CLINICAL REVIEW

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Established Name	Ciclesonide
Trade Name	Omnaris
Therapeutic Class	Corticosteroid
Applicant	NYCOMED
Priority Designation	6S
Formulation	Nasal Aqueous Suspension
Dosing Regimen	Once Daily
Indication	Allergic Rhinitis
Intended Population	2 to <12 years of age

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ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
ANOVA	Analysis of Variance
AR	Allergic rhinitis
CI	Confidence Interval
DSI	Division of Scientific Investigation
ECG	Electrocardiogram
ENT	Ear Nose and Throat
HFA	Hydrofluroalkane
HPA-axis	Hypothalamic-pituitary-adrenal
ICS	Inhaled corticosteroids
ITT	Intention To Treat
i-TNSS	Instantaneous Total Nasal Symptom Score
LS	Least square
MedDRA	Medical Dictionary
PANS	Physicians Assessment of Overall Nasal Signs and Symptoms Severity
PAR	Perennial Allergic Rhinitis
PK	Pharmacokinetic
PNSS	Overall Physician-Assessed Nasal Symptom Score
QD	Every Day
r-TNSS	Reflective Total Nasal Symptom Score
SAR	Seasonal Allergic Rhinitis

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Ciclesonide 200 mcg (2 actuations of 50 mcg each in each nostril) once daily is recommended for the relief of symptoms caused by seasonal allergic rhinitis in children 6 to 12 years of age. The recommendation is based on the results of a well designed pivotal efficacy trial in this age group in subjects with seasonal (SAR) as well as previously documented efficacy in adults. Safety of ciclesonide nasal spray was also demonstrated in the pediatric study and another conducted in subjects with PAR. Adverse events were mild and infrequent, and there was no evidence of an effect on the HPA-axis or the ophthalmologic system that was any greater than expected with inhaled corticosteroid treatment.

Ciclesonide is not recommended for treatment of 6 to < 12 year-olds with PAR. The single study submitted in the original NDA did not support the conclusion that ciclesonide was effective in this age-group and no new studies in subjects with PAR were submitted with the complete response. Ciclesonide is also not recommended for patient 2 to < 6 years of age. The proposed recommended dose of 100 mcg was not shown to be efficacious in any of the pediatric studies, and this dose was administered to too few patients to support the long term safety in this age range.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

No phase 4 study is recommended

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Ciclesonide aqueous nasal spray is a corticosteroid formulated to be administered by nasal inhalation. It is approved for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. In the original application (NDA 22-004), the indication included children as young as 2 years of age. However, efficacy was not demonstrated in the studies submitted at that time. The current complete response includes two new studies and references the pediatric studies submitted with the original application. The new studies include a 2 week efficacy and safety trial in subjects 6 to <12 years of age with SAR (Study 417). Ciclesonide doses of 200 mcg once daily (C200) and 100 mcg once daily (C100) were compared to placebo in during randomized double-blind treatment. The primary efficacy outcome was the average of the AM and PM reflective Total Nasal Symptom Score (r-TNSS) with instantaneous Total Nasal Symptom Score (i-TNSS), the scores on the individual components of the symptom score, and a physician's assessment of

nasal symptoms as secondary efficacy outcomes. Safety was assessed with adverse events, vital signs, and ENT examination. No assessment was made of the HPA-axis.

The second new study was conducted in children 2 to < 6 years of age with PAR (Study 416). The subjects were randomized to C200 or placebo and were treated for 12 weeks. The primary objective of this study was to assess safety. However, the 24-hour r-TNSS was obtained daily and weekly averages were compared between treatment groups over the study period. Safety was assessed with AM plasma cortisol, and routine safety laboratory examinations as well as with adverse events and ENT examinations.

The application also references Study 403 (6 to <12 years of age with PAR) and 405 (2 to < 6 years of age with PAR) that were submitted with the original NDA. Both of these earlier studies were randomized, placebo-controlled, and doses of 25, 100 and 200 mcg ciclesonide were administered. In both of these earlier studies 24-hour urines were collected for cortisol, and these results are included in the current approved label.

The total number of subjects who received ciclesonide in the above studies (403, 405, 416, and 417) was 1096. Of these, 496 received the 200 mcg dose. Of those treated with 200 mcg, 116 were 2 to <6 and 380 were 6 to <12 years of age. For the entire sample, the mean (SD) exposure to C200 was 49.3 (34.5) days: 70.4 (23.7) days in children 2 to <6 years of age and 42.8 days in the 6 to 11 years of age.

1.3.2 Efficacy

In the 6 to <12 age group with SAR (Study 416) there was a statistically significant, but quantitatively small change in mean of the AM and PM r-TNSS in favor of the 200 mcg dose of ciclesonide. The study was powered to detect a difference between placebo and ciclesonide of 0.75, but the LS mean difference observed was 0.39 (p=0.04). The AM i-TNSS was also statistically significantly better in the C200 group than placebo, supporting the conclusion that once daily dosing provided protection throughout the dosing period. Neither the average of the AM and PM r-TNSS nor the AM i-TNSS was improved in the subjects treated with C100 compared to placebo. Similarly, in the PAR study (403) none of the doses resulted in improvement in the r-TNSS compared to placebo. It therefore, appears that ciclesonide is effective is subjects 6 to <12 years of age only for those who have SAR and in the 200 mcg dose.

Only subjects with PAR were studied in the 2 to < 6 year group. The Applicant is proposing a recommended starting dose for this age-group of 100 mcg daily. However, in none of the pediatric studies were any of the efficacy outcomes better in the children treated with C100 than with placebo. The 100 mcg dose was not tested in Study 416 and in Study 405 there were only 30 to 33 subjects per treatment group. In this very small sample size, some of the differences between ciclesonide treatment and placebo were quantitatively large, however, the range of values was wide, and the differences among treatment groups were not statistically significant or dose ordered. As in the adults and older children, the 200 mcg dose of ciclesonide was effective in the 2 to <6 year-olds. The 24-hour r-TNSS averaged over each week of treatment improved by 0.86 points (p=0.021) comparing C200 to placebo treatment. However, the body size and

nasal surface area difference between adults and children age less than 6 years is considerable, and the 100 mcg dose is assumed, by the Applicant, to provide the same effective dose as 200 mcg in the older children and adults.

In the justification of the 100 mcg recommended starting dose in children 2 to < 6 years, the Applicant relied heavily on the physician's assessment of nasal symptoms (PNSS) in Study 405 where the difference between C100 and placebo was large, but the results for this variable were not referred to in Study 416 where the PNSS improved less during treatment with C200 than with placebo. Such selective, retrospective inclusion of a variety of efficacy results (both primary and secondary outcomes and results lacking statistical significance) is not statistically acceptable. Because efficacy with C100 in children 6 to <12 years of age was not demonstrated, it can not be extrapolated to children 2 to <6 years of age.

1.3.3 Safety

The safety review is based on observation of 1096 subjects treated with ciclesonide (496 with the 200 mcg dose). Of those treated with 200 mcg, 116 were 2 to <6 years of age and 380 were 6 to <12 years of age. For the C200 group, the mean exposure was 49.3 days with mean exposure in the younger children 70.4 days and in the older of 42.8 days. This differential is primarily due to the relatively high enrollment in study 417 which only lasted for 2 weeks. There were 398 subjects in the C100 treatment groups: 364 were age 6 to <12 and 34 were 2 to <6 years of age. The mean exposure to C100 was 40.2 days in the 2 to <6 year-olds and 44.6 in the 6 to <12 year-olds.

In general, the adverse events that were reported in this program were mild to moderate and of a classification that is usual for this patient population. The only deaths reported were of two girls who died in the same automobile accident. There were no serious adverse events in either study 416 or 417. From the previously reviewed studies there were 3 serious events in the 6 to <12 year olds: 1 each asthma and abdominal pain in a C200 subject, and a traumatic skull fracture in a placebo subjects. One 2 year-old developed fever and swollen glands 4 weeks after completing 25 mcg ciclesonide.

Common adverse events were reported for 37.6, 40.4, 66.9, and 40.1% of the 6 to <12 year-olds treated with C200, C100, C25, and placebo respectively. The high incidence of events in the C25 group is probably related to the longer exposure (71.5 days compared to 49.3 44.3, and 45.6 days in the C200, C100, and placebo groups, respectively). This was due in turn, to the exclusion of C25 from study 417 which at 2 weeks duration, was substantially shorter than the other trials. Focusing on the comparison between C200 and placebo, the only events that were reported in >2% of the subjects and more frequently in the C200 group were headache, nasopharyngitis, pharyngolaryngeal pain, vomiting, hypersensitivity, allergic rhinitis, and urticaria. Headache and nasopharyngitis were each reported in 6.6% of the C200 subjects. This compared to 5.7% for headache and 5.4% for nasopharyngitis in the placebo subjects. All other events were reported in less than 5% of the subjects and the difference between placebo and C200 was less than 1.0%.

For the 2 to <6 year-olds the incidence of common events was 48.3, 26.5, 21.2, and 42.1% in the C200, C100, C25, and placebo subjects, respectively. The variable incidence of events is again correlated with exposure because neither C100 nor C25 was included in Study 416. Only 9 and 7 events were reported in the younger children treated with C100 and C25, respectively. Focusing on the difference between C200 and placebo, the only MedDRA preferred terms that reported in more than 2% of the subjects and more often in the C200 group than in the placebo subjects were pyrexia, upper respiratory tract infection, otitis media, sinusitis, headache, influenza, platelet count increased and blood pressure increased. The most frequently reported events, pyrexia and upper respiratory tract infection were reported in 12.1 and 9.5%, respectively of the C200 subjects and 10.5% and 6.6% of the placebo subjects. The next most common were otitis media and sinusitis, at 5.2% each in the C200 subjects and 2.6 and 1.3% of the placebo subjects. All other events were reported in less than 5% of the subjects.

Special examinations consisted of ENT exams which showed no perforations or ulcerations in these short term studies, and AM plasma cortisol assessment in Study 416 (2 to < 6 years old). The single AM plasma level is not considered an adequate test of HPA-axis function and the current label, which summarized the findings from the first two studies (403 and 405) will remain unchanged. Routine safety laboratory examinations performed in Study 416 showed no areas for concern.

1.3.4 Dosing Regimen and Administration

Approval of ciclesonide nasal spray in a dose of 200 mcg once daily is recommended for patients 6 years and older. Approval of the 100 mcg once daily dose for patients 2 to <6 years is not recommended because of the failure to demonstrated efficacy with the dose and dose regimen. It is also of note that only 34 subjects age 2 to < 6 years have been treated with this dose of ciclesonide and that the mean length of treatment was 40.2 days. This is not a large enough database to assure safety of this preparation for long-term use.

1.3.5 Drug-Drug Interactions

No drug-drug interaction studies were submitted with this application.

1.3.6 Special Populations

This application is totally directed towards the pediatric population. Studies in subjects <2 years of age have been waived because nasally inhaled corticosteroids may have an unacceptable safety profile in children under 2 years of age.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Ciclesonide is derived from [redacted] and put into a hypotonic aqueous suspension for nasal inhalation. The proposed commercial formulation contains the drug substance, Microcrystalline Cellulose and Carbomethoxycellulose Sodium NF, [redacted] USP, Potassium Sorbate NF, Edetate Disodium USP, Hydrochloric Acid NF and Purified Water USP. The solution is contained in an amber glass bottle equipped with an adapter, [redacted]

The suspension used in the phase 3 trials and in the to-be marketed product contains 50 mcg/ 70 mL actuation. The 200 mcg dose is administered as two activations in each nostril once daily. Stability data support approval with a 24 month shelf-life (see CMC review for details)

2.2 Currently Available Treatment for Indications

There are currently 7 corticosteroid preparations formulated for nasal inhalation (Table 1). They are all indicated for both seasonal and perennial rhinitis, and they are all approved for patient 6 years of age or older. Fluticasone propionate is approved for children as young as 4 years, and both mometasone and fluticasone furoate for children as young as 2 years. All are available as aqueous suspensions and triamcinolone is also marketed as an HFA suspension.

Table 1. Corticosteroid Nasal Sprays Approved for the Treatment of Allergic Rhinitis

Drug	Trade Name	Formulation	Indication*	
Triamcinolone	Nasacort HFA Nasal Aerosol	Microcrystalline suspension in metered-dose aerosol	SAR PAR	≥6
	Nasacort AQ Nasal Spray	Microcrystalline aqueous suspension in manual pump	SAR PAR	≥6
Beclomethasone	Beconase AQ	Microcrystalline aqueous suspension in manual pump	SAR PAR	≥6
Fluticasone propionate	Flonase	Microfine aqueous suspension in metering atomizing spray pump	SAR PAR	≥4
Fluticasone furoate	Veramyst	Aqueous suspension	SAR PAR	≥2
Mometasone	Nasonex	Aqueous suspension in manual pump	SAR PAR	≥2
Budesonide	Rhinocort Aqua	Microcrystalline aqueous suspension in manual pump	SAR PAR	≥6
Flunisolide	Nasarel	Suspension in metered-dose aerosol	SAR PAR	≥6

*SAR – Seasonal Allergic Rhinitis; PAR – Perennial Allergic Rhinitis: ≥ age in years

In addition to nasal corticosteroids, numerous anti-histamines and a leukotriene inhibitor are available for the treatment of allergic rhinitis.

