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RESEARCH**

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STATISTICAL REVIEW(S)



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Statistical Review and Evaluation

CLINICAL STUDY

BLA / Serial Number: NDA 202129 / S0000

Drug Name: Ciclesonide Nasal Aerosol

Proposed Indication(s): Treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.

Applicant: Nycomed Inc. and Sunovion Pharmaceutical Inc.

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1. SUMMARY

1.1 Background

The sponsors have proposed ciclesonide nasal aerosol (ciclesonide NA) delivered via metered-dose inhaler (MDI) for the treatment of symptoms associated with seasonal and perennial allergic rhinitis (SAR and PAR) in adults and adolescents 12 years of age and older. Two-dose levels were evaluated in the phase III clinical development program. The two doses are referred to as 80 µg and 160 µg in this review, approximating ex-actuator 74 µg and 141 µg of ciclesonide, respectively. Three phase III studies were conducted to assess the efficacy and safety of ciclesonide NA. Studies 060-622 and 060-634 (referred to as 622 and 634, respectively) are SAR studies of 2-week duration. Study 060-633 (referred to as 633) is a PAR study of 26-week duration (the efficacy was evaluated at Week 6). This review covers the three studies.

Ciclesonide inhalation aerosol delivered also via MDI was approved in January 2008 for the maintenance treatment of asthma by trade name Alvesco[®]. In addition, ciclesonide nasal spray in aqueous suspension delivered via a pump spray was also approved in 2007 for the treatment of SAR and PAR by trade name Omnaris[®].

1.2 Study Results

The three phase III studies are randomized, double-blind, parallel group, multicenter, and placebo-controlled studies. All studies consist of three treatment groups: placebo, ciclesonide 80 µg, and ciclesonide 160 µg. The endpoints include reflective and instantaneous total nasal symptom scores (TNSS), reflective and instantaneous total ocular symptom scores (TOSS), and rhinoconjunctivitis quality of life questionnaire (RQLQ). The SAR studies (Studies 622 and 634) showed statistically significantly larger symptom reductions in all endpoints in both doses of ciclesonide NA compared to placebo. The PAR study (Study 633) also showed statistically significantly larger symptom reductions in all endpoints in both doses of ciclesonide NA compared to placebo. However, the treatment difference in RQLQ did not achieve clinical important difference defined as 0.5. Overall, ciclesonide 160 µg did not show better benefit compared to ciclesonide 80 µg in the ITT population for both SAR and PAR indications.

Subgroup analyses in Study 633 by gender revealed that the treatment benefit was not consistent between males and females for PAR symptoms. The treatment difference between ciclesonide 80 µg vs. placebo was 0.18, p-value=0.566 for male, while the treatment difference was 0.90, p-value<0.001 for female. Their benefit from ciclesonide 160 µg was numerically larger (treatment difference vs. placebo was 0.50, p-value=0.074) than that from ciclesonide 80 µg for male. These analyses raise questions on whether male could have meaningful benefit from ciclesonide 80 µg and whether they could have greater benefit from the higher dose of ciclesonide NA.

1.3 Conclusions and Recommendations

Based on the evaluation of the three studies, ciclesonide NA 80 µg is efficacious in treating patients with SAR and PAR. However, subgroup analyses by gender in the PAR study raised

questions on whether ciclesonide NA 80 µg is beneficial to male PAR patients and whether the higher dose could be better to the males. If it is necessary to understand these questions using data relevant to the PAR indication and the formulation of ciclesonide NA, more information are needed.

2. EVALUATION INDIVIDUAL STUDIES

3.1 SAR – Studies 622 and 634

Both Studies 622 and 634 are randomized, multicenter, double-blind, placebo controlled, and parallel-group phase 3 studies to evaluate the safety and efficacy of ciclesonide NA 80 µg and 160 µg compared to placebo. The studies started the screening period at Visit 1 followed by a single-blind placebo run-in period at Visit 2 for 7 days. Patients aged 12 years and older with a history of SAR for at least 2 years were recruited to the single-blind placebo run-in period. Patients who had minimum cumulative reflective total nasal symptom score (rTNSS) of 47 out of a possible 84 over any 3 of the last 4 days of the run-in period or who had a minimum cumulative reflective scores for runny nose or nasal congestion of at least 10 out of a possible 21 during any 3 of the last 4 days run-in period were randomized into the three treatment groups in 1:1:1 ratio. Patients started treatment period at Visit 3 (Day 1) for a period of 14 days. Treatment was self-administrated in the morning. Patients visited the clinics at Visit 4 (7 days after the double-blind treatment) and Visit 5 (the end of the double-blind treatment). In order to ensure allergen exposure in SAR studies, mountain cedar pollen counts in the clinical site area had to be elevated for at least 3 consecutive days at levels ≥ 50 grains/m³ prior to the start of the single-blind run-in period. Each site was required to randomize all patients within a consecutive 14-day period. Both studies planned to recruit 660 patients.

Study Endpoints

The efficacy endpoint for SAR nasal symptoms was TNSS, a sum of 4 symptom scores: runny nose, itchy nose, sneezing, and nasal congestion. The endpoint for SAR ocular symptoms was TOSS, a sum of 3 symptoms: itching, tearing, and redness. Each symptom was graded based on 4 scales: 0=absent; 1=mild; 2=moderate; 3=severe. All symptoms were evaluated daily reflectively (rTNSS or rTOSS) and instantaneously (iTNSS or iTOSS) in the morning (AM) and 12-hour later in the afternoon (PM).

Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities (RQLQ(S)) had 28 questions in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). Patients were asked to recall their experiences during the previous week and to give their responses on a 7-point scale (0 = Not Troubled to 6 = Extremely Troubled). The RQLQ(S) was self-administered by patients prior to randomization (Visit 3) and at the end of study (Visit 5).

Onset of action for both nasal and ocular improvement was defined as the first time point at which ciclesonide NA showed significant improvement over placebo with one-sided p-value of ≤ 0.025 using iTNSS or iTOSS and the significant improvement was maintained for some period

of time. Both iTNSS and iTOSS were assessed at 4, 6, 8, 10, and 12 hours post-dose on Day 1 and 6 and 12 hours post-dose on Day 2 in Study 622. In Study 634, the instantaneous time points were collected at the regular AM and PM time points. Onset of action for ocular symptom was not assessed in this review as it was determined that the information would not be presented in label in the mid-cycle review meeting.

The primary efficacy endpoint was the average, over the two-week treatment period, of change from baseline in the mean AM and PM rTNSS daily scores. The baseline score was defined as the average scores collected over the 6-day placebo run-in period.

The key secondary efficacy endpoints included:

1. Change from baseline in average AM and PM iTNSS over the two-week treatment period
2. Change from baseline in average AM and PM rTOSS over the two-week treatment period in a subset of patients whose baseline TOSS was no less than 5.0
3. Change from baseline in Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities (RQLQ(S)) in impaired patients (baseline RQLQ(S) score ≥ 3.0)
4. Onset of nasal improvement

Reviewer's comment: the protocol specified subgroup analyses for TOSS and RQLQ are presented along with the ITT analyses in this review, as the efficacy claim will not be made in subsets of patients for this NDA.

Statistical Methods

Sample Size Determination

Assuming that the standard deviation for the average change from baseline over two weeks in the average of AM and PM rTNSS was 2.1, 200 patients per group expected to provide at least 85% power to detect a difference between treatment groups of 0.7 in the change from baseline in rTNSS with a two-sided alpha level of 0.025.

Analysis Population

The ITT analysis population consisted of all randomized patients who received at least one dose of double-blind study drug.

The PP analysis set included all patients in the ITT analysis set without major protocol violations as well as partial data prior to any major protocol violation.

Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint was analyzed using the Intent-To-Treat analysis set. Treatment groups were compared using ANCOVA with factors of baseline rTNSS, center, and treatment. The protocol specified that comparisons of each active treatment group with placebo were performed at a Bonferroni-corrected significance level of 0.025 (2-sided). This review uses unadjusted p-values and unadjusted significance level which is 0.050 (2-sided).

Reviewer's comments: The level of details of this comment is only relevant to address the concern raised by the secondary statistical reviewer, Dr. Buenconsejo. The statistical evaluation in this review adopts the collective evidence approach which is different from the multiplicity adjustment approach for the following reasons. The establishment of efficacy should rely on information of both doses. That is, if both doses show convincing activity of efficacy which are confirmed in multiple studies, the efficacy of the drug is established. The unadjusted p-values which are less than 0.05 (this significance level can be relaxed to slightly higher level than 0.05 in some cases) are considered convincing efficacy activity for each dose in one study. Once the drug is determined to be efficacious, the next step is to determine the optimal doses. The optimal doses should be identified using collective evidence from all studies and factors such as effect sizes of primary and secondary endpoints as well as safety profiles of each dose. In this process, the adjusted p-values are not useful either. For example, suppose that there are two studies and each yields the results of unadjusted p-values 0.030 and 0.020 for the low and high doses, respectively. The corresponding adjusted p-values using Bonferroni correction are approximated to 0.060 and 0.040 for the low and high dose, respectively (another way of adjusting is to keep the unadjusted p-values and use significant level of 0.025). The p-values of the high dose are better irrespective of the unadjusted and adjusted p-values. therefore there is no need to present the adjusted p-values. Both doses could be considered for approval if the safety profile of the low dose was better than that of the high dose, while the high dose had larger benefit than the low dose, despite the fact that the adjusted p-values are 0.060, larger than 0.05, for the low dose. It is important to point out that the efficacy of the low dose is consistently demonstrated in two studies with unadjusted p-values significant at the level of 0.05 in this hypothetical scenario.

All other secondary efficacy endpoints listed above were analyzed using the same ANCOVA model as for the primary efficacy endpoint.

Missing data handling

If any of the component nasal symptom scores were missing for a particular time point, the TNSS score for that time point was also considered missing. If either AM or PM TNSS was missing, the average of AM and PM TNSS was set to the non-missing (AM or PM) TNSS. TOSS was handled similarly.

The missing data handling approaches for the two studies were somewhat different:

For Study 622: If a single question from the RQLQ(S) is missing, the domain score was still calculated as the average of the non-missing questions within that domain. If more than one question was missing, the domain score was set to be missing. The overall RQLQ(S) score was calculated as the average of the domain scores. If an entire domain score was missing, the overall RQLQ(S) was set to be missing.

For Study 634: The mean RQLQ(S) score for each domain at baseline and post treatment visits was based on non-missing responses. If 50% or more of the responses were absent in a domain, the result for that domain was set to missing. The overall RQLQ(S) score was calculated as the average of the domain scores. If an entire domain score was missing, the overall RQLQ(S) score was set to be missing.

Study results

All the studies were conducted in the United States. Study 622 was conducted at 7 sites in the period of November 15, 2008 to February 17, 2009 and randomized 707 patients. Study 634 was conducted at 7 sites in the period of December 1, 2009 to February 16, 2010 and randomized 671 patients. All of the randomized patients were in ITT population. The number of patients in each treatment arm is summarized in Table 1.

In Study 060-622, 39 patients were identified to have important protocol deviations and distributed in the three treatment groups approximately evenly (see Table 1). Among them, 7 patients were randomized more than once at different study sites, representing 15 patient identifications, which are identified as the following:

0006-S045, 0001-S022,
0001-S047, 0002-S004,
0001-S054, 0006-S099,
0001-S058, 0004-S005, 0006-S067,
0001-S124, 0006-S024,
0003-S089, 0004-S105,
0004-S055, 0001-S142.

In addition, 2 patients, 0002-S074 and 0004-S066, were identified as protocol violation as they previously enrolled in another ciclesonide NA study. These 2 patients were included in the per protocol analyses.

