) (p.3307)
255		UA neg. to 2+ blood (p.3322)
173		UA neg. to 3+ blood (p.3330)
137		ALT 14 to 38 (nl 6-32)(AST 16 to 33)(p.3335)
147	200 QD AM	ALT 37 to 91 (AST 34 to 37)(nl. Bili.) (p.3348)
200		UA Tr. To 2+ Blood, Bili. 0.8 to 1.4 (nl. 0.2 to 1.2)
322		UA Neg. to TNTC, 3+ (p. 3367)
323		AST 28 to 41 (nl. ALT). (p.3395)
148	200 QD PM	ALT 31 to 56 (AST 22-29) (p. 3408)
82		ALT 13 to 106 (A different value was listed for Visit 9C on p. 3411 and p.818 – Vol 1-170. The discrepancy between value for Visit 9C in 14.3.4.1 and 16.2.8.2 had to be clarified with the sponsor in a telecopy dated 6/29/99.), AST 15 to 62. The repeat values on 10/15 of ALT/AST were 29/25 (nl Bili.)AST 15 to 62 (nl Bili.)

272		ALT 25 to 65, AST 24 to 40 (p. 3433)
258		ALT 14 to 244, AST 13 to 435, bili 0.2 to 0.5, LDH 131 to 794, nl Alk.phos. (p. 3442)
192	400 QD AM	ALT 24 to 45, (AST 17 to 26) (p. 3473)
198		ALT 39 to 47 (p. 3474)
287		UA neg. to 3+ Blood (p. 3476)
051		UA neg. to 3+ Blood (p. 3482)
264		ALT 21 to 45 (nl 6-43), LDH 219 to 273, Endpoint WBC was 2.8 (p.3485)
254		ALT 57 to 90 (bili 1.4 to 0.7), Plts 154 to 98 (3467) WBC listed as 1.98 at Visit 9C on p. 881 and 5.47 on p. 3497 (this discrepancy had to be clarified again by the sponsor on 6/29/99 – 5.47 was a repeat value)UA neg. to 3+ Blood, TNTC (p. 3502)
302		LDH 179 to 287 (nl 53-234)
149	Placebo	ALT 22 to 45 (p. 3525)
281		ALT 9 to 76 (AST 14 to 23) (p. 3537)
324		ALT 13 to 51 (p. 3546)
103		ALT 57 SCC to 131 SCR, AST 51 to 51
259		Alkaline Phosphatase is listed as 117 on V9C on p. 932 but is listed as 82 on p. 3560 (it appears from the sponsor's 6/29/99 telecopy that 117 was the repeat lab value) ALT 25 to 76, AST 29 to 47.
178		ALT 24 to 56 (p. 3567)

As in C96-186, a urinalysis showing 2-3+ RBC is seen during study treatment. Those tests that demonstrated 1+ RBC were not tabulated. Only one subject (#286) in the placebo group even showed a new 1+ RBC after treatment. Only one subject in the 200 QD PM showed a new 1+ RBC and other went from 1+ to 2+ RBC. The relationship to drug treatment is unlikely but should be checked for in other trials.

Increases in transaminases are noted. The most prominent is the aforementioned Subject 258 on 200 QD PM where ALT changes from 14 to 244, AST changes from 13 to 435, bilirubin changes from 0.2 to 0.5, and LDH changes from 131 to 794. This change has not been explained. Other changes were less notable as in (1) #147 on 200 QD AM where ALT changes 37 to 91, (2) #82 on 200 QD PM where ALT changes 13 to 106 and AST 15 to 62, (3) #272 on 200 QD PM where ALT changes 25 to 65 and AST 24 to 40. It is not clear whether these changes were drug related or not.

e) Vital Signs

The data on mean values for blood pressure, heart and respiratory rate, and temperature were reviewed. Although weight data is mentioned in the title for this section, none was tabulated. For unclear reasons, data in Section14.3.6. was only supplied for 6 patients in each treatment group even though the protocol specifies that vital signs were to be performed at every visit. The results by subgroup were not reviewed because of the very small numbers whose data was supplied. No conclusions should be drawn from this vital sign data.

The sponsor in a submission dated July 14, 1999 subsequently supplied this data on vital signs. The general mean values for the treatment groups, genders or Caucasian/non-Caucasian did not change with treatment. The number of patients outside the 18-64 year age group was too small to draw any important conclusion. The sponsor also supplied the information on vital signs in a unique manner in this resubmission by supplying a specific listing of subjects with a percent change of at least 30% from the baseline value. Notable changes included:

Subject	Treatment	Change
70	MF DPI 200 BID	HR 88 to 48 Visit 9
77		HR 82 to 52 Visit 5
351		HR 92 to 54 Visit 9/Endpoint
196	MF DPI 200 QPM	HR 88 to 54 Visits7/9/Endpoint
56		HR 76 to 48 Visit 7
336	MF DPI 400 QD	HR 74 to 48 Visit 5
72	Placebo	HR 80 to 56 Visit 5
76		HR 80 to 52 Visit 5/Endpoint

The medications for these subjects were reviewed and none were found to have been on beta-blockers or calcium-channel blockers. Nonetheless, this reviewer does not believe this bradycardia was related to study treatment.

f) Cortrosyn Testing

Cortrosyn testing was performed at 7 selected sites. Measurements were performed at Screening, Baseline (Visit 3 which was already 15 days into the open label MF DPI 200 BID run-in period) and Endpoint. Interestingly, however, the sponsor uses the comparison of Baseline values with Endpoint values – the subjects had already been on 400 mcg a day of MF DPI for 2 weeks at Baseline. Thus, this testing does not really tell us what the steroid effect on MF DPI is because they were already on MF DPI at Baseline. This testing, therefore, is only useful in telling us that subjects were still able to have a change of $\geq$7 mcg/dl with Cortrosyn with a resultant cortisol level above $\geq$18 mcg/dl after 14 weeks of MF DPI. It cannot tell us whether there was a steroid effect of MF DPI.

No significant difference among treatment groups in the change from Baseline to Endpoint in the difference between pre and post-Cortrosyn plasma cortisol levels was noted. Mean post-Cortrosyn plasma cortisol values at Endpoint were significantly lower in the 400 QD AM group than in placebo. Post- Cortrosyn mean plasma cortisol values at Baseline, however, were numerically lower in the 400 QD AM group and the 200 BID groups than in the placebo group. (See table on next page).

The post-Cortrosyn data were re-evaluated by the sponsor using a covariate analysis model that adjusts for differences between treatment groups at Baseline. (See table on page following the next page). This analysis apparently demonstrates that the differences between groups at Endpoint were accounted for in part by the differences between the groups at Baseline. The p value at Endpoint for the difference between 400 mcg QAM and placebo was reduced from <0.01 and 0.01 to 0.05 and 0.05 for post-cortrosyn and difference between post- and pre-cortrosyn, respectively, after the adjustment is made but the difference is still very nearly significant.

Mean AM Plasma Cortisol Levels (mcg/dl)

	MF DPI 200 QD AM (A)		MF DPI 200QD PM (B)		MF DPI 400 QD AM (C)		MF DPI 200 BID (D)		PLACEBO (E)	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Baseline										
Pre-cortrosyn	27	14.28	22	15.14	26	13.82	26	13.12	26	15.75
Post-cortrosyn	27	26.82	22	28.16	26	26.07	26	25.86	26	29.54
Diff. Between Post- and Pre-cortrosyn	27	12.53	22	13.02	26	12.26	26	12.73	26	13.79
Endpoint										
Pre-cortrosyn	24	14.53	22	15.94	25	14.04	24	15.13	20	16.73
Post-cortrosyn	24	26.68	22	28.16	25	25.31	24	27.71	20	31.21
Diff. Between Post- and Pre-cortrosyn	24	12.15	22	12.21	25	11.27	24	12.58	20	14.48
Change From Baseline to Endpoint in the Difference Between Post- and Pre-cortrosyn	**24**	**-0.55**	**22**	**-0.82**	**25**	**-0.70**	**24**	**-0.24**	**20**	**0.28**

Analysis Results

		P-value		Pairwise Comparisons (P Value)									
	P.SD	Treat	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
Baseline													
Pre-cortrosyn	7.35	0.73	0.93	0.69	0.82	0.57	0.47	0.54	0.35	0.77	0.73	0.35	0.20
Post-cortrosyn	7.65	0.39	0.43	0.54	0.72	0.65	0.20	0.35	0.30	0.54	0.92	0.11	0.09
Diff. Between Post- and Pre-cortrosyn	4.25	0.74	0.02	0.69	0.81	0.86	0.29	0.54	0.81	0.54	0.69	0.20	0.37
Endpoint													
Pre-cortrosyn	7.48	0.77	0.98	0.52	0.82	0.78	0.34	0.39	0.71	0.74	0.61	0.24	0.48
Post-cortrosyn	7.27	0.11	0.23	0.49	0.51	0.63	0.04	0.18	0.84	0.18	0.25	**<0.01**	0.12
Diff. Between Post- and Pre-cortrosyn	4.13	0.15	<0.01	0.96	0.46	0.72	0.07	0.44	0.76	0.08	0.27	**0.01**	0.13
Change From Baseline to Endpoint in the Difference Between Post- and Pre-cortrosyn	**4.55**	**0.94**	**0.15**	**0.84**	**0.90**	**0.82**	**0.55**	**0.93**	**0.67**	**0.44**	**0.72**	**0.47**	**0.70**

Mean AM Plasma Cortisol Levels (mcg/dl) - A covariate analysis model adjusting for differences between treatment groups at Baseline

	MF DPI 200 QD AM (A)		MF DPI 200 QD PM (B)		MF DPI 400 QD AM (C)		MF DPI 200 BID (D)		Placebo (E)	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Baseline										
Pre-cortrosyn	27	14.28	22	15.14	26	13.82	26	13.12	26	15.75
Post-cortrosyn	27	26.82	22	28.16	26	26.07	26	25.86	26	29.54
Diff. Between Post- and Pre-cortrosyn	27	12.53	22	13.02	26	12.26	26	12.73	26	13.79
Endpoint										
Pre-cortrosyn	24	14.35	22	14.96	25	14.75	24	16.09	20	15.89
Post-cortrosyn	24	26.88	22	27.39	25	26.85	24	28.85	20	29.72
Diff. Between Post- and Pre-cortrosyn	24	12.35	22	12.27	25	11.75	24	12.73	20	14.08
Change From Baseline to Endpoint in the Difference Between Post- and Pre-cortrosyn	**24**	**-0.55**	**22**	**-0.82**	**25**	**-0.70**	**24**	**-0.24**	**20**	**0.28**

		Analysis Results												
		P-value		Pairwise Comparisons (P Value)										
	P.SD	Treat	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
Baseline													
Pre-cortrosyn	7.35	0.73	0.93	0.69	0.82	0.57	0.47	0.54	0.35	0.77	0.73	0.35	0.20
Post-cortrosyn	7.65	0.39	0.43	0.54	0.72	0.65	0.20	0.35	0.30	0.54	0.92	0.11	0.09
Diff. Between Post- and Pre-cortrosyn	4.25	0.74	0.02	0.69	0.81	0.86	0.29	0.54	0.81	0.54	0.69	0.20	0.37
Endpoint													
Pre-cortrosyn	4.46	0.63	0.31	0.64	0.75	0.18	0.26	0.88	0.39	0.50	0.30	0.40	0.88
Post-cortrosyn	4.79	0.19	0.11	0.72	0.98	0.16	0.06	0.70	0.31	0.12	0.15	**0.05**	0.56
Diff. Between Post- and Pre-cortrosyn	3.81	0.36	<0.01	0.95	0.59	0.73	0.14	0.64	0.69	0.13	0.37	**0.05**	0.25
Change From Baseline to Endpoint in the Difference Between Post- and Pre-cortrosyn	**4.55**	**0.94**	**0.15**	**0.84**	**0.90**	**0.82**	**0.55**	**0.93**	**0.67**	**0.44**	**0.72**	**0.47**	**0.70**

The sponsor tabulated the number of subjects at the specified testing sites who did not meet criteria for testing. i.e., did not meet protocol-specified values for unstimulated (≥ 5 mcg/dl), stimulated (≥18 mcg/dl) cortisol, and change in cortisol (≥7 mcg/dl). There was a suggestion of more subjects at the Baseline timepoint than at the Screening timepoint that did not fulfill these criteria; there were 9 at compared with 15 at Baseline after completing 2 weeks of MF DPI 200 BID. After 12 more weeks of therapy at Endpoint, however, there were still only 15 such subjects.

Distribution of Subjects who Did not Meet Protocol-Specified Criteria for Cortrosyn Testing

	MF DPI 200 QAM	MF DPI 200 QPM	MF DPI 400 QAM	MF DPI 200 BID	Placebo	Total
Screening						
Pre-Cortrosyn value < 5 mcg/dl	0	0	0	0	0	0
Post-Cortrosyn value < 18 mcg/dl	0	1	0	1	0	2
Difference Between Post- and Pre-cortrosyn value < 7 mcg/dl	1	2	2	1	0	6
Post-Cortrosyn value < 18 mcg/dl and Difference Between Post- and Pre-cortrosyn value < 7 mcg/dl	0	0	1	0	0	1
Baseline						
Pre-Cortrosyn value < 5 mcg/dl	0	1	1	0	0	2
Pre-Cortrosyn value < 5 mcg/dl and Post-Cortrosyn value < 18 mcg/dl	0	1	0	0	0	1
Post-Cortrosyn value < 18 mcg/dl	0	0	1	0	0	1
Difference Between Post- and Pre-cortrosyn value < 7 mcg/dl	0	0	4	3	3	10
Post-Cortrosyn value < 18 mcg/dl and Difference Between Post- and Pre-cortrosyn value < 7 mcg/dl	0	0	1	0	0	1
Endpoint						
Pre-Cortrosyn value < 5 mcg/dl	2	0	0	1	1	4
Post-Cortrosyn value < 18 mcg/dl	0	1	0	0	0	1
Difference Between Post- and Pre-cortrosyn value < 7 mcg/dl	0	1	4	2	1	8
Post-Cortrosyn value < 18 mcg/dl and Difference Between Post- and Pre-cortrosyn value < 7 mcg/dl	0	0	1	1	0	2

While testing was done at Screening, this data was only available as individual line listings. The means at Screening were not available in tabulated form and no statistical analyses comparing the values at Screening with those at Baseline or Endpoint were available. Such tabulated data and analysis will be requested of the sponsor.

g) EKG Results

An ECG was only performed at Screening and thus could not be used to reflect drug effect. All abnormalities noted were judged by the investigator to have been not clinically significant.

h) Safety Conclusions for C96-196

1. Investigators and Investigational Centers

There were 132 subjects in the 3 month phase and 128 subjects in the 9 month phase involved at 21 participating centers.

2. Objectives/Rationale

The objective of this randomized, multicenter, double-blind, placebo-controlled, parallel groups trial was to evaluate the efficacy and safety of MF DPI (400 BID and 800 BID) vs placebo in reducing oral prednisone requirements in subjects with severe asthma.

a) Primary

The primary efficacy variable was the percent change from Baseline at Endpoint (last available data in the 3-month phase) in daily prednisone requirement.

b) Secondary

Secondary efficacy variables included FEV_1, $FEF_{25-75\%}$, FVC, daily peak flow, symptom scores, Proventil use, nighttime awakenings and assessments of response to therapy.

c) Safety Data

Adverse events, laboratory test results, vital signs, ECGs, results of physical examinations, Cortrosyn test results, and MF concentrations were summarized and tabulated for the 3-Month Phase and for the 9-Month Phase if assessed (i.e., MF concentrations were not assessed during the 9-Month Phase).

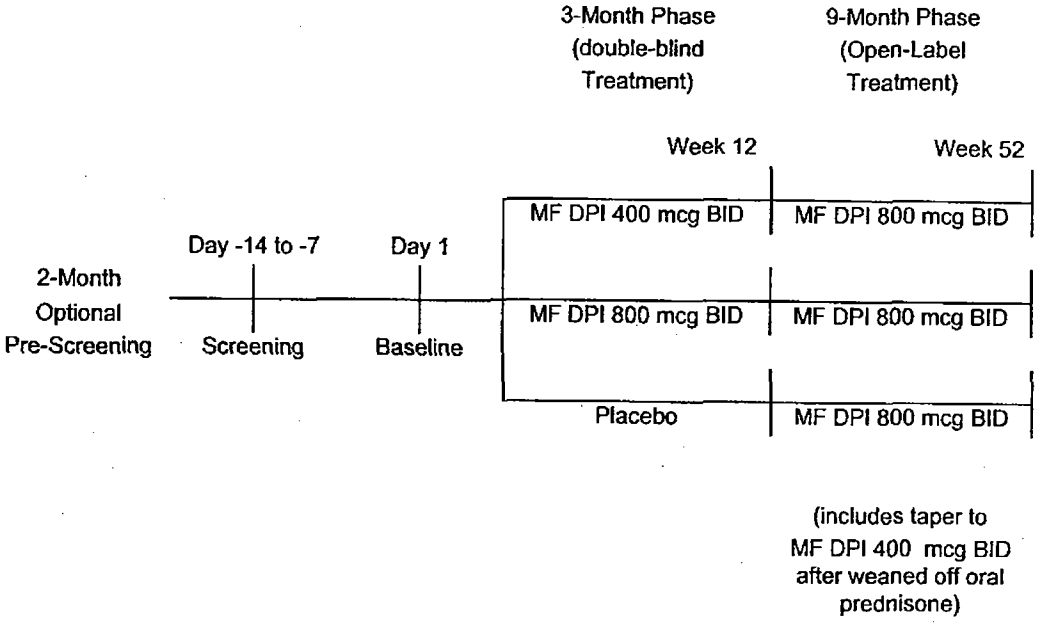
3. Study design

This was a Phase III, randomized, multicenter study of two dose regimens (400 BID and 800 BID) of MF powder compared to placebo in the treatment of asthma in subjects previously maintained on oral prednisone. Subjects must have required daily or alternate-daily oral corticosteroids for ≥5 of 6 months prior to randomization. For the 2 weeks prior to the Screening visit, the oral steroid used must have been prednisone and the dose must have been 5-30 mg daily or 10-60 mg every other day. The minimum effective oral steroid dose for the subject must have been established, as documented by attempts at oral steroid dosage reduction in the previous 6 months. An optional pre-screening period of up to 2 months was allowed for any subject who required having the minimum effective oral steroid dose established. After a run-in period of 1 to 2 weeks, subjects were treated with study drug using double-blind conditions for a period of 3 months. The long-term safety of mometasone was evaluated in a subsequent 9 month, open-label treatment phase.

Eligible subjects were randomized at Baseline (Visit 2) to receive one of the following: MF DPI 400 BID, MF DPI 800 BID, or placebo in a 1:1:1 ratio according to a computer-generated code. Numbers were to be assigned sequentially as subjects qualified for entry into the study. Subjects entering the study who were maintained on <12.5 mg/day (or <25 mg on alternate days) of prednisone were enrolled in ascending order (low-dose stratum), while subjects entering the study who were maintained on ≥12.5 mg/day (or ≥25 mg on alternate days) of prednisone were enrolled in descending order (high-dose stratum).
Subjects who completed the entire 3-Month Phase or who discontinued treatment early for reasons other than an adverse event or for noncompliance were encouraged to continue with

open-label treatment with MF DPI. These subjects were to receive open label treatment with MF DPI 800 BID, which could be tapered down to a minimum of 400 BID once the subject had been weaned off prednisone.

4. Summary of Study Protocol



a) Study Population

This study was designed such that 6-18subjects would be enrolled at each of approximately 20 study centers to provide a total of approximately 145 enrolled subjects, including 135 subjects who met the criteria for the evaluation of the primary endpoint. It was projected that approximately 100 subjects would be enrolled in the 9-month phase to provide long-term safety data.

(1) Inclusion Criteria

The following criteria were unique to C96-137 as compared to other trials in this NDA:

- Subjects must have had a history of asthma for at least 1 year. (as compared to 6 months)
- The subject's baseline FEV_1 must have been greater than or equal to 40% and less than or equal to 85% of predicted at the Screening and Baseline Visits (was 55-85%)
- Subjects must have demonstrated evidence of an increase in absolute FEV_1 of ≥12%, with an absolute volume increase of at least 200 ml, after reversibility testing (with beta agonists or corticosteroids), at Screening or within the past 12 months.
- Subjects must have required daily or alternate day oral corticosteroid therapy to control asthma for at least 5 out of the 6 months prior to study enrollment. Prednisone must have been taken during the 2 weeks immediately before the Screening visit and the dose must have been 5-30 mg daily or 10-60 mg every other day.
- Subjects must have had documented evidence of previous attempts at oral corticosteroid dose reduction within the last 6 months, to establish that the current dose is the minimum effective dose.

(2) Exclusion Criteria

The exclusion criteria were similar to that for C96-196 with the following additions:

- Subjects who were treated with troleandomycin within the last month.
- Subjects who have required ventilator support for respiratory failure secondary to their asthma within the last 6 months (was 5 years).
- Subjects who required in-patient hospitalization for asthma control within the previous 1 month. (was 3 months)
- Subjects who experienced an asthma exacerbation requiring hospitalization during the run-in period.
- Subjects who required an increase in the dose of oral prednisone or any asthma medication other than Proventil during the run-in period.
- Centers 02, 05, 06, 10, 14, 15, 16, 17, 18 and 20 only: Subjects whose normal sleep/wake cycle was inverted (i.e. night shift workers).

(3) Removal of Subjects from Therapy

Subjects who experienced a clinically significant worsening of their asthma during the study were to be discontinued. A worsening included: 1) hospitalization for asthma, 2) significant increases or additions of any asthma medication (with the exception of inhaled Proventil or oral prednisone), 3) the subject required a third burst of prednisone.

Subjects who discontinued the study in this phase were eligible to enter the 9-Month Phase at the time of discontinuation except if the reason for discontinuation was non-compliance or adverse events that would contraindicate further treatment with study drug.

b) Treatments Administered

During the *Pre-screening period* (up to 2 months prior to Screening), attempts at reduction could be made for those subjects who had not already had the minimum effective oral steroid dose established. The dose was to be reduced by appropriate dose steps until the subject experienced a worsening of asthma as defined by either objective or subjective parameters. The dose level above that at which worsening occurred was to be regarded as the minimum effective dose. The oral steroid that was taken in the 2 weeks prior to the Screening visit must have been prednisone, and the dose must have been 5-30 mg daily or 10-60 mg every other day. If the subject was taking any inhaled corticosteroids, the dose was to be adjusted as necessary so that it was within the protocol-specified dose range for the 2 weeks prior to Screening as specified in the Inclusion criteria.

During the *Run-in period* (between Screening and Baseline Visits), all subjects were to continue to take their prescribed medications including oral and inhaled corticosteroids. The subject's prescribed inhaled corticosteroid was to be discontinued at the Baseline visit and study drug was to be initiated. Subjects were not to take Proventil unless needed or before exercise.

At the Baseline visit for the 3 month phase, subjects were randomized to 12 weeks with one of the following:

	AM	PM	
	MF DPI	MF DPI	Total mcg/day
Group 1	200 mcg x 2	200 mcg x 2	MF 800 mcg
Group 2	400 mcg x 2	400 mcg x 2	MF 1600 mcg
Group 3	Placebo x 2	Placebo x 2	Placebo (0)

Subjects completing the 3-Month Phase or discontinuing early for reasons other than adverse event or noncompliance could be rolled over to receive 9 months of open-label treatment. The initial dose was to be 800 mcg BID. But could be tapered down once the subject had been weaned off prednisone. The dose was not to be reduced below 400 mcg BID. The subject was to receive a 200 mcg device and was to be instructed to take 4, 3 or 2 inhalations twice daily, according to the dose level of mometasone that was being used as follows:

AM	PM	
MF DPI	MF DPI	Total mcg/day
200 mcg x 4	200 mcg x 4	1600 mcg
200 mcg x 3	200 mcg x 3	1200 mcg
200 mcg x 2	200 mcg x 2	800 mcg

Subjects were advised to rinse their mouth with water or a suitable mouthwash after study drug administration.

(1) Concomitant/Restricted Medications

The list of permitted medications was similar to C96-196 except that prednisone, nasal and ocular steroids, and cromolyn and nedocromil was permitted in this study. The subject was also allowed to utilize, but was to attempt to withhold, the following medications for a specific interval before each visit: 1) Nebulized beta agonist or ipratropium bromide: 4 hours, 2) Oral beta agonists or salmeterol: withhold last dose before PFTs, and 3) Ipratropium bromide (MDI): 2 hours.

This trial prohibited the same medications as previous studies with some modification. These washouts were also used for subsequent PFTs at Baseline and during the study. The subject was allowed to utilize, but was to attempt to withhold, the following medications, similar to C96-196, were prohibited prior to Screening but times were generally shorter than those for the other studies:

Medication	Washout Time prior to Screening visit
- B-adren. bronchodilators, syrups, tablets	withhold last dose before PFTs (was 24 hours)
- Beta-adrenergic bronchodilators, sustained-release tablets	same as above (was 48 hours)
- Bronchodilators, inhaled	2 hours (was 6)
- Ipratropium bromide (MDI)	2 hours (was 12 hrs –2 weeks)
- Nebulized beta-agonists/ipratropium bromide	4 hours (was 6)
- Salmeterol	withhold last dose before PFTs (was 1-2 weeks)

It was originally not clear what is meant for Salmeterol to "withhold last dose before PFTs." I would not understand this as it is written in the protocol and would not know what to tell a subject. Salmeterol obviously could influence the spirometry data and the sponsor should clarify the definition of salmeterol withholding.

A clarification of the salmeterol procedure was provided by the sponsor in a document dated 8/27/1999. The sponsor felt that withholding long-acting beta-agonists for substantially longer than the normal BID-dosing interval could potentially interfere with the trial's primary endpoint since these drugs may reduce the need for prednisone bursts. As a compromise, and because spirometry was a secondary endpoint, the sponsor decided to measure spirometry at the trough of the BID regimen. The sponsor goes on to say that in those instances where the previous bronchodilator dose was less than 12 hours, they accepted the fact that there may have been some impact on the spirometry endpoint. The sponsor says that relatively few patients were taking BID salmeterol. In the double-blind phase of this study, the numbers of subjects using salmeterol were 13/46, 11/43, and 6/43 in the MF DPI 400 BID, 800 BID, and placebo arms, respectively. The sponsor says that for these patients, the time of the last salmeterol dose prior to their visit was generally 10-15 hours. At the double-blind endpoint for these patients, all but 10 patients (4, 4 and 3, respectively) had their visit more than 10 hours since their last salmeterol dose.

c) Assessments/Study Procedures

Study Procedures – 3 Month Phase

		3-Month Phase (Double-Blind Treatment)				
Treatment Days	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Visits 5-14	Visit 15
	Day -14 to -7	Day 1	Day 4	Week 1	Weeks 2-11 (1-week intervals)	Week 12
Obtain Informed Consent	X					
Review Inclusion/Exclusion Criteria	X	X				X
Prednisone Dose Review/Adjustment	X	X	X	X	X	X
Medical/Disease History	X					
Concomitant Medications Review	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
Oropharyngeal Exam	X	X	X	X	X	X
Pulmonary Auscultation	X	X	X	X	X	X
Pulmonary Function Tests	X	X	X	X	X	X
Reversibility Test	X					
Hematology, Blood Chemistry, Urinalysis	X					X
Pregnancy Test	X					X
Cortrosyn Test	X					X
Mometasone Furoate Concentration						X
Electrocardiogram	X					X
Chest X-ray	X					

Dispense Diary	X	X		X	X	X
Review Diary		X	X	X	X	X
Dispense Peak Flow Meter	X					
Dispense Study Medication		X			X	X
Response to Treatment Evaluation			X	X	X	X
Quality of Life Assessment		X				X
Adverse Events Evaluation	X	X	X	X	X	X
Compliance Check/Collect Medication			X	X	X	X

Study Procedures – 9 Month Phase			
Treatment Days	9-Month Phase (Open-Label Treatment)		
	Visits 16-19	Visits 20-27	Visit 28
	Weeks 13-16 (1-week intervals)	Weeks 20-48 (4-week intervals)	Week 52
Obtain Informed Consent			
Review Inclusion/Exclusion Criteria			
Prednisone Dose Review/Adjustment	X	X	X
Medical/Disease History			
Concomitant Medications Review	X	X	X
Physical Examination, Weight	X	X	X
Height			
Vital Signs (temperature, blood pressure, pulse, respiratory rate)	X	X	X
Oropharyngeal Exam	X	X	X
Pulmonary Auscultation	X	X	X
Pulmonary Function Tests	X	X	X
Reversibility Test			
Hematology, Blood Chemistry, Urinalysis		X	X
Pregnancy Test		X	X
Cortrosyn Test			X
Mometasone Furoate Concentration			
Electrocardiogram			X
Chest X-ray			
Dispense Diary	X	X	
Review Diary	X	X	X
Dispense Peak Flow Meter			
Dispense Study Medication		X	
Response to Treatment Evaluation	X	X	X
Quality of Life Assessment		X	
Adverse Events Evaluation	X	X	X
Compliance Check/Collect Medication	X	X	X

The details of the procedures were generally the same as those trials described previously in this NDA review. Further specific details on the visit procedures include:

- Spirometry – Each visit, three measurements were performed. The effort with the highest FEV_1 was recorded as the best effort.

- Quality of Life Assessment - A self-administered health-related quality of life (HQOL) questionnaire for subjects with asthma which is comprised of the validated acute form of the Short-Form Health Survey, a segment of the SF-36, and a validated asthma specific HQOL module. HQOL was measured using the SF-36 and an asthma-specific scale. The SF-36 assesses eight domains of health over the previous week: physical functioning, role physical, bodily pain, general health perceptions, vitality, social functioning, role emotional, and mental health. The asthma-specific scale assesses breathlessness, mood, social impact, asthma concerns, psychosocial impact, and physical symptoms. As with the SF-36, the asthma specific scale uses the past week as the reference period for assessment.

- Prednisone Dose Adjustment
  During Pre-Screening, if such documentation of oral steroid dosage reduction in the previous 6 months was not available, the Investigator was to attempt to reduce the oral steroid dose during the pre-screening period in order to establish the minimum effective dose. Between the Screening and Baseline visits, the prednisone dose and the inhaled corticosteroid dose were to remain constant. At Baseline, the prescribed inhaled corticosteroid was discontinued and replaced with the study drug. Prednisone dose adjustment could begin after one week at Visit 4 (Week 1).

  Dosage adjustment criteria were reviewed at each visit. The prednisone dose was to be reduced if the subject met the following criteria:

1. FEV_1 had not decreased by 20% or more from the Baseline value
2. FEV_1 was ≥40% of predicted
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 received the reduced dose until the next visit, when criteria were again reviewed. Reductions were made as follows:

Daily Prednisone
30 mg QD
Reduce in ≤5 mg QD steps
10 mg QD
Reduce in ≤2.5 mg QD steps
5 mg QD
Reduce in 1.0-2.5 mg QD steps
0 mg

Alternate Day Prednisone
60 mg QOD
Reduce in ≤10 mg QOD steps
20 mg QOD
Reduce in ≤5 mg QOD steps
10 mg QOD
Reduce in ≤2.5 mg QOD steps
0 mg

If the subject did not meet the above criteria, the 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 with an alternate-day regimen. For exacerbations, subjects could be rescued with a burst of up to 60 mg/day, tapered down within 2 weeks to a dosage of 2.5 mg above the preburst daily dosage.

During the 3-Month Phase, subjects requiring a second burst were to be maintained on a fixed dose 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.

- Mometasone Dose Adjustment

  Subjects entering the 9-Month Phase initially received 800 BID. This dose was to be maintained for the first 4 weeks of this phase (Visits 16-19). The dose could be reduced at Visit 19, provided that the subject had not received prednisone within the previous 4 weeks and that the subject met dosage adjustment criteria 1, 2, 3, 4 and 5 as described in the prednisone dose reduction criteria section above. The dose could be reduced to 600 BID and this dose must have maintained the subject in a stable condition for at least 4 weeks before the next dose reduction could be attempted. Subjects meeting reduction criteria 1, 2, 3, 4 and 5 at this point could have the dose further reduced to 400 BID which was the minimum permitted dose.

- Diary Data - Each subject was given diary cards at Screening, at Baseline, weekly through Visit 15 (week 12), and then every 4 weeks through Visit 28 (Week 52). The following information was recorded daily in the diary: morning and evening peak expiratory flow, total number of Proventil inhalations, symptoms of asthma (wheezing, difficulty breathing and cough were graded 0-3: 0 = none, 1 = noticeable, 2= annoying, 3 = very uncomfortable), number of nocturnal awakenings requiring Proventil use, adverse events and use of study drug, prednisone and concomitant medications.

- Cortrosyn Testing

  An 8 a.m. (±1 hour) blood sample was drawn for determination of plasma cortisol. An intravenous injection of Cortrosyn was then administered at a dose of 250 μg. Another blood sample was taken 30 minutes after the injection for the measurement of plasma cortisol.

- Mometasone Furoate Concentrations

  Subjects withheld the morning dose of study medication on the day of this visit. At the time the pre-Cortrosyn (8 a.m. ± 1 hour) sample was drawn, the subject had approximately 5 ml of blood drawn to provide a 2.5 ml predose plasma sample for analysis of mometasone concentration. The blood was immediately centrifuged and the plasma transferred to a plastic vial. This vial, was immediately frozen at -20°C. Subjects then took their dose of study medication immediately after Cortrosyn administration.

- Clinical Asthma Exacerbation

  A clinical asthma exacerbation (CAE) was defined as a worsening of asthma requiring hospitalization, emergency treatment or an increase in prednisone of >10 mg/day or >20 mg every other day.

d) Statistical and Analytic Plans

(1) Efficacy Analyses

The primary objective of the study was to evaluate the ability of MF DPI to reduce daily prednisone requirement compared with placebo. Endpoint is defined as the last determination during the 3-month phase for which the subject had non-missing data. For each subject, this primary variable at Endpoint was calculated as:

$$[Prednisone_{(Endpoint)} - Prednisone_{(Baseline)}] / Prednisone_{(Baseline)} \times 100$$

The comparison of 800 BID and placebo was identified in the protocol as the primary analysis. The primary efficacy variable at Endpoint was to be analyzed for all randomized subjects using a two-way ANOVA, which extracted sources of variation due to treatment, center and treatment-by-center interaction. Pairwise comparisons were to be based on the least squares means of the MF DPI doses and placebo (from the ANOVA). Since all pairwise comparisons addressed independent questions and the comparison between 800 mcg BID and placebo was identified as the primary efficacy analysis, if the test for no difference between 800 BID and placebo was significant, then each comparison was to be performed at the 0.05 (two-sided) level of significance, with no adjustment for multiple comparisons. In addition to the analysis at Endpoint, all three pairwise comparisons between the three treatment groups were to be made with respect to the percent change from Baseline in daily prednisone requirement for each scheduled visit, using the same two-way ANOVA described above.

All other efficacy variables were to be analyzed at each time point using the same two-way ANOVA noted above. This includes daily prednisone requirement (actual change from baseline), FEV_1, FVC, FEF_{25-75} and the physician's evaluations of response , as well as subject evaluations recorded on the diary (averaged over each 7-day interval) -- PEFR, asthma symptoms, nocturnal awakenings, and the number of Proventil inhalations. Kaplan-Meier survival time estimates were to be used to assess time to discontinuation because of asthma worsening and the time to discontinuation was to be analyzed using the log-rank test.

The primary analysis was based on the All Treated Subjects data set, rather than the Efficacy-Evaluable data set. The Efficacy-Evaluable analysis was used only to confirm the findings of the All-Treated-Subjects analysis.

(2) Summary of Safety Data

Adverse events that were reported during the 3-Month Phase were to be summarized by treatment group, severity, relationship to treatment, and by outcome, subgroup (sex, age and race), and seriousness. Lab data, vital signs, and body weight were to be summarized as overall results, as median, minimum and maximum values, as abnormal values, as shifts relative to Baseline and normal ranges, and by subgroup (sex, age and race). Mometasone furoate levels were summarized for the Week 12 visit. Plasma cortisol values were to be analyzed for the Screening, Week 12, and Week 52 of the 3-Month Phase, and the end of 9-Month Phase by the same two-way ANOVA described above noting: 1) Pre-Cortrosyn Value, 2) Post-Cortrosyn Value, 3) the Difference between Post- and Pre-Cortrosyn values, and 4) the change from Screening to Endpoint in the Difference between Post and Pre values.

(3) Sample Size

The sample size was chosen to detect, with 90% power and a 5% significance level, a clinically meaningful pairwise difference in the mean percent change from Baseline in daily prednisone requirement between any active treatment group and placebo. With 45 subjects per treatment group, assuming a pooled standard deviation of 0.58 units for the percent change from baseline (58%, considering a mean baseline dose of 10.0 mg), mean treatment differences of approximately 0.4 units (40%) or more would be detectable with power greater than 90%.

(4) Changes in Study Conduct or Planned Analyses

- The range of the allowable proportion of actual FEV_1 values relative to predicted values at the Screening and Baseline visits was broadened from 40-85% to 30-95%.

- The original protocol stated that the prednisone requirement had to be 5-30 mg QD or 10-60 QOD between Screening and Baseline and had to be stable during that period. This was relaxed to include subjects taking prednisone 5-35 mg QD, and/or subjects with no dose change for more than 1 day, between Screening and Baseline.

- Subjects demonstrating an increase or decrease in FEV_1 of more than 22%, rather than 20%, between Screening and Baseline were excluded from the study.

- Reversibility testing could have demonstrated an increase in FEV_1 of $\geq$11.8%, rather than $\geq$12%, as long as the absolute change was $\geq$190 ml.

The following changes were specific to the 3 month phase:

- The definition for the ITT data set was changed to an All Treated Subjects data set and an Efficacy-Evaluable data set, and specific criteria for the efficacy data set were developed. Subjects were classified as non-evaluable if one or more of the following deviations was present:

- Baseline FEV_1 was < 30% of the predicted value.
- Variability in FEV_1 between the Screening and Baseline visits was ≥ 22%.
- Subject failed the reversibility test at Screening or historical; that is, did not demonstrate evidence of an increase in absolute FEV_1 of 11.8%, with an absolute volume increase of at least 190 ml.
- The bronchodilator reversibility time was not within 45 minutes.
- Using more than 12 puffs of Proventil on any 2 consecutive days within 5 days of the Baseline visit.
- Prednisone requirement 2 weeks prior to Screening was not 5-30 mg QD or 10-60 mg QOD, or the prednisone dose had not been stable for at least 5 days prior to Screening.
- Prednisone use was not 5-35 mg QD, or the prednisone dose changed for more than 1 day, between Screening and Baseline.
- Compliance was <75% of that specified for treatment in the protocol.

- The original protocol described the primary method of analysis as a two-way ANOVA extracting sources of variation due to treatment, center and treatment-by-center interaction. The analysis model was modified to a reduced, main-effects, two-way ANOVA for the primary efficacy analysis.

- The original protocol mentioned that the Endpoint would be defined as the last visit for the 3-Month Phase of the study. The primary efficacy variable, the % change from Baseline in prednisone dosing, however, is primarily derived from diary data. Therefore, the Endpoint was defined more specifically to be relative to the last day of dosing in the 3-Month Phase.

- The planned analysis of time to discontinuation due to asthma worsening was changed to an analysis of time to asthma worsening, which was defined as the first treatment day on which a subject met any criterion for worsening.

It must be noted that no efficacy analysis was specified in the original protocol for the 9 month phase of the study. The following summaries were proposed after the protocol was finalized. The primary efficacy variable for the 9 month phase was defined as the % change in daily prednisone requirement, and the primary time point was the end of the long-term open label phase. The summary statistics of mean change and mean % change from double-blind baseline were provided for all treated subjects, by their original randomized treatment groups. No between treatment group comparisons were made. Summary statistics of mean change and/or mean % change from double-blind baseline were provided for all other secondary efficacy variables. Summary statistics of mean change from the baseline of open label phase (the end of double-blind treatment) were also provided for all the primary and secondary efficacy variables.

5. Results

a) Study Populations

A total of 132 subjects were randomized at 21 participating centers for the 3 month phase. The numbers of subjects randomized and treated were as follows: 46 for 400 BID; 43 for 800 BID; and 43 for placebo. All treated subjects were evaluated for safety. One subject (C96-137-07 #100) who received 400 BID at the Baseline visit was lost to follow-up after that visit and was included only in the safety summaries. Of the 132, 12 subjects did not meet key eligibility requirements and were excluded from the efficacy-evaluable data set.

Number (%) of Randomized Subjects Who Completed the 3-Month Phase, and the Number (%) Who Discontinued the Study and Reasons for Discontinuance

	400 mcg BID (n=46)	800 mcg BID (n=43)	Placebo (n=43)	Total (n=132)
Number (%) Completed	39 (85%)	36 (84%)	20 (47%)	95 (72%)
Reasons for Discontinuation				
Adverse Event	2 (4%)	1 (2%)	0	3 (2%)
Treatment Failure	3 (7%)	5 (12%)	23 (54%)	31 (23%)
Lost to Follow-up	1 (2%)	0	0	1 (1%)
Non-Compliance	1 (2%)	1 (2%)	0	2 (2%)
TOTAL NUMBER (%) DISCONTINUING	7 (15%)	7 (16%)	23 (54%)	37 (28%)

As can be seen from the above table, the dropout rate for placebo was much higher than for MF DPI. This data, in and of itself, is very supportive of the drug's efficacy.

A total of 128 subjects at 21 centers participated in the 9 month phase of the study. All 128 subjects received at least one dose of MF DPI and were evaluated for safety. With the exception of 5 subjects, including 4 who were previously on 400 BID and one who was previously on 800 BID, these subjects represented all of the subjects randomized to treatment at the Baseline of the 3-Month Phase who received one dose of study medication. One subject (#221) who was not included in the 3 month efficacy data was not included in the 9 month efficacy analysis for consistency.

Number (%)Who Completed the 9-Month Phase, and the Number (%) Who Discontinued and Reasons for Discontinuance

	MF DPI Variable Dose (n=128)
Number (%) Completed	106 (83%)
Reasons for Discontinuation	
Adverse Event	1 (1%)
Treatment Failure	10 (8%)
Subject did not wish to continue	3 (2%)
Non-Compliance	8 (6%)
TOTAL NUMBER (%) DISCONTINUING	22 (17%)

The majority of subjects who discontinued experienced treatment failure or were noncompliant with the protocol.

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

- All Treated Subjects: This data set included all subjects randomized who received at least one dose of study medication (intent-to-treat principle) and who have follow-up data.
- Efficacy-Evaluable Subjects: This data set included all subjects randomized who met the key eligibility and evaluability criteria defined previously. This data set was used for confirmatory efficacy analyses on the primary efficacy variable, % change from baseline in daily prednisone.

Distribution of Subject Subsets Analyzed in the 3 month phase

	400 mcg BID	800 mcg BID	Placebo	Total
All Treated Subjects [a]	46	43	43	132
All Treated Subjects With Follow Up Efficacy Data	45	43	43	131
Subjects Lost to Follow Up After Baseline	1	0	0	1
Efficacy-Evaluable	43	40	37	120
Excluded From Efficacy Evaluable	3	3	6	12

a: Includes 1 subject (C96-137-07 #100) who received 400 BID at Baseline and was lost to follow-up.

A total of 12 subjects were excluded from the Efficacy-Evaluable Data Set for the 3 month phase because of protocol deviations.

	400 mcg BID (n=46)	800 mcg BID (n=43)	Placebo (n=43)	Total (n=132)
Type of Protocol Deviation				
Inclusion/Exclusion Criteria	1	2	5	8
Non-Compliance	1	1	1	3
Prohibited Medication	0	0	1	1
Insufficient Efficacy Data	1	0	0	1
TOTAL # WITH PROTOCOL DEVIATIONS	3	3	6	12

b) Demographics

	400 BID (n=46)	800 BID (n=43)	Placebo (n=43)
Age (years)			
Mean	49	53	55
Min-Max	13-83	22-77	26-79
Distribution of Subjects in Age Categories			
12-17 years	2	0	0
18-64 years	33	34	31
≥65 years	11	9	12
Sex			

	400 BID (n=46)	800 BID (n=43)	Placebo (n=43)
Female	24	27	19
Male	22	16	24
Race			
Caucasian	35	39	37
Black	8	3	3
Hispanic	2	1	3
Asian	1	0	0
Smoking History			
Never Smoked	29	30	23
Has Not Smoked in 6 Months	16	13	20
Smoked in 6 Months	1	0	0
Duration of Asthma Condition (years)			
Mean	21	19	23
Min-Max	2-51	1-51	2-69
FEV_1 % Predicted at Baseline			
Mean	59	61	57
Min-Max	40-84	38-91	26-85
Absolute FEV_1 at Baseline (liters)			
No. of subjects	45	43	43
LS Mean	1.87	1.79	1.78
Baseline AM PEFR			
No. of subjects	45	43	42
LS Mean	324.27	298.95	316.14
Baseline Pred. Use			
No. of subjects	45	43	43
Mean (mg/day)	11.93	12.02	11.56
Min-Max	5.00-30.00	4.00-30.00	5.00-35.00
No Baseline Inhaled Corticosteroids			
No. of subjects	4	11	2
Any Inhaled Corticosteroid			
No. of subjects	42	32	41
Beclomethasone Diproplonate			
No. of subjects	7	5	4
Mean (mcg/day)	444	454	410
Min-Max	168-672	168-840	252-504
Budesonide			
No. of subjects	0	3	0
Mean (mcg/day)	—	1067	—
Min-Max	—	800-1600	—
Flunisolide			
No. of subjects	8	5	7
Mean (mcg/day)	1750	1300	1076[d]
Min-Max	1000-2000	1000-2000	35-2000[d]

	400 BID (n=46)	800 BID (n=43)	Placebo (n=43)
Fluticasone Propionate			
No. of subjects	12	9	15
Mean (mcg/day)	770	953	666[d]
Min-Max	1000-1320	1000-1760	4-1760[d]
Triamcinolone Acetonide			
No. of subjects	15	10	15
Mean (mcg/day)	987	1130	1253
Min-Max	400-2400	800-1600	400-2000

The treatment groups were generally similar for most parameters. While subjects were said to have been titrated to their lowest effective dose for oral steroids before the double blind period, there was no titration of the inhaled corticosteroids. Neither the need for inhaled corticosteroids nor the minimum inhaled corticosteroid dose was established and inhaled corticosteroid use was not controlled.

It must also be noted that the dosages of the individual inhaled corticosteroids, when reported at Baseline, were generally at the high end of the dosage ranges that are typically employed in clinical settings. It appears that there were differences among the treatment groups at Baseline in the number of subjects on inhaled corticosteroids. The 400 BID and placebo groups had proportionately more subjects using inhaled corticosteroids than the 800 BID group. Inhaled corticosteroid use was required to remain stable prior to study entry. The dose of oral prednisone appeared to be similar among the groups and most probably had more of a pharmacologic impact thus negating the differences in previous inhaled steroid use.

6. Analysis of Efficacy

a) Daily Prednisone Requirement

(1) Prednisone Adjustment Before Baseline

The data on prednisone reduction during the 6 months before Screening is listed as being in Section 16.2.14.3 (Volume 110 Update, pp. 11775-11804). The data on prednisone reduction during the period between Screening and Baseline is listed as being in Section 16.2.14.2 (Volume 109 Update, pp. 11756-11773). No real prednisone reduction was accomplished in the period between Screening and Baseline. In the 6 months before Screening, however, there appeared to be several prednisone dose manipulations for generally all subjects. While the subjects did not typically end up on a lower dose than at the start of the 6 months, it does appear that a concerted effort was undertaken to manipulate the prednisone dose to the lowest acceptable at the time.

(2) 3 month phase

Both MF DPI treatment groups were significantly ($p<0.01$) more effective than placebo in reducing daily prednisone requirements at Endpoint. At Endpoint, the mean % reductions of prednisone use were 46.0% and 23.9%, in the 400 and 800 BID groups, respectively. For placebo-treated subjects, mean prednisone requirements increased by 164.4%. The two MF DPI treatments did not differ significantly from each other.

Prednisone Dose (mg/day) Percent Change from Baseline in the 3 month phase

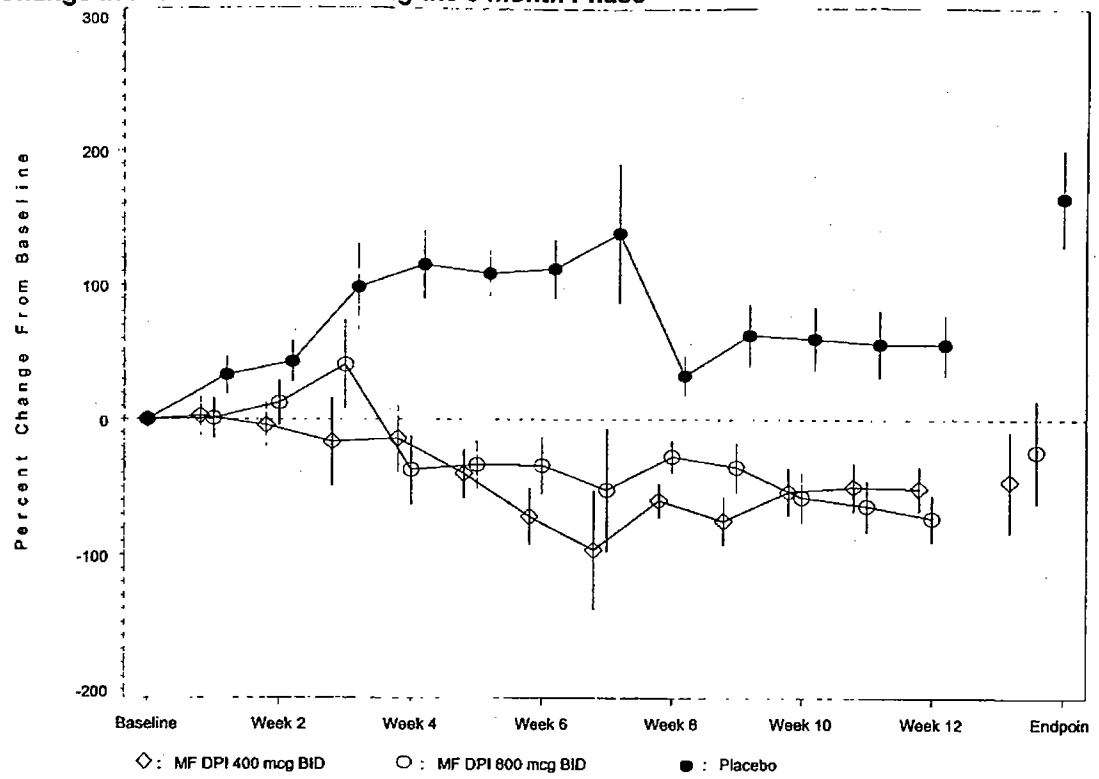
	400 mcg BID (A)			800 mcg BID (B)			Placebo (C)		
	N	Mean % Change	Mean	N	Mean % Change	Mean	N	Mean % Change	Mean
Baseline	45		11.93	43		12.02	43		11.56
Percent Change From Baseline									
Week 1	45	2.7%	-0.44	43	0.9%	-0.14	43	33.1%	2.04
Week 2	44	-4.4%	-1.47	43	12.4%	0.81	42	42.9%	3.07
Week 3	43	-16.5%	-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
Endpoint	**45**	**-46.0%**	**-6.33**	**43**	**-23.9%**	**-3.19**	**43**	**164.4%**	**11.81**

Analysis Results (Percent Change From Baseline)[a]

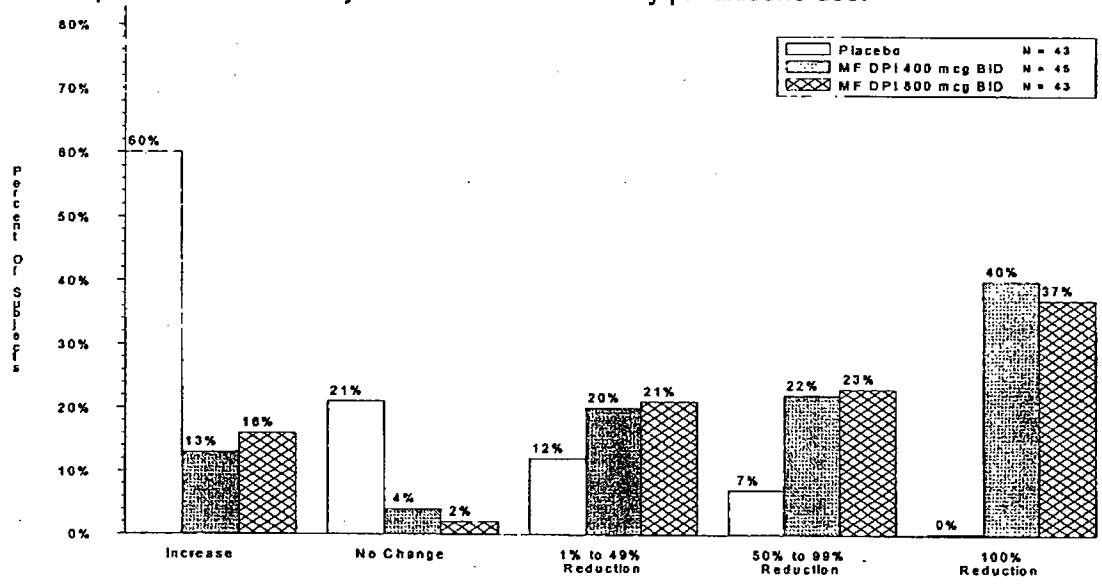
		P-value		Pairwise Comparisons (p-value)		
Time point	Pooled SD	Treatment	Center	A vs B	A vs C	B vs C
Week 1	92.90	0.21	0.46	0.93	0.14	0.12
Week 2	101.16	0.10	<0.01	0.45	**0.04**	0.18
Week 3	199.96	0.05	0.42	0.20	**0.01**	0.21
Week 4	151.13	<0.01	0.58	0.50	**<0.01**	**<0.01**
Week 5	104.86	<0.01	0.02	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**
Endpoint	**228.28**	**<0.01**	**0.84**	**0.66**	**<0.01**	**<0.01**

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

Change in Prednisone Use During the 3 month Phase



Many participants on MF DPI were able to completely discontinue their use of prednisone and others were able to substantially decrease their oral steroid requirement. 40% of subjects in the 400 BID group and 37% of subjects in the 800 BID group, in contrast to none of the subjects in the placebo group, no longer required oral prednisone to manage their asthma. In contrast, 60% of placebo-treated subjects increased their daily prednisone use.



The sponsor performed an analysis based on based on oral prednisone use at Baseline. Subjects were stratified into a low-dose prednisone stratum (< 12.5 mg/day) and a high dose prednisone stratum (≥ 12.5 mg/day). The greatest reductions at Endpoint were observed in high dose subjects in both MF DPI groups.

	(n)	Baseline Prednisone (Mean)	Change in Prednisone use at Endpoint (Mean)	(%)
Daily Prednisone < 12.5 mg at Baseline				
MF DPI 400 mcg BID	32	8.23	-0.33	3.9%
MF DPI 800 mcg BID	26	7.47	0.44	6.3%
Placebo	31	7.89	15.09	226.2%
Daily Prednisone ≥ 12.5 mg at Baseline				
MF DPI 400 mcg BID	13	19.42	-13.27	-68.8%
MF DPI 800 mcg BID	17	19.26	-6.06	-32.5%
Placebo	12	21.07	4.64	36.1%

Thus, subjects already at a lower prednisone dose were essentially only able to maintain their prednisone dose while the largest amount of the decrease was done in that one-third of the subjects on high dose prednisone.

(3)9 month phase

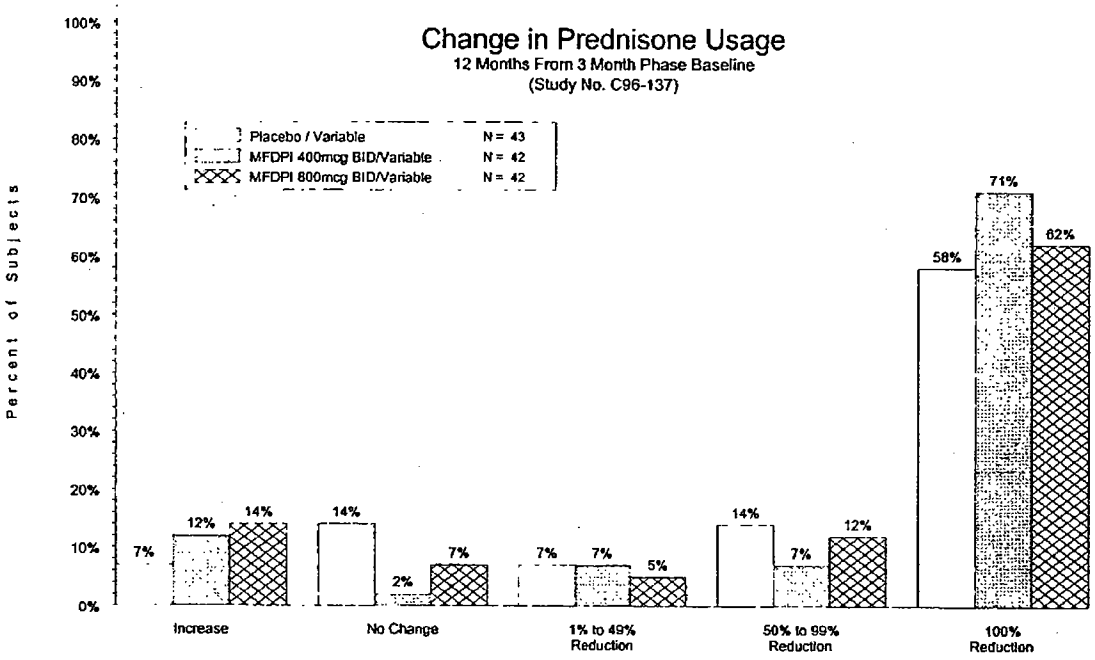
At the endpoint of the 9 month phase, mean % reductions from the 3 month phase Baseline in daily prednisone requirements were 58.1%, 42.5% and 61.6% in subjects previously treated with 400 mcg, 800 mcg and placebo, respectively.

Prednisone Dose (mg/day) Change from the original 3-Month Phase Baseline (For All Subjects who Entered the 9-Month Phase of the Study)

	Mean Oral Prednisone At Baseline					
	MF 400 mcg / MF Variable		MF 800 mcg / MF Variable		Placebo / MF Variable	
	N	Mean	N	Mean	N	Mean
3-Month Phase Baseline	42	11.63	42	12.33	43	11.57
9-Month Phase Baseline	42	6.27	42	7.92	43	21.55

	Change From 3-Month Phase Baseline								
	MF 400 mcg / MF Variable			MF 800 mcg / MF Variable			Placebo / MF Variable		
	N	Mean	(Mean % Change)[a]	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Week 1	42	-4.46	(-12.3%)	41	-4.41	(-32.8%)	42	9.21	(127.5%)
Week 2	42	-6.61	(-42.9%)	40	-6.42	(-57.6%)	42	2.55	(47.7%)
Week 3	41	-8.82	(-75.7%)	40	-6.46	(-47.5%)	42	-0.40	(12.4%)
Week 4	41	-9.02	(-73.5%)	40	-7.53	(-61.8%)	42	-2.02	(-5.6%)
Week 6	40	-9.76	(-87.6%)	41	-6.44	(-58.2%)	40	-1.48	(3.3%)
Week 8	40	-9.62	(-82.2%)	41	-6.78	(-61.5%)	39	-2.87	(-15.8%)
Week 10	39	-10.02	(-86.7%)	40	-7.97	(-71.9%)	39	-3.85	(-15.7%)
Week 12	39	-9.29	(-74.3%)	39	-7.93	(-67.9%)	39	-4.55	(-29.0%)
Week 14	38	-10.34	(-88.9%)	38	-7.71	(-67.2%)	39	-7.06	(-55.5%)
Week 16	36	-9.82	(-83.0%)	38	-8.79	(-72.6%)	39	-7.27	(-55.1%)

Week 18	36	-10.79	(-91.9%)	38	-7.29	(-69.0%)	39	-7.40	(-60.9%)
Week 20	36	-9.41	(-79.0%)	37	-9.27	(-81.3%)	39	-7.62	(-63.4%)
Week 22	36	-9.79	(-83.2%)	36	-10.26	(-84.2%)	38	-5.92	(-33.7%)
Week 24	36	-7.89	(-70.1%)	36	-10.23	(-88.0%)	38	-5.90	(-50.4%)
Week 26	36	-8.74	(-69.4%)	36	-9.14	(-80.0%)	38	-7.02	(-61.3%)
Week 28	36	-10.47	(-88.3%)	36	-8.82	(-77.9%)	37	-8.06	(-71.9%)
Week 30	36	-8.29	(-71.5%)	35	-10.01	(-86.8%)	36	-8.17	(-70.5%)
Week 32	36	-8.75	(-76.6%)	35	-9.15	(-81.4%)	36	-7.89	(-66.3%)
Week 34	35	-10.18	(-86.1%)	35	-8.87	(-72.2%)	35	-7.56	(-65.5%)
Week 36	35	-9.40	(-81.9%)	35	-8.77	(-69.3%)	35	-8.09	(-68.1%)
Week 38	35	-10.85	(-91.8%)	35	-8.63	(-70.0%)	35	-8.82	(-77.3%)
Week 40	31	-9.95	(-87.9%)	31	-9.63	(-88.0%)	33	-8.97	(-81.6%)
Endpoint	**42**	**-7.36**	**(-58.1%)**	**42**	**-4.11**	**(-42.5%)**	**43**	**-7.35**	**(-61.6%)**



In those subjects who were able to complete all 52 weeks of the study, the mean reductions in daily prednisone requirements were even more impressive. The reductions in prednisone requirements were greater at the end of the 9 month phase than at the end of the 3 month phase, demonstrating that longer duration of treatment with MF DPI is effective in further reducing daily prednisone requirements, even among subjects in the placebo group, whose mean daily prednisone requirements had increased beyond Baseline requirements following 3 months of treatment. Those subjects originally in the placebo group during the 3 month blinded phase were able to reduce their prednisone dosage at least as good as those subjects originally on active MF DPI treatment.

The sponsor performed a confirmatory analysis in the aforementioned efficacy-evaluable data set. A similar pattern of response was noted but for unclear reasons there

appeared to be a greater difference between Endpoint and Week 12 for the efficacy-evaluable data set.

A subgroup evaluation of response with stratification of oral prednisone use at Baseline was performed at the Endpoint of the 3 month phase. Two strata were employed during randomization into this study: 1) subjects entering the study who were maintained on <12.5 mg/day, i.e., the low-dose stratum, and 2) subjects entering the study who were maintained on ≥12.5 mg/day, i.e., the high-dose stratum. The results indicated that the response was generally qualitatively similar for high- and low-dose subjects, while the greatest reductions at Endpoint in daily oral prednisone use were observed in high-dose subjects in both MF DPI treatment groups.

Prednisone (mg/day) - Percent Change from Baseline by Prednisone Requirement at Baseline

	400 mcg BID (A)			800 mcg BID (B)			Placebo (C)		
	N	Mean % Change	Mean	N	Mean % Change	Mean	N	Mean % Change	Mean
Daily Prednisone < 12.5 mg at Baseline									
Baseline	32		8.23	26		7.47	31		7.89
Percent Change From Baseline									
Week 1	32	19.5	0.99	26	8.5	0.80	31	51.1	3.46
Week 2	32	27.1	1.36	26	22.4	1.37	30	67.9	5.66
Week 3	31	-12.9	-0.83	26	2.7	0.19	27	123.1	8.13
Week 4	31	15.3	0.72	24	-38.7	-2.70	26	175.3	11.48
Week 5	29	-28.2	-3.01	24	-26.6	-1.84	24	159.8	11.27
Week 6	29	-57.1	-4.89	24	-19.0	-1.11	21	158.3	9.83
Week 7	29	-68.0	-5.67	23	-45.0	-3.40	16	235.3	13.40
Week 8	29	-55.0	-5.23	23	-51.4	-3.61	15	43.9	3.06
Week 9	29	-58.3	-4.81	23	-20.9	-1.80	15	91.7	5.74
Week 10	29	-37.8	-3.08	22	-47.5	-3.55	14	69.0	4.35
Week 11	29	-35.3	-2.31	22	-68.7	-4.92	13	43.7	2.66
Week 12	28	-39.4	-3.13	22	-69.0	-5.02	13	47.8	2.85
Endpoint	**32**	**3.9**	**-0.33**	**26**	**6.3**	**0.44**	**31**	**226.2**	**15.09**
Daily Prednisone ≥ 12.5 mg at Baseline									
Baseline	13		19.42	17		19.26	12		21.07
Percent Change From Baseline									
Week 1	13	-5.5	-0.96	17	-2.6	-0.50	12	-2.9	-0.45
Week 2	12	-19.0	-3.54	17	8.2	1.55	12	-11.6	-2.27
Week 3	12	-24.5	-4.76	17	114.1	17.14	12	13.4	1.60
Week 4	11	-37.5	-6.82	16	-11.8	-2.77	11	-6.3	-1.35
Week 5	11	-33.7	-5.86	15	-24.4	-5.04	11	5.6	0.28
Week 6	11	-38.5	-6.97	15	-38.1	-7.48	11	35.2	5.39
Week 7	11	-59.3	-10.75	15	-20.4	-4.51	10	5.4	0.27
Week 8	11	-64.3	-11.77	15	-30.7	-6.13	10	6.9	0.06
Week 9	11	-68.8	-12.75	14	-54.4	-10.56	8	-9.9	-2.51
Week 10	11	-68.7	-12.84	14	-58.8	-11.33	7	18.6	1.52
Week 11	11	-72.1	-13.52	14	-58.9	-11.28	6	53.6	6.18
Week 12	11	-75.8	-14.27	14	-67.1	-12.89	6	47.8	5.68
Endpoint	**13**	**-68.8**	**-13.27**	**17**	**-32.5**	**-6.06**	**12**	**36.1**	**4.64**

The sponsor performed an analysis by sex, gender and age. Male and female subjects in the placebo group experienced an increase in prednisone dose over the course of the study (mean change of 13.25 to 10.82 mg/day for males and females, respectively.). In the 400 BID group, both male and female subjects decreased their daily dose of prednisone to a similar extent (mean change of -2.24 and -5.57 mg/day for males and females, respectively). In the 800 BID group, males were able to decrease their daily dose while female subjects were essentially unchanged at Endpoint (mean change of -7.51 and -1.06 mg/day for males and females, respectively). Notably, the difference in response for those subjects who continued through Week 12 was small: –7.91 mg for men and –8.2 mg for women. Thus, a differential in response between the sexes is probably unlikely. The dose reduction in prednisone with MF DPI appeared to occur for all age groups and races although a true comparison of response should not be made based on the small numbers involved.

b) FEV_1

(1)3 month phase

Both MF DPI groups were significantly more effective than placebo at Endpoint ($p<0.01$) in improving FEV_1, as well as throughout the study ($p\leq0.04$). The 400 mcg and 800 mcg BID groups did not differ significantly from each other.

FEV_1 (liters) - Change from Baseline – 3 month phase

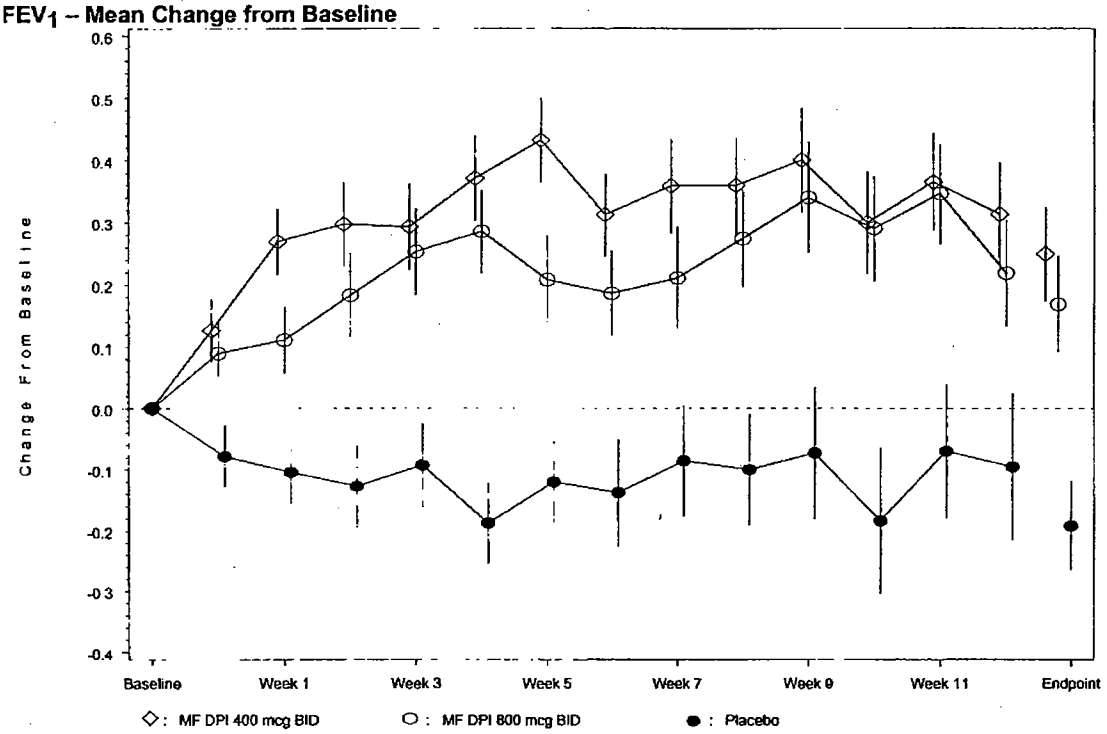
	400 mcg BID (A)			800 mcg BID (B)			Placebo (C)		
	N	Mean	(Mean % Change)[a]	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	45	1.87		43	1.79		43	1.78	
Change From Baseline									
Day 4	38	0.13	(6.9%)	36	0.09	(5.2%)	35	-0.08	(-3.3%)
Week 1	44	0.27	(14.4%)	42	0.11	(6.7%)	41	-0.10	(-5.1%)
Week 2	44	0.30	(17.1%)	43	0.18	(10.9%)	40	-0.13	(-7.5%)
Week 3	41	0.29	(15.7%)	40	0.25	(13.7%)	38	-0.09	(-3.8%)
Week 4	39	0.37	(19.9%)	40	0.29	(16.1%)	36	-0.19	(-10.6%)
Week 5	38	0.43	(23.5%)	35	0.21	(13.8%)	34	-0.12	(-8.5%)
Week 6	40	0.31	(18.7%)	37	0.19	(11.8%)	23	-0.14	(-7.3%)
Week 7	39	0.36	(21.7%)	35	0.21	(15.0%)	24	-0.09	(-4.5%)
Week 8	39	0.36	(21.1%)	37	0.27	(16.2%)	25	-0.10	(-6.8%)
Week 9	38	0.40	(22.9%)	34	0.34	(19.0%)	22	-0.07	(-6.2%)
Week 10	38	0.30	(17.8%)	36	0.29	(17.7%)	18	-0.18	(-11.5%)
Week 11	37	0.37	(19.4%)	35	0.35	(19.4%)	18	-0.07	(-6.1%)
Week 12	38	0.31	(18.7%)	36	0.22	(14.4%)	17	-0.10	(-7.5%)
Endpoint	**45**	**0.25**	**(14.0%)**	**43**	**0.17**	**(9.5%)**	**43**	**-0.19**	**(-12.0%)**

Analysis Results (Change From Baseline)

		P-value		Pairwise Comparisons (p-value)		
Time point	Pooled SD	Treatment	Center	A vs B	A vs C	B vs C
Day 4	0.28	<0.01	0.51	0.58	**<0.01**	**0.02**
Week 1	0.33	<0.01	0.92	0.03	**<0.01**	**<0.01**
Week 2	0.41	<0.01	0.88	0.20	**<0.01**	**<0.01**
Week 3	0.41	<0.01	0.25	0.67	**<0.01**	**<0.01**
Week 4	0.39	<0.01	0.97	0.35	**<0.01**	**<0.01**
Week 5	0.39	<0.01	0.33	0.02	**<0.01**	**<0.01**

Week 6	0.40	<0.01	0.56	0.19	**<0.01**	**<0.01**
Week 7	0.43	<0.01	0.79	0.16	**<0.01**	**0.02**
Week 8	0.43	<0.01	0.80	0.41	**<0.01**	**<0.01**
Week 9	0.47	<0.01	0.29	0.61	**<0.01**	**<0.01**
Week 10	0.48	<0.01	0.69	0.94	**<0.01**	**<0.01**
Week 11	0.43	<0.01	0.10	0.86	**<0.01**	**<0.01**
Week 12	0.46	0.03	0.69	0.41	**<0.01**	**0.04**
Endpoint	**0.46**	**<0.01**	**0.97**	**0.42**	**<0.01**	**<0.01**

FEV_1 – Mean Change from Baseline



These improvements occurred despite the fact that the prime objective was to lower the oral steroid dose. At Endpoint, the mean improvement in FEV_1 was 14.0% and 9.5%, in the 400 mcg and 800 mcg BID groups, respectively, whereas mean FEV_1 for placebo subjects, decreased to -12.0%.

(2) 9 month phase

At the start of open label phase, the mean FEV_1 was lower in subjects who had previously received placebo during the 3 month phase than in subjects who had previously received 3 months of MF DPI. At the Endpoint of the 9 month phase, mean percent change (from the 3-Month Baseline) in FEV_1 was similar in all treatment groups (19.3%, 14.5% and 12.4% in subjects previously treated with 400 mcg, 800 mcg and placebo, respectively). The mean percent change in FEV_1 values for subjects who had received MF DPI during the blinded phase remained relatively constant throughout the subsequent 40 weeks demonstrating that improvements in FEV_1 observed after 3 months of treatment with MF DPI tended to be maintained during long-term treatment. Despite not being originally on MF DPI, those on placebo originally were able to benefit nearly as well as those originally on MF DPI. A pairwise

statistical analysis was not performed to compare the long-term improvements seen in FEV_1 among the treatment groups.

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

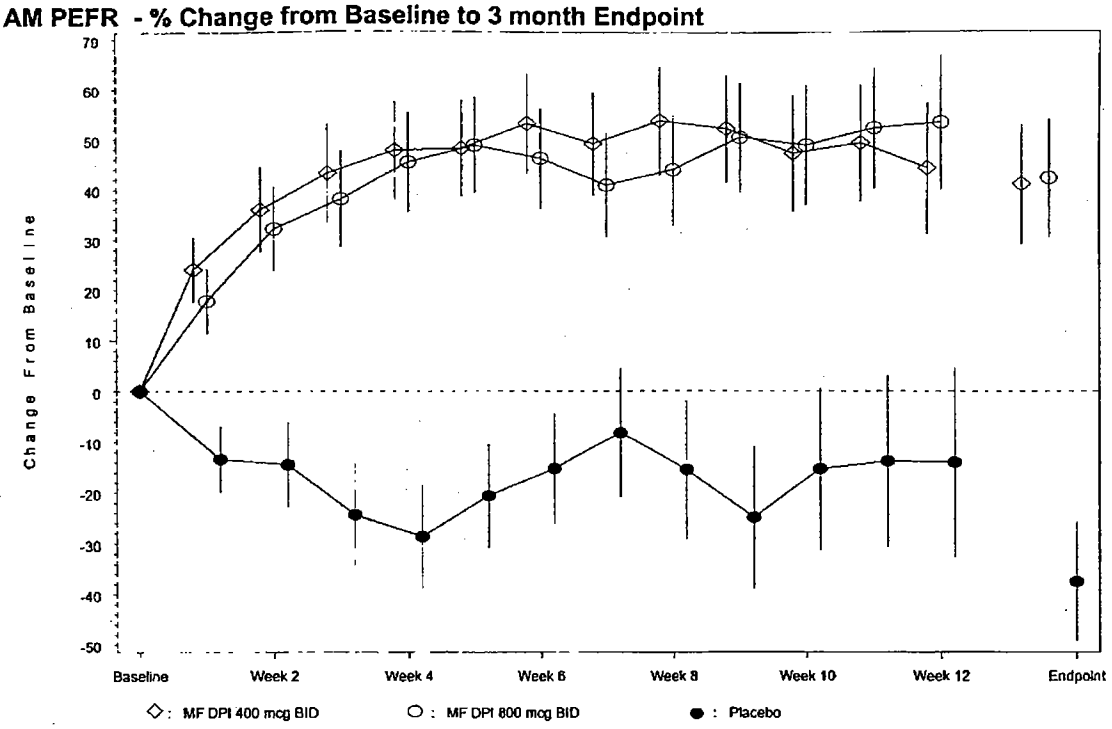
At Endpoint of the 3 month phase, the mean improvement in FVC was 7.1% and 5.5%, in the 400 mcg BID and 800 mcg BID groups, respectively, while for placebo-treated subjects, the mean FVC worsened by 6.9%. Improvement in the $FEF_{25-75\%}$ at Endpoint was 31.3% and 20.8% for the 400 mcg and 800 mcg BID groups, while subjects on placebo experienced a decrease of 13.8%. Both MF DPI treatments were significantly different from placebo for each variable. Interestingly, 400 BID was numerically better than 800 BID for much of the study and at Endpoint for both FVC and $FEF_{25-75\%}$.

