U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	N21-067/SE05-003
Drug Name:	ASMANEX® TWISTHLER®
Indication(s):	Maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older
Applicant:	Schering-Plough Research Institute
Date(s):	Received 03/30/07; User Fee 02/02/08
Review Priority:	Standard
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Keywords: NDA review, clinical Studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The March 30, 2007, supplement (SE05-003) of NDA 21-067 showed that ASMANEX® TWISTHALER® (mometasone furoate) significantly improved lung function in asthmatic children aged 4 to 11 years. In this supplement, Schering Corporation proposed to extend the indicated population for ASMANEX® TWISTHALER® down to children 4 years of age, using a reduced-strength version of the currently marketed device. The new device is code-named MF DPI. The proposed dose is 100mcg mometasone (ex-mouthpiece) inhaled once a day in the evening (QD PM).

The review analyzed three pivotal efficacy studies (Studies P01431, C97380 and CI97300) in pediatrics aged 4 to 11 years. The studies compared the effect of the drug at different times (AM or PM) and frequencies (both AM and PM) of administrations, as well as the drug's dose-response relationship (100mcg vs. 200mcg). Results show that: 1) both 100mcg BID and QD PM treatments provided significant improvements in lung functions, but 100mcg BID had only slightly better improvement, while QD AM results were inconsistent; 2) Increasing MF DPI doses did not appear to offer any further efficacy advantage. Although efficacy results with 100mcg BID dose was replicated in two studies (P01431 and C97380), the 100mcg QD PM dose (the sponsor proposed dose) was only evaluated in one study (P01431).

For Study P01431, based on the primary efficacy endpoint, the change in %predicted FEV_1 between baseline and endpoint, MF DPI treatments were statistically significantly superior to placebo. Both MF DPI dosages (100mcg QD PM and 100mcg BID) provided similar effectiveness for improving %predicted FEV_1. (LS mean: 6.50 and 7.29 for 100mcg QD PM and 100mcg BID, respectively). Other pulmonary function variables supported the efficacy seen in %predicted FEV_1. The use of rescue medication data supported the efficacy of 100mcg QD PM dose with the nominal p-value of <0.021.

Only 5% - 9% of patients were 4-5 years old in the three studies. The efficacy of MF DPI for patients aged 4-5 years had similar trends compared to patients aged 6-11 years.

1.2 Brief Overview of Clinical Studies

ASMANEX® TWISTHALER® [mometasone furoate dry powder inhaler (MF DPI)] was approved for the maintenance treatment of asthma for patients 12 years of age and older in March 2005. At the time of approval, the pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) were deferred and designated as post market study commitments. This efficacy supplement is in accordance with that commitment. The supplement proposed to treat pediatric asthma with a reduced-strength version of MF DPI. The submission included eight studies: 1 short-term HPA-axis study, 2 knemometry studies, 3 efficacy studies, and 2 long-term safety studies.

Table 1 presents the study design and statistical results for the primary efficacy endpoint for the three studies used by the sponsor to support efficacy.

Table 1. Clinical Trials

Study/Center / Study Period	***Study Design***	***Key Inclusion Criteria***	***No. of patients by treatment group entered/completed***	***Primary Endpoints***	***LS Mean (MF DPI-PLA) 95% CI p-value [a]***
P01431 39 centers in US and Latin American 1/01 – 4/02	Multi-center Randomized Double-blind Placebo-controlled Parallel-group	1. Age 4-11 yrs; 2. 60%≤FEV_1<85% predicted; 3. ≥12% increase of FEV_1 after reversibility testing; 4. used ICS for at least 60 days prior to screening;	100mcg QDPM: 98/77 100mcg BID: 99/80 Placebo: 99/67	Change in %predicted FEV_1 from baseline to endpoint (last post-baseline observation)	100mcg QDPM: Δ=6.5 (2.4, 10.6), p=0.002 100mcg BID: Δ=7.3 (3.2, 11.4), p<0.001
C97380 25 centers in US 5/98 – 9/99	Multi-center Randomized Double-blind Placebo-controlled Parallel-group	1. Age 4-11 yrs; 2. 60%≤FEV_1≤90% predicted; 3. ≥12% increase of FEV_1 after reversibility testing; 4. used ICS for at least 30 days prior to screening;	100mcg QDAM: 81/63 200mcg QDAM: 75/55 100mcg BID: 80/72 Placebo: 80/50	Change in %predicted FEV_1 from baseline to endpoint (last post-baseline observation)	100mcg QDAM: Δ=4.3 (-0.2, 8.8), p=0.059 200mcg QDAM: Δ=5.6 (1.0, 10.1), p=0.016 100mcg BID: Δ=8.0 (3.5, 12.5), p<0.001
CI97300 25 centers in US and Central and South America 4/98 – 5/99	Multi-center Randomized Double-blind Placebo-controlled Parallel-group	1. Age 4-11 yrs; 2. 60%≤FEV_1≤90% predicted; 3. ≥12% increase of FEV_1 after reversibility testing; 4. used ICS for at least 30 days prior to screening;	100mcg QDAM: 100/84 200mcg QDAM: 97/76 Placebo: 93/57	Change in %predicted FEV_1 from baseline to endpoint (last post-baseline observation)	100mcg QDAM: Δ=7.6 (2.8, 12.4), p=0.002 200mcg QDAM: Δ=6.8 (2.0, 11.7), p=0.006

ICS: Inhaled Corticosteroids.
A: p-value was from a two-way ANOVA model with treatment and center as covariates; Results from reviewer's analysis.

1.3 Statistical Issues and Findings

There was no special statistical issue. My evaluation of the data supports the sponsor's conclusion of Studies P01431, C97380, and Ci97300. Study P01431 provides evidence of the efficacy of MF DPI 100mcg QD PM dose regimen.

2. INTRODUCTION

2.1 Overview

ASMANEX® TWISTHALER® (mometasone furoate dry powder inhaler (MF DPI)) was initially introduced to the Division of Pulmonary and Allergy Products via IND 46,216. The sponsor originally submitted an NDA (21-067) for ASMANEX® TWISTHALER® 220mcg on November 30, 1998. This NDA was given an approvable action in October 1, 1999 for mostly CMC deficiencies and some clinical as well. Two additional approvable letters were sent on March 14, 2000 and May 17, 2004 for CMC deficiencies while the rest of the clinical issues were adequately addressed in this submission. The September 29, 2004, the sponsor's submission constituted a complete response to Agency's May 17, 2004, action letter and this NDA was approved for the maintenance treatment of asthma for patients 12 years of age and older on March 30, 2005.

The sponsor submitted this application on March 30, 2007 (NDA 21-067/SE5-003) in support of extending the indication for Asmanex to include the treatment of asthma in children ages 4 to 11 years, using a reduced-strength version of MF DPI. The sponsor's submission included eight studies: 1 short-term HPA-axis study, 2 knemometry studies, 3 efficacy studies, and 2 long-term safety studies. This reviewer focused on efficacy studies as outlined in Table 2.

Table 2. Clinical Trials

Study/Center/ Study Period	***Study Design***	***Key Inclusion Criteria***	***No. of patients by treatment group entered/completed***	***Primary Endpoints***
P01431 39 centers in US and Latin American 1/01 – 4/02	Multi-center Randomized Double-blind Placebo-controlled Parallel- group	1. Age 4-11 yrs; 2. 60%≤FEV_1<85% predicted; 3. ≥12% increase of FEV_1 after reversibility testing; 4. used ICS for at least 60 days prior to screening;	100mcg QDPM: 98/77 100mcg BID: 99/80 Placebo: 99/67	Change in %predicted FEV_1 from baseline to endpoint (last post-baseline observation)
C97380 25 centers in US 5/98 – 9/99	Multi-center Randomized Double-blind Placebo-controlled Parallel- group	1. Age 4-11 yrs; 2. 60%≤FEV_1≤90% predicted; 3. ≥12% increase of FEV_1 after reversibility testing; 4. used ICS for at least 30 days prior to screening;	100mcg QDAM: 81/63 200mcg QDAM: 75/55 100mcg BID: 80/72 Placebo: 80/50	Change in %predicted FEV_1 from baseline to endpoint (last post-baseline observation)
CI97300 25 centers in US and Central and South America 4/98 – 5/99	Multi-center Randomized Double-blind Placebo-controlled Parallel- group	1. Age 4-11 yrs; 2. 60%≤FEV_1≤90% predicted; 3. ≥12% increase of FEV_1 after reversibility testing; 4. used ICS for at least 30 days prior to screening;	100mcg QDAM: 100/84 200mcg QDAM: 97/76 Placebo: 93/57	Change in %predicted FEV_1 from baseline to endpoint (last post-baseline observation)

2.2 Data Sources

Documents reviewed were accessed from the CDER document room at: \\...\N21067\SE5_003\

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The main body of my evaluation of efficacy will discuss Study P01431 and encompass two studies (C97380 and Ci97300).

3.1.1 Study P01431

Study Design, Efficacy Endpoints, and Statistical Methodologies

During the year of 2001 and 2002, the sponsor conducted the study P01431 to evaluate the efficacy and safety of two dose regimens (100mcg QD PM and 100mcg BID) of MF compared to placebo in children with asthma previously maintained on inhaled corticosteroids (ICS) (at least of 6 months duration and requiring inhaled corticosteroids for 60 days prior screening). This multi-center, randomized, double-blind, placebo-controlled, parallel-group study was conducted in 34 centers in the U.S. and 5 centers in Latin America. Two-hundred and ninety six males and females with asthma (baseline % predicted FEV_1 must have been at least 60% and no more than 85% at both screening) were stratified by age (4-5 and 6-11) and centrally randomized in a 1:1:1 ratio to MF DPI 100mcg QD PM, MF DPI 100mcg BID, or placebo.

The primary efficacy endpoint was the change in % predicted FEV_1 from baseline to endpoint (last post-baseline observation). The predicted FEV_1 based on the patient's height at Screening, as recorded on the CRF, was calculated as follows:

$$PRED=2.1 \times 10^{-6} \times H^{2.8}$$

Where PRED is the predicted FEV_1, and H is the height (cm) at Screening. If the patient was of African decent (recorded in the database as "Black"), adjustment was made using the formula:

$$PRED=PRED \times 0.88$$

At each visit, including baseline, the value of percent predicted FEV_1 was calculated:

$$\% \text{ predicted } FEV_1 = (\text{actual } FEV_1/PRED) \times 100$$

The primary efficacy analysis at week-12 was based on a test for non-decreasing response with increasing MF DPI dose (0, 100, 200 mcg/day) using a linear contrast of the treatment means, obtained from a two-way ANOVA which extracted sources of variation due to treatment and center. In addition to the test of trend, treatment differences were evaluated using the same two-way ANOVA. Specifically, if the test for non-decreasing response with increasing dose was significant, all pairwise comparisons were made using the least square means from the ANOVA model without adjustment for the multiple comparisons. In addition to the primary analysis at week-12, all three pairwise comparisons among the three treatment groups were made with respect to the change from baseline in %predicted FEV_1 for each scheduled visit, using the same two-way ANOVA described.