In Study 634, 41 patients were identified to have important protocol violations. More of the violations were in the placebo arm than that in the ciclesonide arms (see Table 1). In addition, the sponsor reported 14 patients who previously enrolled in other ciclesonide NA studies, some of them in Study 622. Among the 14 patients, two (0001-S043, 0003-S027) were actually the same patient who enrolled twice. The 14 patients were included in the per protocol population. Sensitivity analysis was performed by this reviewer by removing these 14 patients. The results are the same as the ITT analysis.

Table 1. Patient disposition for Studies 622 and 634

	Study 622			Study 634		
	Placebo	Cic80	Cic160	Placebo	Cic80	Cic160
Randomized	235	237	235	220	226	225
ITT	235	237	235	220	226	225
Per protocol	221(94%)	224(95%)	223(95%)	201(91%)	213(94%)	216(96%)
Discontinued	21(9%)	11(5%)	10(5%)	13(6%)	8(4%)	3(1%)
Adverse event	4	2	1	3	4	2
Protocol violation	2	2	4			
Subj. withdrawal	6	2	0	5	2	0
Lost follow-up	1	0	0	3	2	0
Other	8	5	5	2	0	1

Study conduct

For Study 622, the mean mountain cedar pollen counts at each site were elevated for at least 3 consecutive days at levels ≥ 50 grains per cubic meter, during placebo run-in period. The pollen counts remained elevated during the study. Minimal rainfall amounts were reported at most sites during the study. Elevated pollen counts were also reported in Study 634 during the study, except Sites 007 and 008. The two sites reported lower pollen counts on several days during the first week of double-blind treatment (median raw pollen counts ranged from 44-891 grains/cubic meter). The lower pollen counts at Site #8 during were associated with a large amount of rainfall.

About 80% patients used concomitant medication in both studies. The rates were reasonably balanced among the three treatment groups. Treatment compliance rates were close to 99% in both studies.

The rates of missing data were low in both studies.

Demographic information

All demographic and baseline information were comparable among treatments in the two studies. For Study 622, the mean age was 42 years ranging from 13 to 72 years. About 66% were female, and 93% were white. The mean baseline rTNSS score was 9.3 out of 12 ranging from 5.3 to 12. For Study 634, the mean age was 40 years ranging from 12 to 81 years. About 60% were female, and 88% were white. The mean baseline rTNSS score was 9.3 out of 12 ranging from 5.0 to 12.

Efficacy

Multiple analyses on the primary and secondary endpoints in both studies consistently showed that both doses of ciclesonide NA provided greater reduction in the symptoms associated with SAR than placebo after 2 weeks of treatments. Ciclesonide NA 160 μg did not show better efficacy than ciclesonide NA 80 μg .

For the primary efficacy endpoint rTNSS, the reduction was about 1.0 more in the two doses of ciclesonide NA than that in placebo in both ITT and per protocol populations in both studies. The treatment difference was highly statistically significant. Summary statistics and analysis results in the ITT populations are displayed in Table 2. During the review, the sponsor identified additional patients who were considered for protocol violation because of previous enrollment of other ciclesonide NA studies. Studies 622 and 634 identified 2 and 12 such patients, respectively. Sensitivity analyses were conducted by removing these patients from the ITT populations. The results of the sensitivity analyses are the same as the ITT analyses.

The treatment benefit of ciclesonide NA demonstrated in rTNSS were consistently exhibited in the individual components of rTNSS which include sneezing, runny nose, nasal itching, and nasal congestion. The treatment benefit of the component symptom scores are also summarized in Table 2.

The treatment benefit of ciclesonide NA assessed in iTNSS was also shown in both doses and are summarized in Table 2.

Table 2. Efficacy results for TNSS in the ITT populations for Studies 622 and 634

	Study 622						Study 634					
	Placebo		Cic 80		Cic 160		Placebo		Cic 80		Cic 160	
	N	Score	N	Score	N	Score	N	Score	N	Score	N	Score
rTNSS												
Baseline	235	9.1	237	9.3	234	9.5	220	9.3	226	9.3	225	9.3
2-wk average	234	8.7	237	7.9	234	7.8	218	8.6	226	7.6	225	7.6
Diff form plb			0.9 [0.6,1.3]		1.1[0.7,1.5]				1.0[0.6,1.5]		1.0[0.6,1.5]	
[CI] p-value			<0.001		<0.001				<0.001		<0.001	
iTNSS												
Baseline	235	8.6	237	8.7	234	8.9	220	8.5	226	8.6	225	8.6
2-wk average	234	8.2	237	7.3	234	7.4	218	7.9	226	7.0	225	7.1
Diff form plb			0.9[0.5,1.3]		1.0[0.6,1.4]				0.9[0.5,1.3]		0.8[0.4,1.3]	
[CI] p-value			<0.001		<0.001				<0.001		<0.001	
rTNSS – sneezing												
Baseline	235	2.1	237	2.1	234	2.1	220	2.1	226	2.1	225	2.1
2-wk average	234	1.9	237	1.7	234	1.7	218	2.0	226	1.6	225	1.6
Diff form plb			0.3[0.2,0.4]		0.3[0.2,0.4]				0.3[0.2,0.4]		0.3[0.2,0.4]	
[CI] p-value			<0.001		<0.001				<0.001		<0.001	
rTNSS – running nose												
Baseline	235	2.4	237	2.4	234	2.4	220	2.4	226	2.4	225	2.4
2-wk average	234	2.3	237	2.1	234	2.0	218	2.2	226	1.9	225	2.0
Diff form plb			0.2[0.1,0.3]		0.3[0.1,0.4]				0.3[0.2,0.4]		0.3[0.1,0.4]	
[CI] p-value			<0.001		<0.001				<0.001		<0.001	
rTNSS – nasal itching												
Baseline	235	2.2	237	2.3	234	2.4	220	2.3	226	2.3	225	2.3
2-wk average	234	2.1	237	1.9	234	1.9	218	2.1	226	1.9	225	1.8
Diff form plb			0.2[0.1,0.3]		0.3[0.2,0.4]				0.2[0.1,0.3]		0.3[0.2,0.4]	
[CI] p-value			<0.001		<0.001				<0.001		<0.001	
rTNSS – nasal congestion												
Baseline	235	2.6	237	2.5	234	2.6	220	2.5	226	2.5	225	2.5
2-wk average	234	2.4	237	2.2	234	2.2	218	2.3	226	2.1	225	2.1
Diff form plb			0.2[0.2,0.3]		0.3[0.2,0.3]				0.2[0.1,0.3]		0.2[0.1,0.3]	
[CI] p-value			<0.001		<0.001				<0.001		<0.001	

CI – 95% 2-sided confidence interval

Ciclesonide NA also demonstrated greater symptom reductions in ocular symptoms assessed by both rTOSS and iTOSS (Table 3) and in rhinoconjunctivitis quality of life assessed by RQLQ (Table 4). The greater reductions were shown in both the protocol specified subset analyses and the ITT analyses, in both doses of ciclesonide NA, and in both studies. All analyses consistently indicated that ciclesonide 160 µg did not have greater benefit compared to ciclesonide 80 µg.

Table 3. Efficacy results for TOSS for Studies 622 and 634

	Study 622						Study 634					
	Placebo		Cic 80		Cic 160		Placebo		Cic 80		Cic 160	
	N	Score	N	Score	N	Score	N	Score	N	Score	N	Score
rTOSS in patients with baseline rTOSS≥5.0												
Baseline	148	7.0	164	6.9	160	7.0	165	7.0	159	7.1	161	7.0

2-wk average	147	6.5	164	5.8	160	5.9	164	6.1	159	5.7	161	5.8
Diff form plb			0.6[0.3,1.0]		0.6[0.3,1.0]				0.5[0.2,0.9]		0.34[-0.0,0.7]	
[CI] p-value			<0.001		<0.001				0.006		0.072	
rTOSS in ITT												
Baseline	235	5.7	237	5.8	234	6.0	220	6.2	226	6.2	225	6.2
2-wk average	234	5.5	237	5.0	234	5.2	218	5.7	226	5.3	225	5.3
Diff form plb			0.5[0.3,0.8]		0.5[0.2,0.8]				0.4[0.1,0.7]		0.3[-0.0,0.6]	
[CI] p-value			<0.001		<0.001				0.024		0.055	

CI – 95% 2-sided confidence interval

Table 4. Efficacy results for RQLQ for Studies 622 and 634

	Study 622						Study 634					
	Placebo		Cic 80		Cic 160		Placebo		Cic 80		Cic 160	
	N	Score	N	Score	N	Score	N	Score	N	Score	N	Score
RQLQ in patients with baseline RQLQ\geq3.0												
Baseline	183	4.4	187	4.5	183	4.5	147	4.4	162	4.4	148	4.2
End of trtmnt	180	4.0	186	3.4	181	3.4	145	3.5	162	3.0	148	2.9
Diff form plb			0.6[0.4,0.9]		0.6[0.4,0.9]				0.6[0.3,0.9]		0.6[0.3,0.9]	
[CI] p-value			<0.001		<0.001				0.006			
RQLQ in ITT												
Baseline	234	4.0	237	4.0	232	4.0	220	3.6	226	3.8	225	3.5
End of trtmnt	230	3.7	236	3.2	233	3.2	216	3.1	225	2.7	225	2.5
Diff form plb			0.6[0.4,0.8]		0.6[0.4,0.8]				0.5[0.3,0.8]		0.5[0.3,0.8]	
[CI] p-value			<0.001		<0.001				<0.001		<0.001	

CI – 95% 2-sided confidence interval

Study 622 was designed to evaluate the onset of action at 4, 6, 8, 10, and 12 hours post-dose on Day 1 and 6 and 12 hours post-dose on Day 2 for iTNSS. Onset of nasal improvement was observed for both doses of ciclesonide NA at 36 hours after the first dose. Both the 80 μ g and 160 μ g doses of ciclesonide NA showed statistically significant improvements compared to placebo at 36 hours. This statistically significant effect was observed again at 48 hours after the first dose and was maintained throughout the double-blind treatment period. The onset time was also confirmed in Study 634.

The sponsor reported various subgroup analyses, such as subgroups divided by age category: 12-18 years, 19 to <65 years, and \geq 65 years old, by race, by gender, as well as baseline scores of nasal and ocular symptoms in both studies. As the majority patients were in age group 19 to <65, the numbers of patients in the other age groups were under represented. Similarly, as the majority patients were white, other race groups were under represented. No special subgroup was identified.

In Study 622, significant center-by-treatment interaction was observed in the analysis of the primary endpoint rTNSS (p-value=0.022). By center analyses was therefore performed in both studies and presented in Figures 1 and 2. Centers 0005 and 0007 showed inconsistent efficacy performance compared to the other centers in Study 622.

