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:	Mometasone furoate dry powder inhaler (ASMANEX® TWISTHLER®)
Proposed 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, Growth study

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1 EXECUTIVE SUMMARY

A growth study (Study C97384), as part of an efficacy supplemental for NDA 21-067, was submitted on March 30, 2007 by Schering Corporation for the use of mometason furoate dry powder inhaler (MF DPI) to treat asthmatic children 4 to 11 years of age. The proposed dose for the pediatric population was 110 mcg (100 mcg delivered from mouthpiece) inhaled once a day in the evening (QD PM). This review provides detailed statistical evaluation of the 52-week growth study on the growth effect of MF DPI with three MF DPI dose regimens in comparison to placebo in asthmatic children.

1.1 Conclusions

The results of Study C97384 raise concerns of the effect of MF DPI on children's growth reduction. This study was a randomized, double-blinded, placebo-controlled, parallel-grouped, and multi-center study which recruited 187 asthmatic patients aged 4-9 years and previously maintained on inhaled beta-agonist. The blinded treatment duration was 52 weeks. The numbers of patients randomized to each of the four treatment groups, MF DPI 110 mcg BID, MF DPI 220 mcg QD AM, MF DPI 110 mcg QD AM and placebo, were 44, 50, 48, and 45, respectively. The observed mean growth velocities over 1-year in the MF DPI 110 mcg BID, MF DPI 220 mcg QD AM, MF DPI 110 mcg QD AM, and placebo treatment groups were 5.25, 5.90, 6.06, and 6.26 cm/year, respectively. The differences and the corresponding 2-sided 95% CIs in cm/year of MF DPI 110 mcg BID – placebo, MF DPI 220 mcg QD AM – placebo, and MF DPI 110 mcg QD AM – placebo were -1.01 (-2.20, 0.18), -0.36 (-1.50, 0.78), and -0.19 (-1.34, 0.95), respectively. As the lower bounds of the 2-sided 95% CIs of the treatment differences provide estimates with high confidence, the growth rates in the MF DPI groups could be reduced in comparison to placebo for up to 2.20, 1.50, and 1.34 cm/year for MF DPI 110 mcg BID, 220 mcg QD AM, and 110 mcg QD AM, respectively. The study showed a numerical dose-response growth reduction trend, with the largest effect shown in the MF 110 mcg BID treatment. The results of the study were not robust due to small sample size, high rate of missing data, large measurement error, and low efficacy response.

1.2 Statistical Issues and Findings

The statistical issues discussed in this review include methods used for estimating and analyzing growth velocity, missing data, measurement error, and assay sensitivity for determining treatment differences.

Methods

The sponsor originally proposed an approach which first estimates each patient's growth velocity with linear regression using each individual patient's height measurements during the 1-year treatment period and then evaluates treatment differences using an ANOVA model. The sponsor later changed the method to use a mixed effect model with random intercept and slope to estimate the growth velocities of individual patients, treatment groups, and differences among treatment groups. The reason for the change, according to the sponsor, was to deal with missing data due to early discontinuation of treatment. There are problems in both of the proposed approaches.

It is important to understand that to be a valid estimate of growth velocity, the slope obtained from a linear regression requires a stringent assumption. That is, a child's growth velocity over a 1-year period needs to be constant with a linear growth curve. It is common sense that a child's growth is not in a constant speed in a 1-year period. In fact, to understand a child's growth velocity, one only needs to know how much a child has grown in a given period of time, irrespective to the shapes of growth curves. However, the slope from linear regression could be different depending upon the shape of the growth curves. What makes the slope approach even worse is that for a given growth curve, the slope of linear regression can be different depending upon the data points collected and the frequency of the data points measured.