2.3 Availability of Proposed Active Ingredient in the United States

OMNARIS (Ciclesonide Aqueous nasal spray) was approved for marketing in August 2006. It had not been marketed as of February 1, 2007. No major safety issues have arisen since the approval and no label changes have been submitted.

2.4 Important Issues With Pharmacologically Related Products

Ciclesonide given by inhalation has low systemic bioavailability. However, it is a corticosteroid and therefore has the potential to produce the adverse events associated with corticosteroid administration if it is taken in high enough doses. These adverse effects include adrenal suppression, a poor response to infections and wound healing, delayed bone maturation and growth in children, osteoporosis in older individuals, cataracts and glaucoma.

2.5 Presubmission Regulatory Activity

The original marketing application for OMNARIS (NDA 22-004) was submitted on December 22, 2005, and included a proposed indication for the treatment of symptoms associated with seasonal and perennial rhinitis in patients 2 years of age and older. In August 2006, OMNARIS was approved for the treatment of allergic rhinitis (SAR and PAR) in patients 12 years of age and older. It was not approved for patients < 12 years of age due to the failure to demonstrate efficacy in this age-group, and the concern that very few subjects less than 6 years of age had been treated and that therefore the safety database was not adequate. A separate NDA was created for the portion of the application that related to subjects less than12 years of age and this (NDA 22-124) received an approvable action. During discussions with the Applicant about the approvable action, the Division agreed that if "substantial efficacy" could be demonstrated in the older age group, then it could be extrapolated to the children < 6 years of age.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

A single PK study performed in pregnant rats was submitted. See Pharmtox review for details.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data is taken entirely from the supplement which contains three study reports.

4.2 Tables of Clinical Studies

The submission contains three previously un-reviewed studies, listed in Table 2.

Table 2. New clinical studies submitted with complete response

Study	Subjects	Design	Duration	Dose	Patients	Evaluations
416	2 - <6 y o PAR	Randomized, double-blind, placebo-controlled	12 Wks	200 mcg	125	r-TNSS AE, AM Cortisol
417	6 - <12 y o SAR	Randomized, double-blind, placebo-controlled	2 Wks	100 mcg 200 mcg	618	r-TNSS, PNSS AEs

Studies submitted with the original application (NDA 22-004) are referenced and these are listed in Table 3.

Table 3. Studies submitted with NDA 22-004 and referenced in the complete response

Study	Subjects	Design	Duration	Dose	Patients	Evaluations
405	2 - <6 y o PAR	Randomized, double-blind, placebo-controlled	12 Wks	200 mcg 100 mcg 25 mcg	125	r-TNSS AE, AM Cortisol
403	6 - <12 y o PAR	Randomized, double-blind, placebo-controlled	2 Wks	200 mcg 100 mcg 25 mcg	618	r-TNSS, PNSS AEs

4.3 Review Strategy

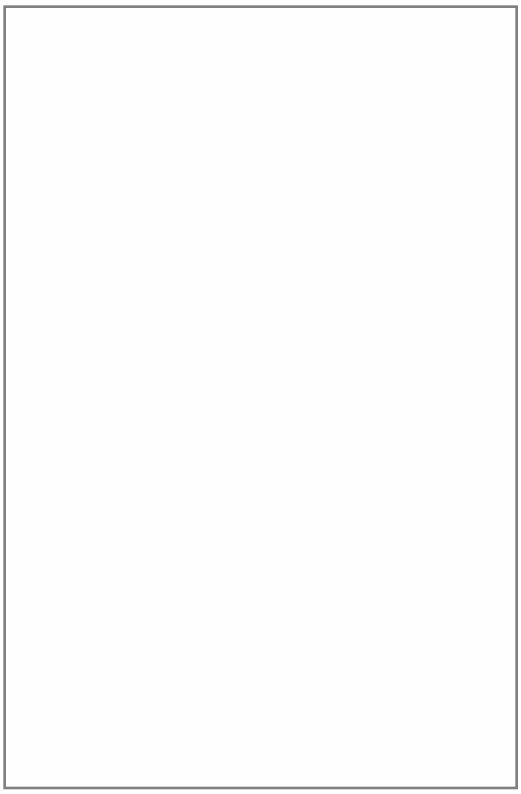
Studies 416 and 417 enrolled subjects ages 2 to < 12 years of age. This is the age range of the proposed indication and the studies were reviewed in detail.

Studies 405 and 403 were reviewed with the original NDA and these reviews are referenced in the current review.

Unless otherwise noted the data in this review was obtained from the study reports submitted with the NDA. Comments from the reviewer and calculations performed by the reviewer are notated in italics.

4.4 Data Quality and Integrity

The primary efficacy variable in Study 417 was the r-TNSS, a symptom score that was recorded by the caregiver into an interactive voice reporting system (IVRS). Operating the IVRS, obtaining the data, and submitting it to the Applicant was the responsibility of [redacted] the company that developed the IVRS. No documentation was submitted with the application to support the efficacy of the system or to describe the correlation between the results obtained with the IVRS and those obtained using the more common paper diary. A request was, therefore made to DSI for an audit of this company and their procedures for monitoring the IVRS, as well as inspections of several sites, to assess the operation of the system from the perspective of the clinical center staff. The sites chosen were as follows:



The preliminary site visit reports have revealed only minor irregularities. The full reports are pending.

4.5 Compliance with Good Clinical Practices

Both study 416 and 417 were conducted according to the Declaration of Helsinki and followed the ICH rules for Good Clinical Practices. Both protocols were review by an independent ethics committed and informed consent was obtained from all subjects.

4.6 Financial Disclosures

All but two of the investigators signed statements that they had no financial interest in ALTANA. Two investigators did not sign statements and had left the respective institutions and could not be located by the time the omission was found.

5 CLINICAL PHARMACOLOGY

5.2 Pharmacodynamics

In Study 416 AM cortisol was measured before and after 12 weeks of treatment with placebo and 200 mcg ciclesonide daily in subject 2 to < 6 years of age. Assays were completed in 40 placebo and 79 ciclesonide 200 mcg once daily (C200) subjects. The samples were single AM plasma levels obtained before 9:300 AM. In this sample, no difference was seen between placebo and ciclesonide treatment (Table 4).

Table 4. AM serum cortisol in Study 416 (Subjects 2 to <6 years of age)

Serum cortisol (mcg/dL) comparing baseline to 1-12 week average	Placebo N=40	C200 N=79
Baseline, mean(SD)	9.85 (3.8)	9.83 (3.9)
Change from Baseline, LS mean (SE)	1.94 (0.7)	0.99 (0.5)
Treatment Difference 95% CI	0.95 -0.72, 2.63	

Serum and 24-hour urines for cortisol were also obtained in the pediatric subjects enrolled in studies 403 and 405, submitted with NDA 22-004. There was a suggestion of a dose response for both variables in Study 405 (2 to <6 years of age). However the number of subjects was too small for reliable statistical inference (Table 5).

Table 5. HPA-axis evaluation in Study 405 (NDA 22-004) subjects age 2 to <6

		C25	C100	C200
Plasma cortisol (mcg/dL)	N Difference from Placebo 95% CI	28 -0.12 -1.8, 1.6	27 -0.36 -2.1, 1.4	28 -1.04 -2.7, 0.7
24-hour urinary cortisol (mcg/day)	N Difference from Placebo 95% CI	16 -1.76 -4.3, 0.8	15 -1.96 -4.5, 0.3	22 -2.04 -4.4, 0.3

All of the data for the 6 to <12 year olds comes from Study 403, submitted with NDA 22-004. For neither the plasma, nor the urinary cortisol was there a dose relationship in the changes comparing placebo to ciclesonide treatment (Table 6). The most dramatic decrease occurred in the urinary cortisol in the subjects treated with ciclesonide 25 mcg (C25). The urinary cortisol

fell less in the 100 mcg (C100) and 200 mcg groups compared to the fall in the 25 mcg group, although the final values were all less than in the placebo subjects. While the number of subjects is higher in the 6 to <12 year old studies, the numbers are still not large, especially considering the vagaries of collecting 24-hour urines in children less than 12 years of age.

Table 6. HPA-axis Evaluation in Subjects 6 to < 12 years of age (Study 403, NDA 22-004)

		C25	C100	C200
Plasma cortisol (mcg/dL)	N Difference from Placebo 95% CI	51 -0.38 -2.1, 1.3	61 0.12 -1.5, 1.7	45 -0.35 -1.4, 2.1
24-hour urinary cortisol (mcg/day)	N Difference from Placebo 95% CI	32 -2.11 -5.3, 1.1	44 -0.08 -3.1, 2.9	35 -0.81 -4.0, 2.4

Reviewer: Because the single plasma measurement of cortisol is not an adequate assessment of HPA-axis function, the currently approved label, which summarizes the results from studies 403 and 450 should remain unchanged.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Proposed Indication

OMNARIS® is indicated for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 2 years of age and older.

6.1.1 Methods

Efficacy was assessed from the results of a randomized, double-blind, placebo-controlled clinical trials in subjects 6 to <12 years of age. The Agency agrees that efficacy can be extrapolated to the 2 to 5 year age group, if it is well documented in adults and older children.

6.1.2 General Discussion of Endpoints

In Study 417, the primary efficacy endpoint was the parent/caregiver recorded Total Nasal Symptom Score (TNSS). The score consisted of four components (runny nose, itchy nose, sneezing, and nasal congestion) which were graded on a 4-point scale (Absent, Mild, Moderate, and Severe). Diary recordings were made of the instantaneous symptoms (i-TNSS - experienced over the prior 10 minutes) and of symptoms recalled over the previous 12 hours (r-TNSS – reflective TNSS). For the primary analysis, the AM and PM r-TNSS values were averaged, and the baseline measurements were compared to the measurements made over the course of the study using a repeated measures ANCOVA. In study 416, in 2 to 5 year-olds, efficacy was not the primary outcome of interest, however the r-TNSS was recorded once daily, the daily recordings were averaged weekly, and these weekly averages were compared among treatment groups. Secondary efficacy measures included instantaneous nasal symptom scores, scores for the individual symptoms, and a physician's assessment of nasal symptoms.

Reviewer: The TNSS is a standard way to assess rhinitis symptoms. For study 417 the caregiver, and if possible the same caregiver, made all of the assessments. This is an improvement over the initial NDA submission where either the parent or subject could have made the assessment, and the individual performing the test could change over the course of the study.

The care givers were instructed to administer the symptoms questionnaire when the child woke up and to call the IVRS within 15 minutes. The IVRS was called again in the evening, at which time the medication time was recorded. According to a response to an FDA query ( ) the Applicant confirmed that there was no paper back-up for the IVRS which means that the caregiver had to remember (or possibly make notes) on the time of medication administration 12 hours prior to the time it was recorded. No edits to the IVRS were allowed. There is no recording of the time the symptom score was obtained as this was assumed to be immediately prior to the call. As described in the review of the study report (pg .), the calls to the IVRS were made throughout the morning and it is not clear when the symptom scores were obtained in

reference to the call or medication administration. However, the distribution of the available variables (time of the call and time of medication administration) was similar in all the treatment groups.

A DSI audit was performed of the CRO that managed the IVRS and of three clinical sites to assess the effectiveness of the IVRS diary. Only minor and infrequent protocol violations were found. The validation documents for the IVRS were reviewed and deemed acceptable by the DSI reviewer. See Section 4.3Data Quality and Integrity.

6.1.3 Study Design

Both trials were randomized, double-blind, and placebo-controlled. The subjects in Study 417 had well documented SAR with positive skin tests to appropriate allergens. Pollen counts were made at each clinical site during the study and all but four subjects were tested at a time when the pollen counts to which they were allergic, were elevated. The study was two weeks in duration which is sufficient to asses the response to a corticosteroid in patients with SAR. There were approximately 200 subjects in each treatment group in Study 417, which should have been adequate to demonstrate efficacy in subjects with SAR. Study 416 was not designed to demonstrate statistically significant changes in symptoms.

As reviewed for NDA 22-004, Study 403 was a randomized, double-blind, placebo-controlled trial of ciclesonide aqueous nasal spray 25, 100, and 200 mcg QD administered to children age 6 to <12 years with PAR for 12 weeks. The primary outcome was the r-TNSS as recorded after 6 weeks of treatment in a paper diary by either the parent or subject. The ITT population included 165 subjects in each dose-group. The 25 mcg dose was totally ineffective, and will not be further referred to in the efficacy review. Study 405 was also reviewed for NDA 22-004. This was a randomized, double-blind, placebo-controlled trial conducted in children 2 to < 6 years of age with PAR.

