CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-124s000

STATISTICAL REVIEW(S)

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 (b) to 11 years of age
Applicant:	Altana Pharmaceuticals, Inc.
Date(s):	Submitted: May 24, 2007
	PDUFA date: Nov. 23, 2007
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.

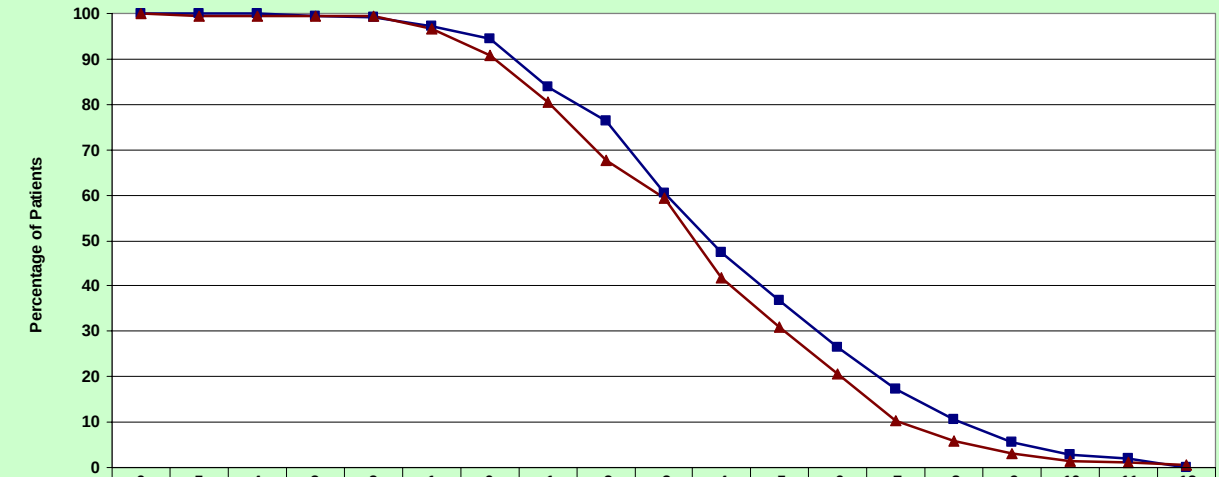
Treatment	Baseline	Change from baseline	Difference: ciclesonide - placebo		
			Difference	2-side 95% CI	2-sided p-value
14 days average AM and PM rTNSS					
Ciclesonide 200 (n=215)	8.25	-2.46	-0.39	(-0.76, -0.02)	0.04
Ciclesonide 100 (n=199)	8.41	-2.38	-0.32	(-0.69, 0.06)	0.103
Placebo (n=204)	8.41	-2.07			
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

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. **(b) (4)**

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.

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/s/

Qian Li
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BIOEQUIVALENCE STATISTICIAN

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:	N22-124
Drug Name:	Ciclesonide Nasal Spray 50mcg
Indication(s):	Proposed Indications: SAR, PAR in patients (b) (4) 11 years of age
Sponsor:	ALTANA Pharmaceuticals, Inc.
Date(s):	Re-submission was received 5/24/07; User Fee 11/23/07
Review Priority:	6 months
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Feng Zhou, M.S. (Statistical Reviewer)
Concurring Reviewers:	Qian Li, Sc.D. (Statistical Team Leader)
Medical Division:	Division of Pulmonary and Allergy Products
Clinical Team:	Carol Bosken, M.D. (Medical Reviewer) Gilbert-McClain, Lydia, M.D. (Medical Team Leader) Badrul A Chowdhury, M.D. (Medical Division Director)
Project Manager:	Collette Jackcon

Keywords: Clinical Studies, NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

ALTANA Pharma has proposed OMNARIS™ (ciclesonide) nasal spray 200mcg QD for the indication of the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in children (b) (4) 11 years old.

Based on my review of the studies conducted in pediatric program, I conclude that there is evidence (Study M1-417) of the decreasing in reflective Total Nasal Symptom Score (rTNSS) in patients 6 to 11 years with SAR and this evidence also is supported by the improvements for the physician-assessed nasal symptom score (PNSS) and instantaneous Total Nasal Symptom Score (iTNSS). In the 12-week study (Study M1-403) trial in patients with perennial allergic rhinitis, none of the ciclesonide doses were statistically significantly different from placebo. The least squares means and 95% confidence intervals for the differences (ciclesonide minus placebo) between ciclesonide 200 mcg, 100 mcg, and 25 mcg treatment groups and placebo were -0.31 (-0.75, 0.13), 0.02 (-0.41, 0.46), and 0.09 (-0.35, 0.53), respectively.

There were two studies for patients 2-5 years old (M1-416 and M1-405). The primary objective of both studies was to evaluate the safety and tolerability of ciclesonide doses. Therefore, there was no declared primary efficacy endpoint. However efficacy measures were collected. The results of primary analysis for Study M1-416 showed efficacy of ciclesonide at a dose of 200mcg/day for the treatment of PAR in patients 2-5 years of age with an effect size of -0.86 (LS Mean). The key secondary endpoint (PNSS) did not reach the statistical significant. This study did not include the 100mcg dose. Study M1-405 failed to show the efficacy of ciclesonide 200mcg and 100mcg. The results from two studies were not consistently support the efficacy of ciclesonide 200mcg in patients 2-5 years old with PAR and ciclesonide 100mcg did not show the efficacy. Therefore, the efficacy of ciclesonide 100mcg (the recommended staring dose by sponsor) for patients 2-5 years old with PAR is unknown.

1.2 Brief Overview of Clinical Studies

Ciclesonide nasal spray was initially introduced to the Division of Pulmonary and Allergy Products via IND 65,488. The sponsor originally submitted NDA (22-004) for ciclesonide 200mcg on December 21, 2005. This NDA was approved on October 20, 2006 for the use of ciclesonide nasal spray in patients 12 years and above with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). A new NDA number (NDA 22-124) was identified for the use of OMNARIS™ (ciclesonide) nasal spray in patients below the age of 12 years with SAR and PAR. The sponsor received an approvable letter for the same indication in patients 2 to 11 years old on October 20, 2006. This submission constitutes a complete response to the approvable letter issued by the Division and is in accordance with the recommendations provided by FDA in response to ALTANA's proposal on December 1, 2006.