The mixed effect model, which can also be considered as a slope approach, adds more confusion in deciphering the data, in addition to the problems of estimating the slope using linear regression. The sponsor's model only fits the linear growth term to estimate the slope. However, when the quadratic growth term (day*day) is added to the model, it is highly significant with p-value<0.01, indicating the linear growth assumption is not appropriate. When dealing with missing data, the mixed effect model assumes missing at random, in addition to the normality assumption imposed to the data, which may not always make sense as a patient's decision of treatment discontinuation is often not random. To illustrate the problem of the mixed effect model, take Patient 158 as an example. This patient had only three height measurements, 130.1, 127.1, and 129.5 cm measured at Day 1, 15, and 29, respectively, was discontinued from the study after experiencing an episode of serious adverse reaction. Clearly the missing height measurement of Patient 158 was not due to a random reason. The estimated growth rate for this patient using the mixed effect was 6.58 cm/year. But why should one believe that 6.58 was a reasonable estimate?

A correct method of the estimation of growth velocity is to use growth change divided by the time period of the change. This estimate represents a child's average growth rate over a period of time and is invariant to the shapes of growth curves. The reviewer's analysis for this NDA used this method to estimate individual patient's growth velocity. An ANOVA model was then used to analyze the treatment difference on the estimated growth velocity.

Measurement error

Data obtained from Patient 158 indicated possible large measurement error in the study. The measurement error could be controlled or minimized by good study design and conduct. To correctly estimate growth velocity, the measurement error at baseline and the end of treatment should be controlled. The measurement error at the two points also has the highest impact in regression approach due to their high leverage. The impact of measurement error was assessed by sensitivity analyses during the review of the study.

Missing data

The rates of discontinuing treatment were high in this study. About 25%, 32%, 21%, and 33% patients did not complete the treatment in MF DPI 110 mcg BID, 220 mcg QD AM, and 110 mcg QD AM, and placebo, respectively. The problems of discontinuation

combined with the measurement error produced unreasonable results, such as negative growth rate seen in Patient 158. The impact of the missing data was also assessed by sensitivity analyses.

Assay sensitivity

The patients enrolled in this study had only mild asthma (baseline % predicted FEV_1>87%). No treatment differences in terms of efficacy were observed in MF DPI 100 and 200 mcg QD AM in comparison to placebo. The MF DPI 100 mcg BID group showed more improvement in % predicted FEV_1 than the placebo group, but the difference was only marginally significant. Given the mild asthmatic patient population, the treatment might not be always needed. Patients that do not have an absolute need to take the medicine on a regular basis may have reduced compliance with the dosing regimen and therefore, the assay sensitivity of detecting treatment difference in safety assessment becomes a concern as the patients may not have actually been receiving the randomly assigned treatment.

2 INTRODUCTION

2.1 Overview

This efficacy supplement was intended for the marketing approval of MF DPI for the indication of maintenance treatment of asthma in patients 4-11 years old. The statistical evaluation of the efficacy portion of MF DPI was reviewed by Ms. Feng Zhou in a separate review document. This review provides detailed evaluation on the growth study, Study C97384, to assess growth effect of MF DPI in pediatric patients.

2.2 Data sources

Electronic document room for NDA21-067 submitted on 3-30-2007. SAS data sets used in this review included Dem and Visitn for Study C97384.

3 STATISTICAL EVALUATION of STUDY C97384

3.1 Study Design

The study objective was to evaluate the effect of three MF DPI regiments on growth velocity in children with asthma who were previously maintained on inhaled beta-agonists.

Study design

This was a multi-center, randomized, double-blinded, placebo-controlled, parallel-grouped study conducted in the United States, in asthmatic children aged 4-9 years and previously maintained on inhaled beta-agonists. Qualified patients were randomized to MF DPI 100 mcg BID, 200 mcg QD AM, 100 mcg QD AM, or placebo in 1:1:1:1 ratio. Randomization was stratified by two age strata, 4-5 and 6-9 years old. Patients went

through a 1-2 week screening period, then entered a 52-week double-blinded treatment period, and continued to a 3-month period follow-up after completion of treatment.

Patients' heights were measured by Harpenden stadiometer at screening, Weeks 1(baseline), 2, 4, 8, 12, 16, 26, 38, and 52 during treatment, and Weeks 56, 60, and 64 during the follow-up period. In addition to the height assessment, bone age measured from left wrist x-ray was obtained before and at the end of treatment.

Efficacy data such as forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25\%-75\%}$) were collected at every clinic visit.