6.1.4 Efficacy Findings

In Study 417 the change in the average of the AM and PM r-TNSS was -2.4 and -2.5 units in the C100 and C200 groups, respectively. The respective difference from the -1.9 change in the placebo group was 0.32 and 0.39. This difference was not significant in the C100 group, but it just reached statistical significance in the C200 group (95% CI = 0.02, 0.76; p=0.04 – Table). It should be noted, however, that the changes in the mean AM r-TNSS did not show efficacy for ciclesonide. The mean difference (95% CI) between C200 and placebo for the AM r-TNSS was 0.35 (-0.04, 0.74). As reviewed in NDA 22-004, none of the changes in the r-TNSS was significant in Study 403.

The AM (predose) i-TNSS can be used as an estimate of the efficacy of the single AM dose to cover the dosing range. In Study 417 the change over the course of the study was -2.1 and -2.2 in the C100 and C200 groups, respectively. As with the r-TNSS the only statistically significant difference was in the C200 group (95% CI = 0.06, 0.81 – Table 7). In Study 403 none of the changes in the AM i-TNSS was statistically significant. It should be noted that in Study 417 the

PM i-TNSS did not show efficacy for C200 and the mean of the AM and PM i-TNSS showed borderline significance for C200 (95% CI = 0.00, 0.73).

Table 7. Change in r-TNSS during Treatment with Ciclesonide in Children 6 to < 11 years of age in Study 417

	Dose	Ciclesonide 100 mcg		Ciclesonide 200 mcg	
	Study N	417 N=199	403 N=164	417 N=215	403 N=163
	Disease	SAR	PAR	SAR	PAR
Outcome	Duration of Treatment (weeks)	2	6	2	6
12 hour AM/PM r-TNSS	Baseline, Mean (SD)	8.4 (1.8)	6.7 (2.1)	8.3 (1.9)	6.7 (2.2)
	Change from Baseline, LS Mean (SE)	-2.4	-1.8	-2.5	-2.1
	Difference from placebo 95% CI p-value	0.32 -0.06, 0.14 0.10	-0.02 -0.50, 0.40 0.92	0.39 **0.02, 0.76** **0.040**	0.31 -0.10, 0.80 0.16
AM i-TNSS	Baseline, N Mean (SD)	197 7.7 (2.0)	164 6.2 (2.4)	215 7.7 (2.2)	163 6.3 (2.2)
	Change from Baseline, LS Mean (SE)	-2.1	-1.6	-2.2	-1.9
	Difference from placebo 95% CI	0.31 -0.07, 0.69	-0.21 -0.0.7, 0.2	0.44 **0.06, 0.81**	0.09 -0.3, 0.5
PNSS	Baseline, N Mean (SD)	199 7.7 (2.3)	163 7.2 (2.8)	215 8.0 (2.4)	157 7.2 (2.7)
	Change from Baseline, LS Mean (SE)	-2.7	-2.8	-3.3	-2.8
	Difference from placebo 95% CI	0.34 -0.21, 0.88	-0.001 -0.60, 0.60	0.92 **0.38, 1.45**	0.80 **0.2, 1.40**

In both studies 417 and 403 the physician's assessment of the nasal symptoms showed more improvement during treatment with 200 mcg ciclesonide than did the caregiver recorded symptom scores. While the 100 mcg dose of ciclesonide did not show efficacy in either study, substantial improvement in the scores was seen for the 200 mcg dose: 0.92 and 0.80 for study 417 and 403, respectively.

In a subset analysis of study 417 it was noted that thee was virtually no evidence of efficacy for the female subjects in either the TNSS (difference from placebo of -0.0) or the PNSS (difference from placebo of -0.02). This gender differential was not seen in the adult studies and differences seen in Study 403 were very small. For the 200 mcg dose of ciclesonide the difference in r-TNSS compared to placebo was 0.37 for the males and 0.22 for females. Neither difference was statistically significant.

Although the original premise was that substantial efficacy demonstrated in the 6 to < 12 year old subjects could be extrapolated to the 2 to < 6 year olds, the Applicant is recommending a starting dose of ciclesonide of 100 mcg daily in the younger age group, not by extrapolation but on the basis of the efficacy results of studies 405 and 416. As shown in Table 8, the only result that shows a significant difference from placebo was in the r-TNSS in Study 416 where the mean (95% CI) difference was 0.86 (0.13, 1.60). The physician's assessment actually showed less improvement in the C200 group than in the placebo group. In Study 405 the differences in the PNSS comparing ciclesonide to placebo were large, but not statistically significant. This was in part due to the small sample size. However, the lack of dose response does not suggest that a simple increase in the sample size would make the changes significant.

Table 8. Summary of Efficacy Outcomes for Subjects 2 to <6 years of age

	Dose	Ciclesonide 100 mcg		Ciclesonide 200 mcg	
	Study N	416 ---	405 N=33	416 N=81	405 N=33
	Disease	PAR	PAR	PAR	PAR
Outcome	Duration of Treatment (weeks)	12	6	12	6
24 hour r-TNSS	Baseline, Mean (SD)	---	5.4 (3.2)	6.7 (2.7)	4..8 (2.7)
	Change from Baseline, LS Mean (SE)	---	-2.6	-2.3	-1.9
	Difference from placebo 95% CI	---	*(0.9)*	0.86 **0.13, 1.60**	*(0.2)*
PNSS	Baseline, N Mean (SD)	---	30 7.0 (2.0)	81 7.2 (2.9)	33 6.1 (2.0)
	Change from Baseline, LS Mean (SE)	---	-3.5	-3.3	-2.9
	Difference from placebo 95% CI	---	1.12 -0.00, 0.2.3	-0.32 -1.5, 0.81	0.57 -0.6, 1.7

6.1.6 Efficacy Conclusions

The analysis of efficacy depends primarily on the results of 2 studies: 417 and 403. In neither was there evidence of efficacy during treatment with 100 mcg ciclesonide daily. After treatment with 200 mcg daily, the mean of the r-TNSS and the AM i-TNSS showed minimal, statistically significant improvement in SAR (Study 417). The difference in statistical significance is in part due to difference is sample size (Study 417 = 215 compared with 163 in Study 403) because the differences in absolute change were very small (0.39 in Study 417 and 0.31 in Study 403). Also the mean baseline scores for the r-TNSS were higher in study 417 which was a factor noted in the robustness of the response in the original NDA review. It should be noted that the studies were powered to detect a difference of 0.75 (Study 417) and 0.60 (Study 403).

Finally, it is curious that the only dose of ciclesonide that was effective in children, is the approved dose for adults. The Applicant stated that this is not unexpected because the pathophysiology of the disease is similar in adults, adolescents and children, and that the area of the nasal mucosa is similar to adults in children as young as 6 years. This seems unlikely on the face of it, and the Applicant's references do not include supporting data [1,2,3]. At least two recent articles documented continuing growth of the nasal septum and nasal volume over the ages 6 to 14. Loosen et al [4] made careful measurements in postmortem specimens obtained from 30 subjects without nasal pathology age 0 to 62 years. They distinguished between the cartilaginous septum and the ossified perpendicular plate (PP). In their specimens, the cartilaginous septum did not increase in size after 2.2 years of age, while the PP grew slowly well past puberty. Ferrario et al [5] conducted a combined longitudinal and cross sectional study in 1013 children ages 6 to 14 years. They used external markers to measure various linear nasal parameters and then calculated the nasal volume. All of the parameters increased gradually over the period of measurement.

[redacted] However, the final proposal is to recommend 100 mcg once daily as the starting e group. The reasoning proposed is that if 200 mcg is effective in larger children, then 100 mcg is probably the same equivalent dose in the smaller children. However, there is no support for this contention in the data submitted. None of the efficacy outcome measures was statistically significant for the 100 mcg dose in any of the pediatric studies. This could be partially due to the small number of subjects who were treated with 100 mcg: only 34 in the 2 to < 6 year age-group. However, lacking any positive findings, this can not be taken as the only cause. It is notable that in the 200 mcg dose group, the r-TNSS was significantly better than in the placebo-treated subjects, but the PNSS was actually worse. This measure, the physician's assessment of nasal symptoms, was a secondary efficacy outcome, and need not be accepted as a critical element in the assessment. However, in the discussion of Study 405 (no more than 33 subjects per treatment group), the results of the PNSS were presented as strong support for the 100 mcg dose. This is despite the fact that there was no dose ordering and no difference was statistically significant.

Ciclesonide appears to be a minimally effective anti-inflammatory agent. Only the highest dose tested has been shown to be effective in any patient population, and the improvement over treatment with placebo is only modest. The variable results (some positive and some negative) shown in Table 9 probably reflect random variation around a mean difference that is close to zero. It is, therefore, not surprising that ciclesonide appears to work better in SAR, because that is usually found to be more responsive to treatment than PAR. What is also apparent in this table is that the physician's assessment correlates very poorly with the diary assessments of nasal symptoms. The diary responses appear to be more consistent and reproducible, and there is no consistent relationship between the two metrics. In the adult SAR study (401) the diary assessment of the r-TNSS showed markedly more improvement compared to placebo than did the physician's assessment, while children 6 to <12 years of age showed more improvement in the physician's assessment than in the diary recorded r-TNSS. The 2 to < 6 year olds in study 416 are a special case. They had a very poor response in the physician's assessment, but a relatively robust response in the r-TNSS as summarized with the repeated measures analysis of

covariance. However, the physician's assessment compared baseline to end of the treatment period while the r-TNSS included measurements obtained over the entire 12 weeks. Had the analysis of the r-TNSS compared baseline to the value at 12 weeks the result would not have been significant. As a matter of fact, the 95% confidence interval for the comparison between C200 and placebo for the r-TNSS outcome crossed zero on each of the three last weeks of the trial.

Table 9. Comparison between Results of Diary-Recorded and Physician-Assessed Nasal Symptoms

				Difference in Scores Between C200 and Placebo		
Study	**Disease**	**Age (years)**	**Dose (mcg)**	**Reflective-Diary**	**Instantaneous AM -Diary**	**Physician****
401	SAR	≥ 12	**200**	**0.90 ***	**0.84***	0.12
402	PAR	≥ 12	**200**	**0.63 ***	**0.53***	**0.62**
404	PAR	≥ 12	**200**	**0.60 ***	---	0.34
403	PAR	6 to <12	200	0.31	0.21	**0.80***
			100	-0.02	-0.09	-0.00
417	SAR	6 to <12	**200**	**0.39 ***	**0.44***	**0.92***
			100	0.32	0.31	0.34
405	PAR	2 to < 6	200	0.2	---	0.57
			100	0.9	---	1.12
416	PAR	2 to < 6	**200**	**0.86 ***	---	-0.32

* 95% confidence interval does not cross zero

** The physician's assessment is for only the symptom score in order to make the comparison between the adult and pediatric results comparable. In the original application (NDA 22-004) the physician's assessment was presented as the average of the signs and symptoms. The data in the current table comes from the following sources: Study Report 401 – Post-text Table 14.2.2.3.4, page 424; Study Report 402 – Post-text Table 14.2.2.3.4, page 522; Study Report 404 – 14.2.3.3, page 502.

In summary, convincing data have not been presented that ciclesonide is effective in children 2 to <6 years of age. Extrapolation from adults and older children might be acceptable if the results were robust in these groups. However, the results for ciclesonide nasal spray suggest efficacy only when the highest dose is administered. Extrapolating the maximum adult dose to children <6 years of age is inappropriate, and the assumption that half the dose would be effective in the younger children is supported by no empirical data.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were two deaths in study 417. Two girls 6 and 7 years of age died in the same automobile accident. One had received 100 mcg ciclesonide for 11 days and the other had completed a

course of 200 mcg ciclesonide. In neither case was the death associated with study drug treatment. There were no deaths in Study 416.

7.1.2 Other Serious Adverse Events

There were no serious adverse events in either study 417 or 416 other than the 2 deaths described, above.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In Study 417, 618 subjects were enrolled and 588 (95.1%) completed the trial. The most common cause for withdrawal was an adverse event which was reported in 2.5, 2.5, and 0.9% of the placebo, C100 and C200 subjects, respectively.

In Study 416, 90.4% (113 of 125 enrolled) completed the study. Only 3 subjects (2 C200 subjects and 1 placebo subject) withdrew due to an adverse event. Lack of compliance was sited as the indication for withdrawal in 4.8% of the placebo and 2.4% of the C200 subjects while 3.6% of the C200 subjects refused to continue compared to none in the placebo group.

7.1.3.2 Adverse events associated with dropouts

In Study 417 there were 14 (2.3%) withdrawals. Two placebo subjects had epistaxis, but no other diagnosis was reported in more than one subject in any treatment group. 17 events were reported as associated with withdrawal: hypersensitivity, sinusitis, upper respiratory tract infection, urinary tract infection, Varicella, injury, asthma, nasal discomfort and pharyngolaryngeal irritation/pain were present in subjects who were withdrawn.

In Study 416 only 2 subjects were withdrawn. One C200 subject had a severe headache and dizziness and another had burning of the nose and eyes after taking the medication. The placebo subject had worsening asthma and a rash.

In a summary, of all the studies included in this application (403, 405, 416, and 417) only 4 MedDRA preferred terms were listed as the cause of withdrawal in more than 1 subject (Table 10). Asthma was most common in the placebo subjects, while epistaxis and nasal discomfort were most common in the C100 subjects. The incidence of withdrawal in the C200 group was the lowest of all the treatment groups.

