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

SECONDARY STATISTICAL REVIEW

NDA/Serial Number:	22-124/000
Drug Name:	Ciclesonide Nasal Spray (Omnaris)
Indication(s):	Proposed for seasonal and perennial allergic rhinitis in patients 2 to 11 years of age
Applicant:	Altana Pharmaceuticals, Inc.
Date(s):	Submitted: May 24, 2007
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Review Priority:	Standard re-submission
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Background

Ciclesonide nasal spray was originally submitted in December, 2005 by Altana Pharma under NDA 22-004 and approved in October, 2006 in patients 12 years of age and older with seasonal and perennial allergic rhinitis (SAR and PAR) for the strength of 200 mcg once daily administered in the morning. The same indications in pediatric patients in age 2-11 years were not approved because of insufficient efficacy evidence based on two pediatric studies in the original submission, Study M1-403 conducted in PAR patients 6-11 years of age and Study M1-405 in PAR patients 2-5 years of age.

This re-submission under NDA 22-124 was for the purpose of addressing the efficacy deficiency of ciclesonide nasal spray in treating pediatric patients with allergic rhinitis. The sponsor submitted two new studies, Study M1-417 conducted in SAR patients 6-11 years of age with two strengths of ciclesonide, 200 and 100 mcg and Study M1-416 in PAR patients 2-5 years of age with ciclesonide 200 mcg. The primary statistical reviewer, Ms. Feng Zhou, provides detailed efficacy assessment to the two studies in her review.

In the overall pediatric clinical program submitted under both NDAs 22-004 and 22-124 for ciclesonide nasal spray, Study M1-417 was used to support SAR claim, while Studies M1-403, M1-417, and M1-405 were used to support PAR claim.

The purposes of this secondary statistical review are to collectively summarize efficacy evaluation of ciclesonide nasal spray for treating both SAR and PAR in pediatric patient population, to discuss analyses which were not covered in the primary statistical review, and to document disagreement with a statistical issue raised in the primary review. This secondary review is based on the primary statistical reviews for NDAs 22-124 and 22-004 as well as study reports relevant to the pediatric program under the two NDAs.

SAR indication

Study design

Study M1-417 was a multi-center, randomized, double-blinded, placebo-controlled, parallel-group study. The primary objective was to evaluate the safety and efficacy of ciclesonide 200 and 100 mcg administered intranasally once a day in the morning in comparison with placebo in pediatric patients with SAR. Patients aged 6-11 years with minimum two years of SAR history were recruited and randomized in 1:1:1 ratio to three treatment groups, ciclesonide 200 and 100 mcg, and placebo. The study included two periods: 7 to 21-days baseline period and 2-week double-blinded treatment period.

The efficacy of SAR was assessed with four nasal symptoms including itch nose, nasal congestion, runny nose, and sneezing. Each of the symptom was rated on a severity scale ranging from 0 to 3 (0=absent, 1=mild, 2=moderate, 3=severe). The nasal symptoms were evaluated by parents/caregivers twice daily in the morning before dose (AM) and in the afternoon (PM). At each evaluation, the nasal symptom scores were assessed reflectively for the past 12 hours and

instantaneously for current. The daily assessments were captured using Electronic Data Capture method utilizing a telephone-based system. In addition, physician assessments of the four nasal symptoms (PANS) were evaluated at 4 scheduled clinic visits, including screening, baseline, Weeks 1 and 2 during treatment.

The primary efficacy endpoint was defined as the average of the AM and PM parent/caregiver reported reflective total nasal symptom scores (rTNSS). The treatment difference on rTNSS was evaluated over the 14-day treatment period. The key secondary efficacy endpoints included PANS assessed at the end of treatment and the average AM and PM parent/caregiver reported instantaneous total nasal symptom scores (iTNSS) over the 14-day treatment period.

The primary analysis used the intent-to-treat (ITT) population which included all randomized patients who took at least one dose of study medicine and had at least one post-randomization efficacy evaluation.

Treatment groups were compared using repeated measures analysis with covariates including treatment, baseline, day (unordered), and the treatment by day interaction. In addition, patient was treated as a random effect. A step-down procedure was used for multiple doses adjustment.

Study Results

The study was conducted at 69 centers in US between March 14, 2006 and October 16, 2006. Six hundred and eighteen patients were randomized and all included in the ITT population. About 5% patients discontinued the study in all three treatment groups. Demographic and baseline characteristics were balanced among the treatment groups: the mean age was 8.8 years; about 57% was male; 82% was caucasian; the baseline rTNSS score was about 8.3.