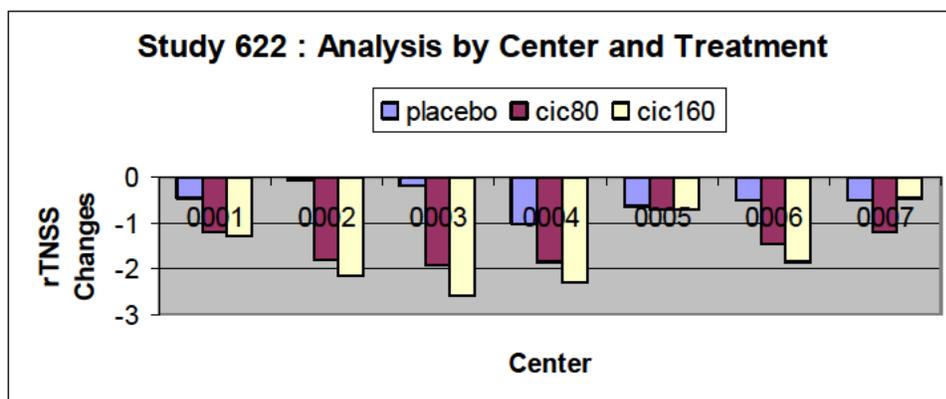


Figure 1. By center analysis for Study 622

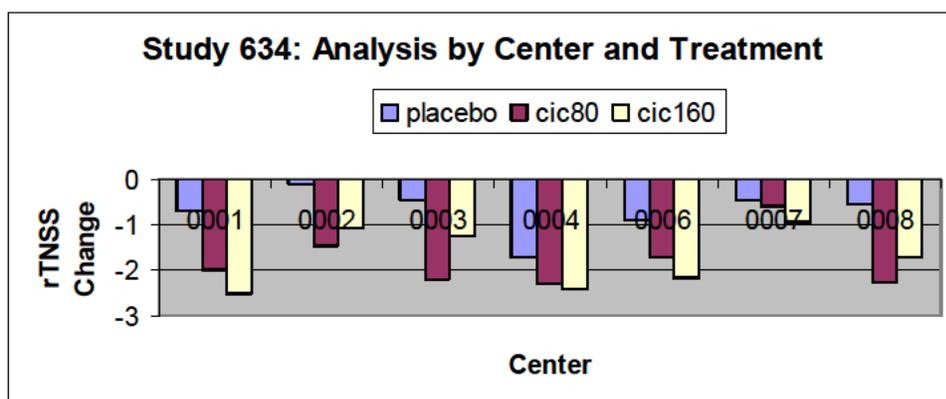


Figure 2. By center analysis for Study 634

3.2 PAR – Study 633

Study Design

The objective of Study 633 is to assess the safety and efficacy of ciclesonide NA in comparison to placebo in patients with PAR. The study design is similar to the SAR studies. Other than the difference in patient population, the notable differences in study design are summarized below:

- Randomization and sample size: the study plans to randomize 1100 patients to ciclesonide 160 µg, 80 µg, or placebo in a ratio of 5:3:3.
- Efficacy endpoints were evaluated over 6 weeks. The primary endpoint is the change from baseline in the averaged daily rTNSS over 6 weeks. The self-administered version of the RQLQ(S) was answered by the patients at the clinical site at Visits 3 (Day 0), Visit 6 (Week 6), and Visit 11 (Week 26).
- TOSS was not assessed
- Missing data handling approach is similar to Study 634. In addition, missing not at random (MNAR) sensitivity analyses for the primary endpoint was performed using the pattern-mixture model, selection model, or shared-parameter model.

Study results

Study 633 was conducted at 46 investigation sites in the United States during the duration from September 01, 2009 to May 18, 2010. One thousand one hundred and eleven (1111) patients were randomized and 1 was excluded in the ITT population. The number of patients in each treatment arm is summarized in Table 5. The rate of important protocol deviation was high, reaching about 30% (322 patients). During the NDA review, the sponsor discovered another 38 protocol violation for patients who previously enrolled other ciclesonide NA studies. Per protocol analyses as well as sensitivity analyses by removing the 38 patients yielded consistent efficacy results as obtained from the ITT analyses.

Table 5. Patient disposition for Study 633

	Placebo	Cic 80	Cic 160
Randomized	307	298	506
ITT	307	298	505
Per Protocol at 6weeks	203(66%)	218(73%)	367(73%)
Discontinued at 6 months	42(14%)	37(12%)	66(13%)
Adverse event	6	8	16
Protocol violation	4	2	8
Subj. withdrawal	12	13	15
Lost follow-up	4	8	9
Other	16	6	18

Study conduct

Over the 6-week double-blind treatment period, 83% patients took concomitant medications. There was no large imbalance among treatment groups in the concomitant medication use. Treatment compliance rate was about 90% during the first 6-week treatment. No large imbalance was observed. The sponsor reported that during audit, Site 0037 had compliance issue. Sensitivity analyses were conducted by removing this site from the ITT population, no large impact of this site on the efficacy results was found.

Regarding missing data, the sponsor reported the following:

Overall, the proportion of patients with missing rTNSS on at least one day during the 6-week double-blind treatment period was 26%: 22% had intermittent missing data and 4% were drop-outs. The proportions of patients with missing data, either intermittent or drop-outs, did not differ by treatment groups. However, the trends in the mean change from baseline in rTNSS values during the first 6-weeks of the double-blind treatment period differed by missing data patterns within treatment groups. In particular, patient drop-outs in the placebo group had mean changes from baseline in rTNSS that remained above zero while patient drop-outs in the active treatment groups had declining mean changes on days that rTNSS scores were available prior to the drop-out date.

The sponsor provided various sensitivity analyses to assess the impact of missing data. All reasonable sensitivity analyses yielded similar efficacy results.

Demographic information

All demographic and baseline information were comparable among treatments. The mean age was 37 years ranging from 12 to 78 years old. About 64% were female, and 83% were white. The mean baseline rTNSS score was 8.5 out 12 ranging from 3.1 to 12.

Efficacy

Multiple analyses including the ITT analyses as well as various sensitivity analyses to assess impact of missing data and per protocol violations showed that the two doses of ciclesonide NA provided greater reduction in nasal symptoms compared to placebo. The greater reduction in nasal symptoms was confirmed in the primary efficacy endpoint rTNSS and many secondary endpoints such as individual symptoms of rTNSS and iTNSS. The treatment differences vs. placebo were 0.7 and 0.5 for ciclesonide 80 µg and ciclesonide 160 µg, respectively for rTNSS. The ciclesonide 160 µg dose did not show extra benefit compared with ciclesonide 80 µg. Summary statistics and testing results for the ITT analyses are presented in Table 6.

Table 6. Efficacy results for TNSS in the ITT population for Study 633

	Placebo		Cic 80		Cic 160	
	N	Score	N	Score	N	Score
rTNSS						
Baseline	307	8.6	298	8.5	505	8.5
6-wk average	305	7.4	298	6.6	504	6.8
Diff form plb				0.7[0.4,1.0]		0.5[0.2,0.8]
[CI] p-value				<0.001		<0.001
iTNSS						
Baseline	307	7.7	298	7.7	505	7.6
6-wk average	305	6.6	298	6.0	504	6.1
Diff form plb				0.6[0.3,0.9]		0.4[0.1,0.7]
[CI] p-value				<0.001		0.006
rTNSS - sneezing						
Baseline	307	1.8	298	1.8	505	1.8
6-wk average	305	1.5	298	1.3	504	1.3
Diff form plb				0.2[0.1,0.3]		0.2[0.1,0.3]
[CI] p-value				<0.001		<0.001
rTNSS – runny nose						
Baseline	307	2.3	298	2.4	505	2.2
6-wk average	305	2.0	298	1.8	504	1.8
Diff form plb				0.2[0.1,0.3]		0.2[0.1,0.3]
[CI] p-value				<0.001		0.002
rTNSS – nasal itching						
Baseline	307	2.1	298	2.1	505	2.1
6-wk average	305	1.7	298	1.6	504	1.6
Diff form plb				0.2[0.1,0.2]		0.1[0.0, 0.2]
[CI] p-value				0.003		0.015
rTNSS – nasal congestion						
Baseline	307	2.4	298	2.5	505	2.4
6-wk average	305	2.2	298	2.0	505	2.1
Diff form plb				0.2[0.1,0.3]		0.1[0.1,0.2]
[CI] p-value				<0.001		0.001

CI – 95% 2-sided confidence interval

A greater improvement in RQLQ in the two doses of ciclesonide NA compared to placebo was also observed in both the sponsor specified subset analysis and analysis using in the ITT population. The treatment differences between ciclesonide NA and placebo were statistically significant, but smaller than 0.5 in the ITT analyses, the defined clinical importance difference for RQLQ.

Table 7. Efficacy analyses for RQLQ for Study 633

	Placebo		Cic 80		Cic 160	
	N	Score	N	Score	N	Score
RQLQ in patients with baseline RQLQ\geq3.0						
Baseline	160	4.1	152	4.2	269	4.1
End of 6-wk	149	3.1	142	2.6	261	2.7
trtment						
Diff form plb			0.6[0.3,0.8]		0.4[0.1,0.6]	
[CI] p-value			<0.001		0.004	
RQLQ in ITT						
Baseline	305	3.2	298	3.1	505	3.1
End of 6-wk	298	2.4	280	2.1	484	2.1
trtment						
Diff form plb			0.3[0.1,0.5]		0.3[0.1,0.4]	
[CI] p-value			0.002		0.002	

CI – 95% 2-sided confidence interval

The sponsor reported various subgroup analyses, such as subgroups divided by age category: 12-18 years, 19 to <65 years, and \geq 65 years old, by race, by gender, as well as baseline scores of nasal symptoms. As the majority patients were in age group 19 to <65, the numbers of patients in the other age groups were under represented. Since over 83% patients were white, the other race groups were under represented.

By-gender analyses revealed inconsistent treatment benefit between male and female. Male did not appear to benefit from ciclesonide 80 μ g. The treatment difference between ciclesonide 80 μ g vs. placebo was 0.18, p-value=0.566 for male, while the treatment difference was 0.90, p-value<0.001 for female. Their benefit from ciclesonide 160 μ g was numerically larger (treatment difference vs. placebo was 0.50, p-value=0.074) than that from ciclesonide 80 μ g for male. As the 95% confidence intervals are crossing 0 and wide for both doses, there is not sufficient information to make statistical inference. These analyses raise questions on whether male could have meaningful benefit from the ciclesonide 80 μ g and whether they could have greater benefit from the higher dose of ciclesonide NA. The by-gender subgroup analyses are displayed in Table 8. In order to answer these questions, more information is needed. Dr. Bueconsejo, the secondary statistical reviewer, believes that these questions can be addressed by information obtained from the SAR indication as well as another ciclesonide formulation for allergic rhinitis. This reviewer does not have sufficient clinical and chemistry knowledge to make such extrapolation. Therefore, the statistical evaluation is focused on the information generated by the PAR patients and the formulation under evaluation.

Table 8. By-gender subgroup analyses for Study 633

	Placebo		Cic 80		Cic 160	
	N	Score	N	Score	N	Score
Male						
Baseline	97	8.6	102	8.3	195	8.5
End of 6-wk	96	7.3	102	6.9	195	6.7
trtment						
Diff form plb			0.2[-0.4,0.8]		0.5[-0.1,1.0]	
[CI] p-value			0.566		0.074	
Female						
Baseline	210	8.6	196	8.7	310	8.5
End of trtment	209	7.4	196	6.4	309	6.8
Diff form plb			0.9[0.5,1.4]		0.5[0.1,0.9]	
[CI] p-value			<0.001		0.009	

CI – 95% 2-sided confidence interval

3. LABEL REVIEW

The label review is focused on Section 14 – Clinical Studies of the proposed label. Reviewer’s comments are summarized as follows:

- Regarding Table 2 in the label, the ITT analyses should be reported for the TOSS and RQLQ analyses, rather than the analyses using subsets of severe patients.
- The clinical meaningful difference was not achieved for RQLQ in PAR patients in the ITT analyses.
- P-values in Table 2 should be either removed or reported using unadjusted p-values. Footnote c for Table 2 should be removed. P-values add no additional useful information when the confidence intervals are presented. The presentation of adjusted p-values not only is unnecessary, but adds confusions to practitioners. The calculation of the adjust p-values is based on the thinking of a school of statisticians who determine drug efficacy with one dose alone in one study. Such statistical practice is against the logic in drug efficacy evaluation because the regulatory decision has seldom been made on one dose in one study when information of multiple studies on multiple doses is available. The efficacy of the ciclesonide NA is established based on the efficacy performance of both doses of ciclesonide NA and confirmed in two studies. It can be calculated that the error rate of claiming efficacy for an ineffective drug is tightly controlled using this approach. Once the drug is determined efficacious, the optimal dose should be identified by factors such as effect sizes of primary and secondary endpoints as well as safety profiles. The adjust p-values play no role in either the determination of efficacy or identification of the optimal doses.
- The onset of action for nasal symptoms in SAR patients was determined at 36 hours after the first dose by Study 622 and confirmed by Study 634.