At the start of the 9 month phase, the mean FVC and $FEF_{25-75\%}$ values were lower in subjects who had received placebo during the 3 month phase. At the Endpoint of the 9 month phase, the mean % change from Baseline in FVC was similar in all treatment groups (10.7%, 9.2% and 13.3% in subjects in the MF DPI 400 mcg, the MF DPI 800 mcg and the placebo treatment groups, respectively). Thus, although the mean change from Baseline in FVC was lower in subjects who received placebo during the 3-Month Phase than in those who received MF DPI, a trend toward improvement in FVC was observed in these subjects during long-term therapy with a variable dose of MF DPI. Similar trends toward improvement during the 9 month phase were observed for $FEF_{25-75\%}$, where mean percent changes between the 3 month phase Baseline and 9 month Endpoint were 43.8%, 27.8%, and 22.4%, respectively in the 400 mcg BID, the 800 mcg BID, and the placebo group, respectively. The mean % change in FVC and $FEF_{25-75\%}$, values for subjects who had received MF DPI during the 3-Month Phase remained relatively constant throughout the 9-Month Phase, demonstrating that improvements in these spirometry parameters tended to be maintained during long-term treatment.

d) PEFR

For the 3 month phase, significant improvements in AM PEFR were seen for both 400 mcg BID (14.4%) and 800 mcg BID (15.6%) compared with placebo (-10.5%).

AM PEFR - % Change from Baseline to 3 month Endpoint



For the 9 month phase, the mean % change from the 3 month Baseline to the 9 month Endpoint was 22% for 400 BID, 15% for 800 BID and 15% for placebo. 400 BID was numerically better throughout much of the open label period compared with 800 BID but because of the open label situation and the fact that the MF DPI was actually variable during this phase, no conclusions should be made as to their comparability. The original placebo group was able to "catch up" during the subsequent 9 months. A pairwise statistical analysis was not performed.

For the PM PEFR, 400 BID and 800 BID were significantly better than placebo at the 3 month Endpoint with increases of 10.5% seen for 400 BID, 11.3% for 800 BID and a decrease of 4.1% for placebo. At the 9 month Endpoint, the respective mean % changes were 17.7 for 400 BID, 10.4 for 800 BID and 15 for the original placebo group. In fact, the original placebo group appeared to be consistently better than the 800 BID group by Week 4 into the open label phase.

e) Asthma Symptoms and Signs

Every morning and evening prior to dosing, the subject rated wheezing, difficulty breathing, and cough on a scale of 0 (none) to 3 (very uncomfortable and interfered with most or all of my normal daily activities/sleep) as had been done in the other trials. The investigator evaluated wheezing at each visit based on pulmonary auscultation of a score of 0 (no wheezing) to 3 (wheezing during tidal volume on expiration and inspiration). The asthma symptom scores again tended to be low at Baseline so it is somewhat difficult how much clinical importance to assign to these variables. The pairwise comparison based on the t-test from the ANOVA indicated that 400 BID was consistently better than placebo (with the exception of Weeks 11 and 12) while 800 BID was better than placebo at Weeks 1-4, and at Endpoint. For unclear reasons, 400 BID again was numerically better than 800 BID but the difference was

never statistically significant. The AM Difficulty Breathing showed very similar results. For AM Cough, both MF DPI treatments were only statistically better than placebo for Weeks 1-4 and Endpoint.

Data for symptoms was gathered for the first 4 weeks of the open label phase. There was marked improvement in the original placebo group for both AM Wheezing and Difficulty Breathing – the scores tended to emulate the numerically lower one for 800 BID rather than for placebo. For AM cough, the placebo group did see an improvement in the score but it remained numerically less than the original MF DPI groups.

For PM Wheezing, 400 BID did consistently better than placebo throughout the 3 month phase while 800 BID was better only at Endpoint. Improvement was seen once placebo switched to variable MF DPI and the overall improvement from the 3 month Baseline was comparable to that for 400 BID. Very similar results were noted for PM Difficulty Breathing. There were no significant differences between MF DPI treatment groups and placebo for PM Cough during the 3 month phase.

The tabulated data on physician's evaluation of wheezing scores. Scores tended to decrease in the MF DPI groups and increase in the placebo group. The 800 BID treatment group tended to be better than placebo only numerically while 400 BID was statistically better early on in the 3 month phase and then only at Week 9 and the Endpoint.

f) Physician's Evaluation of Response to Therapy

At all visits from Day 4 through Week 12 of the 3 month phase, the physician assessed the subject's response to therapy by comparing the current level of symptoms with those noted at Baseline on a scale from 1 (much improved) to 5 (much worse). At Endpoint, the responses to 400 and 800 mcg BID were similar, with the symptoms of approximately 63% to 70% of the subjects being improved or much improved compared with the 9% response with placebo. Conversely, whereas only 16% to 24% of subjects treated with MF DPI had worsening of symptoms, approximately 59% of placebo-treated subjects had worsening of symptoms of asthma at Endpoint.

Physician's Evaluation of Response: Asthma Symptoms Relative to Baseline	MF DPI 400 mcg BID (n=45)	MF DPI 800 mcg BID (n=43)	Placebo (n=43)
Much Improved	12 (27%)	18 (42%)	0
Improved	16 (36%)	12 (28%)	4 (9%)
No Change	6 (13%)	6 (14%)	14 (33%)
Worse	9 (20%)	4 (9%)	17 (40%)
Much Worse	2 (4%)	3 (7%)	8 (19%)

The physician's evaluation of response was better with both MF DPI groups compared with placebo for all time points save one in the 3 month phase. For the 9 month phase, the evaluations continued in an open label fashion and 83% of subjects were thought to show improvement and 9% were thought to be worse off compared with their 3 month Baseline status.

g) B agonist Use During the Study

The 400 BID group used significantly less Proventil than placebo at all time points except Week 10 while the differences in use between the 800 BID group and placebo were only numerical. There were no significant differences between the MF DPI groups at any time point but the numerical difference was consistent. During the 9 month phase, rescue medication usage declined in all treatment groups, but at the Endpoint, the use of Proventil was still numerically higher for the original placebo group. Data on the use of nebulization for this study did not appear complete, as there was only data for the pre-Screening, Screening and Baseline visits. It is difficult to assume that this was the only time period during which nebs were needed in this trial of steroid-using asthmatics.

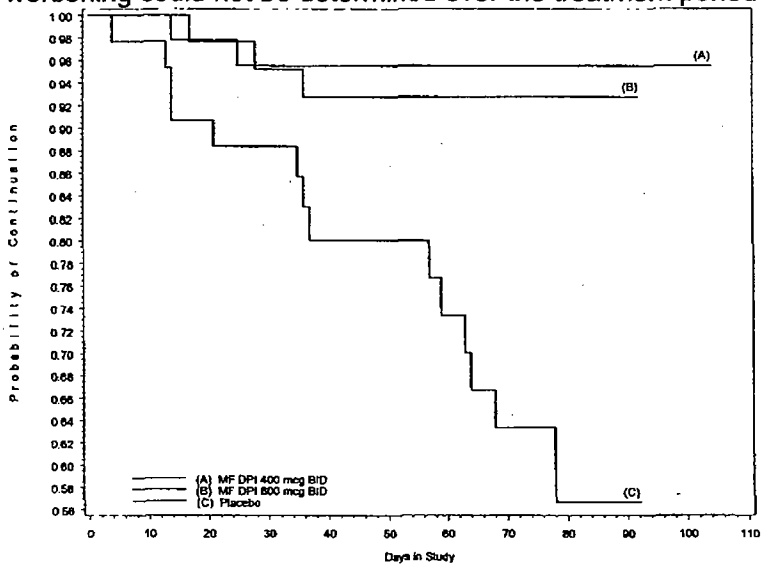
It should be noted that subjects were allowed to take other asthma medications (i.e. Serevent, Atrovent, and Cromolyn-like drugs) during the trial with appropriate washout periods. The sponsor supplied the data on these other drugs in a listing format. Such data is important because an increase in their use could be reflective of the efficacy of the study treatments. In a line listing, however, it is difficult to track changes so it would be worthwhile for the sponsor to supply such data in a summary table over the course of the treatment period.

h) Number of Nocturnal Awakenings Due to Asthma Requiring Proventil

For the 3 month phase Endpoint, both MF DPI groups had significantly fewer awakenings then placebo. Earlier timepoints only tended to involve numerical differences. The MF DPI groups appeared to be remarkably similar. The 400 BID group continued to have a reduction in awakenings during the open label phase and by the end, it had double the amount of reduction as both the 800 BID and placebo groups.

i) Time to Worsening of Asthma

This measure of efficacy reaffirmed that MF DPI was different from placebo. Log rank assessments of these data confirm that both MF DPI treatments are significantly different from placebo ($p<0.01$). Because more than 90% of subjects in each of the active treatment groups had not met the criteria for worsening by the time of their last visit in the 3-Month Phase, median time to worsening could not be determined over the treatment period studied.



Subjects Who Had Worsening of Asthma and Reasons

Reasons for Worsening	400 mcg BID (n = 45)	800 mcg BID (n = 43)	Placebo (n = 43)
Additions of Asthma Medication	0	0	1
Third Burst of Prednisone	0	0	7
Other	1	3	7
Additions of Asthma Medication and Other	1	0	0
Total	2	3	15

j) Distribution of MF DPI Dosing After Long Term treatment

The distribution of subjects taking each MF DPI dose (i.e., 400, 600, and 800 mcg BID) at the end of 9 months of open-label treatment was tabulated. Subjects previously treated with MF DPI in the 3 month phase were similarly distributed with respect to MF DPI doses at Endpoint of open-label treatment. Between 50 and 63% of subjects previously treated with MF DPI were taking 800 BID at Endpoint; whereas approximately 35% of subjects were able to reduce their dose of MF DPI to the lowest permitted dose of 400 BID. At the end of the 9 month phase, 21% of subjects who had previously received placebo were able to reduce their MF dose to the lowest permitted dose of 400 BID.

Distribution of Subjects by Dose of MF DPI at Endpoint of 9 month phase

Dose of MF DPI at Endpoint (mcg)	MF 400 mcg BID/ MF Variable Dose	MF 800 mcg BID / MF Variable Dose	Placebo / MF Variable Dose
	Endpoint of 9-Month Phase		
400 BID	15 (35.7)	15 (35.7)	9 (20.9)
600 BID	6 (14.3)	1 (2.4)	3 (7.0)
800 BID	21 (50.0)	26 (61.9)	31 (72.1)

Thus, the doses at the end of the 9 month phase was very comparable between the original 400 and 800 BID groups. The original placebo group was slightly different – a statistical comparison was not performed.

k) Quality of Life

(1)3 month phase

Health-Related Quality of Life (HQOL) was measured using the SF-36 and an asthma-specific scale. The asthma-specific scale assesses breathlessness, mood, social impact, psychosocial impact, asthma concerns, and physical symptoms. The asthma specific scale was apparently determined from a complex formula relating to questions 12 and 13 which appear to be related specifically to asthma. Each scale uses the past week as the reference period for assessment.

In the protocol, the sponsor said that the hypotheses being tested were: 1) in the 3 month phase, MF DPI subjects show better improvement in HQOL compared with placebo-treated subjects at the study Endpoint, and 2) in the 9 month safety phase, the placebo group from the 3 month phase will show improvement in HQOL after being treated with MF DPI for 12 weeks. The HQOL improvement was expected to be seen in the asthma specific module as

well as physical functioning, role physical and bodily pain in the SF-36 domains. Actual values and changes from baseline between treatment groups were to be compared at Baseline and Endpoint using a two-way ANOVA model.

Efficacy was based on whether the difference in mean scores between groups between Baseline and Endpoint was statistically significant. It is not clear what should be considered a clinically important effect size, only that the mean scores for the groups are statistically different. Of the 132 patients enrolled, 128 patients (97%) completed the quality of life (QOL) questionnaires at both Baseline and post-treatment during the 3 month phase of the study. The baseline score of the subjects showed a significant burden of disease compared with the general U.S. population. SF-36 scores are scaled from 0 to 100, with a higher score representing better functioning. The scores at Baseline showed a significant burden of disease in the study patients compared with the general U.S. population in 4 of the 8 SF-36 domains.

HQOL: Mean Baseline Scores *(SF-36)*

SF 36 Domains	All Treatment Groups Combined (n=128)		General US population (n=2474)	
	Mean	SD	Mean	SD
Physical Function	54.5	22.4	84.2	23.3
Role Physical	55.3	40.8	81.0	34.0
General Health	51.5	22.0	72.0	20.3
Bodily Pain	71.2	22.5	75.2	23.7
Vitality	52.0	18.7	60.9	21.0
Social Functioning	77.1	21.3	83.3	22.7
Role Emotional	74.5	37.0	81.3	33.0
Mental Health	74.0	17.6	74.7	18.0

The asthma specific scale, however, is scored from 0 to 10, with a higher score indicating greater symptoms. The rating scores for these domain questions were 0 = never, 1 = once or twice, 2 = a few times, 3 = fairly often and 4 = very often - each domain was transformed by multiplying by 2.5 to 0-10. The Baseline mean scores of approximately 4 for breathlessness, social impact, asthma concerns and the total indicate that the patients studied have described the effect of their asthma as moderate during the past week. For physical symptoms and psychosocial impact, the mean Baseline scores of approximately 2.5 indicate that limitations due to asthma only occur once or twice over the course of a week

HQOL: Mean Baseline Scores of the *Asthma Specific Scale*

Asthma Specific Scale	All Treatment Groups Combined (n=127)	
	Mean	SD
Breathlessness	3.5	2.1
Mood	2.6	1.7
Social Impact	3.9	2.5
Asthma Concerns	3.9	2.2
Subtotal assoc. with 4 above domains	3.6	1.8
Physical Symptoms	2.6	1.7
Psychosocial Impact	2.3	2.3

At Endpoint, MF DPI subjects had a QOL that was similar to or improved from Baseline, while placebo subjects' QOL generally deteriorated. In the SF-36 results below, both MF DPI groups did numerically better than placebo in all domains but bodily pain. The 800 mcg dose of MF DPI tended to perform better than the lower dose but the pairwise comparison were never significantly different (Vol. 86 Update). The most notable improvement in the MF DPI groups seemed to occur in the physical functioning domain. The MF DPI groups clearly did numerically worse in Bodily Pain, most likely attributable to oral steroid decreases, but this difference was not significant. Role physical and general health were maintained in the MF treatment groups compared to placebo.

HQOL: Summary Statistics and Probability Levels Associated with Comparing the Treatment Groups for the *SF-36* Questionnaire

	Summary Statistics				Unadjusted Probabilities	
	N	Baseline	Endpoint	Change from Baseline	MF DPI 400 mcg BID vs. placebo	MF DPI 800 mcg BID vs. placebo
Physical Component Summary						
MF DPI 400 mcg BID	41	40.2	41.0	.78	**.01**	**<.01**
MF DPI 800 mcg BID	43	38.0	40.5	2.51		
Placebo	42	39.4	34.6	-4.74		
Physical Functioning						
MF DPI 400 mcg BID	42	54.4	66.1	11.6	**<.01**	**<.01**
MF DPI 800 mcg BID	43	52.2	64.3	12.2		
Placebo	43	55.2	49.7	-5.5		
Role Physical						
MF DPI 400 mcg BID	41	57.4	52.4	-5.03	.08	.03
MF DPI 800 mcg BID	43	59.5	58.9	-.61		
Placebo	42	54.4	29.4	-25.1		
General Health						
MF DPI 400 mcg BID	41	55.6	57.5	1.90	.14	**.01**
MF DPI 800 mcg BID	43	50.2	56.5	6.13		
Placebo	43	47.7	44.2	-3.49		
Bodily Pain						
MF DPI 400 mcg BID	41	71.2	60.4	-10.8	.32	.64
MF DPI 800 mcg BID	43	70.0	66.0	-3.9		
Placebo	43	74.2	68.1	-6.1		
Vitality						
MF DPI 400 mcg BID	41	52.9	50.4	-2.43	.10	.08
MF DPI 800 mcg BID	43	54.3	52.3	-2.00		
Placebo	43	50.2	40.8	-9.41		

After adjustment for multiplicity the unadjusted p-values that are less than .01 would be statistically significant at an overall significance level (family wise error rate) of .05.

Please note that the Physical Component Summary is a weighted average of the 8 SF-36 domains.

Within the asthma-specific domains (summary table not shown), both the MF DPI 400 and 800 BID groups reported better QOL than placebo at the Endpoint in all domains. The unadjusted p value of < .01 (needed considering the multiplicity of comparisons) was seen for all comparisons with placebo except for psychosocial impact (0.05) and 400 vs. placebo in Mood (0.02). Consistent with the improved physical functioning observed in the SF-36, breathlessness showed the greatest improvement in the MF groups compared to placebo, that is, the placebo group reported that breathlessness moderately affected them in the past week whereas the MF groups reported that breathlessness effected them mildly in the past week. With the asthma specific scale, the 400 mcg dose tended to do numerically better than the higher dose.

(2)9 month phase

Of the 128 subjects enrolled into the 9 month phase, 116 subjects (91%) completed the quality of life questionnaires at both Baseline and at the 3-month endpoint of the 9-Month Phase. The improvement in HQOL that the MF DPI subjects had achieved at the end of the 3-Month Phase was generally maintained or improved. The subjects who were originally treated with placebo during the 3 month phase exhibited the improved functioning of the subjects who had been previously treated with MF DPI. In other words, the placebo group appeared to gain back what it had lost once it was eventually put on active treatment during the first 3 months of the open-label phase.

Summary Statistics by treatment group at randomization							
SF 36–Domains	Treatment Group	Baseline		3-Month Phase Endpoint		3-month Endpoint of 9-Month Phase	
		N	Mean	N	Mean	N	Mean
Physical Component Summary	MF 400	38	39.6	37	41.5	38	44.7
	MF 800	40	38.3	40	41.5	40	41.0
	Placebo	37	39.4	38	34.8	37	41.4
Physical Functioning	MF 400	38	56.1	38	65.6	38	72.6
	MF 800	40	54.2	40	63.3	40	63.4
	Placebo	38	56.4	38	49.7	38	65.3
Role Physical	MF 400	38	53.3	37	57.4	38	69.1
	MF 800	40	55.6	40	65.6	40	69.4
	Placebo	37	51.4	38	27.6	38	76.1
Bodily Pain	MF 400	38	68.9	37	62.4	38	64.8
	MF 800	40	69.9	40	67.0	40	59.0
	Placebo	38	74.8	38	69.1	38	63.7
General Health	MF 400	38	54.0	37	57.3	38	60.6
	MF 800	40	52.1	40	59.0	40	57.7
	Placebo	38	49.0	38	46.2	37	57.9
Vitality	MF 400	38	50.7	37	50.9	38	55.8
	MF 800	40	54.4	40	55.5	40	55.6
	Placebo	38	49.8	38	41.7	38	54.3

The following table shows the mean scores for the SF-36 domains at the 3 month endpoint of the 9 month phase for all subjects who entered the 9 month phase. At the 3-month endpoint of the 9 month phase, the HQOL status of MF DPI subjects improved in all four domains. The greatest changes were observed within the physical function and role physical domains. Compared with the general U.S. population, however, they continued to lag behind in all domains except for mental health (where they never really differed).

Summary Statistics: SF-36 Domains								
	Baseline			3 month Endpoint of 9-Month Phase			General US Population	
SF-36 Domains	N	Mean	SD	N	Mean	Std	Mean	SD

Physical Function	116	55.6	22.6	116	67.0	25.9	84.2	23.3
Role Physical	115	53.5	42.1	115	71.5	38.2	81.0	34.0
Bodily Pain	116	71.2	23.1	116	62.4	26.9	75.2	23.7
General Health	116	51.7	22.2	115	58.7	20.9	72.0	20.3
Vitality	116	51.7	19.6	116	55.3	22.8	60.9	21.0
Social Functioning	116	75.9	22.7	116	78.4	23.8	83.3	22.7
Role Emotional	116	73.9	37.5	116	78.2	35.5	81.3	33.0
Mental Health	116	74.2	17.9	116	74.6	18.6	74.7	18.1

The following table includes the mean scores of the asthma specific scale for the subjects at baseline and at the 3 month endpoint of the open label phase. Again, these scales are scored from 0 to 10, with a higher score indicating greater symptoms. The subjects typically improved in all of the domains.

Summary Statistics: Asthma Specific Scale						
Asthma Specific Scale	Baseline			3 month Endpoint of 9-Month Phase		
	N	Mean	SD	N	Mean	SD
Breathlessness	116	3.5	2.1	116	1.8	1.9
Mood	116	2.6	1.8	116	2.0	1.8
Social Impact	116	3.8	2.5	116	2.2	2.4
Asthma Concerns	116	3.9	2.3	116	2.3	2.2
Total (of above)	116	3.6	1.8	116	2.1	1.8
Physical Symptoms	116	2.6	1.8	116	1.8	1.8
Psychosocial Impact	116	2.8	2.1	116	1.8	2.1

Breathlessness showed the greatest improvement over Baseline. At Baseline, subjects reported that breathlessness moderately affected them in the past week but at the 3 month endpoint of the 9-Month Phase breathlessness affected them only mildly.

At the 3 month end point of the 9 month phase, there were 67 subjects (30 in the 400 BID group, 23 in the 800 BID group, and 14 in the placebo group) who experienced a 100% reduction of oral steroid and who completed HQOL. The sponsor compared Baseline and Endpoint scores for the eight SF-36 domains for subjects achieving 100% reduction to the US general population norms.

Summary Statistics Comparing Individuals Experiencing 100% Reduction in Oral Steroid Use to US Normative Population for the SF-36 Questionnaire (3-month Endpoint of the 9-Month Phase			
SF-36 Domain	Mean Score		Mean Score
	Baseline	Endpoint	U.S. General Population
Physical Function	60.2	73.5	84.2
Role Physical	55.7	74.6	81.0
Bodily Pain	70.5	61.4	75.2
General Health	53.0	63.1	72.0
Vitality	52.2	57.2	60.9
Social Functioning	78.0	80.4	83.3
Role Emotional	78.1	79.1	81.3
Mental Health	74.8	75.5	74.7

Individuals who achieved a 100% reduction in oral steroid appear to demonstrate QOL improvements. The scores for the four domains that showed substantial decrements at the Baseline (i.e., physical functioning, role physical, general health, and vitality) appeared to have Endpoint levels more closely approaching general US norms than that of all subjects enrolled at 3 months into the 9 month phase.

l) Peak Inspiratory Flow Rate

At only one center (#18), inspiratory flow rates through a functional model of the dry powder inhaler were recorded for 2 subjects at Endpoint for the 3-month phase and for 4 subjects during the 9-Month Phase to gain preliminary information on whether subjects could produce inspiratory rates adequate to generate DPI particles of respirable size. Based on extrapolation of data obtained using [ ] subjects would need to generate an inspiratory flow rate of approximately 30 L/min or more, with a rise time, the time between flow rates of 10 and 30 L/min, of 300 msec or less to provide adequate drug delivery. The subjects examined achieved adequate flow rates to provide functional drug delivery using the DPI.

Subject	Treatment Group.	Study Visit	Peak Inspiratory Flow Rate (L/min)	Rise Time (msec)	Baseline Oral Prednisone Use (mg/day)	Oral Prednisone Use at Visit (mg/day)
3-Month Phase						
016	MF 800 mcg BID	Week 12	76.1	40	10	3
131	MF 800 mcg BID	Week 12	76.1	48	20	7.5
9-Month Phase (Weeks are relative to the 9-Month baseline)						
015	MF/Variable Dose	Week 1	76.1	48	10	1
017	MF/Variable Dose	Week 4	68.1	30	20	12.5
018	MF/Variable Dose	Week 12	60.4	60	15	4
132	MF/Variable Dose	Week 2	72.0	33	30	20

m) Efficacy Conclusions

The results of the efficacy portion of C96-137 can be summarized with noting that a statistically significant difference in response between placebo and both MF DPI doses was found with respect to daily prednisone use, asthma symptoms, and for all measures of pulmonary function at Endpoint of the 3-Month Phase. In general, responses with 400 and 800 mcg BID were similar.

The mean FEV1 % Predicted was 57-61% for the population at the 3 month Baseline. Both doses of MF DPI were able to successfully and significantly lower the mean daily requirement of prednisone compared with placebo. This variable was the primary variable examined for this drug study and was successful in demonstrating the efficacy of MF DPI. Both doses were fairly comparable. Approximately 40% of the subjects on either dose of MF DPI were able to stop their oral prednisone altogether during the 3 month phase. The reductions in prednisone requirements were even greater at the end of the 9 month phase demonstrating that longer duration of treatment with this inhaled corticosteroid is effective in further reducing prednisone need. At the end of 9 months of open label variable MF DPI dosing, the original placebo group was able to reduce its prednisone dose (mean 7.35 mg) as well as the original 400 mg BID group (mean 7.36 mg) and at least numerically better than the 800 BID group

(mean 4.11 mg). All treatment groups had a very comparable % of subjects (58-71%) who were able to completely get off of prednisone. When the dose reduction data was stratified according to the original dosing at Baseline (≥ or < 12.5 mg/day), the greatest reductions in prednisone use were observed in the higher dose subjects in both MF DPI treatment groups. When the data was stratified by gender, responses were similar in the 400 BID group while at Endpoint men seemed to respond better in the 800 BID grouping. When the 12 Week time point was examined, however, this difference was no longer apparent.

The secondary efficacy endpoint of spirometry was examined. Both MF DPI groups were significantly better than placebo in improving FEV_1 at Endpoint and throughout the study . The 400 and 800 BID groups did not differ statistically but 400 mcg tended to be numerically better, at least through the early and middle 3 month phase. The 9 month FEV1 data supported the idea that improvements were maintained while on active therapy. The original placebo group had important gains in their FEV_1 once they were switched over to MF DPI.

Both MF DPI doses showed significant improvement in the FVC and $FEF_{25-75\%}$ compared with placebo. 400 BID was again numerically better than 800 BID for much of the study and at Endpoint for both FVC and $FEF_{25-75\%}$. At the 9 month Endpoint, the mean % improvement in FVC was similar in all treatment groups (10.7%, 9.2% and 13.3% in subjects in the MF DPI 400 mcg, the MF DPI 800 mcg and the placebo treatment groups, respectively). Similar improvements were identified for $FEF_{25-75\%}$, mean changes were 43.8%, 27.8%, and 22.4%, respectively in the 400 mcg BID, the 800 mcg BID, and the placebo groups.

For both AM and PM PEFR, the MF DPI treatment groups were clearly better than placebo in the blinded 3 month phase. Further trends in improvements were noted for the original 400 mcg group during the 9 month phase for both AM and PM PEFR while the 800 BID group showed slight decreases. At the 9 month Endpoint, the 400 BID fared numerically better while the original 800 mcg and placebo groups had very similar outcomes.

Self-administered asthma scoring on Wheezing, Difficulty Breathing, and Cough was again performed in this study. The 3 month blinded data should be considered the most pertinent as open label self administered scoring can be very bias. For AM wheezing, 400 BID was consistently better than placebo (with the exception of Weeks 11 and 12) while 800 BID was better than placebo at Weeks 1-4, and at Endpoint. 400 BID was again numerically better than 800 BID. The AM Difficulty Breathing showed very similar results. For AM Cough, both MF DPI treatments were only statistically better than placebo for Weeks 1-4 and Endpoint.

For PM Wheezing and Difficulty Breathing, 400 BID did consistently better than placebo throughout the 3 month phase while 800 BID was better only at Endpoint. There were no significant differences between MF DPI treatment groups and placebo for PM Cough during the 3 month phase. better early on in the 3 month phase and then only at Week 9 and the Endpoint.

Proventil use was analyzed among the treatment groups. The 400 BID group used significantly less Proventil than placebo at nearly all time points while the differences in use between the 800 BID group and placebo remained only numerical. There were no significant differences between the MF DPI groups at any time point but the numerical difference was

consistent. During the 9 month phase, rescue medication usage declined in all treatment groups.

Nocturnal awakenings requiring the use of Proventil were tabulated and analyzed. The MF DPI groups appeared to be remarkably similar and had significantly fewer awakenings then placebo at the 3 month phase Endpoint.

The time to worsening of asthma was explored cursorily. At the end of 3 months, both MF groups had a less than 10% incidence of asthma worsening while the placebo group had > 33% incidence of meeting a worsening criteria. Overt clinical asthma exacerbations (CAE) were generally infrequent in this study. CAEs were reported more frequently in the placebo treatment group than in either MF DPI groups. During the 3 month phase, there were reports of CAEs in 7 subjects in the 400 BID group, 9 subjects in the 800 BID group, and 23 subjects in the placebo groups. During the 9-Month Phase, CAEs were reported for 42 subjects with 14 subjects having had more than one episode of CAE.

Finally, the sponsor noted improvements in QOL were noted in the 3 month phase which were preserved during the 9 month phase which appeared to reduce the disease burden od asthma and make these subjects more similar to the general population than they had been. The HQOL data was derived from the SF-36 and an asthma specific scale. While this HQOL data was only a secondary variable, it is not known what a clinically relevant effect size is. It is also not clear that the asthma specific scale, or the SF-36, is validated as it pertains to tracking efficacy in asthma patients. Therefore, this data on HQOL as it stands can not be reasonably used in support of the efficacy of MF DPI.

Overall, MF DPI was shown to be efficacious compared with placebo. While there were no significant differences between the doses of MF DPI, 400 mcg BID tended to perform numerically better than 800 mcg BID for many of the variables.

7. Safety Evaluation C96-137

a) Adverse Events

The AE data from C96-137 does not compare well to that of the other trials, yet, because the sponsor is seeking prednisone-sparing labeling with these doses, these AE's must be as closely examined as the AE's in the other trials. It should be remembered that this trial involved higher doses of MF DPI and, more importantly, that these subjects were having their oral prednisone dosages reduced which can cause a series of symtomatology in and of itself.

The most common adverse events occurring in the 3-Month Phase specifically those reported by at least 10% of subjects in any treatment group, included headache, upper respiratory tract infection, viral infection, musculo-skeletal pain, oral candidiasis, sinusitis, dyspepsia, and aggravated allergy. The 9 month phase of the study had similar AE's as the 3 month phase with the addition of dysmenorrhea, back pain, abdominal pain, bronchitis, nasal congestion, rash, rhinitis, and pruritus.

Incidence of Subjects Reporting Frequent (Reported by ≥10% of Subjects in any Treatment Group)

	Number (%) of Subjects	
	3-Month Phase	9 Month Phase

	400 mcg BID (n=46)	800 mcg BID (n=43)	Placebo (n=43)	Variable Dose (n=128)
Headache	7 (15)	14 (33)	15 (35)	55 (43)
Upper respiratory tract infection	7 (15)	15 (35)	6 (14)	64 (50)
Infection, viral	7 (15)	11 (26)	8 (19)	45 (35)
Musculo-skeletal pain	10 (22)	9 (21)	6 (14)	51 (40)
Candidiasis, oral	10 (22)	10 (23)	4 (9)	51 (40)
Sinusitis	10 (22)	6 (14)	8 (19)	37 (29)
Dyspepsia	6 (13)	8 (19)	6 (14)	15 (12)
Allergy aggravated	9 (20)	6 (14)	2 (5)	30 (23)
Arthralgia	6 (13)	5 (12)	3 (7)	22 (17)
Coughing	2 (4)	7 (16)	5 (12)	11 (9)
Fatigue	6 (13)	4 (9)	1 (2)	23 (18)
Myalgia	3 (7)	5 (12)	3 (7)	25 (20)
Dysphonia	3 (7)	5 (12)	1 (2)	18 (14)
Depression	5 (11)	1 (2)	0	9 (7)
Diarrhea	1 (2)	5 (12)	0	7 (5)
Menstrual disorder	1 (4)	3 (11)	0	4 (6)
Dysmenorrhea	1 (4)	1 (4)	0	7 (10)
Back Pain	3 (7)	2 (5)	2 (5)	25 (20)
Abdominal pain	1 (2)	4 (9)	0	15 (12)
Bronchitis	3 (7)	1 (2)	1 (2)	24 (19)
Nasal congestion	3 (7)	3 (7)	3 (7)	17 (13)
Rash	2(4)	3(7)	4 (9)	17 (13)
Rhinitis	4 (9)	3 (7)	4 (9)	29 (23)
Pruritis	2 (4)	0	1 (2)	13 (10)

Many of these AE's have been seen in the previous trials such as headache, musculo-skeletal pain, allergy-aggravated, dysmennorhea and dysphonia and during the first 3 months, the incidence of these specific AE's appears lower than that for C96-186. Other new AE's appear on the list for higher frequency. Most notable seem to be upper respiratory tract infection, viral infection and oral candidiasis. URI and particularly, oral candidiasis, appear to have a higher frequency during MF DPI treatment compared with placebo. Other AE's that appear to be more common with MF DPI during the blinded 3 month phase are allergy aggravated, arthralgia, fatigue, dysphonia, depression, diarrhea, menstrual disorder, dysmenorrhea and abdominal pain.

It is quite interesting to note that the percentages of persons with these AE's increases remarkably during the 9 month open label phase. The sponsor maintains that there was no indication of an increase in incidence with greater duration of treatment for clinically meaningful adverse events that could be associated with use of an orally inhaled product because the incidences of coughing and dysphonia did not increase beyond those observed during the 3 month phase. This reviewer does not believe that such a statement can be definitively made based on this data alone.

The incidence of oral candidiasis was greater during longer (43% - 9 month) than shorter (22%-23% - 3 month)) duration of treatment with MF DPI. The sponsor maintains that adverse events such as upper respiratory tract infection, viral infection, musculoskeletal pain,

back pain, myalgia, fatigue, bronchitis, rhinitis, and nasal congestion should be considered incidental. If these are indeed incidental adverse events, then they would be expected with increased duration of observation, regardless of treatment.

The sponsor supplied an interesting analysis for the 9 month phase stratified in 3 month intervals according to the subjects' total duration of treatment in the 9 month phase.

Number (%) of Subjects Reporting the Most Common Treatment-Emergent Adverse Events During Treatment With MF DPI During the 9-Month Phase, Stratified by Subjects' Total Duration of Treatment During the 9-Month Phase

	Total Duration of Treatment During the 9-Month Phase			
Adverse Events	0 to <3 Months (n=10)	3 to <6 Months (n=7)	6 to <9 Months (n=6)	≥9 Months (n=105)
Upper Respiratory Tract Infection	3 (30)	0	5 (83)	56 (53)
Headache	3 (30)	3 (43)	2 (33)	47 (45)
Candidiasis, Oral	2 (20)	3 (43)	1 (17)	45 (43)
Musculoskeletal Pain	2 (20)	3 (43)	2 (33)	44 (42)
Infection, Viral	0	1 (14)	2 (33)	42 (40)
Sinusitis	1 (10)	1 (14)	3 (50)	32 (30)
Allergy Aggravated	0	1 (14)	1 (17)	28 (27)
Rhinitis	1 (10)	1 (14)	1 (17)	26 (25)
Back Pain	0	0	3 (50)	22 (21)
Myalgia	1 (10)	0	0	24 (23)
Bronchitis	0	2 (29)	4 (67)	18 (17)
Fatigue	0	0	0	23 (22)
Arthralgia	1 (10)	1 (14)	0	20 (19)
Dysphonia	1 (10)	1 (14)	1 (17)	15 (14)
Nasal Congestion	0	0	0	17 (16)
Rash	0	2 (29)	0	15 (14)
Abdominal Pain	1 (10)	1 (14)	0	13 (12)
Dyspepsia	1 (10)	0	0	14 (13)
Dysmenorrhea	1 (20)	1 (25)	0	5 (9)
Pruritus	0	1 (14)	0	12 (11)
Coughing	0	0	0	11 (10)
Depression	0	0	2 (33)	7 (7)
Menstrual Disorder	0	0	0	4 (7)
Diarrhea	0	0	0	7 (7)

The very small numbers of persons exposed less than 9 months in this analysis makes it difficult to give any meaning to the percentages. The following list of adverse events has been edited down to represent those adverse events which this reviewer feels are particularly notable and/or have a clearly higher increased representation in the MF DPI treatment groups.

Incidence Any Treatment-Emergent Adverse Events Reported by ≥1% of Subjects

	Number (%) of Subjects			
	3-Month Phase			9-Month Phase
	MF DPI 400 mcg BID (n=46)	MF DPI 800 mcg BID (n=43)	Placebo (n=43)	Variable Dose (n=128)

Incidence Any Treatment-Emergent Adverse Events Reported by ≥1% of Subjects

	Number (%) of Subjects			
	3-Month Phase			9-Month Phase
	MF DPI 400 mcg BID (n=46)	MF DPI 800 mcg BID (n=43)	Placebo (n=43)	Variable Dose (n=128)
Any Adverse Event	**41 (89)**	**43 (100)**	**32 (74)**	**128 (100)**
allergy aggravated	9 (20)	6 (14)	2 (5)	30 (23)
fatigue	6 (13)	4 (9)	1 (2)	23 (18)
nasal polyp	2 (4)	1 (2)	0	5 (4)
dysphonia	3 (7)	5 (12)	1 (2)	18 (14)
adrenal hypercorticism	0	1 (2)	0	1 (1)
adrenal insufficiency	1 (2)	0	0	1 (1)
artery malformation	0	0	0	1 (1)
ear malformation	0	0	0	4 (3)
abdominal pain	1 (2)	4 (9)	0	15 (12)
diarrhea	1(2)	5 (12)	0	7 (5)
nausea	3 (7)	2 (5)	0	11 (9)
vomiting	1 (2)	3 (7)	0	2 (2)
hepatic function abnormal	0	0	0	1 (1)
arthralgia	6 (13)	5 (12)	3 (7)	22 (17)
musculo-skeletal pain	10 (22)	9 (21)	6 (14)	51(40)
depression	5 (11)	1 (2)	0	9 (7)
dysmenorrhea	1 (4)	1 (4)	0	7 (10)
menstrual disorder	1 (4)	3 (11)	0	4 (6)
candidiasis, oral	10 (22)	10 (23)	4 (9)	51 (40)
sinus congestion	4 (9)	3 (7)	0	10 (8)
upper respiratory tract infection	7 (15)	15 (35)	6 (14)	64 (50)
eye abnormality	3 (7)	3 (7)	1 (2)	3 (2)

This list has been edited to include those AE's which appeared to be more common in the MF DPI group. It is not clear why allergy aggravated should be on the list except that theoretically with the decreases in oral prednisone, systemic allergy symptoms could become more prominent. Likewise with fatigue, nausea, arthralgia, and perhaps abdominal pain, a decrease in prednisone while on MF DPI could make people feel like they were more fatigued or had abdominal pain. Nasal polyp appears to be an incidental finding but should be noted. Dysphonia appears more common with this inhaled steroid product compared with placebo. The hypercorticism is more likely related to the prednisone. The report of adrenal insufficiency is probably related to the oral steroid decrease and is not inherent to the MF DPI itself. Diarrhea and vomiting was seen most commonly in the 800 BID group – the explanation is not apparent. Depression, which was seen most commonly in the 400 BID group, most likely has its origins in the prednisone withdrawal. Dysmennorhea and menstrual disorders are again more common in the MF DPI group compared with placebo. Sinus congestion is seen on this list - perhaps also because of the relative lack of systemic anti-inflammatory properties with MF DPI compared to prednisone. Eye abnormality is also noted and will have to be explored further.

On this list are 5 instances of fetal disorders that were seen in the 9 month phase. There were 4 instances of ear malformation and one instance of artery malformation. One case of artery malformation and 4 cases of ear malformation were also listed in Section 14.3.1.1.2. More information on these fetal events was requested of the sponsor. (The clarification of these events was dated 8/27/99. The incident labeled as "artery malformation" should have been correctly called "arthralgia." The four incidents labeled as "ear malformation" should have been called "peripheral edema." Only the Case Report Form for Subject 114 at Site 13 was available electronically to verify that peripheral edema occurred and not ear malformation. Because the date of the peripheral edema was not available, this could not be verified. The case report forms on these subjects will be requested of the sponsor and the location of these adverse events within the CRF will be queried.

The sponsor mentions a subject in the 9 month phase (Site 3, #58) that had a positive pregnancy test at week 52 of the study. The subject had no reports of problems with her pregnancy and gave birth 4 weeks early to a 9 pound 4 ounce girl with shoulder dystocia. The child was healthy otherwise.

Other than oral candidiasis and dysphonia that were previously discussed, other local adverse events included pharyngitis and coughing. Pharyngitis was reported by 2% of subjects treated with 400 BID, 7% of subjects treated with 800 BID, and 2% of subjects treated with placebo, while coughing was reported by 4% of subjects treated with 400 BID, 16% of subjects treated with 800 BID, and 12% of subjects treated with placebo. In the 9 month phase, pharyngitis was reported by 6% and coughing by 9% of subjects treated with variable doses of MF DPI.

One subject had an adverse event during the open label phase that coded to hepatic function abnormal (subject C96-137-04 #145; Placebo / Variable Dose). This subject experienced elevations were in LDH, ALT, AST, and alkaline phosphatase after having had a viral infection and the flu. A hepatitis screen was negative and there was no history of drug or alcohol abuse. This event was considered by the investigator to be a serious adverse event and unrelated to study medication. Why it was considered unrelated is not clear. The subject did not discontinue from the study. This case is discussed further in section on serious AE's.

b) Severe Adverse Events

During the 3 month phase, 24 % of subjects treated with 400 BID and, 19% of subjects treated with 800 BID reported at least one severe event, compared with 9% of subjects treated with placebo. The most frequently reported severe adverse event was musculo-skeletal pain. There were no life-threatening events during the actual 3 month treatment phase. In the 9 month phase, most adverse events were mild to moderate in severity but four were reported to be life threatening. The life threatening events were: coronary artery disorder (Site 7, #099); appendicitis (Site 8, #023); asthma aggravated (Site 13, #113); and status asthmaticus (Site 22, #180). Forty-one percent of the subjects on variable doses of MF DPI reported at least one severe event. The most frequently reported severe adverse event in the 9-month phase was bronchitis was musculo-skeletal pain. The following list of severe AE's has again been edited by this reviewer.

Number (%) of Subjects

	3-Month Phase			9-Month Phase
	400 mcg BID (n=46)	800 mcg BID (n=43)	Placebo (n=43)	Variable (n=128)
Any Severe or Life-Threatening Adverse Event	**11 (24)**	**8 (19)**	**4 (9)**	**52(41)**
abdominal pain	0	0	0	2(2)
nausea	1(2)	0	0	0
fatigue	1 (2)	0	0	2(2)
headache	1 (2)	0	0	3(2)
hepatic function abnormal	0	0	0	1(1)
arthralgia	1 (2)	0	0	0
fracture	1 (2)	0	0	2(2)
fracture, bone	0	0	0	1(1)
muscle weakness	0	0	0	1(1)
musculo-skeletal pain	2 (4)	1 (2)	1 (2)	4(3)
myalgia	0	0	0	2(2)
osteoporosis	0	0	0	1(1)
insomnia	1 (2)	0	0	0
asthma aggravated	0	1 (2)	0	4(3)
bronchitis	2 (4)	1 (2)	0	5(4)
coughing	0	0	0	1(1)
dyspnea	0	1 (2)	0	1(1)
status asthmaticus	0	0	0	1(1)
upper resp. tract infection	0	1 (2)	0	4(3)
eye abnormality	1 (2)	0	0	0

This list of edited adverse events remains long to include many of those AE's originally thought to be more common with MF DPI in the all adverse event list as well as an eye abnormality noted as severe. One severe event during the 3 month phase was considered by the investigators to be treatment-related: this event consisted of musculo-skeletal pain reported in one subject (C96-137-09 #062) who was treated with 400 BID. The one 9 month phase event considered treatment-related consisted of osteoporosis in one subject (C96-137-10#027) who was treated with 800 BID during the 3 month phase and variable dose MF DPI BID in the 9 month phase.

c) Serious Adverse Events

Eleven subjects had serious adverse events reported during the 3 month phase and 26 were reported during the 9 month phase of the study.

Center/Subject	Sex/ Age/ Race	Adverse Event(s)	Date of Onset	Investigator Designated Relationship	Status
3 month Phase: MF DPI 400 mcg BID					
C96-137-08 #023	M/21/C	spinal disorder (h/o MVA [ ]		unlikely	hospitalized
C96-137-12 #115	F/66/C	pneumonia		unlikely	hospitalized
		sinusitis		unlikely	hospitalized
		asthma aggravated		unlikely	hospitalized
C96-137-12 #223[f]	F/31/N	asthma aggravated		unlikely	hospitalized
C96-137-15 #003	M/77/C	confusion		unlikely	hospitalized

Center/Subject	Sex/ Age/ Race	Adverse Event(s)	Date of Onset	Investigator Designated Relationship	Status
		dyspnea		unlikely	hospitalized
		fever		unlikely	hospitalized
		headache		unlikely	hospitalized
		nausea		unlikely	hospitalized
		pneumonia		unlikely	hospitalized
		sepsis		unlikely	hospitalized
C96-137-15 #005	F/47/C	blindness		unlikely	hospitalized
3 month Phase: MF DPI 800 mcg BID					
C96-137-22 #176	M/63/C	diarrhea		unlikely	hospitalized
		fever		unlikely	hospitalized
		nausea		unlikely	hospitalized
		vomiting		unlikely	hospitalized
		infection, viral		unlikely	hospitalized
		diverticulitis		unlikely	hospitalized
3 month Phase: Placebo					
C96-137-12 #120	F/44/N	procedure (toe surgery)		unlikely	hospitalized
No Treatment (Screening Subject Only)					
C96-137-02 #604	F/47/N	asthma aggr., intubated 3 days		unlikely	life-threatening, hospitalized
C96-137-04 #609	F/44/C	menstrual disorder (prev. h/o bleeding, D&C)		Unlikely (never rec. study drug)	hospitalized
C96-137-05 #606	M/70/C	carcinoma		unlikely	hospitalized, cancer
C96-137-07 #603	M/41/C	asthma aggravated		Unlikely (never rec. study drug)	hospitalized
9 month Phase: Variable Dose					
MF DPI 400 mcg BID in 3-Month Phase					
C96-137-03#046	M/75/C	basal cell carcinoma		unlikely	cancer
C96-137-04#091	F/33/C	cholelithiasis		unlikely	hospitalized
		tumor, benign		unlikely	hospitalized
C96-137-04#148	M/72/C	joint disorder (acromioplasty)		unlikely	hospitalized
		abdominal pain		unlikely	hospitalized
		gastric polyps		unlikely	hospitalized
C96-137-05#076	M/70/C	hernia		unlikely	hospitalized
C96-137-07#099	M/72/C	chest pain		unlikely	life threatening, hospitalized
		coronary artery disorder		unlikely	life threatening, hospitalized
		angina pectoris		unlikely	life threatening, hospitalized
C96-137-08#023	M/21/C	intestinal disorder (appendicitis)		unlikely	life threatening, hospitalized
C96-137-11#067	F/58/C	spinal disorder		unlikely	hospitalized
		back pain		unlikely	
C96-137-12#120	F/45/C	asthma aggravated		Unlikely (apparent smoke exposure)	hospitalized
		asthma aggravated		not provided	hospitalized
		asthma aggravated		not provided	hospitalized
		asthma aggravated		unlikely	hospitalized
		asthma aggravated		unlikely	hospitalized
C96-137-13#113	M/17/C	asthma aggravated		unlikely	life threatening,

Center/Subject	Sex/ Age/ Race	Adverse Event(s)	Date of Onset	Investigator Designated Relationship	Status
					hospitalized
C96-137-15#034	M/55/C	hepatic enzymes increased		unlikely	medically significant
C96-137-22#180	M/35/N	respiratory insufficiency		unlikely	life threatening, hospitalized
		status asthmaticus		unlikely	life threatening, hospitalized
MF DPI 800 mcg BID in 3-Month Phase					
C96-137-01#221	F/70/C	gallbladder disease		unlikely	hospitalized
C96-137-04#096	M/59/	chest pain		unlikely	hospitalized
		myocardial infarction		unlikely	hospitalized
C96-137-04#149	F/28/C	asthma aggravated		unlikely	hospitalized
		bronchitis		unlikely	hospitalized
C96-137-08#024	F/47/C	asthma aggravated		unlikely	hospitalized
		cellulitis		unlikely	hospitalized
		depression		unrelated	
		osteoporosis		not provided	hospitalized
		tachycardia		not provided	
		dyspnea		not provided	
		colonization, bacteria		not provided	
		fracture		not provided	hospitalized
C96-137-09#061	F/49/C	asthma aggravated		not provided	hospitalized
		dyspnea		not provided	hospitalized
C96-137-12#116	F/50/C	dehydration		unlikely	hospitalized
Placebo in 3-Month Phase					
C96-137-02#059	F/31/C	abdominal pain		unlikely	hospitalized
		peptic ulcer		unlikely	hospitalized
C96-137-04#145	M/26/C	hepatic enzymes increased		unlikely	medically significant
		pneumonia		unlikely	hospitalized
		dehydration		unlikely	hospitalized
		fever		unlikely	hospitalized
C96-137-04#150	F/72/C	ECG abnormal		unlikely	hospitalized
		pain		unlikely	hospitalized
		paresthesia		unlikely	hospitalized
		bronchitis		unlikely	hospitalized
C96-137-09#066	M/70/C	pneumonia		unrelated	hospitalized
C96-137-11#069	M/59/C	prostatic cancer		unlikely	hospitalized, cancer
C96-137-13#114	M/59/C	pneumonia		unlikely	hospitalized
		asthma aggravated		unlikely	
C96-137-15#031	M/66/C	fracture, bone		unlikely	hospitalized
C96-137-15#032	M/72/C	angioedema		unlikely	hospitalized
C96-137-22#177	F/73/C	breast neoplasm, malignant		unlikely	cancer

The sponsor makes note that subject #223 in the 400 BID group was not previously included in the adverse event listings, but does appear in other listings for the study.

Upon review of this list for serious adverse events, those for asthma exacerbation, menstrual disorder (#609), hepatic enzymes increased (#034 and #145), loss of vision (#005) and ECG abnormal (#150) should be noted. Aggravation of asthma should be tracked obviously because it is reflective of the treatment's efficacy. It is probably unreasonable to

expect that no aggravation of asthma would be seen, particularly in a population dependent on oral prednisone for their condition. The other serious adverse events on the list appear to be incidental.

Of the serious events for the 3 month phase, 2 subjects reported aggravation of asthma and one had blindness. This latter subject (#005) reported a near total loss of vision in the left eye, and subsequently had surgery for ethmoidal and sphenoidal mucoceles. The subject had a CT scan before being randomized that showed a mass in the left orbital path. It would seem difficult to attribute this situation to the study medication. Subject #115's middle lobe pneumonia and sinusitis had to be an important part of the asthma aggravation. Subject #223 had been off study medication for 4 weeks and was scheduled to be discontinued for noncompliance when she was hospitalized with an asthma exacerbation that required a steroid burst. She was then discontinued for treatment-noncompliance.

In the 9 month phase, Subject #120 had 5 asthma aggravations during the open label phase only. Subject #113 was admitted on two occasions for an asthma exacerbation, the second of which involved the ICU.

Subject #034 was a 55 year old Hispanic male with a past history of alcoholism who had an SGPT of 32 and an SGOT of 23 at Screening on 3/19/97 and 14/18 when he was rolled over into the open label phase on 6/27/97. The sponsor says that Pre-Screening values for SGOT and SGPT were 124 and 134 U/L, respectively (p.202). No further data was available in the NDA on when these Pre-Screening laboratories were performed. At entry into the 9-Month Phase, values were 18 and 14 U/L. He was discontinued from the study on 8/7/97 due to poor compliance and on [ ]' the SGPT and SGOT were elevated at 177 and 139, respectively. The sponsor says that the patient had been stressed when attempting to reduce the prednisone and had reverted to drinking. Typically, however, the SGOT would be elevated higher than the SGPT in the case of alcohol abuse. Nonetheless, it would seem quite atypical for him to have such an elevation attributable to drug therapy more than one month after being removed from the study and notably for a reason of nonadherence while he was under study treatment. A repeat of his liver enzymes 27 days after the abnormal result showed the SGPT/SGOT to be 22/18.

Subject #180 was a 35 year old male who was intubated for one day following acute bronchospasm. There was a question of aspiration and possible infiltrate, however, the investigator considers the event was triggered by a tooth abscess.

Subject # 149 was a 28 year old female who developed a cough productive of yellow sputum and chills on [ ] A dose reduction in MF DPI from 800 to 600 was attempted on 8/1/97. The patient was admitted with an asthma exacerbation on [ ] The investigator considered the event "unlikely to be related to mometasone but due to the attempt at dosage reduction." She was returned to 800 BID on 11/11 and remained on MF DPI at the time these summaries were compiled.

Subject #24 was a 47 year old female admitted for asthma aggravation for 2 days and remained on open label MF DPI, as well as prednisone, after discharge.

Subject #61 was hospitalized with asthma/difficulty breathing on [ ] Her physician added Accolate that was prohibited in the protocol and the patient was discontinued from the

study on 6/11/97. Investigator causality was not provided but the sponsor considered the event unrelated to MF DPI treatment.

Subject #145 was a 26 year old male who rolled over into the open label phase on 6/9/97. The patient developed a viral illness on [ ] and other family members were said to have developed "flu-like" symptoms. Lab tests on [ ] showed LDH 594, ALT 437, AST 189, and an alkaline phosphatase of 301. A hepatitis screen on [ ] was negative. On [ ] an improvement in the values was noted with AP 82, ALT 102, AST 47 and LDH 190. The patient continued to receive MF DPI and no cause was identified.

Subject #150 was a 72 year old female with a h/o hypertension and diabetes who rolled over in 5/13/97. At Visit 15 (at the end of the double blind phase for which she received placebo), the ECG showed flipped T waves. Cardiac enzymes, an echo and a repeat ECG were negative. After an event on — during which she developed jaw pain/left arm numbness after her car broke down. She r/o for MI and on — had a normal dobutamine thallium.

d) Discontinuation Because of Adverse Events

Three subjects in the 3 month phase, all treated with MF DPI, did not complete treatment because of adverse events: 2/46 (4%) subjects treated with 400 BID and 1/43 (2%) subjects treated with 800 BID. Two subjects, on MF variable dose in the 9 month phase, did not complete treatment because of adverse events. Subject #113 discontinued treatment in this phase of the study for life threatening asthma aggravated (mentioned in Serious AE's) and Subject #177 discontinued treatment for a severe malignant breast neoplasm. Both adverse events were considered to be unrelated to treatment.

Center/Subject	Sex/ Age/ Race	Day Reported	Adverse Event(s)	Severity	Relationship
		3-Month Phase: MF DPI 400 mcg BID			
C96-137-15 #003	M/77/C	27	pneumonia	severe	unrelated
C96-137-15 #005	F/47/C	8	eye abnormality	severe	unrelated
		3-Month Phase: MF DPI 800 mcg BID			
C96-137-02 #056	M/77/C	27	arthralgia	moderate	unrelated
			dyspepsia	mild	unrelated
			paresthesia	moderate	unrelated
			edema, peripheral	moderate	unrelated
			insomnia	mild	unrelated
		9-Month Phase: Variable Dose			
C96-137-13 #113	M/16/C	266(4)	asthma aggravated	life-threatening	unrelated
C96-137-22 #177	F/72/C	184	breast neoplasm, female	severe	unrelated

Subject #046 (400 BID) discontinued in the 3 month phase for treatment failure and moved directly into the open label phase and is not included the above table. Subject #003 discontinued treatment for an adverse event (pneumonia) and was incorrectly reported in the adverse event module of the Case Report Form as having interrupted treatment so this subject is not listed in the above table.

e) Laboratory Values

During the 3 month phase, labs were to be tested at Screening and at Visit 15.

The listing of the abnormal laboratory values was in Volumes 78-79 and were reviewed. The individual laboratory data was found beginning in Volume 101. The values listed below are Week 12 or Screening to Week 12 unless mentioned otherwise.

46 (Site 3)	400 BID	WBC 11.8 to 16.13 (p. 930)
23 (Site 8)		Glucose 109 to 146 (p.943)
115 (Site 12)		Platelets 253 to 0 (p.953) (No other bloodwork is avail. for Wk 12) (The sponsor was requested to clarify this data point and in a response dated 8/27,1999this value should have been listed as missing.)
50 (site 19)		SGPT 35 to 46, LDH 193 to 285 (p. 970)
70 (Site 11)	800 BID	Hct. 45 to 51 (p.999)
110 (Site 13)		Platelets 160 to 97 and 81 on Week 5 (p. 1005)
220 (Site 1)	Placebo	SGOT 27 to 47 on Week 4 (p. 1023)
150 (Site 4)		Creatinine 1.4 to 1.7 on Week 9 (p. 1031)(1.8 on Week 24)
071 (Site 11)		SGPT 30 to 51 on Week 11 (p.1049)
10 (Site 17)		WBC 8.91 to 15.8 on Week 4 (p. 1065)

During the 9 month open label MF variable phase, labs were tested at Visits 21, 24 and 28 (Week 52).

87	800 BID	AP 116 Final (was 61 at SCR, 62 at Wk 12) p.8940
217	Placebo	SGPT 22 @ SCR, 17@ Wk. 12, 50 @ Wk. 24, p. 9092
220	Placebo	SGPT 22 @ SCR, 39 @ Wk. 24, SGOT 47 @SCR, T. bili. 1.6 @ SCR, p. 9092.
221	400 BID	WBC 11.8 @ SCR, 16.13 @ Wk. 4, 15.21 @ Wk. 24
101	800 BID	Hct 41 @ SCR, 39 @ Wk. 12, 28 @ Wk. 36, 32 @ Wk. 40 normal LDH, p. 8984, PLTS 333 @ SCR, 578 @ Wk. 36
99	400 BID	SGPT 18 @ SCR, 27 @ Wk. 12, 38 @ Wk. 36, AP 58 SCR to 79 Wk. 12 to 176 Wk. 36
25	Placebo	SGOT 29 @ SCR, 17 @ Wk. 5, 39 @ Wk. 36, p. 9164
69	Placebo	SGPT 34 @ SCR, 24 @ Wk. 5, 73 @ Wk. 52; SGOT 23 @ SCR, 53 @ Day 340.
70	800 BID	Cre 1.4 @ SCR, 1.4 @ Wk 12, 2.4 @ Wk. 36, 1.7 Wk 40

71	Placebo	SGPT 30 @ SCR, 51 @ Wk. 11, 44 @ Wk. 13, p. 9172
72	400 BID	SGPT 28 @ SCR, 76,88 Final (No abnormal value listed for SGPT on Day 473), SGOT 28 to 43 @ Final.
115	400 BID	SGPT 28 @ SCR, no Wk 12 value, 50 @ Wk. 40, p. 8876.
120	Placebo	SGOT 23 @ BSL, 9 @ Wk. 12, 43 @ Final, p. 9180.
110	800 BID	Platelets 160 @ SCR, 97 @ Wk 5, 83 @ Final (43d Study drug), 133 @ Day 53 (11), p. 9032.
109	Placebo	SGPT 25 @ SCR, 23 @ Wk. 12, 45 on Day 295, p. 9188.
113	400 BID	SGPT 47 @ SCR, 80 @ Day 354 (4). SGOT 42 @ BSL. p. 8884.
1	400 BID	SGPT 19 @ SCR, 22 @ Wk 12, 40 @ Wk 24, p. 9204.
80	400 BID	SGPT 12 @ SCR, 11 @ Wk. 12, 61 @ Day 253, p. 8900.
14	Placebo	SGPT 18 @ SCR, 38 on Day 55 in open label phase, p. 9228.
49	400 BID	SGPT/SGOT 18/15 @ SCR, 14/18 @ Wk. 12, 54/43 @ Wk. 24, p.8924.
178	400 BID	SGPT/SGOT 15/24 @ SCR, 14/16 @ Wk. 12, 55/41 @ Week 24, p. 8932.

During both phases, there appeared a number of instances where there was a meager elevation in the transaminases of approximately 20-30 units or less. The following increases were somewhat more notable:

#69 (3 month placebo – Site11) SGPT 34 at Screening to 24 on Week 5 to 73 at Day 340. There was also a rise of 30 in the SGOT to 53 over this time period.

#80 (3 month phase 400 BID) SGPT rises from 12 at Screening to 61 on Day 253.

#178 (3 month phase 400 BID) SGPT rises from 15 at Screening to 55 on Week 24 and Sgot goes from 24 to 41.

#145 and #34 have been previously discussed.

There also appear to be periodic increases in the WBC and not all have been listed above – particularly if the subject already had a baseline elevation. Subject #101 (3 month phase 800 BID) has a hematocrit which decreases from 41 at Screening to 28 at Week 36. More detail on this subject is given in the next page. Subject 115 is listed as having 0 platelets

at Week 12 – no other labs were available for this visit so it is likely that there was a processing error for the information.

The sponsor defined clinically significant abnormalities as values for blood chemistry values ≥2.6 times the upper limit of normal. Other abnormal values were: hemoglobin concentration ≤9.4g/dL, platelet count ≤74,000/μL, or white blood cell count ≤2,900/μL. The following page was presented in the discussion provided by the sponsor. Subject #145 and #34 were removed because they have been discussed previously. Other baseline abnormality presentations were edited out.

Appears This Way
On Original

Listing of Subjects with Clinically Significant Laboratory Values in C96-137 (All visit weeks are relative to Baseline at the beginning of the 3-Month Phase.)

Center/Subject	Visit	Laboratory Parameter (units)	Value	Lower Limit	Upper Limit	Comments
			3-Month Phase: MF DPI 800 mcg BID			
C96-137-06 #108	Follow-up	hemoglobin (g/dl)	9.4	11.6	16.4	Hemoglobin value 10 mg/dl at Screening. Isolated low value reported at end of 3-Month Phase.
			9-Month Phase: Variable Dose			
C96-137-06 #108 (800 mcg BID in 3-month phase)	Week 12 Week 15	hemoglobin (g/dl) hemoglobin (g/dl)	9.4 9.1	11.6	16.4	Hemoglobin value 10 mg/dl at Screening. Hematocrit 31%-32% at Screening and Weeks 12 and 15. Hemoglobin recovered to 13.2 g/dl at final test at end of study, and hematocrit was 40%.
C96-137-07 #101 (800 mcg BID in 3-month phase)	Week 36	hemoglobin (g/dl) hemoglobin (g/dl)	8.5 8.9	11.5	15.8	Hemoglobin value 13.3 g/dl at Screening. Value dropped suddenly at Week 36, then recovered with continued treatment to 10.5 g/dL at Week 40 and 12.2 g/dl at final test at end of study. Hematocrit dropped from 41% at Screening to 28% at Week 36, then recovered to 40% at final test.
C96-137-08 #024 (800 mcg BID in 3-month phase)	Week 40	glucose (mg/dl)	304	70	115	Value was 88 mg/dL at Screening. Values were high at 182 and 171 mg/dL at Weeks 12 and 24, respectively, then peaked at 304 mg/dl at Week 40. Value was within the normal range at end of study (113 mg/dL) despite continued treatment. Subject was diabetic and had multiple problems during treatment, including aggravated asthma requiring additional prednisone, cellulitis of the right leg, and depression requiring hospitalization
C96-137-15 #032 (placebo in 3-month phase)	Week 24	total bilirubin (mg/dl)	3.4	0.2	1.2	Total bilirubin was 0.8 mg/dL at Screening and 1.2 mg/dL at the end of the study. Abnormality was an isolated value that resolved with continued treatment. Alkaline phosphatase, LDH, SGOT, and SGPT were not affected.

The median results for the laboratories were reviewed (Vol.79). The only appreciable changes in the 3 month phase appeared to occur in the WBC where the median changed from 9.32 to 7.16 for 400 BID, for 9.43 to 7.8 for 800 BID and 9.01 to 10.31 for placebo. This decrease in the WBC could possibly be attributable to the decrease in oral steroids in those subjects being treated with MF DPI. The WBC median at the end of the 12 month study was 7.87. Cholesterol also appeared to decrease from 215 to 197 with 400 BID, 230 to 217 with 800 BID and 220 to 230 with placebo. This also could potentially be secondary to the decrease in prednisone with MF DPI. No other changes among in the median of the lab parameters was appreciated. The medians by gender for the 3 month phase were reviewed. No important differential in the lab parameter response between the sexes could be discerned.

f) Vital Signs

Vital signs were performed for every visit (Beginning in Volume 80). The means for the 3 month phase data was reviewed and did not reveal any important changes. Monitoring or, at least, reporting weight data was again a problem with only baseline data reported for 6, 3, and 9 subjects in the 400, 800 and placebo groups respectively. The means for the vital signs also did not appear to change during the MF variable phase. More comprehensive weight data was available for the 9 month phase The mean decreased approximately 5 lbs. from available 183.6 at baseline to 179 at Week 48 and178.2 at Endpoint. Gender data in vital signs for both phases were examined. The only potential difference noted was with weight where the mean baseline for women changed from 184.7 to 177.3 and for men from 182.3 to 179.2. The number of Non-Caucasians and those not in the 18-64 age group was relatively small.

The data on weight during the 3 month open phase was subsequently submitted by the sponsor on July 14, 1999. No important changes in the means among treatment groups occurred between Baseline and Endpoint.

g) EKG Data

EKGs were performed at Screening, Week 12 and Week 52 and are in Volume 109 beginning on page 11476. No data on the intervals or rate was made available. The following abnormalities were noted between Screening and the respective visit during the 3 month phase. Subject #101 (800 BID) was found to have low anterior forces and a nonspecific T wave abnormality at Week 12 compared with Baseline (p. 11497) which were thought to be not clinical significant. Subject #63 (800 BID) was noted to have Mobitz Type II with frequent PVC's at Week 12 compared with Screening (p. 11499). This abnormality was felt to be clinically significant. Subject #38 (800 BID) was noted to have nonspecific inferior T wave abnormalities compared at Week 12 compared with Screening (p. 11502). Subject #150 (Placebo) was noted to have flipped T waves on Week 9 compared with Screening. The patient was referred to a cardiologist. An echo and EKG were performed and were felt to be not clinically significant (p. 11513). Subject #75 (Placebo) was noted to have nonspecific lateral T wave abnormalities at Week 12 compared with Screening (p. 11514). Patient #66 was noted to be in a chaotic atrial dysrhythmia at Week 12, which was new, compared to Screening (p. 11517). Subject #9 (Placebo) was noted to have a nonspecific T wave abnormality at Week 5 compared with Screening (p. 11522).

In the MF variable phase, Subject #87 had a nonspecific intraventricular conduction delay on Day 281 that was deemed not clinically significant. Subject #161 was noted to have a possible old inferior infarction with ST-T changes in the septal lead that was not noted on previous EKGs but was deemed not clinically significant. Subject #96 was noted to have new poor R wave progression at Day 288 compared with earlier EKGs that again was deemed not clinically significant. Subject #73, previously with a LAFB was noted to have a complete LBBB with 1st degree AV block on day 286. Subject #110 had a normal EKG at Screening, non-diagnostic Q waves in inferior leads at Week 5 (3 month phase). Eight days into the open label phase "cannot r/o inferior infarction on or before 17/3/97. Patient will follow up with cardiac consult." This consult was done with a stress echo to follow with no details in this section provided (p. 11536). Subject #131 was noted to have new ST changes in the septal leads on Day 174. No further detail was given but it was not felt to be clinically significant.

These above changes were noted and most were felt to be not clinically significant. It is not readily possible to discern any effect of MF DPI.

h) Plasma Cortisol Concentrations

Plasma cortisol concentration in response to Cortrosyn stimulation was performed at Baseline and Endpoint at 10 selected centers. The assay used in this study was inappropriate since the subjects were taking concomitant prednisone during the study. As a consequence of cross-reactivity between prednisone and prednisolone in the radioimmunoassay (RIA) used for the evaluation of plasma cortisol, the results obtained could not be interpreted. While the cross-reactivity of prednisone is low in the RIA, it should be noted that prednisone is converted in vivo to prednisolone, which is highly cross-reactive. The results obtained are confounding and will not be presented for further elaboration.

i) Plasma Mometasone Concentrations

MF concentrations were measured using a validated high pressure liquid chromatography (HPLC) assay with tandem mass spectrometry detection (LC/MS/MS) in plasma samples collected before and 30 minutes after dosing with study medication on Visit 15 (Week 12) from 43 subjects at ten study centers. The limit of quantitation (LOQ) of the LC/MS/MS assay was 50 pg/ml.

Since only two samples were obtained per patient, a formal PK analysis was not possible. In placebo subjects, plasma MF concentrations were detected in 2/16 subjects. These concentrations were close to the LOQ, and were considered to be spurious. In the 400 BID group, MF was quantifiable in 3/12 predose and 8/12 postdose samples. Mean plasma MF concentrations were 56.1 pg/ml and 148.0 pg/ml, respectively, in these predose and postdose samples, and were characterized by large inter-subject variability. In contrast to the 400 BID group, MF was quantifiable in most predose (11/15) and postdose (14/15) samples in the 800 BID treatment group, indicating the presence of low plasma concentrations. Mean plasma MF concentrations were 105.0 pg/ml and 215.0 pg/ml, respectively, in predose and postdose samples. Overall, postdose plasma MF concentrations were considered low in the 400 and 800 BID groups, and were characterized by large inter-subject variability.

j) Safety Conclusions for C96-137

A total of 132 subjects were evaluated in the 3 month phase of the study; 128 were evaluated in subsequent 9 month phase. Because subjects were eligible for this study because they utilized prednisone, the safety data in this study has a higher degree of complication compared with the other studies for this NDA. It was overall difficult to discern the adverse events attributable to MF DPI from those of oral steroids from those secondary to the reduction on oral steroid dosage.

The most common adverse events (>10% in any treatment group) occurring in the 3 month phase included headache, upper respiratory tract infection, viral infection, musculo-skeletal pain, oral candidiasis, sinusitis, dyspepsia, and aggravated allergy. The 9 month phase of the study had similar AE's as the 3 month phase with the addition of dysmenorrhea, back pain, abdominal pain, bronchitis, nasal congestion, rash, rhinitis, and pruritus.

Many of these more common AE's have been seen in the previous trials such as headache, musculo-skeletal pain, allergy-aggravated, dysmennorhea and dysphonia and during the first 3 months, the incidence of these specific AE's appears lower than that for C96-186. New AE's appeared on the list for higher frequency. Most notable seem to be upper respiratory tract infection, viral infection and oral candidiasis. URI and oral candidiasis were more common with MF DPI compared with placebo. During the 3 month phase, other AE's that seemed to be more common with MF DPI were allergy aggravated, arthralgia, fatigue, dysphonia, depression, diarrhea, menstrual disorder, dysmenorrhea and abdominal pain.

In general, the percentage of persons with each AE increased during the 9 month phase. The incidence of oral candidiasis was somewhat higher in this study (22%-23% - 3 month) relative to the other studies in this NDA and increased during longer (43% - 9 month) duration of treatment with MF DPI.

The adverse events of allergy aggravated, fatigue, nausea, arthralgia, and perhaps abdominal pain were more common with MF DPI in the 3 month phase and may possibly be explained by the decreases in oral prednisone enabled by MF DPI. Nasal polyp also was increased but may be an incidental finding.

Dysphonia and sinus congestion was also more common with MF DPI. Diarrhea and vomiting, pharyngitis and probably coughing were most common in the 800 BID group. Depression, seen most commonly in the 400 BID group, most likely has its origins in the prednisone withdrawal. Dysmennorhea and menstrual disorders are again more common in the MF DPI group compared with placebo. An increased incidence of eye abnormalities was also noted with MF DPI and an explanation is not apparent. Among those adverse events listed as serious, there were a number of asthma exacerbations requiring hospitalizations.

In the 9 month phase, there were 4 instances of ear malformation and one instance of artery malformation which will need to be explored further.

Most notable among the laboratory abnormalities seen with MF DPI was Subject #145 (Placebo / Variable Dose).who experienced elevations were in LDH, ALT, AST, and alkaline phosphatase after having flu-like symptoms. A hepatitis screen was negative and there was no

history of drug or alcohol abuse. The explanation for the event was not apparent. There were a number of instances of elevations of transaminases of 20-30, the clinical significance of which are unclear. The relationship of MF DPI to these elevations is also unclear but has been noted in other studies with this product.

Vital signs did not appear to change with treatment except for an apparent decrease in weight that seemed to be more evident in women. This decrease in weight could be related to the decreases in prednisone.

H. C96-135 (Update Vol. 2-38)

"Long-Term Safety Study Of Mometasone Furoate Dry Powder And Beclomethasone Dipropionate In The Treatment Of Asthma In Subjects Previously Maintained On Inhaled Corticosteroids"

1. Investigators and Investigational Centers

There were 239 subjects involved at 21 centers throughout the United States.

2. Objectives/Rationale

The objectives of this randomized, multicenter, evaluator-blind, Phase III study was to characterize the long-term safety of MF DPI (200 BID, 400 BID, 800 QD) compared with beclomethasone dipropionate (Vanceril; 168 BID) in subjects previously maintained on inhaled corticosteroids. There was no placebo-control treatment group. The purpose of the study was to provide data on the safety of MF DPI when administered for one year. Secondarily, the study also collected efficacy parameters, to evaluate the effect of MF DPI in comparison to BDP in the long-term treatment of asthma. Since this study was primarily a safety study, it was not designed to examine changes from Baseline in the efficacy variables.

a) Primary

The primary safety variables of interest were adverse events and Cortrosyn stimulation test results.

b) Secondary

Other safety variables included laboratory tests, ECGs, vital signs, and physical examination, including oropharyngeal and ophthalmic examination. Efficacy variables included FEV_1, $FEF_{25-75\%}$, FVC), daily peak flow, symptom scores, Proventil use, nighttime awakenings requiring Proventil use, and assessments of response to therapy.

3. Study Design/Protocol

After informed consent, subjects entered into a Run-in period of 1 to 2 weeks, during which they continued treatment with their usual inhaled corticosteroid. At Baseline (Visit 2), subjects stopped treatment with their usual inhaled corticosteroid and were randomized to treatment (MF DPI 200 mcg BID, MF DPI 400 mcg BID, MF DPI 800 mcg QD or BDP 168 mcg BID [336 mcg/day], in a 1:1:1:1 ratio according to a computer-generated randomization for 52 weeks. BDP was considered an active comparator.

a) Study Population

This study selected adult and adolescent subjects who had been maintained on inhaled corticosteroids before entering the study. It was designed to enroll approximately 12-16 subjects at each of approximately 20 study centers for a total of approximately 240 enrolled subjects (180 on MF DPI) to yield approximately 120 subjects treated with MF DPI for one year.

(1) Inclusion Criteria

The inclusion criteria were the same as those for C96-136 with the following differences.

- The subject's Baseline FEV_1 must have been greater than or equal to 60% (as compared to 55%) and less than or equal to 90% (as compared to 85%) of predicted at the Screening and Baseline visits when all restricted medications had been withheld for the specified intervals.
- Subjects must have been using daily 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 medication within the limits outlined below:

Drug	Minimum Dose	Maximum Dose	mcg/day
Flunisolide (Aerobid)	4 puffs/day	8 puffs/day	1000-2000
Triamcinolone acetonide (Azmacort)	6 puffs/day	16 puffs/day	600-1600
Beclomethasone dipropionate (Vanceril or Beclovent)	6 puffs/day	20 puffs/day	252-840
Fluticasone propionate (Flovent)	88 mcg BID	220 mcg BID	176-440

- At selected centers, the subject must have had an unstimulated baseline (8 AM ± 1 hour) plasma cortisol level of ≥5 mcg/dl and a stimulated level of ≥18 mcg/dl 30 minutes after Cortrosyn stimulation.