The sponsor submitted two new studies (M1-417 and M1-416) under this NDA on Mary 24, 2007 (NDA 22-124) in support of use of ciclesonide nasal spray in patients ages (b) (4) 11 years with SAR (b) (4). Table 1 presents the study design and primary efficacy results for two studies and two old studies (M1-403 and M1-405) which were submitted under NDA 22-004.

Table 1. Clinical Trials

Study / Center / Study Period	***Study Design***	***Key Inclusion Criteria***	***No. of subjects by treatment group entered/completed***	***Primary Endpoints***	***LS Mean (CIC-PL) 95% CI p-value*** [a]
M1-417 (SAR) 69 centers in US 3/14/06 – 10/16/06 2 weeks + 1 week run in period	Multi-center Randomized Double-blind Placebo-controlled Parallel-group	1. Age 6-11 yrs 2. at least 2 years history of SAR 3. Positive of standard skin prick test	200mcg: 215/205 100mcg: 199/190 Placebo: 204/193	Mean change from baseline in average of AM and PM reflective TNSS over the 2-weeks	200mcg: Δ=-0.39 (-0.76, -0.02), p=.040 100mcg: Δ=-0.32 (-0.69, 0.06), p=0.103
M1-416 (PAR) 3 centers in US 11/22/05 – 6/26/06 12 weeks + 1 weeks run in period	Multi-center Randomized Double-blind Placebo-controlled Parallel-group	1. Age 2-5 yrs 2. at least 90 days history of PAR 3. Positive of standard skin prick test	200mcg: 81/75 Placebo: 42/38	Mean change from baseline in average of AM and PM reflective TNSS over the 12-weeks	200mcg: Δ=-0.86 (-1.6, -0.13), p=0.021
M1-403 (PAR) 69 centers in US 12/21/05 – 10/16/06 12 weeks + 1 week run in period	Multi-center Randomized Double-blind Placebo-controlled Parallel-group	1. Age 6-11 yrs 2. at least 2 years history of SAR 3. Positive of standard skin prick test	200mcg: 165/149 100mcg: 166/151 25mcg: 169/147 Placebo: 165/139	Mean change from baseline in average of AM and PM reflective TNSS over the 6-weeks	200mcg: Δ=-0.31 (-0.75, 0.13), P=0.166 100mcg: Δ=0.02 (-0.41, 0.46), p=0.911 25mcg: Δ=0.09 (-0.35, 0.53), p=0.681
M1-405 (PAR) 3 centers in US 11/22/05 – 6/26/06 12 weeks + 1 weeks run in period	Multi-center Randomized Double-blind Placebo-controlled Parallel-group	1. Age 2-5 yrs 2. at least 90 days history of PAR 3. Positive of standard skin prick test	200mcg: 33/32 100mcg: 33/32 25mcg: 33/32 Placebo: 34/33	Mean change from baseline in average of AM and PM reflective TNSS over the 12-weeks	200mcg: Δ=0.04 (-0.72, 0.80), p=0.909 100mcg: Δ=-0.13 (-0.90, 0.65), p=0.746 24mcg: Δ=-0.03 (-0.79, 0.73), p=0.930

A: p-value was from a repeated measure ANCOVA with treatment, baseline, day, and treatment by day interaction. Day was an unordered categorical variable. An AR(1) model in conjunction with treating patient as a random effect was used to model intra-patient correlation.

1.3 Statistical Issues and Findings

There was no special statistical issue.

2. INTRODUCTION

2.1 Overview

Ciclesonide nasal spray was initially introduced to the Division of Pulmonary and Allergy Products via IND 65,488. The sponsor originally submitted NDA (22-004) for ciclesonide 200mcg on December 21, 2005. This NDA was approved on October 20, 2006 for the use of ciclesonide 200mcg daily in patients 12 years and above with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). A new NDA number (NDA 22-124) was identified for the use of ciclesonide nasal spray in patients below the age of 12 years with SAR and PAR. The sponsor received an approvable letter for the same indication in patients 2 to 11 years old on October 20, 2006. This submission constitutes a complete response to the approvable letter issued by the Division and is in accordance with the recommendations provided by FDA in response to ALTANA's proposal on December 1, 2006.

The sponsor submitted two new studies (M1-417 and M1-416) under this NDA on Mary 24, 2007 (NDA 22-124) in support of use of ciclesonide nasal spray in patients ages 2 to 11 years with SAR and PAR. Table 2 presents the description of these two studies under this review.

Table 2. Clinical Trials

Study/Center/ Study Period	***Study Design***	***Key Inclusion Criteria***	***No. of subjects by treatment group entered/completed***	***Primary Endpoints***
M1-417 (SAR) 69 centers in US 3/14/06 – 10/16/06 2 weeks + 1 week run in period	Multi-center Randomized Double-blind Placebo-controlled Parallel-group	1. Age 6-11 yrs 2. at least 2 years history of SAR 3. Positive of standard skin prick test	ciclesonide 200mcg: 215/205 ciclesonide 100mcg: 199/190 Placebo: 204/193	Mean change from baseline in average of AM and PM reflective TNSS, consisting of nasal congestion, rhinorrhea, nasal itching, and sneezing, over the 2-weeks
M1-416 (PAR) 3 centers in US 11/22/05 – 6/26/06 12 weeks + 1 weeks run in period	Multi-center Randomized Double-blind Placebo-controlled Parallel-group	1. Age 2-5 yrs 2. at least 90 days history of PAR 3. Positive of standard skin prick test	ciclesonide 200mcg: 81/75 Placebo: 42/38	Mean change from baseline in average of AM and PM reflective TNSS, consisting of nasal congestion, rhinorrhea, nasal itching, and sneezing, over the 12-weeks

2.2 Data Sources

Documents reviewed were accessed from the CDER document room at: \\...\N22124\. The data sets used in this review were as following: AT, DM, DY, IN, RE, and PA.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The Main body of my evaluation of efficacy will discuss two new studies (M1-417 and M1-416) individually.