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/s/

QIAN H LI

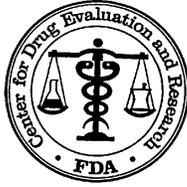
12/21/2011

This review was submitted to DARRTS on 12-16-2011.

JOAN K BUENCONSEJO

12/21/2011

I concur with Dr. Li's principal conclusion that ciclesonide nasal aerosol 74 mcg per day is efficacious in treating patients with SAR and PAR. However, Dr. Li and I have different views in interpreting the findings from subgroup analysis, as well as on multiplicity. Please refer to my secondary review.



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 (SECONDARY REVIEW)

NDA/BLA Serial Number: NDA 202129/serial number 0000

Drug Name: Ciclesonide Nasal Aerosol

Indication(s): Treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.

Applicant: Nycomed Inc. and Sunovion Pharmaceutical Inc.

Date(s): Received: 03-21-2010
PDUFA Due Date: 01-21-2012

Review Priority: Standard

Document Reviewed: primary review by Qian Li, PhD

Biometrics Division: Division of Biometrics II

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Keywords: NDA review, Clinical Studies, Multiplicity, Subgroup Analysis

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1 INTRODUCTION

This is a secondary statistical review considering the findings and conclusions of the primary statistical reviewer, Dr. Qian Li. I concur with Dr. Li's principal conclusion that ciclesonide nasal aerosol 74 mcg per day is efficacious in treating patients with SAR and PAR. However, Dr. Li and I have different views in interpreting the findings from subgroup analysis, as well as on multiplicity.

Dr. Li did not fully address my comments in her original draft review (second draft review dated December 13, 2011). Her views on multiplicity, and the language she used to address this (see Label Review) remains concerning and in my opinion not totally in line with the Office of Biostatistics's view. She also continues to overstate the findings from subgroup analysis. However, after I showed her my secondary review, she subsequently edited her draft version to refute my comments (third draft review dated December 15, 2011). Because she only wanted to submit the third draft version in DARRTS, I believe it is necessary that I include her second draft review (Section 2) and my secondary review (Section 3) in this document.

2 PRIMARY STATISTICAL REVIEW BY DR. QIAN LI

2.1 SUMMARY

2.1.1 Background

The sponsors have proposed ciclesonide nasal aerosol (ciclesonide NA) delivered via metered-dose inhaler (MDI) for the treatment of symptoms associated with seasonal and perennial allergic rhinitis (SAR and PAR) in adults and adolescents 12 years of age and older. Two-dose levels were evaluated in the phase 3 clinical development program. The two doses are referred to as 80 µg and 160 µg in this review, approximating ex-actuator 74 µg and 141 µg of ciclesonide, respectively. Three phase 3 studies were conducted to assess the efficacy and safety of ciclesonide NA. Studies 060-622 and 060-634 (referred to as 622 and 634, respectively) are SAR studies of 2-week duration. Study 060-633 (referred to as 633) is a PAR study of 26-week duration (the efficacy was evaluated at Week 6). This review covers the three studies.

Ciclesonide inhalation aerosol delivered also via MDI was approved in January 2008 for the maintenance treatment of asthma by trade name Alvesco[®]. In addition, ciclesonide nasal spray in an aqueous suspension delivered via a pump spray was also approved in 2007 for the treatment of SAR and PAR by trade name Omnaris[®].

2.1.2 Study Results

The three phase 3 studies are randomized, double-blind, parallel group, multicenter, and placebo-controlled studies. All studies consist of three treatment groups: placebo, ciclesonide 80 µg, and ciclesonide 160 µg. The endpoints include reflective and instantaneous total nasal symptom scores (TNSS), reflective and instantaneous total ocular symptom scores (TOSS), and rhinoconjunctivitis quality of life questionnaire (RQLQ). The SAR studies (Studies 622 and 634) showed statistically significantly larger symptom reductions in all endpoints in both doses of ciclesonide NA compared

to placebo. The PAR study (Study 633) also showed statistically significantly larger symptom reductions in all endpoints in both doses of ciclesonide NA compared to placebo. However, the treatment difference in RQLQ did not achieve clinical important difference defined as 0.5. Ciclesonide 160 µg did not show better benefit compared to ciclesonide 80 µg in the ITT population for both SAR and PAR indications. However, subgroup analyses in Study 633 in gender revealed that the treatment benefit was not consistent between males and females for PAR symptoms. Male did not appear to benefit from ciclesonide 80 µg. Their benefit from ciclesonide 160 µg was numerically larger than ciclesonide 80 µg. This raises a question on whether male could benefit better from the higher dose of ciclesonide NA in treating PAR.

2.1.3 Conclusions and Recommendations

Based on the evaluation of the three studies, ciclesonide NA 80 µg is efficacious in treating patients with SAR and PAR. More information should be collected to determine if male PAR patients can benefit better from ciclesonide 160 µg.

2.2 Evaluation Individual Studies

2.2.1 SAR – Studies 622 and 634

Both Studies 622 and 634 are randomized, multicenter, double-blind, placebo controlled, and parallel-group phase 3 studies to evaluate the safety and efficacy of ciclesonide NA 80 µg and 160 µg compared to placebo. The studies started the screening period at Visit 1 followed by a single-blind placebo run-in period at Visit 2 for 7 days. Patients aged 12 years and older with a history of SAR for at least 2 years were recruited to the single-blind placebo run-in period. Patients who had minimum cumulative reflective total nasal symptom score (rTNSS) of 47 out of a possible 84 over any 3 of the last 4 days of the run-in period or who had a minimum cumulative reflective scores for runny nose or nasal congestion of at least 10 out of a possible 21 during any 3 of the last 4 days run-in period were randomized into the three treatment groups in 1:1:1 ratio. Patients started treatment period at Visit 3 (Day 1) for a period of 14 days. Treatment was self-administrated in the morning. Patients visited the clinics at Visit 4 (7 days after the double-blind treatment) and Visit 5 (the end of the double-blind treatment). In order to ensure allergen exposure in SAR studies, mountain cedar pollen counts in the clinical site area had to be elevated for at least 3 consecutive days at levels ≥ 50 grains/m³ prior to the start of the single-blind run-in period. Each site was required to randomize all patients within a consecutive 14-day period. Both studies planned to recruit 660 patients.

Study Endpoints

The efficacy endpoint for SAR nasal symptoms is TNSS, a sum of 4 symptom scores: runny nose, itchy nose, sneezing, and nasal congestion. The endpoint for SAR ocular symptoms is TOSS, a sum of 3 symptoms: itching, tearing, and redness. Each symptom was graded based on 4 scales: 0=absent; 1=mild; 2=moderate; 3=severe. All symptoms were evaluated daily reflectively (rTNSS or rTOSS) and instantaneously (iTSS or iTTOSS) in the morning (AM) and 12-hour later in the afternoon (PM).

Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities (RQLQ(S)) has 28 questions in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal

symptoms, eye symptoms, and emotional). Patients were asked to recall their experiences during the previous week and to give their responses on a 7-point scale (0 = Not Troubled to 6 = Extremely Troubled). The RQLQ(S) was self-administered by patients prior to randomization (Visit 3) and at the end of study (Visit 5).

Onset of action for both nasal and ocular improvement was defined as the first time point at which ciclesonide NA showed significant improvement over placebo with one-sided p-value of ≤ 0.025 using iTNSS or iTOSS and the significant improvement was maintained for some period of time. Both iTNSS and iTOSS were assessed at 4, 6, 8, 10, and 12 hours post-dose on Day 1 and 6 and 12 hours post-dose on Day 2 in Study 622. In Study 634, the instantaneous time points were collected at the regular AM and PM time points. Onset of action for ocular symptom is not assessed in this review as it was determined that the information will not be presented in label in the mid-cycle review meeting.

The primary efficacy endpoint was the average, over the two-week treatment period, of change from baseline in the mean AM and PM rTNSS daily scores. The baseline score was defined as the average scores collected over the 6-day placebo run-in period.

The key secondary efficacy endpoints included:

1. Change from baseline in average AM and PM iTNSS over the two-week treatment period
2. Change from baseline in average AM and PM rTOSS over the two-week treatment period in a subset of patients whose baseline TOSS was no less than 5.0
3. Change from baseline in Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities (RQLQ(S)) in impaired patients (baseline RQLQ(S) score ≥ 3.0)
4. Onset of nasal improvement

Note, the protocol specified subgroup analyses for TOSS and RQLQ are presented along with the ITT analyses in this review, as efficacy claim is not made in a subgroup of patients for this NDA.

Statistical Methods

Sample Size Determination

Assuming that the standard deviation for the average change from baseline over two weeks in the average of AM and PM rTNSS was 2.1, 200 patients per group expected to provide at least 85% power to detect a difference between treatment groups of 0.7 in the change from baseline in rTNSS with a two-sided alpha level of 0.025.

Analysis Population

The ITT analysis population consisted of all randomized patients who received at least one dose of double-blind study drug.

The PP analysis set included all patients in the ITT analysis set without major protocol violations as well as partial data prior to any major protocol violation.

Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint was analyzed using the Intent-To-Treat analysis set. Treatment groups were compared using ANCOVA with factors of baseline rTNSS, center, and treatment. The protocol specifies that comparisons of each active treatment group with placebo were performed at a Bonferroni-corrected significance level of 0.025. This review does not use the adjusted p-values as the efficacy is established by both doses of ciclesonide NA. That is, if both doses show activity of efficacy which are confirmed in multiple studies, the efficacy of the drug is established. Once the drug is determined efficacious, the optimal dose should be identified by factors such as effect sizes of various endpoints and safety profile. Therefore, there is no need to adjust p-values and the unadjusted p-values are presented in this review.

All other secondary efficacy endpoints listed above were analyzed using the same ANCOVA model as for the primary efficacy endpoint.

Missing data handling

If any of the component nasal symptom scores were missing for a particular time point, the TNSS score for that time point was also considered missing. If either AM or PM TNSS was missing, the average of AM and PM TNSS was set to the non-missing (AM or PM) TNSS. TOSS was handled similarly.

The missing data handling approaches for the two studies were somewhat different:

For Study 622: If a single question from the RQLQ(S) is missing, the domain score was still calculated as the average of the non-missing questions within that domain. If more than one question was missing, the domain score was set to be missing. The overall RQLQ(S) score was calculated as the average of the domain scores. If an entire domain score was missing, the overall RQLQ(S) was set to be missing.

For Study 634: The mean RQLQ(S) score for each domain at baseline and post treatment visits was based on non-missing responses. If 50% or more of the responses were absent in a domain, the result for that domain was set to missing. The overall RQLQ(S) score was calculated as the average of the domain scores. If an entire domain score was missing, the overall RQLQ(S) score was set to be missing.

Study results

All the studies were conducted in the United States. Study 622 was conducted at 7 sites in the period of November 15, 2008 to February 17, 2009 and randomized 707 patients. Study 634 was conducted at 7 sites in the period of December 1, 2009 to February 16, 2010 and randomized 671 patients. All of the randomized patients were in ITT population. The number of patients in each treatment arm is summarized in Table 1.

In Study 060-622, 39 patients were identified to have important protocol deviations and distributed in the three treatment groups approximately evenly (see Table 1). Among them, 7 patients were randomized more than once at different study sites, representing 15 patient identifications, which are identified as the following:

0006-S045, 0001-S022,
0001-S047, 0002-S004,

0001-S054, 0006-S099,
 0001-S058, 0004-S005, 0006-S067,
 0001-S124, 0006-S024,
 0003-S089, 0004-S105,
 0004-S055, 0001-S142.

In addition, 2 patients, 0002-S074 and 0004-S066, were identified as protocol violation as they previously enrolled in another ciclesonide NA study. These 2 patients were not excluded in the per protocol analyses.