The secondary efficacy variables included FEV_1, FEV, FEF 25-75%, AM and PM PEFR, symptoms scores, rescue medication use, nocturnal awakenings due to asthma, response to therapy, and healthy quality of life assessments. The sponsor did not provide any multiplicity adjustment for the secondary variables.

According to the protocol, analyses and summaries of safety and efficacy data were based on the following subsets of patients:

- All Randomized Patients (ITT): all analyses and summaries of data were based on all randomized patients who received at least one dose of the double-blind study medication (intent-to-treat principle).
- Efficacy-Evaluable Patients (EES): confirmatory analyses of the primary efficacy variables were based all randomized patients who met key evaluable criteria, which were established prior to un-blinding of the study.

Based on previous studies, the sponsor determined that a sample of size 315, assuming a pooled standard deviation of 14.3 in %predicted FEV_1 change from baseline, would be required to detect an effect size of 7.0 (or more) between any pair of treatment groups with 90% power.

Patient Disposition, Demographic and Baseline Characteristics

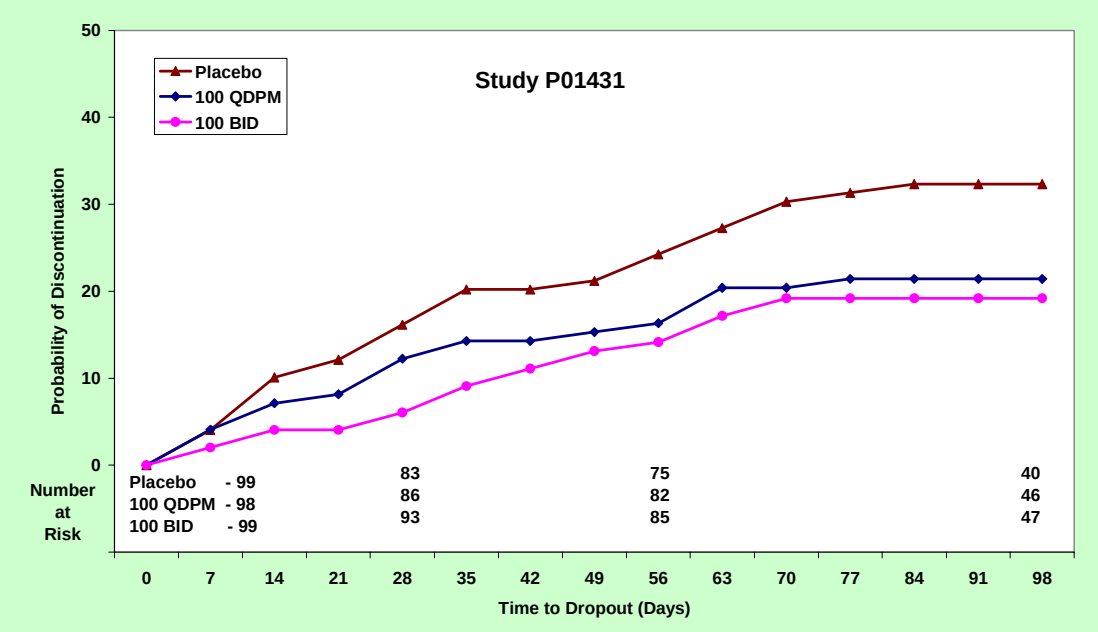
Two hundred and ninety-six patients were eligible for entry into the double-blind treatment period and were randomized. As shown in Table 3, about 10% more placebo treated patients discontinued compared to MF DPI treated patients. Most discontinuations were due to a lack of efficacy and adverse event. Twenty-five (8%) ITT patients (100 mcg QD PM, 9 patients; 100 mcg BID, 11 patients; and placebo, 5 patients) had one or more protocol deviations and were excluded from the efficacy-evaluable data set (EES).

Table 3. Patients' Accountability N (%), (ITT)

Study P01431	***Placebo (n=99)***	***100mcg QD PM (n=98)***	***100mcg BID (n=99)***
Randomized patients	99 (100)	98 (100)	99 (100)
Completed treatment period	67 (68)	77 (79)	80 (81)
Discontinued	32 (32)	21 (21)	19 (19)
Reason of early discontinuation			
Treatment failure	18 (18)	9 (9)	9 (9)
Adverse event	11 (11)	3 (3)	4 (4)
Non-compliance	1 (1)	4 (4)	2 (2)
Did not meet protocol eligibility	0	4 (4)	2 (2)
Did not wish to continue	2 (2)	1 (1)	2 (2)
ITT population	99	98	99
EES population	94	89	88

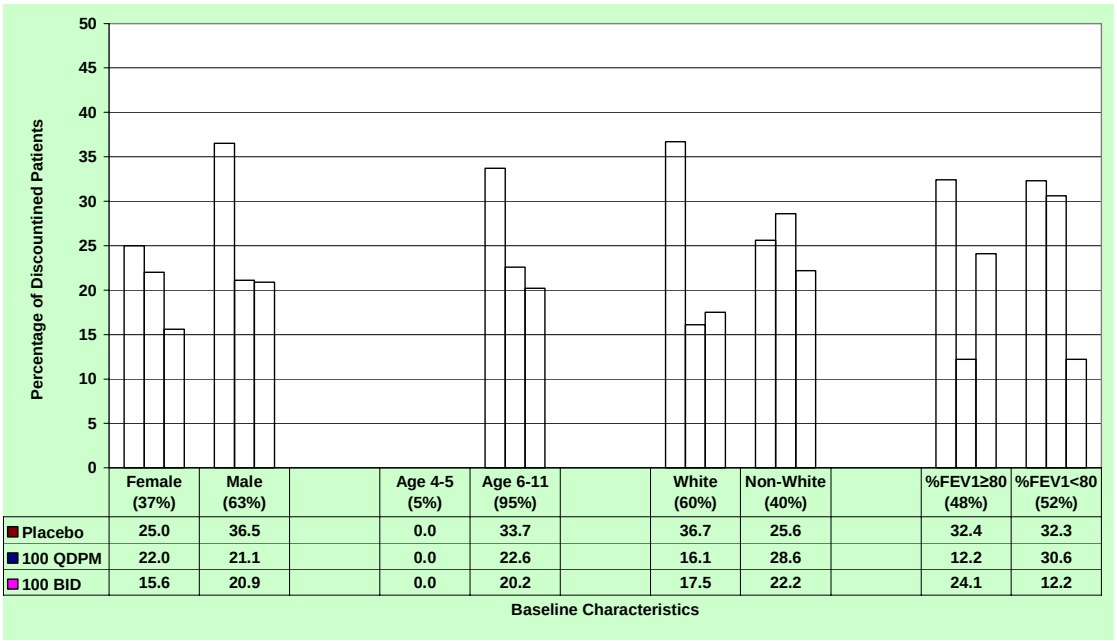
I additionally explored the dropout. Figure 1 presents the cumulative incidence curve for premature discontinuations in Study P01431. The patients treated with placebo had 10% more dropouts compared to patients treated with MF DPI and dropouts happened as early as the first week.

Figure 1. Time to Study Drug Discontinuation - Cumulative Incidence Curve



As shown in Figure 2, for severe asthmatic patients (baseline %predicted FEV_1 <80%), 100mcg BID had the lowest dropout rate compared to other treatment groups. For mild asthmatic patients, 100mcg QD PM had the lowest dropout rate. The dropout rate in placebo group was 15% higher compared to MF DPI groups for male, older age (6 – 11), or white patients.

Figure 2. Percentage of Discontinued Patients by Demographics and Baseline Characteristics



	Female (37%)	Male (63%)		Age 4-5 (5%)	Age 6-11 (95%)		White (60%)	Non-White (40%)		%FEV1≥80 (48%)	%FEV1<80 (52%)
Placebo	25.0	36.5		0.0	33.7		36.7	25.6		32.4	32.3
100 QDPM	22.0	21.1		0.0	22.6		16.1	28.6		12.2	30.6
100 BID	15.6	20.9		0.0	20.2		17.5	22.2		24.1	12.2

Descriptive demographics and baseline characteristics were summarized for the randomized patients who received at lease one dose of double-blind study medication in Table 4. The treatment groups were similar with regard to sex, age, race, weight, and most baseline disease characteristics. Notable differences between groups included a lower mean baseline AM PEF in the placebo group (210.9 L/min) compared to the MF DPI groups (237.0 and 237.7 L/min). The ages of patients ranged from 4 to 11 years with a mean age of 9. In the study, 60% of patients were Caucasian, 16% were African-American, and 22% were Hispanic. Thirty-five percent of the population was female.

Table 4. Patients' Demographic and Baseline Characteristics N (%), (ITT)

Study P01431	***Placebo (n=99)***	***100mcg QD PM (n=98)***	***100mcg BID (n=99)***
Age			
Mean (SD)	8.2 (1.9)	9.0 (1.8)	8.7 (1.8)
Median	8.0	9.0	9.0
Range	4 – 11	4 – 11	4 – 11
4 – 5 years	4 (4.0)	5 (5.1)	5 (5.1)
6 – 11 years	95 (96.0)	93 (94.9)	94 (94.9)
Sex			
Female	36 (36.4)	41 (41.8)	32 (32.3)
Male	63 (63.6)	57 (58.2)	67 (67.7)
Race			
Caucasian	60 (60.6)	56 (57.1)	63 (63.6)
Black	12 (12.1)	16 (16.3)	11 (11.1)
Hispanic	24 (24.2)	22 (22.4)	22 (22.2)
Asian	0	1 (1.0)	1 (1.0)
Native American	0	1 (1.0)	2 (2.0)
Other	3 (3.0)	2 (2.0)	0
Weight [a] (kg)			
Mean (SD)	33.7 (12.7)	35.4 (10.9)	35.2 (11.3)
Median	31.0	34.3	34.0
Range	15.0 – 90.0	15.0 – 81.8	15.9 – 79.5
Height [a] (cm)			
Mean (SD)	132.5 (13.4)	136.1 (11.9)	134.8 (12.5)
Median	131.6	136.5	137.0
Range	98.0 – 175.2	102.0 – 159.7	104.1 – 164.9
Duration of Asthma (years)			
Mean (SD)	5.3 (2.7)	5.9 (2.7)	5.8 (2.7)
Median	5.4	6.0	6.0
Range	1 – 10	1 – 11	1 – 11
Baseline %predicted FEV_1			
Mean (SD)	77.04 (6.76)	79.13 (7.02)	79.72 (8.21)
Median	77.40	79.93	81.59
Range	58.47 – 97.05	60 – 97.81	51.33 – 99.58
Baseline AM PEF (liters/min)			
Mean (SD)	210 (60)	237 (59)	237 (69)
Median	210	349	231
Range	99 – 345	126 – 424	69 – 436

a: Determined at Screening. * Results from reviewer's analysis.

