

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-004**

**STATISTICAL REVIEW(S)**



## STATISTICAL REVIEW AND EVALUATION

### STABILITY REVIEW

<b>NDA NO.:</b>	22-004
<b>SERIAL NO.:</b>	
<b>DATE RECEIVED BY CENTER:</b>	July 21 and Aug. 2, 2006
<b>DRUG NAME:</b>	Ciclesonide
<b>DOSAGE FORM:</b>	Nasal Spray
<b>INDICATION:</b>	Allergic Rhinitis
<b>SPONSOR:</b>	Altana Pharma USA
<b>DOCUMENTS REVIEWED:</b>	Justification of Specification (July 21, 2006) and Electronic Data Sets (Aug. 2 and 10, 2006)
<b>PROJECT MANAGER:</b>	Colette Jackson
<b>STATISTICAL REVIEWER:</b>	Roswitha Kelly, M.S. OB/DB6
<b>CHEMISTRY REVIEWER:</b>	Arthur Shaw, Ph.D., ONDQA/DPA1/Branch 2

**Distribution:** NDA22004/Ciclesonide Nasal Spray  
OND/ODEH/DPAP/Colette Jackson  
ONDQA/DPA1/Arthur Shaw, Ph.D.  
ONDQA/DPA1/Prasad Peri, Ph.D.  
OTS/OB/DB6/Yi Tsong, Ph.D.  
OTS/OB/DB6/Stella Machado, Ph.D.  
OTS/OB/DB6/Roswitha Kelly, M.S.  
OTS/OB/Lillian Patrician, M.S., MBA  
OTS/OB/DB6/Robert O'Neill, Ph.D.

File Directory: c:\ciclesonide\N22004\_Ciclesonide\_nasal\_F.doc

21 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Roswitha Kelly  
9/1/2006 01:32:47 PM  
BIOMETRICS

Yi Tsong  
9/1/2006 01:37:07 PM  
BIOMETRICS



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

## Statistical Review and Evaluation

### CLINICAL STUDIES

NDA/Serial Number: N22-004  
Drug Name: Ciclesonide Nasal Spray 50mcg  
Indication(s): Proposed Indication: SAR, PAR in adults and children ages 2 year and older  
Applicant: Altana Pharmaceuticals, Inc.  
Date(s): Received 12/22/05; User Fee 10/22/06  
Review Priority: Standard

Biometrics Division: Division of Biometrics II (HFD-715)  
Statistical Reviewer: Feng Zhou, Statistical Reviewer  
Concurring Reviewers: Ruthanna C Davi, (Biometrics Team Leader)

Medical Division: Division of Pulmonary and Allergy Drug Products (HFD-570)  
Clinical Team: Carol Bosken, M.D. (Medical Reviewer)  
Badrul A Chowdhury, M.D. (Medical Division Director)  
Project Manager: Collette Jackcon (HFD-570)

Keywords: Clinical Studies, NDA review, Dropouts

## Table of Contents

<b>LIST OF TABLES</b> .....	<b>3</b>
<b>LIST OF FIGURES</b> .....	<b>3</b>
<b>1. EXECUTIVE SUMMARY</b> .....	<b>4</b>
1.1 CONCLUSIONS AND RECOMMENDATIONS .....	4
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES .....	4
1.3 STATISTICAL ISSUES AND FINDINGS .....	5
<b>2. INTRODUCTION</b> .....	<b>10</b>
2.1 OVERVIEW.....	10
2.2 DATA SOURCES .....	12
<b>3. STATISTICAL EVALUATION</b> .....	<b>13</b>
3.1 EVALUATION OF EFFICACY.....	13
3.1.1 <i>Dose-finding and Pivotal Efficacy Trials</i> .....	13
3.1.2 <i>Onset of Action</i> .....	31
3.1.3 <i>Pediatric Studies</i> .....	36
3.2 EVALUATION OF SAFETY .....	43
<b>4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS</b> .....	<b>43</b>
4.1 GENDER, RACE, AGE, AND OTHERS.....	43
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS .....	45
<b>5. SUMMARY AND CONCLUSIONS</b> .....	<b>45</b>
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE .....	45
5.2 CONCLUSIONS AND RECOMMENDATIONS .....	48
<b>6. ATTACHMENTS</b> .....	<b>49</b>
6.1 ATTACHMENT 1 .....	49
6.2 ATTACHMENT 2.....	55
6.3 ATTACHMENT 3.....	58
6.4 ATTACHMENT 4.....	66

## List of Tables

Table 1. Design and Statistical Results of Dose-finding and Two Pivotal Studies.....	5
Table 2. The Results of the Secondary Variables for Dose-finding and Two Pivotal Studies.....	7
Table 3. Change from Baseline in Average AM and PM Reflective Individual Nasal Symptoms.....	8
Table 4. Clinical Trials.....	12
Table 5. ITT Patients' Accountability N (%), Dose-finding Study.....	14
Table 6. ITT Patients' Accountability N (%), Study for Two Pivotal Studies.....	15
Table 7. ITT Subjects' Demographics and Baseline Characteristics, Dose-finding Study SAR002.....	16
Table 8. ITT Subjects' Demographics and Baseline Characteristics.....	17
Table 9. Overview of Changes from Baseline in Primary Efficacy.....	20
Table 10. Change from Baseline in Primary Efficacy Variables: AM and PM Reflective TNSS.....	21
Table 11. Robustness of the Primary Analysis Model for the Pivotal Studies.....	22
Table 12. Mean Change from Baseline of Average of AM and PM Reflective TNSS.....	23
Table 13. Change from Baseline in Average AM and PM Reflective Individual Symptoms Score.....	27
Table 14. The Results of the Secondary Variables for Two Pivotal Studies.....	30
Table 15. Hourly Assessment of Instantaneous TNSS on Day1- Day 5.....	33
Table 16. Patient Demographic and Other Baseline Characteristics – ITT Analysis Set.....	34
Table 17. ITT Patients' Accountability N (%), Studies for SAR.....	37
Table 18. ITT Subjects' Demographics and Baseline Characteristics, Studies for SAR.....	38
Table 19. Mean of Primary and Key Secondary Variables of Study PED403.....	41
Table 20. Mean of Primary and Key Secondary Variables of Study PED405.....	42
Table 21. LS Mean Change from Baseline of Average of AM and PM Reflective TNSS over 14-Days, SAR401.....	43
Table 22. LS Mean Change from Baseline of Average of AM and PM Reflective TNSS over 42-Days, PAR402.....	44

## List of Figures

Figure 1. Primary Analysis of Combined (AM and PM) Reflective TNSS for Three Studies.....	6
Figure 2. Raw Mean of Average AM and PM Reflective Individual Nasal Symptom Score.....	8
Figure 3. LS Mean and 95% CI of Change from Baseline of Average AM and PM Reflective TNSS over 14-Days by Subgroup for Study SAR401.....	9
Figure 4. LS Mean and 95% CI of Change from Baseline of Average AM and PM Reflective TNSS over 42-Days by Subgroup for Study PAR402.....	9
Figure 5. LS Mean Change from Baseline of Average of AM and PM reflective TNSS.....	24
Figure 6. LS Mean Change from Baseline of AM or PM TNSS.....	25
Figure 7. Change from Baseline of Average AM and PM Reflective TNSS by Treatment Day.....	26
Figure 8. Change from Baseline of Average AM and PM Reflective TNSS by Treatment Day.....	26
Figure 9. Raw Mean of Average AM and PM Reflective Individual Symptom Score.....	27
Figure 10. Change from Baseline of Average of AM & PM Reflective TNSS by Center, SAR401.....	28
Figure 11. LS Mean Change from Baseline of Average of AM and PM reflective TNSS.....	29
Figure 12. Change from Baseline of Average of AM and PM Instantaneous TNSS by Race Group for Study SAR406.....	35
Figure 13. Change from Baseline of Average of AM and PM Instantaneous TNSS by Race Group for Study SAR407.....	35
Figure 14. LS Mean Difference of Changes from Baseline in Primary and Secondary Variables for Study PED403.....	41
Figure 15. LS Mean Difference of Changes from Baseline in Reflective TNSS and PNSS.....	42
Figure 16. LS Mean and 95% CI of Change from Baseline of Average AM and PM Reflective TNSS over 14-Days by Subgroup for Study SAR401.....	44
Figure 17. LS Mean and 95% CI of Change from Baseline of Average AM and PM Reflective TNSS over 42-Days by Subgroup for Study PAR402.....	45

## **1. EXECUTIVE SUMMARY**

According to the sponsor (Altana), Ciclesonide 50mcg Nasal Spray is an anti-inflammatory with low glucocorticoid receptor affinity and following intranasal application, Ciclesonide is enzymatically converted to the active metabolite, C21-desisobutyryl-ciclesonide (des-Ciclesonide, des-CIC). The sponsor also indicates that Des-CIC has potent anti-inflammatory activity with affinity for the glucocorticoid receptor 120 times higher than that of the parent compound, Ciclesonide and that the main mechanism of corticosteroid action in allergic rhinitis is considered due to anti-inflammation.

The sponsor submitted this application on December 22, 2005 (NDA 22-004) in support of usage in the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and children 2 years of age and older.

### **1.1 Conclusions and Recommendations**

The efficacy evaluation of studies SAR401 and PAR402, the phase-III, randomized, multi-center, double-blind, parallel-group, and placebo-control trials, demonstrated that Ciclesonide 50mcg Nasal Spray is statistically significantly superior to placebo in improving the Total Nasal Symptoms Score after a dosage regimen of two sprays per nostril once daily (200mcg per day) in adult and adolescent patients 12 years of age and older with SAR or PAR, respectively. The efficacy evaluation of study SAR002, the phase-II, randomized, multi-center, double-blind, parallel-group, and placebo-control, and dose-finding study, demonstrated that Ciclesonide 200mcg per day is the minimum effective dose regimen in adult patients 18 years and older of age with SAR. The efficacy evaluation of study SAR406, one of two EEU studies, demonstrated that the onset of action is within 1 hour after administration of Ciclesonide Nasal Spray 200mcg per day. That one hour of onset of action was not confirmed by SAR407, the second EEU study, or the two pivotal studies. In studies SAR401 and PAR402, the onset of effect was seen within 24 – 48 hours. The improvement in instantaneous TNSS was maintained over the full 24-hour dosing interval.

Subgroup analyses indicated that the effectiveness of Ciclesonide Nasal Spray 200mcg per day was not demonstrated (statistically) in the subjects who are 12-17 years old, 65 years old and older, 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 when conducting multiple analyses, but the magnitude of effect size is very small in 12-17 years old subgroup.

### **1.2 Brief Overview of Clinical Studies**

The sponsor’s submission included eleven studies outlined in Table 4. Study M1-401 (hereafter referred to as SAR401) was the pivotal study for SAR and M1-402 (hereafter referred to as PAR402) was the pivotal study for PAR. Two studies had the similar design, which was a double-blind, randomized, multi-center, placebo-controlled, parallel-group studies to evaluate the efficacy and safety of once-daily, intranasally administered Ciclesonide 200mcg in adult and

adolescent patients 12 years and older with SAR or PAR. Study TBN-CL-02 (hereafter referred to as SAR002), the dose-finding study for SAR, was a double-blind, randomized, placebo-controlled, multi-center, dose-ranging study to evaluate the efficacy and safety of Ciclesonide 25, 50, 100, and 200mcg doses once daily in patients 18 years and older with SAR. The patients in these three studies had at least a two-year history of SAR or PAR and a positive skin test to the local spring pollen. There was a one-week, single-blind, placebo run-in period followed by 2-weeks (SAR002) or 4-weeks (SAR401) or 6-weeks (PAR402) double-blind treatment period.

### 1.3 Statistical Issues and Findings

Table 1 summarizes the design and statistical results for the primary efficacy endpoint for the dose-finding and two pivotal studies under review.

Table 1. Design and Statistical Results of Dose-finding and Two Pivotal Studies

<b>Study (# of centers)</b>	<b>Study Population Age &amp; Gender (N)</b>	<b>Design</b>	<b>Treatment groups (N)</b>	<b>Primary Efficacy Variable</b>	<b>LS Mean of PL - CIC 95% CI p-value<sup>a</sup></b>
<b>SAR002</b> 6 centers in USA 2-weeks study	Age range: Male: 16 – 66 (214)	Randomized Multi-center Double-blind Parallel-group	Ciclesonide 200mcg (144)	Mean Change from Baseline in SUM of AM and PM reflective TNSS, consisting of Nasal Congestion, Rhinorrhea, Nasal Itching, and Sneezing, over the 14-Days	200mcg: $\Delta = 1.35$ (0.23, 2.41), 0.012
	Female: 18– 65 (512)	Placebo-controlled	100mcg (145)		100mcg: $\Delta = 0.88$ (-0.17, 1.93), 0.099
			50mcg (143)		50mcg: $\Delta = 0.44$ (-0.61, 1.49), 0.413
			25mcg (146) Placebo (148)		25mcg: $\Delta = 0.36$ (-0.69, 1.41), 0.506
<b>SAR401</b> 6 centers in USA 4-weeks study	Age range: Male: 12 – 86 (115)	Randomized Multi-center Double-blind Parallel-group	Ciclesonide 200mcg (164)	Mean Change from Baseline in AVERAGE of AM and PM reflective TNSS, consisting of Nasal Congestion, Rhinorrhea, Nasal Itching, and Sneezing, over the 14-Days	PL - CIC = 0.90 (0.45, 1.36) <0.001
	Female: 12– 73 (212)	Placebo-controlled	Placebo (163)		
<b>PAR402</b> 37 centers in USA 6-weeks study	Age range: Male: 12 – 75 (166)	Randomized Multi-center Double-blind Parallel-group	Ciclesonide 200mcg (238)	Mean Change from Baseline in AVERAGE of AM and PM reflective TNSS, consisting of Nasal Congestion, Rhinorrhea, Nasal Itching, and Sneezing, over the 42-Days	PL - CIC = 0.62 (0.28, 0.97) < 0.001
	Female: 12– 74 (305)	Placebo-controlled	Placebo (233)		

a: p-value is from a repeated measures ANCOVA with treatment, baseline, day, and treatment by day interaction;

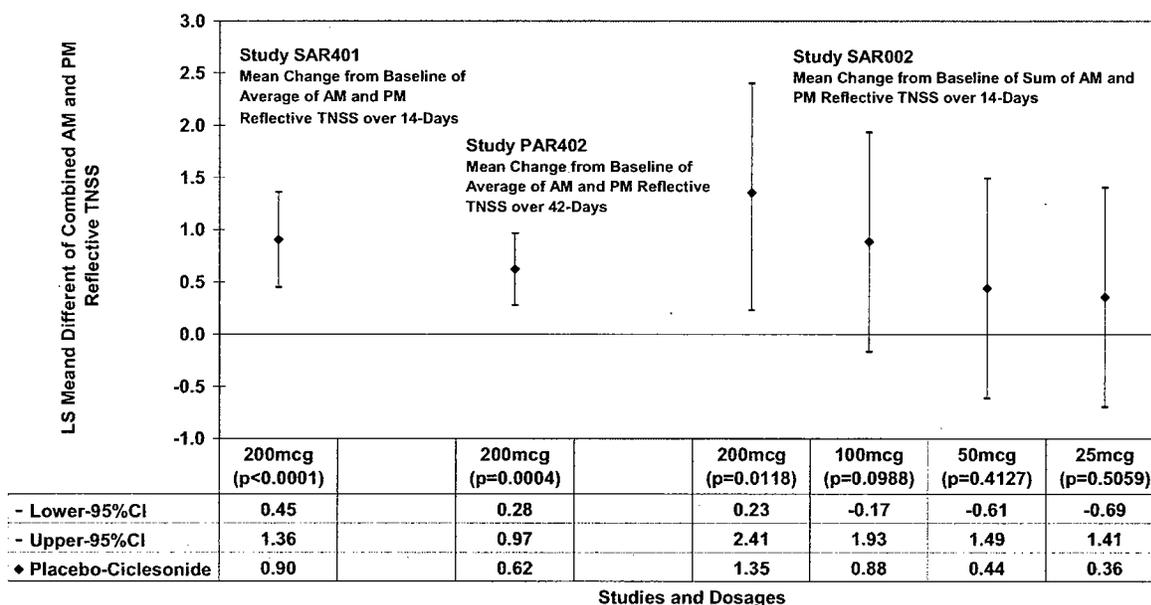
In the original NDA submission, there were several errors in the electronic data and statistical programming for the primary analysis. This reviewer received the NDA assignment on January 15, 2006 and found the following errors after the filing meeting, which was on February 13, 2006. The project manager sent the fax communicating these issues to the sponsor on March 20, 2006 and the sponsor responded to the fax on March 23, 2006 and admitted the errors in the NDA submission and corrected electronic data and tables were submitted on March 29, 2006 and

April 7, 2006. (See attachments for details)

1. Errors in Lab data
2. Incorrect SAS Code for the primary efficacy analysis
3. Duplication in the CDISC-SDTM diary data
4. Incorrect Data Value in dose-find study SAR002

Based on reviewing the corrected data sets with corrected SAS code, the primary efficacy results of Ciclesonide Nasal Spray 200mcg once daily relative to placebo are shown in Figure 1. For both studies SAR401 and PAR402, the primary efficacy endpoint (mean change from baseline in average of AM and PM reflective TNSS) showed that Ciclesonide Nasal Spray 200mcg once daily was statistically significantly better than Placebo as evidenced by the 95% confidence intervals for the least squares mean differences being completely above zero (Placebo – Ciclesonide). In the dose-finding study SAR002, the primary efficacy endpoint (mean change from baseline in sum of AM and PM reflective TNSS) clearly showed that efficacy of Ciclesonide Nasal Spray was dose related; only 200mcg/day dose was statistically significantly better than placebo and 100mcg/day dose showed a trend of positive efficacy, but was not statistically significantly better than placebo.

Figure 1. Primary Analysis of Combined (AM and PM) Reflective TNSS for Three Studies



### Key Secondary Efficacy Variables

For Study SAR401 and Study PAR402, the key secondary efficacy variables were as follows:

- Average AM and PM patient-assessed instantaneous TNSS over Days 1-14
- Physician Assessed Nasal Signs and Symptoms (PANS) at Endpoint
- Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (adult and adolescent) at Endpoint

To account for multiplicity among the primary and key secondary efficacy variables, a clinical decision rule was used. That is sequential testing was employed. If the medication was found to be effective with respect to the primary efficacy measure, the secondary variables were tested for statistical significance starting with the instantaneous TNSS over Days 1-14. If the p-value from the test of the average of AM and PM patient-assessed instantaneous TNSS over Days 1-14 was  $\leq 0.05$ , then PANS at endpoint was examined. If the p-value for the test of PANS at endpoint was  $\leq 0.05$ , then the RQLQ at endpoint result was examined. Therefore, the type I error rate was strictly controlled for the primary and key secondary measures.

Table 2 displays the reviewer's analysis results of the key secondary efficacy variables, which showed that Ciclesonide Nasal Spray 200mcg once daily was better than placebo in improving the average of AM and PM instantaneous TNSS. The PANS and RQLQ did not reach the statistical significance at the endpoint in Study SAR401. Study PAR402 reached the statistical significance in PANS and RQLQ at the endpoint.

Table 2. The Results of the Secondary Variables for Dose-finding and Two Pivotal Studies

Treatment	Baseline Mean (SD)	Change from Baseline		Treatment Comparison Placebo vs. Ciclesonide		
		N	LS Mean (SE)	LS Mean Difference	95% CI	p-value
<b>Average AM and PM Instantaneous TNSS (Day 1-14) SAR002</b>						
Ciclesonide 200	9.00 (1.87)	144	-1.966 (0.18)	0.7735	(0.27, 1.28)	0.0026
Ciclesonide 100	8.79 (1.84)	145	-2.126 (0.18)	0.4347	(-0.06, 0.93)	0.0876
Ciclesonide 50	8.77 (1.95)	142	-2.116 (0.18)	0.1497	(-0.35, 0.65)	0.5581
Ciclesonide 25	9.00 (1.81)	145	-2.192 (0.15)	0.1594	(-0.34, 0.66)	0.5321
Placebo	8.38 (1.84)	147	-1.327 (0.15)	-	-	-
<b>Average AM and PM Instantaneous TNSS (Day 1-14) SAR401</b>						
Ciclesonide 200	8.40 (2.24)	163	-2.192 (0.15)	0.8657	(0.44, 1.29)	<0.001
Placebo	8.33 (2.08)	162	-1.327 (0.15)	-	-	-
<b>Average AM and PM Instantaneous TNSS (Day 1-42) PAR402</b>						
Ciclesonide 200	7.07 (2.15)	232	-2.28 (0.14)	0.5419	(0.21, 0.89)	0.0017
Placebo	7.09 (2.27)	229	-1.74 (0.14)	-	-	-
<b>PANS (Day 1-14) SAR401</b>						
Ciclesonide 200	7.97 (1.58)	163	-1.982 (0.16)	-0.0051	(-0.44, 0.43)	0.9816
Placebo	8.07 (1.44)	161	-1.988 (0.16)	-	-	-
<b>PANS (Day 1-42) PAR402</b>						
Ciclesonide 200	6.90 (1.99)	216	-2.090 (0.15)	0.3966	(0.015, 0.778)	0.0415
Placebo	6.80 (2.04)	216	-1.693 (0.15)	-	-	-
<b>RQLQ (Day 1-14) SAR401</b>						
Ciclesonide 200	3.96 (1.05)	151	-1.391 (0.11)	0.1827	(-0.125, 0.491)	0.2437
Placebo	3.78 (0.98)	152	-1.208 (0.11)	-	-	-
<b>RQLQ (Day 1-42) PAR402</b>						
Ciclesonide 200	3.34 (1.06)	195	-1.298 (0.09)	0.2848	(0.066, 0.504)	0.0109
Placebo	3.38 (1.08)	193	-1.013 (0.08)	-	-	-

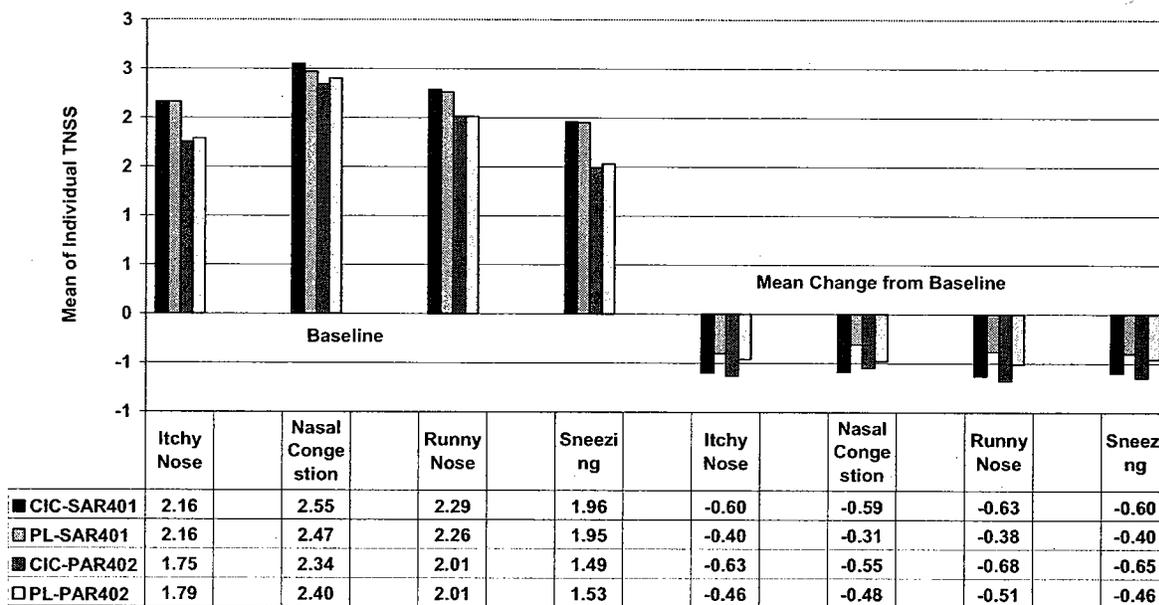
The individual nasal symptoms scores, the changes from baseline of average of AM and PM reflective symptom scores for individual symptoms of the TNSS over 14-days (Study SAR401) or 42-days (Study PAR402) are summarized in Table 3. Figure 2 shows the patients treated with Ciclesonide 200mcg nasal spray had improvements versus placebo in all four nasal symptoms except the nasal congestion component did not reach statistical significance in Study PAR402.