3.1.1 Study M1-417

Study Design and Endpoints

This was a multi-center, randomized, double-blinded, placebo-controlled, parallel-group study evaluating the efficacy and safety of two dose regimens of intranasally administered ciclesonide 200mcg (2 sprays in each nostril) and 100mcg (1 spray in each nostril) once daily in the morning for 2 weeks in patients with a history of SAR to relevant seasonal allergen (pollen) for a minimum of two years. The study was conducted in pediatric patients with SAR at 69 investigational centers in the US. Following a run-in period of 1-2 weeks, 618 males and females 6 to 11 years of age with AR were centrally randomized in a 1:1:1 ratio to ciclesonide 200mcg or 100mcg, or placebo. There were 4 scheduled visits: Screening, Baseline, Weeks 1 and 2.

The primary objective of this study was to evaluate the efficacy of ciclesonide administered intranasally as a spray formulation at two dose levels (200 mcg and 100 mcg, once daily) compared with placebo in the treatment of SAR in pediatric patients (6-11 years of age). Primary efficacy endpoint was the mean change from baseline in average of AM and PM patients/caregiver reported reflective TNSS (rTNSS) over the 2-week treatment period. The primary efficacy analysis based on the repeated measures analysis of covariance (ANCOVA) with covariate adjustment for treatment, baseline, day and the treatment-by-day interaction. Treatment and day 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. This analysis also applied to the secondary efficacy variables of iTNSS.

Key secondary efficacy measures were: 1.Physician-assessed nasal symptom score at day-14 (PNSS); 2.Parent/caregiver-reported average AM and PM instantaneous TNSS (iTNSS) over the 2-week treatment period. Changes from baseline in the physician-assessed nasal symptom (PNSS) score between each active treatment group and placebo were compared inferentially at day-14 using an ANCOVA model with factors of pooled center, treatment and baseline score.

Utilizing knowledge gained from Study M1-403, the sponsor determined that a sample of size 217 would be required to detect an effect size of 0.75 with 90% power and a standard deviation of 2.4.

An Interactive Voice Response System (IVRS) was used for collecting the patient's diary data and other information. The analyses were performed on the intent-to-treat (ITT) population which included the randomized patients who had at least one post-baseline value for efficacy.

In this NDA the approval will be based on the primary endpoint. Key secondary endpoints will be supportive and will not be in label claim. Therefore it is not necessary to propose a rule to adjust for multiple comparisons and there is no issue for multiple comparison adjustment.

However, the sponsor proposed a rule as shown below. A sequential approach was used across the comparison of doses and across variables (primary and key secondary). 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. Any future attempt at a label claim on the key secondary endpoints should be assessed using overall type I error.

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.

Patient Disposition, Demographic and Baseline Characteristics

Of the 618 patients randomized in the study, 588 patients were completed 2 weeks double-blinded period. As shown in Table 3, percentages of patients discontinued were similar between the treatment groups.

Table 3. Patients' Accountability N (%)

Study MI-417	***ciclesonide 200mcg QD (n=215)***	***ciclesonide 100mcg QD (n=199)***	***Placebo (n=204)***
Randomized patients	215 (100)	199 (100)	204 (100)
Completed treatment period	205 (95.3)	190 (95.5)	193 (94.6)
Discontinued	10 (4.7)	9 (4.5)	11 (5.4)
Reason of early discontinuation			
Lack of efficacy	2 (0.9)	0	1 (0.5)
Adverse event	2 (0.9)	5 (2.5)	6 (3.0)
Lack of compliance	0	1 (0.5)	0
Did not meet protocol eligibility	2 (0.9)	1 (0.5)	0
Did not wish to continue	2 (0.9)	0	3 (1.5)
Death	1 (0.5)	0	0
Other	0	1 (0.5)	1 (0.5)
ITT population	215	199	204
PP population	191	176	184

Descriptive demographics and baseline characteristics were summarized for the randomized patients who received at lease one dose of double-blind study medication. The ages of patients ranged from 6 to 11 with a mean age of 9. In the study, 82% of patients were Caucasian, 15% were African-American, and 3% were other. Forty-three percent of the population was female. Baseline characteristics included allergen challenge results, and rTNSS. A detailed composition of the study population with respect to demographic and baseline characteristics is presented in Table 4. Demographic and baseline characteristics were similar across the treatment groups.

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

Study MI-417	***ciclesonide 200mcg QD (n=215)***	***ciclesonide 100mcg QD (n=199)***	***Placebo (n=204)***
Age			
Mean (SD)	8.8 (1.7)	9.0 (1.7)	8.7 (1.6)
Median	9.6	9.7	9.4
Range	6 – 11	6 – 11	6 - 11
Sex			
Female	86 (40.0)	92 (46.2)	91 (44.6)
Male	129 (60.0)	107 (53.8)	113 (55.4)
Race			
Caucasian	161 (74.9)	162 (81.4)	173 (84.8)
Black	42 (19.5)	29 (14.6)	24 (11.8)
Asian	4 (1.9)	3 (1.5)	3 (1.5)
American Indian, Alaska Native	2 (0.9)	1 (0.5)	2 (1.0)
Pacific Islander	1 (0.5)	1 (0.5)	1 (0.5)
Other	6 (2.8)	3 (1.5)	2 (1.0)
Type of Skin Test			
Historical Skin Prick	46 (21.4)	45 (22.6)	45 (22.1)
Current Skin Prick	169 (78.6)	154 (77.4)	159 (77.9)
Allergen Challenge Results (mm)			
Mean (SD)	7.7 (5.1)	7.3 (4.5)	7.0 (4.7)
Median	6	6	5
Range	3 – 40	3 – 26	0 – 30
Average (AM, PM) rTNSS			
Mean (SD)	8.2 (1.9)	8.4 (1.8)	8.4 (1.8)
Median	8.1	8.5	8.1
Range	3.9 – 12	4.4 – 12	4.1 – 12

