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:	N21-658/N000
Drug Name:	Ciclesonide metered dose inhaler (ALVESCO™)
Proposed Indication(s):	Maintenance treatment of asthma as prophylactic therapy in patients years of age and older
Applicant:	Nycomed Inc.
Date(s):	Received July 10, 2007
Review Priority:	Standard
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Keywords: NDA review, Growth Study

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1. EXECUTIVE SUMMARY

1.1 Conclusions

A 52-week growth study (Study 343) was included in this re-submission, dated July 10th, 2007 under NDA21-658, for ciclesonide metered dose inhaler (MDI) to assess its growth effect in asthmatic children in comparison to placebo. The study was a randomized, double-blind, parallel-group study including two doses of ciclesonide, 40 and 160 mcg per day, and placebo, administrated in the morning. The study enrolled 661 patients aged 5 to 8.5 years. These patients were equally randomized to placebo (221), ciclesonide MDI 40 mcg (221), and ciclesonide MDI 160 mcg (219). The mean baseline % predicted FEV_1 was about 95% at randomization. The estimated average growth velocities were 5.83, 5.85, and 5.62 cm/year for placebo, ciclesonide MDI 40 mcg, and ciclesonide MDI 160 mcg, respectively. The differences of the growth velocities and the corresponding 2-sided 95% CIs were 0.02(-0.18, 0.21) and -0.21(-0.41, -0.02) for ciclesonide MDI 40 mcg – placebo and ciclesonide MDI 160 mcg – placebo, respectively. Although the lower bounds of the 2-sided 95% CIs for the differences were larger than the margin -0.5 cm/year, specified in the study protocol for a claim of no worse than placebo, the validity of the study results is questionable. The facts that this study was conducted in a patient population with very mild asthma and no efficacy was observed in the two doses of ciclesonide MDI raised a concern in assay sensitivity of detecting treatment differences in growth velocities.

1.2 Statistical Issues and Findings

The main issue of the study is the enrolled patient population which had very mild asthma with baseline average % predicted FEV_1 about 95%. This patient population might not need to use medication to control their disease, which leads to the question of patients' incentive of taking the medicine. The efficacy results further elevated this concern. In this study, only 3 out of 661 patients (2 in placebo and 1 in ciclesonide MDI 160 mcg) discontinued treatments due to lack of efficacy. There was no treatment difference in efficacy among the three treatment groups in FEV_1 assessment. The patient population selected and the lack of efficacy response raised the concern of assay sensitivity of detecting treatment difference in growth velocities in this study due to possible non-compliance.

One puzzling observation was a large difference in growth velocities between the run-in period and the double-blind treatment period in all treatment groups. To understand if this significant period effect was due to an age difference as the patients were 6 months older when entering the double-blind treatment period than the run-in period, the growth velocities were calculated by 6-month intervals in the double-blind treatment period. However, the growth rates were similar between the first 6 months and the last 6 months. It was not clear how this significant period effect should be interpreted.

2. INTRODUCTION

2.1 Overview

This re-submission intended to address efficacy and safety deficiencies identified from the original submission of ciclesionde MDI under NDA 21-658 for maintenance treatment of asthma. The statistical evaluation of the efficacy portion of ciclesonide MDI was reviewed by Dr. Ted Guo in a separate review document. This review provides detailed evaluation on the growth study, Study 343, to assess growth effect of ciclesonide MDI in children.

2.2 Data sources

Electronic document room for NDA21-658 submitted on 7-10-2007.

3. STATISTICAL EVALUATION OF STUDY 343

3.1 Study Design

The study objective was to evaluate the effect of ciclesonide MDI 40 and 160 mcg (ex-actuator) administered once daily in the morning on growth velocity in comparison to placebo in children with mild persistent asthma over a 12-month treatment.

This was a multicenter, randomized, double-blinded, placebo-controlled, parallel-group study in asthmatic children aged 5-7.5 years for girls and 5-8.5 years for boys. The patient population included patients who had mild persistent asthma for more than 3 months at screening. This study was divided into three periods: a 6-month run-in period with placebo, a 12-month double-blind treatment period, and a 2-month follow-up period. Qualified patients were randomized to ciclesonide 40 or 160 mcg, or placebo in 1:1:1 ratio at the end of the 6-month screening period. Randomization was stratified by center and age strata, where girls were divided by age 7 and boys by 8.