Results and Conclusions

The results of the sponsor's primary analysis are shown in Table 5. The sponsor concluded that MF DPI significantly improved %predicted FEV_1. Because the mean of baseline %predicted FEV_1 was significantly different between treatment groups, I performed additional analysis including the baseline %predicted FEV_1 as a covariate in the primary ANOVA model. The

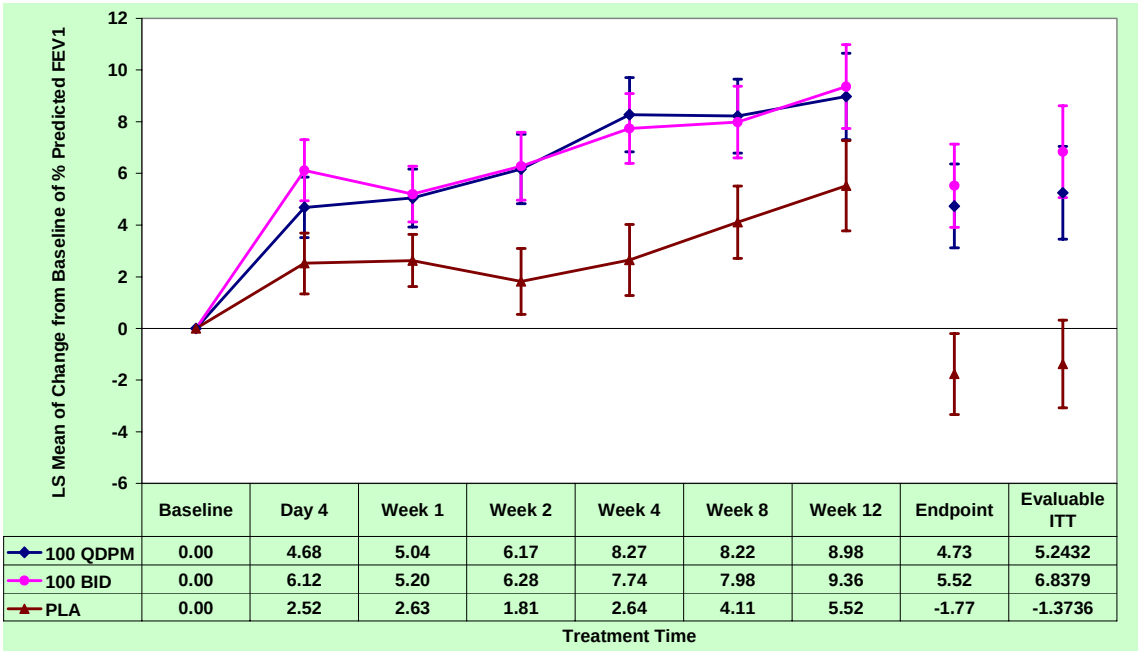
result of this analysis was consistent with the primary analysis results. Table 5 and Figure 3 show a significant improvement in both MF DPI groups compared with placebo in %predicted FEV_1 from baseline at week-12 ($p \leq 0.002$). The slight difference between the MF DPI groups was not significant (p=0.704). Statistically significant differences were first observed at Day 4 (p=0.015) between 100mcg BID and placebo and at Week 2 between 100mcg QD PM and placebo (p=0.011). The analysis results based on the percent change from baseline of %predicted FEV_1 also supported the efficacy of MF DPI groups (mean: 8.8% for 100mcg BID, 8.3% for 100mcg QDPM, 0.0% for placebo). The comparison between MF DPI doses with placebo reached the statistical significant (LS mean: 6.5; 95%CI (2.4, 10.6) for 100mcg QDPM; LS mean: 7.3; 95%CI (3.2, 11.4) for 100mcg BID).

Table 5. Primary Efficacy Endpoint - %Predicted FEV_1 – Change from Baseline, (ITT)

Study P01431	***Placebo***	***100mcg QD PM***	***100mcg BID***	***100mcg QD PM vs. Placebo***	***100mcg BID vs. Placebo***
	N, LS Mean	N, LS Mean [a]	N, LS Mean	LS Mean (p-value)	LS Mean (p-value)
Baseline	99, 77.3	98, 79.2	99, 79.7	1.91 (0.048)	2.36 (0.015)
Change from Baseline					
Day 4	86, 2.52	89, 4.68	84, 6.12	2.17 (0.129)	3.60 (0.015)
Week 1	97, 2.63	90, 5.04	95, 5.20	2.41 (0.077)	2.57 (0.056)
Week 2	93, 1.81	91, 6.17	94, 6.28	4.35 (0.011)	4.46 (0.009)
Week 4	87, 2.64	89, 8.27	95, 7.74	5.2 (0.002)	5.10 (0.004)
Week 8	76, 4.11	79, 8.22	83, 7.98	4.10 (0.021)	3.87 (0.029)
Week 12	66, 5.52	74, 8.98	79, 9.36	3.46 (0.099)	3.84 (0.067)
Endpoint (LOCF) [b]	**99, -1.77**	**98, 4.73**	**99, 5.52**	**6.50 (0.002)**	**7.29 (<0.001)**
Evaluable ITT	**94, -1.37**	**89, 5.24**	**88, 6.84**	**6.62 (0.003)**	**8.21 (<0.001)**

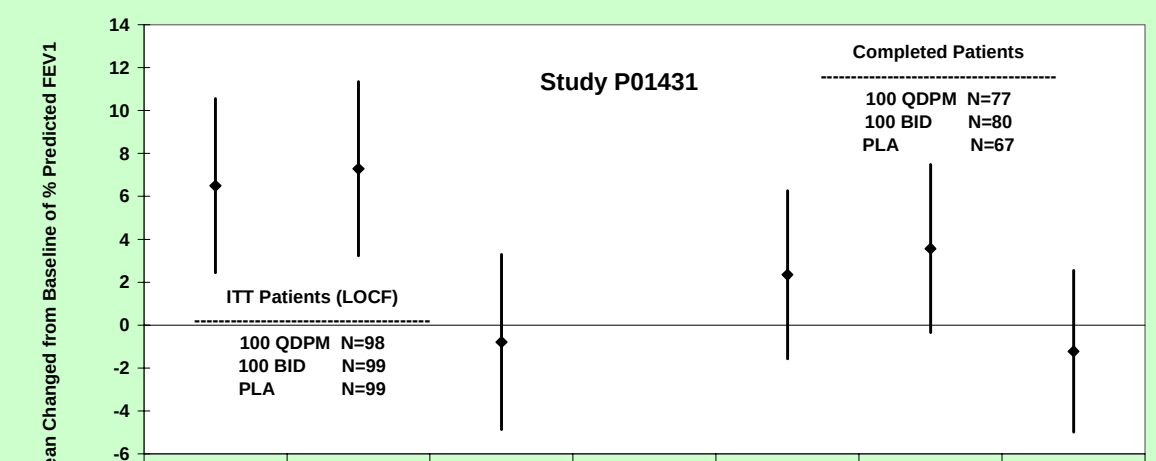
a: LS Means are obtained from the two-way ANOVA model with treatment and center effects.
b: Endpoint is last non-missing visit for patient.

Figure 3. % Predicted FEV_1 Change from Baseline (All Treated Patient): LS Mean +/- SE



Due to the informative dropout, I compared the analysis results based different population (ITT vs. completed patients (CP)). Figure 4 shows the treatment comparison between three treatment groups in the change from baseline of %predicted FEV_1 at endpoint for ITT (LOCF) and completed patients. The analysis results based on CP population did not confirm the primary analysis results based on the ITT population using LOCF imputation methods for both MD DPI groups. The magnitude of effect sizes were only half of effect sizes which based on the ITT population.

Figure 4. LS Mean and 95%CI of % Predicted FEV_1 Change from Baseline at Endpoint



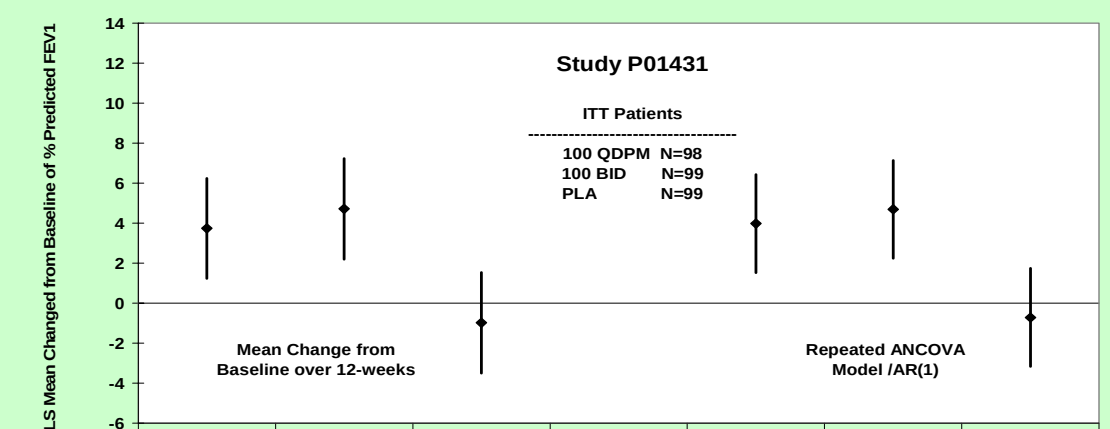
	100 QDPM vs. PLA (p=0.002)	100 BID vs. PLA (p<0.001)	100 QDPM vs. 100 BID (p=0.703)		100 QDPM vs. PLA (p=0.240)	100 BID vs. PLA (p=0.075)	100 QDPM vs. 100 BID (p=0.524)
95%CI - LL	2.44	3.22	-4.86		-1.58	-0.36	-4.99
95%CI - UL	10.56	11.35	3.29		6.27	7.49	2.55
◆ LS Mean Diff.	6.50	7.29	-0.79		2.35	3.57	-1.22

Treatment Comparisons

In addition, I performed the analysis using repeated ANCOVA model with covariate adjustment for treatment, baseline, week and the treatment-by-week interaction. Treatment and week were treated as unordered categorical variables. A first order autoregressive (AR[1]) structure, in combination with treating patient as a random effect, was used to model intra-patient correlation. I also performed the sponsor's primary analysis model (ANOVA) based on mean change from baseline of % predicted FEV_1 without LOCF. Figure 5 shows the results of two estimations which show that the statistically significant differences were observed between 100mcg QD PM and placebo ($p<0.004$) and 100mcg BID and placebo ($p<0.001$).