Results and Conclusions

The Results of Efficacy Analysis –

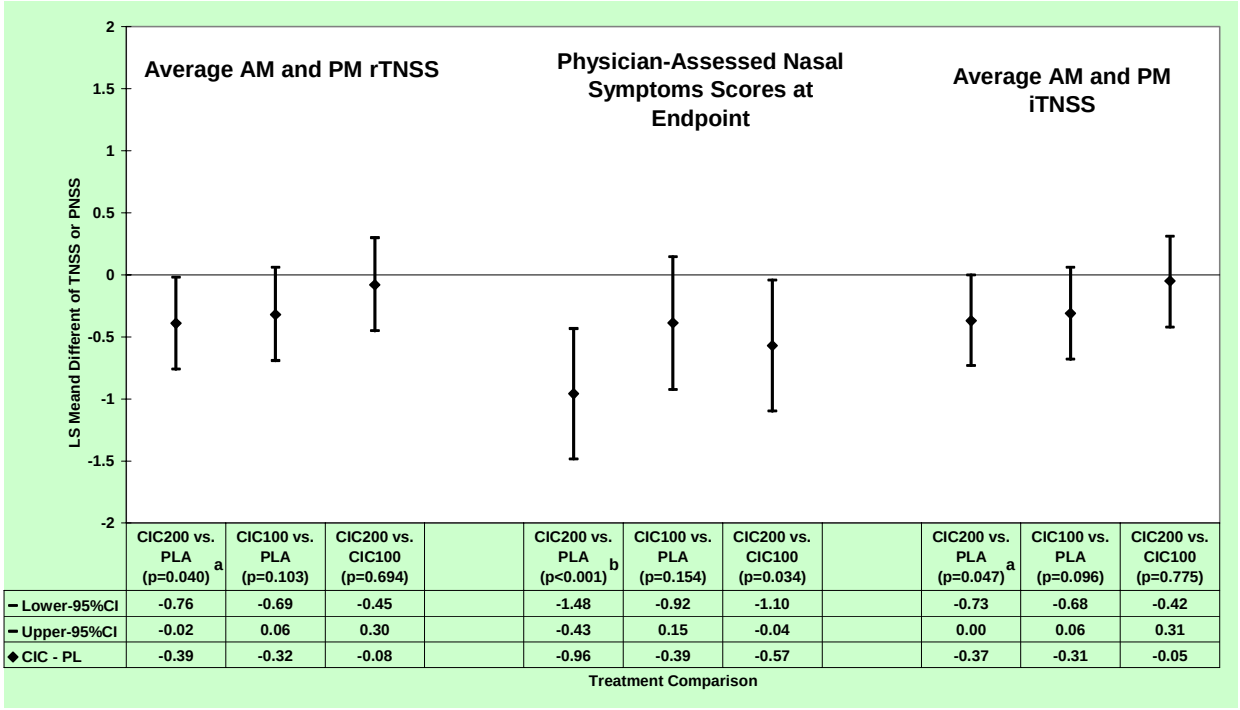
The results of the sponsor's primary analysis are shown in Table 5 and Figure 1. The sponsor concluded that the decrease in rTNSS averaged over 2 weeks was larger for patients in the ciclesonide 200mcg group (LS Mean: -2.46) than in the placebo group (LS Mean: -2.07), providing an estimated LS Mean difference of -0.39 (95%CI: -0.76, -0.02; p=0.04). This observed treatment difference (LS Mean: -0.39) was smaller than expected (LS Mean: -0.75). For the key secondary endpoints (PNSS and iTNSS), the ciclesonide 200mcg was significantly better than placebo. The ciclesonide 100mcg did not show to be effective. My evaluation of the data in both ITT and PP analyses sets are consistent with the sponsor's analyses.

Table 5. Analysis Results of Primary and Key Secondary Variables of Study M1-417

Treatment	Baseline	Change from Baseline		
	Mean (SE)	Mean (SE)	Median (Range)	LS Mean (SE)
Average AM and PM rTNSS (Weeks 1- 2)				
Ciclesonide 200 (n=215)	8.25 (0.13)	-2.40 (0.15)	-2.07 (-9.32, 3.57)	-2.46 (0.13)
Ciclesonide 100 (n=199)	8.41 (0.13)	-2.36 (0.14)	-2.32 (-8.64, 3.0)	-2.38 (0.14)
Placebo (n=204)	8.41 (0.13)	-2.05 (0.14)	-1.80 (-10.03, 2.68)	-2.07 (0.14)
Physician-Assessed Nasal Symptoms Scores at Endpoint [a] (PNSS)				
Ciclesonide 200 (n=215)	7.96 (0.17)	-3.34 (0.22)	-4.00 (-11.00, 8.00)	-3.51 (0.21)
Ciclesonide 100 (n=199)	7.73 (0.16)	-2.56 (0.22)	-2.00 (-10.00, 7.00)	-2.94 (0.22)
Placebo (n=205)	7.57 (0.17)	-2.15 (0.22)	-2.00 (-10.00, 7.00)	-2.56 (0.21)
Average AM and PM iTNSS (Weeks 1- 2)				
Ciclesonide 200 (n=215)	7.46 (0.14)	-2.19 (0.15)	-2.14 (-9.4, 3.6)	-2.24 (0.13)
Ciclesonide 100 (n=199)	7.49 (0.14)	-2.14 (0.14)	-2.14 (-7.9, 1.9)	-2.18 (0.13)
Placebo (n=204)	7.62 (0.15)	-1.87 (0.14)	-1.71 (-9.1, 3.3)	-1.87 (0.13)

a: Endpoint, defined as the last on treatment assessment, improvements from baseline were seen in all treatment groups for the physician-assessed nasal symptom score.