Study endpoints

The primary safety endpoint was growth velocity during the one year treatment period. The efficacy endpoints included % predicted FEV_1, FEF25-75%, FVC, PEFR, short acting beta agonist use as rescue medication, nebulized beta-agonist treatments, nocturnal awakenings due to asthma which required short acting beta agonist use, discontinuation due to worsening asthma, response to therapy evaluation, and asthma exacerbations.

Statistical methods

The growth velocity would be estimated as the slope obtained from a linear regression of standing height vs. time for each patient in the original protocol. The growth velocities were then to be analyzed using two-way analysis of variance method including treatment and center as covariates. This method was changed to a mixed effect method which included random slope and intercept to estimate the individual patient's growth velocity, growth velocity of each treatment group, and treatment differences in growth velocity between treatments. The sponsor claimed that the change was before data blinding and the reason of this change was due to early dropouts that would not allow for precise estimation using the linear regression method.

The reviewer disagreed with the protocol specified approaches. The issues of the sponsor's approaches were documented in Section 1.2 for statistical issues and findings. The reviewer used the change from baseline divided by the time period of the change to estimate individual patient's growth velocity and then used an ANOVA model including treatment indicator, gender and age as covariates to assess treatment difference.

The sponsor defined two analysis data sets: All treated patients included all randomized patients who had received at least one dose of study medication. Full analysis subset included all treated patients with at least one follow-up evaluation. The full analysis subset was used for the analysis of the primary endpoint.

Study results:

Patient disposition

One hundred and eighty-seven patients were randomized at 29 US study centers. The study was conducted between May 28, 1998 and July 28, 2000. Among the 187 randomized patients, 44, 50, 48, and 45 patients were randomized to MF DPI 100 mcg BID, 200 mcg QD AM, 100 mcg QD AM and placebo, respectively. All the patients were in the all treated population and 3 patients were removed from the full analysis population. Overall, 72% (135) patients completed the study. Table 1 displays dropout frequencies by treatment and reason.

Table 1: Discontinuation frequencies by treatment and reasons during treatment.

	Number (%) of Patients			
	MF DPI			
	100 mcg BID	200 mcg QD	100 mcg QD	Placebo
	44	50	48	45
Discontinued	11 (25)	16 (32)	10 (21)	15 (33)
AE	2 (5)	4 (8)	2 (4)	0
Trt Failure	1 (2)	2 (4)	3 (6)	4 (9)
Lost to follow-up	2 (5)	4 (8)	1 (2)	6 (13)
Did not continue *	3 (7)	6 (12)	2 (4)	3 (7)
Noncompliance	3 (7)	0	2 (4)	2 (4)

* For reasons unrelated to treatment.
Source: Table 6 in Page 80 of the study report for Study C97-384.

Demographic and baseline information

No large imbalance among treatment groups was observed in demographic and baseline information. The mean age was 6.5 years; the majority was 6-9 years old; the majority was male patients (fewer female, 20%, in placebo group and more than 30% in the other groups); the majority was Caucasian. The mean baseline % predicted FEV1 was about 87%. Some patients' % predicted FEV1 was above 100%.

Major protocol violation

Forty-nine patients used prohibited medications with exposure for more than 15 days of systemic or additional inhaled corticosteroids, more than 84 days of nasal corticosteroids, or growth hormone. Among the 49 patients, 9 in MF DPI 100 mcg BID, 15 in MF DPI 200 mcg QD AM, 10 in MF DPI 100 mcg QD AM, and 15 in placebo.

Growth analyses

The sponsor's analysis using the mixed effect model is displayed in Table 2. The sponsor's analysis suggested statistically significant growth reduction in MF DPI 200 mcg QD AM in comparison to placebo. However, statistically significant treatment difference does not represent the worst effect on growth reduction. The worst growth effect should be determined by the lower bounds of the 2-sided 95% CIs of the differences in growth velocities between MF DPI versus placebo. The MF DPI 100 mcg BID had the lowest lower bound for the difference of growth velocity.

Table 2: Sponsor's analysis on growth velocity using a mixed effect model.