Table 3. Change from Baseline in Average AM and PM Reflective Individual Nasal Symptoms

Study	N		Baseline (Mean ± SD)		Change from Baseline (LS Mean ± SE)		LS Mean Difference, P-value, 95%CI PL - CIC
	CIC	PL	CIC	PL	CIC	PL	
<b>Average AM and PM Reflective Individual TNSS - Itch Nose (Scale 0 to 3)</b>							
SAR401 <sup>1</sup>	162	162	2.16 (0.63)	2.16 (0.64)	-0.61 (0.04)	-0.41 (0.04)	0.1996, p=0.0017 (0.075, 0.324)
PAR402 <sup>2</sup>	232	229	1.75 (0.72)	1.79 (0.74)	-0.66 (0.04)	-0.48 (0.04)	0.1803, p=0.0004 (0.080, 0.280)
<b>Average AM and PM Reflective Individual TNSS - Nasal Congestion (Scale 0 to 3)</b>							
SAR419	162	162	2.55 (0.47)	2.47 (0.45)	-0.60 (0.04)	-0.34 (0.04)	0.2545, p<0.001 (0.140, 0.369)
SAR420	232	229	2.34 (0.50)	2.40 (0.54)	-0.57 (0.04)	-0.47 (0.04)	0.0972, p=0.0595 (-0.004, 0.198)
<b>Average AM and PM Reflective Individual TNSS - Runny Nose (Scale 0 to 3)</b>							
SAR401	162	162	2.29 (0.58)	2.26 (0.53)	-0.63 (0.05)	-0.40 (0.05)	0.2312, p<0.001 (0.096, 0.366)
SAR420	232	229	2.01 (0.66)	2.01 (0.66)	-0.69 (0.04)	-0.51 (0.04)	0.0535, p=0.0010 (0.071, 0.282)
<b>Average AM and PM Reflective Individual TNSS - Sneezing (Scale 0 to 3)</b>							
SAR419	162	162	1.96 (0.69)	1.95 (0.64)	-0.61 (0.05)	-0.41 (0.05)	0.1995, p=0.0023 (0.072, 0.327)
SAR420	232	229	1.49 (0.75)	1.53 (0.72)	-0.67 (0.04)	-0.47 (0.04)	0.0492, p< 0.001 (0.104, 0.298)

1: Average of 14-days; 2: Average of 42-days.

Figure 2. Raw Mean of Average AM and PM Reflective Individual Nasal Symptom Score



**Subgroup Analyses** – Figure 3 and Figure 4 show the results of the usual subgroup analyses for studies SAR401 and PAR402. The efficacy of Ciclesonide Nasal Spray 200mcg once daily was not demonstrated in the subjects who were 17 years old and younger, 65 years old and older, black, or of “other” races in both studies. However, statistically significant results are not

expected in all subgroups due to the reduced sample size and natural variation expected when conducting multiple analyses, but the magnitude of effect size is very small in 12-17 years old subgroup.

Figure 3. LS Mean and 95% CI of Change from Baseline of Average AM and PM Reflective TNSS over 14-Days by Subgroup for Study SAR401

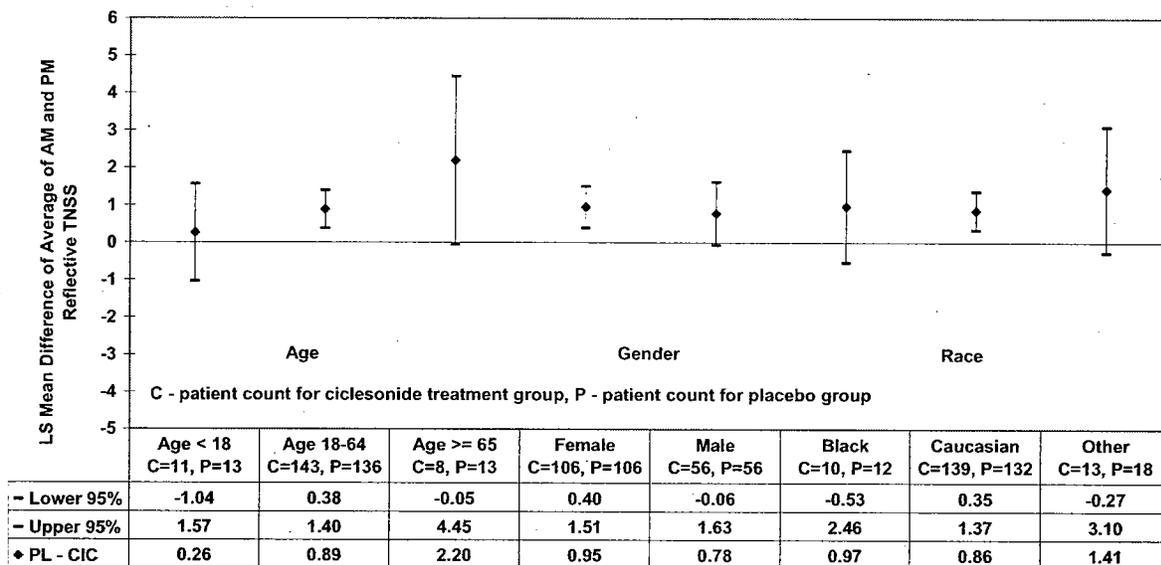
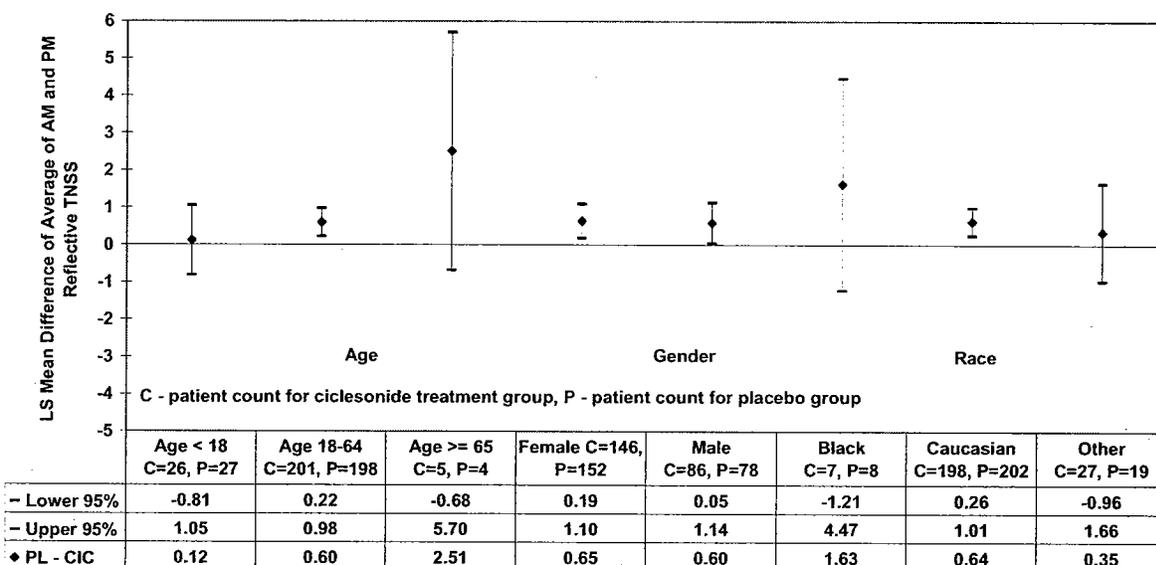


Figure 4. LS Mean and 95% CI of Change from Baseline of Average AM and PM Reflective TNSS over 42-Days by Subgroup for Study PAR402



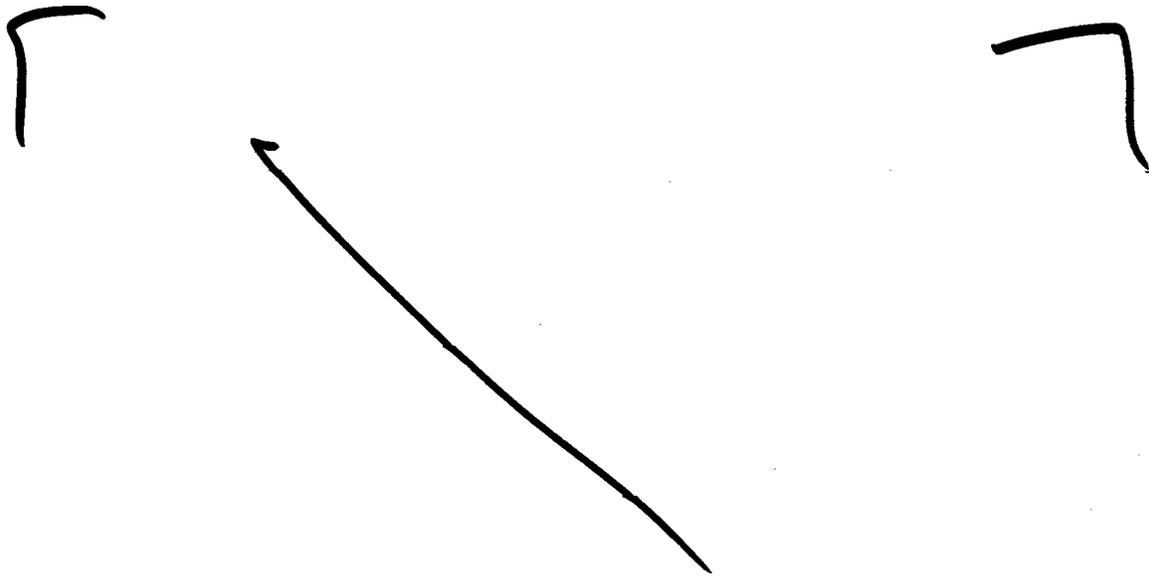
## 2. INTRODUCTION

### 2.1 Overview

According to the sponsor (Atlanta), Ciclesonide 50mcg Nasal Spray is an anti-inflammatory with low glucocorticoid receptor affinity and following intranasal application, Ciclesonide is enzymatically converted to the active metabolite, C21-desisobutyryl-ciclesonide (des-Ciclesonide, des-CIC). The sponsor also indicates that Des-CIC has potent anti-inflammatory activity with affinity for the glucocorticoid receptor 120 times higher than that of the parent compound, Ciclesonide and that the main mechanism of corticosteroid action in allergic rhinitis is considered due to anti-inflammation.

The sponsor submitted this application on December 22, 2005 (NDA 22-004) in support of usage in the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and children 2 years of age and older.

The sponsor proposed the following statements be added to the clinical studies section for the package insert: (p4-5, drafet-package-insert-pdf-file.pdf)



1   Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

  ✓   § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

The sponsor's submission included eleven studies as outlined in Table 4. One is clinical pharmacology (TBN-CL-001), one dose-finding study (TBN-CL-002), and the remaining nine are clinical studies evaluating the efficacy and/or safety of Ciclesonide nasal spray (M1-401, through -409).

Table 4. Clinical Trials

<b>Study</b>	<b>Type</b>	<b>Population</b>	<b>Duration</b>	<b>Ciclesonide Dose (mcg)</b>	<b>N</b>
<b>TBN-CL-001</b>	PK/PD	18 to 55 healthy and asymptomatic SAR	14 days	400 BID	6
				400 BID	6
				400 QD	6
				200 QD	6
				100 QD	6
				50 QD	6
<b>TBN-CL-002</b>	Dose Range in SAR	18 yrs and older	14 days	25 QD	145
				50 QD	145
				100 QD	143
				200 QD	146
				Placebo	148
<b>M1-401</b>	SAR – Pivotal	12 yrs and older	28 days	200 QD	164
				Placebo	163
<b>M1-402</b>	PAR – Pivotal	12 yrs and older	42 days	200 QD	238
				Placebo	233
<b>M1-403</b>	PAR	6 to 11 yrs	84 days	200 QD	165
				100 QD	166
				25 QD	169
				Placebo	165
<b>M1-404</b>	Long Term Safety in PAR	12 yrs and older	12 month	200 QD	400
				Placebo	200
<b>M1-405</b>	Long Term Safety in PAR	2 to 5 yrs	43 days	200 QD	33
				100 QD	33
				25 QD	33
				Placebo	34
<b>M1-406</b>	Onset of Action in SAR	18 yrs and older	1 day	200 QD	251
				Placebo	251
<b>M1-407</b>	Onset of Action in SAR	18 yrs and older	1 day	200 QD	210
				Placebo	210
<b>M1-408</b>	HPA axis PAR	18 to 60 yrs	43 days	200 QD	53
				Placebo	53
<b>M1-409</b>	HPA axis PAR	18 to 60 yrs	43 days	200 QD	53
				Placebo	53

## 2.2 Data Sources

Documents reviewed: \\Cdsub1\Evsprod\N22004\

### 3. STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy

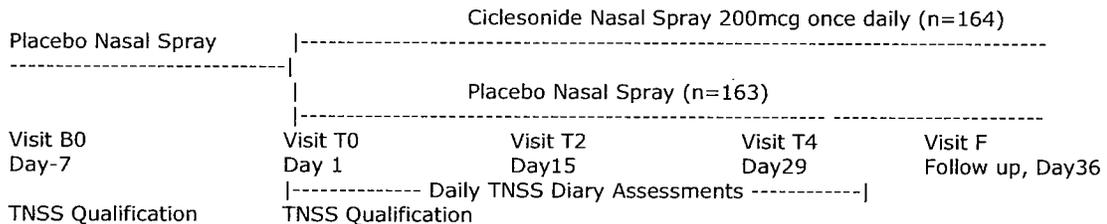
The evaluation of efficacy will include three parts. 1. Dose-finding and pivotal efficacy trials. 2. Onset of action studies. 3. Pediatric studies.

##### 3.1.1 Dose-finding and Pivotal Efficacy Trials

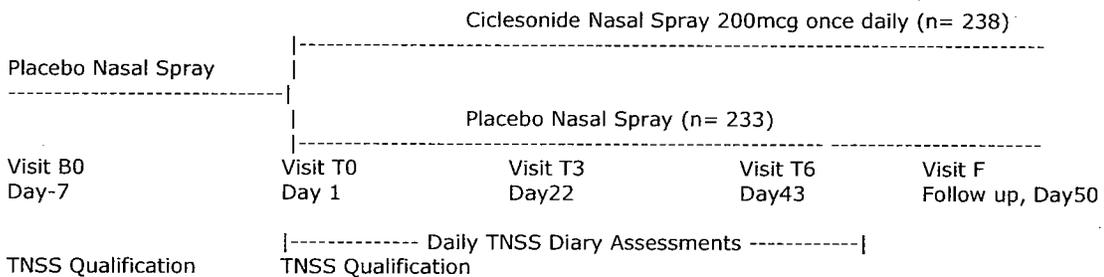
###### 3.1.1.1 Design

Study M1-401 (hereafter referred to as SAR401) was the pivotal study for SAR and M1-402 (hereafter referred to as PAR402) was the pivotal study for PAR. The two studies had similar designs. Each was a double-blind, randomized, multi-center, placebo-controlled, parallel-group study to evaluate the efficacy and safety of once-daily, intranasally administered Ciclesonide 200mcg in adult and adolescent patients 12 years and older with SAR or PAR. Study TBN-CL-02 (hereafter referred to as SAR002), the dose-finding study for SAR, was a double-blind, randomized, placebo-controlled, multi-center, multi-dose study to evaluate the efficacy and safety of Ciclesonide 25, 50, 100, and 200mcg doses once daily in patients 18 years and older with SAR. The patients in these three studies had at least a two-year history of SAR or PAR and a positive skin test to the local spring pollen. Each study had a one-week, single-blind, placebo run-in period followed by 2-weeks (SAR002) or 4-weeks (SAR401) or 6-weeks (PAR402) double-blind treatment period. (See the study flow charts below.)

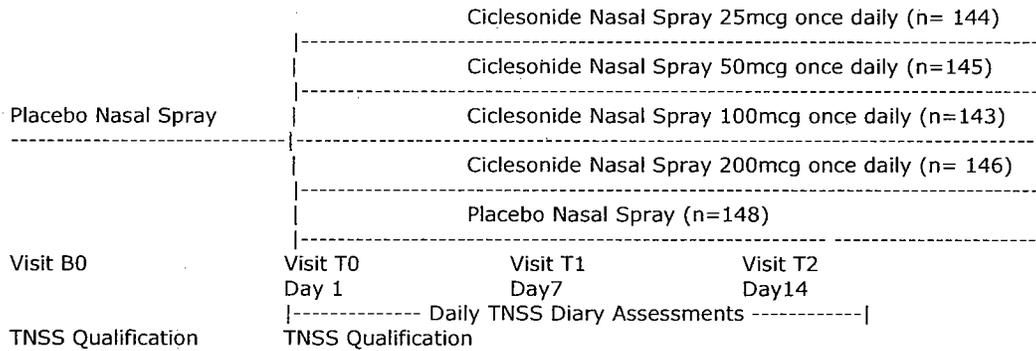
###### Study SAR401



###### Study PAR402



## Study SAR002



### 3.1.1.2 Objective

The objectives of the two pivotal studies were to evaluate the effectiveness and safety of Ciclesonide Nasal Spray 200mcg once daily in the treatment of patients 12 years of age and older with SAR or PAR. The objective of the dose-finding study was to find the minim effective dose of Ciclesonide Nasal Spray in the treatment of patients 18 years of age and older with SAR.

### 3.1.1.3 Patient Disposition

Table 5 summarizes the patient's disposition for the dose-finding study. A total of 726 subjects (ITT population) who satisfied the inclusion and exclusion criteria were randomly assigned to receive ciclesonide 200, 100, 50, 25mcg, and Placebo in Study SAR002. Seven hundred and three subjects (96.8%) completed their study. The percent of discontinuation were similar in the treatment groups. Three patients (IDs 00020092, 00050105, and 00050137) were excluded from full analysis set.

Table 5. ITT Patients' Accountability N (%), Dose-finding Study

	<b>SAR002 (n=726)</b>				
	<b>CIC 200mcg</b>	<b>CIC 100mcg</b>	<b>CIC 50mcg</b>	<b>CIC 25mcg</b>	<b>Placebo</b>
Entered	144	145	143	146	148
Completed	143 (99.3)	139 (95.5)	139 (97.2)	140 (95.5)	142 (95.5)
Discontinued	1 (0.7)	6 (4.1)	4 (2.8)	6 (4.1)	6 (4.1)
<b>Reason of early discontinuation</b>					
Adverse Event	0	3	1	1	2
Non-Compliance/disqualify	1	0	3	2	1
Lack of Efficacy	0	2	0	2	1
Pt. Withdraw Consent	0	0	0	1	1
Lost Follow-up					
Predefined Discontinuation					
Criterion Fulfilled					
Others	0	1	0	0	1
<b>Analysis Population</b>					
The full analysis set	144	145	142	145	147
The valid case set	135 (93.8)	128 (88.3)	131 (91.6)	132 (90.4)	133 (89.9)
The total set	144	145	143	146	148

Data: Dispos.xpt; Code: Demog.sas.

Table 6 summarizes the patient's disposition for the two pivotal studies. A total of 327 subjects (ITT population) who met the criteria were randomly assigned to receive ciclesonide 200mcg or placebo in Study SAR401. Two hundred and ninety two subjects (89.3%) completed the study. The percent of subjects discontinuing was slightly higher in ciclesonide 200mcg treatment group than the placebo group. Three patients (IDs 34541245, 48201348, and 52051262) were excluded from the full analysis set. A total of 471 subjects (ITT population) who met the criteria were randomly assigned to receive Ciclesonide 200mcg or placebo in Study PAR402. Four hundred and nine subjects (86.9%) completed the study. Ten patients (IDs 34122299, 34802682, 37472632, 38992594, 39092199, 39092200, 46092327, 46092677, 52202337, and 53982650) were excluded from full analysis set.

Table 6. ITT Patients' Accountability N (%), Study for Two Pivotal Studies

	<b>SAR401 (n=327)</b>		<b>PAR402 (n=471)</b>	
	<b>CIC 200mcg</b>	<b>Placebo</b>	<b>CIC 200mcg</b>	<b>Placebo</b>
Entered	164	163	238	233
Completed	143 (87.2)	149 (91.4)	206 (86.6)	203 (87.1)
Discontinued	21 (12.8)	14 (8.6)	32 (13.4)	30 (12.9)
<b>Reason of early discontinuation</b>				
Adverse Event	4	5	11	11
Non-Compliance/disqualify	4	1	3	1
Lack of Efficacy	3	4	0	3
Pt. Withdraw Consent	1	1	4	2
Lost Follow-up	2	1	0	1
Predefined Discontinuation				
Criterion Fulfilled	2	2	7	7
Others	5	0	7	5
<b>Analysis Population</b>				
The full analysis set	162	162	232	229
The valid case set	149 (90.9)	155 (95.1)	219 (92.0)	217 (93.1)
The total set	164	163	238	238

Data: Dispos.xpt; Code: Demog.sas.

### 3.1.1.4 Demographic and Baseline Characteristics

The demographics and baseline characteristics for all randomized patients (ITT) for the dose-finding study SAR002 are summarized in Table 7. The majority of the subjects were Caucasian (95%). The demographic and baseline characteristics were balanced except there were slightly less white subjects in the 200mcg group (89%) than other treatment groups (96%). In the original NDA submission, the sponsor sent in the wrong analysis data set for Instantaneous TNSS for Study SAR002. The correct data was sent in on March 30, 2006. (See attachment for details) This presentation is based on the corrected data set. The baseline value of average of AM and PM reflective and instantaneous TNSS were lower in the placebo group, so the primary analysis models need to adjust for the baseline. (In the protocol of study SAR002, the primary analysis was based on a model that did not include baseline as a covariate).

Table 7. ITT Subjects' Demographics and Baseline Characteristics, Dose-finding Study SAR002

	<b>SAR002 (n=726)</b>				
	<b>CIC 200mcg (n=144)</b>	<b>CIC 100mcg (n=145)</b>	<b>CIC 50mcg (n=143)</b>	<b>CIC 25mcg (n=146)</b>	<b>Placebo (n=148)</b>
<b>Sex</b>					
Female	104 (72.2)	95 (65.5)	105 (73.4)	104 (71.2)	104 (70.3)
Male	40 (27.8)	50 (34.5)	38 (26.6)	42 (28.8)	44 (29.7)
<b>Race</b>					
White	129 (89.6)	142 (97.9)	137 (95.8)	138 (94.5)	142 (96.0)
Black	12 (8.3)	3 (2.1)	5 (3.5)	5 (3.4)	3 (2.0)
Asian	2 (1.4)	0	0	1 (0.7)	0
Others	1 (0.7)	0	0	1 (0.7)	0
<b>Age</b>					
12 - 17	0	0	0	0	1 (0.7)
18 - 45	79 (54.9)	103 (71.0)	93 (65.0)	98 (67.1)	103 (69.6)
Over 45	65 (45.1)	42 (29.0)	50 (35.0)	48 (32.9)	44 (29.7)
Mean (SD)	41.8 (12.0)	37.8 (11.6)	40.7 (11.1)	40.4 (10.5)	38.7 (11.6)
Median	42.6	35.9	40.8	40.7	38.3
Range	18.2 - 66	18 - 65	19.9-64.7	18.3-64.5	16.2-65.4
<b>Type of Skin Test</b>					
Current Skin Prick	144 (100%)	145 (100%)	143 (100%)	146 (100%)	148 (100%)
<b>Antigen Challenge Results (mm)</b>					
Mean (SD)	8.8 (3.89)	8.2 (3.63)	8.5 (3.69)	8.8 (3.74)	8.5 (4.01)
Median	8	8	8	8	7
Range	3 - 22	3 - 20	3 - 22	3 - 24	3 - 25
<b>Control Results (mm)</b>					
Mean (SD)	0.3 (0.88)	0.3 (0.92)	0.4 (1.18)	0.3 (1.03)	0.4 (0.95)
Median	0	0	0	0	0
Range	0 - 5	0 - 5	0 - 5	0 - 5	0 - 5
<b>AVG(AM,PM) Reflective TNSS</b>					
Mean (SD)	9.4 (1.6)	9.4 (1.7)	9.2 (1.8)	9.3 (1.7)	8.9 (1.7)
Median	9.36	9.51	9.38	9.27	8.92
N, Range	144, 6 - 12	145, 5 - 12	142, 4 - 12	145, 5 - 12	147, 5 - 12
<b>AVG(AM,PM) Instantaneous TNSS</b>					
Mean (SD)	9.0 (1.9)	8.8 (1.8)	8.8 (2.0)	9.0 (1.8)	8.4 (1.8)
Median	9.1	9.0	9.0	9.1	8.5
N, Range	144, 4 - 12	145, 2.5 - 12	142, 2.8 - 12	145, 4.6 - 12	147, 3.5 - 12

Data: DE.xpt; AT.xpt; RE.xpt; IN.xpt; Code: Demog.sas

The demographics and baseline characteristics for all randomized patients (ITT) for Study SAR401 and PAR402 are summarized in Table 8. The majority of the subjects were Caucasian (86%). The demographic and baseline characteristics were balanced across treatment groups.