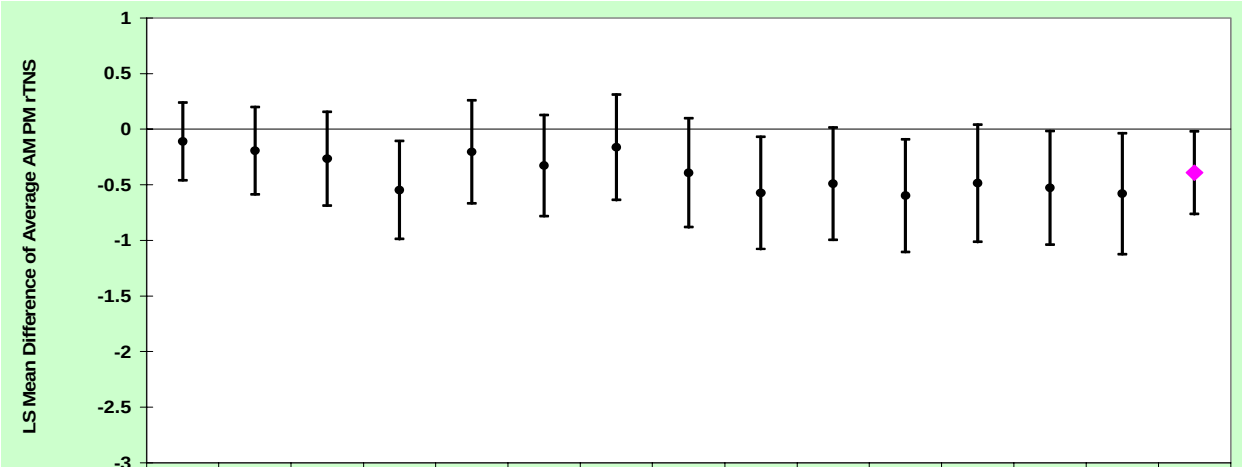
Figure 1. Analysis Results of Primary and Secondary Efficacy Variables for Study M1-417



a: p- value was from a repeated measures ANCOVA with treatment, baseline, day, and treatment by day interaction. Day was an unordered categorical variable. An AR(1) model in conjunction with treating patient as a random effect was used to model intra-patient correlation. Baseline: average of TNSS over the last 7 days of the Baseline Period prior to randomization.
b: p- value was from an ANCOVA with treatment, baseline, and pooled center. Baseline: measurement at the T0 Visit. Endpoint: last Treatment Period measurement.

I additionally explored the daily treatment effect over 2-weeks study period. The least squares mean decrease from baseline in average rTNSS over each study day during 2-week was numerically greater in the ciclesonide group than placebo group (Figure 2).

Figure 2. LS Mean Change from Baseline in Average AM and PM of rTNSS by Day

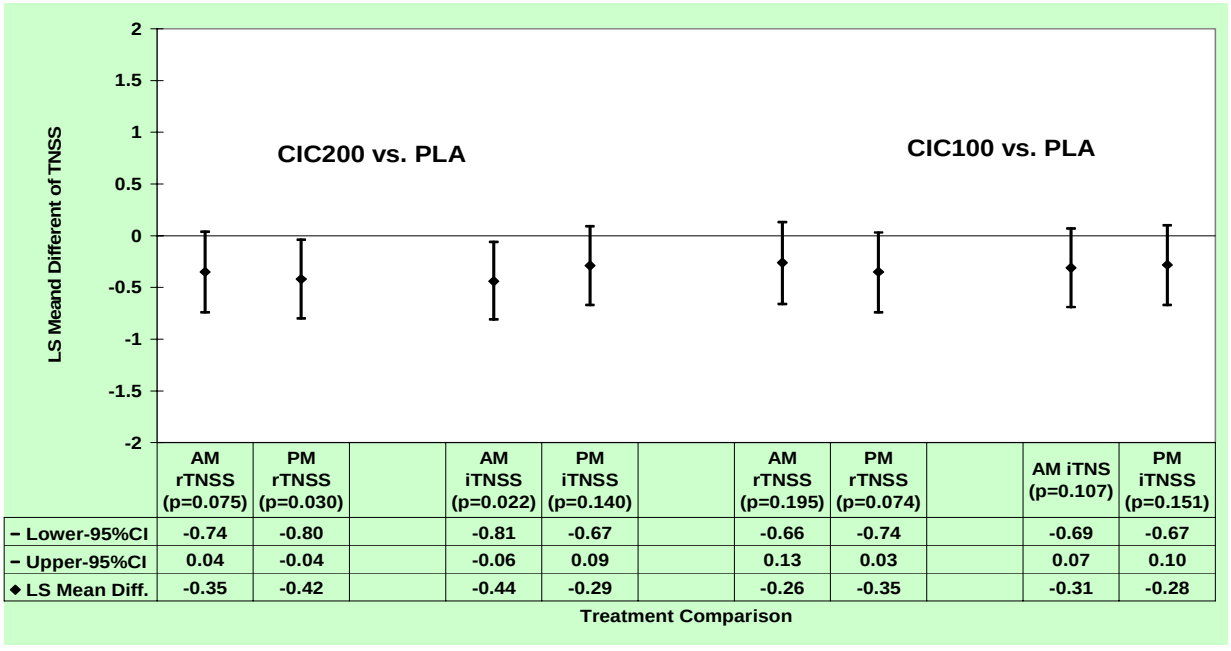


	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 1-14
– 95%CI - LL	-0.46	-0.58	-0.69	-0.99	-0.67	-0.78	-0.64	-0.88	-1.08	-1.00	-1.10	-1.01	-1.04	-1.12	-0.76
– 95%CI - UL	0.24	0.20	0.16	-0.11	0.26	0.13	0.31	0.10	-0.07	0.02	-0.09	0.04	-0.02	-0.04	-0.02
● CIC200-PLA	-0.11	-0.19	-0.26	-0.55	-0.20	-0.33	-0.16	-0.39	-0.57	-0.49	-0.60	-0.49	-0.53	-0.58	-0.39

Treatment Days

Figure 3 displays the LS Mean difference between ciclesonide and placebo in terms of the mean change from baseline in AM or PM reflective or instantaneous TNSS over 2 weeks. The results show that only ciclesonide 200mcg was significantly better than placebo in the PM rTNSS and the AM iTNSS.