Patients' heights measured by stadiometer in cm were assessed

- During the screening period at Visits 1, 2, 3 (-6 months, -3 months and -2 weeks),
- At randomization which was at Visit 4 (time=0),
- During the treatment period at Visits 5-12 (Week 2 and Months 1,2,3,4,6,8, and 10);
- During the follow-up period at Visit 14 (Month 14).

Note that even though the treatment was discontinued early, patients were asked to return to clinic as scheduled for height assessments. Bone age measured by wrist x-ray was obtained at the baseline (Visit 3) and at the end of double-blind treatment (Visit 13). In addition, pulmonary function tests were performed at every clinic visit.

Patient compliance with study medication was assessed based on the patient's diary records and canister weights measured at each clinic visit.

<u>Study endpoints</u>

The primary growth endpoint was growth velocity during the 12-month double-blind treatment period. The secondary endpoint included the change from baseline in bone age. The efficacy endpoints included absolute and relative changes of FEV_1 from baseline to the last on-treatment observations.

Statistical methods

Several analysis populations were defined in the study protocol and its amendments, which included three modified intent-to-treat (mITT) populations, a per protocol (PP) population, and a safety population. The mITT population used for the primary analysis was defined as all randomized patients who completed at least 4 months of treatment or more during the double-blind treatment period. The PP population excluded important protocol deviations based on criteria determined prior to unblinding. The PP criteria were listed on Pages 86-7 in the study report. The safety population comprised all patients who received at least one dose of double-blind study medication.

The sponsor's primary analysis was to estimate the growth velocity using linear regression slopes of height vs. time for each patient. Other approaches of estimating the growth velocity mentioned in the protocol and the growth study report included a 2-point method and linear regression fixing baseline. The 2-point method is to estimate the growth velocity using growth change divided by the time period for the change. The treatment differences in growth velocity were analyzed using the analysis of covariance approach (ANCOVA) with covariates including treatment, pooled center, baseline growth velocity, height at randomization, age and age^2 at randomization, gender, gender by age interaction, race, previous corticosteroid usage during baseline period, and years of asthma since first diagnosed.

In this review, the 2-point method of estimating growth velocity was used in the majority of reviewer's analyses as this is a correct method irrespective of the shapes of growth curves. The analysis model used by the reviewer included only treatment, age stratum, baseline growth rate, and gender as covariates. The pooled center effect was removed from model because it is not clear how to interpret this artificial effect and its contribution in the analysis. The reviewer also removed several other covariates because these covariates appear to be highly correlated with covariates that were kept in the model.

The sponsor proposed a non-inferiority margin for the purpose [redacted] The proposed non-inferiority margin was -0.5 cm/year for the lower bound of the 2-sided 95% CI for the difference of growth velocities between the ciclesonide treatment groups and placebo. The bases of the margin, according to the sponsor, were the draft guidance for industry for clinical studies in assessing the growth effect of the orally inhaled and intranasal corticorsteriods issued in November 2001, as well as study results from comparing growth in pre-pubertal children treated with fluticasone propionate at a dose of 100 μg twice daily or placebo. This margin was not discussed during the review process as three review disciplines including

clinical, clinical pharmacology, and statistics concluded that the study results are unreliable.

The efficacy endpoints for the change of FEV_1 from baseline to the last on-treatment measurements were also analyzed in the mITT population using an ANCOVA model with covariates including treatment, center, baseline measurement, age at randomization, and gender.

3.2 Study results

Patient disposition

Six hundred and sixty-one patients were randomized at 63 US centers and 22 South American centers (12 in Argentina, 4 in Chile, and 6 in Venezuela). The 63 US centers enrolled only about a quarter of the total number of patients. The study was conducted between December 29, 2000 and September 15, 2004. Among the 661 randomized patients, 221, 221, 219 patients were randomized to placebo, ciclesonide MDI 40 mcg, and ciclesonide MDI 160 mcg, respectively. About 92% patients were in the mITT population and 80% in the PP population. Overall, about 16% patients discontinued the double-blind treatment. Table 1 displays patient disposition information and dropout frequencies by treatment and reason.