In Study 634, 41 patients were identified to have important protocol violations. More of the violations were in the placebo arm than that in the ciclesonide arms (see Table 1). In addition, the sponsor reported 14 patients who previously enrolled in other ciclesonide NA studies, some of them in Study 622. Among the 14 patients, two (0001-S043, 0003-S027) were actually the same patient who enrolled twice. The 14 patients were not excluded in the per protocol population. Sensitivity analysis was performed by this reviewer by removing these 14 patients. The results are the same as the ITT analysis.

Table 1. Patient disposition for Studies 622 and 634

	Study 622			Study 634		
	Placebo	Cic80	Cic160	Placebo	Cic80	Cic160
Randomized	235	237	235	220	226	225
ITT	235	237	235	220	226	225
Per protocol	221(94%)	224(95%)	223(95%)	201(91%)	213(94%)	216(96%)
Discontinued	21(9%)	11(5%)	10(5%)	13(6%)	8(4%)	3(1%)
Adverse event	4	2	1	3	4	2
Protocol violation	2	2	4			
Subj. withdrawal	6	2	0	5	2	0
Lost follow-up	1	0	0	3	2	0
Other	8	5	5	2	0	1

Study conduct

For Study 622, the mean mountain cedar pollen counts at each site were elevated for at least 3 consecutive days at levels ≥ 50 grains per cubic meter, during placebo run-in period. The pollen counts remained elevated during the study. Minimal rainfall amounts were reported at most sites during the study. Elevated pollen counts were also reported in Study 634 during the study, except Sites 007 and 008. The two sites reported lower pollen counts on several days during the first week of double-blind treatment (median raw pollen counts ranged from 44-891 grains/cubic meter). The lower pollen counts at Site #8 during were associated with a large amount of rainfall.

About 80% patients used concomitant medication in both studies. The rates were reasonably balanced among the three treatment groups. Treatment compliance rates were close to 99% in both studies.

The rates of missing data were low in both studies.

Demographic information

All demographic and baseline information were comparable among treatments in the two studies. For Study 622, the mean age was 42 years ranging from 13 to 72 years. About 66% were female, and 93% were white. The mean baseline rTNSS score was 9.3 out of 12 ranging from 5.3 to 12. For Study 634, the mean age was 40 years ranging from 12 to 81 years. About 60% were female, and 88% were white. The mean baseline rTNSS score was 9.3 out of 12 ranging from 5.0 to 12.

Efficacy

Multiple analyses on various endpoints in both studies consistently showed that both doses of ciclesonide NA provided greater reduction in the symptoms associated with SAR than placebo after 2 weeks of treatments. Ciclesonide NA 160 µg did not show better efficacy than ciclesonide NA 80 µg.

For the primary efficacy endpoint rTNSS, the reduction was about 1.0 more in the two doses of ciclesonide NA than that in placebo in both studies in both ITT and per protocol populations. The treatment difference was highly statistically significant. Summary statistics and analysis results in the ITT population are displayed in Table 2. During the review, the sponsor identified additional patients who were considered for protocol violation because of previous enrollment of other ciclesonide NA studies. Studies 622 and 634 identified 2 and 12 such patients, respectively. Sensitivity analyses were conducted by removing these patients from the ITT populations. The results of the sensitivity analyses are the same as the ITT analyses.

The treatment benefit of ciclesonide NA demonstrated in rTNSS were consistently exhibited in the individual components of rTNSS which include sneezing, runny nose, nasal itching, and nasal congestion. The treatment benefit of the component symptom scores are also summarized in Table 2.

The treatment benefit of ciclesonide NA assessed in iTNSS was also shown in both doses and are summarized in Table 2.

Table 2. Efficacy results for TNSS in the ITT populations for Studies 622 and 634

	Study 622						Study 634					
	Placebo		Cic 80		Cic 160		Placebo		Cic 80		Cic 160	
	N	Score	N	Score	N	Score	N	Score	N	Score	N	Score
rTNSS												
Baseline	235	9.1	237	9.3	234	9.5	220	9.3	226	9.3	225	9.3
2-wk average	234	8.7	237	7.9	234	7.8	218	8.6	226	7.6	225	7.6
Diff form plb			0.9 [0.6,1.3]		1.1[0.7,1.5]				1.0[0.6,1.5]		1.0[0.6,1.5]	
[CI] p-value			<0.001		<0.001				<0.001		<0.001	
iTNSS												
Baseline	235	8.6	237	8.7	234	8.9	220	8.5	226	8.6	225	8.6
2-wk average	234	8.2	237	7.3	234	7.4	218	7.9	226	7.0	225	7.1
Diff form plb			0.9[0.5,1.3]		1.0[0.6,1.4]				0.9[0.5,1.3]		0.8[0.4,1.3]	
[CI] p-value			<0.001		<0.001				<0.001		<0.001	
rTNSS – sneezing												
Baseline	235	2.1	237	2.1	234	2.1	220	2.1	226	2.1	225	2.1
2-wk average	234	1.9	237	1.7	234	1.7	218	2.0	226	1.6	225	1.6
Diff form plb			0.3[0.2,0.4]		0.3[0.2,0.4]				0.3[0.2,0.4]		0.3[0.2,0.4]	
[CI] p-value			<0.001		<0.001				<0.001		<0.001	
rTNSS – running nose												
Baseline	235	2.4	237	2.4	234	2.4	220	2.4	226	2.4	225	2.4
2-wk average	234	2.3	237	2.1	234	2.0	218	2.2	226	1.9	225	2.0
Diff form plb			0.2[0.1,0.3]		0.3[0.1,0.4]				0.3[0.2,0.4]		0.3[0.1,0.4]	
[CI] p-value			<0.001		<0.001				<0.001		<0.001	
rTNSS – nasal itching												
Baseline	235	2.2	237	2.3	234	2.4	220	2.3	226	2.3	225	2.3
2-wk average	234	2.1	237	1.9	234	1.9	218	2.1	226	1.9	225	1.8
Diff form plb			0.2[0.1,0.3]		0.3[0.2,0.4]				0.2[0.1,0.3]		0.3[0.2,0.4]	
[CI] p-value			<0.001		<0.001				<0.001		<0.001	
rTNSS – nasal congestion												
Baseline	235	2.6	237	2.5	234	2.6	220	2.5	226	2.5	225	2.5
2-wk average	234	2.4	237	2.2	234	2.2	218	2.3	226	2.1	225	2.1
Diff form plb			0.2[0.2,0.3]		0.3[0.2,0.3]				0.2[0.1,0.3]		0.2[0.1,0.3]	
[CI] p-value			<0.001		<0.001				<0.001		<0.001	

CI – 95% 2-sided confidence interval

Ciclesonide NA also demonstrated greater symptom reductions in ocular symptoms assessed by both rTOSS and iTOSS (Table 3) and in rhinoconjunctivitis quality of life assessed by RQLQ (Table 4). The greater reductions were shown in both the protocol specified subset analyses and the ITT analyses, in both doses of ciclesonide NA, and in both studies. All analyses consistently indicated that ciclesonide 160 µg did not have greater benefit compared to ciclesonide 80 µg.

Table 3. Efficacy results for TOSS for Studies 622 and 634

	Study 622						Study 634					
	Placebo		Cic 80		Cic 160		Placebo		Cic 80		Cic 160	
	N	Score	N	Score	N	Score	N	Score	N	Score	N	Score
rTOSS in patients with baseline rTOSS \geq 5.0												
Baseline	148	7.0	164	6.9	160	7.0	165	7.0	159	7.1	161	7.0
2-wk average	147	6.5	164	5.8	160	5.9	164	6.1	159	5.7	161	5.8
Diff form plb			0.6[0.3,1.0]		0.6[0.3,1.0]				0.5[0.2,0.9]		0.34[-0.0,0.7]	
[CI] p-value			<0.001		<0.001				0.006		0.072	
rTOSS in ITT												
Baseline	235	5.7	237	5.8	234	6.0	220	6.2	226	6.2	225	6.2
2-wk average	234	5.5	237	5.0	234	5.2	218	5.7	226	5.3	225	5.3
Diff form plb			0.5[0.3,0.8]		0.5[0.2,0.8]				0.4[0.1,0.7]		0.3[-0.0,0.6]	
[CI] p-value			<0.001		<0.001				0.024		0.055	

CI – 95% 2-sided confidence interval

Table 4. Efficacy results for RQLQ for Studies 622 and 634

	Study 622						Study 634					
	Placebo		Cic 80		Cic 160		Placebo		Cic 80		Cic 160	
	N	Score	N	Score	N	Score	N	Score	N	Score	N	Score
RQLQ in patients with baseline RQLQ \geq 3.0												
Baseline	183	4.4	187	4.5	183	4.5	147	4.4	162	4.4	148	4.2
End of	180	4.0	186	3.4	181	3.4	145	3.5	162	3.0	148	2.9
Diff form plb			0.6[0.4,0.9]		0.6[0.4,0.9]				0.6[0.3,0.9]		0.6[0.3,0.9]	
[CI] p-value			<0.001		<0.001				0.006			
RQLQ in ITT												
Baseline	234	4.0	237	4.0	232	4.0	220	3.6	226	3.8	225	3.5
End of	230	3.7	236	3.2	233	3.2	216	3.1	225	2.7	225	2.5
Diff form plb			0.6[0.4,0.8]		0.6[0.4,0.8]				0.5[0.3,0.8]		0.5[0.3,0.8]	
[CI] p-value			<0.001		<0.001				<0.001		<0.001	

CI – 95% 2-sided confidence interval

Study 622 was designed to evaluate the onset of action at 4, 6, 8, 10, and 12 hours post-dose on Day 1 and 6 and 12 hours post-dose on Day 2 for iTNSS. Onset of nasal improvement was observed for both doses of ciclesonide NA at 36 hours after the first dose. Both the 80 μ g and 160 μ g doses of ciclesonide NA showed statistically significant improvements compared to placebo at 36 hours. This statistically significant effect was observed again at 48 hours after the first dose and was maintained throughout the double-blind treatment period. The onset time was also confirmed in Study 634.

The sponsor reported various subgroup analyses, such as subgroups divided by age category: 12-18 years, 19 to <65 years, and \geq 65 years old, by race, by gender, as well as baseline scores of nasal and ocular symptoms in both studies. As the majority patients were in age group 19 to <65, the numbers of patients in the other age groups were under represented. Similarly, as the majority patients were white, other race groups were under represented. No special subgroup was identified.

In Study 622, significant center-by-treatment interaction was observed in the analysis of the primary endpoint rTNSS (p-value=0.022). By center analyses was therefore performed in both studies and presented in Figures 1 and 2. Centers 0005 and 0007 showed inconsistent efficacy performance compared to the other centers in Study 622.