Sponsor's efficacy results are summarized in Table 1. As can be seen from Table 1, ciclesonide 200 mcg statistically significantly reduced the nasal symptom scores, measured by the average rTNSS over 14-day treatment period, the average iTNSS over 14-day treatment period, and last on-treatment PANS assessment, in comparison to placebo. The symptom reductions in ciclesonide 100 mcg, in comparison to placebo, were not statistically significant measured by the primary and two key secondary endpoints.
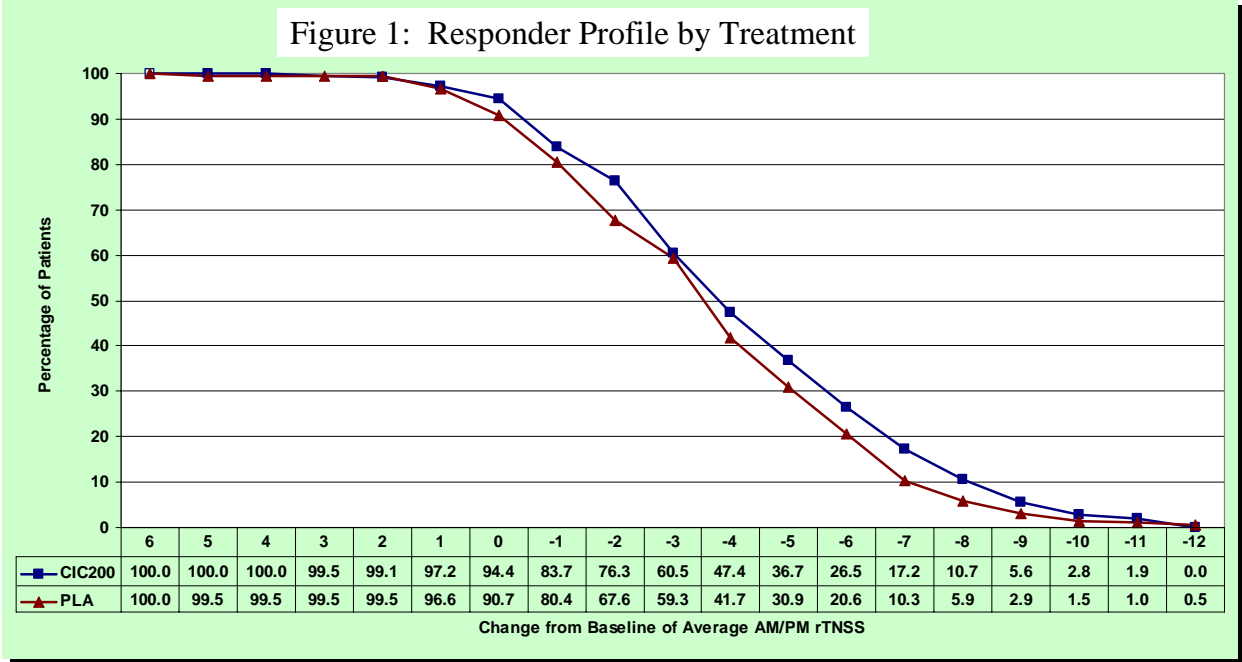
Table 1: Sponsor's efficacy results for Study M1-417.

Treatment	Baseline	Change from baseline	Difference: ciclesonide - placebo		
			Difference	2-side 95% CI	2-sided p-value
14 days average AM and PM rTNSS					
Ciclesonide 200 (n=215)	8.25	-2.46	-0.39	(-0.76, -0.02)	0.04
Ciclesonide 100 (n=199)	8.41	-2.38	-0.32	(-0.69, 0.06)	0.103
Placebo (n=204)	8.41	-2.07			
PANS – last on-treatment assessment					
Ciclesonide 200 (n=215)	7.96	-3.30	-0.92	(-1.45, -0.38)	<0.001
Ciclesonide 100 (n=199)	7.73	-2.73	-0.34	(-0.88, 0.21)	0.223
Placebo (n=204)	7.57	-2.39			
14 days Average AM and PM iTNSS					
Ciclesonide 200 (n=215)	7.46	-2.24	-0.37	(-0.73, -0.00)	0.047
Ciclesonide 100 (n=199)	7.49	-2.18	-0.31	(-0.68, 0.06)	0.096

Placebo (n=204)	7.62	-1.87

Source: based on Table 9 on Page 72, Study report of Study M1-417 submitted under NDA22-214.

The reviewers performed similar analyses on the primary efficacy endpoints by fitting models without patients as a random effect, the interaction terms, as well as the combinations. The results of reviewers' analyses were consistent with the sponsor's results.