(2) Exclusion Criteria

Essentially the same as those for C96-136.

(3) Removal of Subjects from Therapy

In general, subjects who experienced a clinically study were to be discontinued. The criteria included:

- Oral steroids for more then 14 days in 6 months or 28 days in 12 months;
- Hospitalization for asthma on more than two occasions during the study;
- Ventilator support;
- Treatment with additional inhaled corticosteroids.
- 20% or greater decrease in FEV_1 from baseline.
- 25% or greater decrease in AM or PM PEFR from the mean AM baseline value on 2 consecutive days;
- Use of >12 puffs of Proventil or more than two treatments with nebulized beta-agonists on any 2 consecutive days.

b) Treatments Administered

There was first a Run-in Period between the Screening and Baseline visits during which patients continued to take their prescribed inhaled corticosteroid. At the Baseline visit, subjects were randomized to 52 weeks of one of the following, a.k.a. the Treatment Period:

	AM	PM	Total mcg/Day
Group 1	MF DPI 100 mcg x 2 inhalations	MF DPI 100 mcg x 2 inhalations	MF 400 mcg
Group 2	MF DPI 200 mcg x 2 inhalations	MF DPI 200 mcg x 2 inhalations	MF 800 mcg
Group 3	MF DPI 400 mcg x 2 inhalations	none	MF 800 mcg
Group 4	BDP 42 mcg x 4 puffs	BDP 42 mcg x 4 puffs	BDP 336 mcg

Treatment was randomly assigned in a 1:1:1:1 ratio using a computer-generated randomization schedule. A person who was not responsible for performing study evaluations administered treatments in an open-label fashion. It was intended that the person performing the study evaluations remain blinded to the treatment that the subject was receiving.

Subjects were advised to rinse their mouth after study drug administration.

It should be noted that 2 subjects, both at Center 01, were misrandomized. The coordinator did not open the envelopes to determine the subjects' treatment allocation, as was required in the protocol. Instead, drug was simply dispensed from the boxes. As a result, subject #313 was randomized to receive MF DPI 400 BID, but actually received MF DPI 200 BID. Subject #314 was randomized to receive MF DPI 800 QD, but actually received MF DPI 400 BID. Upon discovering this error, the sponsor closed the center to further enrollment. Because of the ITT principle, these 2 subjects were analyzed under the treatment to which they were originally randomized.

c) Concomitant/Restricted Medications

The permitted medication were the same as those for C96-136 with the following differences/allowances:

- Ipratropium bromide (nebulized or MDI) (with 12 hour withhold prior to study visits).:
- Theophylline had to be a stable dose for 2 weeks prior to Screening and no adjustments of dose except as needed for safety reasons.

The following were differences to C96-136 in the prohibited medication list prior to Screening:

Medication	Washout Time Prior to Screening Visit
Beta-adrenergic bronchodilators, syrups and tablets	withhold dose before PFTs
Beta-adrenergic bronchodilators, sustained-release tablets	withhold dose before PFTs
Bronchodilators, nebulized	6 hours
Salmeterol	withhold dose before PFTs
Ipratropium bromide aerosol/nebulized	12 hours
Any systemic bursts of (oral or intravenous) corticosteroids	1 months
Corticosteroids -- intra-articular	1 month

d) Assessment/Study Procedures

The following study procedures have been previously discussed in greater detail in other sections of this NDA review.

Schedule of Study Procedures and Evaluations

Treatment Days		Treatment Period									
	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
	-14 to -7	1	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 26	Week 38	Week 52
Obtain Informed Consent	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
Height	X										
Vital Signs (temperature, blood pressure, pulse, respiratory rate)	X	X	X	X	X	X	X	X	X	X	X
Oropharyngeal examination	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, Urinalysis	X						X		X	X	X
Pregnancy Test	X						X		X	X	X
Plasma MF concentration									X		X
Cortrosyn test	X								X		X
Electrocardiogram	X										X
Chest X-ray	X										
Dispense Diary	X	X			X	X	X	X	X	X	
Review Diary		X	X	X	X	X	X	X	X	X	X
Dispense Peak Flow Meter	X										
Dispense Study Medication		X					X		X	X	
Response to Therapy Assessment			X	X	X	X	X	X	X	X	X
Adverse Events Evaluation		X	X	X	X	X	X	X	X	X	X
Compliance Check/ Collect Medication			X	X	X	X	X	X	X	X	X

e) Statistical and Analytic Plans

The safety (intent-to-treat) population was to consist of all randomized subjects. All summaries of safety data and the efficacy analyses were to be based on this population. All analyses were performed on the set of all treated subjects, and all conclusions were derived from this dataset. An "efficacy subset" was not evaluated in this study. Efficacy analyses were to be focused on the change from Baseline for each efficacy variable. The analysis at each visit or diary interval was to be based on what the sponsor calls a reduced, main effects two-way ANOVA. Pairwise comparisons were to be made using the least square means from the ANOVA model without adjustment for the multiple comparisons. The assessment of response to therapy as a percent of subjects demonstrating improvement or much improvement from Baseline was to be analyzed using Fisher's exact test. Clinical asthma exacerbations were to be summarized and tabulated. Discontinuations due to worsening asthma were to be summarized.

The sponsor says the sample size was based on clinical considerations. The total target population was 240 subjects (180 treated with MF DPI) to have approximately 120 subjects treated with MF DPI for one year. With 60 subjects per treatment group, the probability that one or more subjects reported a given adverse event was 95% for any adverse event with an underlying incidence of at least 5%. Likewise, if the underlying incidence was at least 2%, the probability of observing the event in the study was 70%.

4. Results

There were 239 subjects randomized at 21 study centers. The numbers of subjects randomized and treated in the four groups were as follows: MF DPI 200 BID, 60 subjects; MF DPI 400 BID, 62 subjects; MF DPI 800 QD, 59 subjects; and BDP MDI 168 BID, 58 subjects. A total of 51 subjects (21%) discontinued from the study prior to completion. A greater proportion of subjects in the MF DPI 200 BID (27%) and BDP MDI 168 BID (28%) groups discontinued from the study than in the MF DPI 400 BID (18%) and MF DPI 800 QD (14%) groups. The most common reason for discontinuation was adverse events (28 subjects, 12%). More subjects in the MF DPI 200 BID (18%) and BDP MDI 168 BID (17%) groups discontinued from the study due to adverse events than did subjects in the MF DPI 400 BID (3%) and MF DPI 800 QD (8%) groups.

Number (%) of Randomized Subjects Who Completed the Study, Number (%) Who Discontinued and Reasons for Discontinuation

	MF DPI 200 BID (n=60)	MF DPI 400 BID (n=62)	MF DPI 800 QD (n=59)	BDP MDI 168 BID (n=58)	Total (n=239)
Number (%) Completed	44 (73)	51 (82)	51 (86)	42 (72)	188 (79)
Reasons for Discontinuation					
Adverse Event	11 (18)	2 (3)	5 (8)	10 (17)	28 (12)
Treatment Failure	0	1 (2)	1 (2)	2 (3)	4 (2)
Lost to follow-up	1 (2)	3 (5)	0	0	4 (2)
Did Not Continue for Reasons Unrelated to Treatment	3 (5)	4 (6)	2 (3)	3 (5)	12 (5)
Noncompliance with Protocol	0	0	0	1 (2)	1 (<1)
Did Not Meet Entry Criteria	1 (2)	0	0	0	1 (<1)
Administrative	0	1 (2)	0	0	1 (<1)

Number (%) of Randomized Subjects Who Completed the Study, Number (%) Who Discontinued and Reasons for Discontinuation

	MF DPI 200 BID (n=60)	MF DPI 400 BID (n=62)	MF DPI 800 QD (n=59)	BDP MDI 168 BID (n=58)	Total (n=239)
TOTAL NUMBER (%) DISCONTINUING	16 (27)	11 (18)	8 (14)	16 (28)	51 (21)

There were not many protocol deviations during the study. Three of the 102 subjects who underwent Cortrosyn stimulation testing at Screening had a pre-Cortrosyn cortisol value of <5 mcg/dl and/or a post- Cortrosyn cortisol value of <18 mcg/dl. Subject #276 (MF DPI 800 mcg QD) had a pre-stimulation cortisol value of 4.9 mcg/dl and a post-stimulation value of 23.2 mcg/dl, Subject #001 (BDP MDI 168 BID) had a pre-stimulation value of 17.7 mcg/dl and a post-stimulation value of 12.2 mcg/dl, and Subject #059 (BDP MDI 168 BID) had a pre-stimulation value of 4.0 mcg/dl and a post-stimulation value of 16.7 mcg/dl. These subjects were still included in the study. Unlike some of the other studies in this NDA, a change in plasma cortisol concentrations of <7 mcg/dl between pre- and post-stimulation was not an exclusion criterion for this study.

Summary of Demographic Data

	MF DPI 200 mcg BID (n=60)	MF DPI 400 mcg BID (n=62)	MF DPI 800 mcg QD (n=59)	BDP MDI 168 mcg BID (n=58)
Age (years)				
Mean	40	39	38	41
Min-Max	13-80	12-69	13-79	12-75
Distribution of Subjects in Age Categories				
12 to 17 years	7	5	6	3
18 to 64 years	51	56	49	52
≥65 years	2	1	4	3
Sex				
Female	35	38	30	38
Male	25	24	29	20
Race				
White	51	58	51	51
Black	4	4	4	5
Hispanic	2	0	3	2
Asian	3	0	1	0
Weight (lbs.)				
Mean	165	180	171	180
Min-Max	100-291	93-310	84-255	112-350
Smoking History				
Never Smoked	44	50	44	38
Has Not Smoked in 6 Months	16	12	15	20
Duration of Asthma Condition (years)				
Mean	19	18	20	19

Summary of Demographic Data

	MF DPI 200 mcg BID (n=60)	MF DPI 400 mcg BID (n=62)	MF DPI 800 mcg QD (n=59)	BDP MDI 168 mcg BID (n=58)
Min-Max	1-52	1-57	1-79	1-52
FEV_1 % Predicted at Baseline				
n	58	62	59	58
Mean	75	73	75	74
FEV_1 at Baseline (liters)				
n	58	62	59	58
Mean	2.57	2.41	2.62	2.37

5. Analysis of Efficacy

Because there was no placebo group involved in this study, it is inherently very different from the other studies in the NDA and its efficacy conclusions should not be considered as robust or convincing. The sponsor points out that because this study was primarily a safety study, efficacy evaluations were considered secondary. The study was not designed or powered to detect differences between treatment groups.

There were no significant differences ($p>0.05$) among treatment groups at Baseline for the efficacy analyses, with the exception of $FEF_{25\%-75\%}$ ($p=0.024$). Improvement in all efficacy parameters was evident in all treatment groups over the course of the study and at Endpoint. In general, the greatest numerical improvement in efficacy parameters at Endpoint occurred in the MF DPI 400 BID group, and the least improvement occurred in the BDP MDI 168 BID group. For most efficacy parameters, no statistically significant differences were noted at Endpoint among treatment groups.

a) FEV_1 and FVC

Improvement was seen in all treatment groups and pairwise comparisons among the treatment groups revealed only a rare early significant difference between groups (not shown). No significant differences were detected between the groups at Endpoint.

FEV_1 (liters)

	MF DPI 200 BID			MF DPI 400 BID			MF DPI 800 QD			BDP 168 BID		
	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	58	2.57		62	2.41		59	2.62		58	2.37	
Change From Baseline												
Week 1	57	0.16	(6.20%)	61	0.22	(9.33%)	56	0.07	(3.27%)	55	0.09	(3.43%)
Week 2	58	0.18	(7.06%)	58	0.25	(11.27%)	58	0.09	(4.39%)	55	0.11	(4.58%)
Week 4	55	0.27	(10.86%)	61	0.23	(10.50%)	59	0.11	(5.01%)	57	0.14	(5.90%)
Week 8	51	0.27	(10.75%)	60	0.24	(10.78%)	52	0.12	(5.96%)	55	0.13	(5.52%)
Week 12	49	0.29	(11.31%)	57	0.24	(9.74%)	47	0.27	(11.56%)	51	0.19	(7.89%)
Week 16	48	0.33	(12.97%)	56	0.30	(12.68%)	49	0.27	(11.28%)	48	0.19	(8.27%)
Week 26	38	0.31	(13.01%)	51	0.31	(12.47%)	44	0.23	(10.11%)	41	0.16	(6.70%)

Week 38	36	0.38	(15.14%)	47	0.33	(13.40%)	40	0.29	(11.74%)	38	0.29	(12.43%)
Week 52	34	0.30	(11.89%)	45	0.31	(13.11%)	43	0.30	(12.96%)	39	0.24	(9.04%)
Endpoint	58	0.27	(10.53%)	62	0.28	(12.24%)	59	0.24	(10.40%)	58	0.20	(7.73%)

The sponsor identified a treatment by center interaction for FEV, at Weeks 1, 4, 8, 16, 38, and 52 which was traced back to one Subject #344 who had unusually high post-Baseline values of 106-119% of predicted. Once this subject's data was removed the treatment by center interaction was no longer present but new significant differences in the pairwise comparisons appeared between MF DPI 200 BID and 400 BID versus BDP 168 BID at earlier time points. Still no difference was detected in the pairwise comparisons at Endpoint.

FVC (liters)

	MF DPI 200 BID			MF DPI 400 BID			MF DPI 800 QD			BDP 168 BID		
	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	58	3.46		62	3.36		59	3.64		58	3.37	
Change From Baseline												
Week 1	57	0.14	(4.25%)	61	0.17	(5.97%)	56	0.07	(3.00%)	55	0.05	(0.73%)
Week 2	58	0.23	(6.49%)	58	0.19	(6.96%)	58	0.13	(4.83%)	55	0.10	(2.64%)
Week 4	55	0.25	(8.60%)	61	0.16	(6.07%)	59	0.11	(4.33%)	57	0.14	(3.46%)
Week 8	51	0.20	(6.54%)	60	0.14	(5.18%)	52	0.09	(3.43%)	55	0.09	(2.71%)
Week 12	49	0.30	(9.41%)	57	0.22	(7.43%)	47	0.19	(6.36%)	51	0.21	(5.88%)
Week 16	48	0.32	(9.95%)	55	0.15	(5.25%)	49	0.20	(5.75%)	48	0.14	(4.23%)
Week 26	38	0.39	(12.01%)	51	0.23	(8.26%)	44	0.18	(6.78%)	41	0.14	(4.30%)
Week 38	36	0.43	(12.73%)	47	0.29	(9.11%)	40	0.30	(8.97%)	38	0.34	(10.48%)
Week 52	34	0.47	(15.60%)	45	0.29	(9.57%)	43	0.29	(10.03%)	39	0.26	(7.60%)
Endpoint	58	0.34	(11.20%)	62	0.25	(8.03%)	59	0.25	(8.21%)	58	0.17	(5.01%)

b) FEF_{25-75} and PEFR

Numerical improvements were also seen in all treatment groups for FEF_{25-75} and PEFR; no significant differences between the groups existed after Week 8 for FEF_{25-75} or Week 1 for AM PEFR.

$FEF_{25-75\%}$ (liters/second)

	MF DPI 200 mcg BID			MF DPI 400 mcg BID			MF DPI 800 mcg QD			BDP 168 mcg BID		
	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	58	2.13		62	1.88		59	2.09		58	1.74	
Change From Baseline												
Week 1	57	0.22	(12.73%)	61	0.32	(21.27%)	56	0.07	(7.52%)	55	0.16	(11.86%)

Week 2	58	0.20	(11.17%)	58	0.37	(23.79%)	58	0.10	(7.82%)	55	0.14	(8.24%)
Week 4	55	0.37	(19.80%)	61	0.36	(25.55%)	59	0.13	(11.28%)	57	0.16	(12.56%)
Week 8	51	0.42	(22.53%)	60	0.46	(29.91%)	52	0.17	(17.65%)	55	0.20	(13.04%)
Week 12	49	0.36	(20.18%)	57	0.31	(19.81%)	47	0.32	(25.92%)	51	0.19	(13.47%)
Week 16	48	0.40	(22.23%)	55	0.43	(28.81%)	49	0.38	(29.54%)	48	0.22	(16.26%)
Week 26	38	0.38	(22.13%)	51	0.45	(30.36%)	44	0.23	(22.41%)	41	0.14	(10.64%)
Week 38	36	0.37	(23.72%)	47	0.43	(28.00%)	40	0.25	(24.95%)	38	0.23	(16.14%)
Week 52	34	0.30	(15.88%)	45	0.38	(24.13%)	43	0.32	(23.12%)	39	0.28	(17.26%)
Endpoint	58	0.33	(16.79%)	62	0.38	(25.47%)	59	0.24	(17.97%)	58	0.23	(14.24%)

AM PEFR (liters/minute)

	MF DPI 200 BID			MF DPI 400 BID			MF DPI 800 QD			BDP 168 BID		
	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	59	402.1		62	386.6		59	412.4		58	381.6	
Change From Baseline												
Week 1	59	15.84	(5.5%)	62	11.74	(4.0%)	59	5.35	(1.8%)	58	2.31	(0.8%)
Week 2	59	16.10	(5.2%)	62	22.55	(6.6%)	59	11.96	(3.9%)	58	7.87	(2.9%)
Week 4	59	20.68	(6.5%)	62	20.18	(6.2%)	57	19.63	(5.1%)	57	19.03	(5.5%)
Week 8	56	21.85	(7.2%)	62	31.92	(9.5%)	54	34.77	(9.0%)	57	17.19	(4.7%)
Week 12	54	25.94	(8.6%)	60	33.34	(9.8%)	53	39.37	(10.2%)	55	21.85	(6.0%)
Week 16	51	32.95	(10.2%)	59	41.03	(11.7%)	54	44.42	(11.1%)	54	32.79	(8.9%)
Week 26	49	41.91	(12.5%)	56	43.79	(12.6%)	54	52.00	(13.5%)	49	27.95	(8.7%)
Week 38	45	43.43	(11.8%)	53	39.71	(11.0%)	53	57.12	(15.0%)	46	35.73	(9.4%)
Week 52	41	48.63	(13.1%)	49	44.47	(12.5%)	50	53.90	(14.3%)	43	35.00	(10.3%)
Endpoint	59	37.23	(11.2%)	62	46.50	(13.5%)	59	51.18	(13.3%)	58	27.77	(8.2%)

The PM PEFR data did reveal some difference between the treatment groups. Both the MF DPI 400 BID and MF DPI 800 QD groups reported statistically significant increases in PM PEFR at Endpoint (11.0% and 12.2%, respectively) compared with the BDP MDI 168 BID group (5.9%). Statistically significant differences in pairwise comparisons of treatment groups were also noted at Weeks 8 and 26.

c) Asthma Symptoms

Asthma symptoms were recorded up to Visit 7 only. Improvements were noted in both morning and evening scores for wheezing, difficulty breathing, and cough throughout the study and at Endpoint in all treatment groups. Except for a few time points, no statistically significant differences among treatment groups were found.

AM Wheezing

	MF DPI 200 mcg BID		MF DPI 400 mcg BID		MF DPI 800 mcg QD		BDP 168 mcg BID	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	59	0.60	62	0.56	59	0.51	58	0.61

Change From Baseline								
Week 1	59	-0.16	62	-0.18	59	-0.08	58	-0.10
Week 2	59	-0.18	62	-0.25	59	-0.09	58	-0.10
Week 4	59	-0.19	62	-0.19	57	-0.13	57	-0.18
Week 8	56	-0.15	62	-0.23	54	-0.20	57	-0.14
Week 12	53	-0.13	60	-0.28	51	-0.15	54	-0.20
Endpoint	59	-0.20	62	-0.24	59	-0.22	58	-0.18

The results for PM Wheezing tended to show smaller changes with the least again being seen in the BDP group. For the daily wheezing scores, no significant pairwise differences were identified except at Week 2 when MF DPI 400 BID was significantly greater than BDP 168 BID.

AM Difficulty Breathing

	MF DPI 200 mcg BID		MF DPI 400 mcg BID		MF DPI 800 mcg QD		BDP 168 mcg BID	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	59	0.63	62	0.75	59	0.66	58	0.77
Change From Baseline								
Week 1	59	-0.16	62	-0.23	59	-0.07	58	-0.18
Week 2	59	-0.17	62	-0.31	59	-0.12	58	-0.21
Week 4	59	-0.20	62	-0.24	57	-0.15	57	-0.30
Week 8	56	-0.17	62	-0.32	54	-0.24	57	-0.23
Week 12	53	-0.12	60	-0.31	51	-0.23	54	-0.28
Endpoint	59	-0.16	62	-0.28	59	-0.31	58	-0.25

Similar changes were identified for PM difficulty Breathing although the BDP did not fare quite so well as with the AM symptom (-0.14).

AM Cough

	MF DPI 200 mcg BID		MF DPI 400 mcg BID		MF DPI 800 mcg QD		BDP 168 mcg BID	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	59	0.45	62	0.39	59	0.27	58	0.49
Change From Baseline								
Week 1	59	-0.15	62	-0.11	59	-0.05	58	-0.12
Week 2	59	-0.15	62	-0.13	59	-0.06	58	-0.17
Week 4	59	-0.13	62	-0.04	57	-0.13	57	-0.19
Week 8	56	-0.15	62	-0.13	54	-0.10	57	-0.17
Week 12	53	-0.20	60	-0.15	51	-0.08	54	-0.19
Endpoint	59	-0.21	62	-0.00	59	-0.12	58	-0.10

The difference between MF DPI 200 and 400 BID for AM Cough was 0.05 at Endpoint. For the PM Cough, the largest changes appeared to occur with MF DPI 200 BID although the difference between this treatment group and the others was never significant.

d) Response to Therapy

At Endpoint, the proportion of subjects rated to each of the five response categories was generally similar for all treatment groups. The majority of subjects in each group was evaluated at Endpoint as either much improved or improved: 74% in the MF DPI 200 BID group, 82% in the MF DPI 400 BID group, 74% in the MF DPI 800 QD group, and 62% in the BDP MDI 168 BID group.

Physician's Evaluation of Response to Therapy at Endpoint

	Number (%) of Subjects			
Rating	MF DPI 200 BID (n=59)	MF DPI 400 BID (n=62)	MF DPI 800 QD (n=59)	BDP MDI 168 BID (n=58)
Much Improved	16 (27)	23 (37)	16 (27)	12 (21)
Improved	28 (47)	28 (45)	28 (47)	24 (41)
No Change	12 (20)	9 (15)	13 (22)	18 (31)
Worse	3 (5)	2 (3)	1 (2)	4 (7)
Much Worse	0	0	1 (2)	0

Physician's Assessment of Response to Therapy

	MF DPI 200 BID		MF DPI 400 BID		MF DPI 800 QD		BDP 168 BID	
	N	Mean	N	Mean	N	Mean	N	Mean
Week 1	57	2.50	61	2.41	56	2.54	55	2.56
Week 2	59	2.45	58	2.31	58	2.58	56	2.55
Week 4	56	2.29	62	2.34	59	2.48	57	2.50
Week 8	52	2.29	60	2.13	52	2.39	55	2.37
Week 12	50	1.99	57	2.17	47	2.08	51	2.34
Week 16	49	1.93	56	1.93	49	1.97	48	2.33
Week 26	41	1.97	51	2.05	44	2.13	41	2.44
Week 38	37	1.93	47	1.88	40	1.85	38	2.10
Week 52	35	1.81	45	1.82	44	1.89	39	2.13
Endpoint	59	2.06	62	1.86	59	2.05	58	2.25

At Endpoint and Weeks 16 and 26, the MF DPI 400 BID group experienced the greatest improvement in mean response score, which was statistically significantly different than that of the BDP MDI 168 BID treatment group. All other comparisons at Endpoint were not statistically significant.

e) B-agonist Use During the Study

For all groups, decreases in Proventil use were observed throughout the study. The MF DPI 400 BID group reported the greatest decrease in the number of daily puffs at Endpoint. No statistically significant differences in Proventil use were noted at Endpoint among groups.

Number of Puffs of Proventil

	MF DPI 200 mcg BID		MF DPI 400 mcg BID		MF DPI 800 mcg QD		BDP 168 mcg BID	
	N	Mean	N	Mean	N	Mean	N	Mean

Baseline	60	2.36	62	3.26	59	2.98	58	3.34
Change From Baseline								
Week 1	60	-0.83	62	-0.37	59	-0.27	58	-0.31
Week 2	59	-0.78	62	-0.80	59	-0.33	58	-0.33
Week 4	59	-0.80	62	-0.81	57	-0.45	57	-0.52
Week 8	56	-0.90	62	-1.28	54	-0.61	57	-0.46
Week 12	54	-1.17	60	-1.11	53	-0.73	55	-0.77
Week 16	51	-1.22	59	-1.45	54	-0.66	54	-0.60
Week 26	49	-1.20	56	-1.60	54	-0.88	49	-1.05
Week 38	45	-1.13	53	-1.33	53	-0.91	46	-0.87
Week 52	41	-1.09	49	-1.18	50	-0.95	42	-0.56
Endpoint	60	-0.94	62	-1.16	59	-1.05	58	-0.41

f) Nocturnal Awakenings with Asthma Symptoms Requiring Proventil

In all groups, decreases in the number of awakenings were seen throughout the study. The MF DPI 400 BID group reported the greatest decrease at Endpoint and generally at every timepoint. The differences among treatment groups were not statistically significant.

Number of Nocturnal Awakenings Due to Asthma

	MF DPI 200 mcg BID		MF DPI 400 mcg BID		MF DPI 800 mcg QD		BDP 168 mcg BID	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	60	0.17	62	0.30	59	0.18	58	0.23
Change From Baseline								
Week 1	60	-0.10	62	-0.12	59	-0.01	58	-0.08
Week 2	59	-0.11	62	-0.15	59	-0.04	58	-0.06
Week 4	59	-0.09	61	-0.14	57	-0.03	57	-0.08
Week 8	56	-0.05	61	-0.10	54	-0.04	57	-0.07
Week 12	54	-0.06	59	-0.15	53	-0.09	55	-0.10
Week 16	51	-0.12	58	-0.16	54	-0.08	54	-0.08
Week 26	48	-0.10	55	-0.21	54	-0.09	49	-0.14
Week 38	45	-0.10	52	-0.15	53	-0.11	46	-0.15
Week 52	42	-0.05	48	-0.21	50	-0.11	43	-0.14
Endpoint	60	-0.05	62	-0.17	59	-0.11	58	-0.02

g) Worsening of Asthma/Clinical Asthma Exacerbations

Thirteen subjects (4 in the MF DPI 200 BID group, 1 in the MF DPI 400 BID group, 4 in the MF DPI 800 QD group, and 4 in the BDP MDI 168 BID group) met the criteria for worsening of asthma. Most of these subjects experienced a clinical asthma exacerbation that required emergency treatment.

Clinical Asthma Exacerbations were reported by four subjects in the MF DPI 200 BID group, 10 subjects in the MF DPI 400 BID group, 11 subjects in the MF DPI 800 QD group, and 12 subjects in the BDP MDI 168 BID group.

h) Efficacy Summary for C96-135

The objective of C96-135 was to characterize the long-term safety of three doses of MF DPI compared with BDP in subjects previously maintained on inhaled corticosteroids. Efficacy evaluations were considered secondary, and the study was not designed to detect differences in efficacy parameters between treatment groups. Numerical improvement was noted in all efficacy parameters (FEV_1, FVC, FEF_{25-75}, AM and PM PEFR, asthma symptoms, physician's assessment of response to therapy, B agonist use, and number of nocturnal awakenings) between Baseline and Endpoint for all doses of MF DPI (200 BID, 400 BID, and 800 QD) and for BDP MDI (168 BID). This effect of treatment was consistent over time, and subjects experienced improvement within one week of treatment. No statistically significant differences in efficacy variables were noted among treatment groups with a few exceptions –1) FEV_1: between MF DPI 200 BID and 400 BID versus BDP 168 BID at early time points, 2) MF DPI was greater than 800 QD up to Week 8 and MF DPI 400 BID was greater than BDP at Weeks 2 and 8 for FEF_{25-75}, 3) One early timepoint for each MF DPI dose versus BDP for AM PEFR. 4) For AM Wheezing, MF DPI 400 BID was greater than 800 QD only at Week 2, 4) For AM Difficulty Breathing, MF DPI 400 BID was greater than 800 QD at Weeks 1 and2, 5) the difference between MF DPI 200 and 400 BID for AM Cough was very nearly significant at 0.05 at Endpoint. In general, the currently marketed BDP MDI 168 mcg BID treatment group experienced the least improvement but it must be noted that this was the treatment was open label to the subject and not to the individual doing the respective testing of variables.

6. Safety C96-135

a) Time of Exposure

The respective time of exposure for each of the drug treatments was remarkably similar.

Extent of Exposure by Treatment Group

Length of Exposure	MF DPI 200 mcg BID (n=60)	MF DPI 400 mcg BID (n=62)	MF DPI 800 mcg QD (n=59)	BDP MDI 168 mcg BID (n=58)
≥1 dose	59	60	59	58
≥4 days	58	60	59	58
≥1 month	57	60	58	57
≥3 months	53	59	54	55
≥6 months	49	55	54	51
≥9 months	45	54	52	46
≥12 months	42	50	49	43
Unknown	1	2	0	0
% ≥ 12 mo.	71%	80.6%	83%	74%

The higher daily doses of MF DPI appeared to have a higher completion rate compared with MF DPI 200 BID and BDP.

b) Adverse Events

The most common adverse event in C96-135 was headache (43%-55% for each group). Common with other studies in this NDA, the most prevalent adverse events included allergy aggravated, influenza-like symptoms, viral infection, sinusitis, and pharyngitis.

Incidence of Adverse Events Reported by ≥10% of Subjects in Any Treatment Group.

	MF DPI 200 BID (n=60)		MF DPI 400 BID (n=62)		MF DPI 800 QD (n=59)		BDP MDI 168 BID (n=58)	
	n	(%)	n	(%)	n	(%)	n	(%)
Headache	26	(43)	28	(45)	26	(44)	32	(55)
Allergy, aggravated	21	(35)	21	(34)	16	(27)	15	(26)
Sinusitis	19	(32)	13	(21)	15	(25)	12	(21)
Infection viral	17	(28)	21	(34)	18	(31)	13	(22)
Pharyngitis	15	(25)	12	(19)	10	(17)	14	(24)
Candidiasis, oral	14	(23)	11	(18)	10	(17)	9	(16)
Nasal congestion	11	(18)	12	(19)	14	(24)	8	(14)
Musculo-skeletal pain	11	(18)	12	(19)	13	(22)	7	(12)
Upper resp. tract infection	10	(17)	13	(21)	8	(14)	11	(19)
Bronchitis	10	(17)	13	(21)	9	(15)	12	(21)
Dyspepsia	10	(17)	4	(6)	5	(8)	8	(14)
Influenza-like symptoms	9	(15)	21	(34)	10	(17)	15	(26)
Myalgia	9	(15)	8	(13)	2	(3)	7	(12)
Back pain	6	(10)	9	(15)	10	(17)	4	(7)
Coughing	6	(10)	8	(13)	13	(22)	6	(10)
Rhinorrhea	6	(10)	7	(11)	3	(5)	5	(9)
Dysmenorrhea	3	(9)	7	(18)	6	(20)	7	(18)
Fever	5	(8)	10	(16)	6	(10)	6	(10)
Abdominal pain	5	(8)	6	(10)	1	(2)	5	(9)
Asthma, aggravated	4	(7)	5	(8)	4	(7)	7	(12)
Rhinitis	3	(5)	6	(10)	4	(7)	5	(9)
Respiratory disorder	1	(2)	3	(5)	1	(2)	6	(10)
Vaginitis, fungal	0	(0)	0	(0)	0	(0)	4	(11)

Because there was no placebo control in this study, it is particularly difficult to discern which adverse events were attributable to MF DPI. Among the above adverse events, there is not a definitive difference between MF DPI and BDP but a few adverse events such as viral infection, nasal congestion, musculo-skeletal pain, back pain, and coughing appeared to be slightly more common with MF DPI. There was a suggestion of a MF DPI dose response with these adverse events except for viral infection. On the otherhand, headache, aggravated asthma, respiratory disorder and fungal vaginitis appeared to be more common with BDP. Notably, the incidence of dysmennorhea was lowest in the MF DPI 200 BID group.

Oral candidiasis or pharyngitis did not appear to be any more common with MF DPI than with BDP.

Edited List of Adverse Events (with incidence less than 10% in any treatment group)

	Number (%) of Subjects			
	MF DPI 200 mcg BID (n=60)	MF DPI 400 mcg BID (n=62)	MF DPI 800 mcg QD (n=59)	BDP MDI 168 mcg BID (n=58)
Any Adverse Event	**56(93)**	**58(94)**	**57(97)**	**56(97)**
chest pain	2(3)	4(6)	3(5)	0
dysphonia	3(5)	2(3)	2(3)	0
menstrual disorder	3(9)	0	0	1(3)
otitis media	4(7)	4(6)	1(2)	0
dyspnea	1(2)	1(2)	2(3)	0
epistaxis	2(3)	1(2)	2(3)	0
sinus congestion	4(7)	5(8)	3(5)	3(5)
micturition frequency	2(3)	1(2)	1(2)	0
conjunctivitis	4(7)	1(2)	2(3)	1(2)

Chest pain, dysphonia, otitis media, micturition frequency, dyspnea, and epistaxis are particularly notable for they appear only with MF DPI and not BDP. Other than dysphonia, these adverse events have not been particularly notable in other studies for this NDA thus far and, with the possible exclusion of otitis media, were particularly unusual or infrequent and probably reflect incidental findings. It is not clear why otitis media should be so notable among the MF DPI subjects but at least a dose response relationship is not apparent.

Four subjects were noted to have cataracts during the study and two were noted to have increased intraocular pressure.

Subject #225 was a 30 year-old male (MF DPI 400 BID) had been on BDP 168 BID from 1/97, had no cataracts noted on Screening on 3/10/97 and at the final visit on 4/2/98 was noted to have trace posterior subcapsular changes OU. He had periodically required both inhaled and oral steroids for asthma control prior to the study.

Subject #296 (MF DPI 200 BID) was a 58 year-old female who had been taking fluticasone 176 BID since 1/30/97. No cataracts were noted at Screening on 3/6/97. On — she went to her personal ophthalmologist complaining of difficulty reading a computer screen. Small (trace-1+) posterior subcapsular cataracts were detected in both eyes. The patient was discontinued from the study and placed on a leukotriene modifier.

Subject #148 was a 34 year-old female (MF DPI 800 QD) was found to have a possible early subcapsular cataract OS – notably she had been on Azmacort from 1991 to the commencement of the study as well as periodic Flonase during the study.

Subject #007 was a 61 year-old male (BDP 168 BID) who was noted to have a 3+ posterior subcapsular cataract one year after Screening when no cataracts were noted. He was examined by the same ophthalmologist at each occasion. He had been receiving inhaled steroids for his asthma for approximately 9 years and had also received oral steroid bursts before the study.

The case histories were reviewed for the sponsor by an independent ophthalmologist. He noted that the assessments were not well standardized with respect to examination technique or to grading of opacities. He also noted that in studies such as this, the post-treatment evaluation might be subject to observer bias. The observer is aware that the subject has received long-term treatment with a corticosteroid and therefore tends to conduct a more rigorous assessment, and he may attach more significance to findings. It was also noted that other risk factors for the development of cataract, such as age, prior steroid use, smoking, and possible diabetes were present in these cases making it difficult to determine the association between study treatment and the development of cataract.

Subject #422 was a 26 year-old female (MF DPI 800 QD) who had an intraocular pressure (IOP) of 14/14 on her 3/17/97 Screening and at the final visit on 3/30/98 the pressures were 24/22. She was taking triamcinolone acetonide 200 mcg BID since 1996 and received a 5-day course of prednisone 10 months prior to the study. The patient resumed treatment with triamcinolone after the study and on 5/14/98 her IOP were 16/15.

Subject # 127 was a 48 year-old female (MF DPI 800 QD) previously on Flovent who was noted to have IOP of 16/18 at Screening on 3/26/97 but on 3/30/98 had IOP of 22/21 – notably she

had been on prednisone for 5 days prior to the reading and on 3 previous occasions during the study.

Headache, abdominal pain and musculoskeletal pain appeared to be more common in females in the study but did not have an overrepresentation in MF DPI versus BDP with the possible exception of musculoskeletal pain. Because of the small number of subjects who were not aged 18-64 or who were not Caucasian, a further examination of the AE's among these subgroupings was not warranted.

c) Severe/Life-Threatening Adverse Events

Severe or life-threatening adverse events were reported by 70 subjects. The incidence of severe or life-threatening adverse events was somewhat lower in the MF DPI 200 BID group and MF DPI 800 QD group (20%-22%) compared with the MF DPI 400 BID group and BDP MDI 168 BID group (37%-38%). Six subjects had an event that was categorized as either life-threatening or medically significant and are discussed further in the section on Serious adverse events..

Edited List of Severe/Life-Threatening Treatment-Emergent Adverse Events

	Number (%) of Subjects			
	MF DPI 200 mcg BID (n=60)	MF DPI 400 mcg BID (n=62)	MF DPI 800 mcg QD (n=59)	BDP MDI 168 mcg BID (n=58)
Any Severe/Life-threatening Adverse Event	**13(22)**	**23(37)**	**12(20)**	**22(38)**
allergy, aggravated	1(2)	2(3)	2(3)	1(2)
back pain	0	2(3)	1(2)	0
headache	2(3)	5(8)	1(2)	7(12)
influenza-like symptoms	0	1(2)	0	0
dysphonia	0	0	1(2)	0
hyperglycemia	0	1(2)	0	0
suicide attempt	0	0	0	1(2)
asthma aggravated	1(2)	1(2)	0	3(5)
dyspnea	0	0	1(2)	0
respiratory disorder	0	0	0	1(2)
status asthmaticus	1(2)	0	0	0
hemorrhage, intracranial	1(2)	0	0	0
diplopia	1(2)	0	0	0

d) Serious Adverse Events

Center/Subject	Sex/ Age/ Race	Adverse Event(s)	Relationship	Status
		MF DPI 200 mcg BID		
C96-135-09/029	M/55/C	Hiatal Hernia	unlikely	Hospitalized
C96-135-10/367	F/45/C	Menorrhagia	unlikely	Hospitalized
C96-135-11/298	M/28/C	Hepatic Enzymes Increased	unlikely	Medically Significant (See Below)
C96-135-16/065	M/44/C	Hemorrhage, Intracranial; Loss of consciousness	unlikely	Hospitalized

Center/Subject	Sex/ Age/ Race	Adverse Event(s)	Relationship	Status
C96-135-18/009	F/46/C	Asthma Aggravated	unlikely	Life-threatening, Hospitalized (had additional exacerb.)
C96-135-19/200	F/37/C	Hernia	unlikely	Hospitalized
		MF DPI 400 mcg BID		
C96-135-12/243	F/17/C	Dyspnea (CO poisoning)	unlikely	Life-threatening
C96-135-12/252	F/44/NC	Asthma Aggravated (had dc med. by herself 2 weeks prior)	unlikely	Hospitalized
C96-135--15/267	F/41/C	Breast Neoplasm, Malignant	unlikely	Cancer, Medically Significant
C96-135-15/270	F/49/C	Uterine Fibroid	unlikely	Hospitalized
C96-135-19/199	F/41/C	Abdominal Pain (had vaginal hysterectomy)	unlikely	Hospitalized
C96-135-20/172	F/46/C	Menstrual Disorder	unlikely	Hospitalized
		MF DPI 800 mcg QD		
C96-135-12/255	F/51/NC	Arthritis Aggravated	unlikely	Hospitalized
C96-135-17/149	F/23/C	Cholelithiasis	unlikely	Hospitalized
		BDP MDI 168 mcg BID		
C96-135-04/419	M/42/C	Fracture, Bone (slipped in mud)	unlikely	Hospitalized
C96-135-10/361	F/52/C	Procedure (D&C and urethral dilation)	not provided	Hospitalized
C96-135-15/266	M/21/C	Suicide Attempt with tetracycline (depressed over family events)	unlikely	Hospitalized
C96-135-16/059	F/24/C	Abdominal Pain, Cholelithiasis, Pancreatitis, Vomiting	unlikely	Hospitalized
C96-135-17/147	M/68/C	Mucosal Erosion, Mod. Throat Dysplasia thought due to reflux.	unlikely	Medically Significant
C96-135-21/485	F/30/C	Dyspnea, Asthma Aggravated	unlikely	Hospitalized

Subject #65 was hospitalized after being found unconscious and was found to have a parietal lesion with acute hemorrhage of unclear etiology, possibly representing a primary CNS tumor or a ruptured arteriovenous malformation. Subject #298 (Site 111), a 28-year-old male in the MF DPI 200 BID group, was discontinued from the study due to significant increases in AST (value of 315 IU/L, normal range: 11-36 IU/L) and LDH (value of 928 IU/L, normal range: 53-234 IU/L) at Week 12. The subject was discontinued from the study one week later. Screening values were normal, physical exam was reported to be unremarkable, and the subject was asymptomatic. A screen for Hepatitis A and B were negative. Two days later the AST was 313 and LDH was 418. Five days later, the AST and LDH were 55 and 155, respectively. The investigator considered the event possibly due to either a viral etiology or unreported alcohol consumption. The rest of the serious AE's are essentially self-explanatory and in most cases do not appear to be related to drug treatment with the possible exception of the asthma exacerbation and the liver enzyme increase noted in Subject#298.

e) Discontinuation Because of Adverse Events

There appeared to be fewer subjects discontinuing due to AE's in the MF DPI 400 BID group (2 subjects, 3%) and MF DPI 800 QD group (5 subjects, 8%) than in the MF DPI 200 BID group (11 subjects, 18%) and BDP MDI 168 BID group (10 subjects, 17%). This reviewer's critique of this list shows that the majority of these events should not be related to drug treatment except for those subjects/events that are in bold. These treatment-related events tend to be oral candidiasis, dysphonia, pharyngitis, menstrual disorder, myalgia, or influenza-like symptoms.

Center/Subject	Sex/ Age/ Race	Day of Onset	Adverse Event(s)	Severity	Relationship
MF DPI 200 mcg BID					
C96-135-03/219	**F/28/C**	**8**	**Menstrual disorder**	**Mild**	**Possible**
C96-135-03/221	**F/48/C**	**8**	**Dysphonia**	**Mild**	**Probable**
C96-135-06/099	**F/47/C**	**17**	**Candidiasis, Oral**	**Moderate**	**Related**
		25	**Pharyngitis**	**Moderate**	**Unrelated**
		25	**Coughing**	**Moderate**	**Unrelated**
C96-135-09/026	M/44/C	43	Somnolence	Mild	Possible
C96-135-11/296	F/58/C	99	Cataract Subcapsular	Mild	Possible
C96-135-11/298	**M/28/C**	**84**	**Hepatic Enzymes Increased**	**Moderate**	**Unrelated**
C96-135-14/078	F/33/C	188	Pregnancy Unintended	Mild	Unrelated
C96-135-16/058	**F/27/C**	**143**	**Myalgia**	**Moderate**	**Possible**
C96-135-16/065	M/44/C		Loss of Consciousness	Severe	Unrelated
		172 (1)	Hemorrhage Intracranial	Severe	Unrelated
C96-135-18/009	F/45/C	244	Upper Resp. Tract Infection	Moderate	Unrelated
		245 (1)	Status Asthmaticus	Life-threatening	Unrelated
		246 (2)	Headache	Mild	Unrelated
		246 (2)	Insomnia	Mild	Unrelated
		247 (3)	Coughing	Mild	Unrelated
		248 (4)	Dyspepsia	Mild	Unrelated
C96-135-21/482	**F/14/C**	**272 (1)**	**Influenza-like Symptoms**	**Moderate**	**Unrelated**
MF DPI 400 mcg BID					
C96-135-13/459	**F/57/C**	**46**	**Candidiasis, Oral**	**Moderate**	**Related**
C96-135-19/199	F/40/C	315	Abdominal Pain	Severe	Unrelated
MF DPI 800 mcg QD					
C96-135-04/414	M/28/C	16	Bronchitis	Moderate	Unrelated
C96-135-05/343	**F/31/C**	**29**	**Fibromyalgia**	**Moderate**	**Unrelated**
C96-135-12/255	F/51/NC	32 (1)	Arthritis	Moderate	Unrelated
C96-135-18/012	**M/34/C**	**19**	**Dysphonia**	**Severe**	**Related**
		32 (1)	**Candidiasis, Oral**	**Moderate**	**Related**
C96-135-20/169	F/62/C	324	Headache	Mild	Unrelated

Center/Subject	Sex/ Age/ Race	Day of Onset	Adverse Event(s)	Severity	Relationship
			BDP MDI 168 mcg BID		
C96-135-04/412	**F/38/C**	**230**	**Candidiasis, Oral**	**Moderate**	**Possible**
C96-135-05/337	F/52/C	1	Headache	Severe	Probable
		3	Face Edema	Mild	Probable
C96-135-07/123	M/37/C	178	Abdominal Mass	Mild	Possible
C96-135-15/266	M/21/C	116	Suicide Attempt	Life-threatening	Unrelated
C96-135-16/059	F/24/C	130	cholelithiasis	Severe	Unrelated
		130	Pancreatitis	Severe	Unrelated
C96-135-17/1479	M/67/C	334	Mucosal Erosion NOS	Moderate	Unrelated
C96-135-18/007	M/61/C		Cataract	Moderate	Probable
C96-135-19/204	F/49/C	56	Palpitation	Mild	Unrelated
C96-135-21/481	**F/63/C**	**275**	**Influenza-like Symptoms**	**Moderate**	**Unrelated**
C96-135-21/485	**F/29/C**	**199 (1)**	**Asthma Aggravated**	**Severe**	**Unrelated**

f) Laboratory Events

The sponsor submitted a list of "clinically significant" abnormalities were defined as values for blood chemistry values ≥2.6 times the upper limit of normal, hemoglobin concentration ≤9.4g/dl, platelet count ≤74,000/µl, or white blood cell count ≤2,900/µl but a more extensive list was identified by this reviewer during the 12 months of C96-135. This list does not generally include subjects who had abnormalities at Screening or those who had a transaminase change less than or equal to 20.

Subject #	Abnormality/Visit	Notes
MF DPI 200 mcg BID (Vol. 17 - 4 month Supplement)		
470	AST/ALT 34/70 on Week 12	19/23 Scr, 14/25 Week 38
073	AST/ALT 35/69 on Week 26	22/37 Scr, 36/65 Day 385
065	ALT 93 on Day 190	26 Scr, nl AST.
200	ALT 41 on Week 38	20 at Scr, nl AST
175	WBC 13.18 on Day 366	8-9 previously
482	AST 37 on Day 289	10-17 prev., nl ALT
298	LDH 928 on Day 84, 418 Day 86	167 Scr, 155 Day 91 (Final)
	AST/ALT 315/72	24/20 Scr
MF DPI 400 mcg BID (Vol. 17 4 month Supplement)		
435	ALT 36 at Week 12	16 Scr, nl AST
295	AST/ALT 60/110 at Week 38	30/45 Scr, 25/55 Day 365
314	WBC 13.22 on Day 372	6.55 to 8.84 prev.
MF DPI 800 QD (Vol. 17/18 4 month Supplement)		
434	ALT 85 on Week 26	30 Scr, 61 Day 364, nl AST
395	ALT 74 Day 372	35 Scr, TBILI 1.4- 1.7 throughout, nl AST
292	ALT 41 Week 12	17 Scr, nl AST
271	AST/ALT 46/38, Wk 38	15/10 Scr (TBILI 1.3 Scr, 0.9 Wk 38)
205	ALT 66 at Wk 26,AST 30	16 Scr
175	AST/ALT 53/77 Day 366	27/35 Scr, 25/39 Day 380

BDP 168 mcg BID	(Vol. 18/19 4 month Supplement)	
443	WBC 2.35 Week 26	6.12 Scr, 4.14 Day 370
447	AST/ALT 43/139 Day 365	16/22 Scr, ALT 74 Day 372 (TBILI 1.3 to 1.6 throughout)
419	AST/ALT 46/57Week 38	32/35 Scr
027	ALT 73 Day 107, TBILI 1.4	35/0.8 Scr, Day 107 was Final.
468	ALT 41, AP 160 Week 38 ALT 62, AP 124 Day 373	26/94 at Scr.
074	AST/ALT 91/84 Week 26	31/18 Scr, 31/23 Day 393
147	Glucose 178 Week 26	86 Scr
	TBILI 1.9 Week 12	1.2 Scr, 1.2 Day 350

Of the above abnormalities, a few appear to stand out. These include: 1) MF DPI 200 BID -Subjects #470 (ALT 23 to 70), #65 (ALT 26 to 93), #298 (previously discussed), 2) MF DPI 400 BID – Subject #295 (ALT 45 to 110 – because of the baseline elevation of the ALT, albeit meager, the subject may have had some baseline liver abnormality), 3) MF DPI 800 QD – Subjects # 434 (ALT 30 to 85), #395 (ALT 35 to 74 – subject had somewhat elevated total bilirubin throughout some may have had some baseline liver problem), #205 (ALT 16 to 66) , #175 (AST/ALT 27/35 to 53/77) and 4) BDP 168 BID – Subjects #447 (AST/ALT 16/22 to 43/139), #027 (ALT 35 to 73 and TBILI 0.8 to 1.4), #074 (AST/ALT 31/18 to 91/84). It is difficult to discern which transaminase rises are incidental and which can be attributable to MF DPI treatment. It is difficult to determine the clinical significance of these elevations and to this reviewer's knowledge it is difficult to know what the baseline variation in transaminases is in the general population. The package labeling for BDP does not note any possible transaminase elevation. Of the above laboratory changes, it appears that Subject#298's changes are the most clinically important and cannot be readily explained.

The medians of the laboratory parameters for the treatment groups at 3, 9, and 12 months compared to Baseline were examined and no important changes were noted at these time points. There were too few subjects aged <12 to 17 years or ≥65 years, or who were non-Caucasian, to make any meaningful assessment with respect to age or race.

g) Plasma Cortisol Concentrations

Twenty-seven subjects treated with MF DPI 200 BID, 27 treated with MF DPI 400 BID, 23 treated with MF DPI 800 QD, and 25 treated with BDP 168 BID underwent Cortrosyn stimulation testing at 10 selected centers. Measurements were performed at Screening, Week 26, and Week 52.

Mean Plasma Cortisol Levels (mcg/dl)

	MF DPI 200 mcg BID (A)		MF DPI 400 mcg BID (B)		MF DPI 800 mcg QD (C)		BDP 168 mcg BID (D)	
	N	Mean	N	Mean	N	Mean	N	Mean
Screening								
Pre-Cortrosyn	27	13.04	27	13.55	23	16.11	25	15.31
Post-Cortrosyn	27	28.01	27	28.25	23	27.94	25	28.97
Difference: Post - Pre	27	14.97	27	14.70	23	11.84	25	13.67
Week 26								
Pre-Cortrosyn	25	13.33	24	13.80	22	15.56	24	16.95

Mean Plasma Cortisol Levels (mcg/dl)

	MF DPI 200 mcg BID (A)		MF DPI 400 mcg BID (B)		MF DPI 800 mcg QD (C)		BDP 168 mcg BID (D)	
	N	Mean	N	Mean	N	Mean	N	Mean
Post-Cortrosyn	24	26.42	24	25.88	22	26.69	23	29.59
Difference: Post - Pre	24	12.52	24	12.09	22	11.16	23	12.21
Change From Screening	24	-2.10	24	-2.40	22	-0.48	23	-1.98
Week 52								
Pre-Cortrosyn	19	12.81	21	12.97	20	14.37	20	15.27
Post-Cortrosyn	19	26.35	21	25.15	20	25.93	20	30.77
Difference: Post - Pre	19	13.54	21	12.18	20	11.55	20	15.50
Change From Screening	19	-1.08	21	-1.92	20	-0.64	20	2.54

Analysis Results

		P-value		Pairwise Comparisons (P-values)					
	SD	Treatment	Center	A-B	A-C	A-D	B-C	B-D	C-D
Screening									
Pre-Cortrosyn	50.18	0.378	0.681	0.795	0.132	0.253	0.206	0.374	0.697
Post-Cortrosyn	53.01	0.958	0.894	0.907	0.973	0.636	0.884	0.720	0.626
Difference: Post - Pre	22.20	0.092	0.702	0.833	**0.021**	0.322	0.035	0.433	0.183
Week 26									
Pre-Cortrosyn	56.47	0.322	0.901	0.829	0.316	0.096	0.431	0.153	0.534
Post-Cortrosyn	54.05	0.324	0.491	0.798	0.905	0.145	0.710	0.090	0.191
Difference: Post - Pre	18.91	0.750	0.374	0.731	0.294	0.803	0.475	0.926	0.426
Change From Screening	17.81	0.432	0.286	0.807	0.200	0.921	0.128	0.734	0.240
Week 52									
Pre-Cortrosyn	75.20	0.779	0.589	0.955	0.579	0.381	0.608	0.401	0.748
Post-Cortrosyn	79.22	0.195	0.097	0.672	0.883	0.127	0.782	**0.048**	0.093
Difference: Post - Pre	28.21	0.103	0.444	0.424	0.251	0.254	0.709	**0.050**	0.023
Change From Screening	30.77	0.069	0.715	0.636	0.805	**0.046**	0.465	**0.013**	0.077

At Baseline, there was a significant difference in the pre-post difference between the MF DPI groups 200 BID and 800 QD. At Week 52, there were significant differences between the change in pre-post values of MF DPI 200 BID/400 BID and BDP. No differences had been noted at Week 26.

A statistically significant treatment-by center interaction ($p \leq 0.031$) was identified by the sponsor for pre-Cortrosyn cortisol values at Screening, Week 26, and Week 52, and for post-Cortrosyn cortisol values at Week 26 for three subjects, all assigned to BDP MDI 168 BID, who had unusually high basal plasma cortisol concentrations, which remained high throughout the study. A review of the CRFs indicated that these three subjects were taking oral contraceptives, which could explain the high values.

Despite the removal of these 3 subjects from the analysis ((p.2288, Vol. 9), the differences at Week 52 between MF DPI 200 BID and BDP (p=.034), MF DPI 400 BID and BDP (p= .010) remained and was very nearly significant for the difference between MF DPI 800 QD and BDP (p= .055). It should be noted, however, that the difference between pre- and post-Cortrosyn stimulation was particularly high for the BDP group, even compared with its Week 26 value. Furthermore, the differences within treatment groups over the course of treatment appeared to change by only 1.0 to 2 mcg/dl between Screening and Week 52 for the MF DPI 200 BID and 400 BID groups and 0.5-0.6 for the 800 QD group so it can not be definitively stated that MF DPI is any more likely to produce adrenal suppression, based on the results of

this single small study, than BDP. Of course, more definitive, more sensitive testing could have been done by testing for overnight or 24 hour urine cortisol to discern if there is any real difference in adrenal suppression between these two products.

Individual abnormalities in plasma cortisol concentrations also were noted. A summary of the subjects with a pre-stimulation plasma cortisol concentration of <5 mcg/dl, a post-stimulation concentration of <18 mcg/dl, or an increase in response to Cortrosyn stimulation of <7 mcg/dl was generated.

Number of Subjects with Individual Abnormalities

	MF DPI 200 mcg BID	MF DPI 400 mcg BID	MF DPI 800 mcg QD	BDP 168 mcg BID	Total
Screening	N=27	N=27	N=23	N=25	N=102
Pre-Cortrosyn value < 5 mcg/dl	0	0	1	1	2
Post-Cortrosyn value < 18 mcg/dl	0	0	0	2	2
Difference between Post- and Pre-Cortrosyn value < 7 mcg/dl	0	1	3	2	6
Total Number of Subjects	0	1	4	3	8
Week 26	N=24	N=24	N=22	N=23	N=93
Pre-Cortrosyn value < 5 mcg/dl	1	2	1	0	4
Post-Cortrosyn value < 18 mcg/dl	1	2	1	0	4
Difference between Post- and Pre-Cortrosyn value < 7 mcg/dl	3	5	4	3	15
Total Number of Subjects	4	6	4	3	17
Week 52	N=19	N=21	N=20	N=20	N=80
Pre-Cortrosyn value <.5 mcg/dl	1	2	1	0	4
Post-Cortrosyn value < 18 mcg/dl	3	1	3	0	7
Difference between Post- and Pre-Cortrosyn value < 7 mcg/dl	4	3	3	0	10
Total Number of Subjects	5	5	5	0	15

While at Screening there appeared to be more individuals with abnormalities in the MF DPI 800 QD and BDP groups, at the end of 52 weeks, those with abnormalities were equally distributed among the MF DPI groups only and, interestingly, none were seen in the BDP group. Compared with Screening, there was a gain of 4-5 in the MF DPI 200 BID group, 4-5 in the MF DPI 400 BID group, 0-1 in the MF DPI 800 QD group and 3 less in the BDP group at Week 52. This data on outliers gives the impression that MF DPI may have a greater potential of adrenal suppression in some individuals than BDP but this data on outliers did not show a dose response. The data on means was somewhat controversial but also did suggest a difference between MF DPI and BDP.

h) Plasma Mometasone Concentrations

Mometasone furoate concentrations were measured using a validated high pressure liquid chromatography (HPLC) assay with tandem mass spectrometry detection (LC/MS/MS) in plasma samples collected before and 30 minutes after dosing with study medication. Samples were obtained pre- and post-dosing at Weeks 26 and 52 from 19, 20, and 19 subjects in the MF DPI 200 BID, MF DPI 400 BID, and MF DPI 800 QD groups, respectively, and 20 subjects in

the BDP group. Concentrations below the limit of quantitation (LOQ) of this assay (50.3 pg/ml) were reported as zero.

Plasma MF Concentrations

	Week 26		Week 52	
	Pre-Dose	30 min Post-Dose	Pre-Dose	30 min Post-Dose
MF DPI 200 mcg BID (n=19)				
No. Samples Reportable	3	4	18	18
No. Samples Above LOQ	1	2	7	13
Mean (pg/ml)	28	34	54	103
Minimum Value (Above LOQ) (pg/ml)	84.0	55.3	52.5	76.6
Maximum Value (pg/ml)	84.0	80.6	364	381
MF DPI 400 mcg BID (n=20)				
No. Samples Reportable	3	3	19	18
No. Samples Above LOQ	1	2	12	13
Mean (pg/ml)	53	107	101	156
Minimum Value (Above LOQ) (pg/ml)	159	136	52.4	83.4
Maximum Value (pg/ml)	159	185	569	618
MF DPI 800 mcg QD (n=19)				
No. Samples Reportable	1	1	19	18
No. Samples Above LOQ	none	none	7	15
Mean (pg/ml)	0	0	26	125
Minimum Value (Above LOQ) (pg/ml)	none	none	58.5	55.3
Maximum Value (pg/ml)	0	0	103	259
BDP MDI 168 mcg BID (n=20)				
No. Samples Reportable	4	3	18	18
No. Samples Above LOQ	none	none	none	none
Mean (pg/ml)	0	0	0	0
Maximum Value (pg/ml)	0	0	0	0

LOQ = limit of quantification = 50.3 pg/ml; levels below LOQ were reported as 0.

At Week 52, plasma MF was quantifiable in 7 of 18, 12 of 19, and 7 of 19 pre-dose samples in the MF DPI 200 BID, MF DPI 400 BID, and MF DPI 800 QD groups, respectively. Mean pre-dose plasma MF values in these three groups were 54, 101, and 26 pg/ml, respectively. MF was quantifiable in 13 of 18, 13 of 18, and 15 of 18 post-dose samples at this time point in the three groups, respectively, with mean post-dose plasma MF values of 103, 156, and 125 pg/ml, respectively. The pre- and post-dose mean plasma MF values were low and characterized by a large inter-subject variability. The low plasma MF values observed in this study appear to be consistent with what the sponsor believes to be the low systemic bioavailability of MF.

i) Vital signs

Vital signs and weights were examined among the treatment groups over the 12 month period. An increase of 1.9 to 4.4 mm Hg. was noted in the systolic and diastolic pressures in all

the treatment groups. It is not possible to attribute this to drug treatment and the clinical significance of these changes is doubtful. A weight gain of 4.2 lbs. was noted for the MF 800 QD group compared with 0.9 for the other MF groups and 1.9 for the BDP group. No differential response based on gender was noted.

j) EKG Results

EKGs were performed at Screening and at Week 52. The sponsor again provided sparse information on the EKGs for this study. No data on intervals was provided. The sponsor relates that none of the changes noted in the EKG's were felt to be clinically relevant.

	Abnormality (change from Baseline)
MF DPI 400 BID	
270	Early repolarization (NCS)
055	"Consider posterior infarction. MD feels this is due to V2 lead placement. Consider LAFB."
174	Inferior QT lower in inferior leads (p. 7189, Vol. 22; unclear from sponsor what is old or changed and a request for clarification was made. In a response dated 7/7/99, the sponsor says that the baseline ECG was normal and the Week 52 ECG was read by the machine as showing "Inferior Q wave and old R in anterior leads, probable old inferior infarction and possible old anterior infarction." The investigator noted on the ECG the following:" no significant abnormality and no change from previous.")
MF DPI 800 QD	
53	Not clear in original submission (p. 7195) (A clarification was requested of the sponsor and in a response dated 7/7/99, the investigator noted that the "RSR in V1 or V2" and "consider left atrial enlargement" were questionable due to lead placement and that all abnormalities were not clinically significant in the Baseline ECG. The Week 52 ECG was machine read as "RSR' in V1 or V@ and poor R-wave progression" but the investigator noted not clinically significant for these findings.
64	Poor R wave progression, probable early repolarization pattern.
484	RSR' in V1 or V2, LVH by voltage
486	Borderline intraventricular conduction delay (p. 7197)
BDP 168 BID	
419	L anterior fascicular block
59	Probable early repolarization pattern.
063	RSR in V1 or V2, consider left atrial enlargement.

k) Safety Conclusions for C96-135

Similar to other studies in this NDA, the most prevalent adverse events were headache, allergy aggravated, influenza-like symptoms, viral infection, sinusitis, and pharyngitis. Viral

infection, nasal congestion, musculo-skeletal pain, back pain, and coughing appeared to be slightly more common with MF DPI compared with BDP. There was a suggestion of a MF DPI dose response with these four adverse events except for viral infection. Interestingly, headache, aggravated asthma, respiratory disorder and fungal vaginitis appeared to be more common with BDP. Of the treatment groups in this study, the incidence of dysmennorhea was lowest in the MF DPI 200 BID group. Local adverse events such as oral candidiasis and pharyngitis did not appear to me any more likely with mometasone compared with BDP.

Among the less common adverse events, chest pain, dysphonia, otitis media, micturition frequency, dyspnea, and epistaxis, although uncommon, appear only with MF DPI and not BDP. Other than dysphonia, these probably represent incidental findings. Headache, abdominal pain and musculoskeletal pain appeared to be more common in females but did not have an overrepresentation in MF DPI versus BDP with the possible exception of musculoskeletal pain. Four instances of newly diagnosed cataract and two instances of increased intraocular pressure were noted during the study. The cases of cataract may have been subject to observer bias and more rigorous exam according to the sponsor because of the patient's noted history of long term corticosteroid usage. Other risk factors for cataracts, most notably prior steroid use, were also present so it is difficult to discern the cause and effect of the MF DPI treatment. None of the two cases of increased IOP involved large elevations, changes in the optic disc or visual acuity.

Among the serious adverse events, the most notable was an unexplained liver enzyme elevation in Subject #298 in the MF DPI 200 BID group, who was discontinued at Week 12 with an increase in AST of 315 IU/L and an LDH of 928 IU/L. The investigator considered the event possibly due to either a viral etiology or unreported alcohol consumption. The rest of the serious AE's are essentially self-explanatory and in most cases do not appear to be related to drug treatment with the possible exception of the cases of asthma exacerbation.

A number of instances of transaminase elevation greater than 20 IU/L were documented during the study. Their clinical relevance or relationship to drug treatment is unknown. It should be stated that instances of elevation were noted in both the MF and BDP treatment groups. The cortisol testing program did definitively reveal any differences between MF DPI and BDP nor did it definitively rule out HPA axis suppression. MF plasma concentrations were monitored in C96-135. In general, pre- and post-dose mean plasma MF values were low and characterized by large inter-subject variability.

No clinically relevant changes in vital signs, and mean laboratory tests were noted during the study. None of the changes documented in the EKGs were felt to be clinically significant by the investigators.

I. C96-134 (Vol. 77- 100)

1. Investigators and Investigational Centers

There were 365 subjects involved at 20 centers, all within the United States.

2. Objectives/Rationale

The objectives of this randomized, multicenter, double-blind, placebo-controlled, parallel groups Phase II/III study was to characterize the efficacy and safety of three doses of MF DPI (MF DPI 100 mcg BID, 200 mcg BID, and 400 mcg BID) compared to placebo.

a) Primary

The primary efficacy variable was the change from Baseline to Endpoint (last available observation) in FEV_1.

b) Secondary

Secondary efficacy variables included FEF_{25-75}, FVC, daily PEFR, symptom scores, Proventil use, nighttime awakenings, assessments of response to therapy, and time to worsening of asthma.

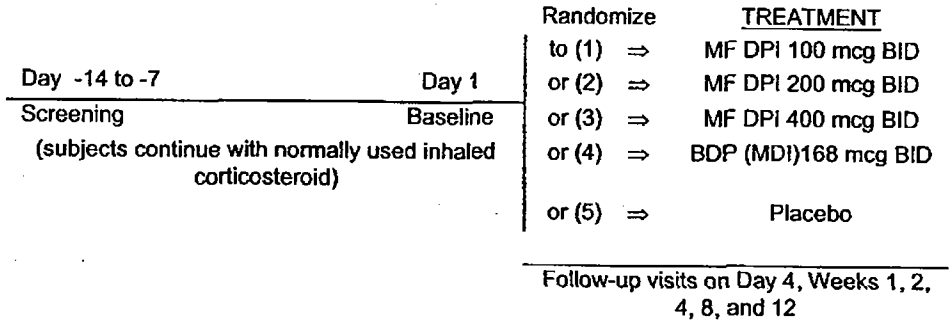
c) Safety

Safety variables included adverse events, laboratory tests, vital signs, and physical examination including oropharyngeal examination. Cortrosyn stimulation tests were performed at 5 selected centers.

3. Study Design

This was a Phase II/III, randomized, dose ranging study of MF DPI compared to placebo and beclomethasone dipropionate (BDP) in the treatment of asthma in approximately 300 subjects previously maintained on inhaled corticosteroids. After a run-in period of 1-2 weeks, during which time subjects continued with their normally used inhaled corticosteroid, subjects were to be switched to and treated with double-blind study drug for 12 weeks. Subjects were randomized at Baseline (Visit 2) to receive one of the following: MF DPI 100 BID, MF DPI 200 BID, MF DPI 400 BID, BDP 168 mcg BID (336 mcg/day), or placebo in a 1:1:1:1:1 ratio according to a computer-generated code.

4. Summary of Study Protocol



a) Study Population

The study was designed to recruit 15-35 subjects at approximately 20 centers to insure 300 subjects who met the criteria for the evaluation of the primary Endpoint.

(1) Inclusion and Exclusion Criteria

Same as C96-135.

(2) Removal of Subjects from Therapy

Same as C96-135 except that there was no criteria in this protocol to remove subjects based on the requirement for oral steroid treatment. A subject could also be removed from this protocol because of an asthma exacerbation requiring hospitalization.

b) Treatments administered

(1) Run-in Period

Between Screening and Baseline Visits, subjects continued to take their previously prescribed inhaled corticosteroid between Screening and Baseline visits.

(2) Double-blind Treatment Period

At the Baseline visit, subjects were randomized to 12 weeks treatment with one of the following:

	AM		PM		
Treatment Group	**MF DPI**	**BDP MDI**	**MF DPI**	**BDP MDI**	**Total (mcg/day)**
Group 1	100 mcg x 1	Placebo x 4 puffs	100 mcg x 1	Placebo x 4 puffs	MF 200 mcg
Group 2	200 mcg x 1	Placebo x 4 puffs	200 mcg x 1	Placebo x 4 puffs	MF 400 mcg
Group 3	400 mcg x 1	Placebo x 4 puffs	400 mcg x 1	Placebo x 4 puffs	MF 800 mcg
Group 4	Placebo x 1	42 mcg x 4 puffs	Placebo x 1	42 mcg x 4 puffs	BDP 336 mcg
Group 5	Placebo x 1	Placebo x 4 puffs	Placebo x 1	Placebo x 4 puffs	Placebo 0 mcg

Treatments were administered in a double-blind manner using a double-dummy technique (each subject received both a DPI and MDI inhalation device). The three dosage strengths of MF DPI (100 mcg, 200 mcg, and 400 mcg) were indistinguishable from each other and from the placebo DPI device. The BDP MDI active control and corresponding placebo were indistinguishable from each other. Each subject took one inhalation from the dry powder inhaler (DPI) followed by 4 inhalations from the metered-dose inhaler (MDI) every morning and evening approximately 12 hours apart.

Subjects were advised to rinse their mouth after study drug administration.

(3) Concomitant/Restricted Medications

The list of permitted medications were essentially the same as those for C96-135 except that cromolyn-like medication and systemic bursts of steroids were prohibited.
The following medications were restricted prior to Screening:

Medication	Washout Time Prior to Screening Visit
- Beta-adrenergic bronchodilators, syrups and tablets	24 hours
- Beta-adrenergic bronchodilators, sustained-release tablets	48 hours
- Bronchodilators, inhaled	6 hours
- Bronchodilators, nebulized	6 hours

- Salmeterol	1 week
- Cromolyn sodium, nedocromil, inhaled	2 weeks
- Ipratropium bromide aerosol/nebulized	12 hours
- Any systemic bursts of (oral or intravenous) corticosteroids	1 month
- Corticosteroids -- nasal or ocular	2 weeks
- Corticosteroids -- intramuscular	3 months
- Corticosteroids -- intra-articular	1 month
- High potency topical corticoids for dermatological use	1 month
- Astemizole	3 months
- Hydroxyzine	5 days
- Long-acting antihistamines	72 hours
- Short-acting antihistamines	24 hours
- Immunotherapy	24 hours
- Oral decongestants (long-acting)	72 hours
- Oral decongestants (short-acting)	24 hours
- Zafirlukast (Accolate)	2 weeks

c) Assessments/Study Procedures

		Treatment Period						
	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Treatment Days (Week)	-14 to-7	1	Day 4	8 (Wk 1)	15 (Wk 2)	29 (Wk 4)	57 (Wk 8)	85 (Wk 12)
Obtain Informed Consent	X							
Review Inclusion/ Exclusion Criteria	X	X						
Medical/Disease History	X							
Concomitant Medications Review	X	X	X	X	X	X	X	X
Physical Examination, Weight	X							X
Height	X							
Vital Signs (temperature, blood pressure, pulse, respiratory rate)	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							X
Pregnancy Test	X							X
Cortrosyn Test	X							X
Mometasone Furoate Concentrations								X
EKG	X							
Chest Roentgenogram	X							
Dispense Diary	X	X				X	X	
Review Diary		X	X	X	X	X	X	X
Dispense Peak Flow Meter	X							
Dispense Study Medication		X				X	X	
Response to Therapy Assessment			X	X	X	X	X	X
Adverse Events Evaluation		X	X	X	X	X	X	X
Compliance Check/ Collect Medication			X	X	X	X	X	X

The above procedures/measurements were generally performed in a similar manner as similar procedures in other studies for this NDA.

d) Statistical and Analytic Plans

As in other studies (except for C96-135), there were two subject data sets: 1) ITT (all randomized subjects), and 2) Efficacy Data set (randomized subjects who met key eligibility and evaluability criteria. This data set was only for confirmatory efficacy analyses.)

The primary efficacy variable was the change from Baseline in FEV_1 and the primary time point was the Endpoint visit. A test for non-decreasing response with increasing MF DPI doses was identified in the protocol as the primary analysis. This primary efficacy variable at Endpoint was to be analyzed for all randomized subjects using a two-way ANOVA that extracted sources of variation due to treatment and center and treatment-by-center interaction. The primary efficacy analysis for demonstrating the activity of MF DPI was to be based on a linear contrast of the least squares means of the MF DPI doses and placebo (from the ANOVA) using a 5% significance level. Since all pairwise comparisons addressed independent questions, and the linear contrast among placebo and three MF DPI doses was identified in the protocol as the primary efficacy analysis, if the test for non-decreasing response with increasing dose was significant, then each comparison was to be performed at the 0.05 (two-sided) level of significance, with no adjustment for multiple comparisons. In discussion with the FDA statistician, Dr. Gebert, it was felt that the sponsor's plan for analysis did adequately address the issue of multiple comparisons in this situation.

In addition to the analysis at Endpoint, all ten pairwise comparisons among the five treatment groups were to be made with respect to the change from Baseline in FEV_1 for each scheduled visit, using the same two-way ANOVA.

All other continuous efficacy variables as well as the plasma cortisol values were to be analyzed at each time point using the same two-way ANOVA. For time to discontinuation because of asthma worsening, Kaplan-Meier survival time estimates were to be analyzed using the log-rank test.

The study was designed to enroll 300 subjects or 60 subjects per treatment group. The sample size was chosen to detect (with 90% power and 5% significance level) a clinically meaningful pairwise difference in the FEV_1 mean change from Baseline (the primary efficacy variable) between any active treatment group and placebo. With 60 subjects per group, assuming a pooled standard deviation of 0.45 units for FEV_1 change from Baseline (based on Study No. C94-127), mean treatment differences of approximately 0.27 units (approximately 11% of Baseline) or more would be detectable with power greater than 90%.

e) Protocol Deviations

Similar to several other studies for this NDA, the range of the allowable proportion of actual FEV_1 values relative to predicted values at the Screening and Baseline visits was broadened from 60% to 90% to 55% to 95% and reversibility testing could have demonstrated an increase in FEV_1 of $\geq$10.5%, rather than $\geq$12%, so long as the absolute change was $\geq$200 ml. Finally, because too few subjects who received an active treatment satisfied the criteria for asthma worsening, the median time to asthma worsening could not be determined from the results so only descriptive statistics were provided.

5. Results

a) Study Population Characteristics

A total of 365 subjects was randomized at 20 study centers. All subjects received at least one dose of study medication. The numbers in the five groups were as follows: 76 for MF DPI 100 BID; 70 for MF DPI 200 BID; 74 for MF DPI 400 BID; 71 for BDP 168 BID; and 74 for placebo.

A total of 87 subjects (12 treated with MF DPI 100 mcg BID, 9 treated with MF DPI 200 mcg BID, 12 treated with MF DPI 400 mcg BID, 15 treated with BDP, and 39 treated with placebo) discontinued the study prior to scheduled completion.

Number (%) of Randomized Subjects Who Completed the Entire Treatment Period and Number (%) Who Discontinued the Study and Reasons for Discontinuance

	Treatment Group					
	MF DPI 100 BID (n=76)	MF DPI 200 BID (n=70)	MF DPI 400 BID (n=74)	BDP 168 BID (n=71)	Placebo (n=74)	Total (n=365)
Number (%) Completed	64 (84%)	61 (87%)	62 (84%)	56 (79%)	35 (47%)	278 (76%)
Reason for Discontinuation						
Adverse Event	4 (5%)	2 (3%)	3 (4%)	6 (8%)	8 (11%)	23 (6%)
Treatment Failure	5 (7%)	5 (7%)	6 (8%)	5 (7%)	28 (38%)	49 (13%)
Lost to Follow-up	0	0	0	1 (1%)	0	1 (<1%)
Discontinued for Reasons Unrelated to Treatment	1 (1%)	2 (3%)	1 (1%)	0	2 (3%)	6 (2%)
Non-Compliance	2 (3%)	0	2 (3%)	2 (3%)	0	6 (2%)
Did not Meet Entry Criteria	0	0	0	1 (1%)	1 (1%)	2 (<1%)
TOTAL NUMBER (%) DISCONTINUING	12 (16%)	9 (13%)	12 (16%)	15 (21%)	39 (53%)	87 (24%)

While 7% of subjects treated with any dose of MF DPI or BDP discontinued because of treatment failure, 38% of placebo subjects discontinued treatment for this reason. Eleven percent of placebo subjects discontinued because of adverse events compared with 3% to 8% of subjects who received MF DPI or BDP.