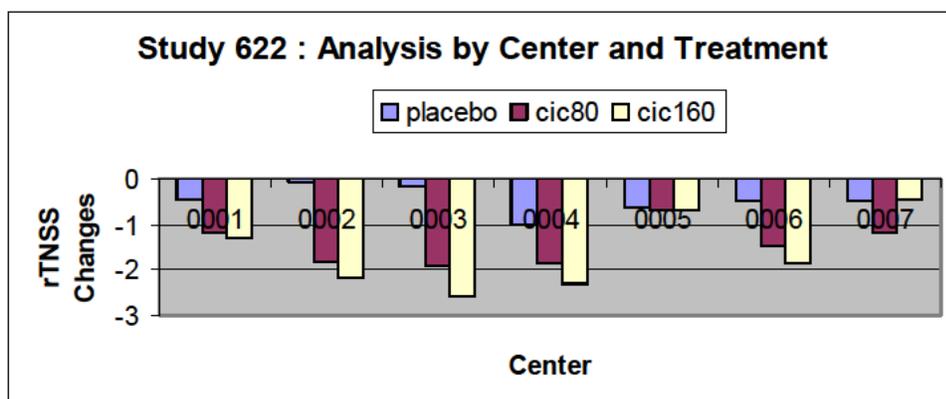


Figure1. By center analysis for Study 622

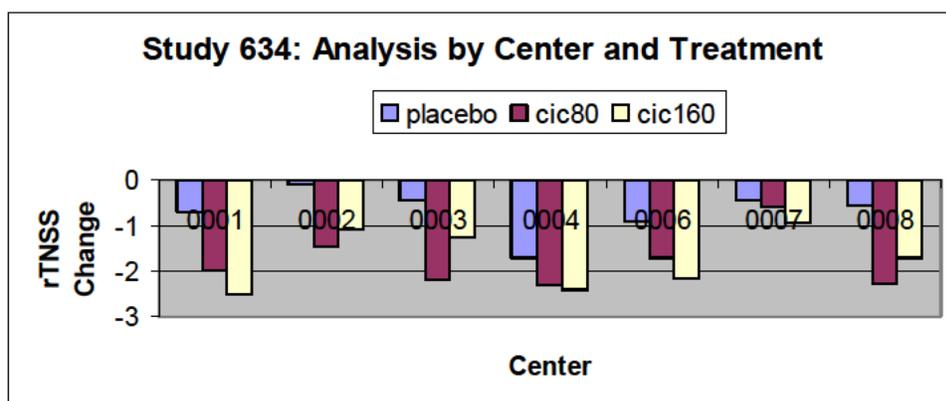


Figure 2. By center analysis for Study 634

2.2.2 PAR – Study 633

Study Design

The objective of Study 633 is to assess the safety and efficacy of ciclesonide NA in comparison to placebo in patients with PAR. The study design is similar to the SAR studies. Other than the difference in patient population, the notable differences in study design are summarized below:

- Randomization and sample size: the study plans to randomize 1100 patients to ciclesonide 160 µg, 80 µg, or placebo in a ratio of 5:3:3.
- Efficacy endpoints were evaluated over 6 weeks. The primary endpoint is the change from baseline in the averaged daily rTNSS over 6 weeks. The self-administered version of the RQLQ(S) was answered by the patients at the clinical site at Visits 3 (Day 0), Visit 6 (Week 6), and Visit 11 (Week 26).
- TOSS was not assessed
- Missing data handling approach is similar to Study 634. In addition, missing not at random (MNAR) sensitivity analyses for the primary endpoint was performed using the pattern-mixture model, selection model, or shared-parameter model.

Study results

Study 633 was conducted at 46 investigation sites in the United States during the duration from September 01, 2009 to May 18, 2010. One thousand one hundred and eleven (1111) patients were randomized and 1110 were included in the ITT population. The number of patients in each treatment arm is summarized in Table 5. The rate of important protocol deviation was high, reaching about 30% (322 patients). During the NDA review, the sponsor discovered another 38 protocol violation who previously enrolled other ciclesonide NA studies. Per protocol analyses as well as sensitivity analyses by removing the 38 patients yielded consistent efficacy results as obtained from the ITT analyses.

Table 5. Patient disposition for Study 633

	Placebo	Cic 80	Cic 160
Randomized	307	298	506
ITT	307	298	505
Per Protocol at 6weeks	203(66%)	218(73%)	367(73%)
Discontinued at 6 months	42(14%)	37(12%)	66(13%)
Adverse event	6	8	16
Protocol violation	4	2	8
Subj. withdrawal	12	13	15
Lost follow-up	4	8	9
Other	16	6	18

Study conduct

Over the 6-week double-blind treatment period, 83% patients took concomitant medications. There was no large imbalance among treatment groups in the concomitant medication use. Treatment compliance rate was about 90% during the first 6-week treatment. No large imbalance was observed. The sponsor reported that during audit, Site 0037 had compliance issue. Sensitivity analyses were conducted by removing this site from the ITT population, no large impact of this site on the efficacy results was found.

Regarding missing data, the sponsor reported the following:

Overall, the proportion of patients with missing rTNSS on at least one day during the 6-week double-blind treatment period was 26%: 22% had intermittent missing data and 4% were drop-outs. The proportions of patients with missing data, either intermittent or drop-outs, did not differ by treatment groups. However, the trends in the mean change from baseline in rTNSS values during the first 6-weeks of the double-blind treatment period differed by missing data patterns within treatment groups. In particular, patient drop-outs in the placebo group had mean changes from baseline in rTNSS that remained above zero while patient drop-outs in the active treatment groups had declining mean changes on days that rTNSS scores were available prior to the drop-out date.

The sponsor provided various sensitivity analyses to assess the impact of missing data. All reasonable sensitivity analyses yielded similar efficacy results.

Demographic information

All demographic and baseline information were comparable among treatments. The mean age was 37 years ranging from 12 to 78 years old. About 64% were female, and 83% were white. The mean baseline rTNSS score was 8.5 out of 12 ranging from 3.1 to 12.

Efficacy

Multiple analyses including the ITT analyses as well as various sensitivity analyses to assess impact of missing data and per protocol violations showed that the two doses of ciclesonide NA provided greater reduction in nasal symptoms compared to placebo. The greater reduction in nasal symptoms was confirmed in the primary efficacy endpoint rTNSS and many secondary endpoints such as individual symptoms of rTNSS and iTNSS. The treatment differences vs. placebo were 0.7 and 0.5 for ciclesonide 80 µg and ciclesonide 160 µg, respectively for rTNSS. The ciclesonide 160 µg dose did not show extra benefit compared with ciclesonide 80 µg. Summary statistics and testing results for the ITT analyses are presented in Table 6.

Table 6. Efficacy results for TNSS in the ITT population for Study 633

	Placebo		Cic 80		Cic 160	
	N	Score	N	Score	N	Score
rTNSS						
Baseline	307	8.6	298	8.5	505	8.5
6-wk average	305	7.4	298	6.6	504	6.8
Diff form plb			0.7[0.4,1.0]		0.5[0.2,0.8]	
[CI] p-value			<0.001		<0.001	
iTNSS						
Baseline	307	7.7	298	7.7	505	7.6
6-wk average	305	6.6	298	6.0	504	6.1
Diff form plb			0.6[0.3,0.9]		0.4[0.1,0.7]	
[CI] p-value			<0.001		0.006	
rTNSS - sneezing						
Baseline	307	1.8	298	1.8	505	1.8
6-wk average	305	1.5	298	1.3	504	1.3
Diff form plb			0.2[0.1,0.3]		0.2[0.1,0.3]	
[CI] p-value			<0.001		<0.001	
rTNSS – runny nose						
Baseline	307	2.3	298	2.4	505	2.2
6-wk average	305	2.0	298	1.8	504	1.8
Diff form plb			0.2[0.1,0.3]		0.2[0.1,0.3]	
[CI] p-value			<0.001		0.002	
rTNSS – nasal itching						
Baseline	307	2.1	298	2.1	505	2.1
6-wk average	305	1.7	298	1.6	504	1.6
Diff form plb			0.2[0.1,0.2]		0.1[0.0, 0.2]	
[CI] p-value			0.003		0.015	
rTNSS – nasal congestion						
Baseline	307	2.4	298	2.5	505	2.4
6-wk average	305	2.2	298	2.0	505	2.1
Diff form plb			0.2[0.1,0.3]		0.1[0.1,0.2]	
[CI] p-value			<0.001		0.001	

CI – 95% 2-sided confidence interval

A greater improvement in RQLQ in the two doses of ciclesonide NA compared to placebo was also observed in both the sponsor specified subset analysis and analysis using in all ITT population. The

treatment differences between ciclesonide NA and placebo were statistically significant, but smaller than 0.5 in the ITT analyses, the defined clinical importance difference for RQLQ.

Table 7. Efficacy analyses for RQLQ for Study 633

	Placebo		Cic 80		Cic 160	
	N	Score	N	Score	N	Score
RQLQ in patients with baseline RQLQ \geq 3.0						
Baseline	160	4.1	152	4.2	269	4.1
End of 6-wk	149	3.1	142	2.6	261	2.7
trtment						
Diff form plb			0.6[0.3,0.8]		0.4[0.1,0.6]	
[CI] p-value			<0.001		0.004	
RQLQ in ITT						
Baseline	305	3.2	298	3.1	505	3.1
End of	298	2.4	280	2.1	484	2.1
trtment						
Diff form plb			0.3[0.1,0.5]		0.3[0.1,0.4]	
[CI] p-value			0.002		0.002	

CI – 95% 2-sided confidence interval

The sponsor reported various subgroup analyses, such as subgroups divided by age category: 12-18 years, 19 to <65 years, and \geq 65 years old, by race, by gender, as well as baseline scores of nasal symptoms. As the majority patients were in age group 19 to <65, the numbers of patients in the other age groups were under represented. Since over 83% patients were white, the other race groups were under represented.

By-gender analyses reveal inconsistent treatment benefit between male and female. Male did not appear to benefit from ciclesonide 80 μ g (treatment difference vs. placebo was 0.18, p-value=0.566). Their benefit from ciclesonide 160 μ g was numerically larger (treatment difference vs. placebo was 0.50, p-value=0.074). As female represented close to 2/3 of the patient population, the overall treatment effect was driven by female. These analyses raise a question on whether male could have greater benefit from the higher dose of ciclesonide NA. The by-gender subgroup analyses are displayed in Table 8.

Table 8. By-gender subgroup analyses for Study 633

	Placebo		Cic 80		Cic 160	
	N	Score	N	Score	N	Score
Male						
Baseline	97	8.6	102	8.3	195	8.5
End of 6-wk	96	7.3	102	6.9	195	6.7
trtment						
Diff form plb			0.2[-0.4,0.8]		0.5[-0.1,1.0]	
[CI] p-value			0.566		0.074	
Female						
Baseline	210	8.6	196	8.7	310	8.5
End of	209	7.4	196	6.4	309	6.8
trtment						
Diff form plb			0.9[0.5,1.4]		0.5[0.1,0.9]	
[CI] p-value			<0.001		0.009	

CI – 95% 2-sided confidence interval

2.3 Label review

The label review is focused on Section 14 – Clinical Studies of the proposed label. Reviewer’s comments are summarized as follows:

- Regarding Table 2 in the label, the ITT analyses should be reported for the TOSS and RQLQ analyses, rather than the analyses using subsets of severe patients.
- The clinical meaningful difference was not achieved for RQLQ in PAR patients in the ITT analyses.
- P-values in Table 2 should be either removed or reported using unadjusted p-values. Footnote c for Table 2 should be removed. P-values add no additional useful information when the confidence intervals are presented. The presentation of adjusted p-values not only is unnecessary, but adds confusions to practitioners. The calculation of the adjust p-values is based on the thinking of a school of statisticians who determine drug efficacy with one dose alone in one study. Such statistical practice is against the logic in drug efficacy evaluation because the regulatory decision has seldom been made on one dose in one study when information of multiple studies on multiple doses is available. The efficacy of the ciclesonide NA is established based on the efficacy performance of both doses of ciclesonide NA and confirmed in two studies. It can be calculated that the error rate of claiming efficacy for an ineffective drug is tightly controlled using this approach. Once the drug is determined efficacious, the optimal dose should be identified by factors such as effect sizes of primary and secondary endpoints as well as safety profiles. The adjust p-values play no role in either the determination of efficacy or identification of the optimal doses.
- The onset of action for nasal symptoms in SAR patients was determined at 36 hours after the first dose by Study 622 and confirmed by Study 634.