Table 10. MedDRA Preferred Term for event leading to withdrawal in all Studies

	Placebo 445	C25 202	C100 398	C200 496
Subjects with one event, n (%)	17 (3.8)	4 (2.0)	10 (2.5)	8 (1.6)
Asthma	7(1.6)	1 (0.5)	2 (0.5)	2 (0.4)
Epistaxis	3 (0.7)	0	3 (0.8)	1 (0.2)
Nasal discomfort	1 (0.2)	0	2 (0.5)	1 (0.2)
Sinusitis	2 (0.4)	1 (0.5)	0	1 (0.2)

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Subjects were queried about adverse events at baseline and at all follow-up visits. Adverse events were not recorded in the diary.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse events were appropriately categorized.

7.1.5.3 Incidence of common adverse events

In Study 417 the overall incidence of total adverse events was higher in the placebo (19.1%) than in the actively treated subjects (16.6, and 12.6% in the C100 and C200 subjects, respectively). No event was reported in >2% of the subjects and more frequently in the placebo than the actively treated subjects.

In Stud 416 the incidence of common adverse events was comparable in the two treatment groups: 58.4 and 60.2% in the placebo and C200 subjects, respectively

7.1.5.4 Common adverse event tables

A listing of all of the adverse events occurring in at least 2% of the 6 to < 12 year old subjects in any treatment group is shown in table 11. There is an unusually high incidence of events in the C25 group, but this is due to the longer exposure in this group because this dose was not included in Study 417 which was substantially shorter than the other studies. The incidence of events in the C200 group was lower (37.6%) than the placebo overall incidence (40.1%) and only the MedDRA preferred terms of headache, nasopharyngitis, vomiting, hypersensitivity, allergic rhinitis, and urticaria were higher in the C200 group. Nasopharyngitis was seen in 1.2% more C200 subjects than placebo. All the other differences were less than 1.0%.

Table 11. Common Adverse Events in Children 6 to <12 years of Age

Preferred Term	Ciclesonide 200 mcg (N=380)	Ciclesonide 100 mcg (N=364)	Ciclesonide 25 mcg (N=169)	Placebo (N=369)
Mean treatment exposure (days)	**42.8**	**44.6**	**77.5**	**41.8**
Patients with one or more treatment-emergent AEs	**143 (37.6%)**	**147 (40.4%)**	**113 (66.9%)**	**148 (40.1%)**
Headache	25 (6.6%)	25 (6.9%)	12 (7.1%)	21 (5.7%)
Nasopharyngitis	25 (6.6%)	19 (5.2%)	16 (9.5%)	20 (5.4%)
Epistaxis	17 (4.5%)	22 (6.0%)	13 (7.7%)	24 (6.5%)
Cough	14 (3.7%)	13 (3.6%)	12 (7.1%)	20 (5.4%)
Pharyngolaryngeal pain	13 (3.4%)	17 (4.7%)	9 (5.3%)	12 (3.3%)
Upper respiratory tract infection	13 (3.4%)	22 (6.0%)	13 (7.7%)	22 (6.0%)
Vomiting	10 (2.6%)	11 (3.0%)	8 (4.7%)	9 (2.4%)
Nasal discomfort	8 (2.1%)	7 (1.9%)	8 (4.7%)	10 (2.7%)
Pyrexia	8 (2.1%)	12 (3.3%)	5 (3.0%)	14 (3.8%)
Asthma	7 (1.8%)	8 (2.2%)	3 (1.8%)	12 (3.3%)
Sinusitis	6 (1.6%)	9 (2.5%)	3 (1.8%)	8 (2.2%)
Hypersensitivity	5 (1.3%)	2 (0.5%)	4 (2.4%)	4 (1.1%)
Rhinitis allergic	5 (1.3%)	1 (0.3%)	5 (3.0%)	2 (0.5%)
Ear infection	3 (0.8%)	3 (0.8%)	4 (2.4%)	3 (0.8%)
Gastroenteritis viral	3 (0.8%)	4 (1.1%)	5 (3.0%)	4 (1.1%)
Urticaria	3 (0.8%)	1 (0.3%)	4 (2.4%)	1 (0.3%)

Data source: Post-text Table 3.5, Post-text Table 4.5 and Post-text Table 6.5

Subjects 6 to <12 with SAR were only enrolled in Study 417. Adverse events were uncommon and for each event they were least common in the C220 group (Table 12). A total of 99 subjects reported events, 39 (19.1%), 33 (16.6%) and 27 (12.6%) in the placebo, C100 and C200 subjects, respectively. Epistaxsis was the more frequently reported event and that occurred in 3.9, 3.6, and 1.4% of the placebo, C100 and C200 subjects, respectively.

Table 12. Adverse events that occurred in >2% of any treatment group in Study 417 (Subjects with SAR and 6 to <12 years of age).

	Placebo N=204	C100 N=199	C200 N=215
Any event	39 (19.1)	33 (16.6)	27 (12.6)
Epistaxis	8 (3.9)	7 (3.5)	3 (1.4)
Headache	4 (2.0)	4 (2.0)	2 (0.9)
Asthma	4 (2.0)	1 (0.5)	1 (0.5)
Nasal Discomfort	7 (3.4)	1 (0.5)	1 (0.5)

Of the 2 - <6 year old subjects enrolled in Study 416, 73 (58.4%) reported adverse events. Upper respiratory tract infection, cough, otitis media, sinusitis, influenza, increased platelet count, increased systolic BP, headache and Nasopharyngitis were reported in a few more subjects in the active treatment group than in the placebo subjects (Table 13).

Table 13 . Common Adverse Events (>3%) that were more frequent in the actively

treated subjects Subjects 2 to < 6 years of Age in Study 416

	Placebo N=42	C100 N=81	Total N=123
Subjects with one event, n (%)	23 (58.4)	50 (60.2)	73 (58.4)
Pyrexia	7 (16.7)	13 (15.7)	20
Upper respiratory tract infection	4 (9.5)	11 (13.3)	15
Cough	4 (9.5)	7 (8.4)	11
Otitis media	2 (4.8)	6 (7.2)	8
Sinusitis	1 (2.4)	6 (7.2)	7
Influenza	1 (2.4)	4 (4.8)	5
Platelet count increased	1 (2.4)	4 (4.8)	5
Increased systolic BP	0	3 (3.6)	3
Headache	0	3 (3.6)	3
Nasopharyngitis	1 (2.4)	3 (3.6)	4

7.1.5.6 Additional Analyses and Explorations

There was no notable difference in the distribution of gender among the treatment groups and no difference in the incidence of AEs between genders. The majority of the subjects were Caucasian in all of the studies. The duration of exposure to C200 was slightly less (42.4 days) in the Black subjects than in the Caucasian (49.7 days) and the Other Races (57.9 days). More of the Black children (34.1%) and children of Other Races (40.4%) were in the 2 to < 6 age range compared to the Caucasian children (18.3%). This is explained by the low prevalence of Caucasian children in study 405. Overall the incidence of any adverse event in the C200 group was 42.1%, 33.0%, and 38.5% in the Caucasian, Black and Other Racial groups, respectively. However, the differential between C200 and placebo was greatest in the Black children (33.0 vs 24.7 in the placebo group). This compares to the Caucasian group (42.1 vs 41.1 in the placebo subjects) and a lower rate in the C200 treated children of other racial groups (38.5% vs 67.6% in the placebo subjects). The disparity in the children of other racial categorization may be an artifact of low numbers as there were only 34 such children treated with the placebo. Also, there was a very high incidence of cough (14.7%), epistaxis (14.7%) and pharyngolarygeal pain (11.8%) in the Other racial group treated with placebo. This compares to an incidence of less than 8% in all of the other treatment groups.

7.1.7 Laboratory Findings

No laboratory analysis was performed in Study 417. In Study 416 an unusually large number of the baseline blood tests were above the upper limit of normal for the laboratory. For instance, 22.7% of the baseline calcium values and 13.4% of the BUN values were reported as being

above the normal range for the laboratory. The elevations were not large and the Applicant suggested that the subjects might have been dehydrated. The baseline plasma cortisol values also appeared to be elevated and the Applicant stated that the incorrect normal values had been reported [redacted]. (For cortisol results see Section 5.2 Pharmacodynamics, pg 13). The results of the routine chemistry and hematology showed no differences in the numbers of subjects who shifted into the abnormal range during the study. There were no differences in the mean values and the shifts in individual values were not large.

7.1.8 Vital Signs

There were no clinically meaningful changes in vital signs in either study 417 or 416.

7.1.12 Special Safety Studies

ENT examinations were performed in both Studies 417 and 416. No perforations, ulcerations, or erosions were seen.

7.1.14 Human Reproduction and Pregnancy Data

No pregnancies were reported.

7.1.16 Overdose Experience

There were no overdoses.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Study 417 (452/2006) was a two week, randomized, double-blind, placebo-controlled trial in subjects 6 to <12 years of age with SAR. There were 204, 199, and 215 subjects enrolled in the placebo C100 and C200 arms of the study. The safety assessment consisted of adverse event reporting and physical examination including ENT exam. No laboratory (including HPA-axis) testing or ECG examination was performed.

Study 416 (451/2006) was a 12 week, randomized, double-blind, placebo-controlled trial in subjects 2- < 6 years of age with PAR. There were 81 children in the C200 group and 42 in the placebo group. The safety evaluation consisted of adverse event enumeration, routine safety laboratory examination, and HPA-axis testing.

7.2.1.2 Demographics

In the children 6 to <12 years of age in study 403, the mean (SD) age was 8.8 (1.7) years, and in Study 417 the mean age was 9.4 (1.7). Fifty-nine percent of the subjects were male in Study 403

compared with 56.5% of the subjects in Study 417. The majority of subjects were Caucasian in both studies (Table 14).

Table 14. Demographic variables for Subjects 6 to <12 years of age

	403 (NDA 22-004)				Study 417 (NDA 22-124)		
	Placebo	C25	C100	C200	Placebo	C100	C200
Age, mean (SD)	8.7 (1.8)	8.8 (1.6)	8.8 (1.7)	9.0 (1.6)	9.2 (1.7)	9.5 (1.7)	9.4 (1.7)
Male (%)	58.8	52.7	61.8	63.6	55.4	53.8	60.0
Race (%)							
Caucasian	79.4	79.3	80.6	79.4	86.3	82.4	77.2
Black	14.5	10.7	11.5	12.7	11.8	14.6	19.5
Other	9.7	10.0	10.3	8.5	3.9	4.0	6.0

In the 2 to < 6 year old subjects, the mean (SD) age was 3.5 (1.1) years IN Study 405 and 4.2 years in Study 416. In the combined population 50 subjects 2 - 3 years of age and 64 subjects 4 - 5 years of age were treated with 200 mcg ciclesonide daily (Table 15). In Study 405, 56.1% of the subjects were male compared to 43.1% of the subjects in Study 416. Most unusual was the finding that only 28.0% of the subjects in Study 405 were Caucasian compared to 69.1% of the subjects in Study 416.

Table 15 Demographics of Subjects 2 to <6 years of age enrolled in studies of ciclesonide nasal spray

Study	405 (NDA 22-004)				416 (NDA 22-124)	
Dose N	Placebo 34	C25 32	C100 33	C200 33	Placebo 42	C200 83
Age, mean (SD)	3.6 (1.3)	3.3 (1.0)	3.5 (1.0)	3.6 (1.1)	9.2 (1.7)	9.4 (1.7)
Range						
2-3	16	20	17	15	19	35
4-5	18	12	16	18	23	46
Male (%)	52.9	56.3	60.6	54.5	50.0	39.5
Race (%)						
Caucasian	23.5	31.3	27.3	30.3	73.8	66.7
Black	70.6	68.8	72.7	69.7	11.9	9.9
Other	5.9	0	0	0	14.3	23.4

7.2.1.3 Extent of exposure (dose/duration)

In the combined studies (403, 405, 416, and 417) 1096 subjects 2 to <12 years of age were treated with ciclesonide and 496 were treated with 200 mcg. Of the total, 183 subject 2 to <6 were treated with ciclesonide, 116 with 200 mcg. More children over 6 years of age were treated than those < 6 years. However, because Study 417 was only 2 weeks long, the mean duration of treatment was shorter in the older children (42.8 [34.7] days compared to 70.4 [23.7] in the children 2 to <6) (Table 16 & 17).

Table 16. Number of Subjects Treated by Duration Treatment 6 to < 12 years of age

Dose	C25		C100		C200	
Age group, years	6-8	9-11	6-8	9-11	6-8	9-11
N	72	97	142	222	147	233
Exposure, days						
<29	6	6	70	134	91	132
29-55	3	5	4	2	4	0
56-80	4	4	3	4	1	5
>80	59	82	66	82	51	96

A total of 176 subjects age 2 to < 6 years were treated for at least a month and most were treated for 6 weeks. Of these, 116 were treated with 200 mcg and of these 51 were 2 to 3 years of age (Table 18).