Figure 3. LS Mean Change from Baseline of AM or PM TNSS



	AM rTNSS (p=0.075)	PM rTNSS (p=0.030)		AM iTNSS (p=0.022)	PM iTNSS (p=0.140)		AM rTNSS (p=0.195)	PM rTNSS (p=0.074)		AM iTNS (p=0.107)	PM iTNSS (p=0.151)
– Lower-95%CI	-0.74	-0.80		-0.81	-0.67		-0.66	-0.74		-0.69	-0.67
– Upper-95%CI	0.04	-0.04		-0.06	0.09		0.13	0.03		0.07	0.10
◆ LS Mean Diff.	-0.35	-0.42		-0.44	-0.29		-0.26	-0.35		-0.31	-0.28

Treatment Comparison

The Individual Reflective Symptom Score –
Decreases in each individual reflective symptom scores were seen in all three treatment groups. The discussion here focuses only the comparison between ciclesonide 200 mcg and placebo. The decreases over the 2-week treatment period were numerically larger for ciclesonide 200mcg than for placebo for each individual reflective symptom. Only for nasal congestion, appreciable differences compared with placebo were seen for ciclesonide 200mcg and reached the statistically significant. Appreciable treatment differences over the 2-week treatment period (ranging from 0.08 to 0.10) were seen between ciclesonide 200mcg and placebo for the other individual symptoms, indicating that all four individual symptoms contributed to the treatment difference observed in the rTNSS. (Table 6)

Table 6. Change from Baseline in Average AM and PM Reflective Individual Symptoms Score

Symptoms	Baseline (Mean ± SD)		Change from Baseline (LS Mean ± SE)		LS Mean Difference, P-value, 95%CI
	CIC200	PLA	CIC200	PLA	CIC200 – PLA
Itch Nose	2.02 (0.63)	2.10 (0.60)	-0.65 (0.04)	-0.56 (0.04)	-0.09 , p=0.105, (-0.19, 0.02)
Nasal Congestion	2.42 (0.50)	2.41 (0.48)	-0.64 (0.04)	-0.51 (0.04)	-0.13, p=0.014, (-0.23, -0.03)
Runny Nose	2.09 (0.66)	2.16 (0.60)	-0.61 (0.04)	-0.51 (0.04)	-0.10, p=0.086, (-0.22, 0.01)
Sneezing	1.72 (0.71)	1.74 (0.68)	-0.57 (0.04)	-0.49 (0.04)	-0.08, p=0.110, (-0.18, 0.02)

Conclusion –
For patients aged 6 – 11 years old, there was one SAR study (M1-417), the results of the sponsor's primary analysis and my evaluation of the data demonstrated the efficacy of ciclesonide at a dose of 200mcg/day for the treatment of SAR in patients 6-11 years of age with a marginal effect size (LS Mean: -0.39). For the key secondary endpoints (PNSS and iTNSS), the ciclesonide 200mcg was significantly better than placebo; this further supported the efficacy of ciclesonide 200mcg. The ciclesonide 100mcg did not shown to be effective.

3.1.2 Study M1-416

Study Design and Endpoints
This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group study evaluating the safety and tolerability of intranasally administered ciclesonide 200mcg (2 sprays in each nostril) once daily in the morning for 12 weeks in patients 2-5 years old with a history of PAR. The study was conducted at three investigational centers in the US. Following a run-in period of 1-2 weeks, 125 males and females, 2 to 5 years of age with PAR, centrally randomized to ciclesonide 200mcg or placebo in 2:1 ratio. There were 6 scheduled visits: Screening, Baseline, Weeks 3 6, 9, and 12. An Interactive Voice Response System (IVRS) was used for collecting the patients' diary data and other information.

The primary objective of this study was to evaluate the safety and tolerability of ciclesonide 200mcg administered once daily as an intranasal spray for 12 weeks, in pediatric patients 2 to 5 years of age with PAR. Therefore, there was no declared primary efficacy endpoint.

However efficacy measures were collected and included the AM rTNSS (which defined as the sum of the four individual reflective nasal symptom score over the past 24-h including nasal stuffiness/congestion, nasal itching, sneezing, and runny nose from the patient diary) over the 12-week treatment period and PNSS at visits: Screening, Baseline, Weeks 3 6, 9, and 12. The statistical models used for analysis of efficacy measures were similar to the models used for Study M1-417. (See Study M1-417 for detail)

Patient Disposition, Demographic and Baseline Characteristics

Of the 125 patients randomized in the study (83 patients were randomized to ciclesonide 200 mcg and 42 to placebo), 113 patients were completed 12 weeks double-blinded period. As shown in Table 7, percentages of patients discontinued were similar between the treatment groups.

Table 7. Patients' Accountability N (%)

Study MI-416	***Ciclesonide 200mcg QD (n=83)***	***Placebo (n=42)***	***Total (n=125)***
Randomized patients	83 (100)	42 (100)	125 (100)
Completed treatment period	75 (90.4)	38 (90.5)	113 (90.4)
Discontinued	8 (9.6)	4 (9.5)	12 (9.6)
Reason of early discontinuation			
Lack of efficacy	0	0	0
Adverse event	2 (2.4)	1 (2.4)	3 (2.4)
Lack of compliance	2 (2.4)	2 (4.8)	4 (3.2)
Lost to follow-up	1 (1.2)	1 (2.4)	2 (1.6)
Did not wish to continue	3 (3.6)	0	3 (1.6)
Other	1 (1.2)	0	1 (0.8)
ITT population	81 (97.6)	42 (100)	123 (98.4)

Descriptive demographics and baseline characteristics were summarized for the randomized patients who received at lease one dose of double-blind study medication. The ITT analysis set consisted of 53 (43.1%) males and 70 (56.9%) females with age ranged from 2 to 5 years. The ciclesonide group comprised 49 females (60.5%) and 32 males (39.5%) while the placebo group contained an equal number of male and female patients. There was a similar distribution within each treatment group across the age range from 2 to 5 years. The majority of patients were Caucasian (69.1%; 85/123). A detailed composition of the study population with respect to demographic and baseline characteristics is presented in Table 8.