3 SECONDARY STATISTICAL REVIEW

Dr. Li's review covers three Phase 3 studies. These studies were conducted to assess the efficacy and safety of two doses of ciclesonide nasal aerosol (74 mcg or 148 mcg per day). Studies 622 and 634 are SAR studies of 2-week duration. Study 633 is a PAR study of 26-week duration (the efficacy was evaluated at Week 6). The primary efficacy endpoint was the average of change from baseline in the mean AM and PM reflective Total Nasal Symptom (rTNSS) daily scores over the two-week treatment period for the SAR studies, or over the six-week treatment period for the PAR study. Key secondary endpoints were evaluated including the change from baseline in average AM and PM instantaneous Total Nasal Symptoms daily score, change from baseline in average AM and PM reflective Total Ocular Symptoms daily score (SAR studies only), change from baseline in Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities, and onset of nasal improvement. The primary efficacy endpoint was analyzed using the Intent-To-Treat analysis set. Treatment groups were compared using analysis of covariance with factors of baseline rTNSS, center, and treatment. The protocol specifies that comparisons of each active treatment group with placebo were performed at a Bonferroni-corrected significance level of 0.025. The results for the primary endpoint analyses are presented below. Note that Dr. Li referred to the two doses as 80 mcg and 160 mcg, respectively.

	Study 622 (SAR Study)						Study 634 (SAR Study)					
	Placebo		Cic 80		Cic 160		Placebo		Cic 80		Cic 160	
	N	Score	N	Score	N	Score	N	Score	N	Score	N	Score
rTNSS												
Baseline	235	9.1	237	9.3	234	9.5	220	9.3	226	9.3	225	9.3
2-wk	234	8.7	237	7.9	234	7.8	218	8.6	226	7.6	225	7.6
average												
Diff form			0.9		1.1		1.0		1.0			
plb [CI]			[0.6,1.3]		[0.7,1.5]		[0.6,1.5]		[0.6,1.5]			
p-value			<0.001		<0.001		<0.001		<0.001			

	Study 635 (PAR Study)					
	Placebo		Cic 80		Cic 160	
	N	Score	N	Score	N	Score
rTNSS						
Baseline	307	8.6	298	8.5	505	8.5
2-wk	305	7.4	298	6.6	504	6.8
average						
Diff form			0.7		0.5	
plb [CI]			[0.4,1.0]		[0.2,0.8]	
p-value			<0.001		<0.001	

Dr. Li stated that

This review does not use the adjusted p-values as the efficacy is established by both doses of ciclesonide NA. That is, if both doses show activity of efficacy which are confirmed in multiple studies, the efficacy of the drug is established. Once the drug is determined efficacious, the optimal dose should be identified by factors such as effect sizes of various endpoints and safety profile. Therefore, there is no need to adjust p-values and the unadjusted p-values are presented in this review.

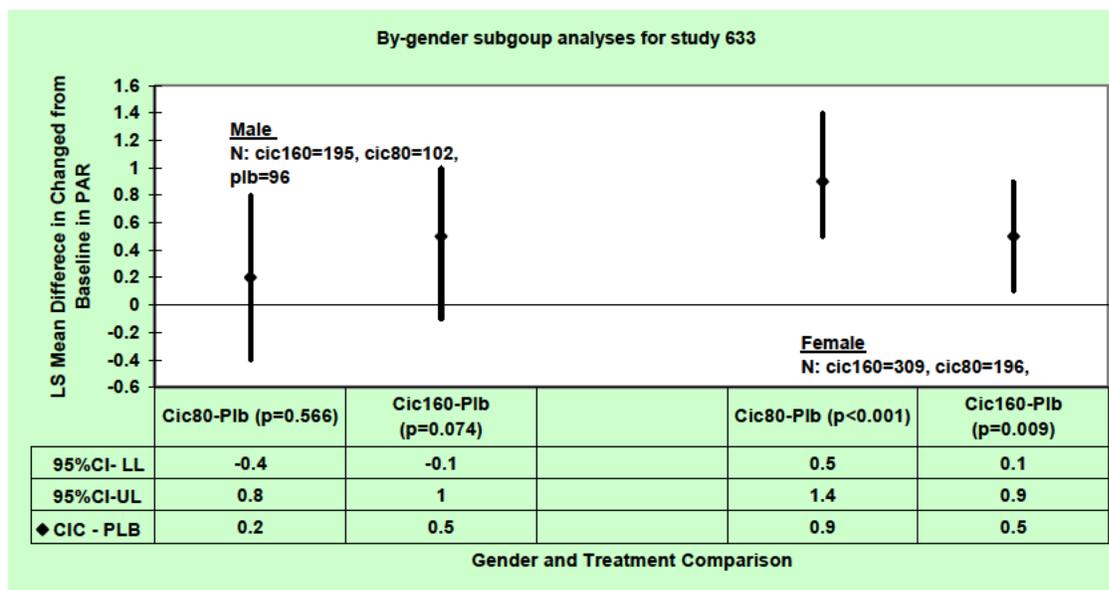
Dr. Li also stated in the labeling section (Section 2.3) that

The presentation of adjusted p-values not only is unnecessary, but adds confusions to practitioners. The calculation of the adjust p-values is based on the thinking of a school of statisticians who determine drug efficacy with one dose alone in one study. Such statistical practice is against the logic in drug efficacy evaluation because the regulatory decision has seldom been made on one dose in one study when information of multiple studies on multiple doses is available. The efficacy of the ciclesonide NA is established based on the efficacy performance of both doses of ciclesonide NA and confirmed in two studies. It can be calculated that the error rate of claiming efficacy for an ineffective drug is tightly controlled using this approach. Once the drug is determined efficacious, the optimal dose should be identified by factors such as effect sizes of primary and secondary endpoints as well as safety profiles. The adjust p-values play no role in either the determination of efficacy or identification of the optimal doses.

I do not completely agree with Dr. Li's statement. Although we do collectively evaluate whether the drug is effective, we also look at the individual doses from individual studies. In each of the trials, two tests of hypothesis were conducted for the primary endpoint (i.e. ciclesonide 148 mcg versus placebo and ciclesonide 74 mcg versus placebo). In general, success on one dose can lead to a conclusion of a drug effect; therefore, there is a multiplicity problem since the probability of finding a difference in one of the dose based on chance alone is larger than 0.05 (i.e. type I error rate). This is in line with the Office of Biostatistics' Draft Guidance on Multiple Endpoints in Clinical Trials. In addition, only one dose is generally approved for treatment of nasal symptoms associated with SAR or PAR, unless additional benefit is shown in another dose.

The applicant proposed to apply Bonferroni-adjustment to compare each of the treatment group with placebo. I agree with Dr. Li that having another trial to corroborate the findings and having strong nominal significance may reduce the probability of error. However, our Agency's standard requires each trial to be convincing on its own to establish efficacy. This implies that each trial is adequately controlled in which the hypotheses are stated in advance, important statistical aspects including multiplicity adjustment should be set out in the protocol, and the analyses be executed the way they were planned.

Dr. Li also reported the results of by-gender analyses. The result for by-gender subgroup analyses for Study 633 (PAR Study) is displayed below.



She stated in Section 2.2.2 of her review that

By-gender analyses reveal inconsistent treatment benefit between male and female. Male did not appear to benefit from ciclesonide 80 µg (treatment difference vs. placebo was 0.18, p-value=0.566). Their benefit from ciclesonide 160 µg was larger (treatment difference vs. placebo was 0.50, p-value=0.074). As female represented close to 2/3 of the patient population, the overall treatment effect was driven by female. These analyses raise a question on whether male could have greater benefit from the higher dose of ciclesonide NA.

In Section 2.1.3, her conclusion is that

Based on the evaluation of the three studies, ciclesonide NA 80 µg is efficacious in treating patients with SAR and PAR. More information should be collected to determine if male PAR patients can benefit better from ciclesonide 160 µg.

Dr. Li overstates the findings of the by-gender subgroup analysis a bit. Although I agree with Dr. Li's assessment that the magnitude of the treatment effects between male and female population appears to be inconsistent (the p-value for the interaction is 0.0598), the direction of the treatment difference is the same across strata, with wide overlapping confidence intervals. In the male population, although the point estimate for the treatment effect appears to be numerically larger in the ciclesonide 148 mcg compared to ciclesonide 74 mcg, the confidence intervals for the treatment difference were wide and overlapping. Based on my discussion with the clinical team, given the clinical similarities between SAR and PAR, the fact that this gender difference was not observed in the two SAR studies calls the finding into question. Further, the gender difference was not observed in the Omnaris program, which is the aqueous version of ciclesonide. Because the evidence that there is gender difference is weak, I do not believe we should ask the applicant to collect more information to determine if male PAR patients can benefit better from ciclesonide 148 mcg.

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/s/

JOAN K BUENCONSEJO

12/19/2011

This is a secondary statistical review considering the findings and conclusions of the primary statistical reviewer, Dr. Qian Li, based on her draft review dated December 13, 2011 which is also included for reference.

THOMAS J PERMUTT

12/19/2011

I concur with Dr. Buenconsejo's secondary review.



STATISTICAL REVIEW AND EVALUATION

Biometrics Division: DBVI

NDA No.:	202129
SERIAL No.:	N-000
DATE REQUESTED:	July 22, 2011
DRUG NAME:	Ciclesonide Nasal Aerosol
DOSAGE FORM:	Canisters
APPLICANT:	Sunovion
NAME OF STATISTICAL REVIEWER:	Meiyu Shen, Ph.D. DBVI
STATISTICAL TEAM LEADER	Yi Tsong, Ph.D. DBVI
NAME OF CHEMISTRY PROJECT MANAGER:	Swati Patwardhan

Meiyu Shen, Ph.D., Mathematical Statistician, DBVI

Concur:

Yi Tsong, Ph.D.
Deputy Director, DBVI

INTRODUCTION

The original Version 1 (V1) actuator (b) (4) was used by the applicant for development studies as well as for all Phase 3 clinical and stability studies. However, (b) (4) the applicant modified the actuator. (b) (4)

The Applicant worked with the manufacturer (b) (4) to create the Version 2 (V2) actuator.

In Section 3.2.P.2.4.5.1, Pharmaceutical development, three primary stability batches of V1 (b) (4) actuators were compared with three batches of V2 (b) (4) actuators for pharmaceutical performance. Two parameters, Particle Size Distribution (PSD) and Spray Content Uniformity (SCU), were evaluated for equivalence by statistical methods.

Objective

The objective of this study was to compare the pharmaceutical performance of the improved actuator V2 (b) (4) with the original actuator V1 (b) (4).

FDA recommended statistical evaluation method in Guidance

The population bioequivalence approach was recommended in the April 2003 draft Guidance for Industry 'Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action' and the guidance document 'In Vitro Nonprofile Bioequivalence Data: Population Bioequivalence – Parallel Designs; Method for Statistical test of Population Bioequivalence criterion'. The criteria for bioequivalence (BE) are based on a population approach for the means of test and reference products, and corresponding standard deviations of the natural logarithm of the appropriate measurement. The population bioequivalence approach relies on (1) a criterion between test and reference parameters to make a comparison (2) a confidence interval for the criterion, and (3) a bioequivalence (BE) upper limit for the criterion. The general approach is to calculate a 95 percent upper bound for the criterion. If this upper bound is less than the upper limit, θ , the test product may be judged bioequivalent to the reference product at the 5 percent level.

The form of the population bioequivalence criterion is:

$$\frac{(\text{difference of means in natural log scale})^2 + \text{difference in variance terms}}{\max(\text{reference variance, scaling variance})}$$

The upper BE limit:

$$\theta_p = \frac{(\ln(\text{average BE limit}))^2 + \epsilon_p}{\sigma_{T0}^2}$$

The upper BE limit therefore depends on 3 values to be specified: (1) average BE limit, (2) variance terms offset, ϵ_p , and (3) scaling variance, σ_{T0}^2 .

Due to the low variability of in vitro measurements, at the present time CDER recommends that the limit not be larger than 90/111. A value of 0.9 is tentatively recommended as the average BE limit. This value should be used in calculating the population BE limit θ_p . CDER recommends

that the variance term offset (ϵ_p) be equal to 0.0. CDER is also considering ϵ_p equal to 0.01 as an acceptable variance term offset. CDER recommends the scaling variance (σ_{T0}^2) be at least 0.1^2 in the non-profile analysis of Statistical information from the April 2003 Draft Guidance and statistical information for In Vitro Bioequivalence data posted on August 18, 1999.