Table 8. ITT Subjects' Demographics and Baseline Characteristics

	<b>SAR401 (n=327)</b>		<b>PAR402 (n=471)</b>	
	<b>CIC 200mcg (n=164)</b>	<b>Placebo (n=163)</b>	<b>CIC 200mcg (n=238)</b>	<b>Placebo (n=233)</b>
<b>Sex</b>				
Female	106 (64.6)	106 (65.0)	150 (63.0)	155 (66.5)
Male	58 (35.4)	57 (35.0)	88 (37.0)	78 (33.5)
<b>Race</b>				
White	141 (86.0)	133 (81.6)	202 (84.9)	206 (88.4)
Black	10 (6.1)	12 (7.4)	10 (4.2)	9 (3.9)
Asian	2 (1.2)	6 (3.7)	9 (3.8)	6 (2.6)
Others	11 (6.7)	12 (7.3)	17 (7.1)	12 (5.1)
<b>Age</b>				
12 - 17	12 (7.3)	13 (8.0)	27 (11.4)	27 (11.6)
18 - 45	93 (56.7)	84 (55.5)	141 (59.2)	140 (60.1)
Over 45	59 (36.0)	66 (40.5)	70 (29.4)	66 (28.3)
Mean (SD)	39.1 (13.9)	40.8 (15.1)	35.7 (14.2)	35.4 (14.2)
Median	38	42	35	34
Range	12 - 73	12 - 86	12 - 75	12 - 73
<b>Type of Skin Test</b>				
Historical Skin Prick	39 (23.8%)	42 (25.8%)	71 (29.8%)	81 (34.8%)
Current Skin Prick	125 (76.2%)	121 (74.2%)	167 (70.2%)	152 (65.2%)
<b>Antigen Challenge Results (mm)</b>				
Mean (SD)	10.2 (5.1)	9.2 (3.4)	8.4 (4.1)	8.2 (3.9)
Median	9	8	8	7
Range	3 - 35	4 - 23	3 - 35	3 - 21
<b>Control Results (mm)</b>				
Mean (SD)	0.9 (1.7)	0.9 (1.7)	0.4 (1.0)	0.3 (0.8)
Median	0	0	0	0
Range	0 - 8	0 - 10	0 - 5	0 - 4
<b>Histamine Results (mm)</b>				
Mean (SD)	9.1 (3.8)	8.9 (3.9)	6.3 (2.4)	6.2 (2.4)
Median	8	8	6	6
Range	3 - 32	3 - 35	0 - 14	1 - 15
<b>AVG(AM,PM) Reflective TNSS</b>				
Mean (SD)	9.0 (1.96)	8.8 (1.82)	7.6 (2.04)	7.7 (2.14)
Median	9.2	9.0	7.5	7.8
N, Range	162, 4-12	162, 4-12	232, 3.17 - 12	229, 2.86 - 12
<b>AVG(AM,PM) Instantaneous TNSS</b>				
Mean (SD)	8.4 (2.24)	8.3 (2.08)	7.1 (2.15)	7.1 (2.27)
Median	8.6	8.4	7.2	6.9
N, Range	2.8 - 12	2.9 - 12	1.93 - 11.79	1.86 - 12

Data: DE.xpt; AT.xpt; RE.xpt; IN.xpt; Code: Demog.sas

### 3.1.1.5 Statistical Methodologies

#### Primary Efficacy Analysis

The primary efficacy measurement in SAR401, PAR402, and SAR002 was the Total Nasal Symptom Score (TNSS) as measured by symptom scores recorded twice daily in the TNSS Diary. Baseline TNSS was defined as the average reflective TNSS from Day -7 to Day 1. The TNSS was comprised of individual symptom scores for runny nose, sneezing, itchy nose, and nasal congestion. Each symptom was scored on a 4-point scale (0=no symptoms; 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms), 12 points for AM TNSS and 12 points for PM TNSS. The baseline score was subtracted from daily TNSS scores to calculate the

change from baseline.

In Study SAR002, the primary efficacy variable was the change from baseline in SUM of AM and PM reflective TNSS over the 2-week treatment period. Change from baseline for each active treatment group over the 2-week study was compared to placebo using a repeated measure ANCOVA according to the restricted maximum likelihood estimation for mixed effect models. This model included treatment, day, and treatment-by-day fixed effect, day was treated as an unordered categorical variable and patient as the random effect and used the compound symmetric structure as covariance structure in the primary analysis model.

$$Y_{ijk} = P_{ij} + T_j + D_k + (T*D)_{jk} + E_{jik}$$
where  $T_j$  is the  $j^{\text{th}}$  treatment,  $P_{ij}$  is the  $i^{\text{th}}$  patients with  $j^{\text{th}}$  treatment,  $D_k$  is the  $k^{\text{th}}$  day, and  $E_{jik}$  is the error term.  $T*D$  is the treatment by day interaction.

In Studies SAR401 and PAR402, the primary efficacy variable was the change from baseline in AVERAGE of AM and PM reflective TNSS over the 2-week (SAR401) or 6-week (PAR402) treatment period. Change from baseline for each active treatment group over the 2-week study (or 6-weeks study) was compared to placebo using a repeated measure ANCOVA according to the restricted maximum likelihood estimation for mixed effect models. This model included treatment, day, and treatment-by-day fixed effect, day was treated as an unordered categorical variable and patient as the random effect and the first order autoregressive structure AR(1) as covariance structure in the primary analysis model.

$$Y_{ijk} = P_{ij} + B_{ijk} + T_j + D_k + (T*D)_{jk} + E_{jik}$$
where  $B_{ijk}$  is the baseline covariate for patients  $i$  in day  $k$  and treatment  $j$ ,  $T_j$  is the  $j^{\text{th}}$  treatment,  $P_{ij}$  is the  $i^{\text{th}}$  patients with  $j^{\text{th}}$  treatment,  $D_k$  is the  $k^{\text{th}}$  day, and  $E_{jik}$  is the error term.  $T*D$  is the treatment by day interaction.

Note: 1. Statistical Analysis Plan Submitted July 1, 2004 stated that the sponsor was not including center in the model because it caused convergence problems in study SAR401; 2. the baseline was not a covariate in the model for study SAR002; 3. three studies used the different covariance structure. See Section 3.1.1.7 Reviewer's analysis for the comments.

#### Key Secondary Endpoints

For Study SAR401 and Study PAR402, the key secondary efficacy variables were as follows:

- Average AM and PM patient-assessed instantaneous TNSS over Days 1-14
- Physician Assessed Nasal Signs and Symptoms (PANS) at Endpoint
- Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (adult and adolescent) at Endpoint

PANS was defined as the average of the sum of the intensity scores (each ranging from 0 to 3) for the Nasal Signs and the sum of the intensity scores (each ranging from 0 to 3) for the Nasal Symptoms. Thus, the maximum value was 12 and the minimum value was 0.

For the items in the RQLQ, patients were asked to recall their experiences during the previous week and to give their responses on a seven-point scale (0=least severe to 6=extremely severe).

As specified in the protocol, the mean non-missing score for each domain and the overall score (average of the scores for all items) at baseline and each treatment visit was used. If 50% or more of the responses were absent in a domain, the result for that domain and the overall score for the patient was set to missing. For the Activities domain, the patients were instructed to list the same three activities at all visits. When a patient had changed the activities listed, the scores for the new activities were used to minimize the number of missing values for the overall RQLQ score. In this context the “Activities” domain represented generic activities, not specific activities.

### Multiplicity

The step down procedure was used to control the Type I error. The test order was the primary efficacy measure was tested first. If the p-value from the test of the primary efficacy was  $\leq 0.05$  then the average AM and PM instantaneous TNSS over Days 1-14 was to be examined; If the p-value from the test of the Instantaneous TNSS over Days 1-14 was  $\leq 0.05$  then the PANS at endpoint was to be examined; If the p-value from the PANS was  $\leq 0.05$  then the RQLR at endpoint was to be examined. Any testing outside of this closed testing procedure was considered exploratory.

### Sample Size

In Study SAR002, the sample size of 625 (125 per treatment arm) was sufficient to ensure a power of 80% to correctly conclude that there was a difference between Ciclesonide and placebo under the assumptions of a common standard deviation of 2.5 and a difference between treatment groups of 0.9 using a two-sided alpha level of 5%.

In Study SAR401 the sample size of 302 (151 per treatment arm) was sufficient to ensure a power of 90% to correctly conclude that there was a difference between Ciclesonide and placebo under the assumptions of a common standard deviation of 2.4 and a difference between treatment groups of 0.9 using a two-sided alpha level of 5%.

In Study PAR402 the sample size of 418 (209 per treatment arm) was sufficient to ensure a power of 90% to correctly conclude that there was a difference between Ciclesonide and placebo under the assumptions of a common standard deviation of 2.2 and a difference between treatment groups of 0.7 using a two-sided alpha level of 5%.

### ITT Population

As defined in the protocol, the “**full analysis set**” was used to describe the analysis set which included all randomized patients who took at least one dose of study medication. The primary efficacy analyses were based on the full analysis set. The “**total set**” consisted of all patients enrolled including patients withdrawn prior to randomization (non-eligible patients) and randomized patients who never took study medication. The safety analyses were based on the full analysis set. The “**valid cases set**” consisted of all patients in the full analysis set without any major protocol violation. The valid case set was determined at a Blind Data Review Meeting (BDRM) held prior to un-blinding of patient treatment. The PP analyses were based on the valid case set.

For the repeated measures analysis, as specified in the protocol, no imputation for missing values was performed as the extent of the missing data had been predicted to be low and assumed to be missing at random. Repeated measures analyses as a maximum likelihood method is valid when there are missing values that are missing-at-random. In the analyses of mean change from Baseline calculations, no imputation for missing values was employed to create endpoint.

#### Interim Analyses

No interim analysis was performed.

### 3.1.1.6 Sponsor's Results and Conclusions

The sponsor's analysis of the primary efficacy endpoint of Study SAR002, SAR401, and PAR402 are provided in Table 9. (p30, clinical-overview.pdf)

Table 9. Overview of Changes from Baseline in Primary Efficacy Variable: Patient-Assessed AM and PM Reflective TNSS

Treatment	Baseline Mean (SD) <sup>a</sup>	LS Mean Change from Baseline (SE)	Treatment Comparison vs. Placebo		
			LS Mean Difference <sup>b</sup>	95% CI	p-value
<b>Summed AM and PM Reflective TNSS (Days 2-14) – TBN-CL-002 –without baseline in the model</b>					
Ciclesonide 200 (n = 144)	18.82 (3.27)	-5.83 (0.39)	-1.64	-2.74, -0.55	0.0033
Ciclesonide 100 (n = 145)	18.71 (3.37)	-5.33 (0.42)	-1.15	-2.24, -0.05	0.0398
Ciclesonide 50 (n = 142)	18.35 (3.61)	-4.79 (0.41)	-0.60	-1.70, 0.50	0.2838
Ciclesonide 25 (n = 145)	18.72 (3.47)	-4.81 (0.36)	-0.62	-1.71, 0.47	0.2648
Placebo (n =146)	17.80 (3.42)	-4.19 (0.39)	--	--	--
<b>Summed AM and PM Reflective TNSS (Days 2-14) – TBN-CL-002-with baseline in the model</b>					
Ciclesonide 200 (n = 144)	18.82 (3.27)	-5.73 (0.39)	-1.35	-2.43, -0.28	0.014
Ciclesonide 100 (n = 145)	18.71 (3.37)	-5.26 (0.39)	-0.88	-1.96, 0.19	0.11
Ciclesonide 50 (n = 142)	18.35 (3.61)	-4.82 (0.39)	-0.44	-1.52, 0.63	0.42
Ciclesonide 25 (n = 145)	18.72 (3.47)	-4.74 (0.39)	-0.35	-1.42, 0.71	0.51
Placebo (n =146)	17.80 (3.42)	-4.38 (0.39)	--	--	--
<b>Average AM and PM Reflective TNSS (Days 1-14) - MI-401</b>					
Ciclesonide 200 (n = 162)	8.96 (1.96)	-2.40 (0.16)	0.90	(0.45, 1.36)	<0.001
Placebo (n = 162)	8.83 (1.82)	-1.50 (0.16)	--	--	--
<b>Average AM and PM Reflective TNSS (Days 1-42) - MI-402</b>					
Ciclesonide 200 (n = 232)	7.59 (2.04)	-2.51 (0.12)	0.63	(0.28, 0.97)	<0.001
Placebo (n = 229)	7.71 (2.14)	-1.89 (0.13)	--	--	--

<sup>a</sup> Baseline means are the average of the TNSS values over the last seven days of the Baseline Period.

<sup>b</sup> Differences for TBN-CL-002 represent ciclesonide minus placebo, whereas, the other studies utilize placebo minus ciclesonide.

### 3.1.1.7 Reviewer's Efficacy Analysis

#### *Efficacy for SAR and PAR –*

This reviewer found a mistake in the sponsor's SAS code, incorrect data values, and duplication in patients' records in the electronic datasets. The sponsor admitted the problems and re-submitted the data sets and tables on March 29, 2006 and April 7, 2006. (See Section 5.1 Statistical Issue for the details)

This reviewer modified the sponsor's primary analysis for Study SAR002 by including the baseline as a covariate and assumed a compound symmetry correlation structure. For studies SAR401 and PAR402, the primary analysis the model included baseline treatment, day, and treatment-by-day as fixed effects. Day was treated as an unordered categorical variable and patient was a random effect and the first order autoregressive structure AR(1) was used in the primary analysis model.

$$Y_{ijk} = P_{ij} + B_{ijk} + T_j + D_k + (T*D)_{jk} + E_{jik}$$

Where  $B_{ijk}$  is the baseline covariate for patients  $I$  in day  $k$  and treatment  $j$ ,  $T_j$  is the  $j^{\text{th}}$  treatment,  $P_{ij}$  is the  $i^{\text{th}}$  patients with  $j^{\text{th}}$  treatment,  $D_k$  is the  $k^{\text{th}}$  day, and  $E_{jik}$  is the error term.  $T*D$  is the treatment by day interaction.

This reviewer reapplied modified primary efficacy analyses to the submitted data using the corrected SAS code. The results of these analyses are displayed in Table 10 and are very similar to those provided by the sponsor and displayed in Table 9.

Table 10. Change from Baseline in Primary Efficacy Variables: AM and PM Reflective TNSS

Treatment	Baseline Mean (SD)	Change from Baseline		Treatment Comparison Ciclesonide vs. Placebo		
		N	LS Mean (SE)	LS Mean Difference	95% CI	p-value <sup>a</sup>
<b>Summed AM and PM Reflective TNSS (Day 2-14) SAR002 <sup>b</sup></b>						
Ciclesonide 200	18.82 (3.27)	144	-5.734 (0.38)	-1.353	(-2.405, -0.23)	0.0118
Ciclesonide 100	18.71 (3.37)	145	-5.266 (0.38)	-0.884	(-1.934, 0.166)	0.0988
Ciclesonide 50	18.35 (3.61)	142	-4.821 (0.38)	-0.440	(-1.494, 0.613)	0.4127
Ciclesonide 25	18.72 (3.47)	145	-4.738 (0.38)	-0.356	(-1.407, 0.694)	0.5059
Placebo	17.80 (3.42)	146	-4.378 (0.38)	-	-	-
<b>Average AM and PM Reflective TNSS (Day 1-14) SAR401 <sup>c</sup></b>						
Ciclesonide 200	8.96 (1.96)	162	-2.401 (0.16)	0.9043	(0.449, 1.359)	< 0.0001
Placebo	8.83 (1.82)	162	-1.496 (0.16)	-	-	-
<b>Average AM and PM Reflective TNSS (Day 1-42) PAR402 <sup>c</sup></b>						
Ciclesonide 200	7.59 (2.04)	232	-2.509 (0.12)	0.6217	(0.276, 0.967)	0.0004
Placebo	7.72 (2.14)	229	-1.888 (0.13)	-	-	-

a: a: p-value is from a repeated measures ANCOVA with treatment, baseline, day, and treatment by day interaction;

b: Differences for SAR002 represent Ciclesonide minus placebo, whereas, the other studies utilize placebo minus Ciclesonide; As protocol specified, assumes a compound symmetry covariance structure with baseline included in the model;

c: As protocol specified, assumes a first order autoregressive covariance structure.

In order to assess the robustness of the primary analysis results to the selection of the variance-covariance matrix, this reviewer reapplied the protocol-specified primary efficacy analyses to the data using autoregressive (1), compound symmetry, and unstructured covariance structures in the mixed effect model. The conclusions from each of these analyses are provided in Table 11 and show that the conclusions are robust in that they are qualitatively consistent regardless of the choice of the variance-covariance matrix and for SAR002 whether or not baseline is included in the model.

Table 11. Robustness of the Primary Analysis Model for the Pivotal Studies  
Treatment Comparison in Change from Baseline of Average AM and PM Reflective TNSS

Treatment	CS <sup>1</sup>		AR(1) <sup>2</sup>		UN <sup>3</sup>	
	LS Mean Difference	p-value	LS Mean Difference	p-value	LS Mean Difference	p-value
<b>Summed AM and PM Reflective TNSS (Day 2-14) SAR002<sup>4</sup></b>						
Ciclesonide 200	-1.64	0.003	-1.64	< 0.001	-1.64	0.003
Ciclesonide 100	-1.14	0.040	-1.14	0.019	-1.14	0.040
Ciclesonide 50	-0.60	0.285	-0.60	0.221	-0.60	0.286
Ciclesonide 25	-0.62	0.266	-0.62	0.203	-0.62	0.267
Placebo	-	-	-	-	-	-
<b>Average AM and PM Reflective TNSS (Day 1-14) SAR401</b>						
Ciclesonide 200	0.90	< 0.001	0.90	< 0.001	0.91	< 0.001
Placebo	-	-	-	-	-	-
<b>Average AM and PM Reflective TNSS (Day 1-42) PAR402</b>						
Ciclesonide 200	0.63	< 0.001	0.62	< 0.001	0.62	< 0.001
Placebo	-	-	-	-	-	-

1: Compound Symmetry. 2: Autoregressive (1). 3: Unstructured. 4: For study SAR002, model did not include the baseline as a covariate as specified in the SAP.

This reviewer did additional sensitivity analyses to assess the impact of the repeated measures approach taken in the primary efficacy analyses and to test for treatment by center interaction. The efficacy variables considered were the mean change from baseline over 2 weeks (Study SAR002 and Study SAR401) or 6 weeks (Study PAR402). A typical ANCOVA model, which showed below, with fixed-effect factors for baseline value, treatment, and center as covariates, was used in the analysis of the average changes from baseline over the 2-weeks (SAR studies) treatment period in average of AM and PM reflective TNSS. In order to allow a direct comparison between Studies SAR002 and SAR401, this reviewer used the average AM and PM reflective TNSS as the efficacy variable instead of the sum AM and PM reflective TNSS which was pre-specified in the protocol of the dose-finding study.

$$Y_{ijk} = B_{ijk} + T_j + C^i + E_{ijk}$$

Where  $B_{ijk}$  is the baseline covariate for patients  $k$  in center  $i$  who have treatment  $j$ ,  $T_j$  is the  $j^{\text{th}}$  treatment,  $C^i$  is the  $i^{\text{th}}$  center, and  $E_{ijk}$  is the error term.

The reviewer's analysis results are displayed in Table 12. The reviewer's analysis results are qualitatively consistent with the primary analysis results, which showed that Ciclesonide Nasal Spray 200mcg once daily is statistically significantly superior to placebo in improving the average of AM and PM reflective TNSS in adult and adolescent patients 12 years old with SAR or PAR.

Table 12. Mean Change from Baseline of Average of AM and PM Reflective TNSS

Treatment	Baseline Mean (SD)	Change from Baseline		Treatment Comparison <sup>1</sup> Placebo vs. Ciclesonide		
		N	LS Mean (SE)	LS Mean Difference	95% CI	p-value
<b>Average AM and PM Reflective TNSS (Day 2-14) SAR002</b>						
Ciclesonide 200	9.40 (1.63)	144	-2.85 (0.19)	0.7152	(0.190, 1.241)	0.0077
Ciclesonide 100	9.36 (1.66)	145	-2.61 (0.19)	0.4719	(-0.052, 0.996)	0.0776
Ciclesonide 50	9.17 (1.78)	142	-2.38 (0.19)	0.2421	(-0.284, 0.768)	0.3664
Ciclesonide 25	9.33 (1.74)	145	-2.33 (0.19)	0.1956	(-0.329, 0.720)	0.4640
Placebo	8.91 (1.69)	146	-2.14 (0.19)	-	-	-
<b>Average AM and PM Reflective TNSS (Day 1-14) SAR401</b>						
Ciclesonide 200	8.96 (1.96)	162	-2.456 (0.16)	0.8986	(0.455, 1.342)	< 0.0001
Placebo	8.83 (1.82)	162	-1.557 (0.16)	-	-	-
<b>Average AM and PM Reflective TNSS (Day 1-42) PAR402</b>						
Ciclesonide 200	7.59 (2.04)	232	-2.575 (0.14)	0.6487	(0.298, 0.999)	0.0003
Placebo	7.72 (2.14)	229	-1.926 (0.15)	-	-	-

1. The ANCOVA model, with fixed-effect factors for baseline value, treatment, and center as covariates

### Minimum Effective Dose for SAR –

In dose-finding study, SAR002, the primary efficacy analysis model did not include baseline as a covariate. The sponsor added the post-hoc analysis using the model include baseline as a covariate. The results from two analyses were different which showed that Ciclesonide Nasal Spray 100mcg daily was statistically significantly superior to placebo in the model without baseline and not in other. The baseline value of average of AM and PM reflective and instantaneous TNSS were lower in the placebo group, so the primary analysis models need to adjust for the baseline. (See Table 7 for detail)

Figure 5 displays the LS Mean difference between Ciclesonide and placebo in terms of the mean change from baseline in average of AM and PM reflective TNSS over 2 weeks for patients 12 years of age and older with SAR using the reviewer’s modified model described in the context of the analyses presented in Table 12. The results clearly show that efficacy of Ciclesonide was dose related; only the 200mcg/day dose of Ciclesonide was distinguishable from placebo at  $p < 0.05$ . Therefore, the data obtained from the Study SAR002 (dose-finding study) and SAR401 (SAR pivotal study) suggest that the 100mcg/day dose of Ciclesonide nasal spray is only marginally effective in the treatment of SAR in adult patients.