Table 17. Duration of exposure to Study Drug in subjects 2 to < 6 years of age

Dose	C25		C100		C200	
Age group, years	2-3	4-5	2-3	4-5	2-3	4-5
N	21	12	17	17	51	65
Exposure, days						
< 29	1	0	1	1	1	3
29-41	0	0	1	0	1	1
42-55	20	12	15	16	15	17
56-80	0	0	0	0	0	1
>80	0	0	0	0	34	43

7.2.3 Adequacy of Overall Clinical Experience

For the 6 to < 12 year old children, 380 subjects treated with 200 mcg ciclesonide (the recommended dose) and followed for an average of 43 days is sufficient to assess safety for a drug that is indicated for SAR. There were no safety signals of concern seen in this application or in the studies submitted with NDA 22-004.

The total database for the 2 to <6 year-old children is larger than the database submitted with NDA 22-004, but it is still inadequate. This is especially true for the 100 mcg dose, which included only 34 subjects. The 2 to <6 year olds all had PAR and would presumably be treated for more than 2 weeks at a time.

The single AM plasma cortisol measurements obtained in the 2 to <6 year old children is inadequate to assess the HPA-axis. Data was obtained in NDA 22-004 and the results are included in the currently approved label. This will not change.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was minimal in this data set because the absence of any abnormalities seen in the previous clinical trials and the low incidence of this type of abnormality in this class of drugs.

7.2.8 Assessment of Quality and Completeness of Data

The clinical data as reported was complete. The official repott of the DSI site visits is pending at the time of this report.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Drug-related adverse events were infrequent and of a type typically associated with corticosteroid therapy. No new safety signal was identified in this dataset.

7.4 General Methodology

Adverse events in the studies reported in this complete response were infrequent, mild, and within the spectrum of those previously reported for this class of drugs. The data were not subjected to pooled analyses and predictive factors were not sought.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Ciclesonide 200 mcg (2 actuations of 50 mcg each in each nostril) once daily is recommended for the relief of symptoms caused by seasonal allergic rhinitis (SAR) in children 6 to 12 years of age. The recommendation is based on the results of a successful trial in patients with SAR and failure to demonstrate effectiveness in patient with PAR in this age-group. Safety of ciclesonide nasal spray in this age group was also demonstrated in all of these studies. Ciclesonide is not recommended for patient 2 to < 6 years of age. The proposed recommended dose of 100 mcg was not shown to be efficacious in any of the pediatric studies, and this dose was administered to too few patients to support the long term safety of this dose in this age range.

8.2 Drug-Drug Interactions

No drug-drug interaction studies were submitted with this application.

8.3 Special Populations

No populations other than the pediatric were studied in this complete response

8.4 Pediatrics

This application is entirely devoted to studies in subjects 2 to < 12 years of age. Studies in subjects less than 2 years of age have been waived because of the unacceptable safety profile of nasal steroids in children under 2 years of age.

8.7 Postmarketing Risk Management Plan

There is no post-marketing risk management plan, and none is required for this product other than routine surveillance and labeling.

9 OVERALL ASSESSMENT

9.1 Conclusions

Treatment with the aqueous solution of ciclesonide for nasal inhalation was associated with little toxicity, but also with only modest efficacy. The approved adult dose of 200 mcg once daily was the only dose that showed efficacy in the 6 to < 12 year old subjects with SAR. And the effect size was only half of that projected in the power analysis. The best response observed was a 0.39 point superiority of the change in r-TNSS comparing 200 mcg ciclesonide to placebo (p=0.04). The only study (403) in subjects with PAR in this age-group was negative. The safety database of 380 subjects treated for over a month and only a few mild to moderate adverse events is acceptable evidence of safety in this age group. Ciclesonide is, therefore recommended for the treatment of SAR, only, in subject 6 to < 12 years of age. The recommended dose is 200 mcg once daily.

The 100 mcg dose of ciclesonide was not effective in any of the pediatric studies. In addition, it was administered to a total of only 34 children age 2 to <6 years (study 405). Therefore, neither efficacy nor safety has been demonstrated. It may well be that 100 mcg is the appropriate dose for the younger children, however without demonstrated effectiveness in the 6 to 12 year-olds, efficacy of 100 mcg once daily can not be extrapolated to children 2 to 5 years of age. We agree that administration of the adult dose is inappropriate in the children less than 6 years of age.

9.2 Recommendation on Regulatory Action

Approval of ciclesonide 200 mcg once daily for children age 6 to <12 years of age with seasonal allergic rhinitis is recommended.

9.3 Recommendation on Postmarketing Actions

No post-marketing actions are recommended.

9.4 Labeling Review

In general, the age range that the revised label covers is 6 years and above

9.5 Comments to Applicant

Labeling comments will be sent to the Applicant.

10 APPENDICES

1 STUDY # 452/2006 (BY9010/M1-417)

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Clinical Trial Designed to Assess the Safety and Efficacy of Ciclesonide (200 mcg and 100 mcg once daily) Applied as a Nasal Spray for Two Weeks in the Treatment of Seasonal Allergic Rhinitis (SAR) in Patients 6 to 11 years of age.

1.1 Protocol

1.1.1 Administrative

Study Dates: March 14, 2006 to October 16, 2006
Clinical Centers: 69 Centers in the US.
Coordinating Investigator: Fred C. Hample Jr, MD

1.1.2 Objective/Rationale

The primary objective of this study was to demonstrate the efficacy of ciclesonide nasal spray administered once daily (200 and 100 mcg) in the treatment of SAR in patients 6 to 11 years of age. A secondary objective was to demonstrate the local safety and tolerability of intra-nasally delivered ciclesonide in this population.

1.1.3 Study Design

This was a 2-week, double-blind, placebo-controlled, parallel study of 618 subjects with SAR randomized into three treatment groups. Subjects were screened 7 to 14 days prior to randomization at which time they had a skin test in addition to the history and physical examination. Patients were kept in the run-in period 21 days if they had been on intranasal corticosteroids prior to screening. During the screening period subjects/caregivers recorded the subject's symptoms in an electronic diary twice daily. If the subject had an appropriate level of symptoms and compliance at the end of the screening period they were randomized to receive either 200 mcg, 100 mcg, or placebo once daily. After randomization they continued to record symptoms twice daily in the diary. Patients were seen at screening, baseline, and after 2 weeks. At baseline and follow-up the subjects had an ear, nose and throat (ENT) examination performed and a physician assessment of rhinitis signs and symptoms (PANS). The primary efficacy variable was the mean of the AM and PM r-TNSS comparing baseline to 1-2 weeks of treatment. Key secondary outcomes included the i-TNSS over 1 – 2 weeks and the physician-assessed nasal

symptom score at endpoint. The nasal signs portion of the PANS were reported as "Other" efficacy outcomes. Safety was assessed with adverse events, physical examination, and routine safety laboratory examinations**.** No assessment of the HPA-axis was made.

1.1.4 Study Population

Inclusion Criteria

- Male or female, 6 to 11 years of age
- A history of physician-diagnosed SAR to a relevant seasonal allergen for a minimum of two years immediately preceding the screening visit. The SAR must have been of sufficient severity to require treatment and be expected to require therapy in the future
- Positive skin test (3mm > control wheal) to an allergen known to induce SAR within 12 months of enrollment. The patient was expected to be exposed to the relevant allergen during the time of the study

Exclusion Criteria

- Pregnancy, nursing or plan to become pregnant.
- Evidence of bronchial, pulmonary, or respiratory tract infections within 14 days of screening
- Antibiotic therapy for a respiratory infection within 14 days of screening
- Active asthma (requiring daily treatment with inhaled corticoseroids or daily β-agonists)
- Had change in immunotherapy injections within 30 days of screening
- Positive for hepatitis B or C virus of human immunodeficiency virus or non-vaccinated exposure
- Any significant nasal physical abnormality including polyps or malformations
- Nasal surgery or trauma within 60 days of screening
- Inability to abide by medication restrictions (Table 19, pg 32).
- Plan to travel outside of the study area for >24 hours during the final 7 days of the baseline period, or > 2 consecutive days during treatment.
- Ingestion of systemic corticosteroids within 60 days of screening
- Use of topical corticosteroids within 30 days of screening
- Change in dose of pimecrolimus or tacrolimus topical preparations within 30 days of screening
- Concurrent participation of a sibling in the study

Randomization Criteria

- No common cold or acute sinusitis during the 7 days prior to randomization
- Adequate recording of symptoms in the diary (failure was defined as missing one or more of the entries on more than 2 days of the last 7 during run-in)
- A minimum TNSS (either AM or PM) of at least 6 for at least 5 of the last 7 days during the run-in

- The score for rhinorrhea or nasal congestion on the TNSS was of moderate severity (minimum score = 2) for 5 of the last 7 days of the run-in

Withdrawal Criteria

There were no specific withdrawal criteria

1.1.5 Study Procedures

Treatment

Ciclesonide nasal spray was provided in canisters containing 0, 25, and 50 mcg ciclesonide per actuation. The subjects were instructed to take two sprays in each nostril each AM. Compliance was assessed by the caregiver's responses to questions about medication use submitted in the diary.

Corticosteroids, antihistamines and immunotherapy were prohibited during the trial and for a specified time before screening/enrollment. The list of specific drugs and times of prohibition are included in Table 18.

Table 18. Prohibited Medications

Type of Medication	Time since last dose prior to B0	Time since last dose prior to T0
Intranasal corticosteroids (except study drugs)	-	21 days
Topical/Oral/Nasal decongestants	-	10 days
Short acting antihistamines including intranasal and ocular	-	14 days
Long acting antihistamines	-	14 days
Over-the-Counter preparations containing antihistamines	-	14 days
Vasoconstrictors	3 days	-
Major tranquilizers	3 days	-
Airozanν (OTC food supplement/diet to reduce leukotrienes)	7 days	-
Cromolyn, nedcromil, or lodoxamide (intranasal, ocular, or oral)	-	14 days
Leukotriene or 5-LO inhibitors	-	14 days
Inhaled/Oral/Intranasal anticholinergics	-	14 days
Tricyclic antidepressants	14 days	-
Monoamine oxidase inhibitors	14 days	-
Any other investigational drug	30 days	-
Inhaled corticosteroids (oral)	30 days	-
Azoles, antifungals	30 days	-
Anti-epileptic drugs	30 days	-
Systemic corticosteroids (intermittent or chronic)	60 days	-
Anti-IgE therapy	60 days	-
Immunosuppressive therapy	60 days	-

Furthermore, the following medications were allowed with limitations:

- Pimecrolimus and tacrolimus topical cream/ointment if initiated 30 days or more prior to the Screening Visit (B0) AND a stable (maintenance) dose used during the study period
- Patients were permitted to receive immunotherapy injections during the study if the patient had been on a stable maintenance regimen for at least 30 days prior to the Screening Visit (B0) and initiation of immunotherapy occurred 90 days or more prior to the Screening Visit (B0). Additionally, the dose of immunotherapy could not change during the study
- Intermittent use of ß-agonists was acceptable for patients with asthma (less than or equal to 3 days per week); however chronic daily use of these agents was not permitted
- Topical (dermatological) corticosteroids <1% hydrocortisone were allowed as needed
- Other drugs to treat concurrent diseases were allowed; however, their dosage was to be kept as constant as possible throughout the study

.

Efficacy Evaluation

Total Nasal Symptom Score was defined as the sum of the scores for four nasal symptoms consisting of runny nose, itchy nose, sneezing, and nasal congestion. Each symptom was rated on a severity scale of 0 to 3.

0 = Absent (no sign/symptom evident)
1 = Mild (sign/symptom clearly present, but minimal awareness; easily tolerated)
2 = Moderate (definite awareness of sign/symptom that is bothersome but tolerable)
3 = Severe (sign/symptom that is hard to tolerate [causes interference with activities of daily living and/or sleeping, for reflective scores])

The maximum AM or PM score was 12 (4 symptoms times a maximum score of 3).
The scores were to be recorded in the morning and evening, approximately 12 hours apart. At each time point, the parent/care-giver recorded and instantaneous (including the ten minutes prior to the call) and a 12-hour reflective score for each symptom. The baseline value was the average of the scores obtained on the 7 days prior to randomization.

The symptoms scores were recorded by the parent/caregiver via the [redacted]Voice™ Interactive Voice Recording System (IVRS). The reporter was responsible for telephoning the clinical center to activate the system. There were two time periods when entries could be made (5:00 AM – 12 noon and 5:00 PM to midnight) and duplicate entries were not accepted by the system. According to the schedule of activities, the instructions for use of the IVRS were reviewed with the parent/caregiver at the baseline and randomization visit. [redacted] the developer of the IVRS, was responsible for collection of the diary data and for data management and transfer to the sponsor. There is no discussion of any validation procedures for the instrumentation or any post-hoc assessment of the accuracy of the patient's reporting. There is no indication of a paper back-up for the IVRS data in the text of the study report or protocol.

Reviewer: Case report forms are available for very few of the subjects. However, a complete listing of investigator comments, taken from the CRFs, is included. In this listing there are

several references to difficulty with use of the IVRS. The system did not allow duplicate entries, but it also locked out caregivers who wanted to enter an appropriate response, but did it too late in the day.