The results of those sensitive analyses were consistent with the results of the primary efficacy analysis and supported the efficacy of MF DPI 100mcg QD PM and 100mcg BID dose regimen.

Figure 5. % Predicted FEV_1 Change from Baseline (ITT Patient)



	100 QDPM vs. PLA (p=0.004)	100 BID vs. PLA (p<0.001)	100 QDPM vs. 100 BID (p=0.444)		100 QDPM vs. PLA (p=0.002)	100 BID vs. PLA (p<0.001)	100 QDPM vs. 100 BID (p=0.568)
95%CI - LL	1.23	2.20	-3.50		1.52	2.24	-3.17
95%CI - UL	6.24	7.23	1.54		6.43	7.14	1.74
◆ LS Mean Diff.	3.73	4.72	-0.98		3.97	4.69	-0.71

Secondary variables -

The sponsor assessed 10 secondary efficacy variables included FEV_1, FEV, FEF 25-75%, AM and PM PEFR, symptoms scores, rescue medication use, nocturnal awakenings due to asthma, response to therapy, and healthy quality of life assessments. I was able to replicate the sponsor's results and Table 6 displays the treatment differences and nominal p-value for the secondary efficacy variables.

Table 6. Other Pulmonary Function Endpoint – Change from Baseline, (ITT, LOCF)

Study P01431	***Placebo***	***100mcg QDPM***	***100mcg BID***	***100mcg QDPM vs. Placebo***	***100mcg BID vs. Placebo***
	LS Mean[a]	LS Mean	LS Mean	LS Mean (p-value)	LS Mean (p-value)
Change from Baseline at Endpoint [b]					
FEV_1 (L)	-0.04	0.09	0.09	0.13 (<0.001)	0.13 (<0.001)
FVC	-0.01	0.09	0.09	0.10 (0.033)	0.10 (0.038)
FEF25%-75%	-0.12	0.14	0.19	0.26 (<0.001)	0.31 (<0.001)
AM PEF (L/min)	-6.9	16.3	11.2	23.2 (<0.001)	18.1 (<0.001)
PM PEF (L/min)	-5.6	14.9	12.9	20.5 (<0.001)	18.5 (<0.001)
Asthma Symptom – Average AM and PM score					
Wheezing	0.13	-0.07	-0.04	-0.21 (0.004)	-0.18 (0.012)
Difficulty Breathing	0.10	-0.06	-0.05	-0.16 (0.112)	-0.16 (0.124)
Cough	0.12	-0.04	0	-0.17 (0.039)	-0.12 (0.134)
Response to Therapy – Mean Score					
	2.99	2.35	2.35	0.64 (<.001)	0.64 (<.001)
Use of Rescue Medication (Proventil) – Daily Number of Puffs Used					
	0.3	-0.4	-0.5	-0.70 (0.006)	-0.77 (0.003)
Use of Rescue Medication – Daily Number of Nebulized Beta Agonist Treatments Used					
	0.09	-0.03	-0.01	-0.12 (0.021)	-0.10 (0.043)
AM Number of Nocturnal Awakenings					
	0.09	-0.04	0.01	-0.13 (0.003)	-0.08 (0.059)

a: LS Means and pooled standard deviations are obtained from the two-way ANOVA model with treatment and center effects.
b: Endpoint is last non-missing visit for patient. * Results from review's analysis.

Conclusion -
Based on the primary efficacy endpoint, change from baseline in %predicted FEV_1 at endpoint, treatment with MF DPI was statistically significantly superior to treatment with placebo and both MF DPI dosages (100mcg QD PM and 100mcg BID) provided similar effectiveness for improving %predicted FEV_1. (LS mean: 4.73 and 5.52 for 100mcg QD PM and 100mcg BID, respectively). Other pulmonary function variables supported the efficacy seen in %predicted FEV_1. The use of rescue medication (Proventil) and beta-2 agonist rescue medication data supported the efficacy of MF DPI dosages.

3.1.2 Study C97380 and Study Ci97300

Study Design, Efficacy Endpoints, and Statistical Methodologies
During the year of 1998 and 1999, the sponsor conducted the study C97380 and Study Ci97300 to evaluate the efficacy and safety of MF DPI 200mcg/daily dose regimen (100mcg BID in Study C97380 and MF DPI 200mcg QD AM in Study Ci97300) compared to placebo in children (aged 4 to 11 years with asthma) who had been previously maintained on inhaled corticosteroids.

Two studies had the similar design except the MF DPI dose regimen. These two multi-center, randomized, double-blind, placebo-controlled, parallel-group study were conducted in 25 centers in the United States (C97380) or 20 center in the United States and Central and South American (Ci97300). Total six-hundred and six males and females with asthma (The patient's FEV_1 must have been greater than or equal to 60% and less than or equal to 90% of predicted normal at the Screening) were stratified by age (4-5 and 6-11) centrally randomized in a 1:1:1:1 (C97380) or 1:1:1 (Ci97300) ratio to MF DPI doses or placebo.

The primary efficacy endpoint was the change in % predicted FEV_1 from baseline to endpoint (last post-baseline observation).

Secondary efficacy variables included FEV_1, FEV, FEF 25-75%, AM and PM PEFR, symptoms scores, rescue medication use, nocturnal awakenings due to asthma, response to therapy, and healthy quality of life assessments. The sponsor did not provide any multiplicity adjustment for the secondary variables. The statistical models used for analysis of efficacy measures were similar to the models used for Study P01431. (See Study P01431 for details)

The sponsor determined that a sample of size with 100 patients per treatment group, assuming a pooled standard deviation of 13.5 for % predicted FEV_1 change from Baseline, a mean treatment difference of approximately 7 (in % predicted FEV_1) or more between any pair of treatment groups would be detectable with a power greater than 90%.

Patient Disposition, Demographic and Baseline Characteristics

As shown in Table 7, about 10% more placebo treated patients discontinued compared to MF DPI treated patients. Most discontinuations were due to a lack of efficacy and adverse event.

Table 7. Patients' Accountability N (%), (ITT)

Study C97380	***Placebo (n=80)***	***100mcg QDAM (n=81)***	***200mcg QDAM (n=75)***	***100mcg BID (n=80)***
Randomized patients	80	81	75	80
Completed treatment period	50 (63)	63 (78)	55 (73)	72 (90)
Discontinued	30 (38)	18 (22)	20 (27)	8 (10)
Reason of early discontinuation				
Treatment failure	13 (16)	8 (10)	8 (11)	3 (4)
Adverse event	12 (15)	7 (9)	8 (11)	1 (1)
Non-compliance	2 (3)	2 (2)	2 (3)	1 (1)
Did not meet protocol eligibility	1 (1)	0	0	1 (1)
Administrative	0	0	1 (1)	0
Did not wish to continue	2 (3)	1 (1)	1 (1)	2 (3)
ITT population	80	81	75	80
Efficacy Evaluable	65	73	64	68
Study Ci97300	***Placebo (n=93)***	***100mcg QDAM (n=100)***	***200mcg QDAM (n=97)***	--
Randomized patients	93 (100)	100 (100)	97 (100)	--
Completed treatment period	57 (61)	84 (84)	76 (78)	--
Discontinued	36 (39)	16 (16)	21 (22)	--
Reason of early discontinuation				
Treatment failure	26 (27)	13 (13)	11 (11)	--
Adverse event	3 (3)	2 (2)	7 (7)	--
Non-compliance	2 (2)	0	0	--
Did not meet protocol eligibility	0	0	1 (1)	--
Lost to follow up	1 (1)	0	0	--
Did not wish to continue	4 (4)	1 (1)	2 (2)	--
ITT population	93	100	97	--
Efficacy Evaluable	84	96	90	--

I additionally explored the dropout. Figure 6 and Figure 7 present the cumulative incidence curve for premature study drug discontinuations in Study C97380 and Study Ci97300. About 10% more placebo treated patients discontinued compared to MF DPI treated patients and dropout happened during the first week. As shown in Figure 8 and Figure 9, in both studies, about 40% of patients dropped out in placebo group. For male or mild patients (whose $\%FEV_1 \geq$ 80 during screening period) treated with placebo had 25% more dropouts compared to MF DPI treated patients. The patients treated with 100mcg BID dose had lowest drop out rate.