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

Study MI-416	***CIC 200mcg QD (n=81)***	***Placebo (n=42)***	***Total (n=123)***
Age			
2 years	14 (17.3)	7 (16.7)	21 (17.1)
3 years	21 (25.9)	12 (28.6)	33 (26.8)
4 years	24 (29.6)	9 (21.4)	33 (26.8)
5 years	22 (27.2)	14 (33.3)	36 (29.3)
Mean (SD)	4.1 (1.1)	4.3 (1.1)	4.2 (1.1)
Median	4.2	4.5	4.4
Range	2.0 – 5.9	2 – 6	2 – 6

Sex			
Female	49 (60.5)	21 (50.0)	70 (56.9)
Male	32 (39.5)	21 (50.0)	53 (43.1)
Race			
Caucasian	54 (66.7)	31 (73.8)	85 (69.1)
Non-Caucasian	27 (33.3)	11 (26.2)	38 (30.9)
Type of Skin Test			
Historical Skin Prick	33 (40.7)	22 (52.4)	55 (44.7)
Current Skin Prick	48 (59.3)	20 (47.6)	68 (55.3)
Allergen Challenge Results (mm)			
Mean (SD)	5.1 (1.9)	5.5 (2.4)	5.2 (2.0)
Median	5	5	5
Range	3 – 16	3 – 14	3 – 16
Average (AM, PM) rTNSS			
Mean (SD)	6.7 (2.7)	7.4 (2.4)	7.0 (2.6)
Median	7.0	7.8	7.1
Range	0.17 – 11.86	1.29 – 11.57	0.17 – 11.86

Results and Conclusions

(b) (4)

Conclusion –
The results of the sponsor's primary analysis and my evaluation of the data from Study M1-416 showed some efficacy of ciclesonide at a dose of 200mcg/day for the treatment of PAR in patients 2-5 years of age with a effect size of (b) (4) (LS mean). The key secondary endpoint (PNSS) did not show that ciclesonide 200mcg was better than placebo. This study did not include the 100mcg dose.

3.2 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Carol Bosken. The reader is referred to Dr. Bosken'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 ciclesonide 200mcg and placebo. I confirmed the sponsor's analyses results. I performed the subgroup analyses using the ANCOVA model for study M1-417 and

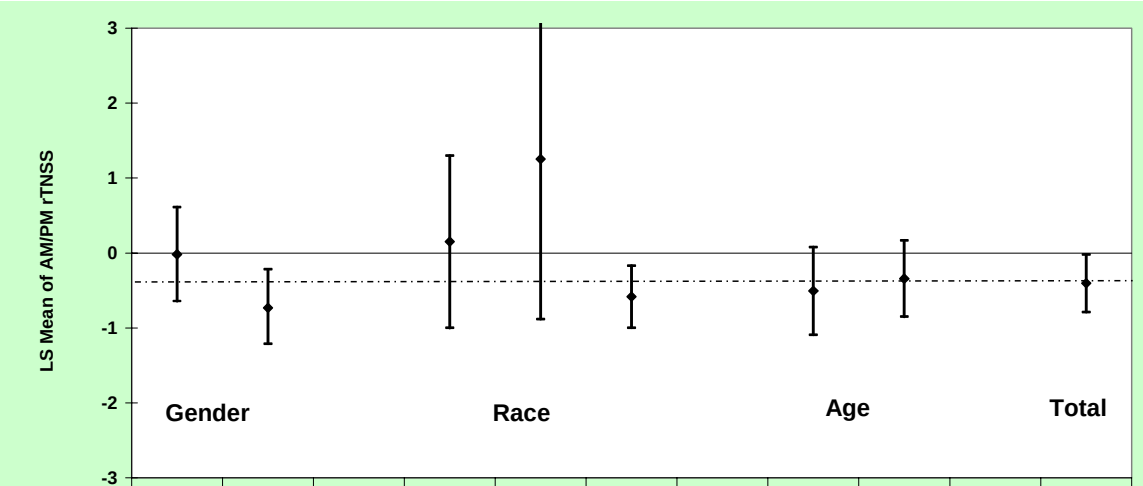
results are displayed in Table 10 and Figure 5. The results show that the treatment-by-gender interactions (p=0.06) with a no effect for female and larger effect for male between ciclesonide 200mcg and placebo; the efficacy of ciclesonide 200mcg was less effective for the subjects who were 9-11 years of age, black or of "other" races. However, statistically significant results are not expected in all subgroups due to the reduced sample size and natural variation expected.

Table 10. Mean Change from Baseline of Average of AM/PM rTNSS over Study Period

	Ciclesonide 200mcg			*Placebo*		
Subgroup (p-Value)†	***N***	***LS Mean***	***SE***	***N***	***LS Mean***	***SE***
Study M1-417 (*Ciclesonide 200mcg: n=215, placebo: n=204, 2-weeks*)						
Gender (p=0.064)						
Male	129	-2.37	0.17	113	-1.64	0.18
Female	86	-2.53	0.22	91	-2.51	0.21
Race Group (p=0.133)						
Black, African American	37	-2.24	0.35	22	-2.39	0.46
White	161	-2.49	0.15	173	-1.91	0.15
Others	17	-2.29	0.61	9	-3.54	0.85
Age Group (p=0.218)						
6-8	87	-2.52	0.21	89	-2.02	0.21
9-11	128	-2.38	0.18	115	-2.03	0.19

† p-Value for treatment-by-subgroup.

Figure 5. Mean Change from Baseline of Average of AM/PM rTNSS over 14-Days, M1-417



	Female (n=177)	Male (n=242)		Black (n=59)	Other (n=26)	White (n=334)		Age 6-8 (n=176)	Age9-11 (n=243)		Total (n=419)
– 95%CI - LL	-0.64	-1.21		-1.00	-0.88	-1.00		-1.09	-0.85		-0.79
– 95%CI - UL	0.61	-0.22		1.30	3.39	-0.17		0.08	0.17		-0.02
♦ CIC200-PLA	-0.02	-0.73		0.15	1.25	-0.58		-0.51	-0.34		-0.41

Gub_groups

4.2 Other Special/Subgroup Populations

There are no other special/subgroup analyses.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There is no special statistical issue.