Treatment	Growth rate (cm/yr)	MF DPI - Placebo Difference (95% CI)	2-sided p-value
Placebo (n=45)	6.52		
100mcg QD (n=48)	6.42	-0.10 (-0.71, 0.51)	0.76

200mcg QD (n=49)	5.82	-0.70 (-1.26, -0.13)	0.02
100mcg BID (n=42)	5.88	-0.64 (-1.40, 0.12)	0.10

Source: Table 29 in Page 129 of the study report for Study C97-384.

The reviewer's analysis on growth velocity based on the change from baseline (two-point) approach is displayed in Table 3. The reviewer's analysis indicated that the MF DPI 100 mcg BID had the largest growth reduction among all the MF DPI treatment groups in comparison to placebo. The lower bound of the 2-sided 95% CI for the treatment difference between the BID dose and placebo was -2.20 cm/year. The reduction in MF DPI 100 mcg BID based on the reviewer's analysis was larger than the result obtained from the sponsor's analysis.

Table 3: Reviewer's analysis on growth velocity estimated using two-point approach.

Treatment	Growth rate (cm/yr)	MF DPI - Placebo Difference (95% CI)	2-sided p-value
Placebo (n=45)	6.26		
100mcg QD (n=48)	6.06	-0.19 (-1.34, 0.95)	0.740
200mcg QD (n=49)	5.90	-0.36 (-1.50, 0.78)	0.535
100mcg BID (n=42)	5.25	-1.01 (-2.20, 0.18)	0.097

Since estimating the slope using a linear regression for an individual patient is currently the recommended approach in the guidance for the industry entitled "Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children," the results of this analysis is displayed in Table 4.

Table 4: Reviewer's analysis on growth velocity estimated using individual regression approach.

Treatment	Growth rate (cm/yr)	MF DPI - Placebo Difference (95% CI)	2-sided p-value
Placebo (n=45)	6.44		
100mcg QD (n=48)	6.15	-0.30 (-1.48, 0.89)	0.623
200mcg QD (n=49)	5.93	-0.51 (-1.69, 0.67)	0.395
100mcg BID (n=42)	5.34	-1.11 (-2.34, 0.12)	0.078

Several sensitivity analyses were performed by the reviewer to assess the impact of early discontinuation and measurement error. One sensitivity analysis was performed by removing patients who had stayed on treatment for less than 3 months. Another was to change all negative growth velocities to 0. The results of the sensitivity analyses showed similar pattern of the dose response relationship in the growth effect to the result based on the reviewer's analysis.

Efficacy evaluation

Based on the sponsor's analyses at the treatment endpoint, which was defined as the last pulmonary function assessment during the treatment period, all the treatment groups including placebo showed improvement in % predicted FEV_1 from baseline. MF DPI 100 mcg BID had the largest increase in % predicted FEV_1 among all the treatment groups, 16.4% on average. The increases of MF DPI 200 and 100 mcg QD AM on average were

13.8% and 14.0%, respectively, and the increase in placebo was 8.3%. The difference of % predicted FEV_1 increase between MF DPI 100 mcg BID and placebo was marginally significant (p-value= 0.054). No differences in % predicted FEV_1 between the other two MF DPI groups and placebo were observed. The efficacy results are summarized in Table 5.

Table 5: Treatment effect in % predicted FEV_1.

Treatment	LS Baseline	LS Chg from Baseline	MF DPI - placebo	
			Difference	2-sided p-value
Placebo (N=43)	84.6	7.69		
110 mcg QD AM (N=46)	86.5	9.39	1.70	0.642
220 mcg QD AM (N=48)	88.0	10.87	3.18	0.384
110 mcg BID (N=40)	89.2	15.00	7.31	0.054

Source: Table 10 on Pages 86-7 in the study report for Study C97384.

This efficacy response was low in the three MF DPI treatment groups. Given the mild asthmatic patient population, the treatment might not be always needed. In a patient population that did not have the absolute need to take the medicine on a regular basis, the assay sensitivity of detecting treatment difference in safety assessment becomes a concern.