A query was sent to the applicant requesting validation of the IVRS and information on the actual use of the system. The response [redacted] *indicated that no paper back-up was used and no changes were permitted in the IVRS recording. The subjects were instructed to call the IVRS by noon or midnight. However, the system actually accepted calls for one hour after that time for caregivers who were late. Therefore, the recording for Midnight to 1 AM was recorded as the PM recording for the day before. The Applicant also submitted a detailed description of the specifications for the operation of the IVRS. However, there is no record of field testing. The test results that are provided relate to the physical functioning of the system, e.g. did the IVRS issue the welcome message, the IVRS confirmed that the date was not a future date, and most of the tasks assessed were administrative tasks performed by the study staff.*

The Physician Assessment of Overall Nasal Signs and Symptoms Severity (PANS) was based on questioning the parent/caregiver on the intensity of the following signs and symptoms:

Signs
- Discoloration of nasal passages
- Swollen nasal passages
- Presence of secretions
- Evidence of post-nasal drip and/of throat irritation

Symptoms
- Runny Nose
- Itchy Nose
- Congestion
- Sneezing

The symptoms were scored with the following scale:

- 0 = absent (no sign/symptom evident)
- 1 = mild (sign/symptom clearly present but minimal awareness; easily tolerated)
- 2 = moderate (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe (sign/symptom that is hard to tolerate [i.e., causes interference with activities of daily living and/or sleeping])

The total of the symptom and total of the sign scores were averaged for the final overall score. The baseline was the score obtained at the randomization visit and the Endpoint was the last on-treatment measurement. Note than only the symptom score (Physicians Nasal Symptom Score – PNSS) was used as a key secondary efficacy variable.

Reviewer: On page 48/4503 says the following: "The PANS was based upon questioning of the patient's parent/caregiver by the investigator at Visits B0, T0, and T1 on the intensity of the

following AR signs and symptoms:". It seems unlikely that a response to a question about the sign of discoloration of the nasal passages would be asked of the care giver. In addition, in previous studies it was stated that the signs for this scale were obtained from the ENT examination.

Safety Evaluation

Safety was assessed with adverse events, vital signs, physical examination, and ENT examinations. The ENT examinations were performed specifically to assess known complications of intranasal corticosteroid administration such as bleeding, perforation or ulceration. Throat examinations were conducted to evaluate evidence of throat irritation, Candida infection, and post-nasal drip.

Pollen Counts

Daily pollen counts were obtained in the vicinity of all of the clinical sites.

1.1.6 Data Analysis

Sample Size

The sample size was calculated on the basis of results obtained during the first two weeks of study M1-403, a previous efficacy assessment of ciclesonide in patients 6 to 11 years of age with PAR. The standard deviation for the average change from baseline in that study was 2.01. A second estimate of 2.4 was obtained from a study of budesonide in a pediatric population with SAR. Using the larger of the values (2.4), it was estimated that 217 patients per group would provide 90% power to detect a difference between treatment groups of 0.75 with a two-sided alpha of 0.05. The estimated number of withdrawals was projected to be low, so 220 patients were randomized to each treatment.

Study Populations

The primary analysis was performed on the intention-to-treat (ITT) population which included all subjects who were randomized and had at least one efficacy evaluation. The per-protocol (PP) population included those who had no major protocol violations.

Efficacy Analysis

The primary efficacy variable was the change from baseline in the mean of the AM and PM 12-hour r-TNSS. The baseline was taken as the average of the mean AM and PM scores obtained during the last 7 days of the screening period. During the Treatment Period, average AM and PM TNSS was calculated by taking the PM TNSS from one calendar day and adding the AM TNSS for the next calendar day and dividing by 2. The average AM and PM r-TNSS was summarized over the 2 weeks of treatment, and treatment groups were compared using repeated measures analysis of covariance (ANCOVA). Covariates included baseline r-TNSS, treatment, day and treatment-by-day interaction terms. A first order autoregressive structure, in combination with treating the patient as a random effect, was used to model intra-patient correlation. No imputation for missing data was performed.

The PANS and the separate symptom score and sign score were summarized at Endpoint. The change from baseline was assessed with an ANCOVA with factors for pooled center, treatment and baseline score included as covariates.

A sequential analysis was planned to protect the Type I error rate (Table 19). Step 1 - If the change in r-TNSS in the subjects treated with C200 was statistically superior at the p <0.05 level to placebo, the analysis would proceed to Step 2. Step 2 included three separate analyses: the comparison of C100 to placebo and C200 to C100 of the r-TNSS outcome as well as a comparison of C200 to placebo for the Physician Assessed Nasal Symptom Score (PNSS, the symptom half of the PANS). If the comparison of the change in PNSS in the subjects treated with C200 was statistically superior to placebo then the analysis proceeded to Step 3, a comparison of the

Table 19. Statistical Plan to Protect the Type I error rate

Step 1	Step 2	Step 4	
r-TNSS ciclesonide 200 vs placebo →	**r-TNSS ciclesonide 200** vs ciclesonide 100		
	r-TNSS ciclesonide 100 vs placebo	→ **PNSS ciclesonide 100 mcg vs** placebo	
	PNSS ciclesonide 200 vs placebo		
Step 3	↓ **i-TNSS ciclesonide 200** vs placebo	↓ → **i-TNSS ciclesonide 100** vs placebo	**Step 5**

effect of C200 to placebo on the i-TNSS outcome. If the results of the comparison of the C200 to placebo on the PNSS **and** the results of the C100 compared to placebo on the r-TNSS outcome were statistically significant then the analysis proceeded to step 4, a comparison of C100 to placebo on the PNSS outcome. If Step 4 was successful, the analysis moved to Step 5, an analysis of C100 vs placebo on the i-TNSS.

Reviewer: This description does not accord with the Agency's understanding of the analysis submitted to the Agency on September 20, 2006 [redacted] *as a SAP. It is the Agency's understanding that success of the C100 dose vs placebo must be successful before the analysis can move to the PNSS or the i-TNSS analyses. This is an important distinction because the C100 dose was not successful in the r-TNSS analysis (see FDA statistical review).*

For the secondary efficacy variables, variations on the TNSS (instantaneous, AM, PM, and individual symptoms) and global evaluations were analyzed with a repeated measures ANOVA similar to the primary variable.

For the safety analysis, the adverse events were tabulated by treatment group. No laboratory analysis was performed. The results of the physical examinations and ENT examinations were summarized.

1.2 Results

1.2.1 Study Population

Disposition

There were 618 subjects randomized and 588 (95.11%) completed the trial. All randomized subjects were included in the safety and the ITT populations. Of the 215 subjects randomized to ciclesonide 200 mcg, 205 (95.3%) completed the trial. For the ciclesonide 100 mcg and placebo groups the respective numbers were 190/199 (95.5%) and 193/204 (94.6%). The most common reason for withdrawal was adverse events which were reported in 2.5, 2.5, and 0.9% of the placebo, C100 and C200 groups, respectively. Three (1.5%) placebo subjects withdrew consent, but all other reasons were reported in less than 1% of the subjects. The per-protocol (PP) populations consisted of 184 (90.2%), 176 (88.4%), and 191 (88.8%) of the placebo, ciclesonide100 and ciclesonide200 subjects, respectively.

Screen and Randomization Failures

The screening failures were reviewed to assess the potential for the IVRS to be a source of problems. Of those screened, 344 were not randomized. Of these, the reason was listed as not meeting the criteria of "Parent/caregiver has completed the AR Assessment Diary" for 132. Most of the other reasons are some form of failure to meet inclusion or exclusion criteria.

Reviewer: In the previous submission, Study 403 enrolled approximately the same number of 6 – 11 year-olds and 317 failed screening. Of the 317, the indication was "Parent/caregiver did not comply with or understand protocol" in only 5. Paper diaries were employed exclusively in Study 403. It is possible that the difference in compliance had something to do with the use of the IVRS in Study 417. However, the list of reasons for failing screening in Study 403 included "Other" in 145 cases compared to 3 cases in Study 417. Unfortunately the "Other" category is not further described so it is difficult to compare the two datasets..

Protocol Violations

Major protocol violations occurred in 9.8, 11.6, and 11.2% of the placebo, C100 and C200 subjects, respectively. The use of prohibited medication was the most frequent violation and occurred most often in the C100 group (8.0%). The incidence was 5.4% and 6.5% in the placebo and cicles200 groups, respectively. Study drug was ingested <60% of the specified times more often in the C200 group (3.7%) than in the other two treatment groups: 2.0% and 2.5% in the placebo and C100 groups, respectively. Minor violations were more evenly distributed with 22.5%, 21.6%, and 24.7% of the placebo, C100 and C200 subjects reporting violations.

Demographics

There were 349 males and 269 females. The mean age was 9.4 years, and 154 (24.9%) were less than 8 years old. The majority were Caucasian (81.9%) with 15.4% Black/African-Americans and 2.7% "Other" (Table 20).

Table 20. Baseline Demographics of ITT population in Study 417

	Placebo N=204	C 100 N=199	C200 N=215	Total N=618
Age, n (%)				
6-7	56 (27.4)	42 (21.1)	56 (26.1)	154 (24.9)
8-9	69 (33.8)	75 (37.7)	70 (32.5)	214 (34.6)
10-11	79 (38.8)	82 (41.2)	89 (41.4)	250 (40.4)
Mean Years (SD)	9.2 (1.7)	9.5 (1.7)	9.4 (1.7)	9.4 (1.7)
Gender (% Male)	55.4	53.8	60.0	56.5
Race (%)				
Caucasian	86.3	82.4	77.2	81.9
Black	11.8	14.6	19.5	15.4
Other	1.9	3.0	3.3	2.7
Hispanic (%)	12.3	12.6	13.0	12.6
Type of skin test (%)				
Historical	22.1	22.6	20.9	21.8
Antigen Challenge (mm)				
Mean (SD)	7.1 (4.7)	7.3 (4.5)	7.7 (5.1)	7.4 (4.8)
Range	3 - 30	3 - 26	3 - 40	3 - 40

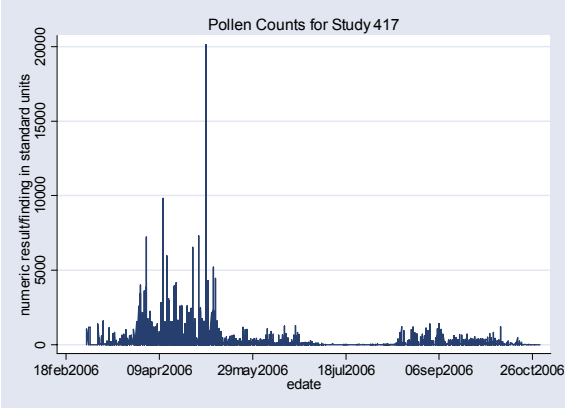
The mean (SD) response to antigen challenge was 7.4 (4.8) mm and 22% were historical as opposed to current tests.

Reviewer: Three subjects (2 C100 and 1 C200) had Diluent Control skin tests > 3 mm. However, in all three, the allergen reactions were more than 3 mm > than the diluent reaction. Four C200, 2 C100, and 4 placebo subjects had histamine tests of <3mm diameter.

Pollen Counts

Pollen counts were obtained daily at all of the clinical sites. A summary of the counts for all the sites is displayed in Figure 1. There is a large peak in the spring and a smaller one in the fall. Most of the counts in the spring are due to tree and grass pollen and the counts in the fall were due to weed pollen.

Figure 1. Summary Pollen Counts for All Sites



Reviewer: The positive skin tests could be grouped broadly into those reacting to trees, grasses, and weeds. Comparing the skin test reactivity to the time of enrollment showed that all but four subjects were enrolled in the season in which the allergen to which they reacted would have been in the atmosphere. Two subjects each in the C100 and C200 groups had skin tests positive for grass or trees and were studied in September. Of these four subjects 3 also had a history of PAR and the fourth had a history of asthma. Two of the subjects had baseline r-TNSS below lower 90th percentile of the group as a whole, but the other two were close to the mean. In addition, all 4 had changes in r-TNSS that were greater than the mean change for the group as a whole. It is unlikely that these 4 subjects substantially affected the results of the study.

Concurrent diseases that might have affected the response to ciclesonide were asthma and PAR. The prevalence of these conditions was similar in the three treatment groups. The prevalence of asthma was 13.6, 12.7, and 14.0% in the placebo, C100 and C200 subjects, respectively. The respective prevalence of PAR was 20.4, 24.1, and 21.4%. (Data taken from medical history datasheet: …\tabulations\mh.xpt.)

A summary of prior medications was taken from 14.1.4.1 (pg 137/4503 of the study report). In general corticosteroid (CS) use was uncommon prior to enrollment. Only 66/618 (10.7%) took nasal CS prior to enrollment. Three (<1%) were recorded as taking an oral inhalation CS and a further 13 (2.1%) used topical CS. Use of nasal CS at baseline was somewhat less (8.3%) in the placebo group than in the active treatment groups (11.6 and 12.1% in the C100 and C200 groups). Of the 66 subjects listed as taking concomitant ICS, 55 had a run-in period of less than 21 days. Only 7 of these are listed as protocol violations and of these 7, 4 have the comment that the drug was taken within 30 days of B0. Only 3 had the correct notation, i.e., within 21 days of T0. In the Applicant's response to the FDA query on these issues [redacted], they reviewed their listed protocol violations and noted that most of the subjects had stopped the ICS prior to 21 days before T0 so that the error was in terminology only. By their reanalysis, there were actually 4 subjects who were entered into the database as having a protocol violation who did not. The final number of violations was small.