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

	Number (%) of Patients		
	Placebo	Ciclesonide 40 mcg	Ciclesonide 160 mcg
Randomized	221	221	219
mITT population	201 (91%)	206 (93%)	202 (92%)
Per Protocol population	176 (80%)	180 (81%)	179 (82%)
Completed 12-month treatment	181 (82%)	181 (82%)	188 (86%)
Reason for discontinue *			
Adverse event	14 (6.3%)	14 (6.3%)	8 (3.7%)
Lack of efficacy	2 (0.9%)	0 (0%)	1 (0.5%)
Did not wish to continue	7 (3.2%)	5 (2.3%)	6 (2.7%)
Lost to follow-up	6 (2.7%)	4 (1.8%)	5 (2.3%)
Poor compliance	3 (1.4%)	5 (2.3%)	4 (1.8%)
Protocol violation	10 (4.5%)	4 (1.8%)	5 (2.3%)
Other	5 (2.3%)	10 (4.5%)	7 (3.2%)

*Patients might report more than one reason for discontinuation.
Source: Table 3 on Page 103 and Table 8 on Page 110 of the study report for Study 343.

Demographic and baseline information

There was no large imbalance across treatment groups in demographic and baseline information. The mean age was about 7 years at randomization. The majority was male (67%), white (71%), and from South American (72%). The mean baseline % predicted FEV_1 was 95% at randomization. The average growth velocity during run-in period was 6.41 cm/year in the mITT population. One observation worth noting about the baseline growth rates was that the growth rate was lower in cicleoside MDI 160 mcg than that in placebo. The reviewer's analysis of baseline growth rates using the 2-point approach is

summarized in Table 2. The model used for the analysis was analysis of variance which included treatment, gender, and age strata as covariates.

Table 2: Reviewer's analysis on growth velocity during run-in period.

Treatment	Growth rate (cm/yr)	Ciclesonide MDI - Placebo Difference (95% CI)	2-sided p-value
Placebo (201)	6.51		
Ciclesonide 40 mcg (206)	6.57	0.06 (-0.22, 0.34)	0.675
Ciclesonide 160 mcg (202)	6.23	-0.27 (-0.56, 0.00)	0.053

Protocol violation and compliance

The sponsor reported that 27 patients had protocol violations. Among the 27 patients, 12, 8, and 7 were in placebo, ciclesonide MDI 40 mcg, and ciclesonide MDI 160 mcg, respectively.

There was about 94% of patients (based on diary data) and 80% patients (based on canister weight) reported over 85% drug compliance across treatment groups. However, the reported compliance rates might not be reliable given the nature of the selected patient population who might not need the treatment for their disease.

Growth analyses

The results of the sponsor and the reviewer's analyses were similar. The lower bounds of the 2-sided 95% CIs of the difference of growth rates between ciclesonide MDI and placebo were within the margin of -0.5 cm/year. Such results appear to indicate that the growth rates in the ciclesonide MDI regimens was not worse than that in placebo if we believe that a difference of 0.5 cm/year is not clinically important, even though the difference was statistically significant. The results of the reviewer's analysis based on the 2-point method are displayed in Table 3.

Table 3: Reviewer's analysis on growth velocity during double-blind treatment period using the 2-point method.

Treatment	Growth rate (cm/yr)	Ciclesonide MDI - Placebo Difference (95% CI)	2-sided p-value
Placebo (201)	5.83		
Ciclesonide 40 mcg (206)	5.85	0.02 (-0.18, 0.21)	0.870
Ciclesonide 160 mcg (202)	5.62	-0.21 (-0.41, -0.02)	0.032

Since estimating the slope using a linear regression for an individual patient is 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 are displayed in Table 4.

Table 4: Reviewer's analysis on growth velocity during double-blind treatment period using linear regression.

Treatment	Growth rate (cm/yr)	Ciclesonide MDI - Placebo Difference (95% CI)	2-sided p-value

Placebo (201)	5.79		
Ciclesonide 40 mcg (206)	5.77	-0.02 (-0.21, 0.16)	0.795
Ciclesonide 160 mcg (202)	5.63	-0.16 (-0.35, 0.03)	0.091

One puzzling observation was a large difference in growth velocities irrespective of treatment assignment between the run-in period and the double-blind treatment period in all treatment groups. This difference can be seen by cross comparing growth velocities displayed in Tables 2 and 3. To understand if this significant period effect was due to an age difference as the patients were 6 months older when entering the double-blind treatment period than the run-in period, the growth velocities were calculated by 6-month intervals in the double-blind treatment period. However, the growth rates were similar between the first 6 months and the last 6 months. It was not clear how this significant period effect should be interpreted. The reviewer further broke down the analysis to age and gender strata. Only two strata out of 12 had numerical trends of slowing down growth rates in every 6-month interval, including run-in and double-blind treatment period. The analyses are summarized in Table 5.