There were a number of protocol deviations during C96-134. Eight subjects were allowed to enroll whose variability in FEV_1 values between the Screening and Baseline visits was ≥20% (20%-33.7%). Two subjects were allowed to enroll whose FEV_1 values at Screening and Baseline visits were not both from 55% to 95% (one 101.6% and one 99.6%). These subjects were excluded from the "Efficacy-Evaluable" data set. Eighty-four of the 365 subjects randomized met a criterion for worsening of asthma. All 84 subjects should have been removed at the time of worsening; 52 subjects were removed immediately, but 32 were not. The numbers ranged from 3-4 for MF DPI 100 and 400 BID and BDP BID to 7 for MF DPI 200 BID and 10 for placebo. Realistically, these numbers should not affect the ITT analysis and any effect should be picked up in the Efficacy-Evaluable set analysis.

Overall, subjects were classified as non-evaluable if one or more of the following major violations was present:

- Baseline FEV_1 was <55% or >95% of the predicted value.
- Variability in FEV_1 between the Screening and Baseline visits was ≥20%.
- Subject failed the reversibility test; that is, did not demonstrate evidence of an increase in absolute FEV_1 of 10.5%, with an increase of at least 200 ml.
- Serevent use within 72 hours of the screening visit.

	MF DPI 100 mcg BID	MF DPI 200 mcg BID	MF DPI 400 mcg BID	BDP 168 mcg BID	Placebo	Total
All Treated Subjects	76	70	74	71	74	365
Efficacy Evaluable	73	67	72	69	69	350

Summary of Demographic Data (All Treated Subjects)

	MF DPI 100 mcg BID (n=76)	MF DPI 200 mcg BID (n=70)	MF DPI 400 mcg BID (n=74)	BDP 168 mcg BID (n=71)	Placebo (n=74)
Age (years)					
Mean	38	36	37	37	37
Min-Max	12-71	12-74	12-68	12-63	13-72
Gender					
Female	41	42	47	47	45
Male	35	28	27	24	29
Race					
White	67	61	61	59	66
Black	7	6	7	7	5
Hispanic	0	2	6	5	0
Asian	0	0	0	0	1
Other	2	1	0	0	2
Weight (lbs)					
Mean	178	180	156	168	167
Min-Max	94-317	95-320	69-313	102-261	82-335
Duration of Asthma Condition (years)					
Mean	21	18	16	18	18
Min-Max	1-65	1-69	1-55	1-52	1-50
FEV_1 % Predicted at Baseline					
Mean	74	76	77	78	74
Min-Max	60-91	56-102	59-95	60-100	60-91
Absolute FEV_1 at Baseline (liters)					
Mean	2.61	2.67	2.49	2.62	2.48
AM PEFR at Baseline (liters/minute)					
Mean	381.36	397.92	365.69	387.86	375.70
Inhaled Corticosteroids at Baseline					
BDP					
no. of subjects	25	30	29	22	27
mean mcg/day	312	328	339	341	356
min-max	126-504	168-672	168-756	252-800	84-1200
Flunisolide					
no. of subjects	10	8	4	9	8
mean mcg/day	1130	1313	1000	1111	1063
min-max	100-2000	1000-2000	500-1500	1000-1500	1000-1500
Fluticasone Propionate					
no. of subjects	9	10	7	5	8
mean mcg/day	435	363	440	550	388
min-max	176-880	176-440	220-880	110-880	110-880
Triamcinolone Acetonide					
no. of subjects	32	22	34	35	31
mean mcg/day	763	768	779	703	794
min-max	400-2400	600-1600	600-1600	300-1500	400-1600

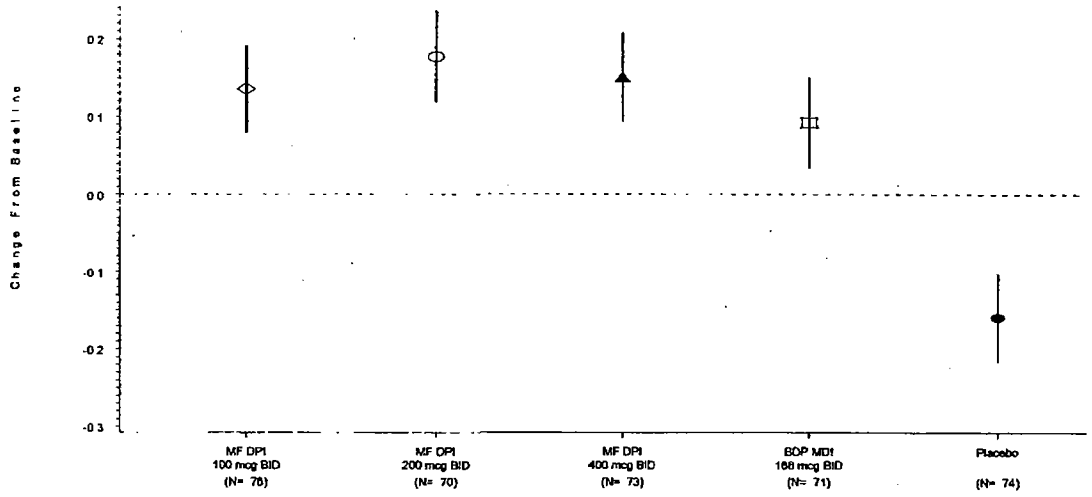
Based on the type and dose of inhaled corticosteroid the subjects were on at Baseline, the stratification of the subjects during randomization was performed in a generally equitable manner.

6. Analysis of Efficacy

a) FEV_1

The sponsor says that there was a statistically significant non-decreasing dose-response relationship for placebo and MF DPI with respect to change from Baseline in FEV_1 at Endpoint and at many individual time points (reviewer note - with the fewest significantly different time points noted with MF DPI 100 BID among the MF treatment groups.) Our statistical reviewer feels that the sponsor's analysis is best characterized as a linear trend test or a Jonckeere-Terpstra test, which he feels, was an appropriate test of the protocol-specified hypothesis. Once there was a demonstration by the trend test of significant activity with active treatment compared with placebo, then a pairwise comparison of each dose with placebo was performed. This test can not determine whether or not there is a dose response.

FEV_1 mean changes from Baseline



There was an imbalance in discontinuation between subjects treated with placebo and those treated with an active drug. The placebo response over time ranged from a small decrease in mean FEV_1 to an increase of 2.5%, compared with increases of approximately 3% to 10% with active drugs, and 6% to 10% with MF DPI 200 mcg, in particular. The increases, although small, are meaningful because subjects entered the study already using inhaled steroids and switched to the assigned treatment at Baseline. The increases suggest a potential improvement in effect over the active treatments taken before the study. This later conclusion, however, could be biased by the fact that the subjects in a study are potentially receiving more interactions with the medical community.

FEV_1 (liters) — Change from Baseline by Treatment Group (All Treated Subjects)

	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	(Mean % Change)	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	**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)

		P-value			Pairwise Comparisons (P Value)									
Time Point	P.SD	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**

L-Trend = Linear contrast of placebo and MF DPI doses

In conclusion, the results at Endpoint for all active treatments were significantly better than results for placebo ($p<0.01$). Despite (1) the decreasing sample sizes over time and (2) the disproportionate discontinuation of placebo subjects due to treatment failure, the results for MF DPI 200 BID were consistently significantly better than those for placebo at all visit time points, a condition not demonstrated with the other active treatments, although results for MF DPI 400 mcg BID were close. Notably, BDP 168 mcg BID was significantly better than placebo only at the Endpoint. It can be seen that MF DPI 200 BID probably works better than 100 BID. This study demonstrates no FEV1 advantage with MF DPI 400 BID over 200 BID.

A confirmatory analysis was done on the Efficacy-Evaluable data set to show significant improvements relative to placebo for all active treatments.

The response between genders was examined (p. 172 – Vol. 77). MF DPI 100 BID and 400 BID appeared to have a better % response in males compared with females while MF DPI 200 BID appeared to be more effective in females. Statistical analysis on the differential response was not performed. The effect of BDP and placebo was comparable in both genders. Only a small percentage of subjects were not in the 18-64 age range so this subgroup analysis is probably not useful. The percentage of non-Caucasians in the study was around 13.6%. In the non-Caucasian group, there was an uncharacteristically successful placebo response as placebo clearly outperformed MF DPI 100 and 200 BID

Response was evaluated in subjects whose Baseline FEV_1 was <75% of the predicted value versus those whose Baseline FEV_1 was ≥75% of the predicted value. The response to active drug was generally more pronounced in the subset with more severe disease (as has been seen in the other studies). MF DPI 200 and 400 BID produced better results than placebo in both subsets, unlike MF DPI 100 BID and BDP 168 BID, and there was no apparent additional benefit with MF DPI 400 mcg BID over 200 mcg BID.

FEV_1 (liters) — Change from Baseline by Treatment Group and by Baseline Predicted FEV_1 (All Treated Subjects)

	MF DPI 100 mcg BID			MF DPI 200 mcg BID			MF DPI 400 mcg BID			BDP MDI 168 mcg BID			Placebo		
	N	Mean	(Mean % Change)[a]	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
FEV_1 < 75% Predicted Value at Baseline															
Baseline	41	2.32		33	2.35		28	2.25		24	2.47		43	2.34	
Change From Baseline															
Day 4	35	0.19	(8.3%)	31	0.21	(9.7%)	26	0.10	(3.2%)	23	0.15	(5.6%)	38	-0.01	(0.4%)
Week 1	39	0.18	(8.0%)	31	0.29	(12.4%)	27	0.13	(5.3%)	23	0.08	(3.2%)	39	-0.04	(-1.7%)
Week 2	38	0.30	(12.9%)	33	0.24	(10.7%)	28	0.21	(7.8%)	24	0.12	(4.6%)	35	-0.01	(-0.2%)
Week 4	40	0.17	(7.4%)	32	0.33	(14.7%)	26	0.16	(6.2%)	22	0.29	(11.0%)	27	0.00	(-1.0%)
Week 8	32	0.24	(10.0%)	31	0.32	(13.3%)	24	0.26	(9.9%)	20	0.22	(8.8%)	21	-0.02	(0.4%)
Week 12	31	0.27	(10.6%)	28	0.40	(17.3%)	23	0.27	(10.5%)	20	0.26	(10.3%)	17	0.08	(3.2%)
Endpoint	**41**	**0.22**	**(8.4%)**	**33**	**0.28**	**(12.1%)**	**28**	**0.12**	**(4.2%)**	**24**	**0.22**	**(8.4%)**	**43**	**-0.17**	**(-7.9%)**
FEV_1 ≥ 75% Predicted Value at Baseline															
Baseline	35	2.97		37	2.98		45	2.65		47	2.72		31	2.70	
Change From Baseline															
Day 4	33	0.07	(2.6%)	35	0.10	(3.3%)	43	0.11	(4.8%)	46	0.04	(1.6%)	29	0.05	(1.7%)
Week 1	34	0.01	(0.3%)	34	0.13	(4.4%)	44	0.15	(5.9%)	44	0.07	(2.5%)	30	0.02	(0.9%)
Week 2	33	0.12	(3.7%)	35	0.16	(5.6%)	44	0.14	(5.6%)	44	0.09	(3.8%)	28	0.02	(0.7%)
Week 4	34	0.13	(3.6%)	35	0.16	(5.4%)	44	0.20	(8.1%)	43	0.10	(4.0%)	26	0.07	(2.7%)
Week 8	32	0.07	(1.7%)	35	0.19	(6.4%)	41	0.19	(7.2%)	39	0.14	(5.2%)	19	0.14	(4.7%)
Week 12	32	0.08	(1.6%)	35	0.14	(4.6%)	38	0.20	(8.2%)	36	0.12	(4.1%)	19	0.05	(1.8%)
Endpoint	**35**	**0.04**	**(0.4%)**	**37**	**0.09**	**(2.6%)**	**45**	**0.17**	**(7.5%)**	**47**	**0.02**	**(0.2%)**	**31**	**-0.14**	**(-5.0%)**

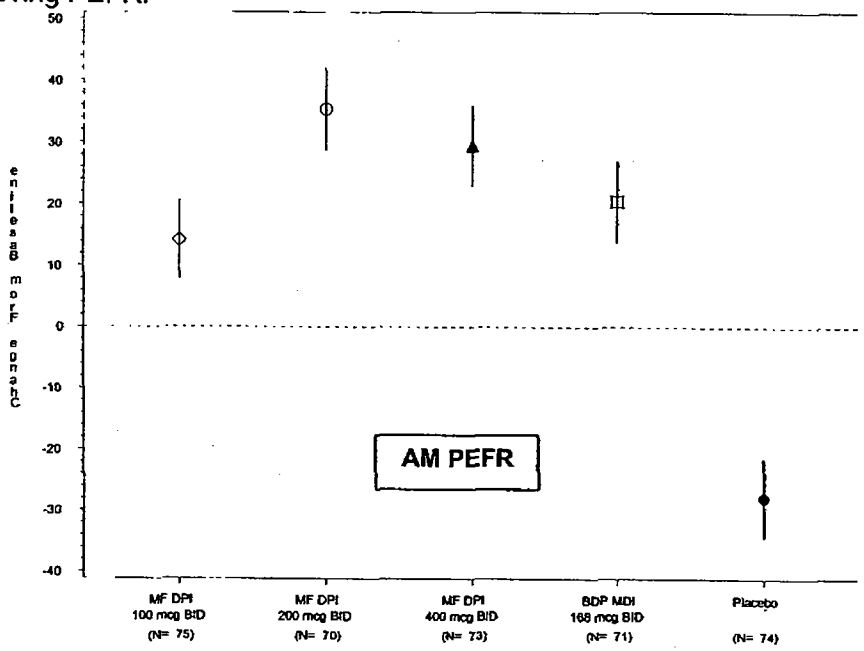
b) FVC and FEF_{25-75}

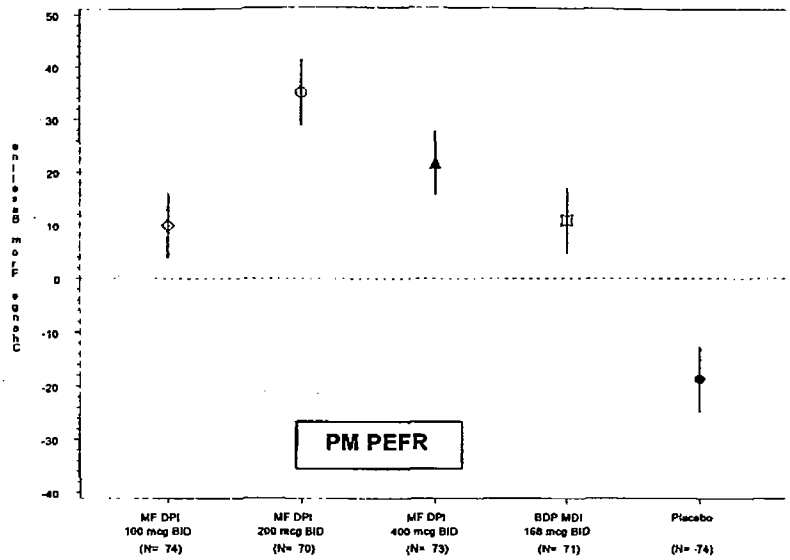
At Endpoint, however, increases of 3.3% to 4.7% with MF DPI and 2% with BDP in the mean FVC were seen and were all significantly different from the mean decrease of 4.7% which occurred with placebo. It should be noted that a mean decrease was seen for placebo only at Endpoint. Earlier timepoints generally showed increases of 4.0 to 7.4% for MF DPI and 1.3 to 6.0% for BDP compared with 1.2 to 4.2% for placebo. It was rare to see earlier timepoints than Endpoint which were significantly higher than placebo. Among the MF DPI treatment groups, the increases in the FVC were similar.

The effect of active treatment on the FEF 25-75 was quite impressive. Decreases in FEF_{25-75} were observed at all time points and at Endpoint with placebo and increases were consistently observed with active treatment: 3.5% to 14.2% with MF DPI 100 BID and BDP 168 BID, and 9.4% to 28.4% with MF DPI 200 and 400 BID. The analysis was significant at all time points and at Endpoint for MF DPI, and all comparisons of MF DPI 200 and 400 mcg BID with placebo were significant ($p<0.01$). At only one early timepoint was the effect of MF DPI significantly different from BDP. The Endpoint comparison and most earlier timepoints were also significant for the pairwise comparison of MF DPI 100 and 200 BID.

c) PEFR

At Baseline, the mean AM PEFR was consistently less than the PM PEFR. Mean increases from Baseline were similar between MF DPI 200 and 400 BID, which were typically 1.5 to 2 times greater than the mean increases for MF DPI 100 BID and BDP for both AM and PM PEFR. All active treatments yielded significantly better results than placebo at Endpoint and at most earlier time points. Overall, MF DPI 200 BID and 400 BID were the most effective in improving PEFR.





d) Asthma Signs and Symptoms

For AM Wheezing and AM Difficulty Breathing, all active treatments were significantly better than placebo at most timepoints throughout the study and at Endpoint. Improvements in the MF DPI 200 and 400 BID treatment groups and the BDP treatment group were comparable and better numerically than the MF DPI 100 BID group.

The effect of active treatment on AM Cough was generally less impressive and active treatment, whether MF DPI or BDP, was better than placebo only at Endpoint. It is interesting to note that BDP was clearly numerically the most effective in reducing AM Cough but this difference was generally not significant.

A more cursory review of the PM symptom score indicates that all active treatment groups were significantly better than placebo at Endpoint and generally at the earlier timepoints for PM Wheezing and Difficulty Breathing. While at early timepoints and at Endpoint, BDP was significantly better than placebo for PM Cough, the significant improvement seen with MF DPI relative to placebo tended to be limited to the Endpoint. BDP seemed to stand apart numerically in its reduction of PM Cough.

The Physician's Evaluation of Wheezing scores were generally not impressive in supporting the efficacy of MF or BDP. At Endpoint, the score for placebo tended to be quite high, perhaps reflective of the reasons for the larger number of subjects dropping out from this group. Other groups tended to have meager decreases in the wheezing scores with probably MF DPI 200 BID showing the greatest effect. MF DPI 100, 200 and 400 BID were significantly better than placebo at Endpoint ($p=0.05$) while the difference for BDP and placebo was only numerical ($p=0.13$).

e) Responses to Therapy

At Endpoint, the responses to MF DPI 200 and 400 BID were nearly equivalent, with the symptoms of approximately two-thirds of subjects being improved or much improved, and noticeably better than the response to placebo. Responses to MF DPI 100 BID and BDP were also subjectively better than those to placebo and slightly less than those to the two higher doses of MF DPI. While only 10% to 15% of subjects treated with an active agent were rated as worse or much worse, 57% of placebo subjects were rated as worse or much worse at Endpoint than at Baseline.

Physician's Evaluation of Response: Level of Symptoms Relative to Baseline	MF DPI 100 mcg BID (n=76)	MF DPI 200 mcg BID (n=70)	MF DPI 400 mcg BID (n=73)	BDP 168 mcg BID (n=71)	Placebo (n=74)
Much Improved	14 (18)	17 (24)	13 (18)	9 (13)	6 (8)
Improved	29 (38)	30 (43)	35 (48)	27 (38)	9 (12)
No Change	25 (33)	16 (23)	16 (22)	24 (34)	17 (23)
Worse	8 (11)	3 (4)	8 (11)	8 (11)	23 (31)
Much Worse	0	4 (6)	1 (1)	3 (4)	19 (26)

This response variable tended to distinguish itself early on for active treatment relative to placebo with significant differences existing with placebo throughout most of the trial.

f) B agonist Use During the Study

All MF DPI groups used less Proventil than did the placebo group. The greatest decreases in Proventil usage occurred in the MF DPI 200 and 400 mcg BID treatment groups. MF DPI 100 BID was significantly better than placebo only at Endpoint. The Endpoint data for placebo differed considerably from the Week 12 data showing the effect of the large number of dropouts in this group.

g) Number of Nocturnal Awakenings

The Baseline number of awakenings requiring the use of Proventil was small, but at Endpoint, all active corticosteroid treatments were significantly better than placebo. There was only an occasional timepoint where a significant difference between active treatment and placebo occurred. The results for MF DPI 200 and 400 BID appear again to stand apart from MF DPI 100 BID and BDP.

h) Time to Worsening of Asthma

Because more than 80% of the subjects in each of the active treatment groups had not met criteria for worsening, a median time to worsening and hence an ANOVA comparison between treatments could not be performed.

First Recorded Reason for Worsening	MF DPI 100 (n=76)	MF DPI 200 (n=70)	MF DPI 400 (n=74)	BDP 168 (n=71)	Placebo (n=74)
Decrease in FEV_1	3	5	3	5	15
Decrease in PEFR	5	5	4	3	6
Clinical Asthma Exacerbation	3	2	1	2	10
CAE and Decrease in FEV_1	0	0	1	1	5
Decrease in FEV_1 and PEFR	0	1	0	0	0
Proventil Use	0	0	0	0	1
Other Asthma Worsening	0	0	0	0	3
TOTAL	11	13	9	11	40

Among placebo subjects, decrease in FEV_1 and clinical asthma exacerbation were the most common, and was much more common than among subjects who received active treatment.

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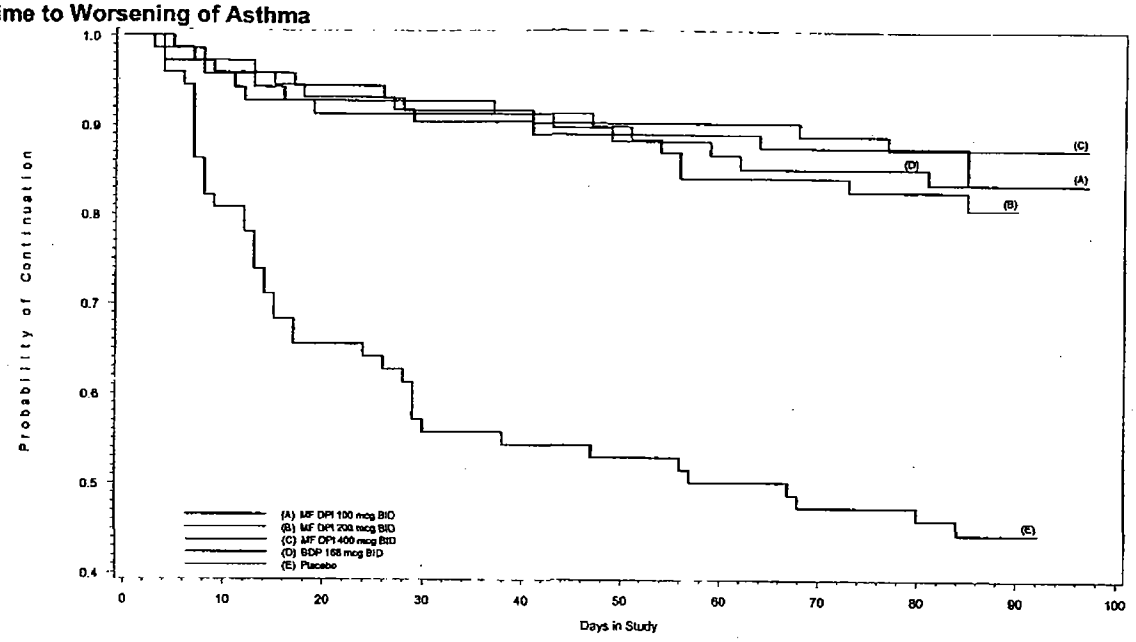
Time to Worsening of Asthma



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i) Peak Inspiratory Flow Rate

At only one center (#03), inspiratory flow rates through a functional model of the dry powder inhaler were recorded in three subjects. The sponsor says this was done to gain preliminary information on whether subjects could produce inspiratory rates adequate to generate DPI particles of respirable size. [ ] Based on previous in vitro data collected while using [ ] subjects needed to generate an inspiratory flow rate of approximately 30 l/min or more, with a "rise time", the time between flow rates of 10 and 30 l/min, of 300 msec or less. The sponsor maintains these subjects achieved adequate flow rates to provide functional drug delivery.

Subject	Treatment Group.	Peak Flow Rate (l/min)	Rise Time (msec)	Baseline FEV_1 (l)	Endpoint FEV_1 (l)
431	BDP 168 mcg BID	58.1	133	2.45	2.61
432	MF 400 mcg BID	53.9	195	2.73	2.79
433	MF 200 mcg BID	70.2	133	4.1	4.31

j) Efficacy Summary for C96-134

The primary efficacy endpoint in this trial was the mean change in FEV_1 from Baseline to Endpoint. MF DPI 200 BID had numerically the largest improvements in FEV_1 and was significantly better at all timepoints. MF DPI 400 BID was significantly better than placebo at al timepoints except for Week 12. The effects of BDP and MF DPI 100 BID were very comparable and were better than placebo at Endpoints as well as Day 4 and Week 2 for MF DPI. An analysis was done in the Efficacy-Evaluable data set that confirmed the above results. Another subgroup analysis compared the response of subjects with FEV1 < 75% predicted with those ≥ 75% predicted. As has been seen in other trials for the NDA, MF DPI was more effective in those subjects with the lower FEV_1. The greatest improvements in the lower FEV_1 subjects was seen with MF DPI 200 BID while the improvements seen in the other active treatment groups were generally equivalent. In those with the better baseline FEV1, MF DPI 200 and 400 BID were equivalent at most timepoints except for Endpoint where the 400 mcg dose outperformed the 200 mcg dose 7.5% to 2.6%.

Significant improvements in FVC were seen with active treatment only at Endpoint and among the MF DPI doses the increases were similar. The improvements in the FEF_{25-75} were much more impressive. Significant differences with placebo were seen at nearly every timepoint for the active treatments with the greatest improvements seen with MF DPI 200 BID and the least with 100 BID. For both AM and PM PEFR, mean increases from Baseline were similar between MF DPI 200 and 400 BID and were typically 1.5 to 2 times greater than the increases with MF DPI 100 BID and BDP.

For AM Wheezing and AM Difficulty Breathing, improvements in the MF DPI 200 and 400 BID and BDP groups were comparable and better numerically than the MF DPI 100 BID group, however, all active treatments were significantly better than placebo at most timepoints.

For AM Cough, all active treatments were better than placebo, but only at Endpoint. For this variable and for PM Cough, BDP clearly had the most beneficial effect. With regards to the Physician's Evaluation of Wheezing scores, MF DPI 100, 200 and 400 BID were significantly better than placebo at Endpoint while BDP and placebo were only numerically different. For Physician's Evaluation of Response to Therapy, two-thirds of subjects improved or were much improved with MF DPI 200 and 400 BID with the responses for MF 100 BID and BDP being somewhat less. For B agonist Use, MF DPI 200 and 400 BID and BDP were statistically superior to placebo and numerically superior to MF DPI 100 BID. In reducing Nocturnal Awakenings, MF DPI 200 and 400 BID fared the best while all active treatments were statistically different from placebo at Endpoint. All active treatments were more or less equivalent in delaying the Time to Worsening of Asthma.

In summary, while all active treatments tended to show efficacy relative to placebo at Endpoint, MF DPI 200 and 400 BID were the most effective. There was no benefit to using MF 400 mcg BID over 200 mcg BID. Notably, BDP was superior to the others products in reducing cough.

7. Safety C96-134

a) Adverse Events

Those adverse events reported by at least 10% of the subjects in any individual treatment group, included headache, aggravated allergy, pharyngitis, viral infection, and sinusitis.

Incidence of Adverse Events Reported by ≥10% of Subjects in Any Treatment Group.

	MF DPI 100 mcg BID (n=76)	MF DPI 200 mcg BID (n=70)	MF DPI 400 mcg BID (n=74)	BDP 168 mcg BID (n=71)	Placebo (n=74)
ANY ADVERSE EVENT	59 (78)	58 (83)	65 (88)	59 (83)	57 (77)
Headache	17 (22)	16 (23)	23 (31)	22 (31)	18 (24)
Allergy aggravated	12 (16)	11 (16)	12 (16)	8 (11)	10 (14)
Pharyngitis	7 (9)	11 (16)	13 (18)	11 (15)	5 (7)
Infection, viral	13 (17)	10 (14)	14 (19)	10 (14)	8 (11)
Sinusitis	9 (12)	7 (10)	9 (12)	11 (15)	7 (9)
Influenza-like symptoms	5 (7)	2 (3)	10 (14)	2 (3)	2 (3)
Candidiasis, oral	3 (4)	4 (6)	12 (16)	2 (3)	1 (1)
Upper respiratory tract infection	7 (9)	8 (11)	13 (18)	7 (10)	7 (9)
Musculo-skeletal pain	6 (8)	6 (9)	9 (12)	9 (13)	7 (9)
Back pain	2 (3)	4 (6)	8 (11)	6 (8)	3 (4)
Dysmenorrhea	4 (10)	4 (10)	2 (4)	2 (4)	3 (7)
Coughing	5 (7)	3 (4)	8 (11)	4 (6)	10 (14)

There appears to be a suggestion of a MF DPI dose response for pharyngitis, oral candidiasis, upper respiratory tract infection, back pain and perhaps musculo-skeletal pain and influenza-like symptoms. Pharyngitis, viral infection, sinusitis, influenza-like symptoms, oral candidiasis, back pain and probably dysmenorrhea was more common with active treatment than with placebo. Viral infection, influenza-like symptoms, oral candidiasis, dysmenorrhea, and coughing appeared to be more common with MF DPI than with BDP.

Local adverse events included pharyngitis, cough and oral candidiasis. Pharyngitis was reported by 9% of subjects treated with MF DPI 100 BID, 16% with MF DPI 200 BID, 18% with MF DPI 400 BID, 15% with BDP, and 7% of subjects treated with placebo. Thus, pharyngitis appeared to have a dose response. Cough was reported 7% with MF DPI 100 mcg BID, 4% with MF DPI 200 BID, 11% with MF DPI 400 BID, 6% with BDP, and 14% with placebo. Oral candidiasis was clearly dose-related and more common with mometasone DPI than with BDP.

The following list of adverse events has been closely edited by this reviewer to highlight adverse event patterns that are notable, i.e. unusual, clearly more common with MF, or which have been issues in other trials.

Incidence of Any Treatment-Emergent Adverse Events Reported by ≥1% of Subjects

	MF DPI 100 mcg BID (n=76)	MF DPI 200 mcg BID (n=70)	MF DPI 400 mcg BID (n=74)	BDP 168 mcg BID (n=71)	Placebo (n=74)
Any Adverse Event	**59 (78)**	**58 (83)**	**65 (88)**	**59 (83)**	**57 (77)**
fatigue	1 (1)	1 (1)	3 (4)	0	1 (1)
dysphonia	2 (3)	2 (3)	2 (3)	1 (1)	1 (1)
dyspepsia	3 (4)	6 (9)	1 (1)	2 (3)	3 (4)
hepatic function abnormal	0	0	1 (1)	2 (3)	1 (1)
myalgia	3 (4)	4 (6)	5 (7)	1 (1)	1 (1)
Psychiatric Disorders	***1 (1)***	***0***	***4 (5)***	***0***	***1 (1)***
anxiety	***0***	***0***	***1 (1)***	***0***	***0***
depression	***0***	***0***	***1 (1)***	***0***	***0***
depression aggravated	***0***	***0***	***0***	***0***	***1 (1)***
insomnia	***1 (1)***	***0***	***1 (1)***	***0***	***0***
irritability	***0***	***0***	***1 (1)***	***0***	***0***
nervousness	***0***	***0***	***1 (1)***	***0***	***0***
asthma aggravated	1 (1)	1 (1)	1 (1)	1 (1)	3 (4)
dyspnea	0	0	0	0	2 (3)
nasal congestion	3 (4)	2 (3)	4 (5)	6 (8)	6 (8)
sinus congestion	3 (4)	1 (1)	2 (3)	2 (3)	2 (3)

Fatigue appears to be an issue with the MF 400 BID dose. Dysphonia and myalgia are more common with the MF DPI than with BDP or placebo and there is somewhat of a dose response for myalgia. Dyspepsia, an intermittent issue in the other trials, shows no real dose response here but does appear to be most common with MF 200 BID. The list of psychiatric disorders are interesting because they are present only with the highest dose of MF DPI (with the exception of aggravated depression) which is plausible. There is no difference among the groups with asthma aggravated but dyspnea is listed only for placebo. Nasal and sinus congestion, issues seen in other trials, showed no particular pattern here.

The sponsor highlights four subjects had increases in activity of hepatic transaminases or related enzymes reported as adverse events: one treated with MF DPI 400 BID; two with BDP 168 BID; and one with placebo. It is not clear why the sponsor only highlighted these four because other elevations were also noted, for instance, larger than that seen in Subject 8. An elevation of bilirubin was not involved in any case:

1. The MF DPI-treated Subject 99 had an increase in liver function tests (AST from 32 to 63 units and ALT from 52 to 111 units) for Day 49 of treatment, when he discontinued because of a raspy voice; follow-up results were not available on this subject.

2. Subject 8 (BDP) had a mild increase in ALT (from 30 to 43 units) reported for the day after the last dose of drug; the investigator reported that the abnormality had resolved 2 weeks later. Subject 12 (BDP) had a moderate increase in the results of liver function tests (AST from 35 to 58 units, ALT from 34 to 73 units, and alkaline phosphatase from 93 to 150 units) considered possibly related to treatment reported for the day after the last dose of drug; results were still high 1 week later.

3. Subject 385 was a 32 year old female who discontinued treatment with placebo after 36 days for due to personal problems unrelated to treatment. Moderate increase in results for ALT and AST (41 to 147 and 54 to 162 units, respectively) and for LDH (214 to 400 units) was reported for a sample collected 6 days after discontinuation; no follow-up results are available. It was noted that the subject had recently had a fight with her husband who had drunk too much

alcohol. The patient was also taking nifedipine, ranitidine, alprazolam, and phenytoin. This was considered a serious adverse event.

The adverse event data was reviewed by gender. Overall, women tended to have a higher percentage of adverse events. Specifically, there was a higher occurrence of musculo-skeletal pain and upper respiratory infection in women.

b) Severe/Life-Threatening Adverse Events

Eight percent of subjects treated with MF DPI 100 BID, 14% of subjects treated with MF DPI 200 BID, 12 % of subjects treated with MF DPI 400 BID, and 18% of subjects treated with BDP reported at least one severe event, compared to 12% of subjects treated with placebo.

Severe or Life-Threatening Treatment-Emergent Adverse Events (All Treated Subjects)

	MF DPI 100 mcg BID (n=76)	MF DPI 200 mcg BID (n=70)	MF DPI 400 mcg BID (n=74)	BDP 168 mcg BID (n=71)	Placebo (n=74)
Any Severe Event	**6 (8)**	**10 (14)**	**9 (12)**	**13 (18)**	**9 (12)**
Body as a Whole - General Disorders					
anaphylactic reaction	0	0	0	0	1 (1)
back pain	0	1 (1)	1 (1)	0	1 (1)
chest pain	0	0	0	0	2 (3)
fatigue	0	0	0	0	1 (1)
fever	1 (1)	0	0	0	0
headache	1 (1)	2 (3)	4 (5)	5 (7)	1 (1)
influenza-like symptoms	0	0	1 (1)	0	0
nasal polyp	0	0	0	1 (1)	0
heart value disorder	0	0	0	1 (1)	0
Collagen Disorders					
arthritis, rheumatoid	0	0	0	1 (1)	0
Gastrointestinal System Disorders					
abdominal pain	2 (3)	0	0	1 (1)	0
dehydration	0	0	1 (1)	0	0
diarrhea	1 (1)	1 (1)	0	0	0
dyspepsia	0	1 (1)	0	0	0
gastroenteritis	0	0	0	1 (1)	0
nausea	1 (1)	0	1 (1)	0	0
vomiting	0	2 (3)	0	0	0
Hearing and Vest. Disorders					
earache	0	0	0	1 (1)	0
Musculo-Skeletal Disorders					
joint disorder	0	1 (1)	0	0	0
joint sprain	0	0	0	1 (1)	0
musculo-skeletal pain	0	1 (1)	1 (1)	0	2 (3)
Resistance Mechanism Disorder					
infection	0	1 (1)	0	0	0
infection, viral	0	0	1 (1)	0	1 (1)

Severe or Life-Threatening Treatment-Emergent Adverse Events (All Treated Subjects)

	MF DPI 100 mcg BID (n=76)	MF DPI 200 mcg BID (n=70)	MF DPI 400 mcg BID (n=74)	BDP 168 mcg BID (n=71)	Placebo (n=74)
asthma aggravated	0	1 (1)	0	1 (1)	0
coughing	1 (1)	0	0	0	3 (4)
dyspnea	0	0	0	0	1 (1)
pharyngitis	0	1 (1)	0	1 (1)	0
sinusitis	0	0	1 (1)	1 (1)	0
upper resp. tract infection	1 (1)	1 (1)	0	0	0
nasal congestion	0	0	0	1 (1)	0
wheezing aggravated	0	0	0	0	2 (3)
sneezing	0	0	0	0	1 (1)
Urinary System Disorders					
urinary tract infection	2 (3)	0	0	0	0
Vascular, Extracardiac					
migraine	0	0	0	1 (1)	1 (1)
White Cell and RES Disorders					
leukopenia	1 (1)	0	0	0	0

The sponsor notes that no subject had a life-threatening adverse event. These severe AE's were scattered about the treatment groups with the possible exception of severe headache that was most prominent in the MF 400 BID and the BDP groups.

c) Serious Adverse Events

Six subjects had serious adverse events.

Center/Subject	Sex/Age/ Race	Adverse Event(s)	Relationship	Status
		MF DPI 100 mcg BID		
C96-134-17/107	M/56/C	leukopenia	unlikely	end-organ toxicity
		leukemia	unlikely	hospitalized, cancer
		MF DPI 400 mcg BID		
C96-134-07/390	F/51/B	asthma aggr, productive cough	unlikely	hospitalized
		BDP 168 mcg BID		
C96-134-10/247	M/32/C	heart valve disorder (aortic insufficiency)	unlikely	hospitalized
		mitral valve prolapse	unlikely	hospitalized
		Placebo		
C96-134-07/385	F/32/B	hepatic enzymes increased	unlikely	end-organ toxicity
C96-134-07/387	F/37/B	asthma aggravated	unlikely	hospitalized
		bronchitis	unlikely	hospitalized
		No Treatment (Screening Subject Only)		
C96-134-08/607	M/14/B	asthma aggravated	unlikely	hospitalized

Subject C96-134-17 #107 (p.4125) treated with MF DPI 100 BID completed the 12 weeks of the study. The subject had a low WBC at Screening (3,340/µl)(normal 3.8 to 10.7 at that site) and the Final Visit (980/µl). Approximately 3 weeks after the end of treatment, the subject was admitted to the hospital with a diagnosis of leukemia. The investigator considered he event to be unlikely related to the study medication since the white cell count was already low at the screening visit (p.572).

Subject C96-134-07 #390 treated with MF DPI 400 BID was hospitalized with aggravated asthma and coughing approximately 3 weeks after being randomized into the study. The investigator believed that the subject had an upper respiratory tract infection that exacerbated her asthma.

Subject C96-134-10 #247 treated with BDP developed shortness of breath shortly after beginning study medication. He was diagnosed with aortic insufficiency, which required aortic valve replacement.

Placebo-treated Subject C96-134-07 #387 was hospitalized with aggravated asthma and bronchitis.

Placebo-treated Subject C96-134-07 #385 experienced elevated hepatic enzymes: activity of AST increased from 54 to 162 units, ALT from 41 to 147 units, and lactate dehydrogenase from 214 to 400 units. The subject admitted to drinking alcohol.

Subject, C96-134-08 #607 was screened for the study but was not randomized to study drug because his FEV_1 was below 60% of predicted at the Baseline visit. He never received study medication. He was admitted to the hospital with aggravated asthma, dyspnea, fever, and coughing.

d) Discontinuation Because of Adverse Events

Twenty-three subjects did not complete treatment because of adverse events.

Center/Subject	Sex/ Age/ Race	Day of Treatment	Adverse Event(s)	Severity	Relation-ship
			MF DPI 100 mcg BID		
C96-134-01/031	F/23/C	57	allergy aggravated	moderate	unrelated
			sinusitis	moderate	unrelated
C96-134-05/065	F/43/B	27	palpitation	moderate	possible
C96-134-09/307	F/36/C	85	asthma aggravated	moderate	unrelated
C96-134-10/250	M/35/C	35	pharyngitis	mild	unrelated
			MF DPI 200 mcg BID		
C96-134-12/345	M/33/C	73	upper resp tract infection	moderate	unrelated
C96-134-13/363	F/39/C	63	upper resp tract infection	severe	unrelated
			MF DPI 400 mcg BID		
C96-134-01/032	F/35/C	35	pneumonia	moderate	unrelated
C96-134-14/082	M/45/C	45	influenza-like symptoms	severe	unrelated
C96-134-14/099	M/41/C	49	dysphonia	mild	probable
			BDP 168 mcg BID		
C96-134-01/025	F/36/B	6	bronchitis	moderate	unrelated
C96-134-06/265	F/44/C	74	sinusitis	moderate	unrelated
C96-134-06/268	F/37/C	74	bronchitis	moderate	unrelated
C96-134-10/247	M/32/C	14	aortic insufficiency	severe	unrelated
C96-134-12/351	F/41/C	21	upper resp tract infection	moderate	unrelated
C96-134-16/208	F/56/C	42	progression of nasal polyposis	severe	unrelated
			Placebo		
C96-134-02/057	M/28/C	2	anaphylactic reaction	severe	Tuna fish
C96-134-03/171	F/15/C	41	sinusitis	moderate	unrelated
			asthma aggravated	moderate	unrelated
C96-134-03/176	M/59/C	68	dyspnea	moderate	unrelated
C96-134-07/387	F/37/B	13	upper resp tract infection	mild	unrelated
			asthma aggravated	moderate	unrelated
			lower resp tract infection	moderate	possible
C96-134-11/005	F/49/C	18	upper resp tract infection	moderate	unrelated
C96-134-13/361	F/15/C	15	infection viral	severe	unrelated
C96-134-14/087	F/37/B	26	chest pain	severe	unrelated
			coughing	severe	unrelated
			fatigue	severe	unrelated
C96-134-14/092	M/27/C	6	chest pain	severe	possible
			wheezing aggravated	severe	possible

This list does not implicate any particular treatment as being over-represented. It should be noted that one subject had to stop the MF DPI 400 BID because of dysphonia and one because of influenza-like symptoms. While the investigator did not attribute the latter AE to treatment, influenza-like symptoms were clearly most common among the MF DPI 400 BID group when all AE's were examined.

e) Laboratory Values

The lab tests among the treatment groups and between genders were reviewed and no important changes in the medians between the groups or gender subgroups were noted. Individual laboratory abnormalities were highlighted by the sponsor. Among these abnormalities the following were notable (Volumes 88-90):

Subject #	Abnormality	Day	Notes
MF 100 mcg BID			
161	Glu 155	Wk 12	108 at Scr (no h/o diabetes)
78	ALT 76	Day 4	51 at Scr
301	Hct 35	Wk 12	43 at Scr
350	Tbili 1.4	Wk 12	1.1 at Scr
85	Tbili 1.4	Wk 12	0.9 at Scr
177	ALT 71	Wk 12	40 at Scr
107	WBC 0.98	Wk 12	Disc. In Serious AE
MF 200 mcg BID			
98	AST/ALT 37/58	Wk 12	27/27 at Scr
138	Glu 263	Wk 12	86 at Scr, 114 3 d later Wk 12 (previous h/o diabetes)
303	Glu 165	Wk 12	102 at Scr (no h/o diabetes)
MF 400 mcg BID			
432	Tbili 2.9	Wk 12	1.6 at Scr, 1.9 1 wk later Wk 12
61	AST/ALT 51/81	Wk 12	22/13 at Scr
122	Tbili 1.5, nl AST/ALT	Wk 12	0.4 at Scr, AST/ALT 47/84 at Scr
204	Tbili 2.1	Wk 12	0.3 at Scr, nl AST/ALT Scr/Wk 12
99	AST/ALT 63/111	Wk 8	39/64 and 32/52 at Scr
BDP 168 mcg BID			
25	WBC 3.38	Day 8	5.44 at Scr
278	AST/ALT 32/51	Wk 12	25/25 at Scr
12	AST/ALT 58/73	Wk 12	35/34 at Scr
	Alk phos 150		93 at Scr, nl bili
125	AST/ALT 67/49	Day 57	16/22 at Scr
114	Tbili 1.4	Wk 12	0.9 at Scr
Placebo			
274	AST/ALT 52/49	Day 15	24/22 at Scr
387	WBC 20.29	Day 15	6.31 at Scr

096	WBC 17.82	Day 15	9.19 at Scr, 10.13 - 2 wks later
	Glucose 168	Day 15	91 at Scr, 71 – 2 wks later (no prev. h/o diabetes listed)
131	WBC 16.22	Day 15	6.04 at Scr, 8.33 – 2 wks later
385	AST/ALT 162/147	Day 29	54/41 at Scr (Disc. in Serious AE)

Again, some increase is seen with the transaminases in selected patients but this is seen both with MF DPI and the already-marketed product, BDP as well as 2 subjects on placebo. The largest increase among the MF groups was Subject 61 whose ALT increased from 13 to 81 and AST from 22 to 51. Some elevation was noted in other subjects in the total bilirubin. Subject 350 and 85's increased from 1.1 to 1.4 and 0.9 to 1.4, respectively, which is not very impressive. Subject 432 already appeared to have some baseline mild elevation. Subject 122 appeared to have a baseline mild elevation of transaminases so it could be that some baseline hepatic abnormality existed to account for the rise in total bilirubin during study to 1.5. Subject 204 rise to 2.1 was not associated with transaminitis – an indirect bilirubin was not available.

It should be noted that 3 subjects without a previous history of diabetes listed in volume 93 were found to have hyperglycemia – one each in the MF DPI 100 and 200 BID groups and the placebo group.

f) Vital signs/ECG

No important changes in the means for vital signs or weight were noted between treatment groups or between genders over the course of the trial. ECGs were performed only at Baseline so a review oft his data was not undertaken as it would not reveal information about the drug effect of MF DPI.

g) Plasma Mometasone Furoate Concentrations

MF concentrations were measured using a high pressure liquid chromatography assay with tandem mass spectrometry detection in plasma samples collected from 90 subjects before and 30 minutes after the last dose at five study sites. Quantifiable concentrations were observed in 2/17 subjects who received MF DPI 100 BID (69.5 and 188 pg/ml), 9/17 who received MF DPI 200 BID (51 to 119 pg/ml), 10/16 who received MF DPI 400 BID (67.7 to 210 pg/ml [second highest value 110 pg/ml]), and in no subject who received BDP or placebo. Quantifiable concentrations appeared to be slightly more prevalent among subjects who received MF DPI 200 or 400 BID than 100 BID, but the values were relatively low and not apparently related to dose.

h) Plasma Cortisol Concentrations

Changes in plasma cortisol were also examined at five selected sites. Approximately 20 subjects were involved in each group. No significant or important numerical differences between the pre- and post-cortrosyn (0.25 mg) level were noted between treatment groups when Screening values were compared with Endpoint values.

A listing of subjects whose prestimulation concentration of plasma cortisol was <5 mcg/dl, whose poststimulation concentration was <18 mcg/dl, or whose response to stimulation was not an increase of at least 7 mcg/dl was generated and reviewed. Sixteen subjects were identified: two treated with MF DPI 100 BID; seven with MF DPI 200 BID; two

with MF DPI 400 BID; four with BDP 168 BID; and one with placebo. Of this list, only five had abnormalities at Week 12 and not at Screening. One (Subject 26 - MF 200 BID) had a basal cortisol of 23.3 which only rose to 27.1. Subject 273 (MF 200 BID) had a basal level of 7.5 that rose to 16.7. Subject 150 (MF 200 BID) had a basal level of 4.8 that rose to 16.8. Subject 149 (MF 400 BID) had a basal level of 7.6 that rose to 17.7. Subject 95 (BDP 168 BID) had a basal level of 17.5 that rose to 24.1. Only Subjects 273, 150 and 149 should be considered to have any level of insufficiency. Nonetheless, the testing was done with the 0.25-mg dose of synthetic ACTH and may not have the true sensitivity to determine whether any true HPA effect caused by the MF DPI drug product.

i) Safety Conclusions for C96-134

Pharyngitis, viral infection, sinusitis, influenza-like symptoms, oral candidiasis, upper respiratory tract infection, back pain and probably dysmenorrhea were more common with corticosteroid treatment than with placebo and viral infection, influenza-like symptoms, oral candidiasis, dysmenorrhea, and coughing appeared to be more common with MF DPI than with BDP. Pharyngitis, candidiasis, URI and back pain even appeared to show a dose response with MF DPI. Of the less common adverse events, fatigue, dysphonia, dyspepsia, and myalgia were more common with MF DPI than either BDP or placebo. It was interesting to note that among the few psychiatric adverse events noted that the majority were with MF DPI 400 BID.

There were no life threatening adverse events with the possible exception of Subject 107 who was diagnosed with leukemia 3 weeks after the trial. Because he had had a somewhat low WBC at Screening, the event was considered unrelated to drug treatment. Of the serious adverse events, none seemed to be plausibly related to treatment. Of the discontinuations because of adverse events, there were plausibly two instances where it may have been attributable to drug including one influenza-like syndrome in a subject on MF DPI 400 BID and pharyngitis in one subject on MF DPI 100 BID.

There were a number of instances of transaminase elevation revealed during the trial. Subject 99 on MF DPI 400 BID had an increase in AST from 32 to 63 and ALT from 52 to 111 for Day 49 of treatment. It is important to point out that this subject had an elevation of his transaminases at Baseline. Subject 61 on MF DPI 400 BID had an increase of AST/ALT to 51/81at Wk 12from 22/13 at Screening. Subject 12 on BDP had an increase of AST from 35 to 58, ALT from 34 to 73, and alkaline phosphatase from 93 to 150. A few other instances of transaminase increase were noted, including two cases in subjects treated with placebo. The relationship of these increases to MF DPI treatment is not clear and should be further discussed in the ISS.

Three subjects without a previous history of diabetes were found to have hyperglycemia during the trial – one each in the MF DPI 100 and 200 BID groups and the placebo group.

No important changes in the means for vital signs or weights were noted during the trial. Post treatment ECGs were not in the protocol. Quantifiable MF levels were found in about half of subjects taking MF DPI 200 and 400 BID but were still relatively low. No differences among the treatment groups as a whole were noted for the Screening and Endpoint cortrosyn stimulation testing but there appeared to be possibly three subjects, all on MF DPI 200 BID, who appeared to have a potential level of HPA axis effect.

J. C96-168 (Vol.140-150)

"Placebo-Controlled, Efficacy And Safety Study Of Mometasone Furoate (Sch 32088) Dry Powder Compared To Beclomethasone Dipropionate (Vanceril®) In The Treatment Of Asthma In Subjects Previously Maintained On Inhaled Corticosteroids"

1. Investigators and Investigational Centers

There were 15 centers involved – all within the United States.

2. Objectives/Rationale

The primary objective of this randomized, multicenter, double-blind, double-dummy placebo-controlled, parallel groups clinical trial was to characterize the efficacy and safety of two doses of MF DPI (100 and 200 BID) compared to placebo in subjects with asthma who were previously maintained on inhaled steroids. The secondary objective was to evaluate the relative efficacy and safety of MF DPI 100 mcg BID, MF DPI 200 mcg BID and beclomethasone dipropionate (BDP MDI) 168 mcg BID.

a) Primary

The primary efficacy variable was change from Baseline in FEV_1 at Endpoint.

b) Secondary

Secondary efficacy variables included FEF_{25-75}, FVC, daily peak flow, symptom scores, Proventil use, nocturnal awakenings, and assessments of response to therapy. Time to discontinuation due to worsening of asthma was also evaluated.

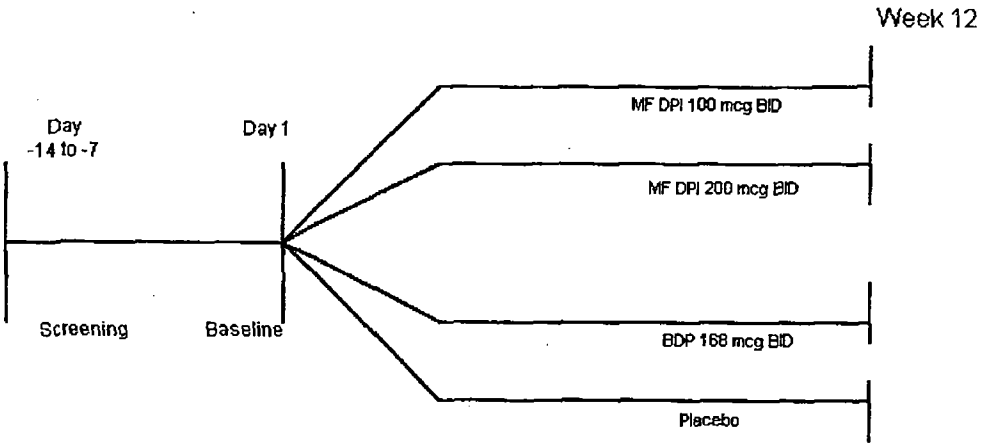
c) Safety

Safety variables included adverse events, laboratory tests, vital signs, and physical examination including the oropharyngeal examination.

3. Study Design

This was a Phase III, randomized, placebo-controlled double-blind, double-dummy, parallel group, study of MF DPI in the treatment of asthma in subjects previously maintained on inhaled corticosteroids. Informed consent was obtained and subjects entered a Run-in period of 1 to 2 weeks, during which they continued treatment with their usual inhaled corticosteroid. At Baseline (Visit 2), subjects stopped treatment with their usual inhaled corticosteroid and were randomized to treatment (MF DPI 100 BID, MF DPI 200 BID, BDP MDI 168 BID [336 mcg/day], or placebo in a 1:1:1:1 ratio according to a computer-generated code with double-blind medications for 12 weeks.

4. Summary Protocol



Follow-up visits on Day 4, weeks 1,2,4,8 and 12.

a) Study Population

The study was designed to enroll approximately 16 (range 12-32) adult and adolescent subjects at each of approximately 15 (range 15-20) study centers to ensure 200 subjects who met the criteria for the evaluation of the primary endpoint.

(1) Inclusion Criteria

Same as C96-196.

(2) Exclusion Criteria

Same as C96-196 and C96-136 (with the only important difference from the latter study being that subjects here were recently on inhaled corticosteroids).

(3) Removal of Subjects from Therapy

Same as 3 month phase of C96-136.

b) Treatments Administered

Subjects continued to take their prescribed inhaled corticosteroid between Screening and Baseline visits (Run-in period). Except for Proventil, nebulized B-agonists and stable dose theophylline, all other asthma medications, including inhaled or oral beta-agonists, anticholinergics, cromolyn, nedocromil, zafirlukast, zileuton, intramuscular, intravenous and oral corticosteroids were prohibited during the Run-in period and for the duration of the study. During the double-blind treatment period, subjects followed one of the following treatment regimens during the study:

	AM		PM		
Treatment Group	MF DPI	BDP MDI	MF DPI	BDP MDI	Total mcg/Day

Group 1	100 mcg x 1 puff	Placebo x 4 puffs	100 mcg x 1 puff	Placebo x 4 puffs	MF 200 mcg
Group 2	200 mcg x 1 puff	Placebo x 4 puffs	200 mcg x 1 puff	Placebo x 4 puffs	MF 400 mcg
Group 3	Placebo x 1 puff	42 mcg x 4 puffs	Placebo x 1 puff	42 mcg x 4 puffs	BDP 336 mcg
Group 4	Placebo x 1 puff	Placebo x 4 puffs	Placebo x 1 puff	Placebo x 4 puffs	Placebo (0)

This was a double-dummy study. Each subject took one puff from the DPI followed by four puffs from the MDI every morning and evening approximately 12 hours apart.

(1) Concomitant/Restricted Medications

Same as C96-196.

c) Assessments/Study Procedures

The safety and efficacy procedures were similar to those in trials previously discussed.

Schedule of Study Procedures and Evaluations for C96-168

		Treatment Period						
	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Treatment Days	Days-14 to-7	1	4 (±1)	8 (±2) (Wk 1)	15 (±2) (Wk 2)	29 (±4) (Wk 4)	57 (±3) (Wk 8)	85 (±3) (Wk 12)
Obtain Informed Consent	X							
Review Inclusion/ Exclusion Criteria	X	X						
Medical/Disease History	X							
Concomitant Medications Review	X	X	X	X	X	X	X	X
Physical Examination, Weight	X							X
Height	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, UA	X							X
Pregnancy Test	X							X
Electrocardiogram	X							
Chest X-ray	X							
Skin Test		X						
Dispense/Collect Diary	X	X	X	X	X	X	X	X
Review Diary		X	X	X	X	X	X	X
Dispense Peak Flow Meter	X							
Dispense Study Medication		X				X	X	
Response to Therapy Assessment			X	X	X	X	X	X
Adverse Events Evaluation		X	X	X	X	X	X	X
Compliance Check/ Collect Meds			X	X	X	X	X	X

d) Statistical and Analytic Plans

(1) Study Populations

The Intent-to-Treat Data Set, as with the other trials discussed thus far, included all randomized subjects. All summaries of safety data and the primary efficacy analyses were to be based on this data set. The efficacy data set were those randomized subjects who met key eligibility and evaluability criteria (did not have major protocol violations). Confirmatory efficacy analyses were to be based on this subject subset.

(2) Efficacy Analyses

The primary efficacy variable at Endpoint was to be analyzed for all randomized subjects (pooled across all centers) using a two-way ANOVA which extracted sources of variation due to treatment and center and treatment-by-center interaction. The primary efficacy analysis for demonstrating the activity of MF DPI was to be based on pairwise comparisons of the least squares means of the MF DPI doses and placebo (from the ANOVA) using a 5% significance level. Since all pairwise comparisons addressed independent questions, and the comparison between MF DPI 200 BID and placebo was the primary efficacy analysis, if the test for no difference between MF DPI 200 BID and placebo was significant, then each comparison was to be performed at the 0.05 (two-sided) level of significance, with no adjustment for multiple comparisons. In addition to the analysis at Endpoint, all six pairwise comparisons between the four treatment groups were to be made with respect to the change from Baseline in FEV_1 for each scheduled visit, using the same two-way ANOVA described above.

All other continuous efficacy variables were to be analyzed at each time point using the same two-way ANOVA. For time to discontinuation because of asthma worsening, Kaplan-Meier survival time estimates were to be calculated and treatment groups were to be compared using the log-rank test.

(3) Sample Size

The study was designed to enroll 200 subjects with 50 subjects per treatment group. The sample size was chosen to detect a clinically meaningful pairwise difference in the FEV_1 mean change from Baseline (the primary efficacy variable) between any active treatment group and placebo with 90% power and 5% significance level. With 50 subjects per group, assuming a pooled standard deviation of 0.45 units for FEV_1 change from Baseline (similar to the other trials thus far, this was based on Study No. C94-127), mean treatment differences of approximately 0.29 units (approximately 12% of Baseline) or more would be detectable with a power greater than 90%.

(4) Changes to the Efficacy Analyses

The same changes in allowable FEV_1 range at Screening and Baseline, reversibility testing, ITT definition (from all randomized subjects to all randomized subjects who received one dose of study drug), two way ANOVA, pooling of small centers for the treatment-by-center interaction term, and "time to discontinuation" to "time of worsening" that have been made in most of the trials discussed were also made in this study.

5. Results

a) Disposition of Subjects

The numbers of subjects randomized and treated in the four groups of the study were as follows: MF DPI 100 BID, 57 subjects; MF DPI 200 BID, 56 subjects; BDP MDI 168 BID, 57 subjects; and placebo, 57 subjects. The majority of subjects in active treatment groups (MF DPI 100 BID, 80.7%; MF DPI 200 BID, 87.5%; BDP MDI 168 BID, 78.9%) completed the study as planned while only 38.6% of the placebo group completed.

Of the 65 subjects that discontinued, the most common reason for discontinuation was treatment failure (38 subjects, 16.7%). The incidence of discontinuation for treatment failure was higher in the placebo group (43.9%) than in any active treatment group (3.6% to 10.5%). The incidence of discontinuation for treatment failure was lower in the MF DPI 200 BID group (3.6%) than in the MF DPI 100 BID (8.8%) group and the BDP MDI 168 BID (10.5%) group. The incidence of discontinuations due to adverse events was also higher in the placebo group (8.8%) than in other treatment groups (1.8% to 3.6%).

Number (%) of Randomized Subjects Who Completed the Study, Number (%) Who Discontinued and Reasons for Discontinuance C96-168

	Treatment Groups									
	MF DPI 100 mcg (n=57)		MF DPI 200 mcg (n=56)		BDP MDI 168 mcg (n=57)		Placebo (n=57)		Total (n=227)	
Number (%) Completed	46	(80.7)	49	(87.5)	45	(78.9)	22	(38.6)	162	(71.4)
Reasons for Discontinuation										
Adverse Event	1	(1.8)	2	(3.6)	1	(1.8)	5	(8.8)	9	(4.0)
Treatment Failure	5	(8.8)	2	(3.6)	6	(10.5)	25	(43.9)	38	(16.7)
Lost to follow-up	2	(3.5)	1	(1.8)	0	(0)	1	(1.8)	4	(1.8)
Did Not Continue for Reasons Unrelated to Treatment	2	(3.5)	2	(3.6)	2	(3.5)	1	(1.8)	7	(3.1)
Noncompliance with Protocol	1	(1.8)	0	(0)	2	(3.5)	2	(3.5)	5	(2.2)
Did Not Meet Entry Criteria	0	(0)	0	(0)	1	(1.8)	0	(0)	1	(0.4)
Administrative	0	(0)	0	(0)	0	(0)	1	(1.8)	1	(0.4)
Total Number (%) Discontinuing	11	(19.3)	7	(12.5)	12	(21.1)	35	(61.4)	65	(28.6)

There were 18 subjects that met criteria for worsening of asthma but were not discontinued as per protocol. There were 8 in the placebo group and 1-5 in the active treatment groups. In addition, 12 subjects had other protocol deviations (which excluded them from the efficacy evaluable data set) including poor compliance(7 subjects), insufficient efficacy data (5 including 2 without any post-baseline data) and FEV1 values not 55-95% predicted at Baseline (4 subjects).

Distribution of Subjects by Analysis Subset and Treatment Group

MF DPI 100 mcg BID	MF DPI 200 mcg BID	BDP MDI 168 mcg BID	Placebo	Total

Subjects Randomized	57	56	57	57	227
All Treated Subjects	57	56	57	57	227
All Treated Subjects with Post-baseline Data	56	55	57	57	225
All Treated Subjects with No Post-baseline Data	1	1	0	0	2
Efficacy Evaluable Subset	54	54	55	52	215
Excluded From Efficacy Evaluable	3	2	2	5	12

b) Demographics

	MF DPI 100 mcg BID (n = 57)	MF DPI 200 mcg BID (n=56)	BDP MDI 168 mcg BID (n=57)	Placebo (n=57)
Age (years)				
Mean	40	40	40	42
Min-Max	13-74	13-68	15-75	15-70
Distribution of Subjects in Age Categories				
12 to 17 years	5	2	3	2
18 to 64 years	50	53	52	54
≥65 years	2	1	2	1
Sex				
Female	33	37	40	39
Male	24	19	17	18
Race				
White	45	48	47	52
Black	3	3	2	2
Hispanic	6	3	5	3
Asian	3	1	2	0
Other	0	1	1	0
Weight (lbs.)				
Mean	176	167	166	179
Min-Max	98-290	120-250	105-255	117-367
Duration of Asthma Condition (years)				
Mean	18	17	23	20
Min-Max	1-55	1-51	1-64	2-50
FEV_1 % Predicted at Baseline				
Mean	76	78	76	75
Min-Max	61-98	60-113	60-96	52-91
FEV_1 at Baseline (liters)				
Mean (raw mean)	2.65	2.59	2.49	2.43
AM PEFR at Baseline (liters/minute)				
Mean	396.51	371.46	370.97	360.79

	MF DPI 100 mcg BID (n = 57)	MF DPI 200 mcg BID (n=56)	BDP MDI 168 mcg BID (n=57)	Placebo (n=57)
Inhaled Corticosteroids at Baseline				
Beclomethasone Dipropionate				
no. of subjects	21	18	18	10
mean mcg/day	300	323	315	323
min-max mcg/day	84-840	168-672	84-672	84-504
Flunisolide				
no. of subjects	5	12	7	8
mean mcg/day	1260	1042	1143	1000
min-max mcg/day	800-2000	500-2000	500-2000	500-1500
Fluticasone Propionate				
no. of subjects	14	8	17	13
mean mcg/day	393	333	380	382
min-max mcg/day	110-440	110*-440	176-440	220-440
Triamcinolone Acetonide				
no. of subjects	17	18	15	26
mean mcg/day	753	617	800	758
min-max mcg/day	400-1600	200-900	400-1600	200-1600

It should be noted that it is not mentioned in the protocol that these subjects were not titrated down, during the run-in period, to their lowest acceptable dose of inhaled corticosteroid. As can be seen, the dose of inhaled corticosteroids was generally balance among the treatment groups and this balance would address, to some degree, the fact that some subjects may not have been previously on their optimal dose. Most subjects were skin prick positive.

6. Analysis of Efficacy

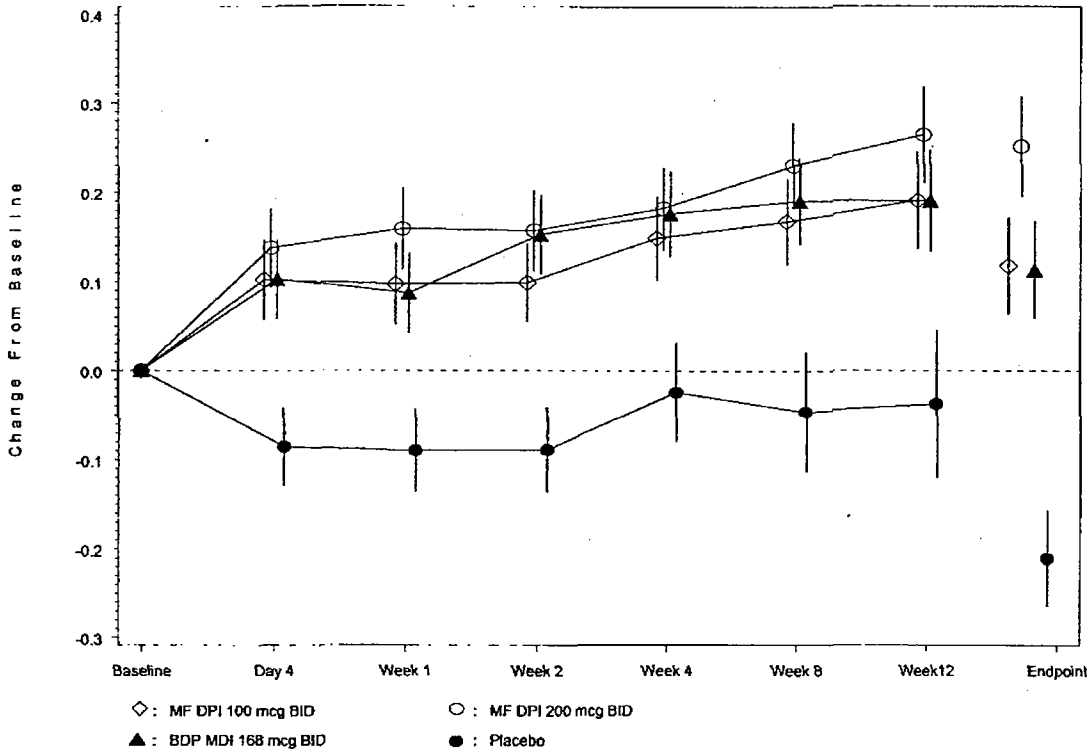
It should be noted that subjects with favorable treatment responses were more likely to contribute data to later post-baseline assessments than subjects with poor treatment responses.

a) FEV_1

All active treatments were significantly different than placebo at Endpoint and at every timepoint during the 12 week period. The magnitude of response appeared to be greatest in the MF 200 BID group and remarkably similar between MF 100 BID and BDP 168 BID. There were no significant differences, however, identified between any of the treatment groups. One must ask, however, why subjects who were previously on inhaled corticosteroids should improve while on BDP during this trial, especially when probably 25% of those randomized were already on BDP.

There were clearly more females than males in this trial. While all groups of active treatment demonstrated improvement in FEV_1, there were interesting differences between the sexes. Response to treatment was similar among active treatment groups in female subjects (MF DPI 100 BID, 7.2%; MF DPI 200 BID, 7.5%; BDP MDI 168 BID, 5.6%). Among male subjects, response to treatment with MF DPI 200 BID (14.2%) was notably greater than the response to treatment with MF DPI 100 BID (1.5%) or BDP MDI 168 BID (4.1%). It does not appear that the sponsor studied whether these differences were significant or not. The 1.5% improvement at Endpoint in males on MF DPI 100 BID may be somewhat misleading as the Week 12 data shows a 7.3% improvement; such a difference must be attributable to the drop-

outs. Among males there were Week 12 data points for 70.8% of MF 200 BID, 100% of MF 200 BID, 70.5% of BDP 168 BID, and only 27.7% of placebo subjects. Not nearly the % of females were missing a data point for Week 12's FEV_1.



Only a small percentage of subjects were not in the 18-64 age range so further comment on age is not warranted. Non-Caucasians showed good improvement in FEV1 with MF DPI 200 BID and BDP relative to placebo but the MF DPI 100 BID did not fare as well and even had a minus 2.3% response at Endpoint.

Changes again were evaluated by the baseline severity of asthma. As has been previously in the other trials examined thus far in this NDA, active treatment produced better results in subjects with more pronounced disease severity (FEV_1 < 75%). In subjects with a baseline FEV_1 of <75% of the predicted value, increases at Endpoint in FEV_1 in were notably highest in the MF DPI 200 BID (14.2%) followed by the BDP MDI 168 BID (10.0%) group then the MF DPI 100 BID (3.7%) group. Subjects in all active treatment groups had better responses than subjects in the placebo treatment group (-10.6% and -6.0 % for the placebo group of FEV_1 ≥75%). In subjects with a baseline FEV_1 ≥75% of predicted, increases at Endpoint were numerically greater in the MF DPI 100 BID group (5.6%) and MF DPI 200 BID group (7.5%) than in the BDP MDI 168 mcg BID group (0.6%).

FEV_1 (liters)

	MF DPI 100 mcg BID (A)			MF DPI 200 mcg BID (B)			BDP MDI 168 mcg BID (C)			Placebo (D)		
	N	Mean	(Mean % Change)[a]	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	56	2.65		55	2.59		57	2.49		57	2.43	
Change From Baseline												
Day 4	44	0.10	(3.4%)	46	0.14	(4.5%)	44	0.10	(4.0%)	46	-0.09	(-3.8%)
Week 1	54	0.10	(3.7%)	54	0.16	(6.0%)	56	0.09	(4.1%)	50	-0.09	(-3.1%)
Week 2	52	0.10	(4.2%)	51	0.16	(5.8%)	52	0.15	(6.7%)	44	-0.09	(-3.1%)
Week 4	50	0.15	(6.3%)	52	0.18	(7.3%)	48	0.18	(7.8%)	35	-0.02	(-0.7%)
Week 8	47	0.17	(7.1%)	49	0.23	(9.1%)	48	0.19	(8.4%)	25	-0.05	(-1.4%)
Week 12	46	0.19	(7.9%)	49	0.26	(10.2%)	43	0.19	(8.9%)	21	-0.04	(-0.8%)
Endpoint	**56**	**0.12**	**(4.8%)**	**55**	**0.25**	**(9.7%)**	**57**	**0.11**	**(5.2%)**	**57**	**-0.21**	**(-8.1%)**

Analysis Results (Change From Baseline)

		P-value		Pairwise Comparisons (P Value)					
Time Point	Pooled SD	Treatment	Center	A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D
Day 4	0.28	<0.01	0.17	0.56	0.99	<0.01	0.56	<0.01	<0.01
Week 1	0.33	<0.01	0.48	0.33	0.87	<0.01	0.26	<0.01	<0.01
Week 2	0.31	<0.01	0.60	0.35	0.38	<0.01	0.94	<0.01	<0.01
Week 4	0.33	0.02	0.46	0.61	0.68	0.02	0.93	<0.01	<0.01
Week 8	0.33	<0.01	0.06	0.35	0.73	0.01	0.56	<0.01	<0.01
Week 12	0.36	0.02	0.21	0.33	1.00	0.02	0.34	<0.01	0.02
Endpoint	**0.40**	**<0.01**	**0.03**	**0.08**	**0.96**	**<0.01**	**0.07**	**<0.01**	**<0.01**

As per protocol, a confirmatory analysis was performed in the Efficacy evaluable data set and, again, all active treatments were significantly different from placebo at Endpoint and at all timepoints. A cursory review of FEV_1 response by study center was performed and there did not appear to be an over-representation of subjects in any one treatment center.

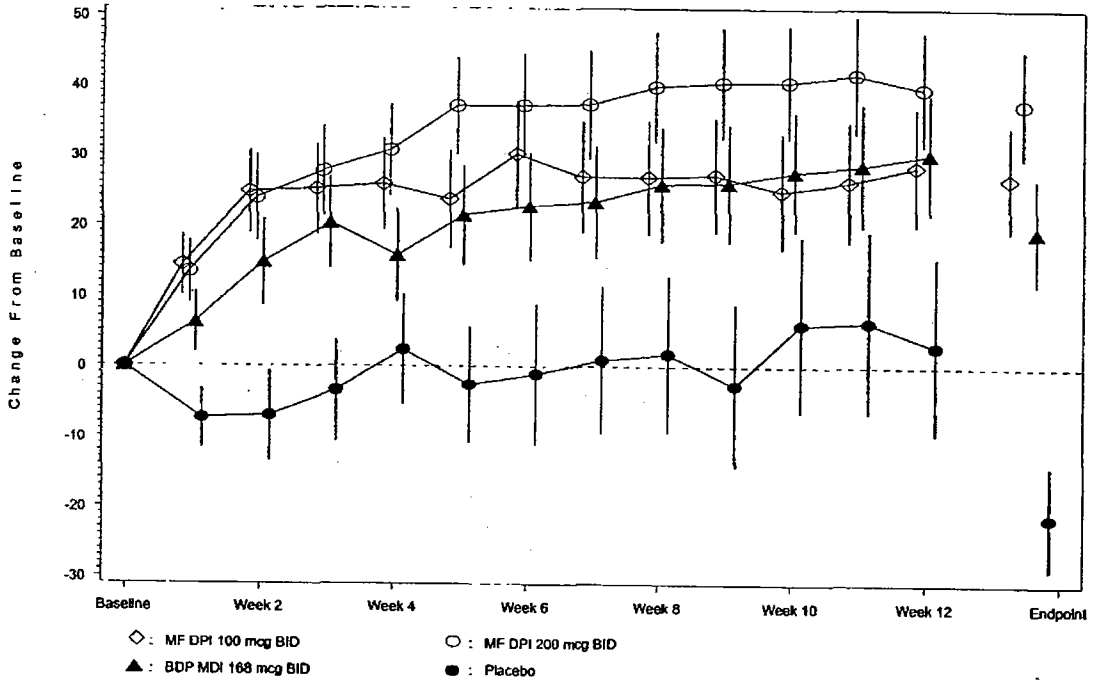
b) FVC and FEF_{25-75}

The FVC data demonstrated statistically better response in the active treatment groups than in the placebo treatment group at Endpoint and at all timepoints. At Endpoint, FVC increased in all active treatment groups (MF DPI 100 BID, 5.5%; MF DPI 200 BID, 7.7%; BDP MDI 168 BID, 5.5%) and decreased in the placebo group (-5.9). There were no statistically significant differences between active treatment groups at Endpoint or at any timepoint. With this variable, while there was little numerical difference among the groups, the greatest effect was still seen with MF DPI 200 BID.

The FEF_{25-75} data showed a consistently significant mean % increase at Endpoint in the active treatment groups (MF DPI 100 BID - 7.0%; MF DPI 200 BID - 20.1%; BDP MDI 168 BID - 7.7%, and a decrease in the placebo group (-9.8%). There were no statistically significant differences between active treatment groups at Endpoint or at any timepoint. No one active treatment group appeared consistently numerically better at specific timepoints, however, at Endpoint, the MF DPI 200 BID group fared numerically best.

c) PEFR

AM PEFR – Change from Baseline over Time and at Endpoint



From the graph above, it is interesting to note that AM PEFR was relatively preserved for placebo (except for the Endpoint) despite the fact that subjects were no longer on their

inhaled corticosteroids. At Endpoint, all active treatments showed a significant difference from placebo for both AM and PM PEFR. For AM PEFR, MF DPI 200 BID fared numerically best at all timepoints from Week 4 on but this difference with other active treatment groups was not significant. For PM PEFR, it was not until Week 7 that MF DPI 200 BID was numerically best.