Figure 6. Time to Study Drug Discontinuation - Cumulative Incidence Curve

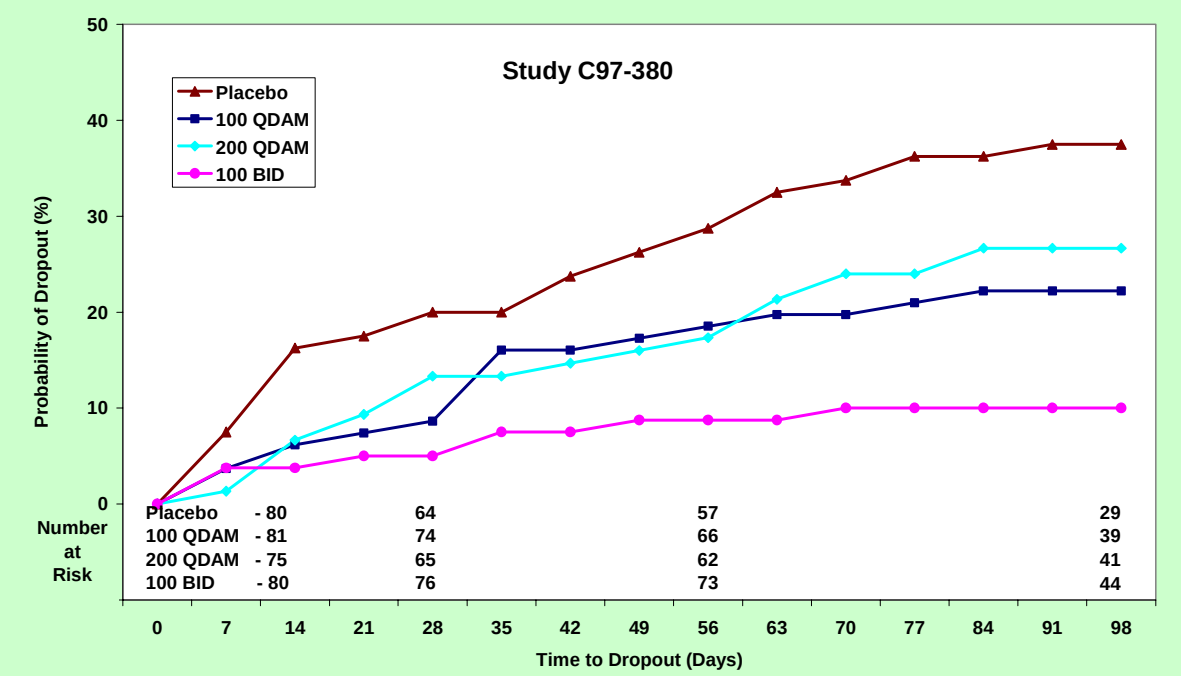


Figure 7. Time to Study Drug Discontinuation - Cumulative Incidence Curve

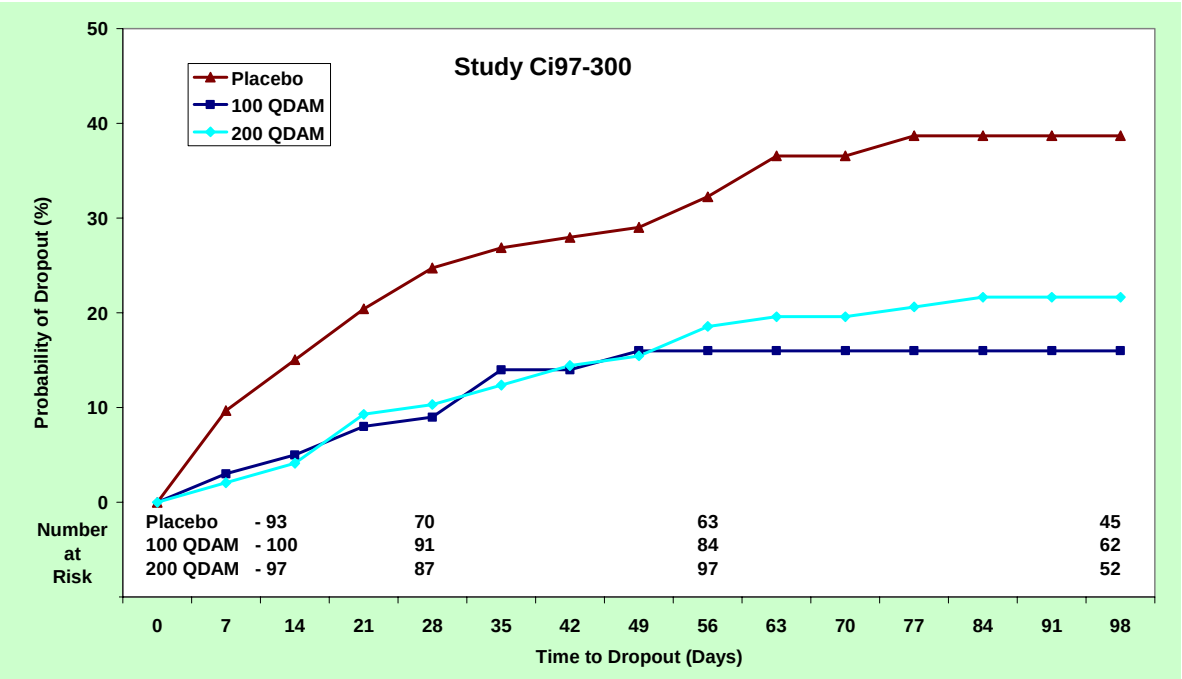
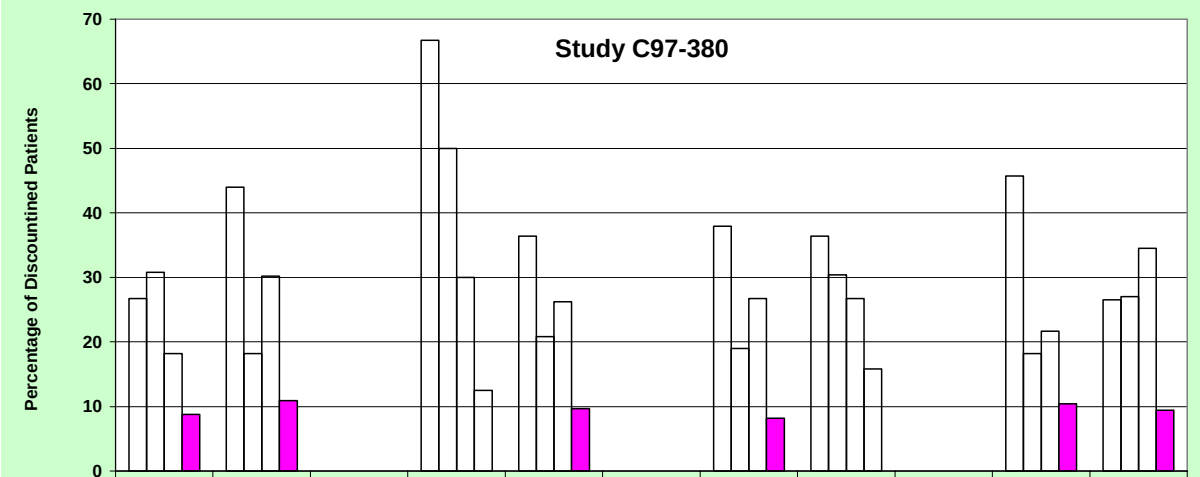


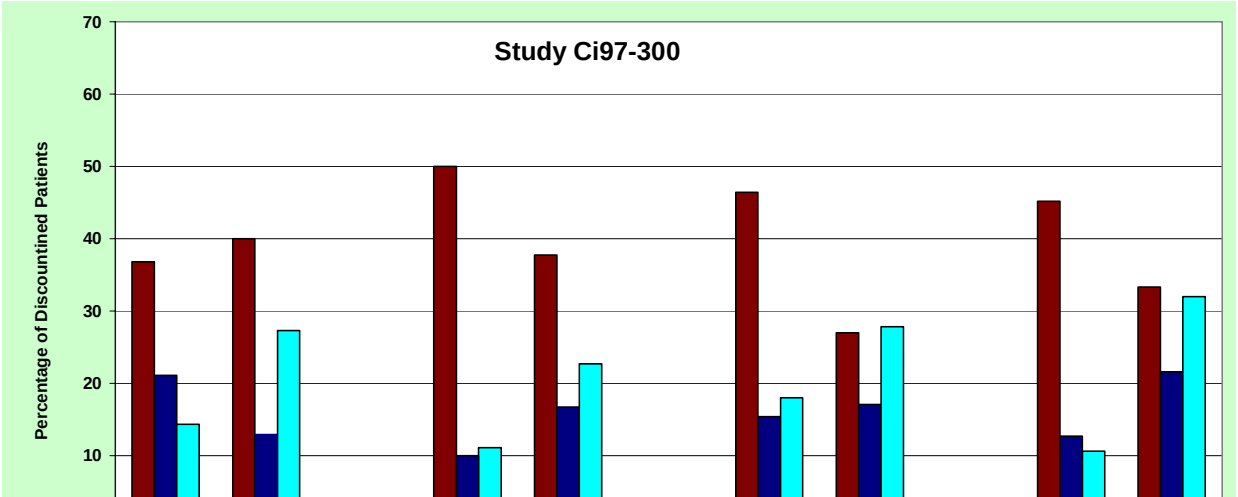
Figure 8. Percentage of Discontinued Patients by Demographics and Baseline Characteristics



	Female (35%)	Male (65%)		Age 4-5 (8%)	Age 6-11 (92%)		White (75%)	Non-White (25%)		%FEV1≥80 (58%)	%FEV1<80 (42%)
Placebo	26.7	44		66.7	36.4		37.9	36.4		45.7	26.5
100 QDAM	30.8	18.2		50.0	20.8		19.0	30.4		18.2	27.0
200 QDAM	18.2	30.2		30.0	26.2		26.7	26.7		21.7	34.5
100 BID	8.8	10.9		12.5	9.7		8.2	15.8		10.4	9.4

Baseline Characteristics

Figure 9. Percentage of Discontinued Patients by Demographics and Baseline Characteristics



	Female (41%)	Male (59%)		Age 4-5 (9%)	Age 6-11 (91%)		White (63%)	Non-White (37%)		%FEV1≥80 (52%)	%FEV1<80 (48%)
Placebo	36.8	40.0		50.0	37.7		46.4	27.0		45.2	33.3
100 QDAM	21.1	12.9		10.0	16.7		15.4	17.1		12.7	21.6
200 QDAM	14.3	27.3		11.1	22.7		18.0	27.8		10.6	32.0

Baseline Characteristics

Descriptive demographics and baseline characteristics were summarized for the randomized patients who received at lease one dose of double-blind study medication for both studies. As shown in Table 8, the treatment groups were similar with regard to sex, age, race, and baseline % predicted FEV_1. Notable differences between groups included a lower mean baseline AM PEF in the placebo group (227 L/min) compared to the MF DPI groups (230 to 253 L/min). The ages of patients ranged from 4 to 11 years with a mean age of 9. In two studies, 70% of patients were Caucasian and 40% of patients were female.

Table 8. Patients' Demographic and Baseline Characteristics N (%), (ITT)

Study C97380 Study Ci97300	***Placebo (n=173)***	***100mcg QDAM (n=181)***	***200mcg QDAM (n=172)***	***100mcg BID (n=80)***
Age				
Mean (SD)	8.5 (1.8)	8.5 (2.0)	8.6 (2.1)	8.5 (1.9)
Median	9	9	9	9
Range	4 – 11	4 – 11	4 – 11	4 – 11
4 – 5 years	11 (6.4)	14 (7.7)	19 (11.1)	8 (10.0)
6 – 11 years	162 (93.6)	167 (92.3)	153 (88.9)	72 (90.0)
Sex				
Female	68 (39.3)	64 (35.4)	64 (37.2)	34 (42.5)
Male	105 (60.7)	117 (64.6)	108 (62.8)	46 (57.5)
Race				
Caucasian	114 (65.9)	123 (68.0)	121 (70.4)	61 (76.3)
Non-Caucasian	59 (34.1)	58 (32.0)	51 (29.6)	19 (23.7)
Height [a] (cm)				
Mean (SD)	134.2 (12.4)	133.8 (13.2)	135.7 (14.3)	135.6 (13.0)
Median	133	135	137	136.5
Range	99 – 168	102 – 165	102 – 178	102 – 159
Duration of Asthma (years)				
Mean (SD)	5.1 (2.7)	5.2 (2.6)	5.3 (3.0)	5.0
Median	5	5	5	5
Range	0.5 – 11	0.5 – 11	0.5 – 11	0.7 – 11
Baseline %predicted FEV_1				
Mean (SD)	80.0 (8.5)	80.5 (8.3)	79.6 (8.1)	80.5 (8.1)
Median	80.3	81.9	80.7	81.6
Range	61.0 – 99.4	59.7 – 112.2	54.3 – 96.3	59.1 – 99.3
Baseline AM PEF (liters/min)				
Mean (SD)	226.7 (66.1)	230.0 (83.7)	247.2 (82.7)	253.2 (79.5)
Median	223.7	227.1	241.3	241.9
Range	63.3 – 488.9	88.7 – 718.7	95.6 - 650	(110 – 637.5)

a: Determined at Screening. * Results from reviewer's analysis.