(b) (4)
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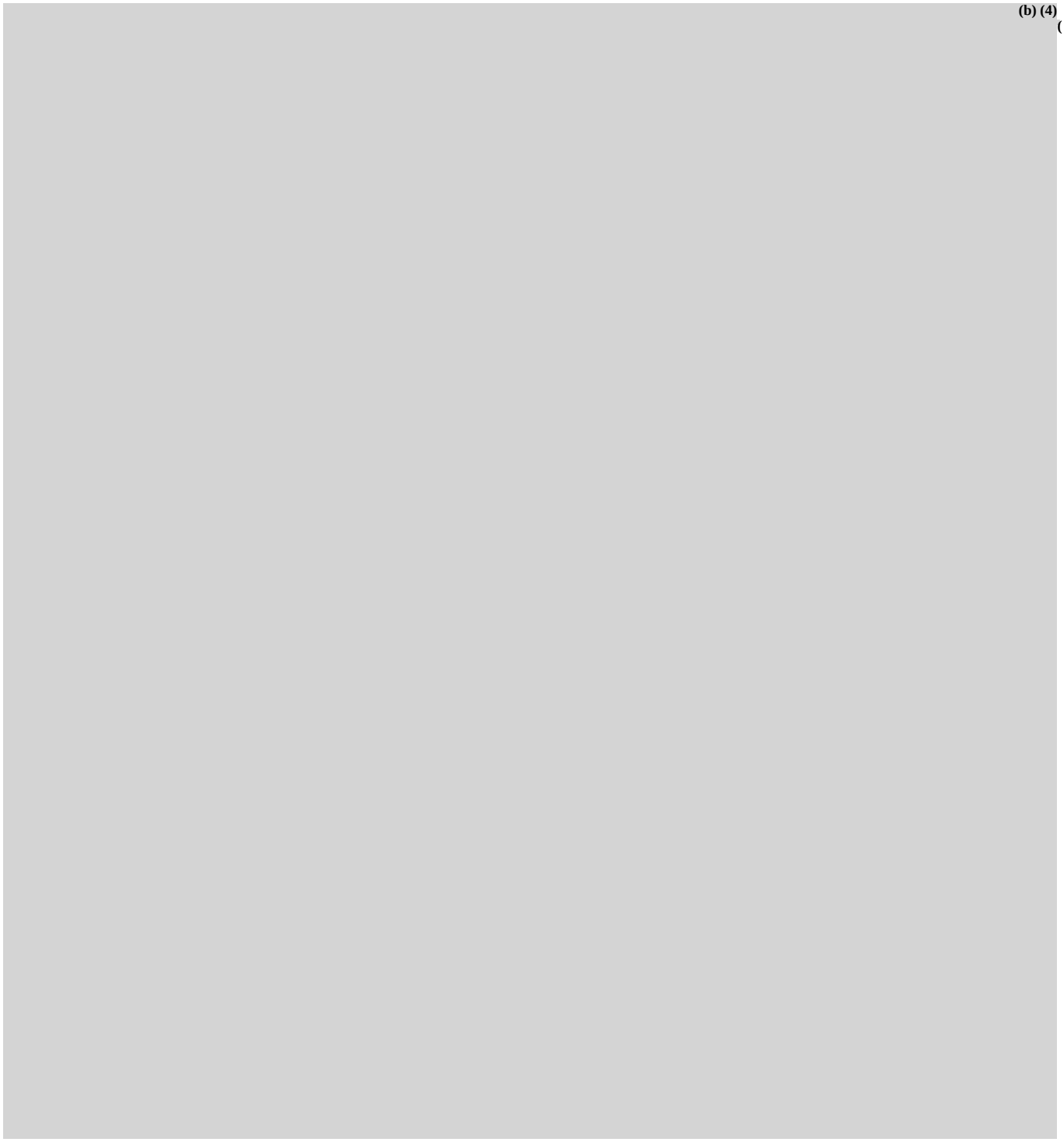

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5.2 Conclusions and Recommendations

ALTANA Pharma has proposed OMNARIS™ (ciclesonide) nasal spray 200mcg QD for the indication of the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in children (b) (4) 11 years old.

Based on my review of the studies conducted in pediatric program, I conclude that there is evidence (Study M1-417) of the decreasing in reflective Total Nasal Symptom Score (rTNSS) in patients 6 to 11 years with SAR and this evidence also is supported by the improvements for the physician-assessed nasal symptom score (PNSS) and instantaneous Total Nasal Symptom Score (iTNSS). In the 12-week study (Study M1-403) trial in patients with perennial allergic rhinitis, none of the ciclesonide doses were statistically significantly different from placebo. The least squares means and 95% confidence intervals for the differences (ciclesonide minus placebo) between ciclesonide 200 mcg, 100 mcg, and 25 mcg treatment groups and placebo were -0.31 (-0.75, 0.13), 0.02 (-0.41, 0.46), and 0.09 (-0.35, 0.53), respectively.

There were two studies for patients 2-5 years old (M1-416 and M1-405). The primary objective of both studies was to evaluate the safety and tolerability of ciclesonide doses. Therefore, there was no declared primary efficacy endpoint. However efficacy measures were collected. The results of primary analysis for Study M1-416 showed efficacy of ciclesonide at a dose of 200mcg/day for the treatment of PAR in patients 2-5 years of age with an effect size of (b) (4) (LS Mean). The key secondary endpoint (PNSS) did not reach the statistical significant. This study did not include the 100mcg dose. Study M1-405 failed to show the efficacy of ciclesonide 200mcg and 100mcg. (b) (4)

5.2.1 Labeling

The sponsor's draft labeling for AR references four studies. After team discuss, I provide one table as following:

Table 3. Mean changes in reflective total nasal symptom score and physician's assessment of nasal symptoms in children 6 to 11 years of age with seasonal allergic rhinitis

Treatment	n	Baseline*	Change from Baseline	Difference from Placebo		
				Estimate	95% CI	p-value**
Reflective total nasal symptom score						
Ciclesonide 200 mcg	215	8.25	-2.46	-0.39	(-0.76, -0.02)	0.040
Ciclesonide 100 mcg	199	8.41	-2.38	-0.32	(-0.69, 0.06)	0.103
Placebo	204	8.41	-2.07			

*Mean of AM and PM score from reflective total nasal symptom score;

** p- value was from a repeated measures ANCOVA with treatment, baseline, day, and treatment by day interaction. Day was an unordered

categorical variable. An AR(1) model in conjunction with treating patient as a random effect was used to model intra-patient correlation. Baseline: average of TNSS over the last 7 days of the Baseline Period prior to randomization.

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Feng Zhou
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Qian Li
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BIOEQUIVALENCE STATISTICIAN
The secondary statistical review is written for this submission.