A supplemental analysis was performed by the sponsor for Days 2-14. As early as Day 2, the AM PEFR for MF DPI 200 BID was significantly different from placebo.

d) Asthma Symptoms

Asthma symptoms were again rated and scores were available for wheezing, difficulty breathing and coughing. For AM wheezing, MF DPI 200 BID fared the best. The decrease in scores for 200 mcg were typically double those seen with 100 mcg at Endpoint and at timepoints from Week 8 forward. The changes with BDP were most similar to those of MF DPI 100 BID. It must be noted that at Endpoint, all active treatments were significantly different from placebo for AM wheezing and for PM wheezing. For PM wheezing, MF DPI 200 BID was numerically the best followed by 100 BID and then BDP.

For AM and PM Difficulty Breathing and their average scores, all active treatments were significantly different from placebo at Endpoint. For the AM score, MF DPI 200 BID did numerically best, but not by much at Endpoint and at other timepoints. MF DPI 100 BID and BDP were significantly better than placebo only at Endpoint (with the exception of Week 8 for MF DPI). The differences among the active treatment groups were again small for PM Difficulty Breathing and MF DPI 100 BID usually fared the best at most timepoints but by very small margins - the largest difference was noted at Endpoint.

For AM Cough, only the MF DPI groups were significantly better than placebo at Endpoint. MF DPI 100 BID clearly fared the best numerically. No active treatment was better than placebo at Weeks 10 and 12 and it was generally only MF DPI 100 BID that was significantly different from placebo at other timepoints. For PM Cough, only the MF DPI 100 BID group was significantly different from placebo at Endpoint.

e) Response to Therapy

As has been done in the other trials so far examined, at all visits from Day 4 through Week 12, the physician assessed the subject's response to therapy by comparing the current level of symptoms with those noted at Baseline on a scale from 1 (much improved) to 5 (much worse).

Summary of Assessment of Response to Therapy at Endpoint

	MF DPI 100 mcg BID N (%)	MF DPI 200 mcg BID N (%)	BDP MDI 168 BID N (%)	Placebo N (%)
Much Improved	8 (14.3)	15 (27.3)	15 (26.3)	2 (3.5)
Improved	27 (48.2)	23 (41.8)	17 (29.8)	5 (8.8)
No Change	15 (26.8)	11 (20.0)	12 (21.1)	14 (24.6)
Worse	3 (5.4)	4 (7.3)	9 (15.8)	19 (33.3)
Much Worse	3 (5.4)	2 (3.6)	4 (7.0)	17 (29.8)

From this data, it is clear that active treatment had an effect according to the evaluating physician. According to these percentages, MF DPI 200 BID fared the best followed by BDP

and then MF DPI 100 BID. The treatment scores show that at Endpoint at all timepoints, all active treatments were significantly different from placebo. While MF DPI 200 BID had the best score at Endpoint, the difference with other active treatments was not significant.

f) B agonist Use During the Study

For this variable, MF DPI 100 BID generally fared the best. Between Baseline and Endpoint, the use of B agonist decreased by 1.18 puffs/day in the MF DPI 100 BID group, 0.94 puffs/day in the MF DPI 200 BID group, and 1.05 puffs/day in the BDP MDI 168 BID group while increasing by 1.31 puffs/day in the placebo group. For most timepoints, the difference from placebo was significant except for Weeks 10 and 12 which may be accounted for by an unusual decrease in Proventil use seen in the placebo group.

There was also data available on nebulizer use. This data was reviewed and the use of nebulizations was very roughly the same among the groups, including placebo.

g) Number of Nocturnal Awakenings

The number of nocturnal awakenings/night was generally low at Baseline (< 0.45 awakenings per night). Furthermore, the number of nocturnal awakenings/night was numerically lower in the active treatment groups (0.14 to 0.28 per night) than in the placebo treatment group (0.41 per night) at Baseline.

For this variable, MF DPI 200 BID fared the best among the active treatments followed by MF DPI 100 BID, but the difference between any form of active treatment and placebo was not significant at Endpoint or at any timepoint. Interestingly for all timepoints (except Endpoint), placebo had clearly the greatest numerical decrease in these awakenings among all groups. This phenomenon was most likely due to the large number of dropouts with placebo as the number of awakenings actually increased at Endpoint in this group.

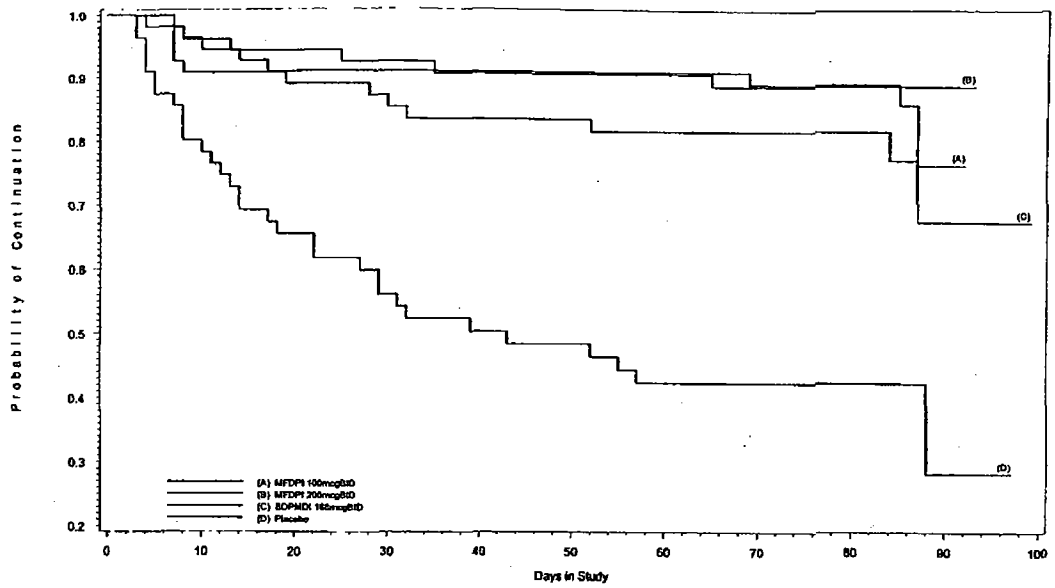
h) Time to Worsening of Asthma

The active treatments were better than placebo, which had a median time to worsening of approximately 40 days. As has been the case with every other trial examined to date in this NDA, median time to worsening could not be determined for these groups over the treatment period studied because more than 80% of subjects in each of the active treatment groups had not met the criteria for worsening by the time of their last visit.

Th figure shows that there was a clear difference between active treatment and placebo. MF DPI 100 BID appears to differ from the other active treatments within the first month while MF DPI 200 BID and BDP separate just before the end of the third month. Overall, 59 subjects met the criteria for asthma worsening (MF DPI 100 BID, 8 subjects; MF DPI 200 BID, 6 subjects; BDP MDI 168 BID, 13 subjects; placebo, 32 subjects).

One of the criteria for worsening of asthma was a clinical asthma exacerbation (CAE) requiring an ER visit or the addition of an asthma medication in addition to those allowed in the protocol. Eight subjects had protocol-defined CAE. CAEs were reported more often in the placebo group (5 subjects) than in either the MF DPI 100 BID (one), MF DPI 200 QD (no subjects), or BDP MDI 168 BID (2) groups.

Time to Worsening of Asthma



Reviewer's Note – The sponsor later points out in the Integrated Summary of Efficacy that because the scheduled treatment duration was 3 months (84 days), small numbers of subjects remained in the study after Day 80. Therefore, larger decrements are noted at timepoints after Day 80 than before in the calculated probabilities of continuing in the trial without asthma worsening.

i) Summary of Efficacy for C96-168

For the primary efficacy endpoint of change in FEV_1, each active treatment was significantly better than placebo at Endpoint and at every timepoint. The best response was in the MF 200 BID group while the response was similar for the MF 100 BID and BDP 168 BID groups. There were no significant differences between active treatments. This trial had a clear over-representation of female subjects for unknown reasons. The efficacy of the active treatments was roughly equal among the female subjects. The male subjects responded much better to the MF DPI 200 BID treatment (14.2%). There was not a favorable response among Non-Caucasians for the MF DPI 100 BID treatment while there was for the other active treatments. The improvement seen in FEV_1 was again more marked in those with a Baseline FEV_1 <75%, however, the MF DPI treatments also appeared to be effective in those with an $FEV_1 \geq 75\%$.

All active treatments were better than placebo FVC and FEF_{25-75} at Endpoint and all timepoints and MF DPI 200 BID was most effective with both variables. At Endpoint, all active treatments showed a significant difference from placebo for both AM and PM PEFR and MF DPI 200 BID was again the best dose fat Endpoint and for at least the later timepoints.

For Wheezing and Difficulty Breathing (DB) scores, all active treatments were significantly better than placebo at Endpoint. MF DPI 200 BID was numerically the best for wheezing and AM DB while 100 BID was best for PM DB. For AM and PM COUGH, MF DPI 100 BID was the best. For PM Cough, it was only the 100 mcg dose of MF DPI that was better than placebo at Endpoint.

For response to therapy, all active treatments were significantly better throughout the trial and MF DPI 200 BID was the best. Interestingly, MF DPI 100 BID was the best among all active treatments that all significantly reduced B agonist use. For the variable Nocturnal Awakenings, placebo fared best at al timepoints except Endpoint when MF DPI 200 BID was the best. It must be noted that the placebo group had a higher # awakenings at Baseline. Active treatment slowed the time to Worsening of Asthma and the MF DPI products fared the best.

In summary, while active treatment was typically better than placebo for most variables at Endpoint, it seemed that MF DPI 200 BID stood apart, albeit only numerically from the rest of the active treatments.

7. Safety

a) Adverse Events

Many of the more common adverse events seen in this trial have been seen previously in other trials.

Incidence of Adverse Events Reported by ≥10% of Subjects In Any Treatment Group

	MF DPI 100 mcg BID (n=57)		MF DPI 200 mcg BID (n=56)		BDP MDI 168 mcg BID (n=57)		Placebo (n=57)	
	n	(%)	n	(%)	n	(%)	n	(%)
Headache	25	(44)	22	(39)	19	(33)	20	(35)
Allergy, aggravated	14	(25)	16	(29)	13	(23)	12	(21)
Dysmenorrhea	5	(15)	7	(19)	3	(8)	5	(13)
Musculo-skeletal pain	5	(9)	10	(18)	8	(14)	5	(9)
Back pain	6	(11)	8	(14)	8	(14)	2	(4)
Pharyngitis	8	(14)	7	(13)	6	(11)	5	(9)
Infection viral	7	(12)	6	(11)	3	(5)	4	(7)
Candidiasis, oral	2	(4)	6	(11)	3	(5)	1	(2)
Nasal congestion	4	(7)	6	(11)	5	(9)	5	(9)
Sinusitis	7	(12)	5	(9)	6	(11)	3	(5)

Interestingly, dysmennorhea does not appear any more common with MF DPI than placebo although there is a slight increase with the higher MF DPI dose. Back pain, pharyngitis and sinusitis appear to be more common with active treatment. Musculo-skeletal pain and oral candidiasis appear to be most common with MF DPI specifically and there appeared to be a dose response.

The following list of adverse events has been edited and it not complete. It has been highlighted to show those clearly more common with active treatment or MF DPI and may or may not have a dose response as well as those that are otherwise particularly notable.

Incidence of Treatment-Emergent Adverse Events Reported by ≥1% of subjects

	MF DPI 100 mcg BID (n=57)	MF DPI 200 mcg BID (n=56)	BDP MDI 168 mcg BID (n=57)	Placebo (n=57)
Any Adverse Event	**49 (86)**	**45 (80)**	**46 (81)**	**40 (70)**
influenza-like symptoms	1 (2)	1 (2)	1 (2)	1 (2)
pain	3 (5)	4 (7)	0 (0)	0 (0)
dizziness	2 (4)	2 (4)	3 (5)	0 (0)
dysphonia	2 (4)	2 (4)	1 (2)	0 (0)

Incidence of Treatment-Emergent Adverse Events Reported by ≥1% of subjects

	MF DPI 100 mcg BID (n=57)	MF DPI 200 mcg BID (n=56)	BDP MDI 168 mcg BID (n=57)	Placebo (n=57)
abdominal pain	2 (4)	5 (9)	4 (7)	1 (2)
dyspepsia	4 (7)	4 (7)	3 (5)	3 (5)
flatulence	0 (0)	4 (7)	0 (0)	0 (0)
gastritis	0 (0)	1 (2)	1 (2)	0 (0)
migraine	2 (4)	2 (4)	1 (2)	1 (2)

Adverse events such as dyspepsia, gastritis and influenza-like symptoms which have appeared as AEs more commonly with MF DPI in at least one trial previously do not appear to be more common with MF DPI in this trial. Pain was most common with MF DPI but it is not specified what is meant by pain (frankly, trials of this caliber should have better descriptors – even for a table). Abdominal pain and dizziness appear to be more common with active treatment in this trial but is not more common with MF DPI compared with BDP. For unclear reasons, flatulence is most common with the high dose of MF DPI here. While migraine headache was more common with MF DPI relative to BDP and placebo, it is only 2 cases n each MF DPI group compared with 1 subject in each of the other groups. Dysphonia appears to be most common with MF DPI.

Headache and pharyngitis was more common among females, but was not more prevalent with active treatment among females. Abdominal pain was more common in females and most prevalent with MF DPI 200 BID (11%) and BDP (8%). Because of the much smaller number of Non-Caucasians, data on the incidence of adverse events and the percentages of subjects involved could be misleading.

b) Severe Adverse Events

Events in this category were reported by 36 subjects. Only one subjects (#231 – Site 11) had one described as life-threatening. This event is further described under Serious Events. The following list of severe AE's has been edited to include those types of AEs previously highlighted in this trial or those that are otherwise notable.

Severe/Life-threatening Adverse Events

	MF DPI 100 mcg BID (n=57)	MF DPI 200 mcg BID (n=56)	BDP MDI 168 mcg BID (n=57)	Placebo (n=57)
Any Severe/Life-threatening AE	**10 (18)**	**11 (20)**	**11 (19)**	**4 (7)**
allergy, aggravated	0 (0)	1 (2)	0 (0)	0 (0)
back pain	2 (4)	1 (2)	2 (4)	0 (0)
headache	2 (4)	4 (7)	4 (7)	1 (2)
influenza-like symptoms	0 (0)	0 (0)	1 (2)	0 (0)
pain	1 (2)	0 (0)	0 (0)	0 (0)
dizziness	0 (0)	0 (0)	1 (2)	0 (0)
abdominal pain	1 (2)	1 (2)	1 (2)	0 (0)
dyspepsia	0 (0)	1 (2)	1 (2)	0 (0)
musculo-skeletal pain	0 (0)	1 (2)	0 (0)	0 (0)
dysmenorrhea	0 (0)	1 (3)	0 (0)	1 (3)
candidiasis, oral	0 (0)	1 (2)	1 (2)	0 (0)
pharyngitis	1 (2)	1 (2)	1 (2)	1 (2)
respiratory insufficiency	0 (0)	1 (2)	0 (0)	0 (0)
migraine	2 (4)	2 (4)	0 (0)	0 (0)

In reviewing this list, AEs such as oral candidiasis, pharyngitis, abdominal pain, musculo-skeletal pain, migraine, back pain, and dizziness which were thought to be more common with active treatment had examples of being severe.

c) Serious Adverse Events

Serious adverse events were reported for two subjects. . Neither event was considered related to treatment by the investigators. Subject #231 (MF DPI 200 BID) was involved in a car accident. She received a nerve root block for treatment for a cervical herniation and had an immediate respiratory arrest. She was resuscitated, and discharged 3 days later. The investigator discontinued the subject subsequent to her release from the hospital. Subject #73 (BDP MDI 168 BID) reported nasal congestion and rhinorrhea for one week prior to hospitalization for shortness of breath (asthma aggravated). The subject attributed her dyspnea to the weather. The subject improved after adjustments to asthma medication and a course of antibiotics and was discontinued from the study for treatment failure.

d) Discontinuation Due to Adverse Events

In addition to the two subjects with serious AEs just discussed, seven subjects discontinued treatment because of adverse events. This included one subject in the MF DPI 100 BID group, one subject in the MF DPI 200 BID group, one subject in the BDP MDI 168 BID group and 5 subjects in the placebo group.

Center/Subject	Sex/ Age/ Race	Day of Onset	Adverse Event(s)	Severity	Relationship
MF DPI 100 mcg BID					
C96-168-13/067	F/49/C	-11	Nasal congestion	Severe	Unrelated
MF DPI 200 mcg BID					
C96-168-10/035	F/40/C	88	Nasal congestion	Moderate	Unrelated
		89	Pharyngitis	Severe	Unrelated
BDP MDI 168 mcg BID					
C96-168-04/043	F/53/C	7	Urticaria	Moderate	Possible
Placebo					
C96-168-02/282	F/37/C	41	Bronchitis	Not available	Unrelated
C96-168-09/141	F/39/C	12	Bronchitis	Moderate	Unrelated
C96-168-10/033	F/51/C	33	Sinus Infection	Moderate	Unrelated
			Upper Respiratory Tract Infection	Severe	Unrelated
C96-168-11/230	F/57/C	22	Allergy aggravated	Moderate	Possible
C96-168-13/074	F/52/C	13	Asthma aggravated	Moderate	Possible

e) Laboratory Values

Changes in the median values for laboratory tests performed from Baseline to Endpoint were reviewed (Vol.1-141) for a differential in response between treatment groups, genders, and Caucasian/Non-Caucasian. One small differential in response was noted between genders in the alkaline phosphatase (AP) (p.830). For females on MF DPI 100 BID, AP went up 57 to 61 while for 200 mcg it went up from 53 to 60. For males, the corresponding changes were 61 to 63 and 68.5 to 68.5. The placebo group actually decreased by 3 for each gender. These changes are not clinically significant and probably do not reflect a true differential in response.

Notable Laboratory Results

Subject	Treatment	Results (Baseline to Endpoint)
260	BDP 168 BID	Chol 189 to 229 (p. 2721)
52		Chol 235 to 329 (p. 2726)
183		Cre 1.1 to 1.8 (p. 2728)
129		Bilirubin 1.2 to 1.7 (p. 2739)
136		UA neg. to 3+ blood (p. 2740)
232		UA neg. to 2+ blood (p. 2753)
215		LDH 153 to 377 (p.2773)
229	MF DPI 100 BID	UA neg. to 2+ blood (p. 2808)
11		WBC 7.73 to 14.14 (p. 2812)
69		Glucose 75 to 139 (p. 2817)(no h/o diabetes)
162		UA neg. to 2+ blood (p. 2819)
294		ALT/AST 57/34 to 75/42 (p.2831)
193		T. bilirubin 2.7 to 3.7, nl transaminases.
194		
264	MF DPI 200 BID	Glucose 183 to 385 (p. 2834) (known diabetic)
188		ALT 24 to 53 (p. 2840)
195		WBC 5.14 to 12.61, UA neg. to 2+ blood (p. 2842)
098		ALT 30 to 47 (p. 2847)
124		AST 17 to 47 (p. 2848)
247	Placebo	Cre 1 to 1.5, Bili 0.8 to 1.4 (p. 2889)
045		UA neg. to 2+ blood (p. 2894)
182		UA neg. to 2+ blood (p. 2897)
154		Glucose 111 to 134, WBC 7.53 to 13.95 (p. 2913)
32		Cholesterol 283 to 326 (p. 2917)
227		Glucose 113 to 154 (p. 2920)
236		ALT/AST 22/18 to 71/38 (p. 2922)
61		AST 25 to 42 (p. 2928)
68		UA neg. to 3+ blood (p. 2929)
269		ALT/AST 15/12 to 58/23 (p. 2942)

There were scattered examples of blood being seen in the urinalysis among the treatment groups – there is no convincing evidence from this trial that it is drug-related. In fact, most cases were noted in the placebo group. The development of a leukocytosis was noted in Subjects #11 and #195 who were on MF DPI. Increases in transaminases were noted in #294 (which already had some baseline elevation of ALT), #188 (ALT 29), #098 (ALT 17), #124 (AST 30) among the MF DPI groups. Increases in transaminases were also noted in the placebo group with #236 (ALT 49), #61 (AST 17) and #269 (ALT 43). Increases in cholesterol were also noted occasionally – here in the non-MF DPI groups. Two instances of glucose increase were noted in MF DPI subjects – one who was a known diabetic.

The following discrepancy in the lab data for C96-168 existed as it was originally submitted. In 16.2.8.2, the Endpoint data for Subject 232 (Urinalysis) and 195 (WBC and urinalysis) do not match the Endpoint data for these same subjects in 14.3.4.1. The sponsor was asked to clarify these issues. In a response for clarification dated 8/27/99, the sponsor says that the discrepancy regarding the urinalysis for Subject 232 (BDP 168 BID) is attributable to the fact that a retest was done and that the 16.2.8.2 listing provided by their contractor incorrectly omitted retest results for parameters with non-numeric vales and carried over the "specimen flag" from the previous attempt. Therefore, the positive value for blood in the urine was erroneously omitted from the listing in 16.2.8.2 and any abnormal values were correctly reflected in 14.3.4.1.

Regarding the data on Subject 195 (MF DPI 200 BID), the retest data was reported in 16.2.8.2 while the original abnormal value was reported in 14.3.4.1.

It appears that true discrepancies do no exist between 16.2.8.2 and 14.3.4.1 but clarification was clearly required in the manner the data was originally presented.

f) Vital Signs/Body Weight/ECG

The means for the vital signs among the treatment groups between Baseline and Endpoint were reviewed. There were no changes in the vital signs suggesting a treatment effect with the possible lone exception of an increase of 4.5-mm Hg in the diastolic blood pressure among males. There was a decrease of 2.8-mm Hg in the male placebo group. No distinctive changes were noted between the Caucasian and Non-Caucasian response.

Although it was listed as part of the protocol, there was no data on weight listed among the data results in 14.3.6.

ECGs were performed only at Baseline and thus can not be used to study drug effect. For this reason, ECGs were not reviewed for this trial.

g) Safety Summary for C96-168

Many of the adverse events seen in this trial have been noted previously in the clinical development program of MF DPI. Musculo-skeletal pain, oral candidiasis, and perhaps migraine and dysphonia appeared to be specifically most common with MF DPI. Pharyngitis, back pain, sinusitis, dizziness, dysphonia, and abdominal pain appeared to be more common with active treatment with inhaled corticosteroids compared with placebo.

Among those AEs listed as severe, there were examples of AEs thought to be more common with active treatment or MF DPI such as such as oral candidiasis, pharyngitis, abdominal pain, musculo-skeletal pain, migraine, back pain, and dizziness. The two AEs listed as serious were not realistically attributable to drug treatment with MF DPI (one was with BDP).

Among the laboratory studies in the MF DPI group., there were 2 instances of leukocytosis, 3 instances of mild transaminase increase (all $\leq$ 30), and one instance of hyperglycemia in a subject not known to be diabetic. There were cases of hematuria, but no

more frequent that that seen in the placebo group. There were no distinctive changes in vital signs with drug treatment and data on weight was not tabulated.

K. C97-049 (Vol. 71-74)

"Multiple-Dose Safety and Tolerance Study of Mometasone Furoate and Lactose Powder Administered by Dry Powder Inhaler in Subjects with Symptoms of Moderate Asthma"

1. Investigator

This was a phase I trial performed at one center, Arkansas Research Medical Testing Center (Little Rock) under the direction of Jerry Herron, M.D. and his staff.

2. Objectives/Statistical Plan

The objective of this multiple-dose, randomized, third-party masked, parallel group, placebo- and positive-controlled study was to evaluate the potential for systemic exposure of mometasone furoate (MF) plus lactose powder administered by DPI (MF/L-DPI) at doses of either 400 mcg twice-daily or 800 mcg twice-daily for 29 consecutive days compared with prednisone administered orally at a dose of 10 mg once-daily in the morning and with placebo DPI in patients with mild to moderate asthma.

a) Primary Endpoint

The primary endpoint was the change in serum cortisol (HPLC assay) between the pre- and 30 minute post-samples obtained from the Day 29 cosyntropin stimulation test. Specifically, for Day 29, serum cortisol data was to be evaluated for each subject by calculating the change between the morning pre-cosyntropin injection serum cortisol and the 30-minute post-cosyntropin value. Treatments were to be compared with respect to this endpoint using a one-way ANOVA. Since the highest dose was likely to show the largest effect on serum cortisol, the primary treatment comparison was to be between 800 µg and placebo.

b) Secondary Endpoints

Serum Cortisol, AUC (0-24 hr) from 11 p.m. to 11 p.m., Cmax, and Tmax were obtained on Days -1, 7, 14, 21 and 28 and urine cortisol level was obtained on Days -2/-1, 6/7, 13/14, 20/21, and 27/28). The AUC value on Day 28 was the most clinically relevant of these secondary endpoints. Urine cortisol was the amount excreted from 11 p.m. to 11 p.m.

These parameters were to be summarized for each treatment group using means, standard deviations and coefficients of variation. In addition, an ANOVA was to be performed on each parameter for each day. These analyses were also to be done for change from Baseline. The contrasts of interest were the comparison of each of the two MF doses to placebo and prednisone on Day 28.

c) Sample Size

The sample size was chosen to detect (with 90% power and 5% level of significance) a clinically meaningful difference between any active treatment group and placebo in the mean change in serum cortisol levels between 30 minutes post- and pre-cosyntropin stimulation test on Day 29 (the primary endpoint). With 16 subjects per treatment group, assuming a pooled standard deviation of 4.3 µg/dl for the primary endpoint described above, mean treatment differences of approximately 5.0 µg/dl or more were to be detectable with a power of 90%.

d) Changes in the Planned Analyses/Conduct

Urine samples were collected for determination of free cortisol content, but due to an excessive percentage of unevaluable data points, the data was not analyzed.

3. Study Design/Procedures

64 subjects were empanelled and confined to the study center for the duration of this 29-day study. Subjects assigned to groups: 16 received MF 400 µg BID (2 inhalations of 200 µg/inhalation), 16 received MF 800 µg BID (2 inhalations of 400 µg/inhalation), 16 received prednisone 10 mg QD (positive control) and 16 received 0 µg (placebo lactose DPI) BID. Cosyntropin stimulation test (30 minute) was administered on Day 29 (post-dose) to determine HPA axis function. Twenty-four hour plasma and urine cortisol collected on Days 7, 14, 21 and 28. Plasma concentrations of SCH 32088 were determined using a validated LC/MS/MS assay with a lower limit of quantitation of 50 pg/ml. Pharmacokinetic analyses were determined from blood samples collected prior to dosing and at specified times during the 12-hour period following dosing on Study Days 7, 14, 21 and 28. This was an investigator-blind study. *(Please note that while this study investigated pharmacokinetics, this review will highlight the pharmacodynamics and safety issues. The Biopharmacology reviewer will review the pharmacokinetics section.)*

	Screen	Day -3	Day -2	Day -1	D 1	D 6	D7	D 13	D 14	D 20	D 21	D 27	D 28	D 29	D 30 F/U
Medical History	X														
Physical Exam.	X														X
PFTs (FVC, FEV_1, FEF_{25-75}, PEFR)	X		X	X	X		X		X		X		X		
Reversiblity Test	X														
Laboratory Tests	X			X											X
Urine continine, HbsAg, HCV and HIV	X														
Serum Pregnancy	X			X											X
Electrocardiogram	X														X
Subjects Confined		X----------X													
Vital Signs	X			X	X----------X									X	X
Samples for Plasma SCH 32088 content and/or serum cortisol concentrations			X	X X		X	X X	X	X X	X	X X	X	X X		
Serum Cortisol (am)	X		X	X			X		X		X		X		X
Cosyntropin Stim. Test	X													X	

Treatment Administration					X----------X										
Urine Samples (24-hr)			X---------X			X-------X		X-------X		X-------X		X-------X			
Serum Creatinine				X			X		X		X		X		
Body Weight	X			X	X		X		X		X		X		
Subjects Discharged															X

- Blood Samples for Serum Cortisol Determination:

At screening and on Day 29 at two hours after the last treatment, blood is collected prior to and 30 minutes after cosyntropin stimulation (250 µg IM). For safety assessments, morning blood samples were to be collected on Days -2 and -1 to establish a Baseline serum cortisol value and on Day 30 for assessment at follow-up.

To determine serum cortisol area under the concentration-time curve from a 24-hour periods on Study Days -2, 7, 14, 21 and 28, blood samples were collected at 11 p.m. on Days -2, 6, 13 and 27 and at 4 a.m., 5 a.m., 6 a.m., 7 a.m., 8 a.m., 9 a.m., 10 a.m., 12 noon, 4 p.m., 8 p.m., and 11 p.m. on Days -1, 7, 14, 21 and 28.

- Urine Samples for Determination of Urine Free Cortisol:

Urine was e collected from 11 p.m. on Day -2 until 11 p.m. on Day -1 (Baseline) and similarly on Days 6-7, 13-14, 20-21, and 27-28 as 24-hour block samples for the determination of urine free cortisol concentrations and total creatinine.

- Cosyntropin Stimulation Test:

At least 14 days prior to the initial dose and approximately two hours after the last morning dose on Day 29, a 30-minute intramuscular cosyntropin stimulation test was to be performed. Immediately following the collection of a blood sample for serum cortisol content, cosyntropin 0.25 mg was injected IM. A second blood sample for serum cortisol determination was collected 30 minutes after the cosyntropin injection.

4. Study Population

A total of 64 male or female subjects with mild to moderate asthma (FEV_1 60-80% predicted) and who required asthma medication ranging in age from 18 to 50 years were to be enrolled into this single-site study.

a) Inclusion Criteria

Notable among the inclusion criteria were:

- 15% improvement of FEV_1 from Baseline after 2 x 90 µg inhalations of albuterol by MDI.
- Between 7 a.m. and 10 a.m., subject was to have a basal serum cortisol between 10 µg/dl and 25 µg/dl at screening.

- Not less than 14 days prior to initiation of study treatment, subject was to have an appropriate response to a 30-minute cosyntropin stimulation test. An appropriate response was defined as an increase in serum cortisol to at least 18 µg/dl, and the post-cosyntropin serum plasma cortisol having an increment of at least 7 µg/dl above the pre-cosyntropin value.
- The enrollment of steroid-naive subjects was preferred. However, patients using inhaled corticosteroids at screening were to be considered; but those using greater than the maximum-labeled doses of an inhaled corticosteroid were to be excluded from entry. (The concomitant therapy of the subjects was reviewed and it did not appear that any of the subjects were on inhaled corticosteroids at Baseline so it appears that these were truly steroid-naïve subjects.)

b) Exclusion Criteria

Notable among the exclusion criteria were:

- Smokers
- No prescription or over-the-counter drugs (except for asthma therapy) for at least two weeks prior to the study nor alcohol within 72 hours prior to drug administration.
- Oral corticosteroids within 6 months, or intramuscular corticosteroids within 1 year, or inhaled corticosteroids at doses greater than the maximum labeled dose.

5. Results

a) Demographics

There were 46 males and 18 females with a mean age of 36.2 years and a mean weight of 178.5 lbs. 59% of the subjects were black.

	Age (years)			Weight (lb.)			Height (in)		
Treatment	N	Mean	Standard Deviation	N	Mean	Standard Deviation	N	Mean	Standard Deviation
A: MF/L DPI 400 µg BID	16	35.3	7.2	16	176.6	30.1	16	69.9	2.7
B: MF/L DPI 800 µg BID	16	35.8	7.9	16	180.9	18.6	16	69.4	3.3
C: Prednisone 10 mg QD	16	36.7	7.7	16	178.4	25.1	16	68.4	4.5
D: Placebo Lactose DPI 0 µg BID	16	37.1	5.2	16	178.2	22.3	16	68.9	3.3

b) Pharmacokinetics

The Biopharmacology reviewer will review the PK data in greater detail. PK data was available from all 32 patients who enrolled and completed MF treatments.

Mean (%CV) PK Parameters

Dose (µg, BID)	Day	Cmax (pg/ml)		Tmax (hr)		AUC(tf) (pg·hr/ml)		AUC(0-12 hr) (pg·hr/ml)		tf (hr)	
400	7	87.8	(64)	1.08	(32)	308	(100)	375	(89)	5.77	(63)
	14	106	(63)	1.69	(31)	473	(95)	559	(87)	6.54	(38)
	21	93.5	(55)	2.46	(83)	364	(81)	523	(65)	6.43	(42)
	28	114	(52)	2.10	(84)	464	(93)	634	(66)	6.67	(50)
800	7	149	(69)	1.19	(27)	741	(70)	819	(64)	9.54	(32)
	14	186	(49)	1.57	(55)	977	(52)	1041	(47)	9.07	(30)
	21	195	(50)	1.73	(77)	1024	(64)	1073	(60)	8.83	(41)
	28	194	(56)	1.64	(66)	1029	(57)	1088	(53)	10.0	(21)

The sponsor says that due to sporadic data it was not possible to determine the terminal phase half-life of SCH 32088. Due to the low concentrations and/or non-quantifiable levels, mean SCH 32088 concentrations at the 400-mcg dose were associated with high variability. At the 800-mcg dose, SCH 32088 concentrations were higher than those observed at the 400-mcg dose, and the mean Cmax did not exceed 195 pg/ml. The variability in mean concentrations in the 800-mcg group, although still large, was somewhat lower than that at the 400-mcg dose. The sponsor reports that the dose adjusted Cmax and AUC values at the 800 mcg and 400 mcg doses were not statistically significantly different. Due to low concentrations and large variability the power to detect a 20% difference between means was low (<20%).

c) Systemic Exposure of SCH 32088 as Assessed by Cortisol Concentration

There was an imbalance between the groups at Baseline in the mean cortisol AUC. The sponsor performed an analysis of covariance with the Baseline as a covariate to determine the effect of this baseline imbalance. The sponsor says that for the AUC, "the contrasts from the ANCOVA support the contrasts of the actual AUC in the ANOVA." The sponsor says that it is reasonable that inferences were based in this study on the analysis of the actual mean cortisol values rather than the mean change from Baseline cortisol values. The sponsor says this was done because the correlation between the Day 29 AUC values and the Baseline AUC values was not substantial. (Reviewer's note – this explanation was not entirely clear to this reviewer. It seems that they tried both an ANCOVA and an ANOVA and did not find much difference between the results.)

Overall, there was a treatment-related decrease in the mean AUC with apparent dose ordering.

Mean Serum Cortisol $AUC_{(0-24)}$ (µg·hr/dl)

Treatment Group	Day	Baseline	7	14	21	28
Placebo lactose BID	AUC	255.5	243.2	202.8	213.4	206.4
	--	--	--	--	--	--
MF 400 µg BID	AUC	242.9	181.9	165.3	173.6	185.3
	%chg[a]	-5	-25[b]	-19[c]	-19[c]	-10
MF 800 µg BID	AUC	210.9	146.7	149.6	160.4	163.0
	%chg[a]	-18[c]	-40[b]	-26[b]	-25[b]	-21[c]
Prednisone 10 mg QD	AUC	215.6	68.5	71.2	68.2	74.3
	%chg[a]	-16	-72[b]	-65[b]	-68[b]	-64[b]

a: % change from placebo at that timepoint.

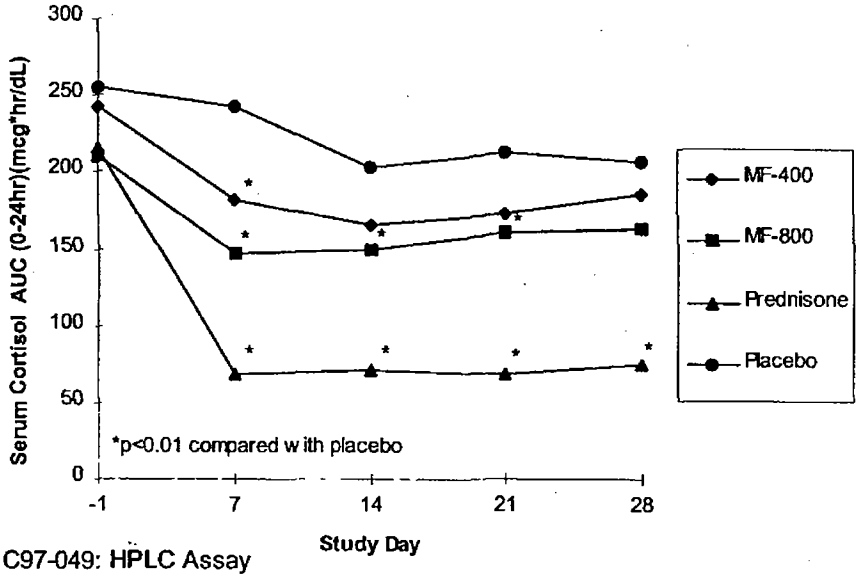
b: p<0.01 with placebo.

c: p<0.05 with placebo.

It should be noted that the above changes reflect the difference from placebo at that particular timepoint. It would be worthwhile to get an analysis comparing the change from Baseline for each particular treatment arm with the change from Baseline for placebo. Such an analysis will be requested from the sponsor. Note that all active treatments were significantly different from placebo during the course of the trial. The Baseline AUC for MF DPI 800 BID was significantly different from placebo at Baseline but clearly decreased with treatment. It is interesting to note that the AUC for placebo decreased considerably over the course of the trial for unclear reasons. The fact that such a decrease occurs makes the difference between the

active product and placebo appear smaller than if the comparison were made with the baseline measurement.

By looking at the graph below, however, it can be seen that, at least for prednisone and MF DPI 400 BID, that the distance between these respective curves and that of placebo increases with treatment. Notably at the 21 and 28 day timepoints, the AUC for the MF DPI 400 BID dose seems to drift up towards the curve for placebo so that by the 28 day timepoint, there is only a 10% difference from placebo. This difference of 10% is mentioned specifically in the sponsor's proposed labeling while for earlier timepoints the difference was 19-25%.



C97-049: HPLC Assay

For MF 400 mcg BID, cortisol AUC values were reduced from placebo values by 25%, 18%, 19% and 10% on Study Days 7, 14, 21 and 28, respectively. The differences were statistically significant on Day 7 ($p<0.01$), Day 14 ($p<0.05$) and Day 21 ($p<0.05$), but not on Day 28. For MF 800 mcg BID, cortisol AUC values were significantly ($p<0.05$) reduced from placebo values by 40%, 26%, 25% and 21% on study Days 7, 14, 21 and 28, respectively, but it must be remembered that there was a significant difference at Baseline. The prednisone group had markedly reduced ($p<0.01$) cortisol AUC values both from placebo by 72%, 65%, 68% and 64% on study Days 7, 14, 21 and 28, respectively, and from the MF 400 mcg and 800 mcg BID treatment groups.

Despite the Baseline differences between placebo and MF DPI 800 mcg BID, because the 400 mcg dose differed for most timepoints from placebo and because 800 mcg is a greater dose than 400 mcg, it is reasonable to assume that 800 mcg would decrease the AUC in a significant manner. It is certainly not possible to discern an important difference between the 400 and 800-mcg dose response.

d) Cosyntropin Stimulation Test

The post-cosyntropin stimulation mean serum cortisol concentration for the MF DPI 800-BID group (20.8 µg/dl) was significantly ($p=0.019$) reduced from the placebo group value (25.0 mcg/dl), while the MF 400 mcg BID group post-stimulation value (23.2 µg/dl) was not significantly different from placebo. The prednisone group had significantly ($p<0.01$) lower

mean serum cortisol concentrations than all other groups before (4.9 mcg/dl) and 30 minutes after (14.5 µg/dl) intramuscular stimulation with cosyntropin 250 mcg. The sponsor did not supply this information in a summary table and the data was only apparently available as line listings making it difficult for this reviewer to draw any conclusions, i.e., by comparing means, difference between post-cosyntropin at screening versus baseline, etc.

An analysis of the comparison between the post-cosyntropin values at Baseline compared and the post-cosyntropin value at Day 29 would be worthwhile and should be requested from the sponsor as well as the data in tabulated form. The sponsor will also be asked to supply information/tabulated data on subjects whose prestimulation concentration of plasma cortisol was <5 µg/dl, whose poststimulation concentration was <18 µg/dl, or whose response to stimulation was not an increase of at least 7 µg/dl.

e) Urinary Cortisol Excretion

Urine free cortisol data were collected but due to an excessive percentage of unevaluable data points (>50% of the data), the data were not analyzed by the sponsor.

6. Safety

a) Adverse Events

34% (11/32) of the patients receiving MF, 13% (2/16) receiving prednisone and 38% (6/16) receiving placebo reported at least one adverse event. The most frequently reported adverse events were headache (10/64 [16%]) and dry throat (11/64 [17%]).

	MF400 µg BID (n=16)	MF 800 µg BID (n=16)	Pred. 10 mg QD (n=16)	Placebo (n=16)
No. of Subjects (%) with AEs	3 (19)	8 (50)	2 (13)	6 (38)
Body as a Whole - General Disorders	1 (6)	3 (19)	1 (6)	5 (31)
Headache	1 (6)	3 (19)	1 (6)	5 (31)
Gastrointestinal System Disorders	**1 (6)**	**1 (6)**	**0 (0)**	**2 (13)**
Abdominal Pain	0 (0)	0 (0)	0 (0)	1 (6)
Diarrhea	1 (6)	0 (0)	0 (0)	0 (0)
Nausea	0 (0)	1 (6)	0 (0)	1 (6)
Respiratory System Disorders	**1 (6)**	**5 (31)**	**2 (13)**	**4 (25)**
Pharyngitis	0 (0)	1 (6)	0 (0)	0 (0)
Throat Dry	1 (6)	4 (25)	2 (13)	4 (25)

From the above list, no AE was seen in any MF DPI group greater than placebo. There were no apparent serious adverse events reported.

b) Spirometry /Physical Exam/ECGs/ Vital Signs

Spirometry was performed several times during the study but the data was only supplied as line listings and was not tabulated. This spirometry data was not reviewed and no conclusions on spirometry are made in this review. Of the abnormalities noted during the screening physical examination including several instances of wheezing, no changes or any new abnormalities were noted at follow-up. The line listings for EKG data were reviewed. There did not appear to be any overt or significant increases in the QTc between screening and follow-up. There was the new finding of an ectopic atrial rhythm and an unusual P axis in Subject #22 (MF DPI 400 BID) at follow-up that was felt to be not clinically significant by the

investigator. There was also the new finding of a sinus bradycardia (HR 56) and an apparently new left ventricular hypertrophy in Subject #62 (MF DPI 400 BID) that was felt to be not clinically significant by the investigator. (Reviewer's note - It is unlikely that this hypertrophy was really new, much less attributable to drug.)

The data on vital signs was also available only as line listings (Volume 73). These line listings for the two MF DPI groups were reviewed and no trends of change or abnormal vital signs with the exception of a number of instances of respiratory rate of 26. Subject #61 had a diastolic blood pressure up to 90-mm Hg on two days during the study but it otherwise started and remained in the 80s.

c) Laboratory Values

The abnormal laboratory values were reviewed. Subject#63 (MF DPI 800 BID) had a hematocrit of 44.5 on Screening, 42.2 at Pre-Treatment, and 31.9 at follow-up. An explanation for this was not available nor did the sponsor in the study report mention the abnormality.

7. Summary of C97-049

Relative to the other studies reviewed thus far, this trial was small and was phase I. The pharmacokinetic data was reviewed only briefly. Plasma concentrations of MF were detectable with both the 400 mcg BID and 800 mcg BID treatments. High variability in the concentrations of SCH 32088 was noted with the 400 mcg dose and somewhat less in the 800 mcg dose. Because of the low concentration and high variability, the power to detect between means was <20%. Numerically, however, the 800 mcg dose clearly had a higher Cmax and AUC.

The primary endpoint of the study as stated in the protocol was the change in serum cortisol between the pre- and 30 minute post-samples obtained from the Day 29 cosyntropin stimulation test. The sponsor briefly described the results of the study in the study report only. Despite the fact that this was the primary endpoint, data was not supplied in a summary table and only line listings were available so a fuller critique by this reviewer was not realistically possible. The sponsor says that the prednisone group (mean 14.5 mcg/dl) had significantly ($p<0.01$) lower mean serum cortisol concentrations than all other groups before and after cosyntropin stimulation. The 800 mcg BID group (mean 20.8 mcg/dl) had a post-cosyntropin mean serum cortisol value significantly ($p<0.05$) less than placebo, while the 400 mcg BID group value (mean 23.2 mcg/dl) was not significantly different from placebo (mean 25 mcg/dl).

There appeared to be a dose dependent decrease in the cortisol AUC over the 29 days. Across the treatment period, serum cortisol $AUC_{(0-24)}$ values were lower for the MF 800 mcg BID group than for the MF 400 mcg BID group. These differences, however, were not found to be statistically significant. The serum cortisol $AUC_{(0-24)}$ values, however, for both the 400 mcg BID group and the 800 mcg BID group were significantly ($p<0.01$) higher than those observed in the prednisone 10 mg treatment group. It is important to note that there were baseline differences in the treatment groups so adjustment in the analysis was made by use of baseline AUC as a covariate in an ANCOVA.

The adverse events seen in this trial were no more common among the MF DPI groups then they were among the placebo group with the possible exception of pharyngitis where one

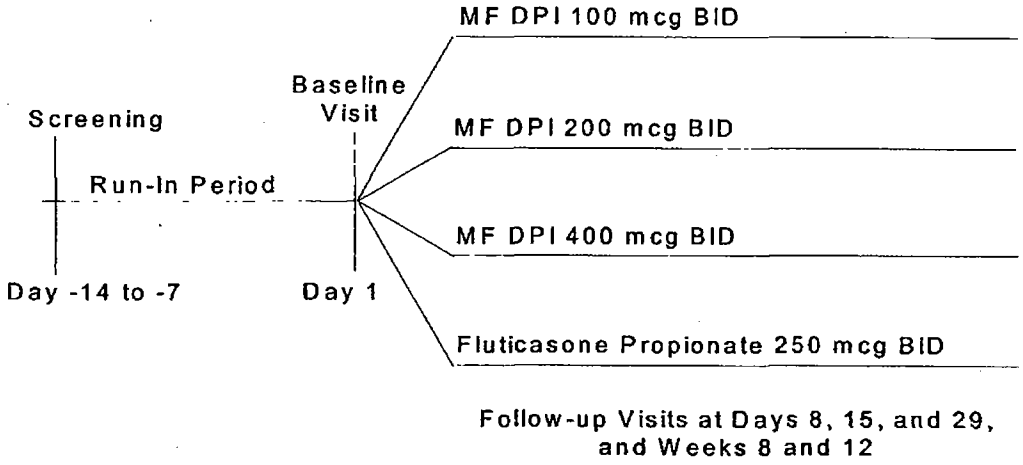
case was noted in the MF DPI 800 BID group and none were noted with placebo. In a review of the laboratory data, one subject in the MF DPI 800 BID treatment group had a hematocrit of 44.5 on Screening and 31.9 at follow-up with no explanation provided. Another subject had left ventricular hypertrophy first noted on the follow-up ECG.

L. I96-111 (Vol. 185-225)

"Efficacy and Safety of Mometasone Furoate (SCH 32088) Dry Powder and Fluticasone Propionate Powder in the Treatment of Asthma"

1. Objectives

The objectives of this randomized, active-controlled, parallel group, international, 60 center study; double-blind (with respect to MF DPI treatment) study were to determine the efficacy and tolerance of twice-daily dosing of MF DPI, at 100, 200, and 400 mcg BID, in subjects with moderate asthma (previously maintained in inhaled corticosteroids, FEV_1 60-90%) and to compare the efficacy and tolerance of these three doses of MF-DPI to that of fluticasone propionate 250 mcg BID over 12 weeks. The sponsor clearly states that it was not the objective of the study to show differences or equivalence between fluticasone propionate and MF DPI.



Inclusion and exclusion criteria were similar to those trials previously reviewed. The list of permitted and prohibited medications was also similar. Subjects had to have been off an oral burst of steroids for one month prior to screening.

The fluticasone propionate (FP) group was not blinded because Diskhaler® placebo devices could not be obtained.

The primary efficacy endpoint was change from Baseline in FEV_1 at Endpoint. The primary comparison was MF DPI 400 mcg BID vs. MF DPI 100 mcg BID. The secondary efficacy variables and safety variables were similar to other trials in this NDA.

The primary efficacy analysis for evaluating the efficacy of MF DPI was to be based on the pairwise comparison of the least squares means of the MF DPI 400 mcg BID and MF DPI 100 mcg BID groups from the ANOVA model using a 5% significance level. Because all pairwise comparisons addressed independent questions, and the comparison between MF DPI

400 BID and MF DPI 100 BID was identified in the protocol as the primary efficacy analysis, if the test for no difference between MF DPI 400 and MF DPI 100 BID was significant, then comparisons of each dose of MF DPI to fluticasone would be made.

2. Efficacy Results

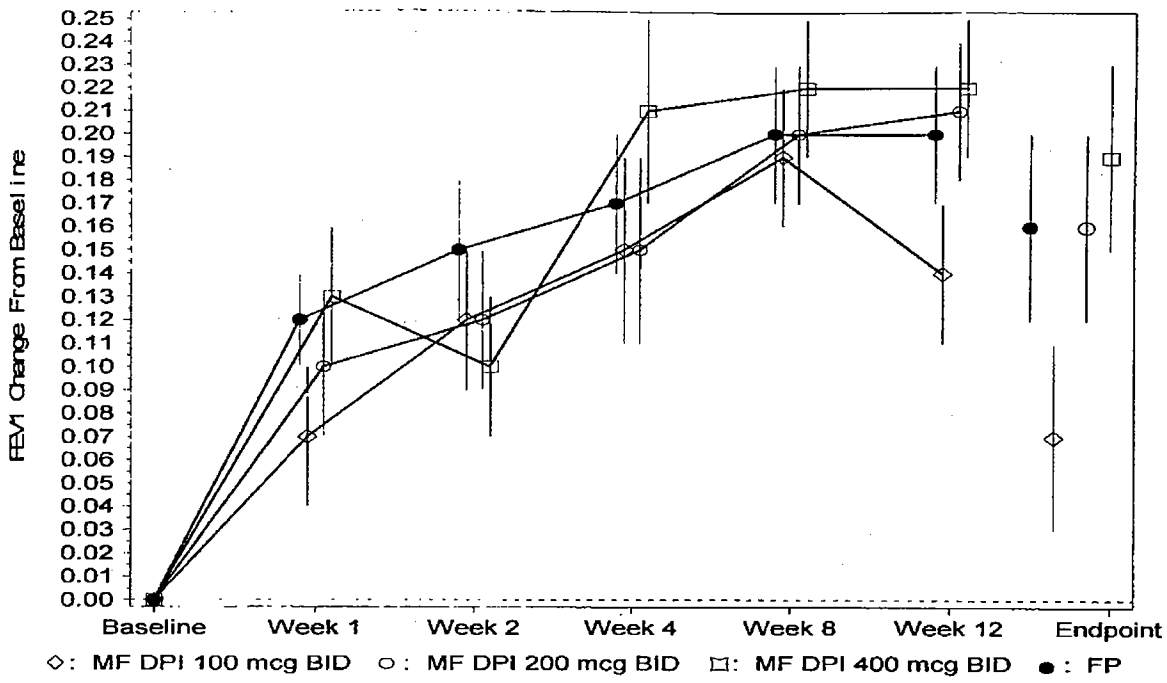
The numbers of subjects treated in the four groups were as follows: MF DPI 100 mcg BID, 182 subjects; MF DPI 200 mcg BID, 182 subjects; MF DPI 400 mcg BID, 184 subjects; and fluticasone propionate, 184 subjects.

The subjects were balanced well at baseline among the treatment groups for age, sex, use of inhaled corticosteroids, FEV_1, and salbutamol use. There was some difference in the baseline AM PEFR (range of means – 362.53 – 382.49).

The increase in FEV_1 from Baseline to Endpoint was significantly greater at Endpoint in the MF DPI 400 mcg BID group than in the MF DPI 100 mcg BID group. There were no significant differences between the MF DPI 200 mcg BID, MF DPI 400 mcg BID, and fluticasone (FP) groups in change in FEV_1 between Baseline and Endpoint. There was no significant difference and hardly any appreciable numerical difference (before Week 12) between MF DPI 100 mcg BID and MF DPI 200 mcg BID or fluticasone propionate in change in FEV_1 between Baseline and Endpoint. By Week 4, there were numerical differences between MF DPI 400 mcg BID and the other treatments. At Week 12, the MF DPI 100 BID dose appeared to separate from the other doses.

FEV_1 (liters) - Change from Baseline

	MF DPI 100 mcg BID			MF DPI 200 mcg BID			MF DPI 400 mcg BID			FP		
	N	Mean	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Baseline	179	2.53		182	2.43		181	2.38		183	2.46	
Change From Baseline												
Week 1	175	0.07	(3.2%)	176	0.10	(5.1%)	177	0.13	(6.1%)	178	0.12	(5.8%)
Week 2	168	0.12	(5.9%)	176	0.12	(6.2%)	175	0.10	(5.8%)	179	0.15	(7.8%)
Week 4	164	0.15	(6.5%)	171	0.15	(6.9%)	169	0.21	(8.9%)	177	0.17	(8.4%)
Week 8	155	0.19	(7.2%)	160	0.20	(8.8%)	161	0.22	(9.8%)	161	0.20	(9.2%)
Week 12	144	0.14	(6.0%)	147	0.21	(8.7%)	155	0.22	(10.3%)	153	0.20	(9.3%)
Endpoint	179	0.07	(3.9%)	182	0.16	(7.5%)	181	0.19	(8.8%)	183	0.16	(8.0%)

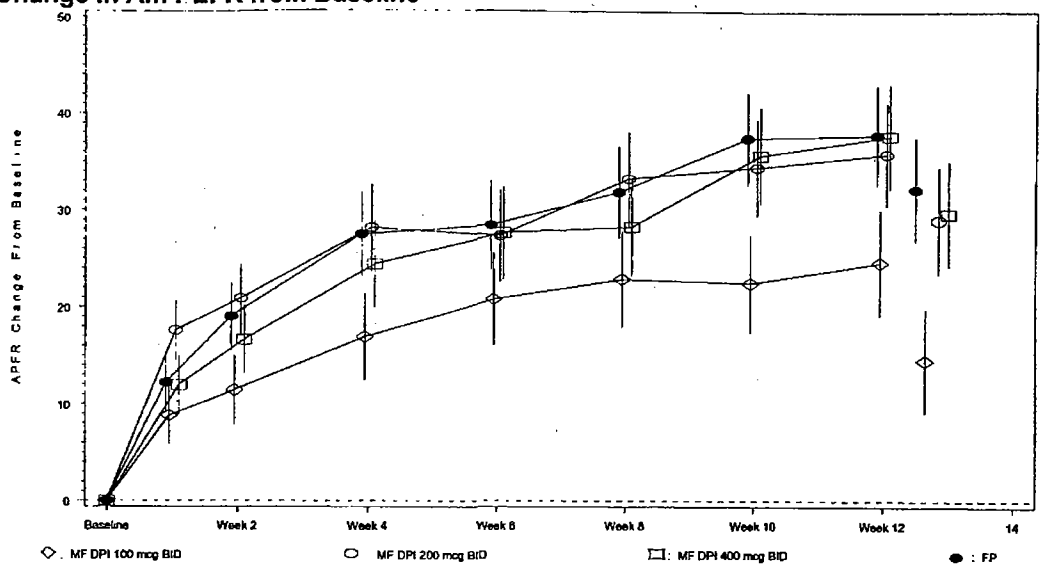


Response was again evaluated in subjects whose Baseline FEV_1 was <75% of predicted versus those whose Baseline FEV_1 was ≥75% of predicted. All active treatments except MF DPI 200 BID had a greater % effect in those Baseline FEV_1 was <75% of predicted.

For FVC, the % increases from Baseline at Endpoint were 3.3%, 4.5%, 5.6%, and 4.8% for the MF DPI 100 mcg BID, MF DPI 200 mcg BID, MF DPI 400 mcg BID, and fluticasone propionate groups, respectively. There were no statistical differences between the groups in FVC. For FEF_{25-75}, the MF DPI 200 BID and MF DPI 400 BID groups were statistically superior to the MF DPI 100 BID group at Endpoint and numerically superior to the fluticasone group. The percentage increases from Baseline at Endpoint were 6.4%, 15.6%, 22.9%, and 22.0% for the MF DPI 100 BID, MF DPI 200 BID, MF DPI 400 BID, and fluticasone groups, respectively.

At Endpoint, the mean increase in AM PEFR was significantly greater in the MF DPI 400 BID (p=0.03; 10.1%), MF DPI 200 BID (p=0.04, 9.5%), and fluticasone (p=0.01, 11.3%) groups than in the MF DPI 100 BID (5.1%) group. At Endpoint, the mean increase in PM PEFR was significantly greater in the MF DPI 400 BID (9.2%), MF DPI 200 BID (7.8%), and fluticasone (10.1%) groups than in the MF DPI 100 BID (3.2%) group.

Change in Am PEFR from Baseline



AM wheezing scores decreased from Baseline to Endpoint in all treatment groups. While there were no statistically significant differences between groups, mean decreases in the MF DPI 400 BID (-0.11) and fluticasone propionate (-0.13) groups were numerically greater than the MF DPI 200 BID (-0.04) or MF DPI 100 BID (-0.01) group. Aside from the Endpoint, the scores for MF DPI 200 BID were roughly equivalent to the scores of FP and slightly less than for MF DPI 400 BID. PM wheezing scores decreased from Baseline to Endpoint to a greater extent in the MF DPI 400 BID (-0.09) and FP (-0.12) groups than in the MF DPI 200 BID (-0.05) group, with no statistically significant differences being noted for these groups at this time point. Mean PM wheezing in the MF DPI 100 BID group rose slightly (0.01) at Endpoint, and was significantly different (p=0.03) from FP at this time point. In general, however, the scores for PM Wheezing were equivalent at other timepoints for MF DPI 200 and 400 BID and FP.

AM and PM scores for difficulty breathing (DB) decreased from Baseline to Endpoint in all treatment groups, with statistically significant ($p \leq 0.04$) differences being noted between the FP (AM, -0.20; PM, -0.22) group and the MF DPI 100 BID (AM, -0.02; PM, -0.03) and MF DPI 200 BID (AM, -0.05; PM, -0.03) groups. Mean decreases in the MF DPI 400 BID (AM, -0.11; PM -0.14) group were numerically, but not significantly greater than those of the MF DPI 200 BID and MF DPI 100 BID groups. For other timepoints in AM and PM DB, FP and MF DPI 400 BID were numerically better than the other doses.

For AM and PM Cough at Endpoint, there were no significant differences at Baseline but FP and MF DPI 400 BID were numerically greater than the other doses.

At all visits, physician's response to therapy was again assessed.

Physician's Evaluation of Response to Therapy at Endpoint

Rating	MF DPI 100 mcg BID (n=179)	MF DPI 200 mcg BID (n=182)	MF DPI 400 mcg BID (n=181)	FP 250 mcg BID (n=183)
Much Improved	31 (17.2)	48 (26.4)	41 (22.7)	37 (20.2)
Improved	65 (36.1)	61 (33.5)	67 (37.0)	76 (41.5)
No Change	56 (31.1)	55 (30.2)	56 (30.9)	54 (29.5)
Worse	18 (10.0)	9 (5.0)	12 (6.6)	8 (4.4)
Much Worse	10 (5.6)	9 (5.0)	5 (2.8)	8 (4.4)

The percentage of subjects evaluated as much improved or improved was similar in the MF DPI 200 BID (60%), MF DPI 400 BID (60%), and FP (62%) groups, and slightly less in the MF DPI 100 BID (53%) group. Mean scores were significantly ($p<0.03$) lower (indicating a better response) in the MF DPI 200 BID (2.29), MF DPI 400 BID (2.33), and FP (2.33) groups, than in the MF DPI 100 BID (2.54) group.

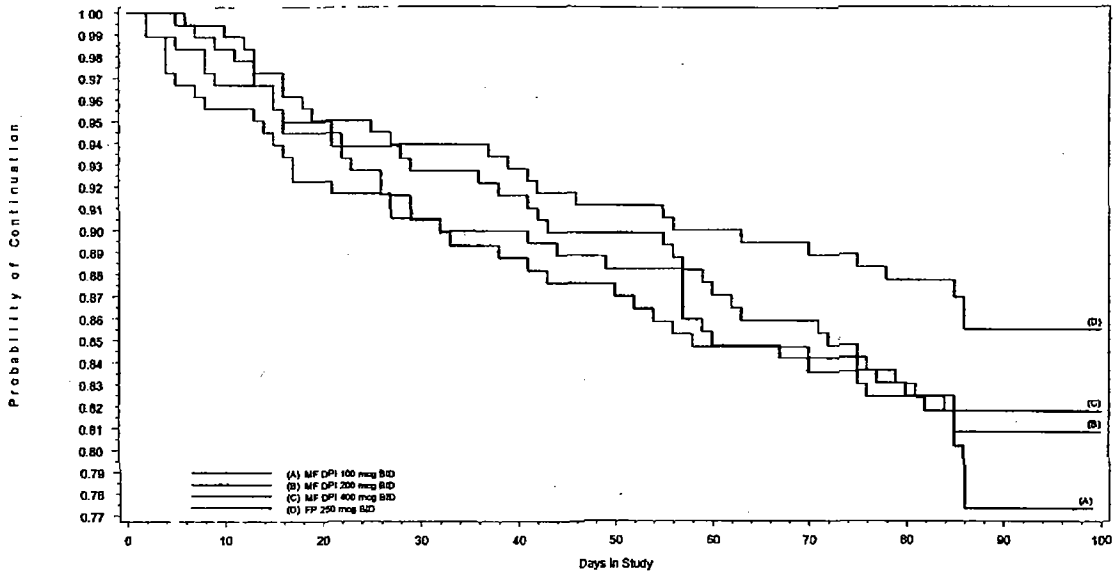
Due to differences in local labeling and in per inhalation mcg strength, the daily mcg use of salbutamol was used in analysis.

	MF DPI 100 BID		MF DPI 200 BID		MF DPI 400 BID		FP	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	170	333.07	173	355.57	167	303.17	174	278.07
Change From Baseline								
Week 1	170	-69.91	169	-94.93	163	-75.63	170	-53.08
Week 2	163	-69.26	163	-89.81	165	-55.30	166	-33.41
Week 4	155	-90.42	158	-118.94	156	-81.80	160	-75.65
Week 6	149	-93.34	160	-121.21	149	-93.85	153	-63.14
Week 8	147	-92.58	156	-137.63	149	-92.73	154	-62.18
Week 10	142	-80.22	152	-143.51	145	-109.48	145	-62.60
Week 12	135	-51.71	150	-149.10	138	-109.61	144	-73.85
Endpoint	170	-13.23	173	-94.84	167	-38.10	174	-52.06

There appear to be differences in use at Baseline but the sponsor says the differences are not significant. While the baseline mean for MF DPI 200 BID was the highest, it also had the greatest numerical decrease in the absolute mean. Statistically significant differences in salbutamol use were noted at Endpoint only between MF DPI 100 BID (-13.23 mcg/day) and MF DPI 200 BID (-94.84 mcg/day). It is not clear the whether the baseline differences were a covariate in this analysis. If one simply looks at the means among the groups at the Endpoint, they would be: MF DPI 100 BID (319.84). 200 (260.73), 400 (265.07) and FP (226.01). Thus, while the FP group ended up with the smallest mean, it also started with the lowest mean. The sponsor will be asked to clarify whether baseline use was used as a covariate: if it was not, such an analysis will be petitioned.

In the number of nocturnal awakenings, decreases were observed at Endpoint for the MF DPI 400 BID (-0.06) and fluticasone propionate (-0.14) groups. At other timepoints, MF DPI 400 BID tended to have a greater numerical decrease. At Endpoint, MF DPI 100 BID and 200 BID actually had an increase of 0.07/night and 0.01/night, respectively.

With Time to Worsening of Asthma, log-rank tests did not show a significant difference among the treatment groups.



The curves generally appear equivalent for the MF DPI groups. FP tended to separate itself from MF DPI for much of the trial in this variable, although the difference was not apparently significant. More detail of this can be noted in the table below.

Reason for First Worsening:	MF DPI 100 mcg BID	MF DPI 200 mcg BID	MF DPI 400 mcg BID	FP 250 mcg BID
Decrease in FEV_1	9	6	6	5
Decreases in PEFR	13	14	16	12
Clinical Asthma Exacerbation (CAE)	6	10	7	6
Overuse of Salbutamol	2	2	2	1
Decrease in FEV_1 and PEFR, and CAE	1	0	0	0
Decrease in PEFR and CAE	1	1	1	0
Other	4	0	0	0
Total Subjects Experiencing Worsening	36	33	32	24

The sponsor then goes on to present in Section 11.4.1.7 that CAEs were reported at some time during the study by 13 subjects in the MF DPI 100 BID group, 11 subjects in the MF DPI 200 BID group, 9 subjects in the MF DPI 400 BID group, and 9 subjects in the FP group. In Section 16.2.4, the sponsor says that this CAE list is a subset of the subjects who met criteria for Worsening of Asthma, however, it is not clear why these numbers do not match the numbers in the Time to Worsening table above. The sponsor will be asked to clarify these differences.

3. Efficacy Conclusions

Because there was no placebo utilized in this trial, differences were analyzed between active treatment groups, one of which was unblinded. Based on significant changes in FEV_1 between Baseline and Endpoint which was the primary efficacy variable in this study, the MF DPI 400 BID dose was more effective than MF DPI 100 BID for improving FEV_1 in subjects with moderate asthma who were previously maintained on inhaled corticosteroids. At other time

points aside from Week 12, the changes in FEV_1 were generally equivalent. While there was some increase in FVC, there were no important differences in treatment groups in the FVC response. For FEF_{25-75}, PEFR, and physician response to therapy, all treatments were better than MF DPI 100 BID at Endpoint. For Wheezing and Difficulty Breathing Scores as well as nocturnal awakenings, there were improvements during the treatment period and MF DPI 400 BID and FP tended to do better than the other treatments. Baseline numerical differences confused the understanding of the salbutamol use for this reviewer. No significant differences were noted in the Time to Worsening of Asthma, but FP appeared to do numerically the best.

Thus, I96-111 did appear to show some differences between MF DPI 100 BID, 200 BID and 400 BID in some variables, but for the primary response variable of FEV_1, the 200 BID and 400 BID doses appeared to be fairly comparable.

4. Safety I96-111

a) Adverse Events

It must be remembered during the scrutiny of these adverse events that these subjects had been on inhaled corticosteroids (ICS) before study entry Similar to C96-168,186, and 196). They therefore may represent a pre-selected population of subjects who, because they have already been exposed to ICS previously, may not have all the side effects that someone not previously exposed to ICS would have. Furthermore, if a subject had previously had a bad experience with an ICS product, they would be less apt to participate in such a trial.

Incidence of Adverse Events Reported by ≥10% of Subjects in Any Treatment Group

	MF DPI 100 mcg BID (n=182)	MF DPI 200 mcg BID (n=182)	MF DPI 400 mcg BID (n=184)	FP 250 mcg BID (n=184)
Headache	35 (19)	27 (15)	34 (18)	33 (18)
Infection, Viral	32 (18)	21 (12)	29 (16)	43 (23)
Rhinitis	20 (11)	15 (8)	17 (9)	15 (8)
Pharyngitis	30 (16)	23 (13)	22 (12)	28 (15)
Oral Candidiasis	2 (1)	12 (7)	18 (10)	18 (10)

Interestingly, viral infection appears to be more common with FP in this trial. There appears to be a clear dose response in oral candidiasis with MF DPI but the incidence of the 400 BID group is no higher than that of the FP group.

The following list has been edited to show those adverse events which were of note periodically in other trial for this NDA thus far reviewed, those which had an interesting dose response in the MF DPI group or those which were particularly different between the MF DPI and FP groups.

Incidence of Any Treatment-Emergent Adverse Events Reported by ≥2% of Subjects

	MF DPI 100 mcg BID (n=182)	MF DPI 200 mcg BID (n=182)	MF DPI 400 mcg BID (n=184)	FP 250 mcg BID (n=184)
Any Adverse Event	**116 (64)**	**109 (60)**	**121 (66)**	**121 (66)**
back pain	3 (2)	9 (5)	4 (2)	6 (3)
fatigue	4 (2)	4 (2)	6 (3)	1 (1)
influenza-like symptoms	1 (1)	4 (2)	5 (3)	2 (1)
pain	5 (3)	4 (2)	11 (6)	3 (2)

Incidence of Any Treatment-Emergent Adverse Events Reported by ≥2% of Subjects

	MF DPI 100 mcg BID (n=182)	MF DPI 200 mcg BID (n=182)	MF DPI 400 mcg BID (n=184)	FP 250 mcg BID (n=184)
hypertension	0 (0)	2 (1)	6 (3)	4 (2)
dysphonia	3 (2)	9 (5)	9 (5)	13 (7)
abdominal pain	9 (5)	6 (3)	4 (2)	8 (4)
dyspepsia	6 (3)	2 (1)	3 (2)	3 (2)
nausea	2 (1)	4 (2)	4 (2)	7 (4)
arthralgia	6 (3)	1 (1)	5 (3)	4 (2)
musculo-skeletal pain	4 (2)	8 (4)	5 (3)	5 (3)
myalgia	6 (3)	6 (3)	7 (4)	1 (1)
dysmenorrhea	3 (3)	5 (5)	4 (4)	8 (7)
coughing	7 (4)	8 (4)	15 (8)	12 (7)
nasal congestion	10 (5)	12 (7)	9 (5)	12 (7)
sinusitis	4 (2)	4 (2)	3 (2)	3 (2)

Back pain, abdominal pain, dyspepsia, arthralgia, musculo-skeletal pain, nasal congestion, and sinusitis (complaints seen in other trials) do not exhibit a dose response here nor do they appear any more common with MF DPI than with FP. Fatigue does not exhibit a dose response, but overall appears to be more common with MF DPI overall than with FP for unclear reasons. Influenza-like symptoms have some suggestion of a dose response and are more common with MF DPI. It is not clear, however, what is the difference in the terms viral infection and influenza-like symptoms: remember the former appeared to be more common with FP. Hypertension, although uncommon, appeared to have a dose response and the MF DPI 400 BID group had 6 subjects compared with 4 in the FP group, probably not an important difference. Coughing also had an MF DPI dose response but was no more common than that seen with FP. Dysphonia and dysmennorhea, commonly seen in other trials thus far, appear in this study to be perhaps more common with FP.

Of some note, One subject #015 in the MF DPI 200 BID group reported phlegm and a burning sensation of mild severity in trachea after dosing on Day 2 and discontinued the study for this adverse event.

Headache, abdominal pain, musculoskeletal pain, and viral infection were more common in females across all treatment groups. Other differences were not reviewed in depth for this trial.

b) Severe/Serious Adverse Events

Severe AEs were reported by 5% of the subjects. No subject had a life-threatening event. The severe AEs were scattered widely among the list of all AEs.

Nine subjects reported serious adverse events (see table below) within 3 months of randomization. Subject #611 (Site 37) experienced elevated liver enzymes between Screening and Baseline (ALT, 127 mcg/L; AST, 309 mcg/L) and she had not received study medication at the time of the event and was not enrolled into the study.

Center/Subject	Sex/ Age/Race	Adverse Event	Relationship	Status
Screening (Not Randomized)				

I96-111-37/611	F/56/C	Liver enzymes increased	Unlikely	Not randomized
MF DPI 100 mcg BID				
I96-111-35/003	F/38/C	Bronchospasm, coughing, dyspnea, fever, sinusitis, wheezing approx. 1 month after discontinuing the study for viral infection and sinusitis	Unlikely	Hospitalized; Discontinued treatment previously
I96-111-55/112	M/54/C	Abdominal pain, duodenal ulcer, hematemesis, rectal bleeding	Unlikely	Hospitalized; study drug interrupted but patient eventually completed the study
MF DPI 200 mcg BID				
I96-111-51/111	M/73/C	Colon carcinoma	Unlikely	Cancer; Hospitalized; Discontinued study
MF DPI 400 mcg BID				
I96-111-35/006	M/48/C	Angina pectoris	Unlikely	Hospitalized, completed the study
I96-111-46/050	F/73/C	Angina pectoris, chest pain, dyspnea, palpitation	Unlikely (had discontinued heart drugs)	Hospitalized; Discontinued study
FP 250 mcg BID				
I96-111-02/012	M/74/C	Paresthesia (thought due to small stroke)	Unlikely	Medically significant: Discontinued study for AE of pneumonia
I96-111-15/020	F/51/NC	Retinal detachment surgery	Unlikely	Hospitalized; procedure scheduled prior to subject's participation in the study
I96-111-44/038	F/22/C	Abdominal pain, fever, leukocytosis, nausea (undetermined etiology)	Unlikely	Hospitalized

It is not probable that any of the serious AEs during the study were attributable to drug.

c) Discontinuation Because of Adverse Events

There did not appear to be a pattern of occurrence with respect to treatment group, and no particular risk was associated with MF DPI treatment relative to FP.

List of Subjects Who Discontinued Treatment Because of Adverse Events

Center/Subject	Sex/ Age/Race	Day of Onset	Adverse Event(s)	Severity	Investigator's Relationship
MF DPI 100 mcg BID					
I96-111-05/012	F/18/C	26	Bronchitis	Moderate	Unrelated
I96-111-06/012	M/52/C	2	Asthma aggravated	Severe	Unrelated
I96-111-15/061	F/46/C	Unknown	Myalgia	Moderate	Possible
I96-111-25/145	F/62/C	18	Alopecia, Nervousness, Sweating increased	Moderate	Probable
			Nausea	Severe	Probable
I96-111-27/051	M/43/NC	3	Pharyngitis	Moderate	Unrelated
I96-111-35/003	F/38/C	66	Viral infection	Moderate	Unrelated
		66	Sinusitis	Severe	Unrelated

List of Subjects Who Discontinued Treatment Because of Adverse Events

Center/Subject	Sex/ Age/Race	Day of Onset	Adverse Event(s)	Severity	Investigator's Relationship
I96-111-36/008	F/41/C	75	Asthma aggravated	Moderate	Possible
I96-111-44/037	F/33/C	27	Tachycardia	Moderate	Unrelated
			Hyperthyroidism	Moderate	Unrelated
I96-111-47/114	M/41/NC	45	Glucose tolerance abnormal	Mild	Possible
			MF DPI 200 mcg BID		
I96-111-21/071	F/44/C	1	Dysphonia	Moderate	Related
I96-111-23/047	F/68/C	16	URI	Moderate	Possible
I96-111-35/002	F/35/C	43	Coughing, URI	Moderate	Unrelated
I96-111-37/015	F/72/C	2	Sputum increased	Mild	Possible
I96-111-51/111	M/73/C	83	Colon carcinoma	Severe	Unrelated
I96-111-62/018	F/68/C	1	Coughing, Dyspnea, Sputum Increased, Wheezing	Severe	Probable
		6	Hypertension	Moderate	Possible
			MF DPI 400 mcg BID		
I96-111-05/025	F/45/C	70	Bronchitis	Severe	Unrelated
			Fever	Moderate	Unrelated
I96-111-05/050	M/46/C	22	Hypertonia	Moderate	Unrelated
		22	Musculo-skeletal pain	Severe	Unrelated
		24	Dyspnea	Mild	Unrelated
I96-111-06/005	F/42/C	8	Hypertension	Mild	Possible
I96-111-09/005	M/31/NC	29	Coughing, Dyspnea, Sputum increased, and Wheezing	Moderate	Possible
I96-111-24/030	F/57/C	23	Infection aggravated	Moderate	Possible
I96-111-36/001	F/67/C	9	Dysphonia	Moderate	Possible
I96-111-42/018	F/50/C	70	Viral Infection	Moderate	Unrelated
I96-111-44/039	F/23/C	21	Pneumonia	Severe	Unrelated
I96-111-46/050	F/72/C	35	Angina pectoris	Severe	Unrelated
			FP 250 mcg BID		
I96-111-02/012	M/74/C	37	Pneumonia	Moderate	Unrelated
I96-111-02/014	M/65/C	5	Respiratory Disorder	Moderate	Unrelated
I96-111-23/041	F/18/C	50	Oral Candidiasis	Mild	Probable
I96-111-25/021	M/59/C	Unknown	Eye Abnormality	Not reported	Not reported
I96-111-26/013	F/18/5	20	Pharyngitis	Severe	Related
I96-111-36/025	M/58/C	11	Dysphonia	Moderate	Probable
I96-111-52/023	M/25/C	78	Viral Infection	Moderate	Unrelated
I96-111-64/170	F/44/C	53	Asthma Aggravated	Moderate	Unrelated

There are some notable cases within this list. Subject #51 (MF DPI 100 BID) discontinued because of moderate pharyngitis. Subject #114 (MF DPI 100 BID) discontinued because of abnormal glucose tolerance. Subject #71 (MF DPI 200 BID) , #1 (MF DPI 400 BID), and #25 (FP 250 mcg BID) discontinued because of dysphonia. Two subjects (#18 - MF DPI 200 BID; #5 - MF DPI 400 BID) discontinued because of hypertension thought possibly attributable to drug treatment. It must be noted that Subject #18 also had dyspnea and

increased sputum around this time. Drug induced hypertension, however, is probably unlikely in these two noted subjects because of the short duration of drug treatment.

d) Laboratory Values

No important changes in the median values of the laboratory values were noted between Baseline and Endpoint.