Table 5: Growth rates by 6-month interval and by gender and age strata

					Double-blind treatment period			
Treatment	Gender	Age(yrs)	Run-in period		First 6 months		Last 6 month	
			N	Mean±SD	N	Mean±SD	N	Mean±SD
Placebo	Female	≤7 years	39	6.52 ±1.32	38	5.80±1.64	34	6.05±1.68
		>7 years	28	6.54±1.60	28	5.86±1.26	26	5.89±1.15
	Male	≤8 years	92	6.42±1.64	88	5.67±1.50	85	6.00±1.32
		>8 years	42	6.46±1.16	41	5.13±1.50	39	5.45±1.62
Ciclesonide MDI 40 mcg	Female	≤7 years	43	6.96±1.43	42	5.87±1.08	39	6.34±1.39
		>7 years	24	6.05±1.07	22	6.32±1.61	21	5.21±1.30
	Male	≤8 years	100	6.66±1.28	96	5.61±1.68	92	5.99±1.56
		>8 years	39	6.11±1.02	38	5.24±1.39	35	5.51±1.17
Ciclesonide MDI 160 mcg	Female	≤7 years	47	6.38±1.61	46	5.99±1.34	44	5.44±1.31
		>7 years	24	5.98±1.41	24	5.14±1.61	23	5.87±1.35
	Male	≤8 years	93	6.43±1.36	92	5.58±1.39	86	5.74±1.22
		>8 years	38	5.62±1.97	37	5.42±1.55	37	5.05±1.45

Efficacy evaluation

Based on the sponsor's analyses, at the treatment endpoint, which was defined as the last pulmonary function assessment during the double-blind treatment period, all the treatment groups showed no improvement in the predicted FEV_1 from the baseline. There was a small similar increase in FEV_1 calculated as percent change from the baseline. No treatment difference was observed among the three treatment groups. The sponsor's efficacy results are summarized in Table 6.

Table 6: Treatment effect in % predicted FEV_1.

Parameter Treatment	N	Baseline mean	Change from baseline LS mean ± SE	Difference vs. placebo LS mean ± SE	2-sided 95% CI	p-value
FEV_1 percent predicted						
Placebo	201	92.97	-3.74 ± 0.817	–	–	–
Ciclesonide 40 µg/day	206	96.26	-3.62 ± 0.801	0.11 ± 1.104	(-2.06, 2.28)	0.9193
Ciclesonide 160 µg/day	202	94.87	-2.45 ± 0.808	1.28 ± 1.103	(-0.88, 3.45)	0.2458
Percent change in FEV_1 [a]						
Placebo	201	1.407	9.56 ± 1.001	–	–	–
Ciclesonide 40 µg/day	206	1.435	8.89 ± 0.988	-0.67 ± 1.355	(-3.33, 1.99)	0.6213
Ciclesonide 160 µg/day	202	1.419	10.32 ± 0.997	0.77 ± 1.356	(-1.90, 3.43)	0.5719

CI = confidence interval; LS = least squares; mITT = modified intention-to-treat; N = mITT population; SE = standard error.

[a] FEV_1 at baseline measured in liters.

Differences vs. placebo are calculated as ciclesonide minus placebo.

Source: Table 39 on Page 148 in the study report for Study 343.

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 does not have the absolute need to take the medicine on a regular basis, the assay sensitivity of detecting treatment differences in a safety assessment becomes a concern as compliance with the dosing regimen is questionable.

4 Findings in special/subgroup populations

The sponsor performed several subgroup analyses in gender, age groups, regions, baseline growth rates (< 4cm/year, ≥4 cm/year) and some other post-hoc subgroups. No major treatment-by-subgroup interactions were observed in these analyses of growth velocities.

5 Label Review and recommendation

[redacted] If any growth study results are to be displayed in the label, [redacted] as the fact that the study did not show treatment difference in efficacy should be mentioned in the label.

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/s/

Qian Li
1/4/2008 02:37:46 PM
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This version incorporated Ruthanna Davi's comments. An old version of this review was mistakenly sent in DFS
on Dec. 20th, 2007.

Ruth Davi
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