1.2.2 Efficacy Results

Primary Efficacy Outcome: Reflective TNSS

The primary efficacy variable was the mean of the AM and PM r-TNSS comparing baseline with the change over the 2-Week treatment period. The data was obtained from a daily diary that was completed by the parent/caregiver by calling an automated answering machine (IVRS). There is no report of a hardcopy back-up for this system and this was confirmed by the applicant in a response to our query [redacted]). However, the amount of missing data was small and equally distributed across the treatment-groups. For instance for the possible maximum 30 entries for nasal congestion a mean of 25.4, 25.9, and 25.8 were completed for the placebo, C100 and C200 subjects, respectively.

During the course of the trial, a problem was noted in the instructions given by the IVRS. At the onset of the call the system asked the caller the following question:

> "How were your child's Nasal Congestion symptoms in the last 10 minutes on a scale from 0 to 3, with 0 being absent, 1 being very mild, 2 being moderate, and 3 being severe."

All of the subsequent questions were in the following format:

> "How were your child's Sneezing symptoms in the last 10 minutes on a scale from 0 to 3, with 0 being absent and 3 being severe."

The term "very mild" was used only once, but it contradicted the terminology used in all other portions of the protocol and in the instructions given to the care givers by the clinic staff. In Appendix 16.1.9 (pg 905/4503) it is stated that "In all other instructions including written instructions, received by the parent/caregiver the '1' score was labeled 'mild'. However, the copy of the "General IVRS Instructions" Section 21.2 (pg 660/4502) defines '1' as 'very mild' in two places and the page has the following note at the bottom: "This document will be provided to the parent/caregiver at the Screening Visit (B0) – this is only a representative sample".

A post hoc analysis was submitted to show that the differences in terminology did not affect the results. It was concluded from this data (reproduced in Table 21) that the distribution of symptom scores was similar in Studies 402 and 403 (paper diaries) compared to the scores in Study 417 (electronic diary and inconsistent instructions) and so the differences in data collection were inconsequential.

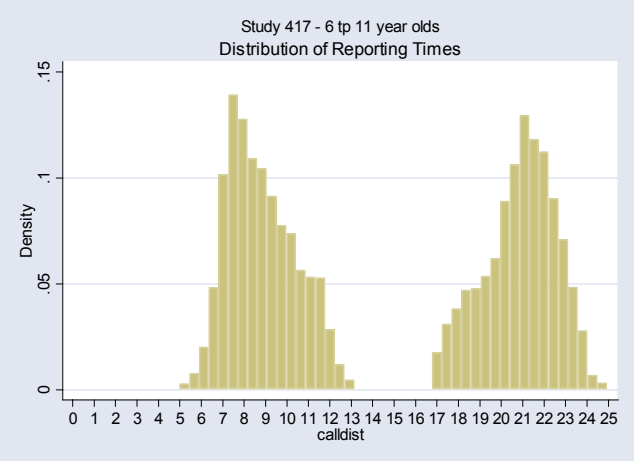
Table 21 Distribution of symptom scores in adult and pediatric studies of allergic rhinitis

Study	0-Absent	1-Mild (Very Mild)	2-Moderate	3-Severe
Itchy Nose				
401	15.2%	32.9%	32.5%	19.4%
403	30.7%	34.2%	26.8%	8.3%
417	18.7%	36.9%	31.4%	12.9%
Nasal Congestion				
401	7.0%	21.9%	40.2%	31.0%
403	11.1%	29.8%	40.3%	18.7%
417	7.8%	29.2%	40.0%	23.0%
Runny Nose				
401	13.2%	30.1%	34.1%	22.6%
403	30.4%	31.3%	25.9%	12.5%
417	17.5%	33.2%	32.3%	17.0%
Sneezing				
401	23.9%	32.1%	28.0%	16.0%
403	42.7%	29.5%	19.8%	8.0%
417	29.2%	35.9%	25.3%	9.6%

Reviewer: The distributions in Table 22 are similar, but not identical comparing the three studies. In particular, Study 403 (children 6 to <12 with PAR) had a relatively high percentage of subjects with no symptoms and a relatively low percentage with severe symptoms. These three studies were performed in two different age groups (adult and adolescent – Study 401 and children 6 to <12 – Study 403 and 417) and in two different disease entities (SAR – Study 401 and 417 and PAR – Study 403). Further, the mean symptom scores were higher in Study 417 (8.3) than in study 403 (6.6). It is not appropriate to conclude that a similarity of symptom scores, in disparate populations, proves that there was no important bias introduced into the results due to the data collection procedures. See FDA statistical review for further details.

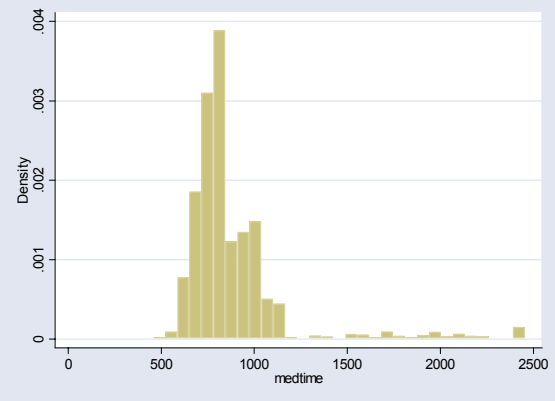
The AM score was supposed to have been recorded upon arising, prior to any activity, and the caregiver was supposed to call the IVRS within 15 minutes of obtaining the scores. From the diary dataset it can be calculated that the entire range of times that the IVRS was open was used for data entry. The mean time of the AM call was 8:55 AM with a range of 5:04 AM to 12:59 PM. The mean time of the PM call was 9:01 PM with a range of 5:00 PM to 12:58 AM. The intrquartile range was 7:39 – 10:05 AM for the morning call and 8:00 – 10:12 PM for the evening call. The time the call was made is depicted graphically in Figure 2.

Figure 2 . Time of call to IVRS



The medication time, as reported by the care giver at the evening call, had a highly skewed distribution with the mode between 7:48 and 8:18 AM and a long tail throughout the rest of the day (Figure 3).

Figure 3. Time of medication administration.



Without additional information, it is difficult to know how to interpret this data. It is unlikely that a large number of 6 to 11 year-olds awakened after 9:00 AM which would have to be the case if the calls were made within 15 minutes of the child's rising and measuring the symptom score. Examination of the distribution of call times suggests a bias towards making the call in the middle of the day. Comparison of the reported medication time and the AM call time, suggests that the call was actually delayed for some time after the medication was administered. This in turn, suggests that the care giver either had to remember the time the medication was administered or to have written him/herself a note. Unfortunately, there is no recording of the time the symptom score was obtained because it was assumed that the call was made immediately upon completion of the symptom questionnaire.

In a response to an FDA query, the Applicant said the following:

> *"As identified by the FDA reviewer, parents were instructed to perform the AM evaluation immediately upon arising, prior to any activity, and prior to taking study*

medication. This instruction was given to ensure that accurate symptoms were recorded prior to any activities that could reduce the symptoms associated with allergic rhinitis such as showering or bathing. If parents failed to perform this assessment in the recommended manner, it is likely that the AM symptoms would have been less severe and thus being able to demonstrated efficacy with ciclesonide nasal spray in this age group could have been difficult."

It appears that the Applicant is assuming the phone call was made late, but immediately after the score was obtained and before the medication was administered. This seems an unlikely explanation for calls made at 10 and 11 AM since most of the study was performed during the school year. A more likely explanation is that the child arose early, took the medication, answered the questions and then went off to school. At a quieter time in the morning the caregiver then called in the results of the morning's activities. If this were the case then recall bias could have affected the results.

There is no notation when the symptom score was obtained relative to the AM dose of study drug. If any of the symptom scores were obtained after the medication was administered the results would be biased towards better scores in the subjects who received active treatment. Finally, without correlation studies to compare the responses to the IVRS to the responses submitted on a paper diary it is impossible to know if this performance is any different from what it would have been if paper diaries had been used. When the distribution of call times and medication times was plotted separately for each treatment group the distributions were essentially identical so this is an unlikely source of bias in the treatment group comparisons.

The reported baseline values for the 12-hour average AM and PM r-TNSS varied between 8.3 and 8.4. The mean scores fell in all of the treatment groups, and the difference in the change during treatment comparing placebo to active treatment was significant for the 200 mcg dose (Mean difference = 0.39, p = 0.04, Table 22). The LS mean fall in score did not differ significantly in the children treated with placebo and C100. Nor was there a significant difference in the response to the 100 mcg and 200 mcg dose of ciclesonide.

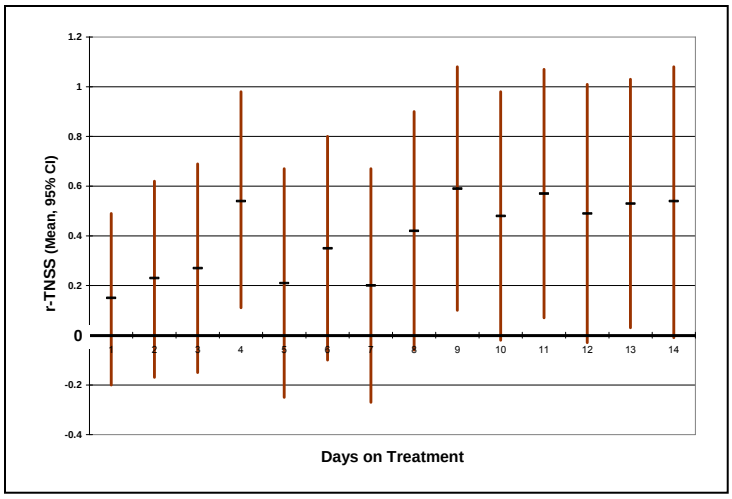
Table 22. Change in r-TNSS in 6 to <12 Year-Olds with SAR After Treatment for 2 Weeks*

	Placebo N=204	C 100 N=199	C200 N=215
Baseline, Mean (SD)	8.4 (1.8)	8.4 (1.8)	8.3 (1.9)
Change from Baseline, LS Mean (SE)	-2.1 (0.14)	-2.4 (0.14)	-2.5 (0.13)
Difference from placebo 95% CI p-value		0.32 -0.06, 0.69 0.10	0.39 0.02, 0.76 0.040
Difference from C100 95% CI p-value			0.08 -0.30, 0.45 0.69

* The results are taken from Text Table 9 with the change from baseline rounded off to one decimal point.

The PP analysis confirmed the ITT analysis in 184 placebo, 176 C100, and 191 C200 subjects. The mean difference (95% CI) comparing C200 to placebo was 0.39 (0.01, 0.78) and the mean difference comparing C100 to placebo was 0.44 (0.05, 0.83). The difference between the two ciclesonide doses was -0.05.

Figure 4. Daily r-TNSS



The daily r-TNSS values are shown in Figure 4. The means increased over the first 4 days but fell on the subsequent 4 days. During the last week of treatment the values were close to the Day 4 mean. Of note, the lower limit of the confidence interval was not consistently above zero. As late as day 10, 12, and 14 the response was not statistically significant.

When the AM and PM r-TNSS were analyzed separately it could be seen that the score fell more in the afternoon (12 hours after the dose) than in the AM (24 hours after the dose) including in the placebo subjects. The mean difference (95% CI) between C200 and placebo for the AM r-TNSS was 0.35 (-0.04, 0.74). The result of the PM r-TNSS analysis was a mean difference (85% CI) of 0.42 (0.04, 0.80).

For the individual symptoms, the baseline reflective scores were the highest for nasal congestion. All of the scores in all of the treatment groups fell over the two weeks of treatment, but the difference between placebo and C200 was very small except for nasal congestion. The nasal congestion score mean difference (95% CI) between active and placebo treatment was 0.13 (0.03, 0.23) for the 200 mcg dose and 0.12 (0.01, 0.22) for the 100 mcg dose.

Secondary efficacy outcome measures

The baseline values of the Average AM and PM Instantaneous TNSS (i-TNSS) varied between 7.5 and 7.6. The mean scores fell in all of the treatment groups (Table 23). The mean difference (95% CI) in the change during treatment comparing placebo to active treatment was 0.37 (0.00, 0.73) and 0.31 (-0.06, 0.68) in the C200 and C100 subjects, respectively. The scores for the PM i-TNSS fell to a slightly greater extent than the scores for the AM i-TNSS in all of the treatment groups. However, the difference between C200 and placebo was greater for the AM scores. The mean (95% CI) for the difference between C200 and placebo was 0.44 (0.06, 0.81) for the AM i-TNSS and 0.29 (-0.09, 0.67) for the PM i-TNSS.