It must be noted in this trial unlike others so far reviewed that there were repeats of subject #'s.

The list of laboratory values that fell outside the normal range were reviewed.

Subject/Site	Treatment	Abnormality (Screening to Week 12)
08/2	MF DPI 100 BID	AST/ALT 32/76 to 52/115 (p. 5715)
13/5		ALT 19 to 60 (p. 5731), (nl. 6-34)
38/20		Uric Acid 314-626 (nl. 196-446) (p. 5835)
35/28		Tbili. 12 to 27 (nl. 3-21)(p.5891)
22/52		AST/ALT 36/59 to 58/124; nl. Bili, Alk. Phos. (p. 6059)
15/09	MF DPI 200 BID	Tbili 0.7 to 1.5 (nl. 0.1 –1.0 mg/dl); nl. Transaminases (p.6211)
51/18		ALT 26 to 43, nl. Bili. (p. 6275)
33/20		AST/ALT 31/27 to 50/45; Bili 9 to 14 (still within nl. range for bili).
37/24		ALT 25 to 72; nl. AST/Bili/Alk. Phos. (p. 6347)
31/31		AST/ALT 29/27 to 122/39 (Alk. Phos. was high at Screening and no value was available for Week 12) Tbili 12 to 21 (nl. 3 – 21) (p. 6371)
49/37		ALT 14 to 51; nl. Bili and AST (p. 6411)
47/45		AST/ALT19/15 to 42/75; nl. Bili and Alk. Phos. (p.6451)
21/52		ALT 28 to 47 (p. 6499)
160/64		Tbili 12 to 31 (nl. 3-21)(p. 6587) (AST 33 to 35, nl.9-34)
02/19	MF DPI 400 BID	ALT 22 to 53 (p. 6723)
12		Positive HCG (p.6836)
77/21	FP 250 BID	AST/ALT 38/74 to 83/125 : nl. Bili. and Alk. Phos (p.7171)
16/48		AST/ALT 18/24 to 24/46 (off drug 6 days) (p. 7363)

Interestingly, most of the laboratory abnormalities listed appear for MF DPI 200 BID; there is not a dose response present here. Subjects # 8, 22, and 77 had increases in transaminases but there were abnormalities at Baseline. The most impressive rises in the transaminases occurred in Subject # 31 (MF DPI 200 BID) where the AST rose from 29 to 122. A rise in uric acid was noted in one subject; this test has not been part of the protocols of the previous trials reviewed. Bilirubin increases were noted in Subject #35, 15, 31 (still within the normal range but was associated with an increase in the AST) and 160 in the MF DPI groups. No large increases in bilirubin were seen in the FP group.

Data was available on AM cortisol levels at Baseline and Endpoint. There were no important changes in the median value but it is difficult to agree with the sponsor's statement in

the study report that there was no evidence of clinically relevant HPA axis suppression because this reviewer believes that such suppression was not looked for with adequately sensitive means to make such a statement.

The vital signs by treatment group, by gender and by the Caucasian/Non-Caucasian designation were reviewed. There were no important differences for the vital signs. The data for the weights is not believed to be accurate at Week 12 and Endpoint for females in the MF DPI 200 BID and FP groups where the range of weights is listed as 45-665 kg and 44 –835 kg, respectively. The data for the weight range on Caucasians in these same treatment groups is also not believed to be accurate.

ECGs were performed only at Screening and thus will not be reviewed for drug effect.

e) Safety Conclusions

Interpretation of this trial must be tempered by the fact that there was no placebo group with which to compare the incidence of adverse events and laboratory abnormalities. Complaints noted in other trials such as pharyngitis, headache, rhinitis, back pain, abdominal pain, dyspepsia, arthralgia, musculo-skeletal pain, nasal congestion, and sinusitis did not exhibit a dose response in this study nor did they appear any more common with MF DPI than FP. There was a clear dose response with MF DPI for oral candidiasis but the incidence was not greater than that for FP. Likewise, viral infection appeared to be more common with FP while influenza-like symptoms and fatigue seemed to be more common with MF DPI. Dysphonia and dysmennorhea appear in this study to be perhaps more common with FP. The pattern for hypertension seemed to indicate a dose response for MF DPI but it was far from definitive.

There was not a common pattern of severe or serious AEs readily attributable to drug treatment. Discontinuations occurred for many reasons during the study. Instances of dysphonia, pharyngitis and perhaps abnormal glucose tolerance were among those thought possibly attributable to drug treatment.

There were increases in transaminases noted among specific individuals in all treatment groups with the largest seen in one patient in the MF DPI 200 BID treatment group. AM cortisol data was available but such data is not a sensitive measure of treatment-induced HPA axis suppression. There were no important changes in median values for vital sign data over the course of the trial but the data on weight will need to be clarified by the sponsor.

M. I96-112 (Vol. 226-269)

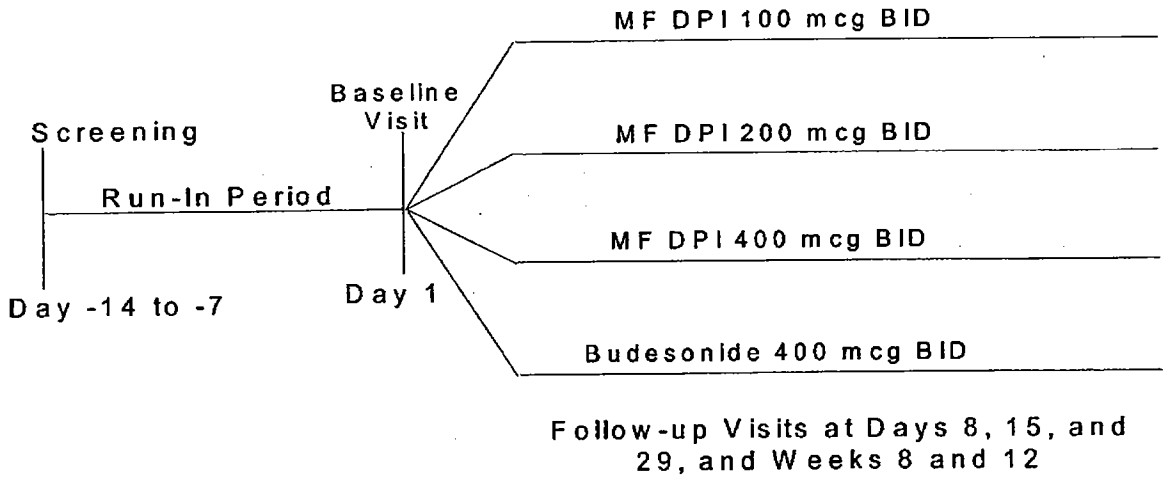
"Efficacy and Safety of Mometasone Furoate (SCH 32088) Dry Powder and Budesonide Powder (Pulmicort Turbuhaler) in the Treatment of Asthma"

1. Objectives

This study was very similar to C96-111 meaning that it was a very large international study comparing MF DPI with an active comparator over 3 months. The primary objective as stated of this randomized, active-controlled, parallel group, 62 center, double-blind (blinded to both the investigator and the subject for MF DPI but only evaluator blind for budesonide) study was to determine the efficacy and tolerance of twice-daily dosing of MF-DPI, at three dose levels (100, 200, and 400 mcg BID) in subjects with moderate asthma. The secondary

objective was to compare the efficacy and tolerance of the three doses of MF-DPI to that of budesonide (Pulmicort Turbuhaler) administered twice daily. All subjects had been previously maintained on inhaled corticosteroids.

The primary efficacy variable was change from Baseline in FEV_1 at Endpoint and the secondary efficacy and safety variables were typical for other studies in this NDA.



The primary efficacy analysis for evaluating the efficacy of MF DPI was to be based on the pairwise comparison of the least squares means of the MF DPI 400 BID and MF DPI 100 BID (from the ANOVA) using a 5% significance level. If this difference was not significant then it appears the plan was to perform a statistical pairwise comparison of each dose of MF DPI to budesonide as a secondary analysis.

The inclusion, exclusion and removal from therapy criteria and concomitant/prohibited medications were the same as that for C96-111. Similarly, salmeterol was discontinued at Run-in and for the duration of the study. Again, three measurements of spirometry were performed at each visit and the effort with the highest FEV_1 was recorded as the best effort.

2. Efficacy Results

There were 730 subjects randomized at 57 centers with the following involvement in each group: MF DPI 100 mcg BID, 185 subjects; MF DPI 200 mcg BID, 176 subjects; MF DPI 400 mcg BID, 188 subjects; and budesonide, 181 subjects.

The primary comparison for efficacy was to be MF DPI 400 BID versus MF DPI 100 BID. The protocol stated that if this comparison was significant, then other pairwise comparisons were to be made at the 0.05 (two-sided) level of significance without adjustments for multiple comparisons. Although this primary comparison was not significant (p=0.11), the sponsor states that the remaining comparisons, especially the comparisons of MF DPI to BUD and the results of these comparisons were presented for completeness. For each comparison, the nominal (unadjusted) p-value is presented. In light of the protocol-specified analysis plan, however, the sponsor emphasizes that these analyses should be considered as secondary, exploratory analyses, and the results should be interpreted as such.

FEV_1 (liters) - Change from Baseline

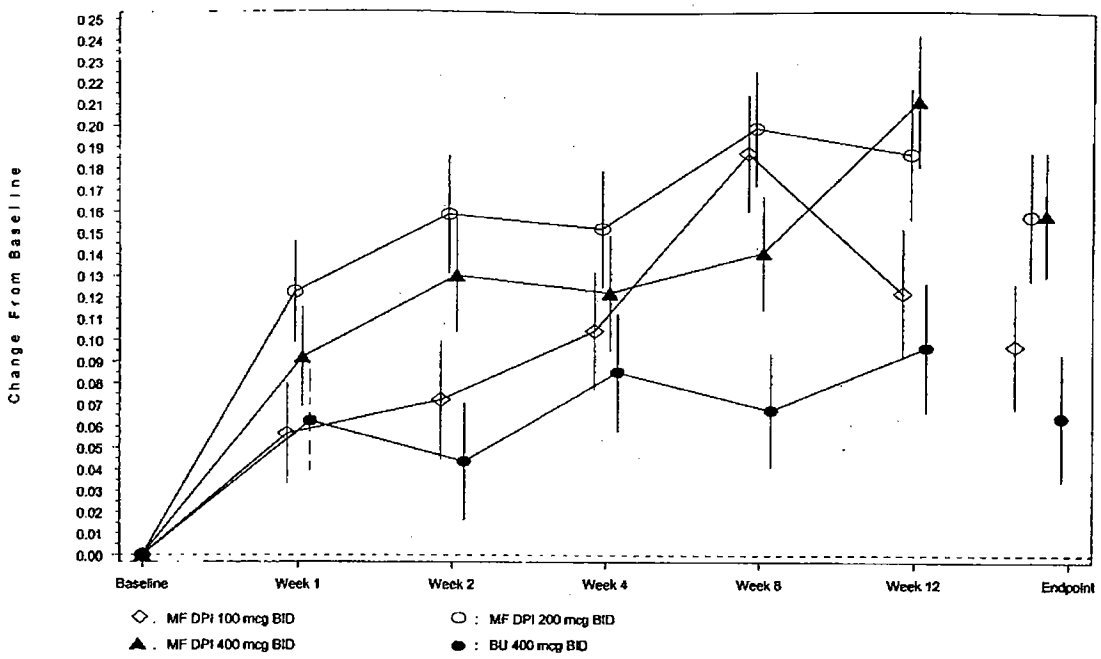
	MF DPI 100 mcg BID (A)			MF DPI 200 mcg BID (B)			MF DPI 400 mcg BID (C)			BUD (D)		
	N	Mean	% Dif.	N	Mean	% Dif.	N	Mean	% Dif.	N	Mean	% Dif.
Baseline	183	2.49		174	2.52		184	2.54		179	2.47	
Change From BSL												
Week 1	178	0.06	(3.6%)	172	0.12	(5.8%)	176	0.09	(4.7%)	175	0.06	3.6%
Week 2	168	0.07	(4.1%)	165	0.16	(7.0%)	177	0.13	(5.9%)	172	0.04	2.7%
Week 4	169	0.10	(6.1%)	165	0.15	(6.9%)	174	0.12	(6.0%)	168	0.09	4.5%
Week 8	154	0.19	(9.3%)	156	0.20	(8.6%)	161	0.14	(6.8%)	156	0.07	4.0%
Week 12	149	0.12	(6.3%)	142	0.19	(7.6%)	143	0.21	(9.3%)	143	0.10	4.6%
Endpoint	183	0.10	(5.3%)	174	0.16	(6.6%)	184	0.16	(7.2%)	179	0.06	3.1%

Analysis Results (Change From Baseline)

		P-Value		Pairwise Comparisons (P-value)					
Time Point	Pooled SD	Treat-ment	Center	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
Wk 1	0.29	0.13	<.01	0.04	0.26	0.85	0.33	0.06	0.35
Wk 2	0.33	<.01	0.01	0.02	0.10	0.42	0.42	<.01	0.01
Wk 4	0.33	0.31	0.01	0.20	0.62	0.60	0.41	0.07	0.31
Wk 8	0.31	<.01	<.01	0.75	0.20	<.01	0.10	<.01	0.04
Wk 12	0.34	0.02	<.01	0.11	0.03	0.53	0.55	0.03	0.01
EP	0.36	0.03	<.01	0.12	0.11	0.39	0.98	0.02	0.01

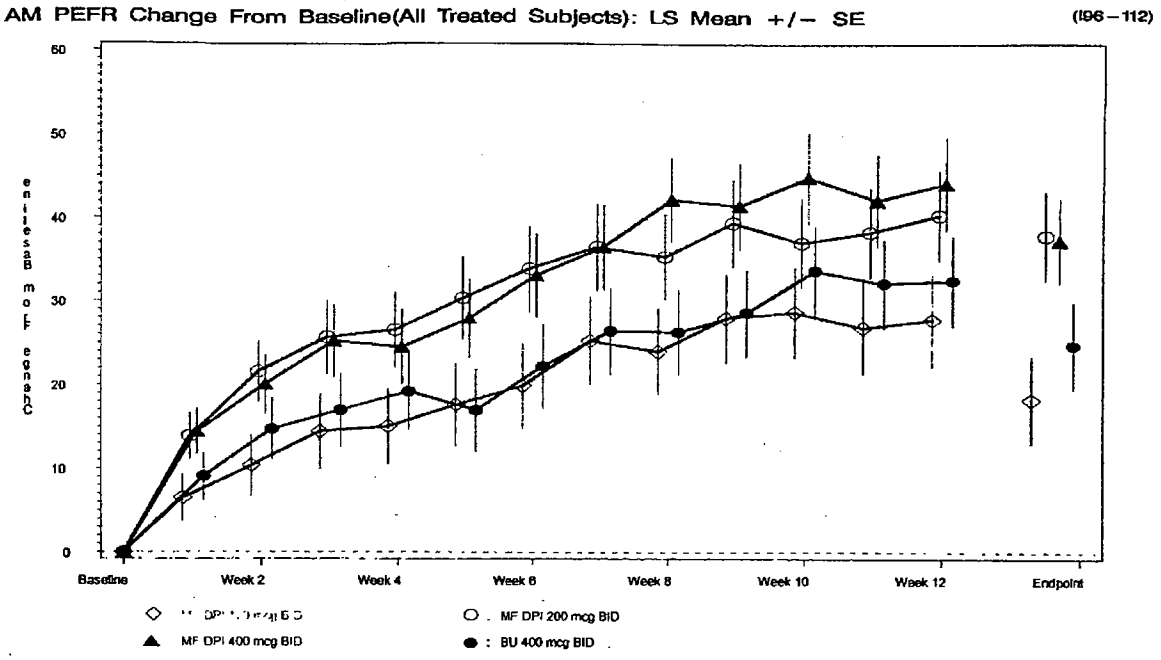
There were only numerical differences in the primary comparison between MF DPI 100 and 400 BID. There was no essential difference, numerical or otherwise, between the 400 and 200 BID doses at Week 12 and Endpoint but these two doses tended to fare numerically better than 100 BID and much better than budesonide throughout the trial. At earlier timepoints it seem that 200 BID is numerically a better dose than 400 BID. Interestingly, budesonide fared numerically the worst throughout the trial. Indeed, the differences between the two higher doses of MF DPI and budesonide were significant at Endpoint and Weeks 8 and 12.

FEV_1 Change From Baseline Over Time



At Endpoint, there were no statistical differences among the treatment groups for FVC. The FVC response for MF DPI 200 and 400 BID were roughly equivalent, followed by 100 BID and then budesonide. For FEF_{25-75}, MF DPI 200 and 400 BID were statistically superior to budesonide only at Endpoint. For most of the treatment period, the MF DPI doses were roughly equivalent and numerically superior to budesonide.

For AM PEFR, MF DPI 200 and 400 BID were statistically superior to 100 BID. The Endpoint response of the two higher MF DPI doses was equivalent. Budesonide appeared to have a response intermediate between MF DPI 100 BID and the two higher doses.



For PM PEFR, MF DPI 400 BID (11.2%) was significantly better than 100 BID (6%) and budesonide (6.3%) at Endpoint. In general, there appeared to be a dose response among the MF DPI doses and budesonide fared similarly to MF DPI 100 BID.

Among the wheezing and difficulty breathing (DB) scores, treatment with MF DPI 400 BID was superior to that with MF DPI 100 BID. At Endpoint, the improvement in AM wheezing scores was significantly greater in the MF DPI 400 BID group (-0.27) than in the MF DPI 100 BID group (-0.07) and the budesonide group (-0.10). Overall for AM Wheezing, there was a dose response for MF DPI with budesonide very similar to MF DPI 100 BID. For PM Wheezing, MF DPI 400 BID was the best and was significantly better than 100 BID and budesonide at Endpoint. The next best numerical response was for 200 BID followed by budesonide and then 100 BID. Results based on AM difficulty breathing scores at Endpoint also demonstrated that improvement was significantly superior with MF DPI 400 BID (-0.24) compared with MF DPI 100 BID (-0.10). For AM DB and for PM DB, there was a dose response with MF DPI and budesonide had an intermediate response at Endpoint between that for 100 and 200 BID. For AM Cough, there were no statistical differences among the treatment groups at Endpoint. Budesonide and MF DPI 400 BID fared the best numerically for AM Cough as well as PM Cough followed by 200 and then 100 BID.

For physician's designated response to therapy, the percentage of subjects evaluated at Endpoint as much improved or improved was similar in the MF DPI 100 BID group (60%), MF DPI 200 BID group (63%), and MF DPI 400 BID group (65%) and lower in the BUD 400 BID group (50%). At Endpoint, mean scores were significantly lower (meaning better) in the MF DPI 400 BID (2.25) group compared to the MF DPI 100 BID group (2.43) and the BUD 400 mcg BID group (2.53). Mean scores were also significantly lower in the MF DPI 200 BID group (2.33) compared to the BUD 400 mcg BID group.

The sponsor says that there was no significant baseline differences between the milligram dose of salbutamol used each day among the treatment groups. It must be noted, however, that there was a numerical difference at baseline with 282 milligrams for 200 BID compared with 252-258 for the other treatment groups. The dose reduction seen with 200 BID was significantly better than for budesonide. Although the difference between MF DPI groups was not statistically significant, numerically the use of salbutamol decreased to a greater extent in the MF DPI 200 BID group (-90.66 mcg per day) than in the MF DPI 400 BID group (-72.13 mcg per day) and the MF DPI 100 BID group (-45.86 mcg per day). Budesonide had the smallest decrease in use numerically.

Mean decreases in the number of nocturnal awakenings requiring salbutamol were observed at Endpoint for all treatment groups (MF DPI 100 BID, -0.06; MF DPI 200 BID -0.09; MF DPI 400 BID, -0.16; and budesonide, -0.07). No significant differences were noted between the MF DPI groups or between each MF DPI group and the budesonide group. In general, 400 BID fared the best followed by 200 BID/budesonide and then 100 BID.

As in the other trials, survival analysis of time to asthma worsening was performed. In C96-112, log rank tests did not reveal a significant difference among the treatment groups. There was overall a high completion rate among all treatment groups. Among all treatment groups, worsening asthma was seen in: MF DPI 100 BID, 32 subjects; MF DPI 200 BID, 26 subjects; MF DPI 400 BID, 30 subjects; and budesonide, 25 subjects). Thus, despite the other parameters that appear to show improved efficacy with MF DPI 400 BID over budesonide, budesonide had numerically fewer instances of worsening asthma than 400 BID but was very comparable to that for 200 BID.

3. Efficacy summary

MF DPI 400 BID generally appeared to be the most effective dose for many parameters in this trial but statistical differences with other MF DPI doses were not often seen. The primary endpoint was change from baseline in FEV_1 and 200 BID and 400 BID were similar at Endpoint and Week 12. Both doses did better than budesonide. For other spirometry endpoints, 200 and 400 BID tended to perform similarly and budesonide was similar to 100 BID.

For the asthma scores of wheezing and difficulty breathing, there was typically a dose response for MF DPI. For response to therapy, MF DPI 200 and 400 BID were better than 100 BID and budesonide. MF DPI 200 BID fared the best with reduction in salbutamol dose and 400 BID was numerically the best in reduction of nighttime awakenings with asthma problems.

4. Safety C96-112

As in C96-111, there was no placebo group in this trial. For this safety review, adverse events and laboratory/vital sign data can only be compared among the treatments groups.

a) Adverse Events

Incidence of Adverse Events Reported by ≥10% of Subjects in Any Treatment Group

	MF DPI 100 mcg BID (n=185)	MF DPI 200 mcg BID (n=176)	MF DPI 400 mcg BID (n=188)	BUD 400 mcg BID (n=181)
Number (%) of Subjects Reporting Any AE	**117 (63%)**	**110 (63%)**	**114 (61%)**	**110 (61%)**
Headache	38 (21%)	43 (24%)	33 (18%)	32 (18%)
Infection, viral	24 (13%)	36 (20%)	40 (21%)	30 (17%)
Pharyngitis	22 (12%)	20 (11%)	22 (12%)	18 (10%)
Rhinitis	23 (12%)	17 (10%)	12 (6%)	16 (9%)

There is a suggestion of a dose response for viral infection and MF DPI dose but there probably is no real difference among them or with budesonide. Among these other common AEs, their incidence did not appear to be any higher than that for budesonide. The following list of all adverse events has been edited to present those clearly more common with one drug treatment or those that have a dose response.

Incidence of Adverse Events Reported by ≥2% of Subjects in Any Treatment Group

	MF DPI 100 mcg BID (n=185)	MF DPI 200 mcg BID (n=176)	MF DPI 400 mcg BID (n=188)	BUD 400 mcg BID (n=181)
Any Adverse Event	**117 (63%)**	**110 (63%)**	**114 (61%)**	**110 (61%)**
Dysphonia	8 (4%)	7 (4%)	11 (6%)	5 (3%)
Nausea	6 (3%)	5 (3%)	2 (1%)	0
Dyspepsia	5 (3%)	8 (5%)	8 (4%)	7 (4%)
Abdominal pain	4 (2%)	5 (3%)	6 (3%)	2 (1%)
Musculo-skeletal pain	6 (3%)	4 (2%)	10 (5%)	8 (4%)
Myalgia	6 (3%)	6 (3%)	3 (2%)	6 (3%)
Dysmenorrhea	1 (1%)	4 (4%)	3 (3%)	2 (2%)
Candidiasis, oral	4 (2%)	6 (3%)	5 (3%)	3 (2%)
Nasal congestion	6 (3%)	3 (2%)	6 (3%)	3 (2%)

Dysphonia appeared to be somewhat more common with MF DPI but not impressively so. Nausea and abdominal pain were also more common with MF DPI. Dyspepsia and perhaps nasal congestion are on this list because it had been mentioned in other trials but does not appear to be any more common than with budesonide. There is a suggestion of a dose response with musculo-skeletal pain with MF DPI but is not any more common than with budesonide. Dysmennorhea also may be more common with a higher dose. For unclear reasons, the incidence of oral candidiasis is quite low in this tria relative to that seen in other trials. The instructions to rinse after use in this protocol report do not appear to be any different that those for the other trials.

The sponsor says that one subject in the MF DPI 200 mcg BID group had a treatment-emergent adverse event that coded to abnormal hepatic function (I96-112-19/017). No abnormalities in this subjects laboratory testing could be identified. The sponsor will be asked for clarification. Another subject with marked elevations is discussed in the serious AE section below.

Severe/Life-threatening Treatment-Emergent Adverse Events

Adverse Event Type	MF DPI 100 mcg BID (n=185)	MF DPI 200 mcg BID (n=176)	MF DPI 400 mcg BID (n=188)	BUD 400 mcg BID (n=181)
Any Severe/Life-threatening AE	**12 (6%)**	**12 (7%)**	**12 (6%)**	**11 (6%)**
vasospasm	0	1 (1%)	0	0

back pain	1 (1%)	1 (1%)	1 (1%)	1 (1%)
cramps, legs	1 (1%)	0	0	0
fatigue	1 (1%)	2 (2%)	0	0
headache	2 (1%)	3 (2%)	2 (1%)	2 (1%)
headache, aggravated	0	0	1 (1%)	0
malaise	0	0	1 (1%)	0
abdominal pain	0	1 (1%)	0	0
diarrhea	1 (1%)	0	0	0
dyspepsia	0	0	0	1 (1%)
bone disorder	0	1 (1%)	0	0
musculo-skeletal pain	1 (1%)	0	0	0
amnesia	0	1 (1%)	0	0
dysmenorrhea	0	0	0	1 (1%)
prostatitis	0	0	0	1 (1%)
infection, viral	1 (1%)	1 (1%)	2 (1%)	0
asthma, aggravated	1 (1%)	0	0	1 (1%)
bronchitis	0	1 (1%)	2 (1%)	1 (1%)
coughing	2 (1%)	0	2 (1%)	1 (1%)
laryngitis	0	1 (1%)	1 (1%)	0
nasal congestion	1 (1%)	0	1 (1%)	0
pharyngitis	0	1 (1%)	1 (1%)	2 (1%)
pleurisy	0	0	0	1 (1%)
respiratory disorder	2 (1%)	0	0	0
rhinitis	0	0	1 (1%)	2 (1%)
status asthmaticus	0	0	0	1 (1%)
migraine	0	1 (1%)	1 (1%)	0

A dose response or differential presentation of severe adverse events between treatment groups is not apparent from this list. Only one subject (#5, site 44, budesonide) was reported to have a life-threatening event (asthma aggravation).

Serious Adverse Events

Center/Subject	Sex/ Age/ Race	Adverse Event(s)	Relationship	Status
		Screening (Not Randomized)		
44/608	F/22/C	Aggravated asthma	Unlikely	Hospitalized, not randomized
		MF DPI 100 mcg BID		
37/027	F/19/NC	Coughing, dyspnea, aggravated asthma	Unlikely	Hospitalized 1 day, additional therapy
55/123	M/65/C	Chest pain (h/o angina)	Unlikely	Hospitalized, additional therapy, continued study
		MF DPI 200 mcg BID		
04/047	M/62/C	Amnesia for 6 hours, vasospasm of vertebral artery?	Unlikely	Hospitalized, additional therapy, resumed study
06/003	M/35/C	Pain, neck	Not provided	Disabled, additional therapy
47/024	M/29/C	Pain, stomach (undetermined etiology)	Unlikely	Hospitalized, resumed study
		MF DPI 400 mcg BID		
22/041	F/43/C	Uterine fibroid surgery	Unlikely	Hospitalized
59/051	F/32/NC	Hepatic enzymes increased	Not provided	Medically significant, additional therapy (See below)

Serious Adverse Events

Center/Subject	Sex/ Age/ Race	Adverse Event(s)	Relationship	Status
		Budesonide 400 mcg BID		
21/129	F/28/C	Varicella	Unlikely	Hospitalized, additional therapy, resumed study
21/038	F/58/C	Menstrual disorder (though to be related to menopause)	Unlikely	Hospitalized
44/005	M/48/C	Bronchitis, pleural fibrosis, aggravated asthma	Unlikely	Hospitalized, additional therapy (considered to be life-threatening)

Subject #51 (Site 59 - MF DPI 400 mcg BID) was a 32-year-old female who had a normal SGOT value of 16 U/L and a normal SGPT value of 28 U/L at Screening. At Visit 7, the subject had an SGOT value of 339 U/L and an SGPT value of 548 U/L and the study medication was discontinued. Follow-up laboratory values were SGOT 29 U/L and SGPT 50 U/L. The investigator reported that the subject had similar elevations in the past in relation to severe colds; at this time the subject reported influenza as an ongoing adverse event. The investigator reported that there were no clinical signs or laboratory findings of viral hepatitis. The investigator considered the event unlikely related to study drug.

There appeared to be an over-representation of subjects discontinuing because of adverse events in the MF DPI 100 BID and budesonide treatment groups. It should be noted that some of the subjects listed below have also been mentioned in the serious AE list.

Subjects Who Discontinued Treatment Because of Adverse Events

Center/Subject	Sex/Age/Race	Day of Onset	Adverse Event(s)	Severity	Relationship
			MF DPI 100 mcg BID		
02/051	F/61/C	17	bronchitis	moderate	unrelated
20/027	M/61/C	78	arthralgia	mild	unrelated
37/027	F/19/NC	23	asthma, aggravated	severe	unrelated
39/011	F/48/C	3	headache	moderate	probable
		6	diarrhea	moderate	probable
		4	nausea	moderate	probable
47/023	F/58/C	19	cough	severe	probable
		19	headache	severe	probable
		19	myalgia	moderate	probable
47/033	F/49/C	17	nasal congestion	severe	unrelated
			MF DPI 200 mcg BID		
01/020	M/67/C	17	dysphonia,	mild	probable
			pharyngitis	mild	probable
			MF DPI 400 mcg BID		
06/001	F/50/NC	14	palpitation	moderate	possible
23/127	F/43/C	37	asthenia	mild	possible
24/089	M/34/C	48	candidiasis, oral	moderate	probable
			Budesonide 400 mcg BID		
01/003	M/63/C	78	bronchitis	mild	unrelated
03/007	F/28/C	82	infection, viral	moderate	unrelated
08/070	F/19/C	27	infection, viral	moderate	unrelated
44/001	M/50/C	5	prostatitis	severe	unrelated
44/005	M/48/C	32	asthma, aggravated	life-threatening	possible
46/016	M/64/C	61	infection, viral	moderate	unrelated
59/041	M/32/C	34	pharyngitis	moderate	probable

b) Laboratory Values

The following laboratory abnormalities were notable: (Transaminase changes were noted if there was a change greater than 20 units and it brought the total above 40. Those with baseline elevations were typically not noted.)

Subject	Site	Treatment	Note (generally Screening to Week 12)
16	16	MF DPI 100 mcg BID	AST/ALT 30/27 to 38/52
39	30		ALT 22 to 50
21	33		Tbili 0.6 to 3.0 (nl 0.2-2.0) (AST 37 to13 (nl 9-37)
45	46		AST/ALT 26/31 to 67/113 (Day 89) to 32/28 Day 117(off med. 28 days)
11	50		WBC 9.9 to 18.9 (Day 88 (5 days)
106	51		AST/ALT 62/75 to 105/121, Bili. Ok)(sponsor determined this was related to alcohol consumption)
140	52		ALT 23 to 47 (Week 8)
66	25	MF DPI 200 mcg BID	Bicarbonate 25 to 15
19	33		AST/ALT 24/13 to 43/42, AP 225 to 568 Tbili. 0.2 to 1.9 (nl 0.2 – 2.0, thus still wnl)
15	33		Tbili. 0.2 to 7.3
20	16	MF DPI 400 mcg BID	AST 30 to 65
69	25		AST/ALT 22/26 to 40/52
34	37		AST/ALT 50/133 to 50/112 Tbili. 29 to 53 (nl 3-21)
44	46		AST/ALT 15/12 to 29/48 (Day 88) to 14/16 (Day 129(41))
72	54		Tbili. 22 to 45. AST/ALT ok.
60	57		Cholesterol 2.66 to 277 (nl. 3.62-6.75 mmol/l listed in one section, 0-200 in another) (appears to be change in units)
51	59		AST/ALT 16/28 to 339/548 (discussed earlier)
13	60		AST/ALT 18/14 to 28/48 Tbili 9 to 15 (nl. 3-21)
18	01	Budesonide 400 mcg BID	AST/ALT 19/28 to 35/66
09	02		AST/ALT 12/8 to 57/69
76	26		AST 23 to 50
02	34		AST 25 to 68, ALT 31 to 25, Tbili. 7 to 17 (nl 3-21)
18	36		AST 51 to 22, Tbili 9. 7 to 26 (nl 3-21)
42	46		AST/ALT 26/24 to 39/46
65	54		K 4.4 to 5.8
25	58		Glucose 80 to 57
12	60		WBC 7.22 to 15.8 (day 92(4))

Examples of mild transaminase increase were noted in al treatment groups. Of the above abnormalities, a few were particularly notable. There were isolated bilirubin increases in the MF DPI subjects # 21, 15 and 72. Subject #34 had a baseline elevation of bilirubin and ALT and the bilirubin rose further during the trial while the ALT decreased slightly. Subject #45(MF DPI 100 mcg BID) had a more marked elevation of AST/ALT on Day 89 that had normalized by a repeat on Day 117.

One site (#12 – C. Bisbal, M.D.) had glucose and creatinine values that were well out of the range of the site's given normal ranges both at Screening and at Week 12. The sponsor will be requested to clarify this data.

The median values of the laboratory testing for each treatment group were reviewed and no important changes in the median values were noted over the treatment period. No decrease was noted in the am plasma cortisol level between Baseline and Endpoint. This does not mean, however, that there was definitive evidence that no HPA axis suppression occurred during MF DPI treatment. Remember also that these subjects had been on inhaled corticosteroids at Baseline. There were no important changes in the means of vital signs or weight over the treatment period nor was there a differential response based on gender.

5. Safety Conclusions I96-112

The incidence of AEs with an expression of greater than 10% in any treatment group were not any more common with MF DPI than with budesonide. Dysphonia, nausea and abdominal pain appeared to be somewhat common with MF DPI. Dyspepsia, dysmennorhea, oral candidiasis, myalgia and nasal congestion did not appear to be any more common with MF DPI.

There were examples of minor transaminase elevations seen in all treatment groups. One subject in the MF DPI 400 BID group had a marked AST/ALT elevation to 339/548 that had largely normalized at follow-up. This elevation was attributed to influenza. There were no important changes in the median of group laboratory values or in the means of vital signs/weights.

N. I96-113 (Vol. 270-301)

" Effect and Safety of Three Daily Dose Levels of Mometasone Furoate Dry Powder in the Treatment of Asthmatics requiring High Dose Inhaled Corticosteroids."

1. Objectives/Rationale

The primary objective of this 3 month randomized, parallel group, international, double blind study was to determine the efficacy and tolerance of twice-daily dosing of MF DPI at 3 daily dose levels (200, 400 or 600 mcg BID) in subjects with moderately severe to severe asthma who required high dose daily maintenance ICS. There was no placebo group in this study. Subjects were to have been on daily ICS for at least 30 days prior to Screening and were to be on a stable dose for the 2 weeks prior to Screening. The primary efficacy endpoint was change from Baseline in FEV_1 at Endpoint and the secondary variables were the same as those in previous trials for this NDA. The primary comparison was to be between MF DPI 600 BID and 200 BID

A 3 month record of daily ICS use was obtained. They must have been on a stable regimen for the 2 weeks prior to Screening within the range below (expressed in mcg/day):

Flunisolide	>1000 (up to 2000)
Triamcinolone acetonide	>800(up to 1600)
Beclomethasone	>1000 (up to 2000)
Budesonide	>800 (up to 2000)
Fluticasone propionate	>500 (up to 1000)

Subjects could not have been on oral steroids for more than 21 days in the preceding 6 months. Other inclusion/exclusion criteria appeared to be similar to I96-111 and 112. Subjects were off of long acting B agonists for the treatment period.

The study was to enroll 150 subjects per treatment arm to detect with an 80% power and 5% significance level to detect treatment differences of 15 cc. as has been the case with previous trials.

2. Efficacy Results

There were 507 subjects randomized at 53 centers.

Inhaled Corticosteroids Dose at Baseline	MF DPI 200 BID	MF DPI 400 BID	MF DPI 600 BID
Beclomethasone Dipropionate			
no. of subjects	47	53	59
mean mcg/day	1362	1342	1401
Budesonide			
no. of subjects	68	57	59
mean mcg/day	1182	1161	1207
Flunisolide			
no. of subjects	7	10	5
mean mcg/day	1279	1245	1250
Fluticasone Propionate			
no. of subjects	45	46	49
mean mcg/day	844	918	901

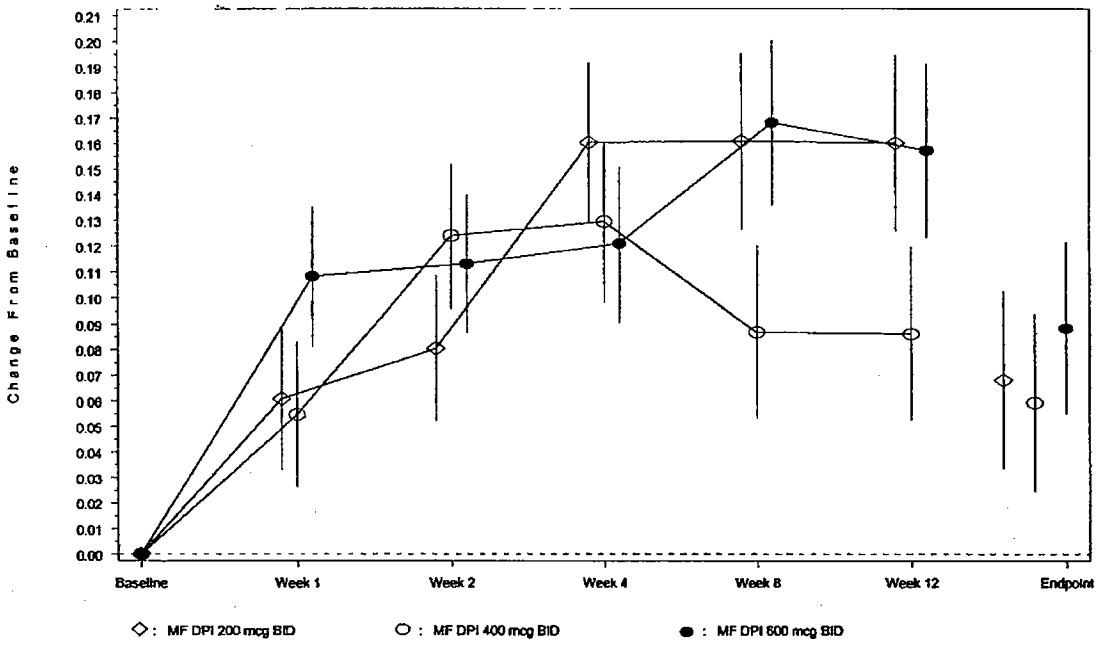
There were improvements in the FEV_1 with all 3 doses. There were no significant differences in the pairwise comparisons of change from Baseline of FEV_1 at Endpoint. It is interesting to note that the data for MF DPI 200 BID and 600 BID track each other closely for FEV_1 and appear to continue to increase through Week 8. The 400 BID dose tracks with the other doses also up to Week 4 when there appears to be a drop-off for unclear reasons, especially noting the large number of subjects in the trial. At Endpoint, the difference between 400 and the other doses is less apparent and 600 BID is slightly numerically better. Thus, no real difference in FEV_1 improvement is noted between 200 and 600 BID and FEV_1 improved despite the fact that subjects were already on ICS doses that were considerably higher than that seen, for instance, in I96-112. Each dose of MF DPI also appeared to be more numerically effective in those subjects with a Baseline FEV_1 <75% of predicted.

FEV_1 (liters) — Change from Baseline by Treatment Group

	MF DPI 200 mcg BID (A)			MF DPI 400 mcg BID (B)			MF DPI 600 mcg BID (C)		
	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	168	2.43		163	2.47		173	2.51	
Change From Baseline									
Week 1	164	0.06	(3.6%)	157	0.05	(2.9%)	165	0.11	(4.8%)
Week 2	161	0.08	(4.2%)	158	0.12	(5.6%)	170	0.11	(5.0%)
Week 4	151	0.16	(7.8%)	155	0.13	(5.9%)	159	0.12	(5.3%)
Week 8	135	0.16	(7.5%)	141	0.09	(4.4%)	144	0.17	(7.4%)
Week 12	139	0.16	(7.5%)	144	0.09	(4.2%)	140	0.16	(6.7%)
Endpoint	**168**	**0.07**	**(4.2%)**	**163**	**0.06**	**(3.5%)**	**173**	**0.09**	**(4.4%)**

Analysis Results (Change From Baseline)

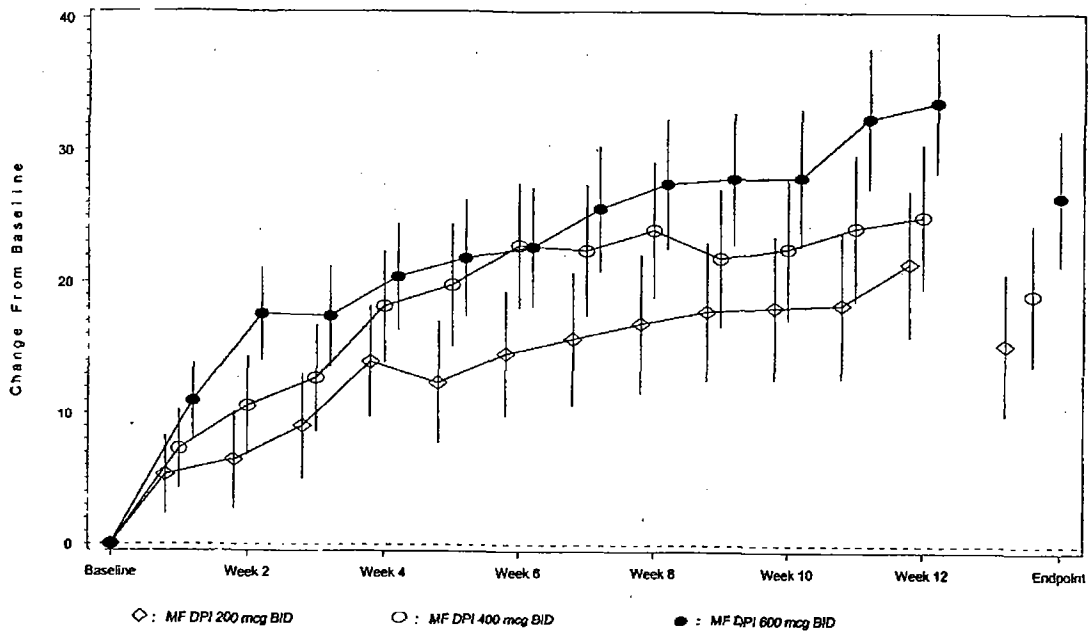
		P-value		Pairwise Comparisons (P Value)		
Time point	Pooled SD	Treatment	Center	A vs B	A vs C	B vs C
Week 1	0.31	0.25	0.24	0.86	0.17	0.13
Week 2	0.31	0.43	0.06	0.21	0.35	0.75
Week 4	0.34	0.58	0.05	0.43	0.32	0.83
Week 8	0.34	0.09	0.07	0.08	0.87	0.05
Week 12	0.35	0.14	0.01	0.08	0.95	0.09
Endpoint	**0.38**	**0.78**	**0.04**	**0.84**	**0.63**	**0.49**



FVC increased slightly (0.01 to 0.05 liters at Endpoint) in all treatment groups and there were no significant differences at Endpoint or at any other timepoint. The numerical differences between groups were small. Changes in FEF_{25-75} also showed increases with MF DPI treatment

and there were again no significant differences at Endpoint or at any other timepoint. The improvements seemed to be better than with FVC and by Endpoint, this variable had improved by 12.5, 7.9 and 12.9% in the 200, 400 and 600 BID groups respectively. The numerical increases with 400 BID tended to be less than that seen with 200 and 600 BID.

For AM PEFR, there were again no significant differences at Endpoint or at any other timepoint between the treatment groups. There was general improvement that continued throughout the 12 week trial. There was somewhat more of a dose response than has been seen with the other variables with 600 BID followed by 400 and then 200 numerically. The dose response in improvement was even more clearly seen in the PM PEFR data at Endpoint and throughout the trial. There were Endpoint improvements of 4.8%, 6.4% and 7.4% for the 200, 400 and 600 mcg doses, respectively.



There appeared to be improvements win the asthma scores with all does during treatment. There were no significant differences at Endpoint or at any other timepoint between doses for any of the AM or PM asthma scores of Wheezing, Difficulty Breathing (DB) and Cough. For AM or PM wheezing, there was no numerical dose response. For AM DB and AM/PM Cough, the 200 BID dose appeared to work numerically the best while for PM DB the edge in improvement went to the 600 mcg dosing.

For physician-designated response to therapy, the majority of subjects in each treatment group was evaluated at Endpoints as improved or much improved in 58%, 56% and 61% for the 200, 400 and 600 mcg doses, respectively. There were no significant differences in the mean response scores but the 600 mcg dose appeared to be numerically superior to the other doses.

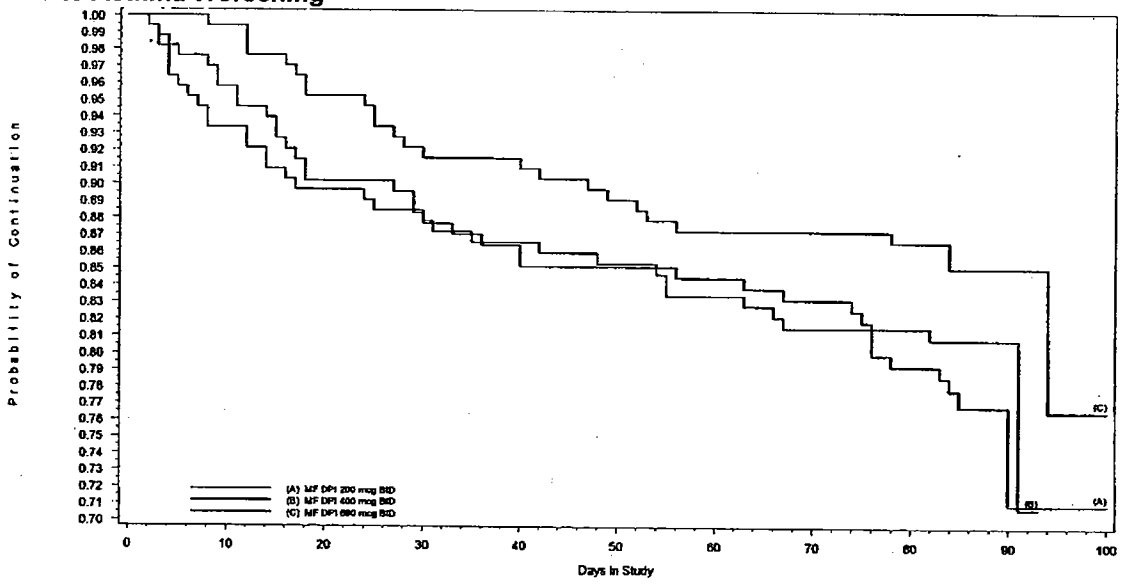
Physician's Evaluation of Response to Therapy at Endpoint

Rating	MF DPI 200 BID (n=168)	MF DPI 400 BID (n=163)	MF DPI 600 BID (n=173)
Much Improved	27 (16)	23 (14)	29 (17)
Improved	70 (42)	68 (42)	76 (44)
No Change	55 (33)	55 (34)	48 (28)
Worse	13 (8)	15 (9)	16 (9)
Much Worse	3 (2)	2 (1)	4 (2)

For salbutamol use during the study, there were growing decreases during MF DPI treatment during the first 6 weeks of treatment that generally stabilized. There were no significant decreases between groups and at Endpoint, 400 and 600 mcg did somewhat numerically better than 200 mcg. For nocturnal awakenings, the number at Baseline was low but further decreases were seen in each treatment group. While the results at Endpoint were nearly equivalent, there was a dose response at the other timepoints.

Log-rank tests showed no significant differences among the treatment groups for time to worsening of asthma. The curves for 200 and 400 BID are nearly superimposable while 600 BID appears to separate itself for nearly the whole treatment period. Fewer subjects in the 600 BID group (15%) experienced a worsening than either the 200 BID (23%) or 400 BID (19%) groups.

Time to Asthma Worsening



3. Efficacy Summary

All doses of MF DPI used in this study demonstrated improvement in the variables examined despite the fact that the subjects had been on fairly high doses of ICS at Baseline. There were no significant differences at Endpoint for any of the variables examined. For FEV_1, 600 BID was numerically better at Endpoint, but for other timepoints was generally comparable

to 200 BID. Like FEV_1, 200 and 600 mcg were numerically superior to 400 mcg for the FEF_{25-75}. For AM and PM PEFR, there tended to be a numerical dose response. For the asthma scores, there were no significant differences and the numerical superiority varied among the doses. For the reduction in salbutamol use, 400 and 600 mcg were numerically better than 200 mcg. At timepoints other than Endpoint (where doses were comparable), a dose response was noted. For the response to therapy variable and time to worsening curve, the 600 mcg dose was best.

4. Safety I96-113

a) Adverse Events

While the AE data in this study cannot clearly tell us what is attributable or not to MF DPI, the presence of a dose response may help to do so. The incidence of adverse events was slightly higher in the 600 mcg BID group (72%) than in the other two treatment groups (64% and 58% in the 200 and 400 mcg BID groups, respectively).

Incidence of Adverse Events Reported by ≥10% of Subjects in Any Treatment Group

Adverse Event	MF DPI 200 mcg BID (n=168)	MF DPI 400 mcg BID (n=166)	MF DPI 600 mcg BID (n=173)
Headache	29 (17)	36 (22)	39 (23)
Infection, Viral	32 (19)	28 (17)	32 (18)
Throat Dry	15 (9)	18 (11)	12 (7)
Candidiasis, Oral	8 (5)	7 (4)	20 (12)

A dose response seems to be apparent only for oral candidiasis among these most common AEs.

Incidence of Any Treatment-Emergent Adverse Events Reported by ≥2% of Subjects

	200 mcg BID (n=168)	400 mcg BID (n=166)	600 mcg BID (n=173)
Any Adverse Event	**108 (64)**	**97 (58)**	**125 (72)**
back pain	9 (5)	6 (4)	8 (5)
fatigue	6 (4)	3 (2)	9 (5)
influenza-like symptoms	7 (4)	6 (4)	6 (3)
pain	2 (1)	7 (4)	11 (6)
dysphonia	2 (1)	9 (5)	14 (8)
dyspepsia	5 (3)	2 (1)	8 (5)
nausea	5 (3)	4 (2)	10 (6)
arthralgia	2 (1)	4 (2)	3 (2)
myalgia	3 (2)	10 (6)	3 (2)
insomnia	4 (2)	4 (2)	5 (3)
dysmenorrhea	2 (2)	3 (4)	2 (2)
menstrual disorder	1 (1)	3 (4)	5 (5)
nasal congestion	12 (7)	10 (6)	7 (4)
pharyngitis	8 (5)	9 (5)	12 (7)
sinus congestion	0 (0)	3 (2)	1 (1)
sinusitis	5 (3)	6 (4)	7 (4)

Back pain, fatigue, influenza-like symptoms, arthralgia, myalgia, insomnia, dysmennorhea, sinus congestion and sinusitis did not show an increasing incidence with

increasing dose. There does appear to be a dose response for pain (The sponsor says that the general term "pain" fall encompasses 57 different literal terms (e.g., ache in neck, arm pain, cervical pain, hand ache, knee pain, pain in leg, sciatica pain, sore jaw, thoracic pain), dysphonia, menstrual disorder (again, the definition is not apparent) and perhaps dyspepsia and pharyngitis. A reverse dose response appears to be present for nasal congestion.

The proportion of subjects with one or more severe/life-threatening adverse events was similar among all three MF DPI groups (5% to 9%), although the highest percentage was found in the 600 mcg group. Two subjects (#18, Site 11 and #3, Site 3) had events that were categorized as life-threatening (asthma exacerbation that required hospitalization) and are also listed among the serious AEs.

Incidence of Severe/Life-Threatening Adverse Events

Adverse Event Type	MF DPI 200 mcg BID (n=168)	MF DPI 400 mcg BID (n=166)	MF DPI 600 mcg BID (n=173)
Any Severe/Life-Threatening Adverse Event	**8 (5)**	**10 (6)**	**15 (9)**
hot flushes	0	0	1 (1)
back pain	1 (1)	0	0
headache	2 (1)	4 (2)	4 (2)
dysphonia	0	1 (1)	0
vertigo	0	0	1 (1)
diarrhea	1 (1)	0	0
intestinal perforation	1 (1)	0	0
nausea	0	0	1 (1)
vomiting	1 (1)	0	0
sleep disorder	0	0	1 (1)
uterine contractions	0	0	1 (1)
candidiasis, oral	0	0	1 (1)
infection, viral	2 (1)	1 (1)	1 (1)
asthma aggravated	2 (1)	1 (1)	1 (1)
bronchitis	2 (1)	1 (1)	0
nasal congestion	0	0	1 (1)
pharyngitis	0	1 (1)	1 (1)
respiratory disorder	1 (1)	1 (1)	1 (1)
rhinitis	0	0	1 (1)
sinusitis	0	0	1 (1)
throat dry	0	1 (1)	0
urinary tract infection	0	1 (1)	0
migraine	1 (1)	0	2 (1)

Serious Adverse Events

Center/Subject	Sex/ Age/ Race	Adverse Event	Relationship	Status
MF DPI 200 mcg BID				
I96-113-17/044	F/50/C	Asthma Aggravated	Unlikely	Hospitalized; Discontinued
I96-113-21/112	F/78/C	Sigmoid colon tear, Pneumonia, UTI, Colonic Polyp	Unlikely	Hospitalized; Discontinued
MF DPI 400 mcg BID				
I96-113-11/018	F/53/C	Coughing, Pharyngitis, Pleural Pain, Asthma Aggravated, URI	Not Provided	Hospitalized; Discontinued
I96-113-16/068	F/58/NC	Hypertension Aggravated	Unlikely	Hospitalized

MF DPI 600 mcg BID				
I96-113-03/003	F/51/C	Asthma Aggravated, URI	Unlikely	Hospitalized
I96-113-09/094	F/38/NC	Spontaneous abortion	Unlikely	Medically Significant; Discontinued
I96-113-22/013	F/59/C	Varicose Veins	Unlikely	Hospitalized
		Nausea, Sinusitis, Vertigo, and Vomiting	Unlikely	Hospitalized

Among the above serious AEs, the incident of spontaneous abortion is notable but the relationship to drug treatment is unknown (the investigator considered the event unlikely related to study medication.) The rest of the AEs are not plausibly related to study treatment with the possible exception of aggravated hypertension.

Nineteen subjects did not complete treatment because of adverse events. There was no apparent pattern of occurrence among the three treatment groups, nor any particular risk associated with one treatment group compared with the others.

List of Subjects Who Discontinued Treatment Because of Adverse Events (those subjects in bold are also listed among the serious adverse events)

Center/Subject		Day of Onset	Adverse Event(s)	Severity	Relationship
MF DPI 200 mcg BID					
I96-113-01/043	F/56/C	14	asthma aggravated	moderate	possible
I96-113-03/005	F/48/C	9	eczema aggravated	moderate	possible
I96-113-08/023	F/36/C	74	respiratory disorder	severe	unrelated
I96-113-17/044	**F/50/C**	**63**	**asthma aggravated**	**severe**	**unrelated**
I96-113-21/112	**F/78/C**	**16**	**intestinal perforation**	**severe**	**unrelated**
I96-113-25/012	F/56/C	37	nasal congestion	moderate	unrelated
I96-113-32/045	F/69/C	42 (6)	infection aggravated	mild	unrelated
I96-113-38/017	F/23/C	15	fatigue, headache	moderate	possible
MF DPI 400 mcg BID					
I96-113-11/018	**F/53/C**	**6**	**asthma aggravated**	**severe**	**possible**
I96-113-12/002	F/17/C	24	bronchitis	severe	unrelated
I96-113-16/196	F/31/C	6	fibromyalgia	moderate	unrelated
I96-113-25/033	M/75/C	29	dysphonia	severe	related
MF DPI 600 mcg BID					
I96-113-03/003	**F/51/C**	**29**	**asthma aggravated**	**life threatening**	**unrelated**
I96-113-06/148	F/60/C	42	candidiasis, oral	severe	probable
I96-113-07/081	F/45/C	24	infection, bacterial	moderate	unrelated
I96-113-09/094	**F/38/B**	**16**	**pregnancy, unintended**	**moderate**	**unrelated**
I96-113-11/017	F/57/C	17	respiratory disorder	severe	unrelated
I96-113-15/052	F/50/C	1	rhinitis	severe	unrelated
I96-113-29/030	F/59/C	47 (4)	procedure	mild	unrelated

b) Laboratory Values/Vital Signs

The sponsor submitted a list of laboratory results that were outside of the normal range and the following were notable. The urinalysis data was not carefully reviewed.

Subject #	Site	Treatment	Note (Screening to Week 12)
20	01	MF 200 BID	Ca 2.22 to 9.8, Phos 1.58 to 5.7
92	09		ALT 20 to 62 (Tbili was 24 to 10)
229	14		Tbili 17 to 27 (nl. 3-21 µmol/L)
02	24		WBC 7.5 to 13.93: Day 102 (18)
16	26		AST/ALT 14/18 to 45/67

Subject #	Site	Treatment	Note (Screening to Week 12) (continued)
25	28		Tbili 17 to 28 (nl. 3-21 µmol/L)
87	34		Glucose 6.2 to 9.7 (nl. 3.9 – 6.7 mmol/L)
02	40		AST/ALT 24/37 to 38/64
31	42		Hematocrit 37 to 32
09	56		Tbili. 0.5 to 7.0 (nl. 0.1 to 1.2 mg/dl)
131	10	MF 400 BID	AST/ALT 28/31 to 38/52
158	14		AST/ALT 21/11 to 41/27
27	28		Tbili. 14 to 27
05	04	MF 600 BID	ALT 31 to 54
148	06		AST/ALT 23/19 to 141/40 (Day 57) to 22/21 (Day77(14)). No change in Tbili.
17	11		WBC 8.53 to 17.9, AST/ALT 15/10 to 24/43 Alk. Phos. 36 to 134.
166	15		Hct. 0.4 to 0.31 (nl. 0.34 to 0.48)
70	16		AST/ALT 23/16 to 43/60
62	25		AST/ALT 17/16 to 35/60
09	57		ALT 31 to 71

The transaminase elevation was particularly notable in Subject #148. There were isolated bilirubin elevations in Subjects # 229,25, 09, and 27. The medians of the laboratory data among the three treatments were reviewed and no important changes were noted. There were no important changes in the median value of the a.m. cortisol after 12 weeks.

There were no important changes in the mean value of the vital signs between treatment groups or between genders. The mean weight for the 600 mcg BID group increased from 80.1 kg to 89.8 kg for the entire group and, for females specifically, the mean weight increased from 73.5 at Baseline to 89.7 at Endpoint. It is believed, however, that this is an error because the high value for the group at Endpoint and at 12 weeks is 675 kg. The sponsor will be asked to clarify this point.

5. Safety Summary I96-113

Headache, viral infection, dry throat, and oral candidiasis were the most common AEs noted in this 12 week trial comparing three BID doses of MF DPI. There appeared to be a dose response for oral candidiasis despite the fact that subjects were instructed to rinse after drug administration. There was also a dose response for "pain," dysphonia and "menstrual disorder" and perhaps dyspepsia and pharyngitis. The serious adverse events did not appear to be clearly attributable to MF DPI. There was an incident of a subject having a spontaneous abortion. Among the laboratory abnormalities were some mild increases in transaminases as well as isolated increases in total bilirubin. The AST increased from 23 to 141 in one subject on MF DPI 600 BID without a change in the bilirubin. There were no important changes in the vital signs with treatment. An increase in the listed weight of women on 600 mcg BID is believed to be erroneous and due to a data processing error.

O. Other Studies

There were other trials submitted in this NDA which were not closely reviewed but which do appear to merit mention.

1. Protocol I96-401 (Holgate/Arshad)

"Effect of Mometasone Furoate (SCH 32088) Dry Powder on AMP-Induced Bronchoconstriction in Asthma"

The primary objective of this single center, three way crossover trial was to evaluate the effect of MF DPI 50 mcg BID and MF DPI 100 mcg BID on AMP-induced bronchoconstriction compared to that of placebo in 15 asthmatic subjects (were to be off inhaled corticosteroids for at least 1 month). Each subject received three 2-week treatment periods separated by washout periods of 4 weeks. The primary efficacy variable was the change in $\log_{10}PC_{20}$ FEV_1 (expressed in terms of doubling dilutions) from pretreatment to post-treatment in each treatment phase, where $\log_{10}PC_{20}$ FEV_1 is the log concentration of AMP [mg/ml] required to decrease FEV_1 20%. Eligible asthmatics were to have demonstrated sensitivity to inhaled AMP at Screening. (PC_{20} $FEV_1 \leq 100$ mg/ml).

Treatment with MF DPI 50 mcg BID and treatment with MF DPI 100 mcg BID increased PC_{20} FEV_1 by approximately three doubling dilutions (2.81 and 3.11 DD, respectively), compared to treatment with placebo and thus demonstrate that treatment with both doses of MF DPI decreased airway responsiveness to AMP. Mean increases in FEV_1 across treatment phases were significantly greater during treatment with MF DPI 50 mcg BID (0.235 L) and MF DPI 100 mcg BID (0.343 L) than during treatment with placebo (0.009 L).

2. Protocol I96-402 (O'Byrne)

"Effect of Inhaled Mometasone Furoate (SCH 32088) Dry Powder on Allergen-Induced Asthmatic Responses and Airway Inflammation"

Each of 11 subjects received MF DPI at 50, 100, and 400 mcg BID and placebo in 4 separate 6-day treatment phases, separated by 3 washout periods of at least 3 weeks each. The key variables were the early (0-2 hours) and late (3-7 hours) asthmatic responses to allergen inhalation, allergen-induced bronchial hyperresponsiveness as determined by methacholine PC_{20}, and total and activated eosinophil counts in induced sputum. The allergen producing the largest skin wheal was diluted in normal saline for the allergen inhalational challenge.

Early asthmatic responses (percent decreases in FEV_1), during treatment with MF DPI (24.25% to 29.06%) were significantly smaller ($p<0.05$) than that observed with placebo treatment (37.42%). The 50 mcg dose had the smallest numerical effect among active treatment groups. Similarly, late asthmatic responses during treatment with MF DPI (6.00% to 12.12%) were significantly smaller than that observed during placebo treatment (23.51%) and dose ordering was demonstrated. There were no statistically significant differences between any two MF DPI treatments for either the early or late response.

Treatment with MF DPI also decreased the response to methacholine challenge. There were significant increases in PC_{20} relative to placebo (1.39 doubling dilutions (DD) to 1.83 DD) at Day 6 of treatment with MF DPI but the differences between each active treatment and placebo was only numerical in a dose responsive manner at Day 4.

Treatment with MF DPI also significantly decreased changes in sputum total eosinophil and EG2 positive eosinophil (activated eosinophil) counts as compared to placebo. On Day 4 (day before allergen challenge), sputum total eosinophil counts decreased after 3 days of treatment with MF DPI 50 mcg BID, MF DPI 100 mcg BID, and MF DPI 400 mcg BID (decreases of 11.6, 17.1, and 26.5 cells/ml of sputum, respectively) compared with an increase of 15.0 cells/ml during treatment with placebo. After allergen challenge on Day 5, sputum total eosinophil counts increased with MF DPI 50 mcg BID and MF DPI 100 mcg BID (8.7 and 13.5 cells/ml of sputum), placebo (76.5 cells/ml) but decreased with MF DPI 400 mcg BID (-12.7 cells/ml of sputum). All MF DPI groups were significantly different than placebo. On Day 6 (no allergen challenge), the 50 and 400 mcg BID doses were significantly different than placebo while 100 mcg was only numerically better. For the same timepoints of Day 4-6, MF DPI 400 mcg was consistently significantly different from placebo, 50 mcg was better at Days 5 and 6 and 100 mcg was only numerically better than placebo.

3. C95-135

C95-135 was a randomized, parallel group, placebo-controlled study. The objective of this study was to evaluate the safety and tolerance of MF DPI 400, 800, and 1200 mcg QAM and 200 mcg BID versus placebo for 28 days in subjects with a history of moderate asthma. Sixty (32 females and 28 males) asthmatic volunteers between the age of 18 and 49 years had a history of moderate asthma (FEV_1 of 60% to 80% predicted) and required treatment. Volunteers had a morning plasma cortisol concentration between 10 mcg/dl and 25 mcg/dl at screening. There were 12 per treatment group and all completed the study. The formulation utilized was micronized lactose/MF mix and was delivered as 100 µg/inhalation.

Prior to study treatment, subjects were taken off their current asthma medications, stabilized on theophylline, and allowed to use albuterol as needed. These subjects were steroid-naïve essentially (One subject in the placebo group had been on BDP 2 puffs prn Up until 2 months prior to first dose of study medication.) Plasma cortisol, urinary free cortisol, plasma MF levels and response to cosyntropin testing were determined.

MF levels were determined on Days 7, 14, 21 and 28. For MF C_{MAX} levels, there was a dose response in the C_{MAX}. The LLOQ was considered to be 50 pg/ml.

	C_{MAX} (pg/ml) on Day			
Treatment	7	14	21	28
200 BID	16.6	19.3	8.5	15.5
400 QAM	55.2	55.6	75	65.6
800 QAM	110.6	80.9	92.5	105.3
1200 QAM	122.9	163.8	200.8	242.6

	AUC (0-12 hr) (pg-hr/ml) (LLOQ = 50 pg/ml)			
Treatment	Day 7	14	21	28
200 BID	31.9	40.9	5.33	10.9
400 QAM	174	175	206	163
800 QAM	444	362	422	462
1200 QAM	693	911	1131	1156

Blood sample data was retrieved over 24 hours, however, only the 12 hour AUC was available in a table. Many data points for 200 BID and 400 QD were below the LLOQ so the sponsor considered the C_{MAX} as the primary variable. It appeared that there was evidence of increasing MF levels for 1200 mcg throughout the treatment period but not for the other doses. The mean C_{MAX} on Day 7 was significantly lower than the C_{MAX} on Day 28.

For the plasma cortisol AUC, there was not an impressive decrease in the cortisol AUC relative to placebo over the 28 days and across treatment groups. Only 400 mcg on Day 28 was statistically different from placebo. The sponsor says that there were no overall treatment effects for C_{MAX} cortisol or 8 a.m. cortisol concentrations.

Mean Plasma Cortisol AUC (mcg-hr/dl)(n=12 per treatment group)						
Parameter	Day	Daily Dose				
		200 BID	400 QAM	800 QAM	1200 QAM	Placebo
$AUC_{(11pm-11pm)}$ % of Placebo	0	246 95%	254 98%	275 106%	273 105%	259
$AUC_{(11pm-11pm)}$ % of Placebo	7	235 89%	230 88%	253 96%	225 86%	263
$AUC_{(11pm-11pm)}$ % of Placebo	14	205 88%	194 83%	251 107%	196 84%	234
$AUC_{(11pm-11pm)}$ % of Placebo	21	185 84%	183 83%	202 91%	189 86%	221
$AUC_{(11pm-11pm)}$ % of Placebo	28	229 94%	202* 82%	253 103%	229 94%	245

* $p < 0.05$ vs. placebo

Subjects had a cosyntropin stimulation test performed only on Day 29. Only individual line listings and not tabulated data were presented (Volume1-60) in this NDA submission. Data on individuals that were outliers (subjects whose prestimulation concentration of plasma cortisol was <5 μg/dl, whose poststimulation concentration was <18 μg/dl, or whose response to stimulation was not an increase of at least 7 μg/dl) was also not presented in a tabulated form. At 30 minutes post-cosyntropin, cortisol was increased by at least 7 μg/dl to values >18 μg/dl. At pre-ACTH, all subjects had cortisol levels of at least 10 μg/dl except for a 9 μg/dl in a placebo subject.

For urinary cortisol levels, there were no significant treatment group differences compared with placebo. A review of the line listings, however, indicates that there was a great

amount of variability in the values so it is difficult to know whether statistical testing would ever be able to discern a difference among treatment groups.

No efficacy evaluations were planned during this study but safety reasons spirometry and PEFR was performed on days 7, 14, 21 and 28. Although there were no consistent dose-related or time-related trends, results were generally greater for the active treatment groups.

Thirteen subjects (22%) reported at least one adverse event during the study; headache 9 (15%), nausea 1 (2%), dry mouth 5 (8%), dry cough 1 (2%), pharyngitis 4 (7%), and rhinitis 1 (2%). Headache and dry mouth were seen as often in the placebo group as in the treatment group. Pharyngitis was seen only in the active treatment group with 1 case each in 400 QD and 800 QD groups and 2 in the 1200 QD group.

The line listings for the laboratory results were reviewed and no pertinent changes could be identified. ECGs were performed at Screening and at follow-up. There did not appear to be any regular or recurrent pattern in interval change. No important changes were noted in the ECGs. In a random sampling of the vital sign line listings, there did not appear to be any important changes. During the study, no subject experienced a body weight gain greater than 5 pounds; one subject in the 1200 QD group had a body weight gain of 5 pounds.

In summation of C95-135, detectable MF levels were present in a dose dependent manner but plasma cortisol, cosyntropin and probably urine free cortisol did not reveal HPA axis effect.

4. C94-071

This trial examined the safety and tolerance of MF DPI – pure powder – in volunteers with history of moderate asthma at doses of 200 mcg qd, 400 mcg qd, 600 mcg qd or placebo qd in groups of 2 subjects each for 28 days. 24 hour plasma cortisol AUC were performed on days 0,7,14,21, and 28.

Treatment Group	Parameter	Day 7	Day 14	Day 21	Day 28	Baseline
A - 200 mcg	$AUC_{(0-24)}$	216	212	225	109[b]	331
N = 12	%Change[a]	-8	-11	-8	-20	+8
B - 400 mcg	$AUC_{(0-24)}$	225	228	227	235	338
N = 12	%Change[a]	-5	-4	-7	-10	+10
C - 600 mcg	$AUC_{(0-24)}$	190 [b]	186 [b]	194 [b]	214 [b]	317
N = 12	%Change[a]	-19	-22	-20	-18	+3
D – Placebo	$AUC_{(0-24)}$	236	238	244	262	308
N = 12						

a = % change from placebo at that timepoint
b = $p<0.05$ compared with placebo.

Thus, the 600 mcg dose of pure MF DPI had a significantly lower cortisol AUC than placebo for the entire treatment period and the 200 mcg qd dose was only significantly different at Day 28. The 400 mcg dose was not significantly different from placebo at any timepoint. For unclear reasons, all groups including placebo had a decrease in the AUC compared with baseline.

5. C94-127

This 16 center randomized, placebo-controlled U.S. trial evaluated the efficacy and tolerance of pure powder MF DPI 100 mcg QD, MF DPI 400 mcg QD, MF DPI 200 mcg BID and placebo in 279 subjects with baseline $FEV_1 \geq 60\%$ for 4 weeks. Subjects must have been using a dose of inhaled corticosteroids for at lease 30 days prior to Screening.

For the primary efficacy parameter of change in FEV_1 from Baseline, all active treatment groups were significantly more effective than placebo at all time points except for MF DPI 100 mcg QD at Day 4. The greatest improvement in the mean percent changes from Baseline at Endpoint for FEV_1 was seen in the MF MDI 200 mcg BID (7.9%), followed by the MF DPI 400 mcg QD (5.6%) and MF DPI 100 mcg QD groups (1.2%) while placebo decreased by 11.5%. A dose response was present for the other timepoints also.

The most frequently reported adverse events were headache, rhinitis, dyspepsia, nasal congestion, pharyngitis, viral infection and sinusitis. Dysphonia was rare but dysmennorhea, coughing, sinus congestion and perhaps sinusitis appeared to be more common with MF DPI than with placebo. Musculoskeletal pain was equally apparent among the treatment groups including placebo.

A subset of 68 subjects received Cortrosyn stimulation testing and there was a mean change of 0.4, -3.8, -0.5 and 1.9 in the 100 qd, 400 qd, 200 BID and placebo groups, respectively, for the difference of pre-treatment and post-treatment between Screening and Endpoint. Other laboratory and ECG data was not reviewed for this trial.

6. 193-009

The purpose of this single-center placebo-controlled German study was to evaluate in 30 healthy male volunteers the potential for systemic bioactivity based on HPA axis function of rising single-doses of pure mometasone furoate powder (SCH 32088) delivered by inhalation with a breath-activated powder inhaler (400 µg, 800 µg, 1600 µg, 3200 µg and placebo) compared with budesonide powder delivered by inhalation with the Pulmicort Turbuhaler, (300 µg, 600 µg, 1200 µg, 2400 µg and placebo) and with orally administered prednisone (5 mg, 10 mg, 20 mg, 40 mg and placebo). Each volunteer was randomly assigned to either the MF, budesonide or prednisone group and received each dose within that treatment group in a rising single-dose fashion with the lowest dose being administered first. The placebo dosing was randomized within the treatment sequence. There was a 72 hours washout period between each dose

The $AUC_{(0\text{-}24)}$ was reduced by 15%, 35%, 56%, and 71% from the placebo value following the MF 400, 800, 1600 and 3200 mcg doses, respectively. The $AUC_{(0\text{-}24)}$ was reduced by 3%, 22%, 36%, and 52% from the placebo value following the budesonide 300, 600, 1200 and 2400 mcg doses, respectively. These decreases were significantly different from placebo for all doses except the very lowest in each treatment group. Both MF and budesonide also caused dose-related decreases in the maximum plasma cortisol concentrations (Cmax) and increased the time to maximum plasma cortisol concentration (Tmax). At the 1600 mcg dose for MF and the 1200 mcg budesonide dose, there were statistically significant differences in changes from placebo noted between mometasone and budesonide in plasma cortisol $AUC_{(0\text{-}24)}$ and Cmax. The shapes of the plasma cortisol profile and the percent $AUC_{(0\text{-}24)}$ reductions (35% and 36%) for mometasone 800 µg and budesonide 1200 mcg were considered to be similar. Cross-

reactivity between prednisone and the radioimmunoassay used to measure plasma cortisol concentrations confounded the 10 mg, 20 mg and 40 mg prednisone data.

A single administration of MF via a powder inhaler elicited a detectable plasma mometasone concentration at all doses.