Results and Conclusions

The results of the sponsor's primary analysis are shown in Table 9. The sponsor concluded that MF DPI significantly improved %predicted FEV_1. I was able to replicate the sponsor's results. Figure 10 shows a significant improvement in MF DPI treatment groups compared with placebo in %predicted FEV_1 from baseline at week-12 except 100mcg QD AM in study C97380 (p=0.059). The magnitude of effect size ranged 4.29 to 7.99 and 100mcg BID had the best effect size among the MF DPI dosages. Table 9 shows statistically significant differences were first observed at Day 4 between 100mcg BID and placebo (p=0.007) and at Week 2 between 100mcg QD AM and placebo (p=0.011).

Table 9. Primary Efficacy Endpoint - %Predicted FEV_1 – Change from Baseline, (ITT)

Study C97380	***Placebo***	***100mcg QDAM***	***200mcg QDAM***	***100mcg BID***	***100mcg BID vs. Placebo***
	LS Mean	N, LS Mean	N, LS Mean	N, LS Mean a	LS Mean (p-value)
Baseline	80, 81.35	81, 80.82	75, 81.15	80, 80.55	-0.78 (0.528)
Change from Baseline					
Day 4	66, 0.52	67, 1.54	56, 2.61	63, 5.38	4.87 (0.007)
Week 1	76, 0.92	78, 3.07	72, 2.41	78, 5.79	4.87 (0.002)
Week 2	72, -0.34	76, 3.6	81, 2.52	78, 5.83	6.17 (<0.001)
Week 4	65, 0.53	75, 4.12	66, 4.35	75, 6.57	6.04 (0.002)
Week 8	58, 1.04	68, 7.63	61, 4.43	71, 10.09	9.05 (<0.001)
Week 12	50, 3.18	63, 6.78	54, 5.49	70, 7.27	4.10 (0.053)
Endpoint (LOCF) b	**80, -1.90**	**81, 2.40**	**75, 3.66**	**80, 6.09**	**8.0 (<0.001)**
Evaluable ITT	**68, -2.76**	**73, 4.37**	**64, 4.47**	**65, 8.02**	**10.78 (<0.001)**
Study Ci97300	***Placebo***	***100mcg QDAM***	***200mcg QDAM***	***100mcg QDAM vs. Placebo***	***200mcg QDAM vs. Placebo***
	N, LS Mean	N, LS Mean a	N, LS Mean	LS Mean (p-value)	LS Mean (p-value)
Baseline	93, 78.88	100, 80.44	97, 78.51	1.56 (0.208)	-0.37 (0.766)
Change from Baseline					
Day 4	81, 2.02	84, 5.17	86, 5.94	3.15 (0.096)	3.92 (0.037)
Week 1	89, 0.55	98, 3.69	96, 4.29	3.13 (0.125)	3.74 (0.069)
Week 2	81, 2.52	96, 7.80	93, 6.47	5.28 (0.011)	3.95 (0.058)
Week 4	73, 2.51	88, 9.17	89, 6.71	6.66 (0.005)	4.20 (0.075)
Week 8	65, 4.02	81, 11.16	80, 7.99	7.14 (0.002)	3.97 (0.088)
Week 12	57, 6.20	79, 10.58	77, 8.76	4.38 (0.058)	2.56 (0.271)
Endpoint (LOCF) b	**93, -1.84**	**100, 5.74**	**97, 5.00**	**7.58 (0.002)**	**6.84 (0.006)**
Evaluable ITT	**84, -1.52**	**96, 6.47**	**90, 6.23**	**7.99 (0.001)**	**7.75 (0.002)**

a: LS Means and pooled standard deviations are obtained from the two-way ANOVA model with treatment and center effects. b: Endpoint is last non-missing visit for patient.

Figure 10. LS Mean and 95%CI of %Predicted FEV_1 Change from Baseline at Endpoint (LOCF)

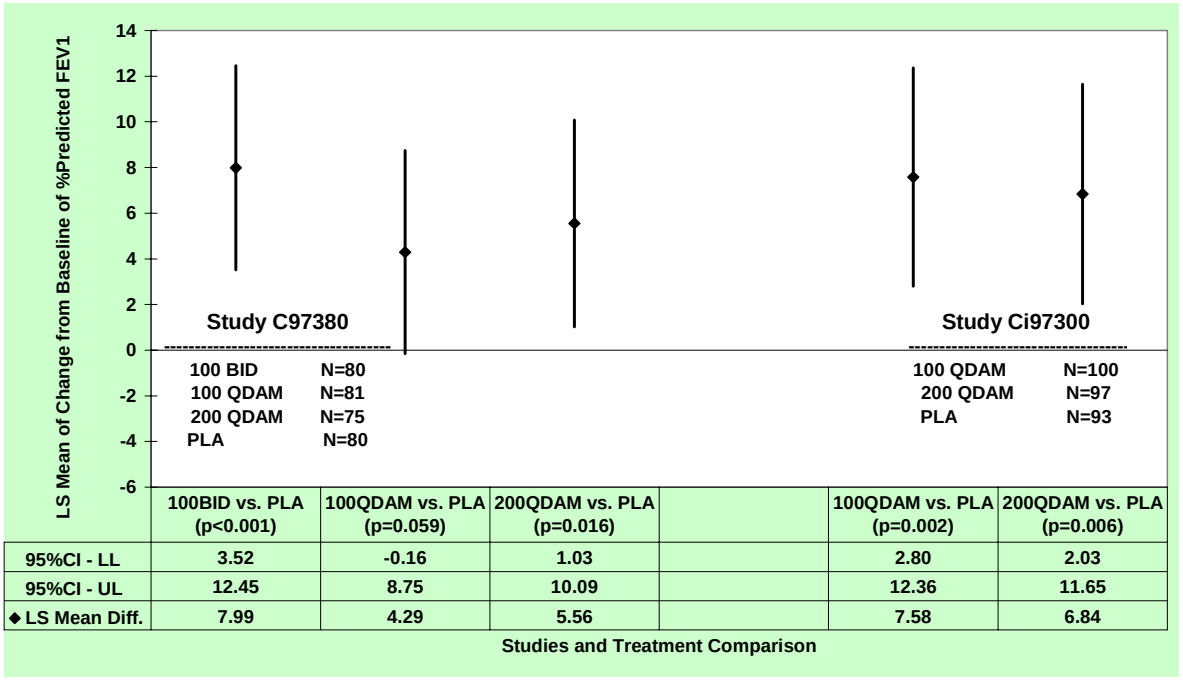
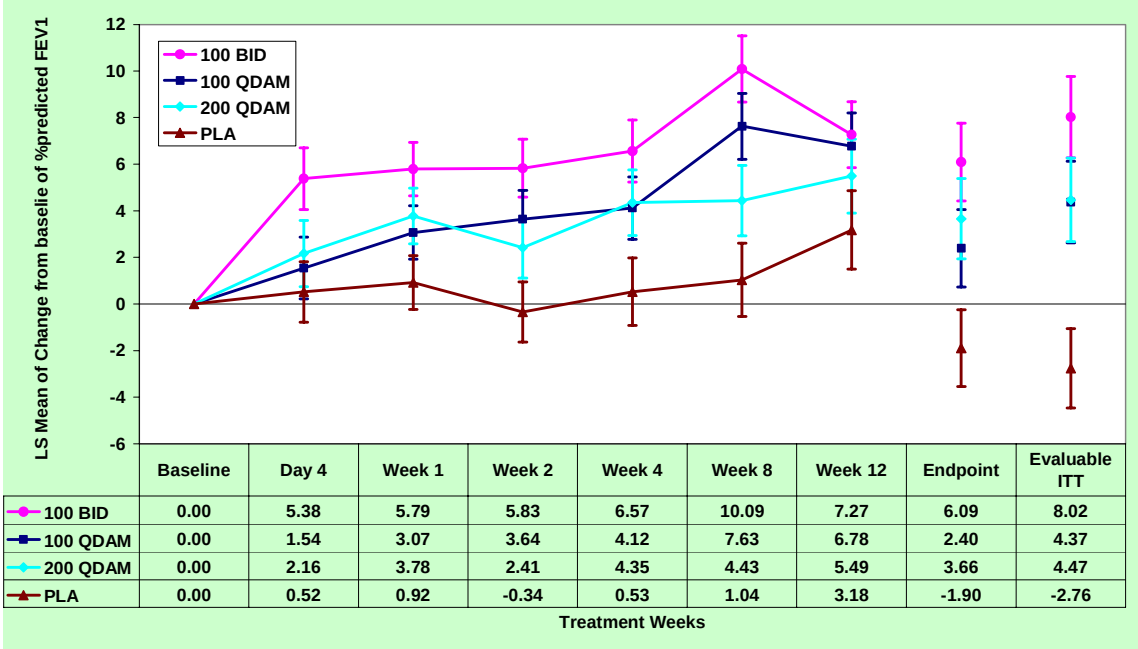


Figure 11 and Figure 12 show the %predicted FEV_1 at each visit and endpoint (LOCF ITT and efficacy evaluable). Graphics show that MF DPI 100mcg BID had the highest effect size and the 200mcg QD AM dose did not appear to offer any further efficacy advantage to the 100mcg QD AM dose.