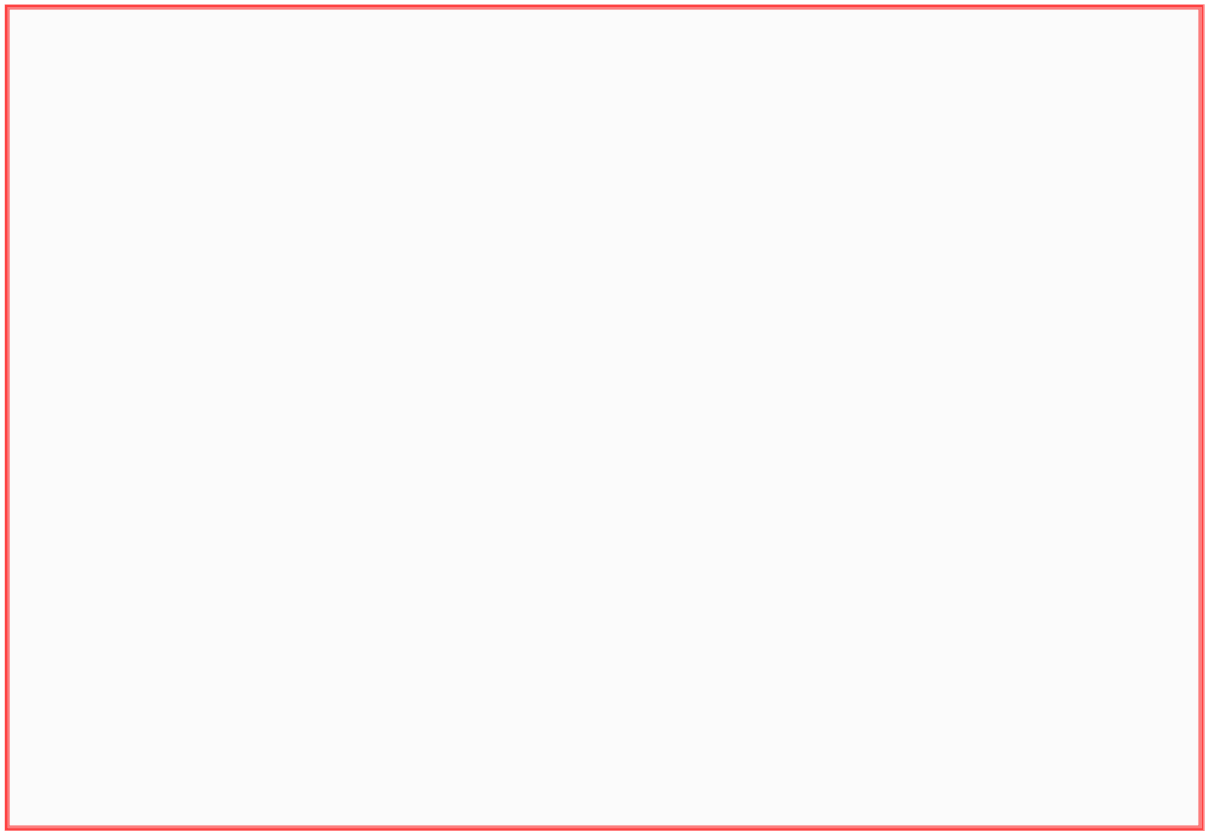
4 Findings in special/subgroup populations

The reviewer performed several subgroup analyses in gender, age groups, and race. The results of the subgroup analyses are summarized in Table 6. As seen from Table 6, numerically, the growth reduction of MF DPI in females seemed to be larger than that in males and the effect in younger age group seemed to be larger than that in the older age group. Since the majority of the patients were Caucasians, the growth rates of Caucasian group are displayed on Table 6.

Table 6: Summary of subgroup analyses by gender, age and race.

Treatment	Gender				Age				Race	
	Female		Male		4-5 years		6-9 years		Caucasians	
	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
Placebo	9	6.77	36	6.03	11	7.67	34	5.70	40	6.27
110 mcg QD AM	14	6.44	34	5.92	14	6.27	34	5.99	40	5.82
220 mcg QD AM	16	5.93	33	5.79	12	6.84	37	5.51	36	6.02
100 mcg BID	16	5.10	36	5.41	14	6.12	28	4.88	31	5.05

5 Label Review and recommendation



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