From the sponsor’s claim (page 29-30 clinical-overview.pdf)

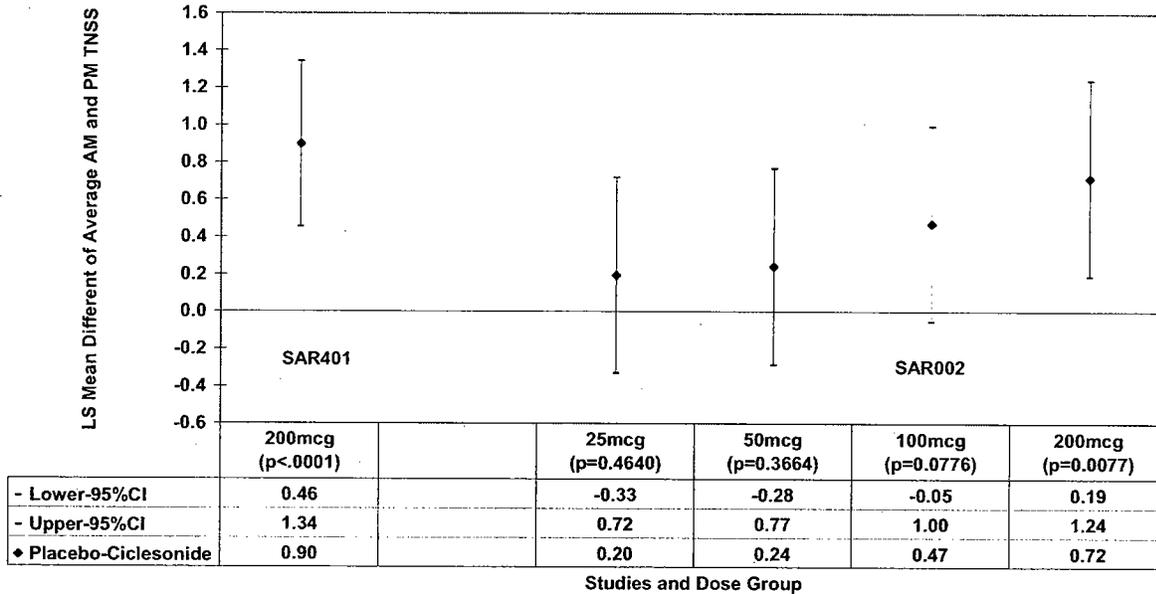
*“One noteworthy consideration in the interpretation of these results is that the analysis of the primary measure was based on a model that did not include baseline as a covariate. The inclusion of baseline as a covariate is recommended in the CPMP’s “Points to Consider on Adjustments for Baseline Covariates” [CPMP, 2003]. Its inclusion in the analyses allows for a more accurate modeling of the data, particularly when baseline values differ appreciably between treatment groups by preventing a regression to the mean bias in treatment estimates. When baseline was incorporated into the statistical model in a post-hoc analysis, only the 200 mcg/day dose of ciclesonide was distinguishable from placebo at  $p < 0.05$ .”*

Table 2.5 - 4 Overview of Changes from Baseline in Patient-Assessed AM and PM Reflective TNSS

Treatment	Baseline Mean (SD) <sup>a</sup>	LS Mean Change from Baseline (SE)	Treatment Comparison vs. Placebo		
			LS Mean Difference <sup>b</sup>	95% CI	p-value
<b>Summed AM and PM Reflective TNSS (Days 2-14) - TBN-CL-002 –without baseline in the model</b>					
Ciclesonide 200 (n = 144)	18.82 (3.27)	-5.83 (0.39)	-1.64	-2.74, -0.55	0.0033
Ciclesonide 100 (n = 145)	18.71 (3.37)	-5.33 (0.42)	-1.15	-2.24, -0.05	0.0398
Ciclesonide 50 (n = 142)	18.35 (3.61)	-4.79 (0.41)	-0.60	-1.70, 0.50	0.2838
Ciclesonide 25 (n = 145)	18.72 (3.47)	-4.81 (0.36)	-0.62	-1.71, 0.47	0.2648
Placebo (n = 146)	17.80 (3.42)	-4.19 (0.39)	--	--	--
<b>Summed AM and PM Reflective TNSS (Days 2-14) – TBN-CL-002-with baseline in the model</b>					
Ciclesonide 200 (n = 144)	18.82 (3.27)	-5.73 (0.39)	-1.35	-2.43, -0.28	0.014
Ciclesonide 100 (n = 145)	18.71 (3.37)	-5.26 (0.39)	-0.88	-1.96, 0.19	0.11
Ciclesonide 50 (n = 142)	18.35 (3.61)	-4.82 (0.39)	-0.44	-1.52, 0.63	0.42
Ciclesonide 25 (n = 145)	18.72 (3.47)	-4.74 (0.39)	-0.35	-1.42, 0.71	0.51
Placebo (n = 146)	17.80 (3.42)	-4.38 (0.39)	--	--	--
<b>Average AM and PM Reflective TNSS (Days 1-14) - M1-401</b>					
Ciclesonide 200 (n = 162)	8.96 (1.96)	-2.40 (0.16)	0.90	(0.45, 1.36)	<0.001
Placebo (n = 162)	8.83 (1.82)	-1.50 (0.16)	--	--	--
<b>Average AM and PM Reflective TNSS (Days 1-14) - M1-402</b>					
Ciclesonide 200 (n = 232)	7.59 (2.04)	-2.51 (0.12)	0.63	(0.28, 0.97)	<0.001
Placebo (n = 229)	7.71 (2.14)	-1.89 (0.13)	--	--	--

<sup>a</sup> Baseline means are the average of the TNSS values over the last seven days of the Baseline Period.  
<sup>b</sup> Differences for TBN-CL-002 represent ciclesonide minus placebo, whereas, the other studies utilize placebo minus ciclesonide.

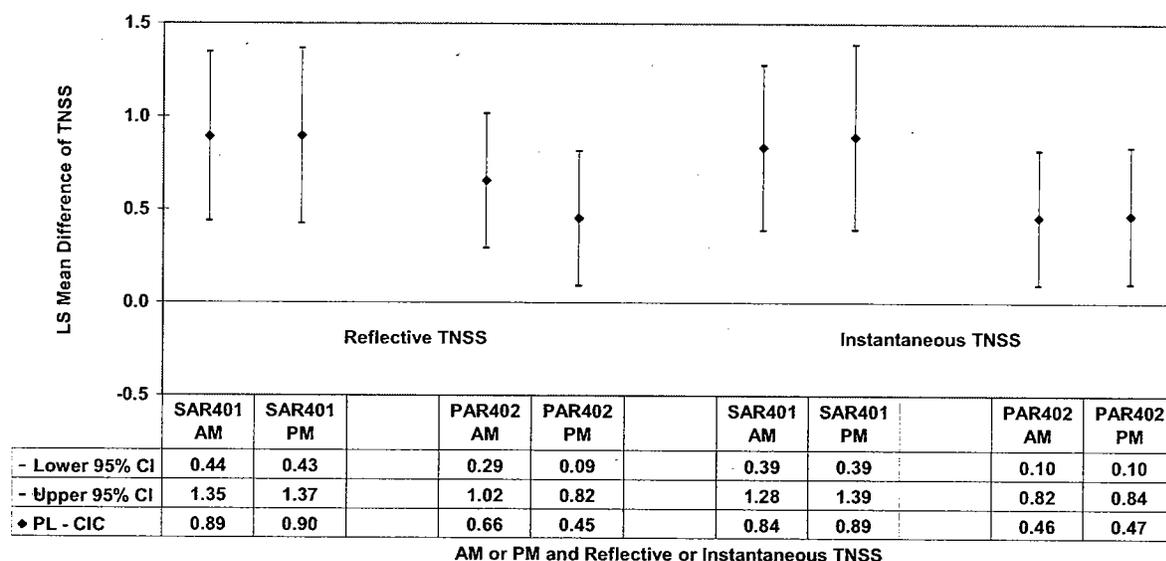
Figure 5. LS Mean Change from Baseline of Average of AM and PM reflective TNSS



**Assessment of Treatment Effect over the Full 24-hours –**

Figure 6 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 (SAR401) or 4 weeks (PAR402) for patients 12 years of age and older with SAR using the reviewer’s modified model described in the context of the analyses presented in Table 12. The results show that the magnitude of the differences between Ciclesonide 200mcg and placebo once daily in the morning for 12-hour reflective TNSS were similar at both the morning (24-hours post-dose) and the evening (12-hours post-dose) time points in the SAR401, greater in the morning in SAR402. Additionally, the individual AM and individual PM instantaneous TNSS showed similar magnitude of effects. These results support the improvement in TNSS was maintained over the full 24-hour dosing interval.

Figure 6. LS Mean Change from Baseline of AM or PM TNSS



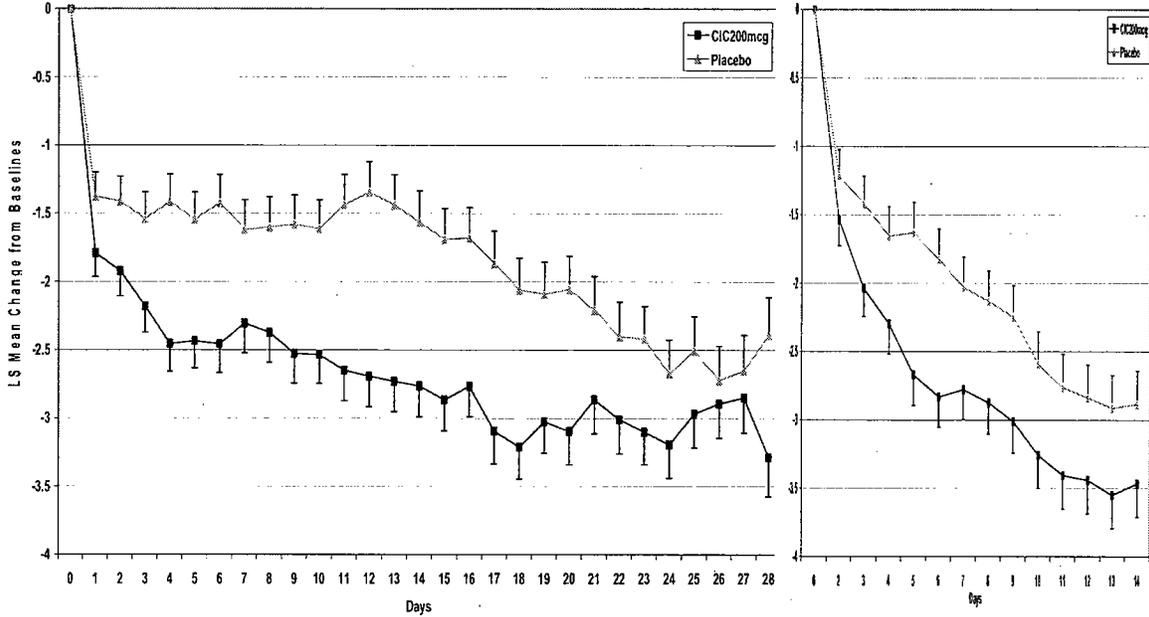
**Assessment of Treatment Effect over Time –**

Figure 7 shows the treatment effect over time for average AM and PM reflective TNSS in the dose-finding study (SAR002) and the SAR pivotal study (SAR401). The graphic on the left represents Study SAR401 and the graphic on the right represents Study SAR002 (only the Ciclesonide 200mcg and placebo groups are shown). The blue lines represent the Ciclesonide 200mcg treatment group and the pink lines represent the Placebo group. The trends over time are similar among the treatment groups in two studies. The magnitude of the difference between Ciclesonide Nasal Spray 200mcg once daily and placebo in the primary efficacy endpoint was fairly consistent across time in both studies except the last week of study SAR401.

Figure 8 shows the treatment effect over time for average AM and PM reflective TNSS in the PAR pivotal study (PAR402). The blue lines represent the Ciclesonide 200mcg treatment group and the pink lines represent the Placebo group. In Study PAR402, a 6 week study, the difference

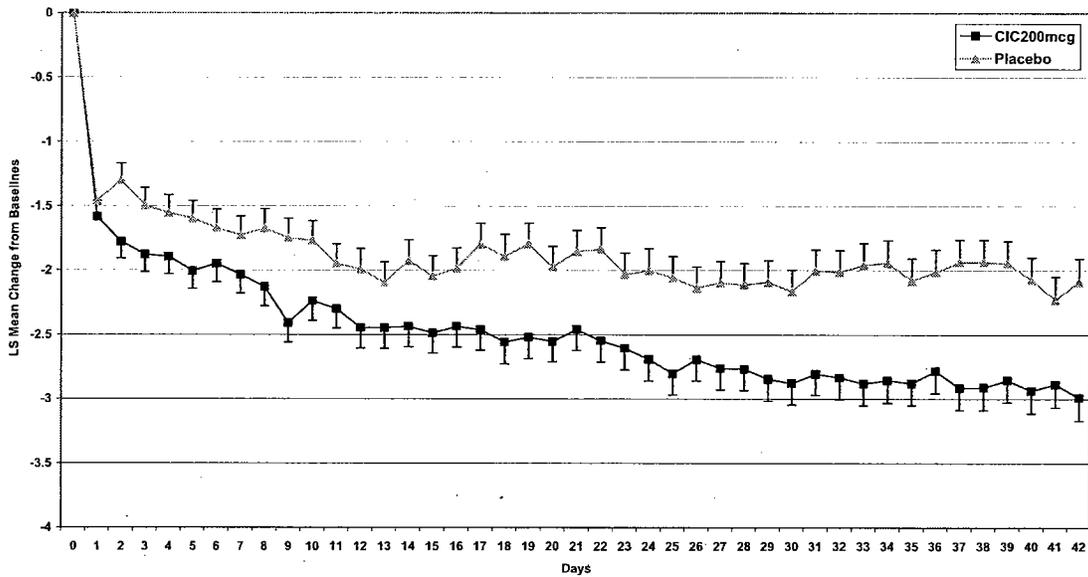
between Ciclesonide 200mcg treatment group and placebo group in the last 2 weeks was bigger than the first 2 weeks.

Figure 7. Change from Baseline of Average AM and PM Reflective TNSS by Treatment Day



In order to allow a comparison of the magnitude of the difference between Ciclesonide 200mcg and placebo across studies, the scales of graphic for three studies are the same.

Figure 8. Change from Baseline of Average AM and PM Reflective TNSS by Treatment Day



**Individual Symptoms Scores of TNSS –**

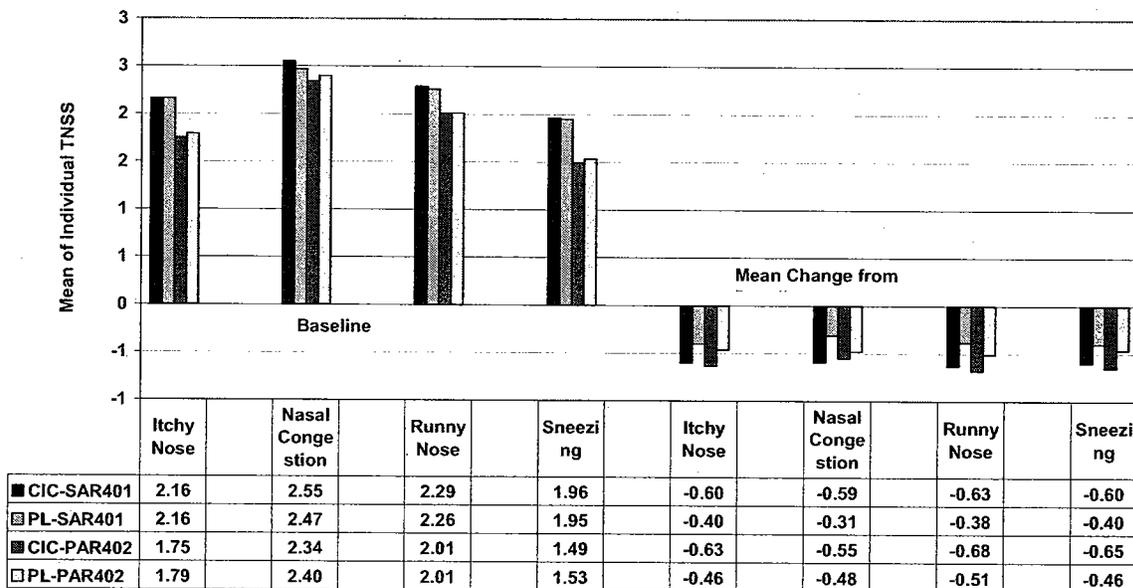
The changes from baseline of average AM and PM reflective symptom scores for individual symptoms of the TNSS over 14-days (Study SAR402) or 42-days (Study PAR402) are summarized in Table 13. Figure 9 shows the patients treated with Ciclesonide 200mcg nasal spray had improvements versus placebo in all four nasal symptoms except the nasal congestion did not reach the statistical significance in Study PAR402.

Table 13. Change from Baseline in Average AM and PM Reflective Individual Symptoms Score

Study	N		Baseline (Mean ± SD)		Change from Baseline (LS Mean ± SE)		LS Mean Difference, P-value, 95%CI PL – CIC
	CIC	PL	CIC	PL	CIC	PL	
<b>Average AM and PM Reflective Individual TNSS – Itch Nose (Scale 0 to 3)</b>							
SAR401 <sup>1</sup>	162	162	2.16 (0.63)	2.16 (0.64)	-0.61 (0.04)	-0.41 (0.04)	0.1996, p=0.0017 (0.075, 0.324)
PAR402 <sup>2</sup>	232	229	1.75 (0.72)	1.79 (0.74)	-0.66 (0.04)	-0.48 (0.04)	0.1803, p=0.0004 (0.080, 0.280)
<b>Average AM and PM Reflective Individual TNSS – Nasal Congestion (Scale 0 to 3)</b>							
SAR419	162	162	2.55 (0.47)	2.47 (0.45)	-0.60 (0.04)	-0.34 (0.04)	0.2545, p<0.0001 (0.140, 0.369)
SAR420	232	229	2.34 (0.50)	2.40 (0.54)	-0.57 (0.04)	-0.47 (0.04)	0.0972, p=0.0595 (-0.004, 0.198)
<b>Average AM and PM Reflective Individual TNSS – Runny Nose (Scale 0 to 3)</b>							
SAR401	162	162	2.29 (0.58)	2.26 (0.53)	-0.63 (0.05)	-0.40 (0.05)	0.2312, p=0.0009 (0.096, 0.366)
SAR420	232	229	2.01 (0.66)	2.01 (0.66)	-0.69 (0.04)	-0.51 (0.04)	0.0535, p=0.0010 (0.071, 0.282)
<b>Average AM and PM Reflective Individual TNSS – Sneezing (Scale 0 to 3)</b>							
SAR419	162	162	1.96 (0.69)	1.95 (0.64)	-0.61 (0.05)	-0.41 (0.05)	0.1995, p=0.0023 (0.072, 0.327)
SAR420	232	229	1.49 (0.75)	1.53 (0.72)	-0.67 (0.04)	-0.47 (0.04)	0.0492, p< 0.0001 (0.104, 0.298)

1: Average of 14-days; 2: Average of 42-days.

Figure 9. Raw Mean of Average AM and PM Reflective Individual Symptom Score



**Pollen Count and Center Effect –**

Mean pollen counts were lower during the first part of the baseline period and the final seven days of patient treatment. Mean of Pollen Counts varied by site for Study SAR401. There is no electronic data for the pollen counts provided in Study SAR002.

The sponsor excluded CENTER from the primary analysis model (repeated model by day) because the convergence problem. This reviewer performed analysis averaged over the full treatment period using an ANCOVA model, which showed below, with fixed-effect factors for baseline value, treatment, and center as covariates and testing for treatment by center interaction.

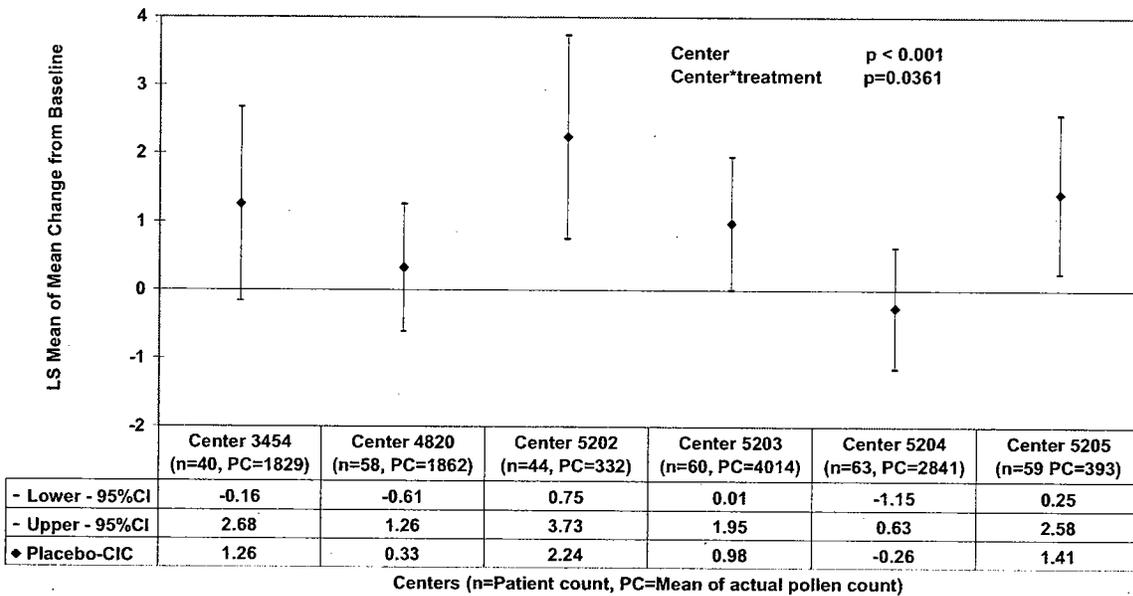
$$Y_{ijk} = B_{ijk} + T_j + C^i + E_{ijk}$$

Where  $B_{ijk}$  is the baseline covariate for patients  $k$  in center  $i$  who has treatment  $j$ ,  $T_j$  is the  $j^{\text{th}}$  treatment,  $C^i$  is the  $i^{\text{th}}$  center, and  $E_{ijk}$  is the error term.

The results are shown in Figure 10 and Figure 11. These analysis indicate that Study SAR401 had a statistical significant center effect and center\*treatment interaction.

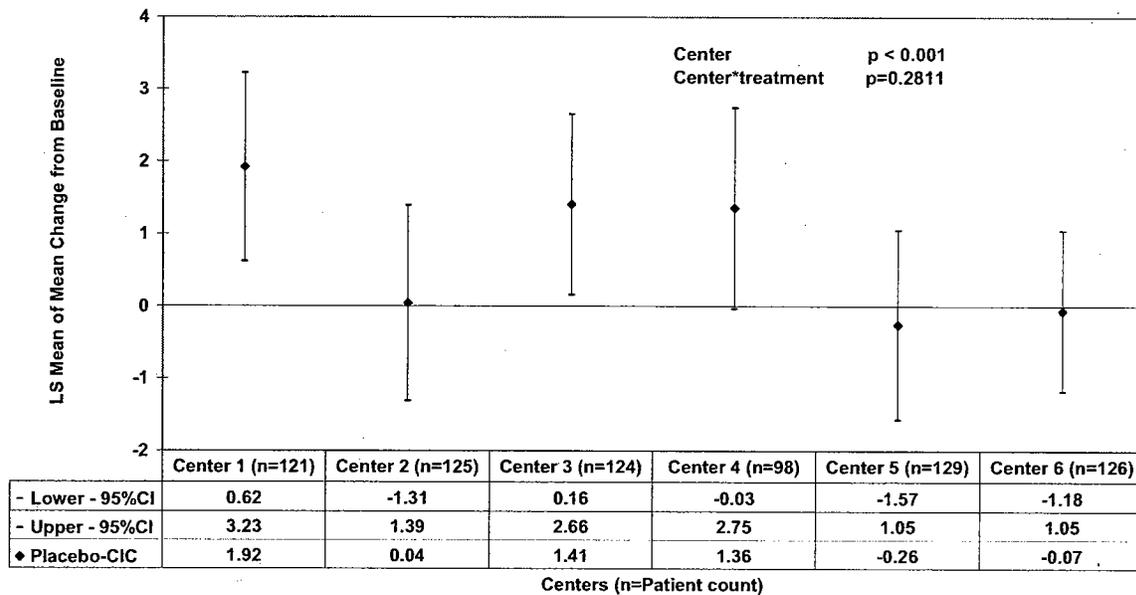
There are four common centers in Study SAR401 (centers 5203, 5204, 4820, and 5205) and SAR002 (center 1, 4, 5, and 6). The medical reviewer ordered the DSI audited for centers 5724, 5202, and 5203. Please see the medical review’s report for the results of the DSI audit.

Figure 10. Change from Baseline of Average of AM & PM Reflective TNSS by Center, SAR401



Note: LS mean from an ANCOVA model (mean change from baseline) include the baseline, center, treatment and center\*treatment as the covariant variables.