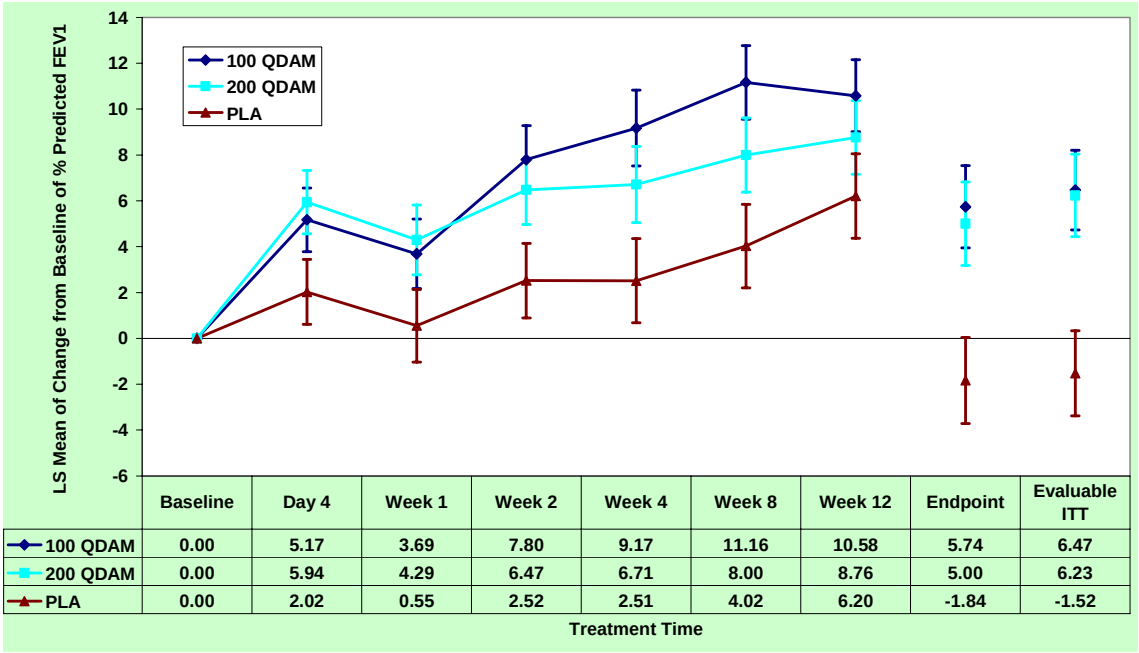
Figure 11. % Predicted FEV_1 Change from Baseline (ITT, Study C97380): LS Mean +/- SE



	Baseline	Day 4	Week 1	Week 2	Week 4	Week 8	Week 12	Endpoint	Evaluable ITT
100 BID	0.00	5.38	5.79	5.83	6.57	10.09	7.27	6.09	8.02
100 QDAM	0.00	1.54	3.07	3.64	4.12	7.63	6.78	2.40	4.37
200 QDAM	0.00	2.16	3.78	2.41	4.35	4.43	5.49	3.66	4.47
PLA	0.00	0.52	0.92	-0.34	0.53	1.04	3.18	-1.90	-2.76

Treatment Weeks

Figure 12. % Predicted FEV_1 Change from Baseline (ITT, Study Ci97300): LS Mean +/- SE



	Baseline	Day 4	Week 1	Week 2	Week 4	Week 8	Week 12	Endpoint	Evaluable ITT
100 QDAM	0.00	5.17	3.69	7.80	9.17	11.16	10.58	5.74	6.47
200 QDAM	0.00	5.94	4.29	6.47	6.71	8.00	8.76	5.00	6.23
PLA	0.00	2.02	0.55	2.52	2.51	4.02	6.20	-1.84	-1.52

Treatment Time

Secondary variables -

The sponsor assessed 10 secondary efficacy variables included FEV_1, FEV, FEF 25-75%, AM and PM PEFR (pre-dosing), symptoms scores, rescue medication use, nocturnal awakenings due to asthma, response to therapy, and healthy quality of life assessments. I was able to replicate the sponsor's results and Table 10 and Table 11 display the treatment differences and nominal p-value for the secondary efficacy variables.

Table 10. Other Pulmonary Function Endpoint – Change from Baseline, (ITT, LOCF)

Study C97380	***Placebo (n=80)***	***100mcg QDAM (n=81)***	***200mcg QDAM (n=75)***	***100mcg BID (n=80)***	***100mcg QDAM vs. Placebo***	***100mcg BID vs. Placebo***
	LS Mean [a]	LS Mean	LS Mean	LS Mean	LS Mean (p-value)	LS Mean (p-value)
Change from Baseline at Endpoint [b]						
FEV_1 (L)	-0.04	0.05	0.06	0.11	0.09 (0.035)	0.15 (.0002)
FVC	0.01	0.09	0.11	0.11	0.07 (0.123)	0.10 (0.046)
FEF25%-75%	-0.16	0.01	0.06	0.25	0.17 (0.029)	0.40 (<.0001)
AM PEF (L/min)	5.00	14.99	5.04	6.03	10.00 (0.261)	1.03 (0.908)
PM PEF (L/min)	11.38	14.20	11.99	9.34	2.83 (0.739)	-2.03 (0.811)
Response to Therapy – Mean Score						
	2.74	2.40	2.32	2.01	-0.34 (0.043)	-0.73 (<.0001)
Use of Rescue Medication (Proventil) – Daily Number of Puffs Used						
	0.20	0.35	0.08	-0.04	0.15 (0.616)	-0.25 (0.401)
Use of Rescue Medication – Daily Number of Nebulized Beta Agonist Treatments Used						
	0.21	0.09	0.05	0.08	-0.12 (0.176)	-0.13 (0.153)
AM Number of Nocturnal Awakenings						
	0.09	0.01	0.05	0.06	-0.09 (0.223)	-0.03 (0.688)

a: LS Means and pooled standard deviations are obtained from the two-way ANOVA model with treatment and center effects.
b: Endpoint is last non-missing visit for patient.
* Results from reviewer's analysis.

Table 11. Other Pulmonary Function Endpoint – Change from Baseline, (ITT, LOCF)

Study Ci97300	***Placebo***	***100mcg QDAM***	***200mcg QDAM***	***100mcg QDAM vs. Placebo***	***200mcg QDAM vs. Placebo***
	LS Mean [a]	LS Mean	LS Mean	LS Mean (p-value)	LS Mean (p-value)
Change from Baseline at Endpoint [b]					
FEV_1 (L)	-0.02	0.09	0.11	0.11 (0.018)	0.13 (0.004)
FVC	0.03	0.08	0.13	0.05 (0.361)	0.10 (0.068)
FEF25%-75%	-0.10	0.09	0.07	0.19 (0.034)	0.18 (0.052)
AM PEF (L/min)	9.75	25.81	15.76	16.06 (0.039)	6.01 (0.442)
PM PEF (L/min)	7.28	24.81	22.09	17.53 (0.013)	14.82 (0.037)
Asthma Symptom – Average AM and PM score					
Wheezing	0.005	-0.05	0.03	-0.06 (0.493)	0.025 (0.770)
Difficulty Breathing	-0.03	-0.10	0.01	-0.06 (0.455)	0.04 (0.601)
Cough	-0.04	-0.17	-0.06	-0.13 (0.232)	-0.02 (0.851)
Response to Therapy – Mean Score					
	-0.09	-0.84	-0.63	-0.74 (<.0001)	-0.54 (0.002)
Use of Rescue Medication (Proventil) – Daily Number of Puffs Used					
	0.08	-0.49	-0.34	-0.57 (0.021)	-0.41 (0.095)
Use of Rescue Medication – Daily Number of Nebulized Beta Agonist Treatments Used					
	0.06	-0.002	0.11	-0.058 (0.421)	0.055 (0.445)
AM Number of Nocturnal Awakenings					
	0.12	-0.05	-0.05	-0.17 (0.025)	-0.18 (0.019)

a: LS Means and pooled standard deviations are obtained from the two-way ANOVA model with treatment and center effects.
b: Endpoint is last non-missing visit for patient.
* Results from reviewer's analysis.

Conclusion –
Based on the primary efficacy endpoint, change in %predicted FEV_1 between baseline and endpoint (week-12), treatments with MF DPI were statistically significantly superior to treatment with placebo except 100mcg QD AM in study C97380 (p=0.059). The magnitude of effect size ranged 4.29 to 7.99 and 100mcg BID had the best effect size among the MF DPI dosages and the 200mcg QD AM dose did not appear to offer any further efficacy advantage to the 100mcg QD AM dose. For Study C97380, the LS mean differences between MF DPI dosages and placebo were 4.29, 5.56, and 7.99 for 100mcg QD AM, 200mcg QD AM, and 100mcg BID, respectively. For Study Ci97300, the LS mean differences between MF DPI dosages and placebo were 7.58 and 6.84 for 100mcg QD AM and 200mcg QD AM, respectively.

In Study C97380, 100mcg QDAM dose was numerically better than placebo in AM PEF and PM PEF with nominal p-value of 0.26 and 0.74; The 100mcg BID data dose was similar to placebo in both AM and PM PEF. In Study Ci97300, 100mcg QDAM dose was significantly better than placebo in AM PEF and PM PEF with nominal p-value of 0.04 and 0.01. The 200mcg QDAM was numerically better than placebo in AM PEF and significantly better than placebo in PE PEF (nominal p-value: 0.04).

3.2 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Karimi-Shah, Banu. The reader is referred to Dr. Karimi-Shah's review for information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age

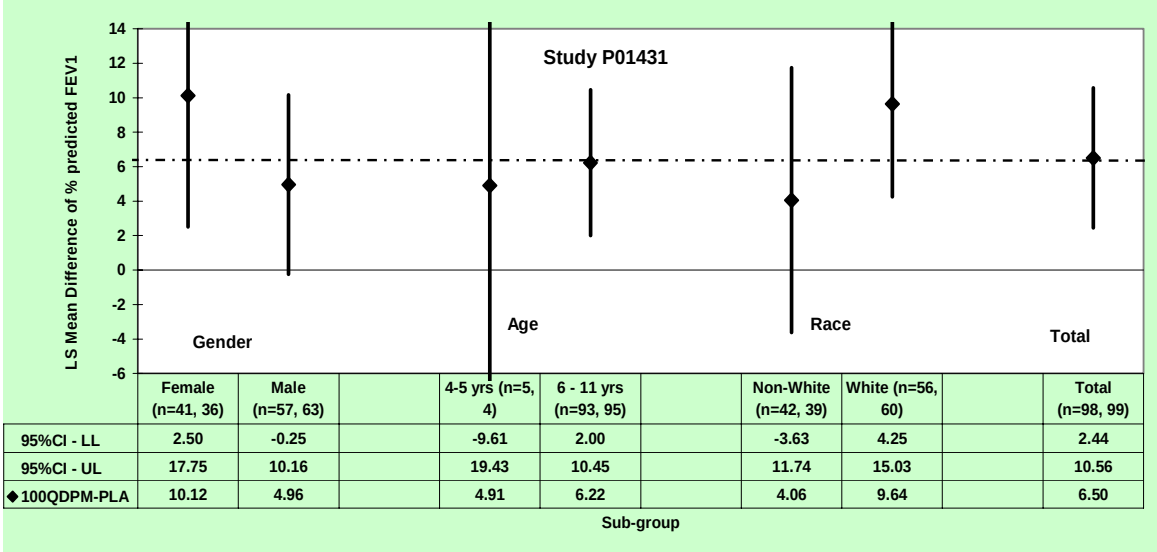
The sponsor performed the subgroup analyses based on gender and race for the primary and key secondary measures. Potential treatment by subgroup interactions were focused on the comparison between MF DPI 100mcg QD PM and placebo. I was able to replicate the sponsor's analyses results. I performed the subgroup analyses using the ANCOVA model for study P01431 and results are displayed in Table 12 and Figure 13. The results show that the treatment-by-race interactions (p=0.098) with a less effect for non-white population; the efficacy of MF DPI 100mcg QD PM was less effective for the patients who were 4-5 years of age or male. There were not enough children younger than 6 years of age (n=14) to make a meaningful comparison; but the efficacy of MF DPI 100mcg QD PM for patients aged 4-5 years had similar trends compared to the patients aged 6-11 years. However, statistically significant results are not expected in all subgroups due to the reduced sample size and natural variation expected.