Increases in transaminases were noted in four volunteers between Screening and at the conclusion of the study:

Subject # 4	Prednisone	ALT 15 to 42
Subject #10	MF	ALT 16 to 29 (10 at follow-up)
Subject #13	MF	ALT 17 to 38
Subject #17	Prednisone	AST/ALT 9/11 to 20/59 (12/18 at follow-up)

P. The Integrated Summary of Efficacy

There were five placebo-controlled multicenter studies undertaken in support of the safety and efficacy of MF DPI (C96-136, 186, 196 134, and 168) and an additional placebo-controlled study (C96-137) which addressed the issue of oral prednisone reduction. This integrated summary of efficacy will largely be based on these large placebo controlled trials and supportive data from the other studies will be included. In these trials and all the other efficacy studies, pulmonary function was assessed by changes in FEV_1, FEF_{25-75}, FVC, and PEFR (AM and PM). The primary efficacy endpoint for the trials (except for C96-137) was the change in FEV_1 between Baseline and Endpoint. Endpoint was defined as the last visit during the treatment period for which the subject had non-missing data. Other efficacy parameters included subject-evaluated asthma symptom scores (wheezing, coughing, and difficulty breathing), use of rescue medication, nocturnal awakenings requiring the use of rescue medication, physician assessment of response to therapy, time to worsening of asthma, and occurrence of clinical asthma exacerbations. Quality of life was assessed by use of a validated acute form of the Short-Form Health Survey (SF-36) and a validated asthma specific HQOL module (which evaluated breathlessness, mood, social impact, asthma concerns, psychological impact, and physical symptoms) as part of Studies C96-136 and C96-137. The population evaluated were based on the Intent-to–treat principle but the sponsor also submitted efficacy evaluable population analyses for the primary endpoint. Data on the secondary efficacy variables of clinical asthma exacerbations, methacholine challenge testing (C96-136) and Peak Inspiratory Flow Rate (C96-136, 134,137 and 186) are not discussed in this ISE.

There were two multicenter international studies (I96-111 and 112) which were non-placebo-controlled and which involved an active control. An additional multicenter international study (I96-113) was also not placebo controlled but did evaluate a dose response among three bid doses of MF DPI. There were two single center placebo-controlled short term studies (I96-401 and 402) which examined the effect of treatment with MF DPI on the AMP or allergen-induced asthmatic response. Three other studies (C94-071, 127 and I93-009) are briefly mentioned in this review that evaluated the pure powder formulation of MF DPI rather than the MF-lactose formulation utilized in the other trials.

The package labeling as submitted by the sponsor in the NDA package seeks approval for 400 mcg qd with a dose reduction to 200 mcg qd to be considered. From 200 mcg qd, the

dose can be increased to 400 mcg qd or 200 mcg bid if more control is needed. For those patients with "severe asthma who may require oral corticosteroids," the recommended starting dose is listed as 400 mcg bid and once reduction of oral steroid is complete, MF DPI should be titrated down to its lowest effective dose.

1. Treatments Administered in Placebo-Controlled Trials

C96-136

	AM Dose	Total mcg/Day
Group 1	100 mcg x 2	MF 200 mcg (AM)
Group 2	200 mcg x 2	MF 400 mcg (AM)
Group 3	Placebo x 2	0

C96-186

Treatment Group	AM	PM	TOTAL (mcg/day)
Group 1	100 mcg MF DPI x 2 puffs	Placebo x 2 puffs	MF DPI 200 mcg QD
Group 2	200 mcg MF DPI x 2 puffs	Placebo x 2 puffs	MF DPI 400 mcg QD
Group 3	100 mcg MF DPI x 2 puffs	100 mcg MF DPI x 2 puffs	MF DPI 400 mcg (BID dosing)
Group 4	Placebo x 2 puffs	Placebo x 2 puffs	Placebo

C96-196

	Regimen	AM	PM	Total mcg/day
Group 1	200 mcg BID	100 mcg x 2	100 mcg x 2	MF 400 mcg
Group 2	400 mcg QAM	200 mcg x 2	Placebo x 2	MF 400 mcg
Group 3	200 mcg QAM	100 mcg x 2	Placebo x 2	MF 200 mcg
Group 4	200 mcg QPM	Placebo x 2	100 mcg x 2	MF 200 mcg
Group 5	Placebo	Placebo x 2	Placebo x 2	0

C96-134

	AM		PM		
Treatment Group	MF DPI	BDP MDI	MF DPI	BDP MDI	Total (mcg/day)
Group 1	100 mcg x 1	Placebo x 4 puffs	100 mcg x 1	Placebo x 4 puffs	MF 200 mcg
Group 2	200 mcg x 1	Placebo x 4 puffs	200 mcg x 1	Placebo x 4 puffs	MF 400 mcg
Group 3	400 mcg x 1	Placebo x 4 puffs	400 mcg x 1	Placebo x 4 puffs	MF 800 mcg
Group 4	Placebo x 1	42 mcg x 4 puffs	Placebo x 1	42 mcg x 4 puffs	BDP 336 mcg
Group 5	Placebo x 1	Placebo x 4 puffs	Placebo x 1	Placebo x 4 puffs	Placebo 0 mcg

C96-168

	AM		PM		
Treatment Group	MF DPI	BDP MDI	MF DPI	BDP MDI	Total mcg/Day
Group 1	100 mcg x 1 puff	Placebo x 4 puffs	100 mcg x 1 puff	Placebo x 4 puffs	MF 200 mcg
Group 2	200 mcg x 1 puff	Placebo x 4 puffs	200 mcg x 1 puff	Placebo x 4 puffs	MF 400 mcg
Group 3	Placebo x 1 puff	42 mcg x 4 puffs	Placebo x 1 puff	42 mcg x 4 puffs	BDP 336 mcg
Group 4	Placebo x 1 puff	Placebo x 4 puffs	Placebo x 1 puff	Placebo x 4 puffs	Placebo (0)

C96-137

	AM	PM	
	MF DPI	MF DPI	Total mcg/day
Group 1	200 mcg x 2	200 mcg x 2	MF 800 mcg
Group 2	400 mcg x 2	400 mcg x 2	MF 1600 mcg
Group 3	Placebo x 2	Placebo x 2	Placebo (0)

Placebo-Controlled Study Population Number Length	Dose	FEV_1 (Yes = $p \leq 0.05$)	FVC	FEF 25-75	AM PEFR	PM PEFR	B agonist use	Noct. Awakenings	Physician Eval.	Asthma Scores					
										AM Wheeze	PM Wheeze	AM Diff. Breathing	PM Diff. Breathing	AM Cough	PM Cough
C96-136 Previously Maintained on B-agonists 365 subjects 3 mo./ 9 mo. open	200µg QD	Yes	.05	Yes	No	No	Yes	No	Yes (.05 v. 400)	Yes	Yes	.05	Yes	No	No
	400µg QD	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No
C96-186 Previously Maintained on B-agonists 306 subjects 12 weeks	200µg QD	No	No	Yes	Less v. 400 & 200 BID	Less v. 400 & 200 BID	Yes	No	Less v. 400 & 200 BID	Less v. 200 BID	Less v. 200 BID	Less v. 200 BID	Less v. 200 BID	No	No
	400µg QD	Yes	No	Yes	Yes	Yes	Yes	No	Yes	.05	Yes	Yes	Yes	Yes	Yes
	200µg BID	Yes	.05	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
C96-196 Previously Maintained on inhaled corticosteroids 286 subjects 12 weeks	200µg QAM	Less v. others	Less v.200 PM	No	Yes	Yes	Yes	Yes	Yes	Yes, .05 v. 200 BID	Yes	Yes, less v. 200 BID	Yes, less v. 200 BID	Yes	Yes
	200µg QPM	Yes	Yes	Yes	Yes	Yes	.05 v. 200 BID	Less v. 200 BID	Yes	Yes	Yes	Yes	Yes, .05 v. 200 BID	Less v. 200 BID	Yes, less v. 200 BID
	400µg QAM	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	200µg BID	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
C96-134 Previously Maintained on inhaled corticosteroids 365 subjects 12 weeks	100µg BID	Yes	Yes	Yes, .05 v. 200 BID	Yes, less v. 200 BID	Yes, less v. 200 BID	Yes	Yes	.05	Yes	Yes	Yes	Yes	Yes	Yes
	200µg BID	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	400µg BID	Yes	Yes	Yes	Yes	Yes	Yes	Yes	.05	Yes	Yes	Yes	Yes	Yes	Yes
	BDP 168µg BID	Yes	Yes	Yes	Yes	Yes, less v. 200 BID	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

C96-168 Previously Maintained on inhaled corticosteroids 227 subjects 12 weeks	100µg BID	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	200µg BID	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
	BDP 168µg BID	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No

Appears This Way
On Original

2. FEV_1

FEV_1 - Change from Baseline by Treatment Group - Placebo-Controlled Studies -

Treatment Group	(n)	Baseline FEV_1 (mean)	Change in FEV_1 at Endpoint (mean)	(%)	Placebo Comparison (p-value)	Other Significant Comparisons (p-value)
C96-186 (Subjects previously used bronchodilators alone; 12 weeks parallel-group)						
MF DPI 200 mcg QD AM	77	2.58	0.27	10.4%	0.09	—
MF DPI 400 mcg QD AM	74	2.64	0.41	16.0%	< 0.01	—
MF DPI 200 mcg BID	79	2.56	0.40	16.1%	< 0.01	—
Placebo	74	2.55	0.14	5.5%	—	—
C96-136 (Subjects previously used bronchodilators alone; 12 weeks parallel-group)						
MF DPI 200 mcg QD AM	72	2.60	0.35	14.8%	< 0.01	—
MF DPI 400 mcg QD AM	76	2.57	0.35	14.2%	< 0.01	—
Placebo	86	2.61	0.06	2.5%	—	—
C96-168 (Inhaled-corticosteroid-dependent subjects; 12 weeks parallel-group)						
MF DPI 100 mcg BID	56	2.65	0.12	4.8%	< 0.01	—
MF DPI 200 mcg BID	55	2.59	0.25	9.7%	< 0.01	—
BDP 168 mcg BID	57	2.49	0.11	5.2%	< 0.01	—
Placebo	57	2.43	-0.21	-8.1%	—	—
C96-134 (Inhaled-corticosteroid-dependent subjects; 12 weeks parallel-group)						
MF DPI 100 mcg BID	76	2.61	0.14	4.8%	< 0.01	—
MF DPI 200 mcg BID	70	2.67	0.18	7.1%	< 0.01	—
MF DPI 400 mcg BID	73	2.49	0.15	6.2%	< 0.01	—
BDP 168 mcg BID	71	2.62	0.09	3.0%	< 0.01	—
Placebo	74	2.48	-0.16	-6.6%	—	—
C96-196 (Inhaled-corticosteroid-dependent subjects; 12 weeks parallel-group) —following 2 weeks of open-label treatment with MF DPI 200 mcg BID						
MF DPI 200 mcg QD AM	58	2.57	-0.22	-8.4%	0.23	—
MF DPI 200 mcg QD PM	54	2.49	0.03	1.5%	< 0.01	p < 0.01 vs 200 mcg QD AM
MF DPI 400 mcg QD AM	58	2.64	-0.01	-1.4%	< 0.01	p < 0.01 vs 200 mcg QD AM
MF DPI 200 mcg BID	58	2.75	-0.03	-0.6%	< 0.01	p = 0.01 vs 200 mcg QD AM
Placebo	58	2.68	-0.30	-9.8%	—	—
C96-137 (Oral-prednisone-dependent subjects; 12 weeks parallel-group)						
MF DPI 400 mcg BID	45	1.87	0.25	14.0%	< 0.01	—
MF DPI 800 mcg BID	43	1.79	0.17	9.5%	< 0.01	—
Placebo	43	1.78	-0.19	-12.0%	—	—

Of the five placebo-controlled trials, three addressed the efficacy of both 400 mcg qd and 200 mcg qd (C96-136, 186 and 196). All three trials found 400 mcg qd to be efficacious for improvement in FEV_1 compared with placebo whether or not the subject had previously been on inhaled corticosteroids (ICS). Only one out of the three trials demonstrated statistical efficacy at Endpoint for 200 mcg QAM. In C96-136 (136), the improvement of 400 mcg qd was comparable to that of 200 mcg qd at Endpoint and for other timepoints the higher dose was actually numerically less. In C96-186 (186), 400 qd was comparable to 200 BID throughout the trial and was numerically (p=0.06) better than 200 qd. The 200 mcg qd dose did not beat placebo (p=0.09) but clearly was numerically better than placebo. For C96-196 (196), 200 mcg QAM was not effective (p=0.23) and did not statistically outperform placebo at any timepoint. These trials, while clearly supporting the efficacy of 400 qd for the primary variable of interest, are not convincing for 200 mcg qam. C96-196 is the only placebo-controlled study in which

subjects previously on ICS were treated with 12 weeks of 400 mcg QAM; furthermore, these subjects had a 2 week run-in period of 200 BID. The sponsor relates that the results of this particular study support a switch from previous (BID) ICS regimens to directly dosing with 400 QAM. While 200 mcg QPM was numerically the most efficacious in C96-196, it should be remembered that spirometry was typically performed in the am making it approximately 12 hours after dosing as opposed to testing 24 hours after dosing for the QAM doses. This shorter dose-test interval may account for the improved efficacy of the 200 QPM dosing; we do not feel that the efficacy of 200 QPM as a daily dosing has been definitively demonstrated.

The effectiveness of 200 mcg BID in improving or maintaining FEV_1 has been shown convincingly in four of the large placebo controlled trials (186,196, 134 and 168). In 186, it was as good as 400 qd. In 196, it was numerically better than 400 QAM and statistically better than 200 QAM but slightly less than 200 QPM. In 134, 200 BID numerically outperformed all other doses (100 BID, 400 BID and BDP). In 168, 200 BID numerically outperformed BDP 168 BID and MF DPI 100 BID.

Two trials (134 and 168) looked at 100 mcg BID and found it statistically better than placebo. In 168, the effect was comparable to BDP 168 BID while in 134 it numerically outperformed BDP and was comparable to 400 BID. Only one trial utilized 200 QPM (196) and found that it numerically outperformed 200 and 400 QAM and 200 BID but, again, spirometry testing was done only approximately 12 hours after dosing.

Over all of these placebo-controlled studies, the change in FEV_1 at Endpoint was not significantly different between any of the MF DPI groups in any study except C96-196, in which FEV_1 decreased significantly more in the MF DPI 200 mcg QD AM group than in the 200 mcg QD PM, 400 mcg QD AM, or 200 mcg BID groups ($p \leq 0.01$). There was a numerical trend for FEV_1 to increase more in the MF DPI 200 mcg BID group than in the 100 mcg BID group in Studies 134 and 168; whereas MF DPI 400 mcg BID showed no numerical advantage over 200 mcg BID in Study 134.

The FEV_1 variable was also examined in subgroups according to $FEV_1 \geq$ or $< 75\%$ predicted, gender, race, and age. A statistical differentiation of effect size was not performed between the groups. In each of the large placebo-controlled trials, MF DPI appeared to be more effective in those subjects with an $FEV_1 < 75\%$ predicted. There did not appear to be any overt differences in the efficacy of MF DPI between genders and there were generally too few non-Caucasians or those outside the age range of 18-64 years to draw any conclusions of a differential in effectiveness.

It should be mentioned that 136 involved a 9 month open label extension in which all treatment groups were randomized into a.m. or p.m. treatment groups of either 200 or 400 mcg. The subjects previously on MF DPI maintained their improvement during the 9 month extension. It is interesting to note that those subjects randomized to the p.m. dosing in the open label phase appeared to have a slight numerical improvement compared with the a.m. dosing.

Other trials also looked at the change in FEV_1 from Baseline. FEV_1 was a secondary endpoint in C96-137. Subjects on either 400 or 800 mcg BID did significantly better than those subjects randomized to placebo during the initial 3 month phase. In fact, these subjects, despite demonstrating a reduction in oral steroid usage had an improvement in their FEV_1 that

was maintained during the 9 month open label phase. Interestingly, subjects on 400 mcg BID appeared to do numerically better than those on 800 mcg BID.

In the two large international non-placebo controlled studies I96-111 and 112, MF DPI was studied along with either fluticasone or budesonide. In 111, there was little numerical difference at most timepoints among MF DPI 100 BID, 200 BID, 400 BID and fluticasone propionate 250 BID but at Endpoint, 400 BID was slightly numerically better than FP and 200 BID and statistically better than 100 BID. In 112, MF DPI 200 BID and 400 BID were very comparable and statistically better than budesonide at Endpoint. In I96-113, where MF DPI 200, 400 and 600 BID were evaluated, no statistical differences existed among the doses; interestingly, 200 and 600 BID were very comparable for most of the trial but at Endpoint, the mean for 600 BID was 20-30 cc better than the lower doses, an effect which is probably not clinically relevant.

FEV_1 - Change from Baseline - Non-Placebo-Controlled Studies

Treatment Group	(n)	Baseline FEV_1 (mean)	Change in FEV_1 at Endpoint (mean)	(%)	Significant Comparisons (p-value)
I96-111 (Inhaled-corticosteroid-dependent subjects; 12 wks parallel-group)					
MF DPI 100 mcg BID	179	2.53	0.07	3.9%	—
MF DPI 200 mcg BID	182	2.43	0.16	7.5%	—
MF DPI 400 mcg BID	181	2.38	0.19	8.8%	p = 0.02 vs MF 100 mcg BID
FP 250 mcg BID	183	2.46	0.16	8.0%	—
I96-112 (Inhaled-corticosteroid-dependent subjects; 12 wks parallel-group)					
MF DPI 100 mcg BID	183	2.49	0.10	5.3%	—
MF DPI 200 mcg BID	174	2.52	0.16	6.6%	p = 0.02 vs BUD 400 mcg BID
MF DPI 400 mcg BID	184	2.54	0.16	7.2%	p = 0.01 vs BUD 400 mcg BID
BUD 400 mcg BID	179	2.47	0.06	3.1%	—
I96-113 (Inhaled-corticosteroid-dependent subjects; 12 wks parallel-group)					
MF DPI 200 mcg BID	168	2.43	0.07	4.2%	—
MF DPI 400 mcg BID	163	2.47	0.06	3.5%	—
MF DPI 600 mcg BID	173	2.51	0.09	4.4%	—

Based on these international studies and on the large domestic placebo-controlled study C96-134, it can be seen that BID dose levels greater than 200 mcg BID resulted in diminishing further benefits.

3. Daily Prednisone Requirement

The primary efficacy variable in C96-137 was the percent change from Baseline at Endpoint in daily oral prednisone use by subjects who were dependent upon oral prednisone. It appears that genuine efforts were made in the Pre-screening period to reduce the prednisone dosage to the lowest tolerated dose. The great majority of subjects (115 out of 132) in this study also were using ICS at Baseline.

Prednisone Use (mg/day) - Change from Baseline

Treatment Group	(n)	Baseline Prednisone (Mean)	Change in Prednisone at Endpoint (Mean)	(%)	Placebo Comparison (p-value)	Other Significant Comparison(s) (p-value)
MF DPI 400 mcg BID	45	11.93	-6.33	-46.0%	< 0.01	—
MF DPI 800 mcg BID	43	12.02	-3.19	-23.9%	< 0.01	—
Placebo	43	11.56	11.81	164.4%	—	—

Subjects on either dose of BID MF DPI were able to significantly reduce their dosage of prednisone. 40% of the 400 BID and 37% of the 800 BID group compared with 0 of the placebo group were able to completely come off of prednisone. It should be noted that 800 BID did not confer any benefit over 400 BID.

During the 9 month open label phase, all subjects were begun on 800 mcg BID and then tapered down to as low as 400 BID once they were off prednisone. At the end of the 9 months, the respective mean decreases among the original 400 BID, 800 BID and placebo groups were – 7.36 mg, -4.11 mg and –7.35 mg. Thus, those subjects originally on placebo were able to "catch up" in their prednisone reduction once they were on mometasone and the original reductions seen in the other groups were largely maintained.

The sponsor performed an analysis based on oral prednisone use at Baseline. Subjects were stratified into a low-dose prednisone stratum (< 12.5 mg/day) and a high dose prednisone stratum (≥ 12.5 mg/day). The greatest reductions at Endpoint were observed in high dose subjects in both MF DPI groups.

	(n)	Baseline Prednisone (Mean)	Change in Prednisone use at Endpoint (Mean)	(%)
Daily Prednisone < 12.5 mg at Baseline				
MF DPI 400 mcg BID	32	8.23	-0.33	3.9%
MF DPI 800 mcg BID	26	7.47	0.44	6.3%
Placebo	31	7.89	15.09	226.2%
Daily Prednisone ≥ 12.5 mg at Baseline				
MF DPI 400 mcg BID	13	19.42	-13.27	-68.8%
MF DPI 800 mcg BID	17	19.26	-6.06	-32.5%
Placebo	12	21.07	4.64	36.1%

The means here indicate that subjects already at a lower prednisone dose were essentially only able to maintain their prednisone dose while the largest amount of the decrease was done in that one-third of the subjects on high dose prednisone. It still must be remembered that approximately 40% of the active treatment group were able to come off prednisone altogether.

4. FVC and FEF_{25-75}

The changes seen in FVC were typically less impressive than those seen for FEV_1. In the large placebo-controlled trials except for 186, there were consistently statistical improvements compared with placebo except for the 200 mcg QAM doses in 186, 196 and borderline (p=0.05) for 136. In 186, a 0.05 difference with placebo was noted only for 200 BID with the rest of the doses having nonsignificant differences with placebo. FEF_{25-75} generally had significant improvements in all MF DPI treatment groups with the exception of the 200 mcg QAM group in 196.

5. PEFR

Improvements in the AM PEFR generally tracked with the PM PEFR. Statistical efficacy compared with placebo was seen in each MF DPI treatment group except for the 200 QAM treatment group in 136 and186. This dose did have a significant difference with placebo in 196.

AM PEFR (liters/minute) - Change from Baseline

Treatment Group	(n)	Baseline AM PEFR (mean)	Change in AM PEFR at Endpoint (mean)	(%)	Placebo Comparison (p-value)	Other Significant Comparisons (p-value)
C96-186 (Subjects used bronchodilators alone; 12 weeks parallel-group)						
MF DPI 200 mcg QD AM	78	377.0	26.13	7.4%	0.72	—
MF DPI 400 mcg QD AM	74	397.5	52.10	15.0%	**< 0.01**	p < 0.01 vs. 200 mcg QD
MF DPI 200 mcg BID	79	362.2	63.58	19.6%	**< 0.01**	p < 0.01 vs. 200 mcg QD
Placebo	74	369.9	22.73	5.8%	—	—
C96-136 (Subjects used bronchodilators alone; 12 weeks parallel-group)						
MF DPI 200 mcg QD AM	72	372.8	15.80	7.5%	0.46	—
MF DPI 400 mcg QD AM	76	369.7	41.29	13.1%	**< 0.01**	p = 0.02 vs. 200 mcg QD
Placebo	86	376.8	7.95	3.0%	—	—
C96-168 (Inhaled-corticosteroid-dependent subjects; 12 weeks parallel-group)						
MF DPI 100 mcg BID	56	396.5	26.73	7.4%	**< 0.01**	—
MF DPI 200 mcg BID	54	371.5	37.35	14.0%	**< 0.01**	—
BDP 168 mcg BID	57	371.0	19.25	6.4%	**< 0.01**	—
Placebo	57	360.8	-21.43	-4.4%	—	—
C96-134 (Inhaled-corticosteroid-dependent subjects; 12 weeks parallel-group)						
MF DPI 100 mcg BID	75	381.4	14.17	4.6%	**< 0.01**	p = 0.02 vs. 200 mcg BID
MF DPI 200 mcg BID	70	397.9	35.37	9.9%	**< 0.01**	—
MF DPI 400 mcg BID	73	365.7	29.49	9.3%	**< 0.01**	—
BDP 168 mcg BID	71	387.9	20.46	5.7%	**< 0.01**	—
Placebo	74	375.7	-27.93	-7.0%	—	—
C96-196 (Inhaled-corticosteroid-dependent subjects; 12 weeks parallel-group) —following 2 weeks of open-label treatment with MF DPI 200 mcg BID						
MF DPI 200 mcg QD AM	58	393.7	-8.93	-1.8%	**< 0.01**	—
MF DPI 200 mcg QD PM	54	391.5	4.30	1.8%	**< 0.01**	—
MF DPI 400 mcg QD AM	58	387.3	-6.03	-1.6%	**< 0.01**	—
MF DPI 200 mcg BID	58	383.5	6.85	2.2%	**< 0.01**	—
Placebo	58	397.0	-36.90	-8.1%	—	—
C96-137 (Oral-prednisone-dependent subjects; 12 weeks parallel-group)						
MF DPI 400 mcg BID	45	324.3	40.97	14.4%	**< 0.01**	—
MF DPI 800 mcg BID	43	299.0	42.21	15.6%	**< 0.01**	—
Placebo	42	316.1	-37.51	-10.5%	—	—

For 136, there was clear dose ordering between 200 QD and 400 QD in the AM and PM PEFR. For 186, there was no difference in the AM and PM PEFR between placebo and 200 QD and 200 BID was numerically better than 400 QD. For 196, a trial in which subjects were previously on ICS and were on MF DPI 200 BID, there were smaller changes in the PEFR in those subjects on MF DPI compared with 136 and 186; the 200 BID dose tended to do the best followed by 200 QPM, then 400 QAM and 200 QAM for both AM and PM PEFR. Interestingly, 200 QPM numerically outperformed 200 QAM at Endpoint for PM PEFR despite the 24 hour lag of peak flow testing for 200 QPM compared to 12 hours for 200 QAM. For AM and PM PEFR in 134, 200 BID was again the best followed by 400 BID and then 100 BID/budesonide. In C96-168, 200 BID was the best for AM PEFR followed by the very similar effects of 100 BID and

BDP; for PM PEFR, there were some differences with 100 and 200 BID performing comparably followed by BDP.

In summarizing this data for PEFR, 200 BID tended to be the most effective of the MF DPI doses and 200 QD was the least effective.

6. Beta agonist Use

All of these changes in B agonist use were significantly better in the MF DPI groups than in the placebo groups, except for the MF DPI 200 QPM group in Study C96-196, and the MF DPI 800 BID group in Study C96-137. Dose ordering was apparent in 136,134, 196 and for the QD doses in 186. Larger decreases were generally seen in those trials involving subjects previously maintained only on B agonists alone.

Proventil Use (puffs/day) - Change from Baseline

Treatment Group	n	Baseline Proventil Use (mean)	Change in Proventil Use at Endpoint (mean)	Placebo Comparison (p-value)	Other Significant Comparison(s) (p-value)
			C96-186		
MF DPI 200 mcg QD AM	78	3.70	-1.84	0.04	—
MF DPI 400 mcg QD AM	74	3.84	-2.22	< 0.01	—
MF DPI 200 mcg BID	79	3.66	-1.99	0.01	—
Placebo	74	4.50	-1.08	—	—
			C96-136		
MF DPI 200 mcg QD AM	72	4.02	-1.58	< 0.01	—
MF DPI 400 mcg QD AM	76	4.18	-2.23	< 0.01	—
Placebo	86	4.09	-0.47	—	—
			C96-168		
MF DPI 100 mcg BID	55	3.21	-1.18	< 0.01	—
MF DPI 200 mcg BID	55	2.86	-0.94	< 0.01	—
BDP 168 mcg BID	56	3.85	-1.05	< 0.01	—
Placebo	57	3.70	1.31	—	—
			C96-134		
MF DPI 100 mcg BID	74	3.67	-0.61	< 0.01	—
MF DPI 200 mcg BID	70	4.04	-1.11	< 0.01	—
MF DPI 400 mcg BID	73	3.40	-1.32	< 0.01	—
BDP 168 mcg BID	71	4.04	-0.99	< 0.01	—
Placebo	74	4.73	0.72	—	—
			C96-196		
MF DPI 200 mcg QD AM	58	2.88	0.54	0.02	—
MF DPI 200 mcg QD PM	54	1.98	0.73	**0.07**	—
MF DPI 400 mcg QD AM	58	2.45	0.21	< 0.01	—
MF DPI 200 mcg BID	58	2.69	-0.15	< 0.01	p = 0.05 vs. 200 mcg QD PM
Placebo	58	2.70	1.53	—	—
			C96-137		
MF DPI 400 mcg BID	44	4.97	-1.83	< 0.01	—
MF DPI 800 mcg BID	43	4.21	-0.88	**0.11**	—
Placebo	41	5.10	0.29	—	—

7. Nocturnal Awakenings Necessitating B agonist Use

There was a mean of less than 1 awakening per night at Baseline in all studies. Awakenings decreased numerically in all MF DPI groups in all studies (except 200 QPM in C96-196) but the difference reached significance only in C96-134, C96-137, and for 3 of 4 MF DPI groups in C96-196. Other than 196, 400 QD appeared to be numerically the most effective when it was utilized in the trial.

Nocturnal Awakenings - Change from Baseline

Treatment Group	n	Baseline Awakenings (mean)	Change in Awakenings at Endpoint (mean)	Placebo Comparison (p-value)	Other Significant Comparison(s) (p-value)
C96-186					
MF DPI 200 mcg QD	78	0.35	-0.22	0.22	—
MF DPI 400 mcg QD	73	0.38	-0.25	0.11	—
MF DPI 200 mcg BID	79	0.29	-0.20	0.35	—
Placebo	74	0.48	-0.12	—	—
C96-136					
MF DPI 200 mcg QD	72	0.41	-0.16	0.20	—
MF DPI 400 mcg QD	76	0.45	-0.22	0.06	—
Placebo	86	0.41	-0.04	—	—
C96-168					
MF DPI 100 mcg BID	56	0.14	-0.09	0.34	—
MF DPI 200 mcg BID	55	0.28	-0.18	0.15	—
BDP 168 mcg BID	56	0.25	0.06	0.87	—
Placebo	56	0.41	0.09	—	—
C96-134					
MF DPI 100 mcg BID	75	0.25	-0.02	< 0.01	—
MF DPI 200 mcg BID	70	0.20	-0.08	< 0.01	—
MF DPI 400 mcg BID	74	0.24	-0.12	< 0.01	—
BDP 168 mcg BID	71	0.23	0.00	< 0.01	—
Placebo	73	0.26	0.31	—	—
C96-196					
MF DPI 200 mcg QD AM	58	0.15	0.07	0.02	—
MF DPI 200 mcg QD PM	54	0.08	0.15	0.13	—
MF DPI 400 mcg QD AM	58	0.09	0.07	0.01	—
MF DPI 200 mcg BID	56	0.30	-0.07	< 0.01	p = 0.03 vs. 200 mcg QD PM
Placebo	58	0.10	0.30	—	—
C96-137					
MF DPI 400 mcg BID	45	0.53	-0.30	< 0.01	—
MF DPI 800 mcg BID	43	0.44	-0.29	< 0.01	—
Placebo	42	0.29	0.18	—	—

8. Physician's Assessment of Response to Therapy

At all visits, the physician investigator assessed the subject's response to therapy by comparing the current level of symptoms with those noted at Baseline, based on a 5-point scale: 1 = much improved, 2 = improved, 3 = no change, 4 = worse, and 5 = much worse. Overall, the percentages of subjects evaluated as much improved or improved were higher in the MF DPI groups than in the placebo groups. Across studies, 62%–80% of the subjects treated with MF DPI were rated as much improved or improved at Endpoint, whereas 4%–53% of the subjects treated with placebo were similarly rated.

Quantitatively, every active-treatment group received a significantly better mean score compared with placebo in these double-blinded studies. This occurred even in the studies involving subjects previously on ICS. Significant improvements were also observed in MF DPI 200 mcg BID groups over MF DPI 200 mcg QD AM groups in both C96-186 and C96-196. 200 BID performed numerically the best in the four trials in which it was involved. Dose ordering was typically not present with this variable.

9. Asthma Scores

Every morning and evening, prior to use of study medication, subjects evaluated the following asthma symptoms as they were experienced during the time since the last evaluation: wheezing, difficulty breathing, and cough on a scale from 0 (none) to 3 (very comfortable and interfered with most or all of my daily activities/sleep). For AM wheezing, all active treatment groups produced at least a p=0.05 difference with placebo except for the 200 mcg QD group in C96-186.

Wheezing Scores - Change from Baseline by Treatment Group – (Placebo-Controlled Studies)

	Baseline Wheezing Scores				Change in Wheezing at Endpoint		Placebo Comparison (p-value)		Other Significant Comparison(s) (p-value)
	n	AM	n	PM	AM	PM	AM	PM	
C96-186 (Subjects used bronchodilators alone; 12 weeks parallel-group)									
MF DPI 200 mcg QD AM	78	0.85	78	0.79	-0.31	-0.30	**0.47**	**0.16**	—
MF DPI 400 mcg QD AM	74	0.79	74	0.78	-0.44	-0.44	0.05	< 0.01	—
MF DPI 200 mcg BID	79	0.92	79	0.87	-0.60	-0.53	< 0.01	< 0.01	p ≤ 0.01 vs. 200 QAM‡
Placebo	74	1.06	74	0.99	-0.23	-0.16	—	—	—
C96-136 (Subjects used bronchodilators alone; 12 weeks parallel-group)									
MF DPI 200 mcg QD AM	72	1.03	72	0.96	-0.40	-0.39	0.02	0.02	—
MF DPI 400 mcg QD AM	76	0.97	76	0.92	-0.39	-0.37	0.03	0.04	—
Placebo	86	0.98	86	0.91	-0.14	-0.13	—	—	—
C96-168 (Inhaled-corticosteroid-dependent subjects; 12 weeks parallel-group)									
MF DPI 100 mcg BID	56	0.43	55	0.48	-0.14	-0.17	< 0.01	< 0.01	—
MF DPI 200 mcg BID	54	0.60	55	0.59	-0.29	-0.27	< 0.01	< 0.01	—
BDP 168 mcg BID	57	0.56	56	0.49	-0.11	-0.07	< 0.01	0.04	—
Placebo	57	0.55	57	0.59	0.32	0.15	—	—	—
C96-134 (Inhaled-corticosteroid-dependent subjects; 12 weeks parallel-group)									
MF DPI 100 mcg BID	75	0.63	74	0.65	-0.15	-0.21	< 0.01	< 0.01	—
MF DPI 200 mcg BID	70	0.53	70	0.53	-0.22	-0.20	< 0.01	< 0.01	—
MF DPI 400 mcg BID	73	0.59	73	0.60	-0.25	-0.29	< 0.01	< 0.01	—
BDP 168 mcg BID	71	0.69	71	0.67	-0.25	-0.23	< 0.01	< 0.01	—
Placebo	74	0.64	74	0.66	0.30	0.21	—	—	—
C96-196 (Inhaled-corticosteroid-dependent subjects; 12 weeks parallel-group) —following 2 weeks of open-label treatment with MF DPI 200 mcg BID									
MF DPI 200 mcg QD AM	58	0.55	58	0.50	0.15	0.14	< 0.01	< 0.01	—
MF DPI 200 mcg QD PM	54	0.28	54	0.27	0.22	0.19	< 0.01	< 0.01	—
MF DPI 400 mcg QD AM	58	0.54	58	0.49	0.12	0.08	< 0.01	< 0.01	—
MF DPI 200 mcg BID	58	0.46	58	0.43	-0.02	0.00	< 0.01	< 0.01	p = 0.05 vs 200 mcg QD PM†
Placebo	58	0.38	58	0.35	0.61	0.49	—	—	—
C96-137 (Oral-prednisone-dependent subjects; 12 weeks parallel-group)									
MF DPI 400 mcg BID	45	0.79	44	0.77	-0.31	-0.29	< 0.01	< 0.01	—
MF DPI 800 mcg BID	43	0.56	43	0.48	-0.19	-0.11	< 0.01	0.03	—
Placebo	42	0.70	42	0.70	0.35	0.17	—	—	—

‡ AM and PM scores. † AM scores only.

The efficacy of MF DPI appears convincing for wheezing; while the active treatment groups were statistically different from placebo, however, it is problematical to discern what a clinically relevant effect size is for this 4 point wheezing score or for the other two asthma scores used in this NDA of Difficulty Breathing or Cough.

Among the international non-placebo controlled trials 111 and 112, there was a dose ordering among the MF DPI groups while for 113, 600 BID was no better than 600 BID.

All MF DPI treatment groups except again for 200 mcg QD in C96-186 produced a significant decrease in the AM and PM Difficulty Breathing scores compared with placebo.

Difficulty-Breathing Scores - Change from Baseline

	Baseline Difficulty Breathing Scores				Change in Difficulty Breathing at Endpoint		Placebo Comparison (p-value)		Other Significant Comparison(s) (p-value)
	n	AM	n	PM	AM	PM	AM	PM	
C96-186 (Subjects used bronchodilators alone; 12 weeks parallel-group)									
MF DPI 200 mcg QD AM	78	0.98	78	0.96	-0.34	-0.34	0.41	0.23	—
MF DPI 400 mcg QD AM	74	1.04	74	1.03	-0.49	-0.53	**0.02**	**< 0.01**	—
MF DPI 200 mcg BID	79	1.10	79	1.11	-0.64	-0.60	**< 0.01**	**< 0.01**	p ≤ 0.01 vs. 200 mcg QD AM‡
Placebo	74	1.14	74	1.08	-0.26	-0.21	—	—	
C96-136 (Subjects used bronchodilators alone; 12 weeks parallel-group)									
MF DPI 200 mcg QD AM	71	1.16	71	1.12	-0.44	-0.44	**0.05**	**0.02**	—
MF DPI 400 mcg QD AM	76	1.10	76	1.09	-0.48	-0.47	**0.02**	**< 0.01**	—
Placebo	86	1.16	86	1.07	-0.20	-0.16	—	—	—
C96-168 (Inhaled-corticosteroid-dependent subjects; 12 weeks parallel-group)									
MF DPI 100 mcg BID	56	0.56	55	0.65	-0.22	-0.31	**< 0.01**	**< 0.01**	—
MF DPI 200 mcg BID	54	0.75	55	0.77	-0.25	-0.23	**< 0.01**	**< 0.01**	—
BDP 168 mcg BID	57	0.69	56	0.74	-0.10	-0.18	**0.02**	**< 0.01**	—
Placebo	57	0.77	57	0.71	0.20	0.14	—	—	—
C96-134 (Inhaled-corticosteroid-dependent subjects; 12 weeks parallel-group)									
MF DPI 100 mcg BID	75	0.82	74	0.87	-0.15	-0.24	**< 0.01**	**< 0.01**	—
MF DPI 200 mcg BID	70	0.79	70	0.78	-0.31	-0.25	**< 0.01**	**< 0.01**	—
MF DPI 400 mcg BID	73	0.83	73	0.87	-0.25	-0.25	**< 0.01**	**< 0.01**	—
BDP 168 mcg BID	71	0.88	71	0.87	-0.29	-0.26	**< 0.01**	**< 0.01**	—
Placebo	74	0.79	74	0.85	0.39	0.26	—	—	—
C96-196 (Inhaled-corticosteroid-dependent subjects; 12 weeks parallel-group) —following 2 weeks of open-label treatment with MF DPI 200 mcg BID									
MF DPI 200 mcg QD AM	58	0.71	58	0.62	0.14	0.16	**< 0.01**	**< 0.01**	p ≤ 0.04 vs. 200 mcg BID‡
MF DPI 200 mcg QD PM	54	0.51	54	0.48	0.17	0.12	**< 0.01**	**< 0.01**	p ≤ 0.05 vs. 200 mcg BID‡
MF DPI 400 mcg QD AM	58	0.66	58	0.64	0.12	0.03	**< 0.01**	**< 0.01**	p = 0.05 vs. 200 mcg BID§
MF DPI 200 mcg BID	58	0.57	58	0.58	-0.11	-0.11	**< 0.01**	**< 0.01**	—
Placebo	58	0.52	58	0.51	0.53	0.46	—	—	—
C96-137 (Oral-prednisone-dependent subjects; 12 weeks parallel-group)									
MF DPI 400 mcg BID	45	0.82	44	0.84	-0.33	-0.38	**< 0.01**	**< 0.01**	—
MF DPI 800 mcg BID	43	0.72	43	0.71	-0.16	-0.14	**< 0.01**	**0.02**	—
Placebo	42	0.76	42	0.79	0.42	0.23	—	—	—

§ AM scores.
† PM scores.
‡ AM and PM scores.

The 200 BID group appears to be numerically the best whenever it is involved in a trial; there is a trend for a better effect compared with 400 QAM (186 and 196) and even when it is compared with higher BID doses (134). In 137, no benefit is seen when the dose is increased from 400 BID to 800 BID. A dose ordering is again present for I96-111 and 112 while among the 200 BID, 400 BID and 600 BID doses of I96-113 there really is no difference.

The data on Cough is not as consistently efficacious among the MF DPI treatment groups although a beneficial effect was evident in some groups.

Coughing Scores - Change from Baseline

	Baseline Coughing Scores				Change in Coughing at Endpoint		Placebo Comparison (p-value)		Other Significant Comparison(s) (p-value)
	n	AM	n	PM	AM	PM	AM	PM	
C96-186									
MF DPI 200 mcg QD AM	78	0.63	78	0.61	-0.24	-0.21	0.20	0.11	—
MF DPI 400 mcg QD AM	74	0.50	74	0.51	-0.32	-0.34	**0.04**	**< 0.01**	—
MF DPI 200 mcg BID	79	0.56	79	0.60	-0.33	-0.34	**0.03**	**< 0.01**	—
Placebo	74	0.64	74	0.59	-0.12	-0.06	—	—	—
C96-136									
MF DPI 200 mcg QD AM	71	0.58	71	0.62	-0.06	-0.16	0.92	0.37	—
MF DPI 400 mcg QD AM	76	0.58	76	0.58	-0.20	-0.19	0.19	0.25	—
Placebo	86	0.65	86	0.67	-0.05	-0.05	—	—	—
C96-168									
MF DPI 100 mcg BID	56	0.31	55	0.38	-0.11	-0.12	**< 0.01**	**0.03**	—
MF DPI 200 mcg BID	54	0.41	55	0.42	-0.05	-0.06	**0.01**	0.10	—
BDP 168 mcg BID	57	0.33	56	0.32	0.02	0.00	0.06	0.31	—
Placebo	57	0.43	57	0.43	0.22	0.11	—	—	—
C96-134									
MF DPI 100 mcg BID	75	0.41	74	0.46	-0.03	-0.15	**< 0.01**	**< 0.01**	—
MF DPI 200 mcg BID	70	0.35	70	0.40	-0.05	-0.10	**< 0.01**	**< 0.01**	—
MF DPI 400 mcg BID	73	0.47	73	0.50	-0.04	-0.08	**< 0.01**	**< 0.01**	—
BDP 168 mcg BID	71	0.43	71	0.47	-0.13	-0.15	**< 0.01**	**< 0.01**	—
Placebo	74	0.52	74	0.51	0.36	0.25	—	—	—
C96-196									
MF DPI 200 mcg QD AM	58	0.39	58	0.35	0.05	0.10	**< 0.01**	**< 0.01**	—
MF DPI 200 mcg QD PM	54	0.22	54	0.20	0.17	0.15	0.07	**0.03**	—
MF DPI 400 mcg QD AM	58	0.39	58	0.39	0.06	0.00	**< 0.01**	**< 0.01**	—
MF DPI 200 mcg BID	58	0.43	58	0.44	-0.09	-0.08	**< 0.01**	**< 0.01**	p ≤ 0.03 vs. 200 mcg QD PM‡
Placebo	58	0.22	58	0.20	0.38	0.38	—	—	—
C96-137									
MF DPI 400 mcg BID	45	0.49	44	0.41	-0.07	-0.01	**0.03**	0.38	—
MF DPI 800 mcg BID	43	0.43	43	0.42	-0.09	-0.07	**0.03**	0.22	—
Placebo	42	0.50	42	0.53	0.30	0.13	—	—	—

‡ AM and PM scores.

Among subjects previously treated with bronchodilators alone, neither the MF DPI 200 or 400 QD groups in C96-136, Interestingly, BDP was not statistically different from placebo in 168 while numerically it was the most effective in 134. C96-136 did not show any statistical difference from placebo nor did the 200 mcg QD group in C96-186. C96-137 showed a statistical difference only for AM Cough. Overall, dose ordering was not very apparent so it is difficult to say which dose is most effective in ameliorating this variable.

10. Time to Worsening

The criteria for asthma worsening were specified in the protocols and were generally the same for each trial. In each of the large placebo-controlled trials, MF DPI treatment groups had lower rates of asthma worsening compared with placebo. Results of log-rank tests showed a significant difference among the treatment groups in all studies with the active-treatment groups being better than placebo. In C96-196, asthma worsening was experienced by about half the number of subjects in the MF DPI 200 QPM and 200 BID groups (11% and 12%) than in the 200 and 400 QAM groups (21% and 24%). This large differential occurred primarily in the last 15 days of the trial. In C96-186, asthma worsening was experienced by about half the number of subjects in the MF DPI 200 BID group (4%) than in the MF DPI 200 and 400 QAM groups (9% and 11%). In C96-134, however, MF DPI 200 BID fared numerically the worst among treatment groups. In general, there was not a consistent relationship between asthma worsening and MF DPI dose.

11. Quality of Life

Health-related QOL was examined in C96-136 and C96-137. The SF-36 and an asthma-specific module that evaluated breathlessness, mood, social impact, asthma concerns, psychosocial impact and physical symptoms measured the quality of life. The SF-36 has not been validated in trials for asthma. It is also not apparent that this asthma-specific module has been verified. At Endpoint, the subjects in the two MF DPI groups in Study C96-136 showed greater numerical improvements from Baseline than those in the placebo group, in both the SF-36 and asthma-specific domains, although no statistically significant differences were observed.

Summary Statistics and Probability Levels for the SF-36 Questionnaire

SF 36 Domains	Summary Statistics (LS mean)				Probabilities
	N	Baseline	End of treatment	Change from Baseline	MF DPI group vs. placebo
Physical Function					
MF DPI 200 mcg QD	70	72.5	79.8	7.3	0.17
MF DPI 400 mcg QD	70	74.0	80.7	6.6	0.24
Placebo	81	72.0	75.1	3.1	—
Role Physical					
MF DPI 200 mcg QD	70	79.1	84.0	4.8	0.21
MF DPI 400 mcg QD	70	75.8	79.8	4.0	0.26
Placebo	81	76.6	73.6	-3.0	—
General Health					
MF DPI 200 mcg QD	69	68.5	69.6	0.75	0.40
MF DPI 400 mcg QD	70	65.0	64.7	-0.30	0.71
Placebo	81	68.5	67.4	-1.11	—

The asthma specific scale in C96-136 also showed the greatest improvement in the MF DPI treatment groups and in a dose-ordered pattern; the only difference for MF DPI with a p value ≤ 0.05, however, was for physical symptoms (and the probability levels were not adjusted for the large number of multiple comparisons made.)

At Endpoint in Study C96-137, both MF DPI groups did numerically better than placebo in all domains but bodily pain. The effect on Bodily pain with MF DPI was attributed to the short-term adverse events associated with the reductions in maintenance doses of oral steroids that

occurred. The 800 mcg dose tended to perform better than the lower dose but the comparison with 400 mcg was never significantly different. Statistical improvements with MF DPI were seen with the physical-functioning domain and with 800 mcg in the general health domain.

Within the asthma-specific domains for C96-137, both the MF DPI 400 and 800 BID groups reported better QOL than placebo at the Endpoint in all domains. The unadjusted p value of < .01 was seen for all comparisons with placebo except for psychosocial impact (0.05) and 400 vs. placebo in Mood (0.02).

While it is apparent that there was at least a numerical improvement in both studies and a statistical improvement in C96-137, it is difficult where to place the value of this data citing the lack of validation of these tools in the asthma population.

12. Onset of Action

The sponsor makes a statement in the proposed package labeling that "improved lung function was observed within 24 hours of the start of treatment in some patients, although maximum benefit was not achieved before 1 to 2 weeks or longer." The sponsor told the Division that the reference for this statement is in the ISE section on "Exploration of Treatment Effect." This section refers to a post-hoc exploration of the time of onset of MF DPI treatment effects in C96-136 and 186, studies that involved subjects not being treated with ICS at Baseline. The sponsor indicates that such an analysis was not performed on any of the placebo- or non-placebo-controlled studies with subjects who had been previously treated with ICS or oral corticosteroids because carry-over effects of the previous medication would make the time of onset of effect difficult to interpret.

An analysis of the pooled diary data was performed by the sponsor to assess the first timepoint at which significant differences from placebo were observed in AM and PM PEFR, AM and PM asthma symptom scores, number of awakenings requiring treatment with B agonist, and daily number of puffs of B agonist.

While a significant difference was noted by Day 2 for AM PEFR for 400 QD and 200 BID versus placebo, it was not consistently different from placebo until Day 4 for the AM PEFR and doses of 400 QD and 200 BID. For PM PEFR, the statistical difference was not consistent until Day 5 for these doses.

	Daily AM PEFR MF DPI mcg						Daily PM PEFR MF DPI mcg					
	200 QD AM		400 QD AM		200 BID		200 QD AM		400 QD AM		200 BID	
Baseline	373.53		382.92		362.16		399.70		403.52		385.65	
(N)	(148)		(150)		(79)		(143)		(141)		(79)	
Day 1	N/A		N/A		N/A		-4.9		-7.1		0.5	
Day 2	-2.9		9.6	*	19.8	*	-1.1		9.6		14.7	*
Day 3	-0.1		9.1		12.4		3.0		7.2		18.2	*
Day 4	5.5		15.0	*	19.7	*	5.4		8.5		2.9	
Day 5	0.9		14.3	*	15.4	*	7.5		15.6	*	17.8	*
Day 6	-8.1		13.0	*	26.7	*	4.5		14.2	*	16.7	*
Day 7	3.7		15.3	*	24.0	*	-2.7		12.5	*	23.4	*
Day 8	2.9		22.7	*	40.4	*	6.6		15.6	*	21.0	*

Day 9	8.2	20.2	*	23.8	*	2.3	9.2		17.0
Day 10	7.0	15.1	*	30.9	*	1.6	12.3	*	16.7
Day 11	10.3	26.8	*	34.4	*	8.2	12.9	*	20.1 *
Day 12	11.8	21.7	*	44.8	*	7.7	19.0	*	27.2 *
Day 13	7.2	18.6	*	41.3	*	9.7	12.8	*	24.3 *
Day 14	9.9	25.8	*	36.6	*	N/A	N/A		N/A

*p<0.05

The PEFR data in C96-136 and 186 was examined separately. For C96-136, MF DPI 400 µg QD was statistically different from placebo by Day 4 for AM PEFR (except for Day 6) For PM PEFR, the difference between 400 QD and placebo was only <0.05 on Days 4-6 and 13 during the first two weeks. For C96-186, 200 BID was statistically different from placebo by Day 2 for AM and PM PEFR (both variables missed on Day 3). The Day 2 data may be somewhat incongruous because the placebo AM PEFR was uncharacteristically low – 0.47 difference from Baseline compared with > 10 for the next 8 days. The 400 QD was different from placebo on Day 6 and again on Day 8 forwards for AM PEFR while for PM PEFR the difference was less than 0.05 only on Days 8,12 and 14. It should also be noted in C96-186 that while the sponsor says there were no significant differences in AM PEFR at Baseline, the 400 QD baseline PEFR was 20 –35 points higher than the other Baseline PEFRs – this could potentially be important when you are examining effect sizes of generally 25 to 65.

The data on the 3 asthma symptom scores was much more sporadic in showing a statistical difference from placebo during these first 14 days. Some consistency of significant differences between 400 QD AM and placebo in PM wheezing (Days 6 through 13) and PM difficulty breathing (Days 5 through 10 and 12); and between 200 BID and placebo in AM difficulty breathing (Days 6 and 7, and 10 through 14). There were nearly no statistical differences for cough. This data on symptom scores should not support an onset of action claim.

The data on nocturnal awakenings showed only a rare and sporadic statistical difference. The data on daily B agonist use was more robust and showed a statistical difference between placebo and 400 QAM from Day 2 forward while interestingly there were only 2 days with a difference for the seemingly comparably successful (in terms of FEV_1) MF DPI 200 BID dose.

In summary of this time to onset issue, a consistent change in AM PEFR was seen by Day 4-7 for 400 QD and for PM PEFR it was Day 5 in one study and was sporadic in the other. For 200 BID, the early onset at Day 2 was more convincing but this dose was examined in only one of the studies. This was a post-hoc analysis of a secondary endpoint. While a decrease in B agonist was seen by Day 2, it was demonstrated at this time only for 400 QAM and was seen rarely for 200 BID, an otherwise successful dose with the primary endpoint of FEV_1.

The sponsor also points out that "maximum benefit was not achieved before 1 to 2 weeks or longer." The following table demonstrates the maximum FEV_1 for each dose in each placebo-controlled study.

Trial	Dose	Week of Max. Mean FEV_1	Highest Mean FEV_1 Change (L)
C96-136	200µg QD	Week 8	0.41
	400µg QD	Week 12	0.36

C96-186	200µg QD	Week 8	0.30
	400µg QD	Week 8	0.53
	200µg BID	Week 12	0.44
C96-196	200µg QAM	Day 4	-0.06
	200µg QPM	Week 8	0.10
	400µg QAM	Week 12	0.06
	200µg BID	Week 2	0.05
C96-134	100µg BID	Week 2	0.21
	200µg BID	Week 12	0.27
	400µg BID	Week 12	0.24
	BDP 168µg BID	Week 8	0.17
C96-168	100µg BID	Week 12	0.19
	200µg BID	Week 12	0.26
	BDP 168µg BID	Week 8	0.19
C96-137	400µg BID	Week 5	0.43
	800µg BID	Week 11	0.35

From the above table, it does not appear that maximum benefit near 1-2 weeks. In general, the FEV_1 continued to increase through Week 8, even Week 12, although the rate of increase was slower near the latter part of the trials.

13. Other Studies

Two crossover challenge studies, I96-401 and 402, were small but are worth mentioning in the ISE because the sponsor discusses them in the proposed labeling. In 401, the dose of adenosine monophosphate required to decrease post-saline FEV_1 by 20% prior to treatment and at the end of treatment was compared for the three two week treatment phases with MF DPI 50 mcg BID, 100 mcg BID, and placebo in 15 asthmatic subjects. Treatment effect was expressed in terms of doubling dilutions (DD) relative to placebo and changes of more than one DD were generally considered clinically meaningful. While there were no significant differences between MF DPI doses, treatment response based on AMP challenge was numerically greater during treatment with MF DPI 100 mcg BID (3.11 DD) than with 50 mcg BID (2.81 DD) and each was significantly great than placebo. Thus, it has been demonstrated in a small study that MF DPI reduced responsiveness to AMP but as the sponsor points out in the labeling, the clinical significance of the fining is not known.

In I96-402, changes in the early (0–2 hours) and late (3–7 hours) phase response to the inhalation of allergen, changes in response to methacholine challenge, and changes in inflammatory cells (eosinophils and EG2 positive eosinophils) in induced sputum were assessed in 11 asthmatic subjects before and during 4 separate 6 day treatment phases with MF DPI 50, 100, 400 BID or placebo. The % decreases in FEV_1 both early and late response to allergen was significantly less with MF DPI than with placebo. While there were no significant differences among MF DPI doses, a dose response was seen.

Percent Decrease in FEV_1 After Allergen Challenge on Day 5 (of 6 day treatment phase)

	MF DPI 50 BID (n = 11)	MF DPI 100 BID (n = 11)	MF DPI 400 BID (n = 10)	Placebo (n = 10)	MF DPI 50 BID (n = 11)	MF DPI 100 BID (n = 11)	MF DPI 400 BID (n = 10)	Placebo (n = 10)
	EARLY RESPONSE				LATE RESPONSE			
	Mean %	Mean %	Mean %	Mean %	Mean %	Mean %	Mean %	Mean %
Post-treatment Pre-challenge FEV_1 (Raw Mean; liters)	3.34	3.47	3.41	3.30	3.34	3.47	3.41	3.30
% Decrease Post-treatment (Raw Mean)	29.60	24.24	26.37	36.82	12.30	10.92	5.865	23.61
% Decrease Post-treatment (LSM)	29.06	24.25	27.80	37.42	12.12	10.92	5.996	23.51

FEV_1 was measured following challenge with normal saline and then methacholine on Days 1, 4 (day before allergen challenge), and 6 (day after allergen challenge) to determine the PC_{20}. The $log_{10}PC_{20}$ FEV_1 was compared at the beginning and on Days 4 and 6 and changes of more than one doubling dilution are generally considered to be clinically meaningful. Allergen-induced (Day6) responsiveness to methacholine was significantly decreased following treatment with any of the three doses of MF DPI, and in a dose responsive manner.

$Log_{10}PC_{20}$ FEV_1

	MF DPI 50 BID (n = 11)	MF DPI 100 BID (n = 11)	MF DPI 400BID (n = 10)	Placebo (n = 10)	MF DPI 50 BID (n = 11)	MF DPI 100 BID (n = 11)	MF DPI 400 BID (n = 10)	Placebo (n = 10)
	DAY 4 (before Day 5 allergen)				DAY 6			
	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Pre-treatment (Raw Mean)	0.308	0.250	0.298	0.192	0.308	0.250	0.298	0.192
Post-treatment (RawMean)	0.458	0.440	0.547	0.258	0.270	0.242	0.425	-0.258
Change (Raw Means)	0.150	0.190	0.249	0.067	-0.038	-0.008	0.126	-0.449
Change (LSM)	0.155	0.192	0.260	0.073	-0.029	0.006	0.102	-0.448

Sputum eosinophils and activated eosinophils (EG2 positive) were measured pre-treatment and on Days 4, 5, and 6. For total sputum eosinophils, all three doses produced significantly fewer eosinophils than placebo on Day 5 whereas on Day 6, only 50 and 400 BID were significantly better than placebo. For EG2 positive eosinophils, 50 and 400 BID and not 100 BID were significantly better than placebo on both days.

The sponsor's statement in the proposed labeling regarding the attenuation of the increase of eosinophils in induced sputum after allergen challenge appears to be accurate but again the clinical significance is not known. The labeling statement using the broader term of "inflammatory cells" should be limited to eosinophils since lymphocytes and neutrophils as well as cytokines do not appear to have been measured.

14. Peak Inspiratory Flow Rates

Peak inspiratory flow rates (PIFR) were examined in a small scale at one site each at four of the placebo-controlled trials. These studies were performed to gain preliminary information on whether subjects could produce inspiratory rates adequate to generate DPI particles of respirable size. Based on extrapolation of data obtained using [ ] subjects needed to generate an inspiratory flow rate of approximately 30 L/min or more, with a rise time, the time between flow rates of 10 and 30 L/min, of 300 msec or less to provide adequate drug delivery. PIFRs were examined in C96-134 (3 subjects), C96-137 (2 subjects), C96-136 (6

subjects), and C96-186 (16 subjects). All but one subject achieved flow rates higher than 30 L/min and rise times of less than 300 msec. Subject C96-186-05 had a rise time of greater than 300 msec but the flow rate was adequate at 50.83 L/min.

Summary Results for Peak Inspiratory Flow Rates at Endpoint - Placebo-Controlled Studies C96-134, C96-136, C96-137, and C96-186.

Treatment Group	Subject	Endpoint PIFR (l/min)	Endpoint Rise Time (msec)	Baseline FEV_1 (l)	Endpoint FEV_1 (l)
C96-186 (Subjects used bronchodilators alone; 12 weeks parallel-group)					
MF DPI 200 mcg QD AM	05/186	73.12	65	2.13	2.22
	05/192	54.66	68	2.19	2.66
	05/195	73.44	60	2.75	3.72
	05/197	69.21	58	2.19	2.41
MF DPI 400 mcg QD AM	05/187	76.68	65	3.39	3.46
	05/189	50.83	495	2.71	2.10*
	05/194	66.32	20	2.69	5.00
	05/198	70.88	35	2.60	2.89
MF DPI 200 mcg BID	05/185	63.67	45	1.99	—
	05/190	76.64	28	2.35	2.90
	05/193	70.84	33	1.53	—
	05/199	76.58	48	2.84	3.53
Placebo	05/188	69.06	38	2.87	2.39
	05/191	58.18	70	2.14	2.20
	05/196	76.65	45	3.13	—
	05/200	75.81	65	2.47	2.91
C96-136 (Subjects used bronchodilators alone; 12 weeks parallel-group)					
MF DPI 200 mcg QD AM	22/278	76.10	50	2.63	3.04
	22/279	67.65	40	1.99	2.14
	22/282	71.25	70	2.51	2.54
MF DPI 400 mcg QD AM	22/281	72.35	40	3.12	2.64
Placebo	22/277	65.62	33	2.91	2.55
	22/280	74.25	18	3.18	—
C96-134 (Inhaled-corticosteroid-dependent subjects; 12 weeks parallel-group)					
MF DPI 200 mcg BID	03/433	70.2	133	4.10	4.31
MF DPI 400 mcg BID	03/432	53.9	195	2.73	2.79
BDP 168 mcg BID	03/431	58.1	133	2.45	2.61
C96-137 (Oral-prednisone-dep. subjects; 12 weeks parallel-group) 3 month phase {Pred. dose}					
MF DPI 800 mcg BID	18/016	76.10	40	1.28 {10.0}	1.77 {3.0}
	18/131	76.12	48	2.34 {20.0}	2.20 {7.5}
C96-137 (Oral-prednisone-dep. subjects; 12 weeks parallel-group) 9 month phase {Pred. dose}					
MF/ Variable Dose	18/015	76.1	48	{10.0}	{1.0}
MF/ Variable Dose	18/015	68.1	30	{20.0}	{12.5}
MF/ Variable Dose	18/015	60.4	60	{15.0}	{4.0}
MF/ Variable Dose	18/015	72.0	33	{30.0}	{20.0}

15. Efficacy Conclusion

Overall, it appears that MF DPI 400 mcg QAM and 200 MCG BID are efficacious. If the 400 QAM dose is approved for patients not previously on inhaled corticosteroids, it would be the first QD ICS to receive this indication. Looking at the FEV_1 and AM PEFR data in C96-186,

it appears that their maximal effects appear to parallel each other chronologically. Although C96-196 also involved both doses, such a comparison is more complicated in that subjects had a two week run-in period of 200 BID so there is not an issue of one dose needing to catch up with the other dose.

The 200 mcg QAM dose does not appear to be an appropriate starting dose in patients not previously on ICS (C96-186) (See also PEFR data in C96-136) and does not appear to be an appropriate starting dose in switching over a patient from another ICS (C96-196). For oral prednisone dependent subjects, both MF DPI 400 BID and 800 BID were successful in reducing mean prednisone dosage (an effect seen best in subjects previously on $\geq$ 12.5 mg of prednisone qd) and, despite the lower doses of prednisone, each dose was able to improve the FEV_1 over a 12 week period. For both variables, 400 BID appeared to numerically outperform 800 BID so there appears to be no inherent advantage with 800 BID dosing.

Q. The Integrated Summary of Safety (ISS)

The ISS will primarily focus on the six-large placebo controlled trials but data from the three large international non-placebo controlled trials will also be discussed. C96-137 will be addressed separately because of the different nature of the adverse events, and presumably the population, because of the oral steroid withdrawal involved. The ISS will address adverse events, severe adverse events and serious adverse events as well as any changes in laboratories, vital signs or EKG with treatment. Cortrosyn stimulation testing was performed in three of the large placebo-controlled studies (C96-134, C96-137, and C96-196) as well as the smaller studies C97-049 and C95-135. Cortisol AUC data was available in C97-049, C95-135 as well as two small studies (C94-071 and I93-009) that utilized pure mometasone furoate instead of the MF-lactose mix used for the pivotal studies.

All adverse events discussed in the ISS as well as those previously presented in this NDA review were considered to be treatment-emergent which includes any adverse event that began on or after the first day of treatment through 30 days after the last day the subject participated in the study, and any adverse event that was observed before the first day of treatment and later reported with a greater severity during study participation after the first day of treatment.

1. Extent of Exposure

Most trials in the NDA were 12 weeks in duration and C96-136 and 137 had 9 month open label phases.

Extent of Exposure: Pooled Data for Placebo and Non-Placebo Controlled Studies (not C96-137)

	MF DPI BID				MF DPI QD						
Length of Exposure	100 n=500	200 n=789	400 n=612	600 n=173	200 (AM) n=209	200 (PM) n=54	400 (AM) n=209	Placebo n=350	BUD BID 400 n=181	BDP BID 168 n=128	FP BID 250 n=184
≥1 Dose	495	786	608	173	205	53	208	346	178	126	184
≥4 Days	491	783	605	172	205	53	208	342	178	126	184
≥1 Week	488	781	601	171	201	53	208	328	177	121	183
≥2 Weeks	471	762	589	171	197	53	205	297	174	117	180
≥4 Weeks	452	745	569	161	195	51	195	261	168	113	177
≥8 Weeks	434	724	543	156	185	47	184	230	163	104	171

≥12 Weeks	372	611	475	126	154	39	148	187	143	88	150
≥14 Weeks	6	61	11	7	3	1	4	7	7	2	6
Unknown	5	3	4	0	4	1	1	4	3	2	0
Days of Exposure											
Mean	77	81	79	80	79	80	78	62	81	74	81
Median	85	84	85	85	85	85	85	84	85	84	85
Max	106	108	126	108	106	99	102	106	128	99	118

The requirements for long term safety exposure appear to have been met. A total of 369 subjects completed the 9 month extensions of C96-136, C96-135 and C96-137.

C96-136	**200 mcg QAM**	**200 mcg QPM**	**400 mcg QAM**	**400 mcg QPM**
	32	29	31	30
C96-135	**200 mcg BID**	**400 mcg BID**	**800 mcg QD**	
	42	50	49	
C96-137	**MF Variable**			
	106			

2. Adverse Events in Placebo Controlled Trials

The data from the five placebo-controlled studies was pooled and presented in descending order of incidence in the table on the following page. Headache did not appear to be dose-related nor did it appear to be more commonly seen with MF DPI than with placebo. Allergy aggravated refers to allergic rhinitis symptoms and neither it nor rhinorrhea or nasal congestion appeared to be more common with MF DPI. Pharyngitis, oral candidiasis and influenza symptoms were more common with MF DPI and the incidence was higher with BID dosing as compared to once daily dosing. In addition, oral candidiasis demonstrated clear dose ordering with the BID dosing. When considering these patterns of pharyngitis and oral candidiasis, it should be noted that subjects in all the large trials were advised to rinse their mouths after using inhaler treatment according to the protocol. The rate of compliance with the rinsing procedure is not known.

Viral infection, sinusitis, upper respiratory tract infection, musculoskeletal pain and back pain were more common with the BID MF DPI dosing than with placebo but the once daily dosing was not. The explanation for this pattern is not apparent. Dysmenorrhea was more evident with MF DPI treatment than with placebo and was clearly more common with the BID dosing. The sponsor mentions that because corticosteroids have been shown to have progestational activity at high concentrations in preclinical and in-vitro studies, female reproductive adverse events were carefully evaluated in the clinical studies

The patterns for abdominal pain and myalgia showed they were more common with MF DPI but no dose response was present. The pattern for dyspepsia incidence in the pooled data was not convincing in showing a greater incidence with mometasone. MF DPI 400 BID was the only dose that appeared to demonstrate a higher incidence of coughing than placebo. The interpretation of the coughing data is complex, however, because as a common symptom of

asthma, it would be expected that a treatment for asthma would decrease the incidence of coughing. This may be a signal that coughing could indeed be inherent to the MF DPI product.

Beclomethasone dipropionate was used as an active comparator in C96-134 and 168. The incidence of myalgia seemed to be less than MF DPI but this lower rate is probably not real as the rate was also lower than placebo. In general, the rates of the BDP adverse events followed either the pattern for the QD or BID dosing of MF DPI.

Because adverse events were treatment emergent, special attention should be given to the patterns seen in those two large trials in which subjects were not previously using inhaled corticosteroids (C96-136 and 186). The blinded, placebo control phase of C96-136 compared 200 QD, 400 QD and placebo. Those AEs by ≥10% of subjects in any treatment group included headache, pharyngitis, viral infection, allergy aggravated, sinusitis, nasal congestion, musculo-skeletal pain, and dysmenorrhea. Pharyngitis was more common in the 400 mcg group (18%) than in either the 200 mcg (8%) or placebo (13%) groups. Musculo-skeletal pain and dysmenorrhea were also more common in the 400 mcg group than in other groups. It is interesting to note that nasal congestion was less common among active treatment groups. Fatigue, tremor, ear disorder/earache, rhinorrhea, sneezing, weight increase, and conjunctivitis were reported out of proportion for 400 mcg relative to 200 mcg and placebo. The AEs of tremor, ear problems, sneezing, weight increase or conjunctivitis did not appear to be important issues in other trials. Back pain and influenza-like symptoms were only slightly more common with MF DPI. Aggravation of asthma, bronchitis, migraine, and coughing were common in the placebo group. Myalgia, dyspepsia, dysphonia and abdominal pain did not appear to be any more common with MF DPI than with placebo. There were a total of two cases of rash in the MF DPI groups.

C96-186 compared 200 QD, 400 QD and 200 BID with placebo. Among those AEs by ≥10% of subjects in any treatment group, pharyngitis, musculo-skeletal pain, dyspepsia, and dysmenorrhea were more common with MF DPI than with placebo while headache and allergy aggravated were not. Pharyngitis appeared to be more common only in the 200 BID group (13%) compared with the other MF DPI or placebo treatment groups (8-9%). Similarly, musculo-skeletal pain was more common in the 200 BID treatment group (10%) than in other treatment groups (3-5%). Among the less common AEs, asthenia and dysphonia had a higher incidence with 400 mcg QD than any other dose or placebo. Reports of nausea, infection (not classified further), and nasal congestion were listed only for MF DPI and no cases were seen for placebo. Oral candidiasis was more common with MF DPI and was seen most often in the 400 QD group. There were two total cases of taste perversion with the 400 mcg total daily dosing groups. The only case of taste perversion in C96-136 was in the placebo group. There was a later case of taste loss in C96-136 during the 9 month open label phase.

Noting this data from the two specific trials in subject not previously on ICS, it appears that oral candidiasis, dysmennorhea, pharyngitis should be in the list of AEs more common with MF DPI than with placebo. Pharyngitis and perhaps musculoskeletal pain are more common with BID dosing and perhaps with 400 mcg QD dosing. While dyspepsia was more common with MF DPI in C96-186, this was not seen in C96-136 or in the pooled placebo trial data. Dysphonia was more common with 400 QD in C96-186 but such an increase with MF DPI was not apparent in the other placebo-controlled trials (of note, there was a lower incidence of dysphonia compared with fluticasone in I96-111 and a higher incidence than budesonide in I96-112).

Besides the 3 month double-blind phase, C96-196 also involved a 9 month open-label extension without the use of placebo groups. During this 9 month phase, subjects received either 200 mcg QAM or QPM or 400 mcg QAM or QPM. Dyspepsia was more common with the 400 mcg dosing. The incidence of nasal congestion and nausea appeared to be more common with am dosing for unclear reasons. Compared with the 3 month phase, the incidence of allergy aggravated doubled during the 9 month phase; this finding was most likely related to the longer duration of allergen exposure in these typically atopic individuals.

Number (%) of Subjects Reporting Common (Reported by ≥5% of Subjects in Any Treatment Group) Treatment-Emergent Adverse Events: Pooled Data for Placebo-Controlled Studies (not C96-137) (This is a limited table submitted by the sponsor and is not inclusive of all AEs seen.)

	MF DPI BID			MF DPI QD			BDP 168 mcg	
Adverse Event	100 mcg (n=133)	200 mcg (n=263)	400 mcg (n=74)	200 mcg (AM) (n=209)	200 mcg (PM) (n=54)	400 mcg (AM) (n=209)	BID (n=128)	Placebo (n=350)
No. (%) with Any AE	**108 (81)**	**205 (78)**	**65 (88)**	**161 (77)**	**44 (81)**	**152 (73)**	**105 (82)**	**265 (76)**
Headache	42 (32)	77 (29)	23 (31)	65 (31)	14 (26)	55 (26)	41 (32)	95 (27)
Allergy Aggravated	26 (20)	59 (22)	12 (16)	41 (20)	11 (20)	49 (23)	21 (16)	69 (20)
Pharyngitis	15 (11)	34 (13)	13 (18)	16 (8)	11 (20)	23 (11)	17 (13)	33 (9)
Infection Viral	20 (15)	29 (11)	14 (19)	24 (11)	4 (7)	25 (12)	13 (10)	41 (12)
Sinusitis	16 (12)	20 (8)	9 (12)	11 (5)	5 (9)	14 (7)	17 (13)	23 (7)
Dysmenorrhea in Females	9 (12)	24 (14)	2 (4)	10 (8)	1 (3)	8 (8)	5 (6)	13 (6)
Upper Respiratory Tract Infection	10 (8)	17 (6)	13 (18)	11 (5)	5 (9)	13 (6)	8 (6)	25 (7)
Musculo-Skeletal Pain	11 (8)	27 (10)	9 (12)	10 (5)	3 (6)	15 (7)	17 (13)	27 (8)
Back Pain	8 (6)	22 (8)	8 (11)	10 (5)	3 (6)	8 (4)	14 (11)	16 (5)
Candidiasis, Oral	5 (4)	19 (7)	12 (16)	4 (2)	1 (2)	9 (4)	5 (4)	8 (2)
Nasal Congestion	7 (5)	17 (6)	4 (5)	21 (10)	6 (11)	10 (5)	11 (9)	29 (8)
Influenza-Like Symptoms	6 (5)	5 (2)	10 (14)	9 (4)	2 (4)	8 (4)	3 (2)	6 (2)
Dyspepsia	7 (5)	19 (7)	1 (1)	13 (6)	2 (4)	5 (2)	5 (4)	15 (4)
Abdominal Pain	4 (3)	11 (4)	0	13 (6)	4 (7)	4 (2)	7 (5)	8 (2)
Coughing	8 (6)	9 (3)	8 (11)	7 (3)	2 (4)	9 (4)	5 (4)	19 (5)
Myalgia	4 (3)	10 (4)	5 (7)	11 (5)	4 (7)	6 (3)	1 (1)	12 (3)
Rhinorrhea	4 (3)	7 (3)	3 (4)	2 (1)	1 (2)	8 (4)	6 (5)	11 (3)

3. Adverse Events in the Non-Placebo Controlled Studies

The AE data from the non-placebo controlled studies must be interpreted with care because MF DPI was dosed BID. Nonetheless, the data is important in that it gives some sense as to a dose response among MF DPI, allows some comparison to two marketed ICS, and BID is given as an option by the sponsor in the proposed package labeling for patients switching from QD dosing and is recommended to those patients on oral corticosteroid therapy.

Number (%) of Subjects Reporting Adverse Events (Reported by ≥5% of Subjects in any Treatment Group): Pooled Data for Non-Placebo Controlled Studies

	MF DPI, BID				FP, BID	BUD, BID
	100 mcg (n=367)	200 mcg (n=526)	400 mcg (n=538)	600 mcg (n=173)	250 mcg (n=184)	400 mcg (n=181)
No. (%) of Subjects with Any AE	**233 (63)**	**327 (62)**	**332 (62)**	**125 (72)**	**121 (66)**	**110 (61)**
Headache	73 (20)	**99 (19)**	103 (19)	39 (23)	**33 (18)**	**32 (18)**
Infection Viral	56 (15)	**89 (17)**	97 (18)	32 (18)	**43 (23)**	**30 (17)**
Pharyngitis	52 (14)	**51 (10)**	53 (10)	12 (7)	**28 (15)**	**18 (10)**
Rhinitis	43 (12)	**46 (9)**	44 (8)	13 (8)	**15 (8)**	**16 (9)**
Nasal Congestion	16 (4)	**27 (5)**	25 (5)	7 (4)	**12 (7)**	**3 (2)**
Bronchitis	12 (3)	**21 (4)**	27 (5)	9 (5)	**7 (4)**	**5 (3)**
Candidiasis, Oral	6 (2)	**26 (5)**	30 (6)	20 (12)	**18 (10)**	**3 (2)**
Coughing	15 (4)	**20 (4)**	31 (6)	7 (4)	**12 (7)**	**10 (6)**
Dysphonia	11 (3)	**18 (3)**	29 (5)	14 (8)	**13 (7)**	**5 (3)**
Allergy	14 (4)	**16 (3)**	18 (3)	9 (5)	**1 (1)**	**4 (2)**
Back Pain	9 (2)	**24 (5)**	18 (3)	8 (5)	**6 (3)**	**6 (3)**
Fatigue	13 (4)	**15 (3)**	14 (3)	9 (5)	**1 (1)**	**3 (2)**
Fever	12 (3)	**12 (2)**	18 (3)	6 (3)	**9 (5)**	**6 (3)**
Throat Dry	3 (1)	**16 (3)**	22 (4)	12 (7)	**1 (1)**	**2 (1)**
Pain	6 (2)	**6 (1)**	18 (3)	11 (6)	**3 (2)**	**0**
Dyspepsia	11 (3)	**15 (3)**	13 (2)	8 (5)	**3 (2)**	**7 (4)**
Nausea	8 (2)	**14 (3)**	10 (2)	10 (6)	**7 (4)**	**0**
Dysmenorrhea	4 (2)	**11 (4)**	10 (3)	2 (2)	**8 (7)**	**2 (2)**
Menstrual Disorder	3 (1)	**2 (1)**	8 (3)	5 (5)	**0**	**2 (2)**

A dose response for MF DPI was evident for oral candidiasis, dysphonia, and dry throat. There was a trend for the incidence of pharyngitis to decrease with increasing doses. Dysmenorrhea was reported in 2%, 4%, 3%, and 2% of subjects treated with MF DPI 100, 200, 400, and 600 mcg BID, respectively, and thus a dose response was not apparent. Menstrual disorders, however, were reported in 1%, 1%, 3%, and 5% of subjects treated with MF DPI 100, 200, 400, and 600 mcg BID, respectively, so a dose response was apparent.