Figure 11. LS Mean Change from Baseline of Average of AM and PM reflective TNSS by Center for Study SAR002 (only include the 200mcg)



Note: LS mean from as ANCOVA model (mean change from baseline) include the baseline, center, treatment and center\*treatment as the covariant variables.

***The Key Secondary Efficacy Variables***

For Study SAR401 and Study PAR402, the key secondary efficacy variables were as follows:

- Average AM and PM patient-assessed instantaneous TNSS over Days 1-14
- Physician Assessed Nasal Signs and Symptoms (PANS) at Endpoint
- Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at Endpoint

To account for multiplicity among the primary and key secondary efficacy variables, a clinical decision rule was used. That is sequential testing was employed. If the medication was found to be effective with respect to the primary efficacy measure, secondary variables were to be tested for statistical significance starting with the instantaneous TNSS over Days 1-14. If the p-value from the test of the average of AM and PM patient-assessed instantaneous TNSS over Days 1-14 was  $\leq 0.05$ , then PANS at endpoint was to be examined. If the p-value for the test of PANS at endpoint was  $\leq 0.05$ , then the RQLQ at endpoint result was to be examined. Therefore the type I error rate was strictly controlled for the primary and key secondary measures.

The reviewer’s analysis results for the key secondary endpoints are displayed in Table 14. The reviewer’s analysis results are consistent with the primary analysis results, which showed that Ciclesonide 50mcg Nasal Spray, administrated as two sprays per nostril once daily, is statistically significantly superior to placebo in improving the combined AM and PM reflective TNSS in adult and adolescent patients 12 years old with SAR or PAR. The average of AM and

PM patient-assessed instantaneous TNSS was statistically significantly higher for the Ciclesonide 200mcg group than the placebo group in all three studies. However, PANS at Endpoint and RQLQ at Endpoint were found to be statistically significantly better for the Ciclesonide 200mcg group than the placebo group for study PAR 402 only.

Table 14. The Results of the Secondary Variables for Two Pivotal Studies

Treatment	Baseline Mean (SD)	Change from Baseline		Treatment Comparison Placebo vs. Ciclesonide		
		N	LS Mean (SE)	LS Mean Difference	95% CI	p-value
<b>Average AM and PM Instantaneous TNSS (Day 1-14) SAR002</b>						
Ciclesonide 200	9.00 (1.87)	144	-1.966 (0.18)	0.7735	(0.27, 1.28)	0.0026
Ciclesonide 100	8.79 (1.84)	145	-2.126 (0.18)	0.4347	(-0.06, 0.93)	0.0876
Ciclesonide 50	8.77 (1.95)	142	-2.116 (0.18)	0.1497	(-0.35, 0.65)	0.5581
Ciclesonide 25	9.00 (1.81)	145	-2.192 (0.15)	0.1594	(-0.34, 0.66)	0.5321
Placebo	8.38 (1.84)	147	-1.327 (0.15)	-	-	-
<b>Average AM and PM Instantaneous TNSS (Day 1-14) SAR401</b>						
Ciclesonide 200	8.40 (2.24)	163	-2.192 (0.15)	0.8657	(0.44, 1.29)	< 0.0001
Placebo	8.33 (2.08)	162	-1.327 (0.15)	-	-	-
<b>Average AM and PM Instantaneous TNSS (Day 1-42) PAR402</b>						
Ciclesonide 200	7.07 (2.15)	232	-2.28 (0.14)	0.5419	(0.21, 0.89)	0.0017
Placebo	7.09 (2.27)	229	-1.74 (0.14)	-	-	-
<b>PANS (Day 1-14) SAR401</b>						
Ciclesonide 200	7.97 (1.58)	163	-1.982 (0.16)	-0.0051	(-0.44, 0.43)	0.9816
Placebo	8.07 (1.44)	161	-1.988 (0.16)	-	-	-
<b>PANS (Day 1-42) PAR402</b>						
Ciclesonide 200	6.90 (1.99)	216	-2.090 (0.15)	0.3966	(0.015, 0.778)	0.0415
Placebo	6.80 (2.04)	216	-1.693 (0.15)	-	-	-
<b>RQLQ (Day 1-14) SAR401</b>						
Ciclesonide 200	3.96 (1.05)	151	-1.391 (0.11)	0.1827	(-0.125, 0.491)	0.2437
Placebo	3.78 (0.98)	152	-1.208 (0.11)	-	-	-
<b>RQLQ (Day 1-42) PAR402</b>						
Ciclesonide 200	3.34 (1.06)	195	-1.298 (0.09)	0.2848	(0.066, 0.504)	0.0109
Placebo	3.38 (1.08)	193	-1.013 (0.08)	-	-	-

### Conclusion –

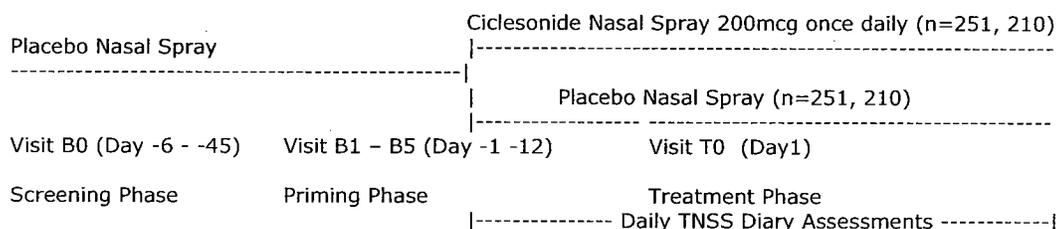
The efficacy evaluation of studies SAR002, SAR401 and PAR402, the phase-II and III, randomized, multi-center, double-blind, parallel-group, and placebo-control trials, demonstrated that Ciclesonide 50mcg Nasal Spray is statistically significantly superior to placebo in improving the Total Nasal Symptoms Score after a dosage regimen of two sprays per nostril once daily in adult and adolescent patients  $\geq 12$  years old with SAR or PAR. The data obtained from the Phase 2 dose-finding study indicated that the 200 mcg/day dose of ciclesonide provided a robust and consistent effect whereas the 100 mcg/day dose was, at best, marginally effective. Lower doses of Ciclesonide were not shown to be effective in the treatment of SAR. The improvement in TNSS was maintained over the full 24-hour dosing interval.

### 3.1.2 Onset of Action

#### 3.1.2.1 Design

Onset of action of Ciclesonide Nasal Spray 200mcg once daily was investigated in both of the pivotal multi-dose clinical studies, SAR401 and PAR402, as well as via two single-dose Environmental Exposure Unit/Chamber Studies, SAR406 and SAR407. Both Studies SAR406 and SAR407 were randomized, double-blind, placebo-controlled, parallel-group, single-center studies, conducted in Ontario (Mississauga and Kingston), using an environmental exposure unit (EEC) to assess the onset of action of Ciclesonide applied as a nasal spray 200mcg/day in the treatment of SAR in patients 18 years and older. (See the study flow charts below.)

#### Study SAR406 and SAR407



SAR401 and PAR402 TNSS diary collection method:

Investigators evaluated patient diary entries at the Randomization Visit (T0), and at each treatment visit (T2 and T4). Immediately prior to administration of the first dose of study medication, patients were to complete the 0-hour field for instantaneous nasal signs and symptoms on the Day 1 patient diary card in the presence of the investigator or designee. Patients were then to administer the first dose of study medication while in the clinic. Four (4) hours after administering the first dose of study medication, patients began recording instantaneous nasal signs and symptom scores in their patient diary every hour through hour 12. At hour 12, nasal and non-nasal signs and symptoms were also to be recorded. On day 2 of treatment, and throughout the rest of the treatment period, upon awakening, and prior to administration of the study medication, bathing, consumption of food or beverage, or strenuous activities, patients were to record their AM instantaneous and reflective nasal and reflective non-nasal signs and symptom scores on their patient diary card. Patients were then to record their evening nasal and non-nasal signs and symptom scores approximately 12 hours after the AM assessment. The sponsor did not submit the hourly instantaneous TNSS for studies SAR401 and PAR402 in the original NDA submission; the hourly instantaneous TNSS were submitted on March 29, 2006. (See attachment for details)

#### 3.1.2.2 Statistical Methodologies

##### Primary Efficacy Analysis

The primary efficacy variable was the time to onset of action, which was defined as the time

from Baseline (Hour 0) until the two-sided p-value for the test of a difference in the average of patient-assessed instantaneous TNSS between intranasal Ciclesonide and placebo was less than 0.05. Additionally, the p-value for the test of a difference between treatments was required to be less than 0.05 for a second time point in order to confirm the onset of effect. Treatment groups were compared at each hour using ANCOVA with covariate adjustment for center, treatment, and baseline.

#### Sample Size

In Study SAR406, a sample size of 241 patients per treatment group was sufficient to provide 90% power to demonstrate a difference of 0.8 at any time point in TNSS using a two-sided alpha level of 0.05. In this study the standard deviation for the change from baseline in TNSS ranged from 2.7 at Hour 1 to 3.09 at Hour 12. This corresponds to a power to demonstrate a difference of 0.8 at any time point ranging from 82% to 91%,

In Study SAR407, a sample size of 206 patients per treatment group was sufficient to provide 85% power to demonstrate a difference of 0.8 at any time point in TNSS using a two-sided alpha level of 0.05. In this study the standard deviation for the change from baseline in TNSS ranged from 2.48 to 3.30. This corresponds to a power to demonstrate a difference of 0.8 at any time point ranging from 69% to 90%. At all hours except Hour 1 the observed standard deviation was larger than the value assumed for sample size estimation.

#### **3.1.2.3 Sponsor's Results and Conclusions**

The sponsor concluded that (draft-package-insert-pdf-file.pdf)



#### **3.1.2.4 Reviewer's Efficacy Analysis**

Table 15 summarizes the results of the primary efficacy analysis – hourly assessment of instantaneous TNSS on Day 1. According to the protocol specified definition of onset of action, one out of four studies had demonstrated onset of action at one hour (Study SAR406). The onset of action was never demonstrated in others studies as there were never two consecutive p-values < 0.05. In study SAR407, the first statistical significant time point was hour 6 with effect size of 0.63; at hour 7, the effect size was 0.63 with p-value of 0.051 and the effect size was never maintained after hour 7. In studies SAR401 and SAR402, the first statistical significant time point were hour 9 or hour 12, but no other significant time point after that.

Table 15. Hourly Assessment of Instantaneous TNSS on Day1- Day 5

Hour	SAR406 (n=402)	SAR407 (n=420)	SAR401 (n=325)	PAR402 (n=461)
	LS Mean (PL-CIC) 2-sided p-value <sup>1</sup>	LS Mean (PL-CIC) 2-sided p-value	LS Mean (PL-CIC) 2-sided p-value	LS Mean (PL-CIC) 2-sided p-value
Hour 1	0.51, p=0.0197 <sup>2</sup>	0.10, p=0.693	-	-
Hour 2	0.47, p=0.0364	0.12, p=0.670	-	-
Hour 3	0.54, p=0.0230	0.37, p=0.197	-	-
Hour 4	0.66, p=0.0042	0.42, p=0.169	0.45, p=0.088	0.04, p=0.826
Hour 5	0.56, p=0.0155	0.39, p=0.210	0.12, p=0.671	0.09, p=0.658
Hour 6	0.72, p=0.0019	0.69, p=0.031	0.42, p=0.148	0.12, p=0.579
Hour 7	0.51, p=0.0277	0.63, p=0.051	0.18, p=0.554	0.20, p=0.351
Hour 8	0.68, p=0.0030	0.53, p=0.102	0.13, p=0.673	0.22, p=0.299
Hour 9	0.78, p=0.0005	0.35, p=0.269	0.38, p=0.258	0.46, p=0.032
Hour 10	0.91, p<0.0001	0.29, p=0.380	0.50, p=0.121	0.31, p=0.160
Hour 11	0.83, p=0.0003	0.26, p=0.418	0.62, p=0.056	0.34, p=0.118
Hour 12	0.88, p=0.0002	0.41, p=0.193	0.71, p=0.022	0.37, p=0.080
Hour 24	-	-	0.29, p=0.293	0.28, p=0.133
Day 2	-	-	0.49, p=0.051	0.49, p=0.007
Day 3	-	-	0.68, p=0.008	0.23, p=0.214
Day 4	-	-	0.95, p<0.001	0.26, p=0.180
Day 5	-	-	0.84, p=0.003	0.37, p=0.061

1. p-value is from comparison of treatment groups using ANCOVA at each time point with covariate adjustment for center, treatment, and baseline. Baseline is the Hour 0 assessment. 2. The highlight indicated the first significant time-point and confirmed time-point.

The sponsor claimed that

Although two EEU studies had identical designs, the patient population was not the same. As indicated in Table 16 the baseline characteristics were different among the two studies. The test results of the patients in Study SAR407 were lower in the Allergy Test, Control Results, and Histamine Results compared to the patients in Study SAR406. The demographic were different in two studies. There were only 4 % minorities in Study SAR407 and Study SAR406 had 40% Minorities; the average ages of subjects in Study SAR407 were 6 years younger than subjects in Study SAR406. Therefore, the two studies can not be pooled for analysis because they had different patients' population. In addition, Figure 12 and Figure 13 display the mean change from baseline of average of AM and PM instantaneous TNSS by Race Group for both EEU studies. The Figure 12 shows the Study SAR406, which had a positive study results, the Caucasian group (60%) had the onset of action at hour 5 and confirmatory time point at hour 9.

Table 16. Patient Demographic and Other Baseline Characteristics – ITT Analysis Set

Variable	SAR406		SAR407	
	Ciclesonide 200 mcg (N=251)	Placebo (N=251)	Ciclesonide 200 mcg (N=210)	Placebo (N=210)
<b>Age (years)</b>				
Mean (SD)	36.62 (11.33)	37.45 (11.89)	32.43 (11.26)	33.42 (12.31)
Median	36	36	30	30
Min, Max	18, 75	18, 74	18, 71	18, 70
<b>Gender (n (%))</b>				
Male	118 (47.0%)	110 (43.8%)	88 (41.9%)	90 (42.9%)
Female	133 (53.0%)	141 (56.2%)	122 (58.1%)	120 (57.1%)
<b>Race<sup>1</sup> (n (%))</b>				
Caucasian	150 (59.8%)	154 (61.4%)	203 (96.7%)	201 (95.7%)
Black	74 (29.5%)	73 (29.1%)	2 (1.0%)	2 (1.0%)
Asian	33 (13.1%)	27 (10.8%)	2 (1.0%)	5 (2.4%)
Native American	4 (1.6%)	3 (1.2%)	2 (1.0%)	4 (1.9%)
Native Hawaiian, or Other Pacific Islander	3 (1.2%)	1 (0.4%)	0	1 (0.5%)
Other	4 (1.6%)	5 (2.0%)	6 (2.9%)	3 (1.4%)
<b>Ethnicity (n (%))</b>				
Hispanic	14 (5.6%)	24 (9.6%)	1 (0.5%)	1 (0.5%)
Non-Hispanic	237 (94.4%)	227 (90.4%)	209 (99.5%)	209 (99.5%)
<b>Smoking History (n (%))</b>				
Never	162 (64.5%)	154 (61.4%)	130 (61.9%)	131 (62.4%)
Former	53 (21.1%)	62 (24.7%)	42 (20%)	51 (24.3%)
Current	36 (14.3%)	35 (13.9%)	38 (18.1%)	28 (13.3%)
<b>Type of skin test (n (%))</b>				
Historical skin prick	141 (56.2%)	156 (62.2%)	65 (31%)	59 (28.1%)
Current skin prick	110 (43.8%)	95 (37.8%)	145 (69%)	151 (71.9%)
<b>Allergy Testing</b>				
Antigen (ragweed) challenge results (mm)				
Mean (SD)	11.39 (5.36)	11.20 (6.48)	10.09 (4.47)	9.68 (4.48)
Median	11	10	9	9
Min, max	3, 35	3, 70	3.0, 29.0	3.0, 26.0
Control results (mm)				
Mean (SD)	2.28 (1.13)	2.50 (1.11)	0.53 (0.62)	0.38 (0.68)
Median	2	3	0	0
Min, max	0, 5	0, 6	0.0, 3.0	0.0, 3.0
Histamine results (mm)				
Mean (SD)	5.86 (1.70)	6.57 (2.24)	3.81 (0.94)	3.70 (1.03)
Median	6	6	4	4
Min, max	2, 14	2, 18	2.0, 8.0	1.0, 8.0

Figure 12. Change from Baseline of Average of AM and PM Instantaneous TNSS by Race Group for Study SAR406

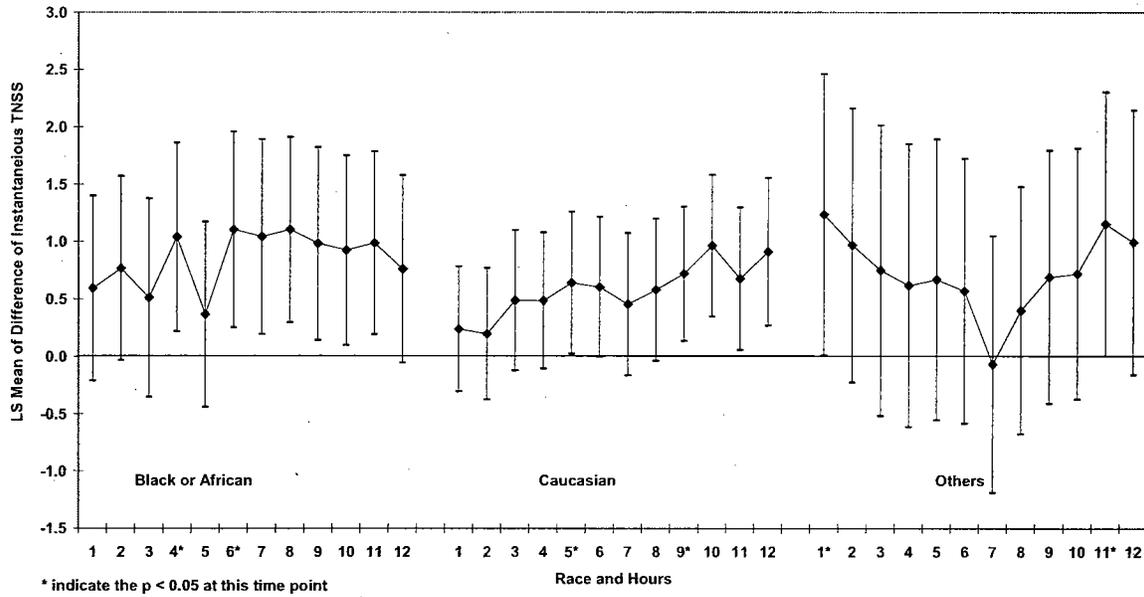
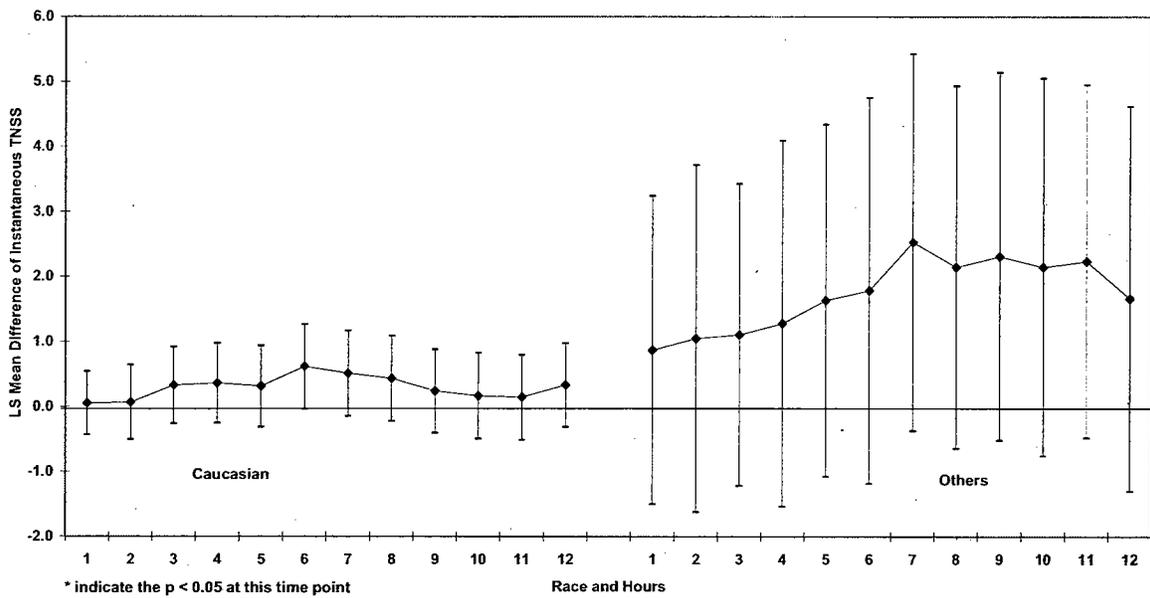


Figure 13. Change from Baseline of Average of AM and PM Instantaneous TNSS by Race Group for Study SAR407



**Conclusion –**

The efficacy evaluation of studies SAR406 and SAR407, the phase-III, randomized, multi-center, double-blind, parallel-group, and placebo-control, single dose environmental exposure unit (EEU) trials, indicated that Ciclesonide Nasal Spray 200mcg once daily had an onset of action after 12 hours. Although, the Study SAR406 had an onset of action within one hour, but the second EEU study (SAR407) did not confirm this finding. The sponsor's [redacted] is not acceptable due to differing patient groups in each study. In outpatient clinical trials (SAR401 and PAR402), the onset of effect was seen within 24 – 48 hours.

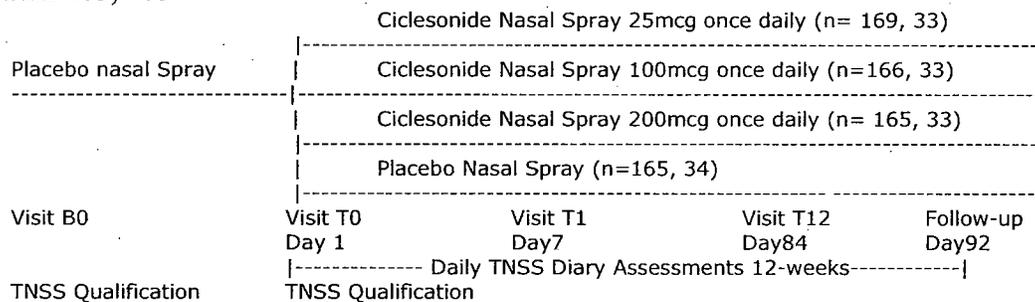
**3.1.3 Pediatric Studies**

**3.1.3.1 Design**

The pediatric program for Ciclesonide Nasal Spray was comprised of two studies. One study, M1-403 (hereafter referred as PED403), was conducted in pediatric patients 6-11 years of age with PAR and was designed as both a safety and efficacy study of 12 weeks in duration. The 12-week study in patients 6-11 years of age was conducted as a randomized, double-blind, parallel-group, placebo-controlled, multi-center clinical trial in pediatric patients with PAR. Patients were randomized to 1 of 4 arms (placebo, Ciclesonide 25, 100 or 200mcg/day) in a ratio of 1:1:1:1.

Study M1-405 (hereafter referred as PED405) conducted in patients 2-5 years of age with PAR was primarily designed as a tolerability and pharmacokinetic/pharmacodynamic study. This study was a single-center, double-blind, placebo-controlled, parallel-group randomized safety trial and various efficacy measures were also incorporated into the study design. (See the study flow charts below.)

**Study PED403, 405**



### 3.1.3.2 Objective

The objectives of these studies were to evaluate the efficacy and safety of Ciclesonide Nasal Spray at three dose levels (200, 100 or 25mcg, once daily) versus placebo in the treatment of PAR in pediatric patients (ages 2-5 and 6-11 years old).

### 3.1.3.3 Patients Disposition

As indicated in Table 17, a total of 665 subjects (ITT population) who satisfied the inclusion and exclusion criteria were randomly assigned to receive Ciclesonide Nasal Spray 200mcg, 100mcg, 25mcg once daily, or placebo in Study PED403. Five hundred and eighty six subjects (88%) completed this study. In PED403, the percent of subjects discontinuing was slightly higher in the Ciclesonide 25mcg treatment group and the placebo group than the other treatment groups.