Table 12. % Predicted FEV_1 Change from Baseline (Study P01431, ITT Patient)

	MFDPI 100mcg QD PM			Placebo		
Subgroup (p-Value)†	***N***	***LS Mean***	***SE***	***N***	***LS Mean***	***SE***
Study P01431 (MFDPI 100mcg QD PM*: n=98, placebo: n=99*)						
Gender (p=0.336)						
Male	57	5.16	2.25	63	-0.004	2.00
Female	41	6.38	2.95	36	-3.34	2.92
Race Group (p=0.098)						
White	56	6.68	2.22	60	-2.95	2.07
Non-White	42	2.94	2.85	39	-1.11	3.06
Age Group (p=0.693)						
4 – 5	5	15.32	3.40	4	10.41	4.29
6 – 11	93	4.17	1.78	95	-2.08	1.69

† p-Value for treatment-by-subgroup.

Figure 13. % Predicted FEV_1 Change from Baseline (LOCF)

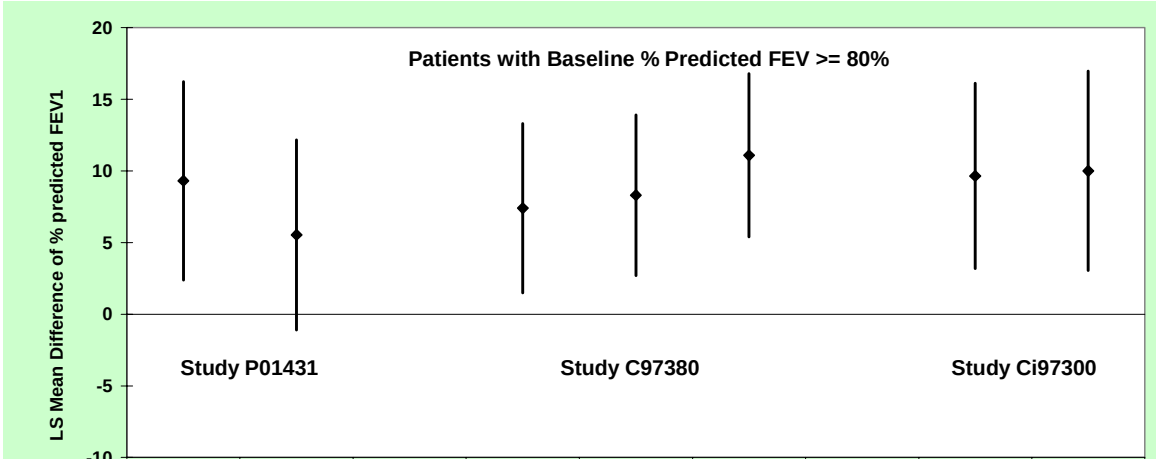


4.2 Other Special/Subgroup Populations

In Study P01431, the sponsor did a subgroup analysis based on patients with baseline %predicted $FEV_1 \geq 80\%$ or < 80%. In other two studies (C97380 and Ci97300), the sponsor did a subgroup analysis based on patients with % predicted $FEV_1 \geq 75\%$ or < 75%. In the summary of clinical efficacy, the sponsor defined the severe patients as the patients whose baseline % predicted FEV_1 was <80% in order to comparing three studies. The sponsor just reported the mean and standard deviation. I performed the subgroup analyses using the same model as the primary analysis model for primary efficacy endpoint. As shown in Figure 14 and Figure **15**, for Study P01431, the result suggested that 100mcg BID dose might be more effective for severe asthmatic patients compared to mild asthmatic patients. This finding was not seen clearly in Study C97380. In other two studies, the magnitudes of effect size of MF DPI groups

were smaller for severe patients compared to mild patients.

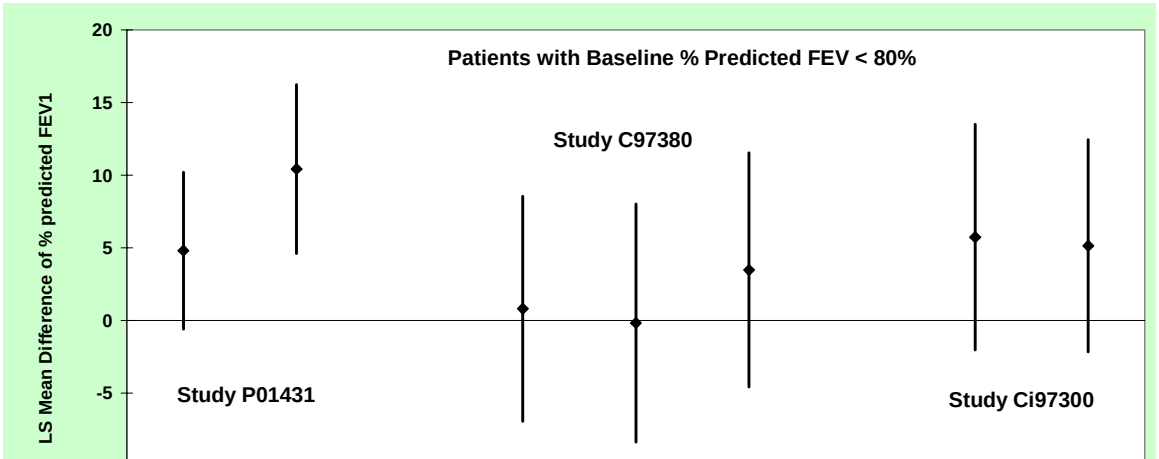
Figure 14. % Predicted FEV_1 Change from Baseline (For Mild Patients) (LOCF)



	100QDPM (n=49) vs. PLA(n=34)	100BID (n=58) vs. PLA(n=34)		100QDAM (n=44) vs. PLA(n=46)	200QDAM (n=46) vs. PLA(n=46)	100BID (n=48) vs. PLA(n=46)		100QDAM (n=61) vs. PLA(n=43)	200QDAM (n=48) vs. PLA(n=43)
95%CI - LL	2.38	-1.09		1.49	2.70	5.40		3.18	3.05
95%CI - UL	16.24	12.17		13.31	13.91	16.78		16.12	16.96
◆ LS Mean	9.31	5.54		7.40	8.30	11.09		9.65	10.01

Sub-group

Figure 15. % Predicted FEV_1 Change from Baseline (For Severe Patients) (LOCF)



	100QDPM (n=49) vs. PLA(n=65)	100BID (n=41) vs. PLA(n=65)		100QDAM (n=37) vs. PLA(n=34)	200QDAM (n=29) vs. PLA(n=34)	100BID (n=32) vs. PLA(n=34)		100QDAM (n=39) vs. PLA(n=50)	200QDAM (n=49) vs. PLA(n=50)
95%CI - LL	-0.60	4.61		-6.95	-8.36	-4.59		-2.03	-2.16
95%CI - UL	10.21	16.23		8.56	8.02	11.54		13.50	12.45
◆ LS Mean	4.81	10.42		0.80	-0.17	3.47		5.73	5.14

Sub-group

5. SUMMARY AND CONCLUSIONS

The March 30, 2007, supplement (SE05-003) of NDA 21-067 showed that ASMANEX® TWISTHALER® (mometasone furoate) significantly improved lung function in asthmatic children aged 4 to 11 years. In this supplement, Schering Corporation proposed to extend the indicated population for ASMANEX® TWISTHALER® down to children 4 years of age, using a reduced-strength version of the currently marketed device. The new device is code-named MF DPI. The proposed dose is 100mcg mometasone (ex-mouthpiece) inhaled once a day in the evening (QD PM).

The review analyzed three pivotal efficacy studies (Studies P01431, C97380 and CI97300) in pediatrics aged 4 to 11 years. The studies compared the effect of the drug at different times (AM or PM) and frequencies (both AM and PM) of administrations, as well as the drug's dose-response relationship (100mcg vs. 200mcg). Results show that: 1) both 100mcg BID and QD PM treatments provided significant improvements in lung functions, but 100mcg BID had only slightly better improvement, while QD AM results were inconsistent; 2) Increasing MF DPI doses did not appear to offer any further efficacy advantage. Although efficacy results with 100mcg BID dose was replicated in two studies (P01431 and C97380), the 100mcg QD PM dose (the sponsor proposed dose) was only evaluated in one study (P01431).

For Study P01431, based on the primary efficacy endpoint, the change in %predicted FEV_1 between baseline and endpoint, MF DPI treatments were statistically significantly superior to placebo. Both MF DPI dosages (100mcg QD PM and 100mcg BID) provided similar effectiveness for improving %predicted FEV_1. (LS mean: 6.50 and 7.29 for 100mcg QD PM and 100mcg BID, respectively). Other pulmonary function variables supported the efficacy seen in %predicted FEV_1. The use of rescue medication data supported the efficacy of 100mcg QD PM dose with the nominal p-value of <0.021.

Only 5% - 9% of patients were 4-5 years old in the three studies. The efficacy of MF DPI for patients aged 4-5 years had similar trends compared to patients aged 6-11 years.

5.1 Labeling

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/s/

Feng Zhou
12/5/2007 12:03:44 PM
BIOMETRICS

Qian Li
12/5/2007 03:30:56 PM
BIOEQUIVALENCE STATISTICIAN
I concur.