Figure 1: Responder Profile by Treatment

	6	5	4	3	2	1	0	-1	-2	-3	-4	-5	-6	-7	-8	-9	-10	-11	-12
CIC200	100.0	100.0	100.0	99.5	99.1	97.2	94.4	83.7	76.3	60.5	47.4	36.7	26.5	17.2	10.7	5.6	2.8	1.9	0.0
PLA	100.0	99.5	99.5	99.5	99.5	96.6	90.7	80.4	67.6	59.3	41.7	30.9	20.6	10.3	5.9	2.9	1.5	1.0	0.5

Change from Baseline of Average AM/PM rTNSS

In addition, analysis of responder profile was conducted to further understand the effect size of ciclesonide in treating pediatric patients with SAR. The analysis was based on the change from baseline of the last on-treatment rTNSS assessment. The responder profiles of both ciclesonide 200 mcg and placebo are presented in Figure 1 (courtesy of Ms. Feng Zhou). As can be seen from the graph, the maximum treatment difference of 8.7% was observed when patients with rTNSS reduction larger than 2 scales were classified as responders. This treatment difference can be interpreted as such that with 50% certainty, when 100 patients were treated with ciclesonide 200 mcg, the most only 8 patients could benefit from the drug.

PAR indication

Study design

The PAR indication was supported by three studies of which the key features and differences of the three studies in design are summarized in Table 2. All studies were conducted as a randomized, double-blind, parallel-group, placebo-controlled, multi-center clinical trials. The efficacy evaluation of the three studies was similarly designed as Study M1-417 for the SAR indication.

Table 2: Key features of study design in PAR studies.

Study	Age range	Treatment/sample size	Treatment duration	Primary endpoint	Secondary endpoints
M1-403	6-11 years	200 mcg/ 165 100 mcg/ 166 25 mcg/ 169 Placebo/ 165	12 weeks	Average AM and PM 12-hour rTNSS over the first 6 weeks of treatment	1) Average of AM and PM rTNSS-12 hour over the 12 weeks of treatment; 2) Last on-treatment PANS assessment during the first 6 weeks of treatment
M1-416	2-5 years	200 mcg/ 81 Placebo/ 42	12 weeks	Average 24-hour rTNSS over 12 weeks of treatment	Last on-treatment PANS assessment;
M1-405	2-5 years	200 mcg/ 33 100 mcg/ 33 25 mcg/ 33 Placebo/ 34	6 weeks	Average 24-hour rTNSS over 12 weeks of treatment	Last on-treatment PANS assessment;

The statistical method was similar to the one used in the SAR study, except that the daily TNSS was average over a week period and the weekly average was used in the analyses.

In efficacy evaluation of treating allergic rhinitis, studies conducted in patients 2-5 years of age are not considered as important as studies in patients 6-11 years of age. This is because it is unlikely to obtain meaningfully assessment to the subjective efficacy symptoms in young kids. For this reason, Study M1-403 conducted in patients 6-11 years of age was designed to evaluate efficacy of ciclesonide with a reasonable sample size, while Studies M1-416 and M1-405 were conducted mainly to assess tolerability of ciclesonide in patients 2-5 years of age and sample sizes were not designed for efficacy assessment. Therefore the results of Study M1-403 are weighed heavier in efficacy evaluation than that of the other two studies.

Study Results:

The study results of the three studies are summarized in Table 3. It is clear from Table 3, Study M1-403, the pivotal study for PAR efficacy indication, completely failed to show efficacy of ciclesonide in all three strengths in treating patients 6-11 years old with PAR by almost all the endpoints. In fact, none of the three studies in any strength of ciclesonide demonstrated consistently reduction in nasal symptoms scores measured by the primary and key secondary endpoints in comparison to placebo, not to mention statistically and clinically meaningful treatment benefit.

Table 3: Sponsor's efficacy results in PAR patients from Studies M1-403, M1-416, and M1-405.

	Baseline	Change from baseline	Difference: ciclesonide - placebo		
			Difference*	2-side 95% CI	2-sided p-value
Study M1-403					
Average AM and PM 12-h rTNSS for Weeks 1-6					
Ciclesonide 200 (n=163)	6.6	-2.1	-0.3	(-0.8, 0.1)	0.164
Ciclesonide 100 (n=164)	6.7	-1.8	0.0	(-0.4, 0.5)	0.917
Ciclesonide 50 (n=162)	6.8	-1.7	0.1	(-0.3, 0.5)	0.687

Placebo (n=162)	6.9	-1.8			

Average AM and PM 12-h rTNSS for Weeks 1-12

Ciclesonide 200 (n=163)	6.6	-2.3	-0.1	(-0.6. 0.3)	0.528
Ciclesonide 100 (n=164)	6.7	-2.0	0.1	(-0.3, 0.6)	0.553
Ciclesonide 50 (n=162)	6.8	-1.9	0.2	(-0.2, 0.7)	0.304
Placebo (n=162)	6.9	-2.2			