Again referring to Table 17, a total of 133 subjects (ITT population) who satisfied the inclusion and exclusion criteria were randomly assigned to receive Ciclesonide Nasal Spray 200mcg, 100mcg, 25mcg once daily and placebo in Study PED405. One hundred and twenty nine subjects (97%) completed their study. The percent of discontinuation were similar in all the treatment groups in this study.

Table 17. ITT Patients' Accountability N (%), Studies for SAR

	<b>PED403 (n=665)</b>				<b>PED405 (n=133)</b>			
	<b>CIC 200mcg</b>	<b>CIC 100mcg</b>	<b>CIC 25mcg</b>	<b>Placebo</b>	<b>CIC 200mcg</b>	<b>CIC 100mcg</b>	<b>CIC 25mcg</b>	<b>Placebo</b>
Entered	165	166	169	165	33	33	33	34
Completed	149 (90.3)	151 (91.0)	147 (87.0)	139 (84.2)	32 (97.0)	32 (97.0)	32 (97.0)	33 (97.1)
Discontinued	16 (9.7)	15 (9.0)	22 (13.0)	26 (15.8)	1 (3.0)	1 (3.0)	1 (3.0)	1 (2.9)
<b>Reason of early discontinuation<sup>1</sup></b>								
Adverse Event	3	5	4	11				
Non-Compliance/ disqualify	1	0	3	2				
Lack of Efficacy	0	2	0	3				
Pt. Withdraw Consent	2	7	6	4				
Lost Follow-up Predefined	4	1	6	4	1	1	1	1
Discontinuation Criterion Fulfilled	3	2	2	4				
Others	3	1	3	1				
<b>Analysis Population</b>								
Full analysis set	165	166	169	165	33	33	33	34
Valid case set	149 (90.3)	151 (91.0)	147 (87.0)	139 (84.2)	32	32	32	33
Total set	165	166	169	165	33	33	33	34

Some patient discontinued for more than one reasons. Data: Dispos.xpt; Code: Demog.sas.

The demographics and baseline characteristics for all randomized patients (ITT) for Study PED403 and PED405 are summarized in Table 18. The majority of the subjects were Caucasian (86%). The demographic and baseline characteristics were balanced across treatment groups.

Table 18. ITT Subjects' Demographics and Baseline Characteristics, Studies for SAR

	<b>PED403 (n=665)</b>				<b>PED405 (n=133)</b>			
	<b>CIC 200mcg (n=165)</b>	<b>CIC 100mcg (n=166)</b>	<b>CIC 25mcg (n=169)</b>	<b>Placebo (n=165)</b>	<b>CIC 200mcg (n=33)</b>	<b>CIC 100mcg (n=33)</b>	<b>CIC 25mcg (n=33)</b>	<b>Placebo (n=34)</b>
<b>Sex</b>								
Female	60 (36.4)	64 (38.6)	80 (47.3)	68 (41.2)	15 (45.5)	13 (39.4)	14 (42.4)	16 (47.1)
Male	105 (63.6)	102 (61.4)	89 (52.7)	97 (58.8)	18 (54.5)	20 (60.6)	19 (57.6)	18 (52.9)
<b>Race</b>								
White	131 (79.4)	133 (80.1)	134 (79.3)	131 (79.4)	10 (30.3)	9 (27.3)	10 (30.3)	8 (23.5)
Black	21 (12.7)	19 (11.5)	18 (10.7)	24 (14.6)	23 (69.7)	24 (72.7)	23 (69.7)	24 (70.6)
Asian	2 (1.2)	4 (2.4)	8 (4.7)	4 (2.4)	0	0	0	0
Others	11 (6.7)	10 (6.0)	9 (5.3)	6 (3.6)	0	0	0	2
<b>Age</b>								
2 Years	-	-	-	-	7 (21.2)	6 (18.2)	7 (21.2)	10 (29.4)
3 Years	-	-	-	-	8 (24.2)	11 (33.3)	14 (42.4)	6 (17.7)
4 Years	-	-	-	-	9 (27.3)	11 (33.3)	6 (18.2)	6 (17.7)
5 Years	-	-	-	-	9 (27.3)	5 (15.2)	6 (18.2)	12 (35.3)
6 - 7	34 (20.6)	44 (26.5)	43 (25.4)	49 (29.7)	-	-	-	-
8 - 9	61 (37.0)	55 (33.1)	61 (36.1)	53 (32.1)	-	-	-	-
10 - 11	70 (42.4)	67 (40.4)	65 (38.5)	63 (38.2)	-	-	-	-
Mean (SD)	8.96 (1.6)	8.78 (1.6)	8.76 (1.6)	8.71 (1.8)	3.6 (1.1)	3.5 (1.0)	3.3 (1.0)	3.6 (1.3)
Median	9	9	9	9	4	3	3	4
Range	6 - 11	5 - 11	6 - 11	6 - 11	2 - 5	2 - 5	2 - 5	2 - 5
<b>Type of Skin Test</b>								
Historical Skin Prick	52 (31.5)	52 (31.5)	53 (31.4)	47 (28.5)	-	-	-	-
Current Skin Prick	113 (68.5)	113 (68.5)	116 (68.6)	118 (68.6)	33	33	33	34
<b>Antigen Challenge Results (mm)</b>								
Mean (SD)	7.15 (3.8)	8.13 (5.4)	7.17 (4.1)	7.28 (4.1)	6.0 (1.3)	6.4 (1.6)	6.2 (1.8)	6.4 (1.4)
Median	6	6	6	6	6	6	6	6
Range	3 - 25	3 - 31	3 - 27	3 - 25	3 - 8	4 - 10	4 - 13	4 - 10
<b>Control Results (mm)</b>								
Mean (SD)	0.09 (0.38)	0.24 (1.07)	0.34 (0.92)	0.18 (0.64)	0.24 (0.6)	0.15 (0.6)	0.39 (0.9)	0.24 (0.7)
Median	0	0	0	0	0	0	0	0
Range	0 - 3	0 - 11	0 - 4	0 - 4	0 - 2	0 - 3	0 - 3	0 - 2
<b>Histamine Results (mm)</b>								
Mean (SD)	5.9 (2.12)	6.5 (2.84)	6.1 (2.58)	6.2 (3.24)	-	-	-	-
Median	6	6	6	5	-	-	-	-
Range	0 - 15	0 - 16	1 - 20	1 - 31	-	-	-	-
<b>AVG(AM,PM) Reflective TNSS</b>								
Mean (SD)	6.56 (2.22)	6.65 (2.14)	6.84 (2.20)	6.87 (2.31)	4.81 (2.67)	5.39 (3.20)	4.48 (2.56)	4.90 (2.71)
Median	6.25	6.23	6.29	6.69	4.42	5	4	4.43
N	163	164	162	162	33	30	32	32
Range	2.4-12	1.8 - 12	2.3 - 12	2.5 - 12	0 - 12	0.6 - 12	1 - 11	0.7 - 12
<b>AVG(AM,PM) Instantaneous TNSS</b>								
Mean (SD)	6.12 (2.19)	6.13 (2.34)	6.31 (2.41)	6.44 (2.55)	-	-	-	-
Median	5.81	5.92	5.93	6.33	-	-	-	-
N, Range	162, 1.3 - 12	164, 1.3 - 12	163, 1.1 - 12	163, 0 - 12	-	-	-	-

Data: DE.xpt; AT.xpt; RE.xpt; IN.xpt; Code: Demog.sas

### 3.1.2.2 Statistical Methodologies

#### Study PED403

The primary efficacy variable was the change from baseline in average of AM and PM reflective TNSS over 1-6 weeks. Key secondary efficacy measures were average of AM and PM patient reported reflective TNSS over the 12 weeks of treatment and Overall Physician Assessment of Nasal Symptom Severity at Endpoint (from Weeks 1–6).

In order to control Type I error rates, a sequential approach was used across both doses and measures. If the p-value for the difference in treatment effect between the 200 mcg dose and placebo was less than or equal to 0.05, then the 100 mcg dose vs. placebo comparison was to be examined. If the p-value for the 100 mcg dose vs. placebo comparison was less than or equal to 0.05, then the 25 mcg dose vs. placebo comparison was to be examined. If a particular dose was found to be effective with respect to the primary efficacy measure, key secondary measures for the dose were tested for statistical significance. The sequential approach across the doses combined with the sequential approach across measures is displayed in the diagram below.

Order of Testing for Determining Statistical Significance vs Placebo			
Start →	200 µg	100 µg	25 µg
Days 1-42 Ref. TNSS	↓ →	↓ →	↓ □
Days 1-84 Ref. TNSS	↓ →	↓ →	↓ □
PANS at Endpoint	□ →	□ →	□

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

A repeated measures analysis of covariance (ANCOVA) model was used for analyses of the difference in treatment effects for the nasal symptom variables using weekly averages, with covariates of baseline, treatment, week, and treatment-by-week. Week was treated as an unordered categorical variable. A first order autoregressive [AR(1)] structure was used to model intra-patient correlation and, in combination with treating patient as a random effect, this yielded a correlation structure in which observations from the same patient were considered to be correlated, with observations closer in time being more correlated. Baseline was defined as the appropriate value measured over the Baseline Period up to 7 days prior to randomization. Estimated treatment differences and 95% confidence intervals for the treatment differences were calculated. No imputation for missing values was performed or planned for in the protocol, as the extent of missing data was expected to be low and the chosen analysis as a maximum likelihood method was valid for missing-at-random missingness.

Study PED403 was 80% powered to detect a difference between placebo and ciclesonide of 0.6 assuming a standard deviation of 1.9 for the mean change from baseline in the overall TNSS over six weeks using a two-sided alpha level of 0.05.

According to the sponsor, the study was powered at 80%, rather than at 90% that is typical of a Phase 3 trial, due to recruitment difficulties in this age population and since the FDA had previously suggested that trends in efficacy in this trial, coupled with definitive and convincing

evidence of efficacy in the adult and adolescent trials, may allow for extrapolation of efficacy from the adult and adolescent trials down to the 6- 11 year old population.

#### Study PED405

As a safety study, there was no primary efficacy variable in the original study design. One amendment, dated July 29, 2004, was made to the study protocol. In addition to personnel changes and other minor administrative changes, the following revisions were included in this amendment:

- An additional objective was added to include the summary of reflective (24-hour) TNSS over the 6 weeks of treatment at various time points and PNSS at endpoint;
- An additional randomization criterion was added mandating that each parent/caregiver must have adequately completed the AR Assessment Diary during the Baseline Period (defined as completing all items on  $\geq 70\%$  of the days);
- TNSS was added to the study as an efficacy component;
- PNSS was added to the study as an additional efficacy component.

#### **3.1.2.3 Sponsor's Results and Conclusions**

The sponsor concluded that (p28, Summary-clin-efficacy-allergic-rhinitis.df)

*"In conclusion, while a statistically significant improvement relative to placebo was not observed for any ciclesonide dose, appreciable trends in efficacy were observed for the 200 mcg/day dose of ciclesonide. These results in addition to the efficacy results from the adolescent*

*"In conclusion, although trends were observed in the PANS, no definitive conclusions regarding efficacy could be drawn. This finding is not unexpected considering that children of this age are unable to reliably verbalize their subjective nasal symptoms to a third party (parent/caregiver or physician)."*

#### **Reviewer's Efficacy Analysis**

##### ***Study PED403***

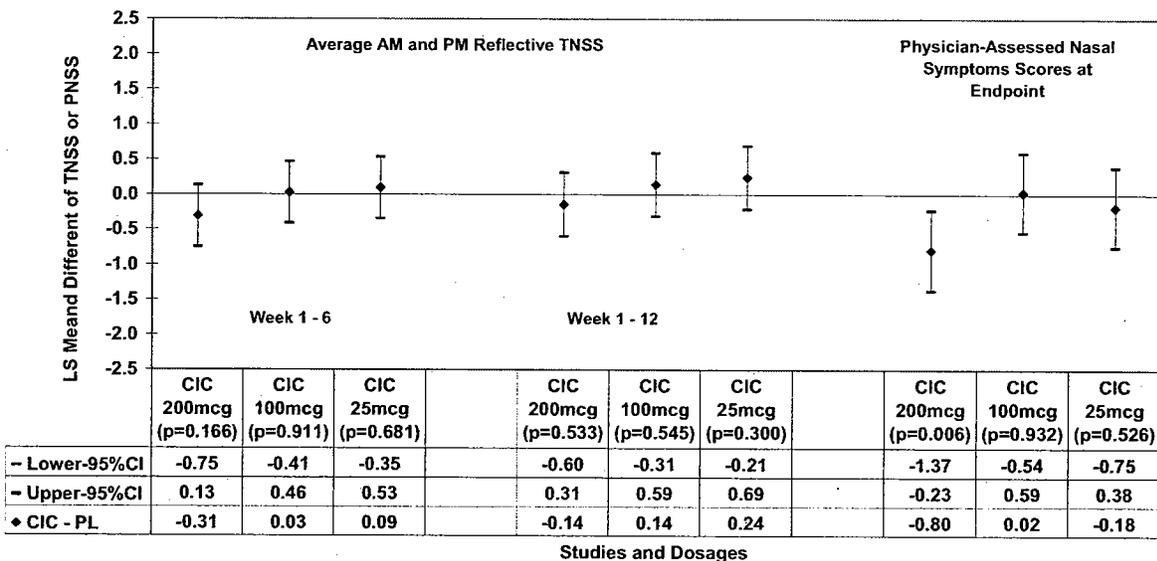
Table 19 and Figure 14 display the results of changes from baseline in reflective TNSS and overview of change from baseline in physician-assessed nasal symptoms scores for study PED403. A decrease from Baseline in the average of AM and PM patient/caregiver-assessed reflective TNSS over Weeks 1-6 was observed in all 4 treatment groups. There were no appreciable treatment differences between the ciclesonide 100 mcg/day, ciclesonide 25 mcg/day and placebo groups. There was an appreciable, but non-statistically significant difference, between the ciclesonide 200 mcg/day and placebo groups of 0.31 (95% CI: -0.75, 0.13; p=0.166)

for Weeks 1-6. By the sequential approach of multiple adjustment, because the p-value for the difference in treatment effect between the 200mcg dose and placebo was greater than 0.05, formal statistical comparison of the change from baseline at endpoint in the overall physician assessment of nasal symptoms was not legitimate even though numerically there was approximately a 0.8 units greater change in the ciclesonide 200 mcg/day group compared to the placebo group and would have a nominal p-value less than 0.05 (p=0.006).

Table 19. Mean of Primary and Key Secondary Variables of Study PED403

Treatment	Baseline	Change from Baseline		
	Mean (SE)	Mean (SE)	Median (Range)	LS Mean (SE)
<b>Average AM and PM Reflective TNSS (Weeks 1- 6)</b>				
Ciclesonide 200 (n=163)	6.6 (2.2)	-2.0 (2.5)	-2.0 (-11.1, 4.1)	-2.1 (0.16)
Ciclesonide 100 (n=164)	6.7 (2.1)	-1.7 (2.4)	-1.5 (-10.4, 4.1)	-1.8 (0.16)
Ciclesonide 25 (n=162)	6.8 (2.2)	-1.8 (2.6)	-1.5 (-9.9, 6.0)	-1.7 (0.16)
Placebo (n=162)	6.8 (2.3)	-1.9 (2.4)	-1.6 (-8.2, 5.4)	-1.8 (0.16)
<b>Average AM and PM Reflective TNSS (Weeks 1- 12)</b>				
Ciclesonide 200 (n=163)	6.6 (2.2)	-2.3 (2.6)	-2.2 (-11.4, 6.7)	-2.3 (0.16)
Ciclesonide 100 (n=164)	6.7 (2.1)	-2.0 (2.6)	-1.8 (-12.0, 4.1)	-2.0 (0.16)
Ciclesonide 25 (n=162)	6.8 (2.2)	-2.0 (2.8)	-1.7 (-9.9, 6.5)	-1.9 (0.16)
Placebo (n=162)	6.8 (2.3)	-2.2 (2.6)	-1.9 (-11.8, 7.4)	-2.2 (0.16)
<b>Physician-Assessed Nasal Symptoms Scores at Endpoint (PANS)</b>				
Ciclesonide 200 (n=157)	7.3 (2.7)	-2.9 (3.2)	-3 (-12, 8)	-2.8 (0.21)
Ciclesonide 100 (n=163)	7.2 (2.8)	-2.0 (3.3)	-2 (-11, 8)	-1.9 (0.20)
Ciclesonide 25 (n=164)	7.0 (2.7)	-2.1 (3.0)	-2 (-10, 6)	-2.2 (0.20)
Placebo (n=155)	6.7 (2.9)	-1.8 (3.1)	-2 (-10, 7)	-2.0 (0.21)

Figure 14. LS Mean Difference of Changes from Baseline in Primary and Secondary Variables for Study PED403



1   Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

## Reviewer's Conclusion



### 3.2 Evaluation of Safety

As no specific endpoints or hypotheses were identified during the review as warranting formal statistical hypothesis testing or examination, a detailed safety review can be found in the medical review and evaluation.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Others

To explore consistency of the treatment effects across the levels of several predefined covariates, treatment-by-covariate interactions were evaluated for the primary efficacy endpoint. The results are displayed in Table 21 and Table 22, which show that the treatment-by-subgroup interactions were not statistically significant indicating that the treatment effect is not statistically significantly difference in the different subgroups examined. Figure 16 and Figure 17 show the efficacy of Ciclesonide Nasal Spray 200mcg was not demonstrated in the subjects who were 12-17 years of age, 65 years old and older, black or of "other" races in both studies. However, statistically significant results are not expected in all subgroups due to the reduced sample size and natural variation expected when conducting multiple analyses.

Table 21. LS Mean Change from Baseline of Average of AM and PM Reflective TNSS over 14-Days, SAR401

<i>Subgroup (p-Value)†</i>	<i>Ciclesonide 200mcg (n=162)</i>			<i>Placebo (n=162)</i>		
	<i>N</i>	<i>LS Mean</i>	<i>SE</i>	<i>N</i>	<i>LS Mean</i>	<i>SE</i>
<b>Gender (p=0.7412)</b>						
Male	56	-2.44	0.30	56	-1.66	0.30
Female	106	-2.38	0.20	106	-1.43	0.20
<b>Race Group (p=0.8569)</b>						
Black, African American	10	-2.71	0.53	12	-1.75	0.48
White	139	-2.31	0.18	132	-1.45	0.19
Others	13	-3.12	0.62	18	-1.71	0.52
<b>Age Group (p=0.5350)</b>						
<18	11	-1.68	0.46	13	-1.42	0.42
18 - 64	143	-2.44	0.18	136	-1.55	0.18
≥ 65	8	-1.68	0.46	13	-1.42	0.42

† p-Value for treatment-by-subgroup.

Table 22. LS Mean Change from Baseline of Average of AM and PM Reflective TNSS over 42-Days, PAR402

Subgroup (p-Value)†	Ciclesonide 200mcg (n=232)			Placebo (n=229)		
	N	LS Mean	SE	N	LS Mean	SE
<b>Gender (p=0.8992)</b>						
Male	86	-2.09	0.19	78	-1.49	0.20
Female	146	-2.69	0.17	151	-2.04	0.16
<b>Race Group (p=0.8273)</b>						
Black, African American	7	-3.19	0.92	8	-1.56	0.85
White	198	-2.49	0.13	202	-1.86	0.13
Others	27	-3.18	0.42	19	-1.83	0.50
<b>Age Group (p=0.2070)</b>						
<18	26	-1.91	0.33	27	-1.79	0.32
18 - 64	201	-2.51	0.14	198	-1.91	0.14
≥ 65	5	-3.09	0.86	4	-0.58	0.97

† p-Value for treatment-by-subgroup.

Figure 16. LS Mean and 95% CI of Change from Baseline of Average AM and PM Reflective TNSS over 14-Days by Subgroup for Study SAR401

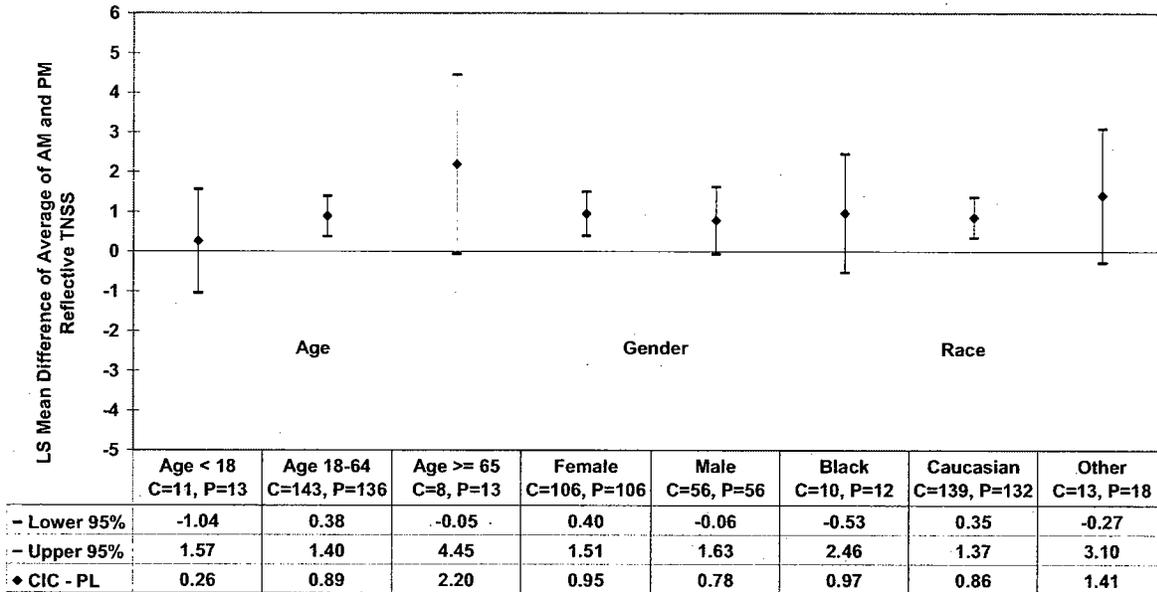
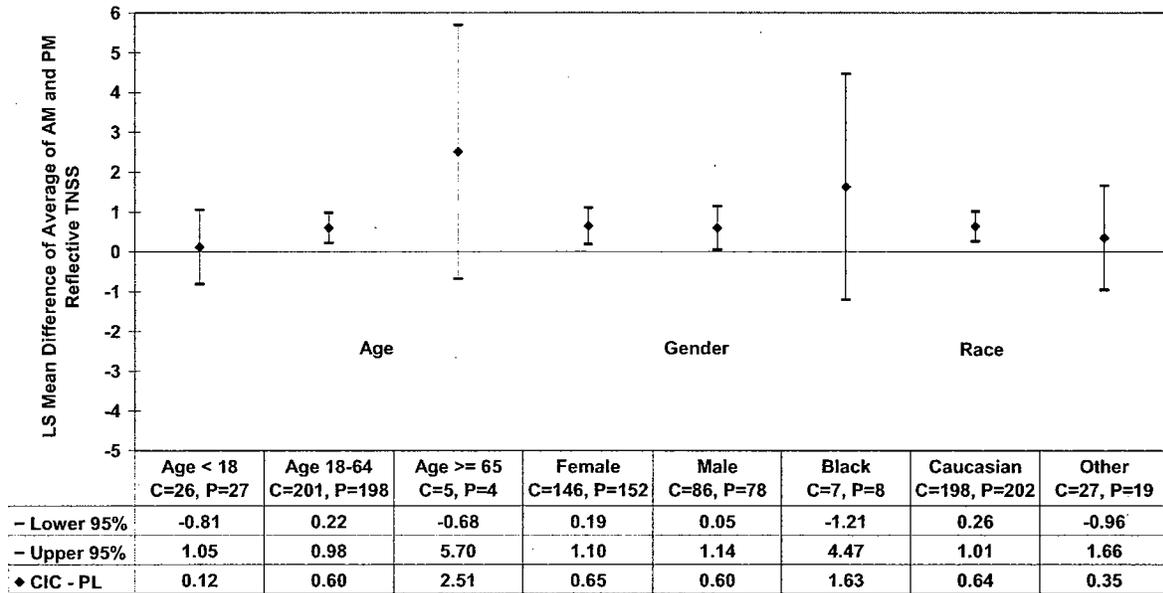


Figure 17. LS Mean and 95% CI of Change from Baseline of Average AM and PM Reflective TNSS over 42-Days by Subgroup for Study PAR402



## 4.2 Other Special/Subgroup Populations

There are no other special/subgroup analyses.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

#### Statistical Issues

The following statistical issues were identified and resolved in the course of this review. The reader is referred to the specified section for details.