Table 1 CDER recommended regulatory constants

Average BE limit	ϵ_p	σ_{T0}	θ_p
0.9	0	≥ 0.1	≤ 1.11

Criterion:

$$((\mu_T - \mu_R)^2 + \sigma_T^2 - \sigma_R^2) / \sigma_R^2 \leq \theta_p$$

Following the method developed by Hyslop, Hsuan, and Holder (Hyslop T., F. Hsuan, D.J. Holder, "A small-sample confidence interval approach to assess individual bioequivalence," STATISTICS IN MEDICINE, 2000; 19:2885-2897.) for the individual bioequivalence criterion, we propose the following method for testing this criterion. The procedure involves the computation of a test statistic which is either positive (does not conclude population bioequivalence) or negative (concludes population bioequivalence). This method is based on the work of Howe (1974) and Ting et al. (1990). The method outlined below assumes equal numbers of canisters per batch, and that three batches for each product will be combined as one "superbatch" for each product for analysis.

Notation:

n_T, n_R : Number of canisters per batch, for T and R products

ℓ_T, ℓ_R : Number of batches of T and R products

$\Delta = \mu_T - \mu_R$: Mean difference of T and R products

σ_T^2, σ_R^2 : Total variance of T and R products

σ_{T0}, θ_p : Regulatory constants

Linearized Criteria:

$$\eta_1 = (\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2) - \theta_p \cdot \sigma_R^2 < 0, \text{ for } \sigma_R > \sigma_{T0}$$

$$\eta_2 = (\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2) - \theta_p \cdot \sigma_{T0}^2 < 0, \text{ for } \sigma_R \leq \sigma_{T0}$$

Estimating the Linearized Criteria:

Begin by computing the separate means and variances for the log of the measure of each product.

Statistical Review of NDA202-129N000

Since three batches is not sufficient to reliably estimate the between batch component, the total variances are estimated as the between canister variance of the "super-batch" consisting of the three batches combined. Compute the total sum of squares for each product and denote them as SST_T and SST_R . Compute:

$MST_T = SST_T / (n_T \cdot \ell_T - 1)$ and $MST_R = SST_R / (n_R \cdot \ell_R - 1)$ (Searle).

Estimate the overall means of each product and compute:

$$\hat{\Delta} = \bar{X}_T - \bar{X}_R = \mu_T - \mu_R$$

$$\hat{\eta}_1 = (\bar{X}_T - \bar{X}_R)^2 + MST_T - (1 + \theta_p)MST_R$$

$$\hat{\eta}_2 = (\bar{X}_T - \bar{X}_R)^2 + MST_T - MST_R - \theta_p \sigma_{T0}^2$$

To test for population bioequivalence, compute the 95% upper confidence bound of either the reference-scaled or constant-scaled linearized criterion. The procedure for computing this is described in the next paragraphs. If this upper bound is negative, conclude population bioequivalence. If the upper bound is positive, do not conclude population bioequivalence.

95% Upper Confidence Bounds of Components:

Use the estimated total variance for T and for R based on $l_T^*n_T-1$ and $l_R^*n_R-1$ degrees of freedom where n_T and n_R are the number of canisters in each of the T and R batches and l_T , l_R are the number of batches of each product.

Using methods developed by Lee and Gurland for the Behrens-Fisher problem and the estimation method provided by Lee and Fineberg, compute two-sided confidence interval for $\hat{\Delta}$ based on the total variances.

Let $E0 = (\bar{X}_T - \bar{X}_R)^2$, $H0 = \max\{LCL^2, UCL^2\}$ using the two-sided interval obtained for $\hat{\Delta} = \bar{X}_T - \bar{X}_R$ which is described above (Hsu et al, 1994).

Let $E1 = MST_T$, compute $H1 = \frac{(\ell_T n_T - 1)E1}{\chi^2_{\ell_T n_T - 1, \alpha}}$

Let $E2rs = -(1 + \theta_p) MST_R$, compute $H2rs = \frac{(\ell_R n_R - 1)E2rs}{\chi^2_{\ell_R n_R - 1, 1 - \alpha}}$

Let $E2cs = -MST_R$, compute $H2cs = \frac{(\ell_R n_R - 1)E2cs}{\chi^2_{\ell_R n_R - 1, 1 - \alpha}}$

For each component above, also compute $U_i = (H_i - E_i)^2$.

95% Upper Confidence Bounds for Linearized Criteria:

$$H_{\eta_1} = (E0 + E1 + E2rs) + (U0 + U1 + U2rs)^{1/2}$$

$$H_{\eta_2} = (E0 + E1 + E2cs - \theta_p \sigma_{T0}^2) + (U0 + U1 + U2cs)^{1/2}$$

Applicant’s Statistical evaluation method

The applicant used the population bioequivalence (PBE) approach for spray content uniformity (SCU) and particle size distribution (PSD). Applicant referred to the 2003 draft guidance for industry ‘Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action’ and the guidance document ‘In Vitro Nonprofile Bioequivalence Data: Population Bioequivalence – Parallel Designs; Method for Statistical test of Population Bioequivalence criterion’. **The applicant used (0.9, 1.11) as the Average BE limit and variance offset ϵ_p equal to 0.**

Table 2 Applicant’s regulatory constants

θ_p	ϵ_p	σ_{T0}
1.11	0	0.1

Applicant also used Chow’s method (Chow, Shao and Wang, In Vitro Bioequivalence Testing, Statistics in Medicine, 2003, 22: 55-68) for the spray content uniformity.

Applicant's analysis

Testing was carried out for SCU and PSD. The upper limit of the 95% Confidence bound of the linearized criteria was less than zero for comparisons of SCU and PSD performed between V1 and V2 actuators. The applicant concluded that the actuators are equivalent.

FDA analysis

1. Population bioequivalent analyses

This reviewer used the CDER recommended regulatory constants listed in Table 1. Population bioequivalent analyses were carried out for the following: (1) SCU and (2) PSD.

1) $\theta_p = 1.11$

The upper limit of the 95% Confidence bound of the linearized criteria was less than zero for comparisons of SCU at the beginning stage and ending stage, PSD of Groups (b)(4) at the beginning stage and at the end stage performed between V1 and V2 actuators. This analysis was listed in Table 3.

2. Average bioequivalent analyses

This reviewer performed average bioequivalence test for (1) SCU and (2) PSD. The two-sided 90% confidence bound of the mean difference between V1 and V2 was within goal post ($-\ln(0.9), \ln(1.11)$) for comparisons of SCU, PSD of Groups (b)(4) at the beginning stage and at the end stage, The result was listed in Table 4.

Conclusions

The analyses showed that they passed the population in-vitro bioequivalence criteria and average bioequivalence criteria. However, the validity of this evaluation relies on the assumption of acceptance of stability batches for V1 in bioequivalence study. Hence, this decision is up to the review chemist.

We didn't evaluate Chow's method for SCU because the constants in Chow's method are derived from simulation and are not recommended in any FDA guidance.

Table 3 FDA population bioequivalence analysis

Product Strength	Variable	Class	Mean	Standard Deviation	$\theta_p = 1.11$ 95% upper limit	Equivalent	
(b) (4)	SCU (end)	V1	3.6127	0.0441	-0.00671	Yes	
	SCU (end)	V2	3.6611	0.0399			
	SCU (beginning)	V1	3.5931	0.0354	-0.00868	Yes	
	SCU (beginning)	V2	3.6228	0.0361			
	SCU (end)	V1	4.3269	0.0384	-0.00892	Yes	
	SCU (end)	V2	4.3622	0.0304			
	SCU (beginning)	V1	4.2696	0.0460	-0.00572	Yes	
	SCU (beginning)	V2	4.3269	0.0388			
	PSD_Group	(b) (4)	V1	2.7522	0.0556	-0.0054	Yes
	PSD_Group	(b) (4)	V2	2.6980	0.0490		
	PSD_Group	(b) (4)	V1	3.2715	0.0352	-0.0084	Yes
	PSD_Group	(b) (4)	V2	3.3000	0.0390		
	PSD_Group	(b) (4)	V1	1.8380	0.0718	-0.0055	Yes
	PSD_Group	(b) (4)	V2	1.8534	0.0768		
	PSD_Group	(b) (4)	V1	2.6823	0.0821	-0.0075	Yes
	PSD_Group	(b) (4)	V2	2.6419	0.0622		
	PSD_Group	(b) (4)	V1	3.2211	0.0312	-0.0092	Yes
	PSD_Group	(b) (4)	V2	3.2446	0.0341		
	PSD_Group	(b) (4)	V1	1.8044	0.0905	-0.0118	Yes
	PSD_Group	(b) (4)	V2	1.8175	0.0584		
	PSD_Group	(b) (4)	V1	3.4541	0.0497	-0.0076	Yes
	PSD_Group	(b) (4)	V2	3.4114	0.0411		
	PSD_Group	(b) (4)	V1	4.0491	0.0260	-0.0098	Yes
	PSD_Group	(b) (4)	V2	4.0623	0.0314		
	PSD_Group	(b) (4)	V1	2.1311	0.1029	-0.0082	Yes
	PSD_Group	(b) (4)	V2	2.1334	0.0767		
	PSD_Group	(b) (4)	V1	3.4070	0.0416	-0.0044	Yes
	PSD_Group	(b) (4)	V2	3.3789	0.0653		
	PSD_Group	(b) (4)	V1	3.9960	0.0259	-0.0098	Yes
	PSD_Group	(b) (4)	V2	4.0062	0.0326		
	PSD_Group	(b) (4)	V1	2.1911	0.0715	-0.0082	Yes
	PSD_Group	(b) (4)	V2	2.1987	0.0667		

Statistical Review of NDA202-129N000

Table 4 FDA average bioequivalence analysis

Product Strength	Variable	LowerCLMean	Mean	UpperCLMean	Average bioequivalent (ln(0.9), ln(1.11)) = (-0.1054, 0.1044)
(b) (4)	SCU (end)	-0.0666	-0.0484	-0.0302	Yes
	SCU (beginning)	-0.0452	-0.0298	-0.0143	Yes
	SCU (end)	-0.0502	-0.0353	-0.0203	Yes
	SCU (beginning)	-0.0757	-0.0573	-0.0390	Yes
	PSD_Group (b) (4)	0.03159	0.05420	0.07682	Yes
	PSD_Group	-0.04455	-0.02852	-0.01249	Yes
	PSD_Group	-0.04751	-0.01542	0.01668	Yes
	PSD_Group	0.00888	0.04031	0.07175	Yes
	PSD_Group	-0.03766	-0.02356	-0.00946	Yes
	PSD_Group	-0.04597	-0.01309	0.01978	Yes
	PSD_Group	0.02295	0.04263	0.06232	Yes
	PSD_Group	-0.02557	-0.01312	-0.00067	Yes
	PSD_Group	-0.04146	-0.00229	0.03687	Yes
	PSD_Group	0.00448	0.02811	0.05174	Yes
	PSD_Group	-0.02288	-0.01018	0.00252	Yes
	PSD_Group	-0.03746	-0.00763	0.02220	Yes

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/s/

MEIYU SHEN
12/06/2011

YI TSONG
12/06/2011

STATISTICS FILING CHECKLIST FOR NDA 202129 / S0000

NDA Number: 202129 / seq0000 Applicant: Nycomed

Stamp Date: 03-March-2011

Drug Name: Ciclesonide

NDA/BLA Type: Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)		x		need V1.0 protocol, DARP
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes (but see comment 1 below)

74-day letter: Comments from Statistics

1. Provide original V1.0 protocols and data analysis and reporting plans for studies 060-622, 060-633, and 060-634.

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/s/

ROBERT ABUGOV
05/02/2011

JOAN K BUENCONSEJO
05/03/2011