The most appropriate comparisons should probably be between MF DPI 200 BID and budesonide 400 BID and fluticasone 250 BID as each would be near a typical starting dose. Using this comparison, viral infection, pharyngitis, oral candidiasis, and dysphonia were as common with budesonide and less common than with fluticasone. There were no essential differences among the products for headache, rhinitis, bronchitis, fatigue or dyspepsia. While dysmenorrhea was most common with fluticasone, there were no cases of menstrual disorder with it. While there was a trend for coughing to be a less frequent complaint for MF DPI subjects, dry throat was somewhat more common for MF DPI. No strong conclusions should be drawn from this data.

4. Adverse Events in C96-137

The nature of the adverse events in this trial should be expected to be different than in the rest of the trials for this NDA because patients were previously on regular doses of oral corticosteroids and the objective of this trial was to successfully lower the prednisone dose. It is also a very different trial because the placebo subjects were actually on higher doses of corticosteroids than the "active treatment" subjects. In addition, higher doses of MF DPI were involved in these trials. It is therefore difficult to discern from this trial what is attributable to MF DPI intrinsically and what is attributable to steroid effect/steroid withdrawal. The AEs noted in this trial should probably not be considered as important as those noted in the other placebo-controlled trials. The following list has been edited to include those AEs with a dose response or differential response between MF DPI and "placebo."

Common AEs (Reported by ≥5% of Subjects in Any Treatment Group in 3 month phase)

	MF DPI, BID		
Adverse Events	400 mcg (n=46)	800 mcg (n=43)	Placebo (n=43)
No. (%) Subjects with Any Adverse Event	**41 (89)**	**43 (100)**	**32 (74)**
candidiasis, oral	10 (22)	10 (23)	4 (9)
musculo-skeletal pain	10 (22)	9 (21)	6 (14)
dyspepsia	6 (13)	8 (19)	6 (14)
allergy aggravated	9 (20)	6 (14)	2 (5)
arthralgia	6 (13)	5 (12)	3 (7)
fatigue	6 (13)	4 (9)	1 (2)
dysphonia	3 (7)	5 (12)	1 (2)
sinus congestion	4 (9)	3 (7)	0
abdominal pain	1 (2)	4 (9)	0
menstrual disorder	1 (4)	3 (11)	0
pharyngitis	1 (2)	3 (7)	1 (2)
edema, peripheral	1 (2)	2 (5)	4 (9)
nausea	3 (7)	2 (5)	0
depression	5 (11)	1 (2)	0
insomnia	1 (2)	1 (2)	3 (7)
edema, legs	0	2 (5)	1 (2)
Pain*	0	2 (5)	0

* The general term "pain" falls under the body system/organ class "Body as a Whole – General Disorders" and encompasses 57 different literal terms (eg, ache in neck, arm pain, cervical pain, hand ache, knee pain, pain in leg, sciatica pain, sore jaw, thoracic pain, etc.)

Oral candidiasis and dysphonia were clearly more common in MF DPI subjects and cannot be related to steroid withdrawal effect. Musculo-skeletal pain, allergy aggravated, arthralgia, fatigue, sinus congestion, abdominal pain, nausea, depression, and pain were more common in the MF DPI groups but are more related to the lower dose of systemic corticosteroids than to an intrinsic effect of MF DPI. Peripheral edema was more common with placebo and should be related to the higher dose of systemic corticosteroids and salt retention. Dyspepsia was no more common with MF DPI than in the "placebo" groups. Menstrual disorder is of particular note and appears to be more common in the MF DPI groups; there is even a trend for a dose response. This evidence suggests that menstrual disorder is an intrinsic problem with MF DPI.

Similar to C96-136, C96-137 involved a 9 month phase extension; during this time, the subjects were treated by open-label initially with 800 mcg BID which could be tapered down

once the subject had been weaned off prednisone. Similar to C96-136, the incidence of allergy aggravated increased and nearly tripled in this case compared with the 3 month phase. As opposed to C96-136, the incidence of several adverse events increased during the 9 month phase. Oral candidiasis increased markedly and during the 9 month phase there was a 40% incidence of this event. Other AEs probably increased because of the reduction in oral corticosteroid dose such as musculo-skeletal pain, fatigue, abdominal pain, nausea, arthralgia, and depression.

5. Severe Adverse Events in Placebo-controlled Trials

With the exception of severe headache and dysmenorrhea, no other severe adverse event was experienced by greater than 2% of subjects in any treatment group. Three percent of subjects treated with MF DPI 200 BID and <1% of subjects treated with placebo experienced severe dysmenorrhea.

There were 5 reports of life-threatening adverse events but only 3 met the protocol definition of life-threatening. They included 2 reports of asthma aggravated (one subject treated with each placebo and MF DPI 200 mcg QD), and one report of respiratory arrest (subject treated with MF DPI 200 mcg BID). The respiratory arrest followed a nerve root block to treat neck pain and muscle spasm resulting from a car accident. These events are also reported under Serious Adverse Events.

Common Severe Adverse Events (Reported by ≥5% of Subjects in Any Treatment Group in the list addressing all Adverse Events): Pooled Data for Placebo-Controlled Studies (not C96-137)

	MF DPI, BID			MF DPI, QD			BDP 168 mcg	
Adverse Event	100mcg (n=133)	200mcg (n=263)	400 mcg (n=74)	200 mcg(AM) (n=209)	200 mcg(PM) (n=54)	400 mcg(AM) (n=209)	BID (n=128)	Placebo (n=350)
No. (%) of Subjects with Any Severe AE	**16 (12)**	**35 (13)**	**9 (12)**	**19 (9)**	**8 (15)**	**28 (13)**	**24 (19)**	**33 (9)**
Headache	3 (2)	11 (4)	4 (5)	5 (2)	2 (4)	7 (3)	9 (7)	3 (1)
Back Pain	2 (2)	3 (1)	1 (1)	2 (1)	0	1 (<1)	2 (2)	2 (1)
Allergy Aggravated	0	4 (2)	0	1 (<1)	0	4 (2)	0	1 (<1)
Sinusitis	0	2 (1)	1 (1)	0	1 (2)	1 (<1)	1 (1)	2 (1)
Musculo-Skeletal Pain	0	5 (2)	1 (1)	0	0	0	0	3 (1)
Coughing	1 (1)	0	0	1 (<1)	0	1 (<1)	0	4 (1)
Abdominal Pain	3 (2)	1 (<1)	0	1 (<1)	0	0	2 (2)	0
Pharyngitis	1 (1)	2 (1)	0	0	0	0	2 (2)	1 (<1)
Upper Resp. Tract Infection	1 (1)	1 (<1)	0	0	0	0	0	3 (1)
Nasal Congestion	1 (1)	1 (<1)	0	1 (<1)	0	0	1 (1)	0
Dysmenorrhea	0	4 (3)	0	0	0	0	0	1 (<1)
Influenza-Like Symptoms	0	0	1 (1)	1 (<1)	1 (2)	0	1 (1)	0
Candidiasis, Oral	0	1 (<1)	0	0	0	1 (<1)	1 (1)	0
Pain	1 (1)	1 (<1)	0	1 (<1)	0	0	0	0
Myalgia	0	1 (<1)	0	0	0	0	0	1 (<1)
Dyspepsia	0	2 (1)	0	0	0	0	1 (1)	0
Infection Viral	0	0	1 (1)	0	0	0	0	1 (<1)

Fever	1 (1)	0	0	0	0	1 (<1)	0	0
Fatigue	0	0	0	0	0	0	0	1 (<1)

It should be highlighted that this table above includes only those listed as severe and represents a subset of the larger list of adverse events reported with an incidence greater than 5% in any treatment group. Because of the small number of severe adverse events, no overt pattern of differential expression between doses and placebo is evident except perhaps severe headache appears to be more common with active ICS treatment than with placebo. Headache as a whole was not found to be more common with MF DPI than with placebo.

Within this list are those adverse events that are believed to be more common with MF DPI than with placebo such as pharyngitis, dysmennorhea and oral candidiasis and those which might be more common with MF DPI such as back pain, musculo-skeletal pain and influenza-like symptoms.

Severe adverse events were also noted in C96-137. The incidence of severe adverse events was considerably higher in this trial as it related to the different patient population and the steroid-reducing nature of the study. The incidence of severe AEs was higher in the MF DPI 400 BID (24%) and MF DPI 800 BID (19%) than in the placebo group (9%) but no one severe AE had more than 2 subjects and no pattern from this data was evident.

6. Serious Adverse Events in Placebo–controlled Trials

Serious adverse events were reported in 21 subjects in the placebo-controlled trials other than C96-137. Of these 21 subjects, 6 were placebo-treated subjects, 3 subjects were diagnosed with serious AEs prior to receiving treatment, and 2 were treated with BDP 168 mcg BID. Aggravated asthma was the most common serious adverse event and reported for 6 subjects.

Serious Adverse Events: Placebo-Controlled Studies (except for C96-137)

Center/Subject	Sex/Age/ Race	Adverse Event(s)	Relationship	Status
MF DPI 100 mcg BID				
C96-134-17/107	M/56/C	leukopenia leukemia	unlikely unlikely	end-organ toxicity hospitalized, cancer
MF DPI 200 mcg BID				
C96-168-11/231	F/41/C	respiratory arrest	unlikely	hospitalized, discontinued
C96-186-21/331	F/48/C	uterine fibroid	unlikely	hospitalized; continued study
MF DPI 400 mcg BID				
C96-134-07/390	F/51/B	asthma aggravated	unlikely	hospitalized
MF DPI 200 mcg (AM) QD				
C96-186-15/166	F/17/NC	dyspnea	unlikely	hospitalized, discontinued
MF DPI 200 mcg (PM) QD				
C96-196-12/258	F/23/NC	hepatic enzymes increased	possibly	additional study visit
MF DPI 400 mcg (AM) QD				

C96-136-07/266	M/36/NC	hepatitis C	unlikely	additional therapy
C96-136-12/129	F/34/C	intestinal disorder	unlikely	hospitalized
C96-136-18/052	F/39/C	elevated SGPT	unlikely	additional therapy
C96-186-23/220	F/24/NC	pelvic inflammatory disease	unlikely	hospitalized (continued study)
BDP 168 mcg BID				
C96-134-10/247	M/32/C	heart valve disorder (aortic insufficiency)	unlikely	hospitalized
		mitral valve prolapse	unlikely	hospitalized
C96-168-13/073	F/22/C	asthma aggravated	unlikely	hospitalized, discontinued (for treatment failure)
Placebo				
C96-134-07/385	F/32/NC	hepatic enzymes increased	unlikely	end-organ toxicity
C96-134-07/387	F/37/NC	asthma aggravated, bronchitis	unlikely	hospitalized
C96-136-14/036	F/27/C	asthma aggravated, acute respiratory distress	unlikely	hospitalized, additional therapy, discontinued
C96-136-19/245	M/28/NC	elevated LFT	unlikely	discontinued
C96-186-19/121	F/36/C	hepatic function abnormal	unlikely	discontinued study early for failure to meet entry criteria
C96-196-06/281	F/34/NC	asthma aggravated	unlikely	additional therapy, hospitalization, study discontinuation
No Treatment (Screening Subject Only/Not Randomized)				
C96-134-08/607	M/14/NC	asthma aggravated	unlikely	hospitalized
C96-186-21/609	F/58/C	procedure (kidney stone removed)	unlikely	hospitalized
C96-186-17/605	F/19/C	asthma aggravated	unlikely	hospitalized

The instances of elevation of LFTs will be discussed in a separate section of this NDA. The other serious adverse events can not be easily attributable to MF-DPI and in many cases are completely non-related such as the case of pelvic inflammatory disease, aortic insufficiency, hepatitis C, and intestinal disorder (subject later had appendectomy and drainage of an ovarian cyst). Subject #331 in C96-186 was hospitalized for a bleeding fibroid uterus and the investigator considered the event to be unlikely to be related to study medication.

Subject #107 in C96-134 treated with MF DPI 100 BID had a low WBC at Screening (3,340/µl)(normal 3.8 to 10.7 at that site) and the Final Visit (980/µl). Approximately 3 weeks after the end of treatment, the subject was admitted to the hospital with a diagnosis of leukemia. The investigator considered he event to be unlikely related to the study medication since the white cell count was already low at the screening visit. It is unlikely that this leukemia was drug-related.

The other instances of dyspnea, bronchitis and aggravation of asthma may potentially argue against the efficacy of a medication or dose but such events will occur in asthmatics and there is better evidence that MF DPI is efficacious in asthma as seen in the ISE of this review.

C96-136 involved a 9 month open label extension and a few serious adverse events were noted.

List of Subjects Who Had Serious Adverse Events During the 9-Month Phase of C96-136

Sex/Age/ Race	Adverse Event(s)	Investigator – designated Relationship	Status
MF DPI 200 mcg QD AM and 200 mcg QD PM			
None			
MF DPI 400 mcg QD AM (previously 400 mcg QD)			
M/40/NC	Back pain	Unrelated	Hospitalized, Additional Therapy
MF DPI 400 mcg QD AM (previously placebo)			
M/35/C	Irritable bowel syndrome	Unrelated	Hospitalized, Additional Therapy, Discontinued
MF DPI 400 mcg QD PM (previously 400 mcg QD)			
F/38/C	ITP	Unrelated	Additional Therapy
F/34/C	Pelvic pain	Unrelated	Hospitalized, Additional Therapy
F/52/C	Cellulitis	Unrelated	Hospitalized, Additional Therapy
MF DPI 400 mcg QD PM (previously placebo)			
F/43/NC	Hepatitis (hepatitis A)	Unrelated	Additional Therapy, Discontinuation

One of these serious adverse events is particularly notable. In C96-136 during the open label phase, Subject 213 (a 38 year old female on 400 QD then 400 QPM) had repeated platelet counts of 30,000/μL and 31,000/μL associated with her last visit in the study; she was referred to a hematologist and the final diagnosis was idiopathic thrombocytopenic purpura. She had no evidence of bleeding. The case report form was reviewed electronically. The study report says that this adverse event was unrelated to study treatment but on the case report form the relationship to treatment, when the low platelet count was initially found, was possible. The platelet counts for Screening, Week 12, Week 26 and 38 were normal. Not much more information on this adverse event appeared to be available.

Serious adverse events did occur in the 3 month blinded phase of the steroid-sparing trial C96-137 but a larger number were noted during the 9 month open label phase.

Center/Subject in C96-137		Adverse Event(s)	Relationship	Status
MF DPI 400 mcg BID				
C96-137-08/023	M/21/C	spinal disorder (h/o MVA)	unlikely	hospitalized
C96-137-12/115	F/66/C	pneumonia	unlikely	hospitalized
		sinusitis	unlikely	hospitalized
		asthma aggravated	unlikely	hospitalized
C96-137-12/223	F/31/N	asthma aggravated	unlikely	hospitalized
C96-137-15/003	M/77/C	Confusion, dyspnea, fever	unlikely	hospitalized
		Headache, pneumonia, sepsis	unlikely	
C96-137-15/005	F/47/C	Blindness (Mucoceles)	unlikely	hospitalized
MF DPI 800 mcg BID				
C96-137-22/176	M/63/C	Diarrhea, fever, viral infection	unlikely	hospitalized
		Nausea, diverticulitis	unlikely	hospitalized
Placebo				
C96-137-12/120	F/44/N	procedure (toe surgery)	unlikely	hospitalized
9 month Phase: Variable Dose				
MF DPI 400 mcg BID in 3-Month Phase				

Center/Subject in C96-137		Adverse Event(s)	Relationship	Status
C96-137-03#046	M/75/C	basal cell carcinoma	unlikely	cancer
C96-137-04#091	F/33/C	cholelithiasis	unlikely	hospitalized
		tumor, benign	unlikely	hospitalized
C96-137-04#148	M/72/C	joint disorder (acromioplasty)	unlikely	hospitalized
		abdominal pain	unlikely	hospitalized
		gastric polyps	unlikely	hospitalized
C96-137-05#076	M/70/C	hernia	unlikely	hospitalized
C96-137-07#099	M/72/C	chest pain	unlikely	life threatening, hospitalized
		coronary artery disorder	unlikely	life threatening, hospitalized
		angina pectoris	unlikely	life threatening, hospitalized
C96-137-08#023	M/21/C	intestinal disorder (appendicitis)	unlikely	life threatening, hospitalized
C96-137-11#067	F/58/C	spinal disorder	unlikely	hospitalized
		back pain	unlikely	
C96-137-12#120	F/45/C	asthma aggravated	Unlikely (apparent smoke exposure)	hospitalized
		asthma aggravated	not provided	hospitalized
		asthma aggravated	not provided	hospitalized
		asthma aggravated	unlikely	hospitalized
		asthma aggravated	unlikely	hospitalized
C96-137-13#113	M/17/C	asthma aggravated	unlikely	life threatening, hospitalized
C96-137-15#034	M/55/C	hepatic enzymes increased	unlikely	medically significant
C96-137-22#180	M/35/N	respiratory insufficiency	unlikely	life threatening, hospitalized
		status asthmaticus	unlikely	life threatening, hospitalized
MF DPI 800 mcg BID in 3-Month Phase				
C96-137-01#221	F/70/C	gallbladder disease	unlikely	hospitalized
C96-137-04#096	M/59/	chest pain	unlikely	hospitalized
		myocardial infarction	unlikely	hospitalized
C96-137-04#149	F/28/C	asthma aggravated	unlikely	hospitalized
		bronchitis	unlikely	hospitalized
C96-137-08#024	F/47/C	asthma aggravated	unlikely	hospitalized
		cellulitis	unlikely	hospitalized
		depression	unrelated	
		osteoporosis	not provided	hospitalized
		tachycardia	not provided	
		dyspnea	not provided	
		colonization, bacteria	not provided	
		fracture	not provided	hospitalized
C96-137-09#061	F/49/C	asthma aggravated	not provided	hospitalized
		dyspnea	not provided	hospitalized
C96-137-12#116	F/50/C	dehydration	unlikely	hospitalized
Placebo in 3-Month Phase				
C96-137-02#059	F/31/C	abdominal pain	unlikely	hospitalized
		peptic ulcer	unlikely	hospitalized
C96-137-04#145	M/26/C	hepatic enzymes increased	unlikely	medically significant
		pneumonia	unlikely	hospitalized
		dehydration	unlikely	hospitalized

Center/Subject in C96-137		Adverse Event(s)	Relationship	Status
		fever	unlikely	hospitalized
C96-137-04#150	F/72/C	ECG abnormal	unlikely	hospitalized
		pain	unlikely	hospitalized
		paresthesia	unlikely	hospitalized
		bronchitis	unlikely	hospitalized
C96-137-09#066	M/70/C	pneumonia	unrelated	hospitalized
C96-137-11#069	M/59/C	prostatic cancer	unlikely	hospitalized, cancer
C96-137-13#114	M/59/C	pneumonia	unlikely	hospitalized
		asthma aggravated	unlikely	
C96-137-15#031	M/66/C	fracture, bone	unlikely	hospitalized
C96-137-15#032	M/72/C	angioedema	unlikely	hospitalized
C96-137-22#177	F/73/C	breast neoplasm, malignant	unlikely	cancer

A review of the above serious adverse events does not make it seem likely that MF DPI should be implicated as the cause. During the 9 month open-label phase of this trial, serious adverse events involved such incidents as chest pain in a 72 –year old male found to have a coronary artery disease, acute myocardial infarction in a 58 year old male, reversible T wave inversion in a 72 year old diabetic female, prostate cancer in a 59 year old male and a vertebral fracture in a 66 year old female should be associated with previous oral steroid therapy or coexistent disease and age and not MF DPI. Subjects #034 and #145 have further data in the upcoming section on laboratory values.

Serious adverse events in the 3 large international non-placebo controlled trials will not be represented in this Integrated Summary of Safety with the exception of Subject #94 in I96-113. This 38 year female subject initiated MF DPI 600 mcg BID on July 30, 1997 and discontinued it on [ ] 1997 (had positive pregnancy tests on [ ]) The sponsor says she had scheduled to terminate her pregnancy on [ ] but on [ ] her family practitioner determined that a spontaneous abortion had occurred. While this event involved a fetal death while possibly on treatment, it was early in the term and most likely not related to treatment. Serious adverse events were also seen in the non-placebo controlled C96-135. Notable among the serious AE's in subjects treated with MF DPI were subject #65 with an intracranial hemorrhage thought to be associated with a primary CNS tumor or an arteriovenous malformation, subject #367 with menorrhagia, and subject #172 with menstrual disorder. The case of increased hepatic enzymes is presented in the laboratory values section.

7. Vital signs

There were overall no important changes in the means reported for vital signs or weight during these clinical trials. In C96-137, the only potential difference noted was with weight where the mean baseline for women changed from 184.7 at Baseline to 177.3 at Endpoint and for men from 182.3 at Baseline to 179.2 at Endpoint. In C96-196, bradycardia to the high 40's-low 50's was seen in 6 patients on MF DPI (who were not also on beta-blockers or calcium channel blockers). There was not decrease in the mean pulse rate and it is not believed that this bradycardia was resultant of MF DPI treatment. In C96-135, a weight gain of 4.2 lbs. was

noted for the MF 800 QD group compared with 0.9 for the other MF groups and 1.9 for the BDP group. Perhaps weight gain is an issue with daily doses of 800 mcg or higher. C96-137, which also involved such doses could not possibly convey such data as the subjects were previously or concurrently on oral steroid therapy which is known to cause weight increase.

For I96-111, the data for the weights is not believed to be accurate at Week 12 and Endpoint for females in the MF DPI 200 BID and FP groups where the range of weights is listed as 45-665 kg and 44–835 kg, respectively. The data for the weight range on Caucasians in these same treatment groups is also not believed to be accurate. In C96-113, the mean weight for the 600 mcg BID group increased from 80.1 kg to 89.8 kg for the entire group and, for females specifically, the mean weight increased from 73.5 at Baseline to 89.7 at Endpoint. It is believed, however, that this is an error because the high value for the group at Endpoint and at 12 weeks is 675 kg. No conclusions can be drawn from these two trials on weight. The sponsor will be asked to clarify these points in these large international trials.

8. Laboratory Data

The median values for laboratory testing were compared between Baseline and Endpoint for the large clinical trials. The median values among the treatment groups for Studies 111, 112, 113, were reviewed and the median values among treatment group and gender were reviewed for Studies 134, 136,186, 196, 168 and 137. No changes in the median values were appreciated with the following possible exceptions:

1. For C96-136, a possible change was noted in cholesterol where the median value increased from 176.5 to 181 for the 200 mcg group, 169.5 to 178.5 for the 400 mcg group and decreased 183.5 to 183 for the placebo group.

2. For C96-186, the one possible change in median was a decrease in the % eosinophils; there was a decrease in the median of 20% for 200 BID, 12.5% for 200 QD, 21.4% for 400 QD and 7% for placebo.

3. For C96-196, the only potentially discernable median change between genders was the 3 point decrease in hematocrit for females from 42 to 39 for 400 QD AM and 2 points for 200 BID and a 0.5 point decrease for placebo. The corresponding decreases for males were 1 point in each group. Because there was a 2 point decrease in the placebo group for males and because a decrease in hematocrit seems otherwise implausible, it is unlikely that the changes reflect drug treatment.

4. For C96-137, the only appreciable changes in the 3 month phase appeared to occur in the WBC where the median changed from 9.32 to 7.16 for 400 BID, from 9.43 to 7.8 for 800 BID and from 9.01 to 10.31 for placebo. This decrease in the WBC could possibly be attributable to the decrease in oral steroids in those subjects being treated with MF DPI. The WBC median at the end of the 12 month study was 7.87. Cholesterol also appeared to decrease from 215 to 197 with 400 BID, 230 to 217 with 800 BID and 220 to 230 with placebo and could also potentially be secondary to the decrease in prednisone with MF DPI.

5. For C96-168, one small differential in response was noted between treatment groups and gender in the alkaline phosphatase (AP). For females on MF DPI 100 BID, AP went up 57 to 61 while for 200 mcg it went up from 53 to 60. For males, the corresponding changes were 61 to 63 and 68.5 to 68.5. The placebo group actually decreased by 3 for each

gender. These changes are not clinically significant and probably do not reflect a true differential in response.

For C96-136, the data on shifting of parameter data between baseline and endpoint was reviewed. No particular notable differences between shifts among the groups was discerned. In general, however, the data presented in shift tables was not otherwise closely reviewed.

Typically, labs were done in these trials at Screening and at Endpoint. They were also performed at the open label Endpoint for C96-136 and 137. Laboratory tests were performed at Screening and Weeks 12, 26, 38 and 52 for C96-135. In general the sponsor highlighted individual laboratory abnormalities in the Clinical Study Report that fulfilled a particular definition. Clinically significant abnormalities were defined for all blood chemistry parameters as ≥ 2.6 times the upper limit of normal. Other abnormal values were: hemoglobin concentration ≤ 9.4g/dl, platelet count ≤ 74,000/μl, or white blood cell count ≤ 2,900/μl. All abnormal laboratory values were presented in the NDA, however, and the following abnormal values were notable (more noteworthy increase are in bold):

Trial	MF DPI Dose	Subject /Site	Transaminase Change	Day	Note	Note
C96-136 3 month phase	400 mcg	130	AST/ALT 24/22 to 35/38	Day 83		
	400 mcg	192	AST 22 to 57	Day 95	AST 21 on Day 127	ALT 17 to 24
	placebo	245	AST/ALT 32/44 to 144/240	Day 85	Severe AE	Drinking up to 20 oz EtOH qd, neg. Hepatitis Screen
	placebo	170	AST/ALT 37/35 to 71/53	Day 85	ALT rose to 53 by Day 15	AST 49-70 U/L, ALT 43-56 in 9 month phase
	200 QD	047	ALT was 87 at Scr, 47 at Week 12, 46 at Week 26, 51 at Week 38, then was 156 at day 368 with 68 at repeat on Day 383		Baseline elevation	
C96-136 9 Month Phase	200 QAM/ 200 QAM	189	AST/ALT 27/47 to 48/122	Week 26	Treatment was continued and the value decreased steadily.	AST/ALT 26/45 on Day 371. Mild BSL elevation of ALT
		047/18	AST/ALT 45/87 to 129/156	Day 368	Elevated at BSL	
	400 QAM/ 400 QAM	130/12	AST/ALT 24/22 to 53/96	Day 363		
	Placebo/ 400 QPM	131/12	AST/ALT 61/69 to 79/117	Day 261	Elevated at BSL	
C96-186	200 BID	235	ALT 46 to 64	Endpoint	AST 31 to 42	Mild BSL Elevation
	200 BID	293	AST/ALT 31/24 to 39/48	Endpoint	ALT(nl 6-43), AST 39 (nl 11-36)	

	200 BID	36/09	AST 29 to 80	Endpoint	ALT 13 to 28	
	200 QD	141/10	ALT 27 to 65	Endpoint	AST 21 to 33	
	200 QD	049	ALT 26 - 39 (nl 6-34)	Endpoint		
	200 QD	251/18	AST/ALT 19/26 to 38/75	Endpoint		
	400 QD	234	ALT 47 to 77		AST 40 to 50	Mild BSL Elevation
	Placebo	158	ALT 38 to 54	Endpoint		
	Placebo	121/19	ALT 147 to 267, AST 128 to 291	Endpoint		High BSL Elevation
	Placebo	339/21	ALT 26 to 48	Endpoint	AST 19 to 27	
C96-196	200 BID	156	ALT 44 to 67 / AST 30 to 36	Visit 9	nl. Bili.	
		137	ALT 14 to 38 (nl 6-32)(AST 16 to 33)	Visit 9		
	200 QAM	147	ALT 37 to 91	Visit 9	No change in AST or bilirubin	
		323	AST 28 to 41 (nl. ALT).	Visit 9		
	200 QPM	82	**ALT 13 to 106, AST 15 to 62**	Visit 9	(nl Bili.) Repeat values nl.	
		272	ALT 25 to 65, AST 24 to 40	Visit 9		
		148	ALT 31 to 56	Visit 9	AST 22-29	
		258	**ALT 14 to 244, AST 13 to 435, LDH 131 to 794**	Visit 9	nl AP, bili 0.2 to 0.5. No explanation is available	
	400 QAM	192	ALT 24 to 45	Visit 9	AST 17 to 26	
		198	ALT 39 to 47	Visit 9		
		264	ALT 21 to 45 (nl 6-43), LDH 219 to 273	Visit 9		
		254	ALT 57 to 90	Visit 9	Repeat value = 68, 17 d later	
	Placebo	149	ALT 22 to 45	Visit 9		
		281	ALT 9 to 76	Visit 9	AST 14 to 23	
		324	ALT 13 to 51	Visit 9		
		103	ALT 57 SCC to 131 SCR	Pre-baseline to Baseline	AST no change @51	BSL elevation
		259	ALT 25 to 76, AST 29 to 47.	Visit 9		
		178	ALT 25 to 56	Visit 9		

C96-137 3 month phase	400 BID	50	ALT 35 to 46, LDH 193 to 285	Week 12		
	Placebo	220	AST 27 to 47	Week 4	(p. 1023)	
		71	ALT 30 to 51	Week 11	(p.1049)	
C96-137 9 month phase	Variable	217	ALT 22 to 50	Wk. 24	p. 9092	
	Variable	220	ALT 22 to 39	Wk. 24	AST 47, T. bili. 1.6 @ SCR, p. 9092.	
	Variable	99	ALT 18 to 38	Wk. 36	AP 58 to 176	
	Variable	25	AST 29 to 39	Wk. 36		
	Variable	69	ALT 34 to 73 ; AST 23 to 53	Wk. 52 Day 340		
	Variable	71	ALT 30 to 51	Wk. 11	44 @ Wk. 13	
	Variable	72	ALT 28 to 76,88; AST 28 to 43	Final	No abnormal value listed for ALT on Day 473	
	Variable	115	ALT 28 to 50	Wk. 40		
	Variable	120	AST 23 to 43	Final		
	Variable	109	ALT 25 to 45	Day 295		
	Variable	113	ALT 47 to 80	Day 354	AST 42 @ BSL	
	Variable	1	ALT 19 to 40	Wk 24		
	Variable	80	ALT 12 to 61	Day 253		
	Variable	14	ALT 18 to 38	Day 55	Had been on placebo in closed phase	
	Variable	49	ALT/AST 18/15 to 54/43	Wk. 24		
	Variable	178	ALT/AST 15/24 to 55/41	Wk.24		
	Variable	34	ALT/AST 14/18 to 177/139	1 month p dc study secondary to compliance	Drinker, Prescreening ALT/AST were 124/134	
	Variable	145	**ALT 437, AST 189, LDH 594, AP 301** (Screening values - 27, 25,47) Tbili only 0.7 Week 36.	Week 36	"Viral illness" hep screen neg., continued MF	No cause was identified. No h/o EtOH or drug abuse. AST/ALT 19/22 at end of study.
C96-135	200 BID	470	AST/ALT 19/23 to 34/70	Week 12		
		073	AST/ALT 22/37 to 35/69	Week 26		
		065	ALT 26 to 93	Day 190	nl AST	
		200	ALT 20 to 41	Week 38	nl AST	
		482	AST 10-17 to 37	Day 289	nl ALT	
		298	**AST/ALT 24/20 to 315/72**	Day 84	LDH 167 to 928 on Day 84: bili/AP nl; AST/ALT55/45 Day 91	Hep. A and B negative
	400 BID	435	ALT 16 to 36	Week 12	nl AST	

		295	AST/ALT 30/45 to 60/110	Week 38	25/55 Day 365	Mild BSL elev. Of ALT
	800 QD	434	ALT 30 to 85	Week 26	nl AST	
		395	ALT 35 to 74	Day 372	TBILI 1.4- 1.7, nl AST	
		292	ALT 17 to 41	Week 12	nl AST	
		271	AST/ALT 15/10 to 46/38	Wk 38	TBILI 0.9 to 1.3	
		205	ALT 16 to 66 AST 30	Wk 26		
		175	AST/ALT 27/35 to 53/77	Day 366	25/39 Day 380	
	BDP 168 BID	447	**AST/ALT 16/22 to 43/139**	Day 365	TBILI 1.3 to 1.6 : ALT 74 Day 372	
		419	AST/ALT 32/35 to 46/57	Week 38		
		027	ALT 35 to 73, TBILI 0.8 to 1.4	Day 107 (Final)		
		468	ALT 26 to 62; AP 94 to 160	Day 373; Week 38		
		074	AST/ALT 31/18 to 91/84	Week 26	31/23 Day 393	
C96-134	100 BID	78	ALT 51 to 76	Day 4		
		177	ALT 40 to 71	Wk 12		
	200 BID	98	AST/ALT 27/27 to 37/58	Wk 12		
	400 BID	61	AST/ALT 22/13 to 51/81	Wk 12		
		99	AST/ALT 39/64 to 63/111	Wk 8		Some BSL elevation
	BDP 168 BID	278	AST/ALT 25/25 to 32/51	Wk 12		
		12	AST/ALT 35/34 to 58/73		Normal bili, AP 93 to 150	
		125	AST/ALT 16/22 to 67/49	Day 57		
	Placebo	274	AST/ALT 24/22 to 52/49	Day 15		
		385	AST/ALT 54/41 to 162/147	Day 29	Subjected admitted to drinking alcohol	Some BSL elevation
C96-168	100 BID	294	ALT/AST 57/34 to 75/42	Endpoint		
	200 BID	188	ALT 24 to 53	Endpoint		
		098	ALT 30 to 47	Endpoint		
		124	AST 17 to 47	Endpoint		
	Placebo	236	ALT/AST 22/18 to 71/38	Endpoint		
		61	AST 25 to 42	Endpoint		
		269	ALT/AST 15/12 to 58/23	Endpoint		
196-111	100 BID	08/2	AST/ALT 32/76 to 52/115	Week 12		ALT high at BSL
		13/5	ALT 19 to 60, (nl. 6-34)	Week 12		
		22/52	AST/ALT 36/59 to 58/124	Week 12	nl. Bili, Alk. Phos	ALT high at BSL
	200 BID	51/18	ALT 26 to 43	Week 12	nl. Bili.	
		33/20	AST/ALT 31/27 to 50/45	Week 12	Bili. 9 to 14 (still in nl. range for bili).	
		37/24	ALT 25 to 72	Week 12	nl. AST/Bili/AP	

		31/31	**AST/ALT 29/27 to 122/39**	Week 12	**Tbili 12 to 21 (nl. 3 – 21)**	AP high at BSL - no value available for Wk 12
		47/45	AST/ALT19/15 to 42/75	Week 12	nl. Bili and AP	
		49/37	ALT 14 to 51	Week 12	nl. Bili and AST	
		21/52	ALT 28 to 47	Week 12		
	400 BID	02/19	ALT 22 to 53	Week 12		
	FP 250 BID	77/21	AST/ALT 38/74 to 83/125	Week 12	nl. Bili. and AP	ALT high at BSL
		16/48	AST/ALT 18/24 to 24/46	Week 12	(off drug 6 days)	
I96-112	100 BID	16/16	AST/ALT 30/27 to 38/52	Week 12		
		39/30	ALT 22 to 50	Week 12		
		45/46	**AST/ALT 26/31 to 67/113**	Day 89	**32/28 Day 117(off med. 28 days)**	No change in the bilirubin.
		106/51	AST/ALT 62/75 to 105/121	Week 12	Bili.Ok) (sponsor - related to EtOH)	BSL elevation
		140/52	ALT 23 to 47	Week 8		
	200 BID	19/33	AST/ALT 24/13 to 43/42	Week 12	AP 225 to 568; Tbili. 0.2 to 1.9 (nl 0.2 – 2.0)	
	400 BID	20/16	AST 30 to 65			
		69/25	AST/ALT 22/26 to 40/52			
		34/37	AST/ALT 50/133 to 50/112		Tbili. 29 to 53 (nl 3-21)	
		44/46	AST/ALT 15/12 to 29/48	Day 88	14/16 (Day 129 (off Rx 41 d.)	
		51/59	**AST/ALT 16/28 to 339/548**		F/U AST/ALT 29/50; Bili 0.45 to 0.6	Reported influenza: has had similar elevations in past with severe colds
		13/60	AST/ALT 18/14 to 28/48		Tbili 9 to 15 (nl. 3-21)	
	Bud 400 BID	18/01	AST/ALT 19/28 to 35/66			
		09/02	AST/ALT 12/8 to 57/69			
		76/26	AST 23 to 50			
		02/34	AST 25 to 68, ALT 31 to 25		Tbili. 7 to 17 nl 3-21)	
		42/46	AST/ALT 26/24 to 39/46			
I96-113	200 BID	92/09	ALT 20 to 62 (Tbili was 24 to 10)			
		16/26	AST/ALT 14/18 to 45/67			
		02/40	AST/ALT 24/37 to 38/64			
	400 BID	131/10	AST/ALT 28/31 to 38/52			
		158/14	AST/ALT 21/11 to 41/27			
	600 BID	05/04	ALT 31 to 54			
		148/06	**AST/ALT 23/19 to 141/40**	Day 57	Last value - 22/21; No change in Tbili.	

		17/11	AST/ALT 15/10 to 24/43		Alk. Phos. 36 to 134	
		70/16	AST/ALT 23/16 to 43/60			
		62/25	AST/ALT 17/16 to 35/60			
		09/57	ALT 31 to 71			

Looking at the above data, it appears that transaminase increases are most often in the 20 to 60 U/L range unless the patient had some baseline elevation of a transaminase. These mild transaminase increases were seen in all treatment groups including beclomethasone, budesonide, fluticasone and placebo. There does not appear to be a dose response with MF DPI in these abnormalities. Their clinical relevance is not clear nor is their relationship to MF DPI although at this point a link is believed to be unlikely. A few transaminase increases were particularly noteworthy and include Subject 82 (C96-196; 200 QPM), Subject 258 (C96-196; 200 QPM), Subject 145 (C96-137; Variable), Subject 298 (C96-135; 200 BID), Subject 31/31 (I96-111; 200 BID), Subject 45/46 (I96-112; 100 BID), Subject 51/59 (I96-112; 400 BID), and Subject 148/06 (I96-113; 600 BID). Another notable increase was in a beclomethasone subject (# 447 in C96-135.) These cases were not associated with increase of bilirubin to outside the normal range (although Subject 31/31 in I96-11 had an increase in bilirubin from 12 to 21 (normal ranges up to 21)).

There were isolated instances of leukocytosis, hematocrit decreases, cholesterol increases, hyperkalemia, hypokalemia, and creatinine increases. Subject # 70 in C96-137 (800 BID) had a creatinine of 1.4 at Screening which increased to 2.4 on Week 36 with a decrease to 1.7 on Week 40.

Instances of hyperglycemia in diabetics and those not previously known to be diabetic during the trial were somewhat more frequent but were still not often seen. Hematuria was not closely reviewed in most trials but was notable in a few trials. In C96-196, there were 3, 2, and 3 instances in the 200 BID, 200 QAM and 400 QAM groups, respectively, where the urinalysis changed from negative (in one case, trace) to at least 2+ blood. Cases of 1+ blood were generally not tabulated. In this same study, only one placebo subject showed even a 1+ Blood. Only one subject in the 200 QD PM showed a new 1+ RBC and other went from 1+ to 2+ RBC. In C96-186, there were 3 cases of at least 2+ blood in the 200 BIG group, 3in the 200 QD group 1 in the 400 QD group and one in the placebo group. In C96-168, the pattern was slightly different with 3 seen in the placebo group, and 2 each in the 100 BID and 200 BID groups.

In C96-137, Subject 87 (800 BID) had an alkaline phosphatase of 61 at Screening but by Day 267 had an isolated increased value of 116. There were cases of bilirubin increases in a number of the trials:

Trial	Dose	Subject/Site	Bilirubin Change	Day	Note	Note
C96-137	Placebo/ Variable	32/15	Tbili 0.8 to 3.4	Week 24	Other LFTs not affected	NI 0.2 –1.2. Tbili was 1.2 at end of study.
C96-135	BDP 168 BID	147	TBILI 1.2 to 1.9	Week 12	1.2 Day 350	
C96-134	100 BID	350	Tbili 1.1 to 1.4	Wk 12		
		85	Tbili 0.9 to 1.4			

	400 BID	432	Tbili 1.6 to 2.9	Wk 12	1.9 1 wk later Wk 12	
		122	Tbili 0.4 to 1.5	Wk 12	AST/ALT 47/84 at Scr	Nl AST/ALT Wk 12
		204	Tbili 0.3 to 2.1	Wk 12	nl AST/ALT Scr /Wk 12	
	BDP 168 BID	114	Tbili 0.9 to 1.4	Wk 12		
C96-168	BDP 168 BID	129	Bilirubin 1.2 to 1.7			
	100 BID	193/05	Total Bilirubin 2.7 to 3.7	Wk 12	Nl. 0.2-1.2 Baseline elevation	Normal AST/ALT
	Placebo	247	Bili 0.8 to 1.4			
I96-111	100 BID	35/28	Tbili. 12 to 27 (nl. 3-21)	Week 12		
	200 BID	15/09	Tbili 0.7 to 1.5		nl. Transamin ases	nl. Tbili 0.1 –1.0 mg/dl
		160/64	Tbili 12 to 31		AST 33 to 35, nl.9-34	nl. Tbili 3-21
I96-112	100 BID	21/33	Tbili 0.6 to 3.0		AST 37 to 13 (nl 9-37)	nl Tbili 0.2-2.0
	200 BID	15/33	Tbili. 0.2 to 7.3			nl Tbili 0.2-2.0
	400 BID	72/54	TBILI. 22 TO 45.		AST/ALT OK	
	Bud 400 BID	18/36	Tblli 9. 7 to 26		AST 51 to 22	nl Tbili 3-21
I96-113	200 BID	229/14	Tbili 17 to 27			nl. Tbili 3-21 µmol/L
		25/28	Tbili 17 to 28			nl. Tbili 3-21 µmol/L
		09/56	Tbili. 0.5 to 7.0			nl. Tbili 0.1 to 1.2 mg/dl
	400 BID	27/28	Tbili. 14 to 27			

There were rare instances of the occurrence of WBC decrease during study. In C96-134, Subject #107 (MF DPI 100 BID) developed a WBC of 0.98 on Week 12. The subject had a low WBC at Screening of 3.34 (normal 3.8 – 10.7). Three weeks after the end of treatment he was admitted with a diagnosis of leukemia. Another subject in this study on BDP 168 BID had a decrease in the WBC from 5.44 to 3.38. In C96-136, Subject 004/16 (400 QD) started with a WBC of 5.47 but had WBC 3.57 on Day 85. In the same study, Subject 134 (Placebo) had a WBC 3.22 on Day 85 and a WBC of 4.59 at Screening that was low normal.

In C96-196, Subject 264 (400 QAM) had a WBC at Endpoint of 2.8 but at Screening did not have one much higher at 3.42. Subject 254/12 (400 QAM) had a baseline platelet count of 154 which decreased to 98 by Endpoint (Repeat was 160 17 days later. WBC was also abnormal at 1.98 at visit 9 (5.38 at Screening) and a repeat value 17 days later was 5.47.

In C96-137, Subject 110/13 (800 BID) had a platelet count of 160 at Screening but by Day 36 of the study had a platelet count of 97 with a repeat of 81 three days later. On Day 53 (11 days off the treatment) and Day 92 (50 days off treatment), the platelet counts were 133 and 137, respectively.

9. Cortisol Testing

Cortrosyn testing was performed at selected study centers as part of Studies C96-134, C96-137, and C96-196. Cortrosyn testing was also performed in C96-135 but the sponsor does not present this data in any depth in the ISS probably because there was no placebo arm. The RIA used in C96-137 was inappropriate because of the cross-reactivity of prednisone with cortisol so data from this study is not usable so data is only available from the other sites.

Subjects whose prestimulation concentration of plasma cortisol was <5 μg/dl, whose poststimulation concentration was <18 μg/dl, or whose response to stimulation was not an increase of at least 7 μg/dl were generally infrequent and were pooled from C96-134 and C96-196.

Cortrosyn Testing from C96-134 and C96-196

	MF DPI BID			BDP 168 mcg BID	Placebo	Total
	100 mcg	200 mcg	400 mcg			
Screening						
Post-Cortrosyn value <18 mcg/dl	0	1	0	0	0	1
Difference Between Post- and Pre-cortrosyn value <7 mcg/dl	1	2	0	3	1	7
Endpoint						
Post-Cortrosyn value <18 mcg/dl	0	1	1	0	0	2
Pre-Cortrosyn value <5 mcg/dl and Post-Cortrosyn value <18 mcg/dl	0	1	0	0	0	1
Difference Between Post- and Pre-cortrosyn value <7 mcg/dl	0	2	0	2	1	5
Pre-Cortrosyn value <5 mcg/dl and Difference Between Post- and Pre-cortrosyn value <7 mcg/dl	0	0	0	1	0	1

There did not appear a particular increase in the number of subjects fitting these criteria at Endpoint compared with Screening.

Mean Plasma Cortisol (mg/dl) - Studies C96-134 and C96-196

Treatment Group	Screening(134)/Baseline(196)				Endpoint			
	n	Pre cortrosyn	Post cortrosyn	Change	n	Pre cortrosyn	Post cortrosyn	Change
C96-134 Inhaled Steroid-Dependent Subjects – 5 sites –18-20 per group at Screening								
MF DPI 100 mcg BID	20	14.67	28.58	13.91	17	15.19	28.83	13.64
MF DPI 200 mcg BID	18	14.22	26.90	12.68	17	14.35	26.16	11.81
MF DPI 400 mcg BID	18	11.73	27.42	15.70	18	12.21	26.59	14.38
BDP 168 mcg BID	20	14.48	29.19	14.71	18	12.83	26.88	14.05
Placebo	20	12.22	27.53	15.31	12	17.00	29.92	12.92
C96-196 (Corticosteroid-dependent subjects; 2 wks 200 BID then 12 wks double-blind)								

	7 sites							
MF DPI 200 mcg QD AM	27	14.28	26.82	12.53	24	14.53	26.68	12.15
MF DPI 200 mcg QD PM	22	15.14	28.16	13.02	22	15.94	28.16	12.21
MF DPI 400 mcg QD AM	26	13.82	26.07	12.26	25	14.04	25.31	11.27
MF DPI 200 mcg BID	26	13.12	25.86	12.73	24	15.13	27.71	12.58
Placebo	26	15.75	29.54	13.79	20	16.73	31.21	14.48

For C96-134, no significant changes were noted in the change between Screening to Endpoint in the difference between pre- and post ACTH stimulation. For C96-196, mean post-Cortrosyn plasma cortisol values at Endpoint were significantly lower in the MF DPI 400 QAM group than in the placebo group but at Baseline, post- Cortrosyn mean plasma cortisol values also were lower in the MF DPI 400 QAM and 200 BID treatment groups than in the placebo group. The sponsor says that after the post-Cortrosyn data were re-evaluated using a covariate analysis model that adjusts for Baseline differences, it was confirmed that differences between treatment groups at Endpoint were due in part to the differences at Baseline. The p value at Endpoint for the difference between 400 mcg QAM and placebo was reduced from <0.01 and 0.01 to 0.05 and 0.05 for "post-cortrosyn" and "difference between post- and pre-cortrosyn," respectively, after the adjustment is made but the difference is still very nearly significant. Despite this definitive lack of difference it should be noted that subjects had been utilizing ICS before entering the study (and were even on 2 weeks of MF DPI 200 BID before Baseline in C96-196) so it seems that the ability of such testing to rule out a steroid effect of MF DPI is not manifest. Furthermore, 250 µg doses of ACTH were utilized: such doses, while traditional, may not be able to rule out any HPA axis suppression and appear to rule out overt adrenal suppression and a statistical analysis involves a comparison of the means.

In C96-135, there were significant differences at Week 52 between the change in pre-post values of MF DPI 200 BID/400 BID and BDP but no significant differences were noted at Week 26. Because 1) the mean pre-post differences from Screening over the course of treatment appeared to decrease by 1.0 to 2 mcg/dl for the MF DPI 200 BID and 400 BID groups and 0.5-0.6 for the 800 QD group, and 2) the Week 52 pre-post difference for BDP, even compared with its 26 week difference, was particularly high, it can not be definitively stated that MF DPI is any more likely to produce adrenal suppression, based on the results of this single small study, than BDP. No dose related effects were noted among treatment groups. A summary of the subjects with a pre-stimulation plasma cortisol concentration of <5 mcg/dl, a post-stimulation concentration of <18 mcg/dl, or an increase in response to Cortrosyn stimulation of <7 mcg/dl was generated in C96-135. While at Screening there appeared to be more individuals with abnormalities in the MF DPI 800 QD and BDP groups, at the end of 52 weeks, those with abnormalities were equally distributed among the MF DPI groups only and, interestingly, none were seen in the BDP group suggesting, perhaps, that MF DPI has a more suppressive effect in some individuals than BDP.

In I96-111 and 112, no decrease was noted in the am plasma cortisol level between Baseline and Endpoint. This does not mean, however, that there was definitive evidence that no HPA axis suppression occurred during MF DPI treatment. These subjects had also been on inhaled corticosteroids at Baseline.

In C95-135, groups of 12 asthmatics were exposed to MF DPI 400 QAM, 800 QAM, 1200 QAM or 200 BID for 28 days. MF levels were present is a dose ordering manner but important

differences between treatments and placebo were not identified for the plasma cortisol AUC, urinary free cortisol or cosyntropin testing.

The small study C97-049 examined serum cortisol, AUC (0-24 Hr) and urine cortisol effects of MF 400 BID, MF 800 BID, Prednisone 10 mg and placebo over 29 days. Urine cortisol testing was not analyzed by the sponsor because of an excessive number of unusable data points. There was a treatment related decrease in the mean serum AUC with apparent dose-ordering.

Mean Serum Cortisol $AUC_{(0-24)}$ (µg·hr/dl)

Treatment Group	Day	Baseline	7	14	21	28
Placebo lactose BID	AUC	255.5	243.2	202.8	213.4	206.4
	--	--	--	--	--	--
MF 400 µg BID	AUC	242.9	181.9	165.3	173.6	185.3
	%chg[a]	-5	-25[b]	-19[c]	-19[c]	-10
MF 800 µg BID	AUC	210.9	146.7	149.6	160.4	163.0
	%chg[a]	-18[c]	-40[b]	-26[b]	-25[b]	-21[c]
Prednisone 10 mg QD	AUC	215.6	68.5	71.2	68.2	74.3
	%chg[a]	-16	-72[b]	-65[b]	-68[b]	-64[b]

a: % change from placebo at that timepoint.
b: p<0.01 with placebo.
c: p<0.05 with placebo.

The post-cosyntropin stimulation mean serum cortisol concentration for the MF DPI 800 BID group (20.8 µg/dl) was significantly reduced from the placebo group value (25.0 mcg/dl), while the MF 400 mcg BID group post-stimulation value (23.2 µg/dl) was not significantly different from placebo. The prednisone group had significantly lower mean serum cortisol concentrations than all other groups before (4.9 mcg/dl) and 30 minutes after (14.5 µg/dl) intramuscular stimulation with cosyntropin 250 mcg.

This data from C97-049, a study in which the subjects were asthmatics but had not recently been on ICS, supports the idea that MF DPI does have an effect on the HPA axis. It should be noted, however, that the doses of MF DPI were higher than those that the sponsor seeks to market in non-prednisone dependent subjects.

There is considerable difference in the 24 hour cortisol AUC results between C97-049 and C95-135. There were differences in the formulation of MF- lactose used between the studies. In C95-135, the doses of 200 BID, 400 BID, 800 BID and 1200 BID were administered with 100 µg/ inhalation while the 400 BID and 800 BID of C97-049 were administered as 2 inhalations of 200 µg BID and 2 inhalations of 400 µg BID respectively. The sponsor will be asked to provide some explanation as to the reason behind the differences in the 24 hour cortisol AUC data between these two studies.

It is this reviewer's conclusion that the sponsor has not definitively demonstrated in this NDA submission that MF DPI does not affect the HPA axis. Studies such as C95-135 showed no effect on the HPA axis while C97-049, using higher doses than those to be marketed, did support the idea of a treatment-related effect. Cosyntropin testing in the large trials were

typically performed on asthmatics treated with ICS at baseline so what was being tested was whether MF DPI had an HPA axis effect above and beyond that of the previous ICS.

Other studies examined the effect of the pure powder form of mometasone furoate. In the four week study C94-127, a subset of 68 subjects received Cortrosyn testing and there was a mean change of 0.4, -3.8, -0.5 and 1.9 in the MF pure powder 100 qd, 400 qd, 200 BID and placebo groups, respectively, for the difference of pre- and post-treatment between Screening and Endpoint. In the small study C94-071, the 600 mcg dose of pure MF DPI had a significantly lower cortisol AUC than placebo for the treatment period of 28 days and the 200 mcg qd dose was only significantly different at Day 28. The 400 mcg dose was not significantly different from placebo at any timepoint. In the small German study I93-009 using pure MF (no lactose mixture) inhalations, the $AUC_{(0-24)}$ was reduced by 15%, 35%, 56%, and 71% from the placebo value following single doses of MF 400, 800, 1600 and 3200 mcg doses, respectively. These decreases were significantly different from placebo for all doses except the very lowest in each treatment group.

Studies on growth and bone density were not part of this NDA submission but are part of the sponsor's mometasone program.

10. Mometasone Furoate Concentrations

The levels observed in two studies were considered relatively low by the sponsor. There was large inter-subject variability. MF concentrations were measured using a validated high pressure liquid chromatography assay with tandem mass spectrometry detection in plasma samples collected before and 30 minutes after dosing with study medication on Visit 15 (Week 12) from 43 subjects at ten study centers in C96-137. The limit of quantitation (LOQ) of the LC/MS/MS assay was 50 pg/ml. In the 400 BID group, MF was quantifiable in 3/12 predose and 8/12 postdose samples. Mean plasma MF concentrations were 56.1 pg/ml and 148.0 pg/ml, respectively. In the 800 BID treatment group, MF was quantifiable in most predose (11/15) and postdose (14/15) samples and mean plasma MF concentrations were 105.0 pg/ml predose and 215.0 pg/ml postdose.

In C96-134, MF concentrations were measured in plasma samples collected from 90 subjects before and 30 minutes after the last dose at five study sites. Quantifiable concentrations were observed in 2/17 subjects who received MF DPI 100 BID (69.5 and 188 pg/ml), 9/17 who received MF DPI 200 BID (51 to 119 pg/ml), 10/16 who received MF DPI 400 BID (67.7 to 210 pg/ml [second highest value 110 pg/ml]), and in no subject who received BDP or placebo. Quantifiable concentrations appeared to be slightly more prevalent among subjects who received MF DPI 200 or 400 BID than 100 BID, but the values were relatively low and not apparently related to dose. The Biopharmacology reviewer is performing a more formal PK review.

11. ECG Data

In general, ECGs were only performed at Baseline. Because these ECGs did not reflect an effect of drug treatment, they were not reviewed in any detail. ECGs were performed both at Baseline and at 3 month and 9 month Endpoints for three trials – C96-136, 137 and at Baseline and Week 52 for C96-135. Typically, the sponsor only submitted descriptions of the ECG and did not supply a listing of the segment intervals. In general, the abnormalities noted were not felt to be clinically significant by the investigator except for Subject #63 in C96-137. No specific

ECGs were requested of the sponsor for review although two subjects in C96-135 were asked for clarification. In general, it does not appear that there is a specific ECG abnormality induced by MF DPI.

In C96-136, an ECG was done at Screening, Week 12 and at Week 52. None of the ECG changes that were seen were considered to be clinically significant by the investigators.

1. Subject 197 (200 QAM) is listed as having a non-specific T wave abnormality and a long QT interval at Week 12. No further ECGs were available for this subject.
2. Subject 094 (200 QAM) is listed with a non-specific T-wave abnormality at Week 12 after a normal Screening ECG. No further ECGs were available for this subject.
3. Subject 063 (Placebo to 200 QPM) is listed with poor R wave progression in V2-4 at Day 288 abnormality whereas it had been normal at Screening and "borderline abnormal" with low QRS voltages in the precordial leads at Week 12.
4. Subject 215 (Placebo to 400 QPM) is listed with nonspecific inferior T wave abnormalities at Day 56 into the 9 month phase (End of study for subject due to lack of compliance notably patient had been off of study medication for 53 days at this point.) – subject had LVH at Screening which was no longer present at Week 12's study.
5. Subject 111 (400 QPM; Site 19) is listed with a "possible infarction and ST abnormality" at Day 114 of the 9 month open label phase. Notably, the subject had been off study medication for 47 days at this point. The subject had previously been listed with a ST abnormality and possible Digitalis effect at Week 12.

For C96-135, again the sponsor relates that none of the following changes from Baseline noted in the EKG's at Week 52 were felt to be clinically relevant:

<u>MF DPI 400 BID</u>	
271	Early repolarization
055	"Consider posterior infarction. MD feels this is due to V2 lead placement. Consider LAFB."
<u>MF DPI 800 QD</u>	
54	RSR in V1 or V2 was seen both at Baseline and Week 52 but only poor R wave progression is specifically listed for Week 52.
65	Poor R wave progression, probable early repolarization pattern.
485	RSR' in V1 or V2, LVH by voltage
486	Borderline intraventricular conduction delay
<u>BDP 168 BID</u>	
420	L anterior fascicular block
60	Probable early repolarization pattern.
063	RSR in V1 or V2, consider left atrial enlargement.

In C96-137, the following abnormalities were noted between Screening and the respective visit during the 3 month phase (all were felt to be not clinically significant except for Subject #63):

1. Subject #101 (800 BID) was found to have low anterior forces and a nonspecific T wave abnormality at Week 12 compared with Baseline.

2. Subject #63 (800 BID) was noted to have a 2nd degree AV block, Mobitz Type II, with frequent PVC's and moderate ST depression at Week 12 compared with Screening (p. 11499). This abnormality was felt to be clinically significant. Notably, the patient had anteroseptal ECG changes which were borderline abnormal at Baseline which were though possibly due to myocardial ischemia.
3. Subject #38 (800 BID) was noted to have nonspecific inferior T wave abnormalities compared at Week 12 compared with Screening.
4. Subject #150 (Placebo) was noted to have flipped T waves on Week 9 compared with Screening. The patient was referred to a cardiologist. An echo and EKG were performed and were felt to be not clinically significant.
5. Subject #75 (Placebo) was noted to have nonspecific lateral T wave abnormalities at Week 12 compared with Screening.
6. Subject #66 was noted to be in a chaotic atrial dysrhythmia at Week 12, which was new, compared to Screening.
7. Subject #9 (Placebo) was noted to have a nonspecific T wave abnormality at Week 5 compared with Screening.

In the 9 month open phase of C96-137:

1. Subject #87 had a nonspecific intraventricular conduction delay on Day 281
2. Subject #161 was noted to have a possible old inferior infarction with ST-T changes in the septal lead that was not noted on previous EKGs.
3. Subject #96 was noted to have new poor R wave progression at Day 288 compared with earlier EKGs.
4. Subject #73, previously with a LAFB was noted to have a complete LBBB with 1st degree AV block on Day 286.
5. Subject #110 had a normal EKG at Screening, non-diagnostic Q waves in inferior leads at Week 5 (3 month phase). Eight days into the open label phase "cannot r/o inferior infarction on or before 17/3/97. Patient will follow up with cardiac consult." This consult was done with a stress echo to follow but no details in this section were provided.
6. Subject #131 was noted to have new ST changes in the septal leads on Day 174. No further detail was given.

R. DSI Review

Three sites from the placebo-controlled trials were selected for review by mutual agreement with the Division of Scientific Investigations (DSI). The sites were chosen because the numbers of subjects at those sites were among the sites with the largest number of participants in that particular trial. These sites, however, did not necessarily have the largest number of participants. The sites that were reviewed include:

1. Study C96-137 – Site 04 (Timothy Craig, D.O., The Milton S. Hershey Medical Center, 500 University Drive, P.O. Box 850, Hershey, PA 17033)

2. Study C96-196 – Site 09 (Jay Grossman, M.D., Allergy Care Consultants, Ltd., 3395 North Campbell Avenue, Tucson, AZ 85719)

3. Study C96-186 – Site 05 (S. David Miller, M.D., New England Research Center, Inc., 49 State Road, Watuppa Building, No. Dartmouth, MA 02747)

The site reviews for Timothy Craig, D.O. and S. David Miller, M.D. were found to have adhered to the Federal Regulations and/or good clinical investigational practices that govern the conduct of clinical investigations and the protection of human subjects. The data at these sites appeared to be acceptable to support drug claims. Each site was given the designation of NAI-no deviation from regulations.

There were two separate inspections of Dr. Grossman performed by DSI: one was for the conduct of the study for NDA 21-067 (PDUFA), and the other was a For Cause Inspection (FCI)(NON-PDUFA Drugs) of Dr. Grossman's conduct of studies involving several other drugs.

The results of our inspection of Dr. Grossman's conduct of the studies in support of NDA 21-067, Mometasone are satisfactory, and the data were deemed to be usable. However, the results of the FCI raised many questions as per DSI. Based on the findings described in the Form 483 for this FCI, DSI believed that the data for these studies was not usable (See memo from H.W. Ju dated August 30, 1999). At the time of this review, the EIR had not yet been completed. Without the formal EIR, the DSI officer could definite conclusion regarding the validity of these studies and a classification was not yet assigned (See memo from H.W. Ju dated August 13, 1999). In summary, DSI believed that Dr. Grossman's conduct of the latter studies was so questionable as to make his conduct of the Mometasone study suspect. It was DSI's recommendation that our statistician not include Dr. Grossman's data for NDA 21-067 but DSI noted that their conclusions were unofficial until they were able to receive and evaluate the completed EIR.

During the PDUFA Drug review dated 4/29 – 5/5/99, the following observations were made by the inspector:

1. There is no written procedure/documents of training of study coordinators in GCPs.
2. Calibration of KOKO Spirometer is not maintained in that:
   - There is no record of daily calibration.
   - Temperature, humidity, and atmospheric pressure used to calibrate machine is taken from instrument that is not NIST traceable.
   - Employee informed me that contrary to instruction manual only temperature is entered.
3. Seven of fourteen patient files examined found no notation of informed consent given.

Dr. Grossman was involved in trials C96-137 (Site 11) and C96-196 (Site 09). He contributed data on 6 subjects to trial C96-137 – one male/female subject in each of the treatment groups (#'s 67, 72 in MF DPI 400 BID, #'s 68, 70 in MF DPI 800 BID, and #'s 69, 71 in placebo (both were treatment failures.) For C96-196, he contributed 4 subjects to the 200 QAM group, 4 subjects in the 200 QPM group, 6 subjects in the MF DPI 400 QAM group, and 6 subjects to the placebo group. A re-analysis of the data in C96-137 and C96-196 without Dr. Grossman's subjects will be requested of the sponsor in an action letter. Of note, he was also involved in the ongoing study (Site 08) which is a two year study on the effects of MF DPI on bone density in young adult asthmatics. The study was not submitted as part of this NDA package.

S. Executive Summary and Conclusion

The purpose of this NDA as stated in the propose package labeling is to obtain approval for the use of MF DPI in patients 12 years of age and older in the maintenance treatment of asthma as a prophylactic therapy and as a treatment in asthma patients who require systemic corticosteroid administration where adding MF DPI may reduce or eliminate the need for systemic therapy. The sponsor seeks to market two strengths of MF DPI, 220 mcg which results in a delivery of 200 mcg, and 440 mcg which results in a delivery of 400 mcg. There were 2 large placebo-controlled trials which examined the efficacy and safety of MF DPI in asthmatic subjects previously maintained on B agonists alone and three large placebo-controlled trials which examined safety and efficacy in asthmatics previously on inhaled corticosteroid therapy. The three large international trials did not utilize a placebo control.

The doses that are believed to be justified and efficacious in this clinical program are 200 μg BID and 400 μg QAM for asthmatics as well as 400 μg BID in those attempting to reduce oral corticosteroid therapy. It is important to note that the to-be-marketed inhalation strengths of 200 μg and 400 μg per inhalation were not utilized in many of the pivotal large clinical trials in this development program. C96-136 dosed MF DPI 400 μg QAM as 2 inhalations of 200 μg: it would be logical for this to be dosed as 400 μg in one inhalation in the to-be-marketed product and this inhalation strength was not tested. C96-186 dosed 400 μg QAM in the same way and 200 μg BID as 2 inhalations of 100 μg BID. C96-196 dosed 200 μg BID as 100 μg in 2 inhalations BID and 400 μg QAM as 2 inhalations of 200 μg QAM. C96-134 and C96-168 dosed 200 μg BID as 200 μg in 1 inhalation BID (a probable to-be-marketed manner.) C96-137 dosed 400 μg BID as 200 mcg in 2 inhalations BID: in the to-be-marketed inhalation strength, 400 μg BID would be more aptly dosed as 400 μg in 1 inhalation BID. The sponsor will be asked to perform pharmacokinetic and pharmacodynamic studies utilizing the nominal doses from the two to-be-marketed inhalation strengths (200 μg and 400 μg) as well as the 100 μg strength that was utilized in many of the pivotal placebo-controlled trials

Analysis of the primary endpoint, change in FEV_1 from baseline, has demonstrated efficacy with the 400 mcg QAM and 200 mcg BID doses of MF DPI in subjects previously maintained on B-agonists alone as well as in subjects previously maintained on inhaled corticosteroids. The efficacy of 200 mcg QAM has not been sufficiently demonstrated as it failed to significantly improve FEV_1 in 2 out of the 3 trials in which it was utilized as well as a number of secondary efficacy endpoints. The primary endpoint in C96-137 was the percent change from Baseline to Endpoint in the daily prednisone requirement. In this one steroid-sparing trial, the efficacy of MF DPI 400 mcg BID has been demonstrated in its ability to allow for the successful reduction of oral corticosteroid therapy. There was no benefit in using 800 mcg BID over 400 mcg BID in steroid-dependent patients.

In clinical trials, the most common adverse event was headache, which was no more common with MF DPI than with placebo. Oral candidiasis was clearly more common with MF DPI than with placebo despite the fact that subjects were advised to rinse their mouths after drug treatment in the protocol; pharyngitis and dysmennorhea are probably also more common with MF DPI. Laboratory abnormalities were noted in the clinical development program but there were no important changes in the median laboratory values between Baseline and Endpoint. There were unexplained elevations in transaminases found, but such abnormalities were also noted in placebo groups as well as in subjects utilizing other forms of inhaled

corticosteroid therapy. There were studies that demonstrated both an effect and a lack of effect of MF DPI on the HPA axis. A lack of HPA axis effect of MF DPI has not been convincingly demonstrated in this clinical program.

Overall, it is believed that MF DPI is an effective and relatively safe product in the maintenance therapy of asthma; MF DPI has also been shown in one trial to be effective in the reduction of oral corticosteroid therapy in those asthmatics requiring such intervention. Because of several outstanding CMC issues at this time, NDA 21-067 is felt to be approvable.

T. Comments/Questions to the Sponsor

Mometasone DPI is approvable in the United States at this time. There are several chemistry and manufacturing deficiencies of which the sponsor is aware that need to be addressed and reviewed. Please also make note of the following comments.

1. In future NDA submissions, it is recommended that dates be included with laboratory testing results and that repeat values clearly be labeled. The fact that dates were not included with the laboratory results unnecessarily complicated and prolonged the review of this NDA. When laboratory testing needed to be repeated, for example, the repeated results were often included in one section of the NDA (16.2.8.2) and not in another (14.3.4.1) for Studies C96-196, C96-168, and C96-196 thus making it appear that there were incongruities in the data presentation.

2. It is important to note that the to-be-marketed inhalation strengths of 200 μg and 400 μg per inhalation were not utilized in many of the pivotal large clinical trials in this development program. There is a general lack of pharmacodynamic data with the 400 μg strength both as a 400 μg QAM and as a 400 μg BID dosing. C96-136 dosed MF DPI 400 μg QAM as 2 inhalations of 200 μg: it would be logical for this to be dosed as 400 μg in one inhalation in the to-be-marketed product and this inhalation strength was not tested in this trial. C96-186 dosed 400 μg QAM in the same manner and 200 μg BID as 2 inhalations of 100 μg BID. C96-196 dosed 200 μg BID as 100 μg in 2 inhalations BID and 400 μg QAM as 2 inhalations of 200 μg QAM. C96-134 and C96-168 did dose 200 μg BID as 200 μg in 1 inhalation BID in a probable to-be-marketed manner. C96-137 dosed 400 μg BID as 200 mcg in 2 inhalations BID: in the to-be-marketed inhalation strength, 400 μg BID would be more aptly dosed as 400 μg in 1 inhalation BID. Please perform a pharmacokinetic and pharmacodynamic study utilizing the same nominal doses (400 μg per day) from the two to-be-marketed inhalation strengths (200 μg and 400 μg) and also include evaluation of a dose response in this trial.

3. In Trial C96-196, the graph for AM PEFR in Figure 3 does not appear to reflect the same data on AM PEFR that is presented in Table 13. Clarify the graph and this discrepancy.

4. In Trial C96-196, please explain why there are so few data points for the FEV_1 on Day 4 for the MF DPI 200 QD AM and MF DPI 200 BID treatment groups for those subjects with FEV_1 <75% predicted and for the MF DPI 200 QD PM and MF DPI 400 QD AM treatment groups - for those subjects with FEV1 $\geq$ 75%

5. In C96-136, Table 50 contains a footnote indicating this list of severe adverse events are related or possibly related to treatment. In the next paragraph in the report, you then say that only one subject had an adverse event that was considered treatment related and severe during the 9 month phase. It is believed that the labeling of the above list in a footnote as treatment-related was in error. Please clarify.

6. In Trial C96-137, subjects were allowed to take other medications for their asthma (i.e. Serevent, Atrovent, and Cromolyn-like drugs) during the treatment period with appropriate washout periods. This data on these other drugs was presented in a listing format. Such data is important because an increase in their use could be reflective of the efficacy of the study treatments. In a line listing, however, it is difficult to track changes. Please supply such data in a summary table over the course of the treatment period.

7. In C96-137, there are listed in Table 43 five instances of fetal disorders that were seen in the 9 month phase. There were 4 instances of ear malformation and one instance of artery malformation. One case of artery malformation and 4 cases of ear malformation were also listed in Section 14.3.1.1.2. More information on these fetal events was requested of the sponsor. The clarification of these events was dated 8/27/99. The incident labeled as "artery malformation" should have been correctly called "arthralgia." The four incidents labeled as "ear malformation" should have been called "peripheral edema." Only the Case Report Form for Subject 114 at Site 13 was available electronically to verify that peripheral edema occurred and not ear malformation. It was difficult to locate this adverse event within the case report form. Please supply the five case report forms on these subjects with errantly coded adverse events and the location of these adverse events within the CRF.

8. In C97-137, a serious adverse event of idiopathic thrombocytopenic purpura was noted at the last visit in Subject 213. Please provide follow-up data on this subject.

9. In Trial C96-186, there were baseline differences among the treatment groups in the AM and PM PEFR. Please perform an analysis factoring in these baseline differences in some way, for example, by using them as a covariate in the analysis.

10. For salbutamol use in I96-111 (Section 11.4.1.4), please clarify whether baseline use of salbutamol was a covariate in the analysis.

11. In Trial I96-111, you present in Section 11.4.1.7 that Clinical Asthma Exacerbations were reported at some time during the study by 13 subjects in the MF DPI 100 mcg BID group, 11 subjects in the MF DPI 200 mcg BID group, 9 subjects in the MF DPI 400 mcg BID group, and 9 subjects in the Fluticasone Propionate group. In Section 16.2.4, you state that this CAE list is a subset of the subjects who met criteria for Worsening of Asthma, however, it is not clear why these numbers do not match the numbers for clinical asthma exacerbations in the Time to Worsening table in Section 11.4.1.7.

12. In Trial I96-111, the data for the weights is not believed to be accurate at Week 12 and Endpoint for females in the MF DPI 200 BID and FP groups where the range of weights is listed as 45-665 kg and 44 –835 kg, respectively. The data for the weight ranges on Caucasians in these same treatment groups is also not believed to be accurate. Please clarify.

13. In Trial C96-112, the glucose values for Site 12 (C. Bisbal, M.D.) both at Screening and at Week 12 appear to be out of the normal range of 3.9 –6.4 mmol/l listed for this site. The creatinine data at Week 12 also appear to be well out of the range of 62-124 µmol/l. Please submit a clarification of the glucose and creatinine data at this site.

14. In Trial I96-113, the mean weight for the 600 mcg BID group increased from 80.1 kg. to 89.8 kg at Endpoint for the entire group and for females specifically, the mean weight increased from 73.5 to 89.7 at Endpoint. It is believed, however, that this is an error because the high value for the group at Endpoint and at 12 weeks is 675 kg. Please clarify this data.

15. In Trials I96-113 and C96-136, "menstrual disorder" was one of the adverse events listed. Please clarify what pain and menstrual disorder mean.

16. In the package labeling under Clinical Trials, a reference made to C96-136 indicates that the subjects entered into this study ' [ ] [ ]" Please clarify what is meant by [ ] alone and justify why these subjects met that criterion.

17. Dr. Jay Grossman was involved in trials C96-137 (Site 11) and C96-196 (Site 09). He contributed data on 6 subjects to trial C96-137 – one male/female subject in each of the treatment groups (#'s 67, 72 in MF DPI 400 BID, #'s 68, 70 in MF DPI 800 BID, and #'s 69, 71 in placebo (both were treatment failures.) For C96-196, he contributed 4 subjects to the 200 QAM group, 4 subjects in the 200 QPM group, 6 subjects in the MF DPI 400 QAM group, and 6 subjects to the placebo group. Based on concerns raised to the Division by the Division of Scientific Investigators (DSI), please supply a re-analysis of the data in C96-137 and C96-196 without Dr. Grossman's subjects.

18. In Trials C95-135 and C97-049, the post-cosyntropin stimulation mean serum cortisol concentration data could not be located in a table format. Please supply this information on means as well as outliers (subjects whose prestimulation concentration of plasma cortisol was <5 µg/dl, whose poststimulation concentration was <18 µg/dl, or whose response to stimulation was not an increase of at least 7 µg/dl) in a summary table. In addition for C97-049, a statistical analysis of the comparison between the post-cosyntropin values at Baseline compared and the post-cosyntropin values at Day 29 for each active treatment versus placebo should be submitted.

19. In Trial C97-049 and C95-135 for the Mean Serum Cortisol $AUC_{(0\text{-}24)}$ (µg·hr/dl) data, please submit an analysis comparing the change in cortisol AUC from Baseline for each particular treatment arm with the change from Baseline for placebo.

20. There is considerable difference in the 24 hour cortisol AUC results between C97-049 and C95-135. There were differences in the inhalation strength of MF-lactose used between the studies. In C95-135, the doses of 200 BID, 400 QD, 800 QD and 1200 QD were administered with 100 µg/inhalation while the 400 BID and 800 BID of C97-049 were administered as 2 inhalations of 200 µg BID and 2 inhalations of 400 µg BID, respectively. Th C_{MAX} data for 1200 mcg QD in C95-135 most closely resembles the C_{MAX} data for 800 mcg BID in C97-049. Please provide an explanation for the differences in the 24 hour cortisol AUC data between these two studies.

21. Pharmacokinetic data for the 100 µg, 200 µg, and 400 µg inhalation strength was not available together in a single study. Using pharmacokinetic data from the to-be-marketed dosage strengths and formulations, discuss what to-be-marketed doses and formulations would be supported by the data available in C95-135?

22. In C96-196, while cortrosyn stimulation testing was performed at Screening, the data was only made available as individual line listings. The means at Screening were not available in tabulated form and no statistical analyses comparing the values at Screening with those at Baseline or Endpoint were available. Please provide this tabulated data with statistical analysis.

23. It is mentioned in the Integrated Summary of Safety that ECGs were performed at Week 12 in C96-134 (Section 8.2.6.1), however, no Week 12 ECGs were mentioned in this study's protocol. Please clarify.