- In the original NDA submission, there were several errors in the electronic data and statistical programming for the primary analysis. This reviewer received the NDA assignment on January 15, 2006 and found the following errors after the filing meeting, which was on February 13, 2006. The project manager sent the fax communicating these issues to the sponsor on March 20, 2006 and the sponsor responded to the fax on March 23, 2006 and admitted the errors in the NDA submission and corrected electronic data and tables were submitted on March 29, and April 7, 2006. (Attachment 1, 2, 3, and 4)

1. Errors in Lab data
2. Incorrect SAS Code for the primary efficacy analysis (see next bullet for more detail)
3. Duplication in the CDISC-SDTM diary data
4. Incorrect Data Value in dose-find study SAR002

- The sponsor's SAS code for the primary analysis was incorrect. *"The FDA is correct that either the time variable should be in the repeated statement or missing data included as records with "." in the SAS data set in order for SAS to properly perform the repeated measures analysis. ALTANA has run preliminary analyses correcting the mistake and does not expect any appreciable impact on results."* (the sponsor's e-mail sent on March 23, 2006) (Section 3.1.7 Reviewer's Efficacy Analyses)
- The protocol specified that the change from baseline for each active treatment group over the 2-week study would be compared to placebo using a repeated measure ANOVA according to the restricted maximum likelihood estimation for mixed effect models. This model would include treatment, day, and treatment-by-day fixed effect and patient as the random effect. The protocol did not pre-specify the covariance structure in the dose-finding study; compound symmetry method was used in the primary analysis model. This reviewer conducted sensitivity analyses to assess the effect of the assumed covariance structure as well as the impact of the repeated measures analysis itself and found that the qualitative conclusions regarding the efficacy of Ciclesonide® Nasal Spray 200mcg versus placebo were robust. (Section 3.1.7 Reviewer's Efficacy Analyses)

• 5

7

L

J

- The sponsor excluded the CENTER as a covariate from the primary analysis model because of the conversion problems for Proc Mixed.

(Study report 208-2004 statistical.pdf p1277)

*“The treatment by center interaction could not be considered in the statistical model because inclusion of center in the model caused conversion problems for Proc Mixed. So, to identify a possible heterogeneity of treatment effects across study centers, individual center results are presented below.*

Average AM and PM Reflective TNSS – Days 1-14					
		Mean Change from Baseline			
Site	N	Ciclesonide	Placebo	Treatment Difference	p-value for treatment
3454	40	-2.63	-1.37	1.27	0.07
4820	58	-1.46	-1.12	0.34	0.46
5202	44	-4.20	-1.91	2.29	0.002
5203	60	-2.20	-1.22	0.98	0.04
5204	63	-1.16	-1.42	-0.25	0.57
5205	59	-3.44	-1.96	1.48	0.01

*Although five of the six study centers had results showing that ciclesonide was numerically superior to placebo in decrease from Baseline in average AM and PM reflective TNSS over Days 1 to 14, the treatment effect for Center 5204 was in the opposite direction. It is unknown whether this result is just noise or is due to something peculiar about this particular center. Four of the six centers had point estimates around 1.0 or higher.”*

This reviewer used an ANCOVA model for the mean change from baseline in average of AM and PM reflective TNSS with baseline, treatment, center, center\*treatment as covariant variables. The center effect ( $p < 0.0001$ ) and the treatment by center interaction ( $p=0.0361$ ) were statistically significant. The following figure shows the treatment effects across study centers. According to this finding, the medical reviewer ordered the DSI audit request on March 2, 2006 on following two sites:

Site 5724 (Study 144/2005 or 405)  
Investigator: Jerry Herron, MD  
Arkansas Research Medical Testing  
1207 Rebamen Park Road  
Little Rock, AR 72202

8501 North Mopac Expressway, Suite 200  
Austin, Texas 78759

Site 5202 (Study 287/2004)  
Investigator: Daniel V. Freeland, MD

Site 5203 (Study 287/2004)  
Investigator: Frank C. Hampel Jr, MD  
Central Texas Health Research  
705 A Landa Street  
New Braunfels, Texas 78130

Subgroup analyses indicated that the effectiveness of Ciclesonide Nasal Spray 200mcg once



**6. Attachments**

**6.1 Attachment 1**

*Appears This Way  
On Original*

*Appears This Way  
On Original*



Food and Drug Administration  
 Center for Drug Evaluation and Research  
 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** March 20, 2005

<b>To:</b> Cheryl Czachorowski Senior Manager, Regulatory Affairs	<b>From:</b> Colette Jackson Regulatory Health Project Manager
<b>Company:</b> ALTANA Pharma	Division of Pulmonary and Allergy Products
<b>Fax number:</b> 973-236-1695	<b>Fax number:</b> 301-796-9718
<b>Phone number:</b> 973-514-4271	<b>Phone number:</b> 301-796-1230
<b>Subject:</b> NDA 22-004	

**Total no. of pages including cover:** 4

**Comments:**

**Document to be mailed:** YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22-004 Ciclesonide Nasal Spray

We are reviewing your new drug application (NDA) and have the following statistical comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

**1. Errors**

a. For LB.xpt, the variables – LBSTNRHI and LBSTNRLO should be data type of “NUM”. There are some records with “Negative” or “NEGATIVE” in LB.xpt. These errors need to be corrected for all the LB.xpt datasets. Please review the CDISC implementation Guide 3.1 Page 74.

b. Ti.xpt has no records. The dataset needs to be re-sent or the dataset name should be removed from define.xml and define.pdf. This occurred in the datasets of Study 76-2005.

**2. Incorrect Code**

We note that the following code was provided in the submission; however, this code is not useful with the data structure used in the submission since missing days were not indicated with periods in the input data set.

\_\_\_\_\_

In addition, using your submitted data, it seems that the DAYS (REANLGRP) variable should be added as repeated effect.

\_\_\_\_\_

Clarify and provide the corrected analysis results for the primary efficacy and key secondary variables for the dose-finding study and the two pivotal studies. In order to show the robustness of the primary analysis model, provide the analysis results using three different covariate structures (AR(1), CS, UN) separately.

### 3. Duplication

Clarify the duplicated records in the CDISC-SDTM data.

For example: diary data - "Z:\m5\53-clin-stud-rep\535-rep-effic-safety-stud\allergic-rhinitis\5351-stud-rep-contr\287-2004\datasets\tabulations\DY.xpt"

Following subjects have more than one record per DYCAT DYTEST DYDTC

Obs	USUBJID
1	34541202
2	34541205
3	34541206
4	34541211
5	34541241
6	48201160
7	52021005
8	52031301
9	52031505
10	52041122
11	52041495
12	52051262
13	52051441
14	52051449
15	52051452

### 4. Incorrect Data Value

We note that the data values are the same in RE.xpt and IN.xpt analysis data set for the dose-finding study. Please provide the correct data set.

### 5. Hourly Diary Data

Provide the hourly assessment of INSTANTANEOUS TNSS on Day 1 analysis data set and the SAS code which creates the data set for the dose-finding study and the two pivotal studies.

### 6. Pollen Count Data

Provide the pollen count data for study TBN-CL-002 (DOSE-FINDING study).

### 7. Review Assistant



"CDISC © 2004. All rights reserved Page 5, V 1.0 December 22, 2004

#### ***Analysis Dataset Creation Documentation***

*Written documentation may include descriptions of the source datasets, processing steps, and scientific decisions pertaining to creation of the dataset. This documentation should clearly distinguish those derivations and decision rules that were specified a priori from those changes and decisions that were data-driven. Key issues for consideration in analysis dataset creation documentation include (but are not limited to):*

*Derived variables*

*Visit windows*

*Omitted observations*

*Multiple observations*

*Imputed data*

*Missing data*

*Dropouts*

*Data item-specific derivations, i.e. changes to a data value for a specific observation.*

#### ***Analysis Dataset Creation Programs***

*Statistical software programs may also be included as part of the analysis dataset documentation. These programs may be classified into three levels of increasing functionality and complexity:*

*As pseudo-code embedded in written documentation of the creation of the dataset*

*As code fragments that a reviewer could include in a program*

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-796-1230.

Drafted: CCJ/March 17, 2006

Initialed: Barnes/ March 17, 2006 Zhou/ March 20, 2006 Davi/March 20, 2006

Finalized: CCJ/March 20, 2006 File: 22004 march 2006 stats fax.doc

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

Colette Jackson  
3/20/2006 01:27:32 PM  
CSO

## 6.2 Attachment 2

Team,

Altana is submitting a response to our March 20, 2006, fax. Please see the e-mail below. Let me know if you have any questions.

# *Colette Jackson*

Regulatory Health Project Manager  
Division of Pulmonary and Allergy Products  
301-796-1230

---

**From:** Cheryl.Czachorowski@altanapharma-us.com [mailto:Cheryl.Czachorowski@altanapharma-us.com]  
**Sent:** Tuesday, March 21, 2006 7:33 PM  
**To:** Jackson, Colette  
**Cc:** Peter.Fernandes@altanapharma-us.com  
**Subject:** Ciclesonide Nasal Spray NDA 22-004 Response to March 20th Fax

Dear Colette,

I would like to provide information relating to the March 20, 2006 facsimile which provided statistical comments and information requests for NDA 22-004 for Ciclesonide Nasal Spray. Please note, the information within this email provides high level response details and a proposed submission timeline. **Additionally, we would like to request further clarification on Comments 1, 2, 6 and 7 (see bolded questions below).** A formal submission providing comprehensive details will be submitted to NDA 22-004 in eCTD format (Comments 3 - 7 can be provided by March 29th and Comment 2 can be provided by April 7th). I will be out of the office for the next 2 days and will be checking voicemail and email and return to the office on Friday, March 24th. If you require immediate phone contact, please contact Peter Fernandes at 973-593-7984.

### **Comment 1:**

The data type for LBSTNRHI and LBSTNRLO have been fixed and now are defined as a data type of "NUM" or numeric for the SDTM lab data for the 403 study. The terms "NEGATIVE" or "Negative" do not appear in these variables after the update. The update and deletion files were submitted in the NDA eCTD Submission Sequence 002 on Friday March 17th. You had stated in a phone communication that it would be desirable to have the information from the March 17 th submission repeated within the response to the other statistical comments identified in the March 20th fax. We are experiencing difficulty in complying with this request for the following reasons:

- Since this submission was submitted in an eCTD format it is technically impossible to resubmit the deletion of the ti.xpt.
- Resubmitting the lb.xpt submitted in 0002 will also be difficult since the system recognizes that the file was submitted in submission sequence 0002. Additionally since the FDA has requested that the Sponsors follow the Accumulative Approach for the STF Lifecycle it would be most efficient to not reappend this stf.xml twice.

Due to the above information, we propose not to resubmit the information to address this comment and that

Sequence 0002 be relied upon for the further review of this issue. *Can you confirm this is an acceptable approach?*

**Comment 2: Incorrect Code** (for Proc Mixed and exploration of other covariance structures)

The FDA is correct that either the time variable should be in the repeated statement or missing data included as records with "." in the SAS data set in order for SAS to properly perform the repeated measures analysis. ALTANA has run preliminary analyses correcting the mistake and does not expect any appreciable impact on results. New tables containing the repeated measures analyses of average AM and PM reflective and instantaneous TNSS (covering the primary and key secondary measures analyzed by repeated measures) will be provided for the M1-401 and M1-402 trials. Since LOCF was used to fill in missing values for the 002 trial, it is not anticipated that this change in programming language would have any impact on the results of the 002 trial. ALTANA will verify that this is the case.

Additionally, ALTANA will perform the repeated measures analyses for the primary measure utilizing the different correlation structures as requested in order to evaluate the robustness of the primary analysis to misspecification of the correlation structure. The results of these analyses will be provided for two pivotal trials as requested in a similar manner to the post-text tables provided in the 401 and 402 trials. As ALTANA does not possess the SAS code for the production of tables in the dose range finding trial, the analyses are planned to be provided as SAS output. *Please let ALTANA know if the FDA would like the information in another format.*

The planned submission timeline for this information is by April 7th. We propose to include this information within 1.11.3 Efficacy Information Amendment. *Is the proposed eCTD location acceptable?*

**Comment 3: Duplication**

Clarification will be provided in a submission targeted for March 29th.

**Comment 4: Incorrect Data Value**

A replacement file for IN.XPT for this study (76/2004) will be submitted. This will be provided in the March 29th submission.

**Comment 5: Hourly Diary Data**

Hourly instantaneous nasal symptom data were not collected in the dose range finding trial, only in the two pivotal studies. Currently in the submission for these two trials, these data are only available in the SDTM datasets.

ALTANA will create analysis data sets for instantaneous TNSS on Day 1 for 401 and 402.

These will be provided in the March 29th submission.

**Comment 6: Pollen Count Data**

Pollen count data for study TBN-CL-002 were collected by the sites. These data were not entered into a clinical database, however, the source data have been obtained from the sites and will be submitted in a pdf file within the March 29th submission. We propose to include this information within 1.11.3 Efficacy Information Amendment. *Is the proposed eCTD location acceptable?*

**Comment 7: Review Assistant**

As the SDTM data sets were derived from the raw data after the analysis of the clinical trials, the ADaM data sets were not created directly from the SDTM data sets. Rather the ADaM data sets were typically created from intermediate data sets utilized in the analysis of the trial. Thus, ALTANA does not have the SAS code for creation of ADaM data sets from SDTM data sets readily available. Furthermore, it is possible that analysis datasets can not be created solely from the SDTM domain data sets. As an alternative, ALTANA can provide the programs and datasets that were used to create the derived analysis datasets. In addition, this comment did not address the specific studies for which this information should be provided and we therefore propose to include this for studies M1-401 and M1-402. *Does FDA feel this comment can be adequately addressed with the proposed information that is intended for submission?* If FDA concurs, this information can be provided in the March 29th submission.

**Cheryl Czachorowski**  
Director, Regulatory Affairs  
ALTANA Pharma US  
210 Park Ave  
Florham Park, NJ 07932  
Office: (973) 514-4271  
Fax: (973) 236-1695

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

Pharma



ALTANA Pharma  
220 Park Avenue  
Florham Park, NJ 07932  
USA

T + (973) 514-4240  
F + (973) 236-1695  
[www.altanapharma-us.com](http://www.altanapharma-us.com)

Via Courier

30 March 2006

Dr. Badrul Chowdhury, Division Director  
Division of Pulmonary and Allergy Drug Products (HFD-570)  
Office of Drug Evaluation II  
Food and Drug Administration (FDA)  
Center of Drug Evaluation and Research (CDER)  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**CICLESONIDE NASAL SPRAY  
NDA 22-004 eCTD SUBMISSION 0005  
AMENDMENT TO A PENDING APPLICATION  
RESPONSE TO AN INFORMATION REQUEST – STATISTICAL COMMENTS**

Dear Dr. Chowdhury:

Reference is made to NDA 22-004 for ciclesonide nasal spray. Additional reference is made to a facsimile dated March 20, 2006 providing statistical comments and information requests. Further reference is made to a telephone contact held on March 23, 2006 requesting information on the allergen utilized in the skin prick tests for study 76/2004 (TBN-CL-002).

The Sponsor's response and detailed information for each FDA comment identified within the March 20, 2006 communication is provided as an attachment to this cover letter. The FDA comment is provided in bolded text, followed by the Sponsor's response.

ALTANA Pharma is providing a response to FDA Comments 1, 2, 4, 5 and 6 within this submission and will provide a response to FDA Comments 2, 3 and 7 in a subsequent submission planned for April 7, 2006. The specific content of the submissions are summarized below.

**March 30, 2006 Submission Detail:**

- Comment 1: Information was submitted previously to NDA eCTD Submission Sequence 0002 on Friday, March 17, 2006 to address this comment; therefore, no new data information provided.
- Comment 2: A summary of the corrected analysis results for the affected primary and key secondary analyses from studies 287/2004 (M1-401) and 363/2004 (M1-402) demonstrating no appreciable impact on results is provided within the attachment to cover letter. Summary tables will be provided in the April 7, 2006 submission (see below).
- Comment 4: A replacement file for dataset in.xpt for study 76/2004 (TBN-CL-002), located in Section 5.3.5.1 of the eCTD is provided.
- Comment 5: New analysis datasets for instantaneous TNSS on Day 1 (diday1ha.xpt) for Studies 287/2004 (M1-401) and 363/2004 (M1-402), located within Section 5.3.5.1 of the eCTD is provided. A new data definition file for each of the datasets, containing the output from proc contents, is also provided.
- Comment 6: Pollen count data for all clinical sites within study 76/2004 (TBN-CL-002) is provided within this submission as a new report labeled 76/2004PC (TBN-CL-002), located within Section 5.3.5.4 of the eCTD.

**April 7, 2006 Submission Detail:**

- Comment 2: Summary tables of analysis results from pivotal studies 287/2004 (M1-401) and 363/2004 (M1-402) for reflective TNSS utilizing three different covariate structures (AR(1), CS, UN) and SAS output for each structure from Study 76/2004 (TBN-CL-002) will be provided.
- Comment 3: Analysis datasets for pivotal Studies 287/2004 (M1-401) and 363/2004 (M1-402) will be provided.
- Comment 7: The programs and datasets that were used to create the derived analysis datasets for Studies 287/2004 (M1-401) and 363/2004 (M1-402), located within Section 5.3.5.1 of the eCTD, will be provided.

This amendment is the fifth amendment (sequence 0005) to NDA 22-004 and is compiled in an eCTD format. As a reminder, please be aware that with the current eCTD technology, the pdf hyperlinks are active within documents (internal hyperlinks) and within a sequence submission but the hyperlinks from this sequence to previous and across other sequences may not work.

A Cumulative Table of Contents (TOC) is being provided in Module 1 under Section 1.2. This Cumulative TOC provides the full eCTD table of contents, which serves to identify all documents submitted to date, along with a reference to the sequence. Documents submitted in the present sequence are listed in blue text and hyperlinked.

ALTANA certifies that all electronic media are free from computer virus. The virus scan for the entire submission was performed using Symantec Antivirus Corporate Edition Program

Dr. Badrul Chowdhury  
March 30, 2006

Page 3

8.1.0.825, scan engine 4.2.0.7. This submission is approximately 122 MB and is being provided on one CD-ROM.

If you have any questions or require additional information to facilitate the review, please contact me at (973) 514-4271, or in my absence, Peter Fernandes at (973) 593-7984. For technical eCTD matters, please contact Edna Hernandez at (973) 593-7909.

Sincerely,  
ALTANA Pharma US, Inc.



Cheryl Czachorowski  
Director of Regulatory Affairs  
Phone: (973) 514-4271  
Fax: (973) 236-1695

Enclosures: 1 CD-ROM, paper copies of original signatures for 1.1.2 FDA Form 356h and 1.2 Cover Letter

**APPEARS THIS WAY  
ON ORIGINAL**

**ATTACHMENT TO COVER LETTER**

The Sponsor's response and detailed information for each comment identified within the March 20, 2006 communication is provided below. The FDA comment is provided in bolded text, followed by the Sponsor response:

**FDA Comment 1. Errors**

- a. **For LB.xpt, the variables – LBSTNRHI and LBSTNRLO should be data type of "NUM". There are some records with "Negative" or "NEGATIVE" in LB.xpt. These errors need to be corrected for all the LB.xpt datasets. Please review the CDISC implementation Guide 3.1 Page 74.**

Sponsor Response: The data type for LBSTNRHI and LBSTNRLO have been corrected to "NUM" for the SDTM lab data for Study 149/2005 (M1-403). Additionally, the terms "NEGATIVE" or "Negative" do not appear in these variables. All other datasets have been verified and do not contain the terms "NEGATIVE" or "Negative" in the LBSTNRHI and LBSTNRLO variables. A replacement SAS transport file for the laboratory domain lb.xpt, initially included within the Tabulation Datasets submitted for Study 149/2005 (M1-403) in Section 5.3.5.1 of the eCTD, was submitted in NDA eCTD Submission Sequence 0002 on Friday, March 17, 2006.

- b. **Ti.xpt has no records. The datasets need to be re-sent or the dataset name should be removed from define.xml and define.pdf. This occurred in datasets of Study 76-2005.**

Sponsor Response: An attribute of "delete" was assigned for the ti.xpt dataset included within the Tabulation Datasets for Study 76/2004 (TBN-CL-002). This was submitted in NDA eCTD Submission Sequence 0002 on Friday, March 17, 2006.

**FDA Comment 2: Incorrect Code**

**We note that the following code was provided in the submission; however, this code is not useful with the data structure used in the submission since missing days were not indicated with periods in the input data set.**



**Clarify and provide the corrected analysis results for the primary efficacy and key secondary variables for the dose finding study and the two pivotal studies. In order to show the robustness of the primary analysis model, provide the analysis results using three different covariate structures (AR(1), CS, US) separately.**

Sponsor Response: The FDA is correct that either the time variable should be in the repeated statement or missing data included as records with "." in the SAS dataset in order for SAS to properly perform the repeated measures analysis. ALTANA has run analyses correcting the mistake, and there is no appreciable impact on the results. Analysis of the average of AM and PM reflective TNSS and the key secondary analysis of the average of AM and PM instantaneous TNSS for the pivotal trials 287/2004 (M1-401) and 363/2004 (M1-402) is provided in Table 1 below. The results within this table also address the issue identified in FDA Comment 3: Duplication. Since LOCF was used to fill in intermittent missing values for Study 76/2004 (TBN-CL-002), this change in programming language would have no impact on the results of the 76/2004 (TBN-CL-002) trial. As later trials [149/2005 (M1-403), 146/2005 (M1-404), 144/2005 (M1-405), 147/2005 (M1-408), 148/2005 (M1-409)] utilized weekly averages for analysis instead of daily values making intermittent missing values much less common, it is assumed that any impact on results from those trials would be even more negligible. All analyses of diary efficacy data potentially affected by this error are available from ALTANA upon request.

Additionally, ALTANA will perform the repeated measures analyses for the primary measure utilizing the different correlation structures as requested in order to evaluate the robustness of the primary analysis to misspecification of the correlation structure. The results of these analyses will be provided for two pivotal trials as requested in a similar manner to the post-text tables provided in the 287/2004 (M1-401) and 363/2004 (M1-402) trials. As ALTANA does not possess the SAS code for the production of tables in the dose range finding trial, the analyses of Study 76/2004 (TBN-CL-002) will be provided as SAS output. The planned submission date for this information is April 7, 2006.

**Table 1 Comparison of Original Analyses to the Corrected\* Analysis in Studies 287/2004 (M1-401) and 363/2004 (M1-402)**

Study	Measure	Original Analyses*			Corrected Analyses*		
		LS Mean Change from Baseline (SE) Cic 200 mcg	LS Mean Change from Baseline (SE) Placebo	Estimated Difference (95% CI) p-value	LS Mean Change from Baseline (SE) Cic 200	LS Mean Change from Baseline (SE) Placebo	Estimated Difference (95% CI) p-value
<b>Primary Analyses</b>							
287/2004 (M1-401)	Average AM and PM Reflective TNSS over Days 1-14	-2.40 (0.16)	-1.50 (0.16)	0.90 (0.45, 1.36) <0.001	Same as Original	Same as Original	Same as Original
363/2004 (M1-402)	Average AM and PM Reflective TNSS over Days 1-42	-2.51 (0.12)	-1.89 (0.13)	0.63 (0.28, 0.97) <0.001	Same as Original	-1.89 (0.12)	0.62 (0.28, 0.97) <0.001
<b>Key Secondary Analyses</b>							
287/2004 (M1-401)	Average AM and PM Instantaneous TNSS over Days 1-14	-2.15 (0.16)	-1.28 (0.16)	0.88 (0.44, 1.31) <0.001	Same as Original	Same as Original	0.87 (0.44, 1.31) <0.001
363/2004 (M1-402)	Average AM and PM Instantaneous TNSS over Days 1-42	-2.22 (0.12)	-1.68 (0.12)	0.54 (0.21, 0.88) 0.001	-2.21 (0.12)	Same as Original	0.53 (0.20, 0.87) 0.002

\*Analyses were corrected for handling of duplicate diary entries and for the handling of missing values in the repeated measures analysis

**FDA Comment 3: Duplication**

Clarify the duplicated record in the CDISC SDTM data.