PANS – last on-treatment assessment for Weeks 1-6

Ciclesonide 200 (n=157)	7.3	-2.8	-0.8	(-1.4, -0.2)	0.006
Ciclesonide 100 (n=163)	7.2	-2.0	0.0	(-0.6, 0.6)	0.998
Ciclesonide 50 (n=164)	7.0	-2.2	0.2	(-0.8, 0.3)	0.429
Placebo (n=155)	6.7	-2.0			

Study M1-416
Average 24-h rTNSS for Weeks 1-12

Ciclesonide 200 (n=81)	6.7	-2.3	-0.9	(-1.6, -0.1)	0.021
Placebo (n=42)	7.4	-1.5			

PANS – last on-treatment assessment for Weeks 1-12

Ciclesonide 200 (n=81)	7.2	-3.3	0.32	(-0.8, 1.5)	0.575
Placebo (n=41)	7.0	-3.6			

Study M1-405
Average 24-h rTNSS for Weeks 1-6

Ciclesonide 200 (n=33)	4.8	-1.6	0.0	(-0.7, 0.8)	0.909
Ciclesonide 100 (n=30)	5.5	-1.8	-0.1	(-0.9, 0.7)	0.746
Ciclesonide 50 (n=32)	4.5	-1.7	-0.0	(-0.8, 0.7)	0.930
Placebo (n=32)	4.9	-1.6			

PANS – last on-treatment assessment for Weeks 1-6

Ciclesonide 200 (n=33)	6.1	-3.0	-0.6	(-1.7,0.6)	0.327
Ciclesonide 100 (n=30)	7.0	-3.5	-1.1	(-2.3, 0.0)	0.054
Ciclesonide 50 (n=32)	5.9	-3.1	-0.7	(-1.8, 0.5)	0.244
Placebo (n=32)	5.6	-2.5			

*Differences were calculated using 3 decimals and then rounded to 1 decimal.
Sources: Table 9 on Page 70, study report of Study M1-403;
　　　　　Table 10 on Page 60 and Table 12 on Page 63, study report of Study M1-416;
　　　　　Table 20 and Figure 15 on Page 42, primary statistical review for NDA 22-004.

Statistical Disagreement

A step-down procedure for determining statistical significance shown in the following diagram was specified for multiplicity adjustment in Study M1-417. The primary reviewer made the following comments in her statistical review:

> "This approach controls type I error within each dose comparison and within variables (primary and key secondary) separately, but does not control the overall type I error. The control of family wise type I error breaks down at the second step after the hypothesis at 200mcg dose on primary (rTNSS) endpoint is rejected. The sequential procedure will lead to testing the hypothesis at 100mcg dose on the secondary endpoint (PNSS) if either of the two parallel hypotheses, the one at 200mcg dose on the secondary (PNSS) endpoint and the one at 100mcg dose on the primary (rTNSS) endpoint, are rejected. The type I error for testing these two hypotheses in parallel are not controlled at 0.05 level.

Order of Testing for Determining Statistical Significance

Start →	200 mcg vs. Placebo		100 mcg vs. Placebo		200 mcg vs. 100 mcg
Days 1-14 Reflective TNSS	↓	→	↓	→	↓
Physician-Assessed Nasal Symptoms at Endpoint	↓	→	↓	→	↓
Days 1-14 Instantaneous TNSS	☐	→	☐	→	☐

Note: Arrows indicate the order of testing, from left to right and from top to bottom.

The disagreement lies in the differences in understanding the diagram of the multiplicity procedure. The secondary reviewer interprets the diagram as follows:
- If the high dose successfully demonstrates efficacy, the efficacy of low dose will be considered; at the same time, the secondary endpoint for the high dose can be considered for labeling if it is clinically meaningful.
- The secondary endpoint of the low dose will be considered for labeling only if the low dose demonstrates efficacy and the secondary endpoint of the high dose is statistically significant.

The primary reviewer's interpretation of this diagram is that the secondary endpoint of the low dose could be claimed in the label if the secondary endpoint of the high dose is statistically significant without the low dose to demonstrate the efficacy. The primary reviewer's interpretation does not seem to make regulatory sense as the secondary endpoint should not be considered for labeling at all if its corresponding dose level does not demonstrate efficacy.

Conclusion

The results of Study M1-417 support the pediatric claim of ciclesonide 200 mcg QD AM in treating patients 6-11 years of age with SAR. As ciclesonide 100 mcg did not demonstrated convincing efficacy in treating pediatric patients with SAR and there are concerns in administrating ciclesonide 200 mcg to patients under 6 years old, the SAR indication is recommended to be approved in pediatric patients 6-11 years old.

As none of the studies conducted in PAR pediatric patients demonstrate convincing efficacy of ciclesonide in any strength, the PAR indication was not recommended to be approved in pediatric patients with PAR.