(an example was provided in the March 20<sup>th</sup> fax and is not repeated here)

Sponsor Response: There are duplicate records in the CDISC-SDTM data for dy.xpt in both pivotal Studies 287/2004 (M1-401) and 363/2004 (M1-402) because the SDTM data are a mirror of the raw data, and the raw data include duplicate records. These data represent patient diary data obtained from a paper diary, and in some cases patients recorded symptom scores on two diary pages for the same date. All data were included in the SDTM dataset. Upon investigation of the duplicate data, it was discovered that the duplicate records had not been handled properly in the analysis datasets for the pivotal

trials in that no prospective rule or sensible post-hoc rule was applied. For later trials [namely 149/2005 (M1-403) and 146/2005 (M1-404)], a rule was established at the blind data review meeting held prior to unblinding on how to handle duplicate diary data. The established rule was as follows: if only one of the two pages has non-missing data, then the data from that page will be used and the page containing only missing data is discarded, if both pages have non-missing data that include identical symptom scores, then the data from one of the pages will be discarded and the other used, and finally, if the pages contain non-missing non-identical symptom scores, then both pages of data will be discarded due to the difficulty in determining which of the two pages is correct. Using this rule, analysis datasets will be re-created from the diary data for the pivotal trials. Additionally, the analyses being rerun in response to FDA Comment 2: Incorrect Code will use the corrected intermediate datasets in terms of handling duplicate dates. Since the number of duplicate values is quite small in relation to the size of the datasets for both 287/2004 (M1-401) and 363/2004 (M1-402), the impact of this correction on results is negligible. Results for the primary and key secondary analyses corrected for both the handling of duplicate dates and the handling of missing data are shown in the table above included in the response to FDA Comment 2: Incorrect Code. Also as stated above, all additional analyses of diary efficacy data potentially affected by the mistakes identified by the FDA are available from ALTANA upon request. Corrected analysis datasets for pivotal Studies 287/2004 (M1-401) and 363/2004 (M1-402) will be provided in a submission planned for April 7, 2006.

**FDA Comment 4: Incorrect Data Value**

**We note that the data values are the same in RE.xpt and IN.xpt analysis data set for the dose-finding study. Please provide the correct data set.**

Sponsor Response: The dataset in.xpt was provided in error and a replacement file for in.xpt for Study 76/2004 (TBN-CL-002) is provided within this submission.

**FDA Comment 5: Hourly Diary Data**

**Provide the hourly assessment of INSTANTANEOUS TNSS on Day 1 analysis dataset and the SAS code, which creates the data set for the dose-finding study and the two pivotal studies.**

Sponsor Response: Hourly instantaneous nasal symptom data were collected in the two pivotal Studies 287/2004 (M1-401) and 363/2004 (M1-402) and were not collected in the dose range finding trial 76/2004 (TBN-CL-002). Within the original NDA, hourly instantaneous nasal symptom data for trials 287/2004 (M1-401) and 363/2004 (M1-402) were only available in the SDTM datasets. ALTANA has created and is providing within this submission, new analysis datasets [287/2004 (M1-401) diday1ha.xpt and 363-2004

(M1-402) diday1ha.xpt] for instantaneous TNSS on Day 1 for Studies M1-401 and M1-402. A new data definition file for each of these datasets, containing the output from proc contents, is also provided.

**FDA Comment 6: Pollen Count Data**

**Provide the pollen count data for study TBN-CL-002 (DOSE-FINDING study).**

Sponsor Response: Daily pollen counts were recorded for all study sites participating in Study 76/2004 (TBN-CL-002). These data were not originally harvested by the study monitors, nor entered into a clinical database; however, the source data have been obtained and are provided as Report 76/2004PC in Section 5.3.5.4 within this submission.

In response to a subsequent phone request for information on skin prick testing, the allergen utilized for skin prick testing at all clinical sites was mountain cedar.

**FDA Comment 7: Review Assistant**

**Provide the SAS programs that created the CDISC-AdAM datasets from CDISC-SDTM datasets. For example, the following code is part of the SAS code (T\_AM-PM\_REFL.pdf) that was provided in the submission. The "TNSS" is the input data set and can not be found in the submission. We can not verify the primary analysis datasets – RE.xpt and IN.xpt (AdAM) from datasets DY.xpt, CM.xpt, EX.xpt and other available datasets (SDTM).**

Sponsor Response: The SDTM datasets were derived from the raw data after the analysis of the clinical trials. The ADaM datasets were not created directly from the SDTM datasets; rather, the ADaM datasets were typically created from intermediate datasets utilized in the analysis of the trial. Thus, ALTANA does not have the SAS code for creation of ADaM datasets from SDTM datasets readily available. Furthermore, it is possible that analysis datasets cannot be created solely from the SDTM domain datasets. Programs and datasets that were used to create the derived analysis datasets will be provided. In addition, this comment did not address the specific studies for which this information should be provided, and we therefore propose to include this for pivotal Studies 287/2004 (M1-401) and 363/2004 (M1-402). The planned submission date for this information is April 7, 2006.

## 6.4 Attachment 4

Back to CUM TOC

Pharma



ALTANA Pharma  
220 Park Avenue  
Florham Park, NJ 07932  
USA

T + (973) 516-0240  
F + (973) 236-1695  
[www.altanapharma-us.com](http://www.altanapharma-us.com)

Via Courier

07 April 2006

Dr. Badrul Chowdhury, Division Director  
Division of Pulmonary and Allergy Drug Products (HFD-570)  
Office of Drug Evaluation II  
Food and Drug Administration (FDA)  
Center of Drug Evaluation and Research (CDER)  
Central Document Room  
5901-B Amundale Road  
Beltsville, MD 20705-1266

**CICLESONIDE NASAL SPRAY  
NDA 22-004 eCTD SUBMISSION 0006  
AMENDMENT TO A PENDING APPLICATION  
RESPONSE TO AN INFORMATION REQUEST – STATISTICAL COMMENTS**

Dear Dr. Chowdhury:

Reference is made to NDA 22-004 for ciclesonide nasal spray. Additional reference is made to an FDA facsimile dated March 20, 2006 providing statistical comments and information requests (IR). Further reference is made to eCTD submission sequence 0005 dated March 30, 2006, which provided a response to 5 out of the 7 comments raised by FDA within the March 20<sup>th</sup> IR.

The purpose of this submission is to provide information to address all other outstanding FDA comments identified within the March 20<sup>th</sup> IR. A detailed description of the Sponsor's response to address FDA comments 2, 3 and 7 is provided as an attachment to the cover letter. The FDA comment is provided in bolded text, followed by the Sponsor's response.

The specific content of this submission is summarized below.

- **Comment 2: complete summary tables containing analysis results from pivotal studies 287/2004 (M1-401) and 363/2004 (M1-402) for the primary (average AM and PM reflective TNSS) and key secondary (average AM and PM instantaneous TNSS) measures utilizing the three different covariate structures (AR(1), CS, UN) are provided.**

Furthermore, as ALTANA does not possess the SAS code for the production of tables in the dose range finding trial, the analyses of Study 76/2004 (TBN-CL-002) are provided as SAS output. All information will be contained within Section 5.3.5.3 Report 164/2006. For reference, the programs utilized to perform these analyses are provided in an analyses program folder within the report.

Comment 3: ADaM datasets using the rule identified in the previous March 30, 2006 submission for the primary and key secondary measure of average AM and PM instantaneous TNSS, labeled re.xpt and in.xpt, respectively, for pivotal Studies 287/2004 (M1-401) and 363/2004 (M1-402) are included as replacement datasets within each study located in Section 5.3.5.1 of this eCTD submission.

Comment 7: raw and intermediate datasets as well as the programs used to create both the intermediate and ADaM datasets for both the reflective and instantaneous TNSS for Studies 287/2004 (M1-401) and 363/2004 (M1-402) are provided within this submission. Specifically, the following files are provided within each study located in Section 5.3.5.1 of this eCTD submission:

New Datasets:

- sm.xpt: raw data for study medication information
- di.xpt: raw data for patient diary information
- tnss.xpt: intermediate data consisting of reflective data used in the analysis for the primary efficacy measure (average AM and PM reflective TNSS)
- inst.xpt: intermediate data consisting of instantaneous data used in the analysis for the secondary efficacy measure (average AM and PM instantaneous TNSS)
- A new data definition file containing the output from proc contents for the raw and the intermediate datasets identified above will be provided as pdf files labeled raw-contents.pdf and imed-contents.pdf within each respective tabulation or analyses dataset folder.
- The datasets sm.xpt and di.xpt are provided within the tabulations dataset folder for each study report, located in section 5.3.5.1 of the eCTD. The datasets tnss.xpt and inst.xpt are provided within the analyses dataset folder for each study report, located in section 5.3.5.1 of this eCTD submission.

Analysis Programs:

- D-TNSS-INTER.txt (and .pdf) and D-INST-INTER.txt (and .pdf): code utilized for the creation of the reflective and instantaneous intermediate datasets, respectively, provided as a text file and also in pdf format.
- D-TNSS-ADAM.txt (and .pdf) and D-INST-ADAM.txt (and .pdf): code utilized for the creation of the ADaM datasets from the reflective and instantaneous intermediate datasets, respectively, provided as a text file and also in pdf format.
- The program code is provided in the analyses programs subfolder for each study report, located in section 5.3.5.1 of this eCTD submission.

This amendment is the sixth amendment (sequence 0006) to NDA 22-004 and is compiled in an eCTD format. As a reminder, please be aware that with the current eCTD technology, the pdf hyperlinks are active within documents (internal hyperlinks) and within a sequence submission. Hyperlinks to previous sequences may not work.

A Cumulative Table of Contents (TOC) is being provided in Module 1 under Section 1.2. This Cumulative TOC provides the full eCTD table of contents, which serves to identify all documents submitted to date, along with a reference to the sequence. Documents submitted in the present sequence are listed in blue text and hyperlinked.

ALTANA certifies that all electronic media are free from computer virus. The virus scan for the entire submission was performed using Symantec Antivirus Corporate Edition Program 8.1.0.825, scan engine 4.2.0.7. This submission is approximately 902 MB and is being provided on one DVD.

If you have any questions or require additional information to facilitate the review, please contact me at (973) 514-4271, or in my absence, Peter Fernandes at (973) 593-7984. For technical eCTD matters, please contact Edna Hernandez at (973) 593-7909.

Sincerely,  
ALTANA Pharma US, Inc.



Cheryl Czachorowski  
Director of Regulatory Affairs  
Phone: (973) 514-4271  
Fax: (973) 236-1695

Enclosures: 1 DVD, paper copies of original signatures for 1.1.2 FDA Form 356h and 1.2 Cover Letter

### ATTACHMENT TO COVER LETTER

The Sponsor's response and detailed information for each comment identified within the March 20, 2006 communication is provided below. The FDA comment is provided in bolded text, followed by the Sponsor response:

#### **FDA Comment 2: Incorrect Code**

**We note that the following code was provided in the submission; however, this code is not useful with the data structure used in the submission since missing days were not indicated with periods in the input data set.**

**Clarify and provide the corrected analysis results for the primary efficacy and key secondary variables for the dose finding study and the two pivotal studies. In order to show the robustness of the primary analysis model, provide the analysis results using three different covariate structures (AR(1), CS, UN) separately.**

Sponsor Response: The mistakes in the handling of intermittent missing data in the repeated measures analysis identified in the first portion of this FDA comment were previously addressed in NDA 22-004 eCTD sequence submission 0005 dated March 30, 2006.

In terms of addressing the robustness of the primary and key secondary analyses to specification of the correlation structure, ALTANA has performed the repeated measures analyses for the primary measure (average AM and PM reflective TNSS) for 287/2004 (M1-401), 363/2004 (M1-402), and 76/2004 (TBN-CL-002) and the key secondary measure (average AM and PM instantaneous TNSS) for 287/2004 M1-401 and 363/2004 (M1-402) utilizing the different correlation structures as requested. As there were no key secondary analyses pre-specified in 76/2004 (TBN-CL-002), no additional analyses were performed for this trial. A summary of the results and comparisons of the analyses for each study are summarized in Table 1, Table 2, and Table 3. There were no appreciable differences between analysis results when different correlation structures were specified.

Additionally, complete summary tables containing analysis results from pivotal studies 287/2004 (M1-401) and 363/2004 (M1-402) for the primary (average AM and PM reflective TNSS) and key secondary (average AM and PM instantaneous TNSS)

measures utilizing the three different covariate structures (AR(1), CS, UN) are provided. Furthermore, as ALTANA does not possess the SAS code for the production of tables in the dose range finding trial, the analyses of Study 76/2004 (TBN-CL-002) are provided as SAS output. All information will be contained within Section 5.3.5.3 Report 164/2006. For reference, the programs utilized to perform these analyses are provided in an analyses program folder within the report.

**Table 1 Repeated Measures Analysis Results for Average AM and PM Reflective and Instantaneous TNSS Utilizing Different Correlation Structures Study 287/2004 (MI-401)**

Correlation Structure	LS Mean Change from Baseline (SE) Cic 200 mcg	LS Mean Change from Baseline (SE) Placebo	Estimated Difference (95% CI) p-value
<b>Average AM and PM Reflective TNSS over Days 1-14</b>			
CS + AR(1)*	-2.40 (0.16)	-1.50 (0.16)	0.90 (0.45, 1.36) p<0.001
AR(1)	-2.40 (0.14)	-1.49 (0.14)	0.91 (0.53, 1.29) p<0.001
CS	-2.40 (0.17)	-1.50 (0.17)	0.90 (0.44, 1.36) p<0.001
UN	-2.40 (0.17)	-1.49 (0.17)	0.91 (0.45, 1.37) p<0.001
<b>Average AM and PM Instantaneous TNSS over Days 1-14</b>			
CS + AR(1)*	-2.15 (0.16)	-1.28 (0.16)	0.87 (0.44, 1.31) p<0.001
AR(1)	-2.16 (0.13)	-1.28 (0.13)	0.88 (0.52, 1.24) p<0.001
CS	-2.15 (0.16)	-1.28 (0.16)	0.87 (0.43, 1.31) p<0.001
UN	-2.15 (0.16)	-1.28 (0.16)	0.88 (0.44, 1.32) p<0.001

\* This is the structure specified in the SAP and used for analyses reported in the CSR.

**Table 2 Repeated Measures Analysis Results for Average AM and PM Reflective and Instantaneous TNSS Utilizing Different Correlation Structures Study 363/2004 (MI-402)**

Correlation Structure	LS Mean Change from Baseline (SE) Cic 200 mcg	LS Mean Change from Baseline (SE) Placebo	Estimated Difference (95% CI) p-value
<b>Average AM and PM Reflective TNSS over Days 1-42</b>			
CS + AR(1)*	-2.51 (0.12)	-1.89 (0.12)	0.62 (0.28, 0.97) p<0.001
AR(1)	-2.51 (0.08)	-1.89 (0.08)	0.62 (0.40, 0.85) p<0.001
CS	-2.52 (0.13)	-1.89 (0.13)	0.63 (0.27, 0.98) p<0.001
UN	-2.49 (0.13)	-1.88 (0.13)	0.62 (0.26, 0.97) p<0.001
<b>Average AM and PM Instantaneous TNSS over Days 1-42</b>			
CS + AR(1)*	-2.21 (0.12)	-1.68 (0.12)	0.53 (0.20, 0.87) 0.002
AR(1)	-2.22 (0.08)	-1.67 (0.08)	0.55 (0.34, 0.76) p<0.001
CS	-2.22 (0.12)	-1.68 (0.12)	0.53 (0.20, 0.87) 0.002
UN	-2.20 (0.12)	-1.67 (0.12)	0.54 (0.19, 0.88) 0.002

\* This is the structure specified in the SAP and used for analyses reported in the CSR.

**Table 3 Repeated Measures Analysis Results for the Sum of AM and PM Reflective TNSS Utilizing Different Correlation Structures – Study 76/2004 (TBN-CL-002)**

Correlation Structure	LS Mean Change from Baseline (SE)					Estimated Difference (95% CI) p-value			
	Cic 200mcg	Cic 100mcg	Cic 50mcg	Cic 25mcg	Placebo	Cic 200 v Pla	Cic 100 v Pla	Cic 50 v Pla	Cic 25 v Pla
CS w/ Random Subject*	-5.83 (0.40)	-5.33 (0.39)	-4.79 (0.40)	-4.81 (0.39)	-4.19 (0.39)	-1.64 (-2.74, -0.55) 0.003	-1.14 (-2.24, -0.05) 0.040	-0.60 (-1.70, 0.50) 0.284	-0.62 (-1.71, 0.47) 0.265
AR(I)	-5.83 (0.35)	-5.33 (0.34)	-4.79 (0.35)	-4.81 (0.34)	-4.19 (0.34)	-1.64 (-2.60, -0.69) p<0.001	-1.14 (-2.10, -0.19) 0.019	-0.60 (-1.56, 0.36) 0.221	-0.62 (-1.57, 0.33) 0.203
CS	-5.83 (0.40)	-5.33 (0.39)	-4.79 (0.40)	-4.81 (0.39)	-4.19 (0.39)	-1.64 (-2.74, -0.55) 0.003	-1.14 (-2.24, -0.05) 0.040	-0.60 (-1.70, 0.50) 0.285	-0.62 (-1.71, 0.47) 0.266
LN	-5.83 (0.40)	-5.33 (0.39)	-4.79 (0.40)	-4.81 (0.39)	-4.19 (0.39)	-1.64 (-2.74, -0.55) 0.003	-1.14 (-2.24, -0.05) 0.040	-0.60 (-1.70, 0.50) 0.286	-0.62 (-1.71, 0.47) 0.267

\* This is the structure specified in the SAP and used for analyses reported in the CSR.

Appears This Way  
 On Original

**FDA Comment 3: Duplication**

**Clarify the duplicated record in the CDISC SDTM data.**

Sponsor Response: The impact on analysis results of the mistake in the handling of duplicate diary data in the intermediate datasets for the 287/2004 (M1-401) and 363/2004 (M1-402) trials was previously addressed in NDA 22-004 eCTD sequence submission 0005 dated March 30, 2006. ADaM datasets using the rule identified in the previous March 30<sup>th</sup> submission for the primary and key secondary measure of average AM and PM instantaneous TNSS, labeled re.xpt and in.xpt, respectively, for pivotal Studies 287/2004 (M1-401) and 363/2004 (M1-402) are included as replacement datasets within each study in Section 5.3.5.1 of this eCTD submission.

As the Sponsor was updating the ADaM datasets, an additional observation was noted that we would like to bring to the statistical reviewer's attention. The Intent-to-Treat (ITT) flag in these datasets was set for each patient based upon the patient being randomized and receiving at least one dose of randomized study medication only. However, the statistical analysis plans (SAP) specified in addition that patients should have at least one post-baseline efficacy observation in order to be included in the ITT analysis set. The result of the utilized classification is that one patient in 287/2004 (M1-401) and 6 patients in 363/2004 (M1-402) were counted in the total number of patients in the ITT analysis set when technically they should not have been, according to the SAP. This classification was consistent across all the core phase 3 ciclesonide nasal spray allergic rhinitis trials [287/2004 (M1-401), 363/2004 (M1-402), 149/2005 (M1-403), 146/2005 (M1-404), 144/2005 (M1-405), 143/2005 (M1-406), 145/2005 (M1-407), 147/2005 (M1-408) and 148/2005 (M1-409)] included in the original NDA, eCTD sequence 0000 dated December 22, 2005. There is no impact on any analysis results, as these randomized and treated patients without a post-baseline efficacy observation have no efficacy data to be included in the efficacy analyses.

**FDA Comment 7: Review Assistant**

**Provide the SAS programs that created the CDISC-AdAM datasets from CDISC-SDTM datasets. For example, the following code is part of the SAS code (T\_AM-PM\_REFL.pdf) that was provided in the submission. The "TNSS" is the input data set and can not be found in the submission. We can not verify the primary analysis datasets – RE.xpt and IN.xpt (AdAM) from datasets DY.xpt, DM.xpt, EX.xpt and other available datasets (SDTM).**

Sponsor Response: The SDTM datasets were derived from the raw data after the analysis of the clinical trials. The ADaM datasets were not created directly from the SDTM datasets; rather, the ADaM datasets were typically created from intermediate datasets utilized in the analysis of the trial. Thus, ALTANA does not have the SAS code for

*Confidential Information*

creation of ADaM datasets from SDTM datasets readily available. Furthermore, it is possible that analysis datasets cannot be created solely from the SDTM domain datasets. Therefore, the raw and intermediate datasets as well as the programs used to create both the intermediate and ADaM datasets for both the reflective and instantaneous TNSS for Studies 287/2004 (M1-401) and 363/2004 (M1-402) are provided within this submission. Specifically, the following files are provided within each study located in Section 5.3.5.1 of the eCTD:

**New Datasets:**

- sm.xpt: raw data for study medication information
- di.xpt: raw data for patient diary information
- tnss.xpt: intermediate data consisting of reflective data used in the analysis for the primary efficacy measure (average AM and PM reflective TNSS)
- inst.xpt: intermediate data consisting of instantaneous data used in the analysis for the secondary efficacy measure (average AM and PM instantaneous TNSS)
- A new data definition file containing the output from proc contents for the raw and the intermediate datasets identified above will be provided as pdf files labeled raw-contents.pdf and imed-contents.pdf within each respective tabulation or analyses dataset folder.
- The datasets sm.xpt and di.xpt are provided within the tabulations dataset folder for each study report, located in section 5.3.5.1 of the eCTD. The datasets tnss.xpt and inst.xpt are provided within the analyses dataset folder for each study report, located in section 5.3.5.1 of the eCTD.

**Analysis Programs:**

- D-TNSS-INTER.txt (and .pdf) and D-INST-INTER.txt (and .pdf): code utilized for the creation of the reflective and instantaneous intermediate datasets, respectively, provided as a text file and also in pdf format.
- D-TNSS-ADAM.txt (and .pdf) and D-INST-ADAM.txt (and .pdf): code utilized for the creation of the ADaM datasets from the reflective and instantaneous intermediate datasets, respectively, provided as a text file and also in pdf format.
- The program code is provided in the analyses programs subfolder for each study report, located in section 5.3.5.1 of the eCTD.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Feng Zhou  
8/29/2006 12:48:17 PM  
BIOMETRICS

Ruth Davi  
8/29/2006 12:55:25 PM  
BIOMETRICS



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

## **Statistical Review and Evaluation**

### **CLINICAL STUDIES**

NDA/Serial Number: N22-004  
Drug Name: Ciclesonide Nasal Spray 50mcg  
Indication(s): Proposed Indication: SAR, PAR in adults and children ages 2 year and older  
Applicant: Altana Pharmaceuticals, Inc.  
Date(s): Received 12/22/05; User Fee 10/22/06  
Review Priority: Standard

Biometrics Division: Division of Biometrics II (HFD-715)  
Statistical Reviewer: Feng Zhou, Statistical Reviewer  
Concurring Reviewers: Ruthanna C Davi, (Biometrics Team Leader)

Medical Division: Division of Pulmonary and Allergy Drug Products (HFD-570)  
Clinical Team: Carol Bosken, M.D. (Medical Reviewer)  
Badrul A Chowdhury, M.D. (Medical Division Director)  
Project Manager: Collette Jackcon (HFD-570)

Keywords: Clinical Studies, NDA review, Dropouts

### FILING CHECKLIST

<b>Item</b>	<b>Check (NA if not applicable)</b>
<b>Index sufficient to locate necessary reports, tables, etc.</b>	<b>Yes</b>
<b>Original protocols &amp; subsequent amendments available in the NDA</b>	<b>Yes</b>
<b>Safety and efficacy for gender, racial, and geriatric subgroups investigated</b>	<b>Yes</b>
<b>Data sets in EDR conform to applicable guidances.</b>	<b>Yes</b>

The submission is filable from a statistical perspective.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Feng Zhou  
3/1/2006 01:40:20 PM  
BIOMETRICS

Ruth Davi  
3/1/2006 01:46:21 PM  
BIOMETRICS