Table 23. Instantaneous TNSS*

Average of AM and PM	Placebo N=204	C 100 N=199	C200 N=215
Baseline, Mean (SD)	7.6 (2.1)	7.5 (2.0)	7.5 (21)
Change from Baseline, LS Mean (SE)	-1.9 (0.1)	-2.2 (0.1)	-2.2 (0.1)
Difference from placebo 95% CI		0.31 -0.06, 0.68	0.37 0.00, 0.73
Difference from C100 95% CI			0.05 0.04, 1.11
AM	N=204	N=197	N=215
Baseline, Mean (SD)	7.8 (2.1)	7.7 (2.0)	7.7 (2.2)
Change from Baseline, LS Mean (SE)	-1.8 (0.1)	-2.1 (0.1)	-2.2 (0.1)
Difference from placebo 95% CI		0.31 -0.07, 0.69	0.44 0.06, 0.81
Difference from C100 95% CI			0.12 -0.25, 0.50
PM	N=204	N=199	N=214
Baseline, Mean (SD)	7.4 (2.2)	7.3 (2.1)	7.2 (2.2)
Change from Baseline, LS Mean (SE)	-2.0 (0.1)	-2.3 (0.1)	-2.3 (0.1)
Difference from placebo 95% CI		0.29 -0.10, 0.67	0.29 -0.09, 0.67
Difference from C100 95% CI			0.00 -0.38, 0.39

* Taken from Text Table 12 with results rounded off to 1 decimal place

The baseline values of the physician's assessment of symptoms (PNSS) varied between 7.6 and 8.0 with the low baseline value in the placebo subjects and the high value in the C200 subjects. The mean scores fell in all of the treatment groups, and the difference in the change during treatment comparing placebo to active treatment was significant for the 200 mcg dose (Mean difference = 0.92, $p<0.001$, Table 24). The LS mean fall in score also differed between the 100 and 200 mcg dose. The scores for nasal signs also fell in all of the treatment groups, but by a smaller amount. The mean difference (95% CI) between active treatment and placebo was 0.64 (0.18, 1.1) for C200 and 0.36 (-0.10, 0.82) for C100.

Table 24. Physicians Assessment *

Nasal symptoms	Placebo N=204	C 100 N=199	C200 N=215
Baseline, Mean (SD)	7.6 (2.5)	7.7 (2.3)	8.0 (2.4)
Change from Baseline, LS Mean (SE)	-2.4 (0.2)	-2.7 (0.2)	-3.3 (0.2)
Difference from placebo 95% CI p-value		0.34 -0.21, 0.88 0.22	0.92 0.38, 1.45 <0.001
Difference from C100 95% CI p-value			0.58 0.04, 1.11 0.034

Table 24. (continued)

Nasal signs	Placebo N=204	C 100 N=199	C200 N=215
Baseline, Mean (SD)	6.4 (2.6)	6.5 (2.3)	6.4 (2.5)
Change from Baseline, LS Mean (SE)	-1.5 (0.2)	-1.8 (0.2)	-2.1 (0.2)
Difference from placebo 95% CI		0.36 -0.10, 0.82	0.64 0.18, 1.1
Nasal signs and symptoms			
Baseline, Mean (SD)	7.0 (2.2)	7.1 (1.9)	7.2 (2.1)
Change from Baseline, LS Mean (SE)	-1.9 (0.2)	-2.3 (0.2)	-2.7 (0.2)
Difference from placebo 95% CI		0.35 -0.10, 0.80	0.78 0.34, 1.22

* Taken from Text Table 14 with results rounded off to 1 decimal place

Subgroup Analysis

Ciclesonide had a greater effect on males than females (Table 25). For the average of the AM & PM r-TNSS there was a negligible response in females (LS mean difference [95% CI] comparing placebo to C200 = -0.00 [-0.58, 0.58]). This is in contrast to a substantial response in males (0.72 [0.24, 1.20]). The results for the i-TNSS were similar. The mean difference comparing the change during placebo treatment to the change during C200 treatment (95% CI) was 0.75 (0.28, 1.23) for males and -0.12 (-0.68, 0.45) for females.

Table 25. Interaction Between Treatment with Ciclesonide 200 mcg QD and Gender

Average AM & PM r-TNSS	Placebo* N=91 / 113	Females N=86	Males N=129
Baseline, Mean (SD) F/M	8.3 (1.8) / 8.5 (1.9)	8.6 (1.8)	8.0 (1.9)
Change from Baseline, LS Mean (SE)	-2.5 (0.2) /-1.7 (0.2)	-2.5 (0.2)	-2.4 (0.2)
Difference from placebo 95% CI		-0.00 -0.58, 0.58	0.72 0.24, 1.20
PNSS			
Baseline, Mean (SD) F/M	8.3 (1.8) / 7.5 (2.7)	8.1 (2.3)	7.9 (2.5)
Change from Baseline, LS Mean (SE)	-2.8 /-2.0	-2.8 (0.4)	-3.7 (0.3)
Difference from placebo 95% CI		-0.02 -0.93, 0.88	1.77 1.05, 2.49

* Placebo events are reported as N=female/male

The Physician's assessment of nasal symptoms showed an appreciable response in males but none in females. The mean difference (95% CI) comparing placebo to C200 was 1.77 (1.05, 2.49) for males and -0.02 (-0.93, 0.88) for females.

Reviewer: The difference in response comparing the two genders previous Adult SAR or PAR studies. Nor was it seen in the study of 6 to < 12 year olds with PAR (Study 403)/

An analysis of racial differences (Caucasian, Black, Other) showed a larger response in Caucasians than in the other racial groups. However, there were only 37 Black children and 17 "Other" children who were treated with 200 mcg ciclesonide compared to 161 Caucasians, making statistical inference unreliable. The mean difference (95% CI) comparing C200 to

placebo in the r-TNSS was 0.56 (0.16, 0.96) for the Caucasian children, -0.14 (-1.25, 0.98) for the Black children, and -1.23 (-3.22, 0.75) in the Others.

Reviewer: In study 403 (NDA 22-004) conducted in children 6 – 11 years of age with PAR large differences among racial groups were also found in the response of the r-TNSS to ciclesonide. However, they were in the opposite direction. The Caucasian children had a minimal response (difference from placebo = 0.2) compared to the Black children (difference from placebo = 0.2), and "Other" children (difference from placebo = 1.0). It is unlikely that differences in the disease entities (SAR and PAR) are responsible for this differing response to ciclesonide and is more likely due to the unreliable estimate of the response in the small number of non-Caucasian children.

1.2.3 Safety

Extent of Exposure

The mean duration of exposure was 14 days. In the individual treatment groups the exposures means were 14.1, 14.2, and 14.3 days for the placebo, and C100 and C200 mcg groups, respectively.

Adverse Events

Overall, 98 (16.0%) of the subjects reported an adverse events during treatment. The incidence was inversely related to dose (19.1, 16.6, and 12.6% in the placebo, C100, and C200 groups, respectively) (Table 26).

Table 26. Adverse Events Experienced by >2% of Subjects Enrolled

	Placebo N=204	C100 N=199	C200 N=215
Any event	39 (19.1)	33 (16.6)	27 (12.6)
Epistaxis	8 (3.9)	7 (3.5)	3 (1.4)
Headache	4 (2.0)	4 (2.0)	2 (0.9)
Asthma	4 (2.0)	1 (0.5)	1 (0.5)
Nasal Discomfort	7 (3.4)	1 (0.5)	1 (0.5)

The only events that were reported in ≥2% of the subjects were epistaxis, headache, asthma and nasal discomfort. All of these events were reported more frequently in the placebo than the actively treated subjects. Nasal discomfort was particularly notable as it was reported in 7 (3.4%) of the placebo subjects compared with 1 (0.5%) in each of the active treatment groups. Most of the events were mild with only 1.0%, 1.5%, and 1.4% of the subjects reporting severe events in the placebo, C100 and C200 groups, respectively.

Reviewer: If all of the MedDRA terms that refer to epistaxis are combined (Bloody Nasal Discharge; Epistaxis; Epistaxis, intermittent; Epistaxis, increased; Intermittent nosebleed; Mild epistaxis on the right; Nosebleed; Nosebleed, less than 2 episodes; Nasal, left septal bleed) the number of events is 12 (4.9%), 14 (7.0%), and 4 (1.9%) of the placebo, C100 and C200 subjects,

respectively. (Summary of "Epistaxis" in the aedecod variable in the dataset …\tabulations\ae.xpt.)

Serious Adverse Events and Events Leading to Withdrawal

Two deaths occurred during the study, neither of which was related to treatment. Two cousins, girls 6 and 7 years of age, died in an automobile accident. The 7 year-old had received 100 mcg ciclesonide daily for 11 days prior to the accident and the 6 year-old had completed treatment with 200 mcg daily. Neither had reported any adverse events.

Other than the two deaths there were no serious adverse events.

Fourteen (2.3%) of the subjects were withdrawn from the study: 6 (2.9%), 5 (2.5%), and 3 (1.4%) of the placebo, C100, and C200 subjects, respectively. The reasons for withdrawal in the placebo group were hypersensitivity, sinusitis, asthma, and nasal discomfort in one, each, and two cases of epistaxis. In the C100 group there was one case, each, of upper respiratory tract infection, urinary tract infection, asthma, epistaxis, nasal discomfort nasal disorder, pharyngolarygeal pain, and throat irritation. In the C200 group there was one case, each, of sinusitis, varicella, and injury that resulted in withdrawal.

Laboratory Results

No laboratory examination was performed

Physical Examination including ENT

There were no clinically meaningful changes in vital signs or in the general physical examination. On the ENT examination the scores went from normal at baseline to abnormal at the end of the study in slightly more placebo than actively treated subjects (5.1% compared with 3.0% of the C100 and 2.0 of the C200 subjects). On the other hand more C200 subjects (15.3%) changed from abnormal at baseline to normal at the end of treatment (9.0 C100 and 4.9% of the placebo subjects).

1.3 Summary and Discussion

In this two-week, randomized comparison of ciclesonide nasal spray at doses of 100 and 200 mcg once daily and placebo, there was a small response in some of the efficacy variables to the 200 mcg dose in 6 to 11 year-old children with SAR. The primary efficacy variable, the average of the AM and PM reflective TNSS was significantly better in the children treated with 200 mcg ciclesonide (p=0.04), but not those treated with 100 mcg. However, the daily summary of the r-TNSS showed the lower limit of the confidence interval including zero on 10 out of the 14 days on which it was measured. In the last week of treatment the difference was significant on day 9, 11, and 13, but not on days 10, 12, and 14. Of the individual symptom scores, the response was best seen for nasal congestion. Furthermore, the AM r-TNSS and the PM i-TNSS did not show a significant response. The only efficacy variable that showed a robust response was the physician's assessment of the nasal signs and symptoms. The nasal symptoms score was 0.92

points lower in the C200 group compared to placebo and 0.58 points lower than in the C100 group. It is not clear if use of the IVRS to report the parent/caregiver assessment of the TNSS had any independent effect on the results. A few caregivers described difficulty using the system, but no independent assessment of validity of the system was provided. Adverse events were infrequent and mild and more common in the placebo than the active treatment groups. No laboratory examination, including HPA-axis testing was performed.

2 STUDY # 451/2006 (BY9010/M1-416)

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Clinical Trial Designed to Assess the Safety and Tolerability of Ciclesonide, (200 mcg, Once Daily), Applied as a Nasal Spray for Twelve Weeks, in the Treatment of Perennial Allergic Rhinitis (PAR) in Pediatric Patients 2 – 5 years of age.

2.1 Protocol

2.1.1 Administrative

Study Dates: November 11, 2005 to June 26, 2006
Clinical Centers: Three US sites: Long Beach California; Normal Illinois, and San Antonio, Texas
Coordinating Investigator:

2.1.2 Objective/Rationale

The objective of this study was to evaluate the safety and tolerability of 200 mcg once daily ciclesonide administered as a nasal spray for 12 weeks in subject 2 – 5 years of age with PAR. A secondary outcome was to evaluate the effectiveness of the 200 mcg dose of ciclesonide nasal spray in this population.

2.1.3 Study Design

This was a, double-blind, placebo-controlled, parallel study of 125 subjects with PAR randomized into two treatment groups and treated for 12 weeks. Subjects were screened 7 to 14 days prior to randomization at which time they had a skin test in addition to the history and physical examination. During the screening period parents/caregivers recorded the subject's symptoms in the morning. If the subject met randomization criteria at the end of the screening period they were randomized (2:1) to receive either 200 mcg ciclesonide nasal spray once daily or placebo. Subjects were seen by the investigators at 3, 6, 9, and 12 weeks of treatment.

Randomization was carried out with the [redacted] IVRS. But the diary for rhinitis symptoms and adverse events was maintained by the parent/caregiver on paper forms.
Safety was based on adverse events and the physical examination. In addition, a single plasma cortisol was collected at baseline (prior to 9 AM) and at the 6- and 12-week follow-up visits. At randomization and all follow-up visits, the subjects had an ear, nose and throat (ENT) examination performed and a physician assessment of rhinitis symptoms (Physician-Assessed Nasal Symptom Scores (PNSS). Efficacy was assessed with the PNSS and the AM 24-hour r-TNSS comparing baseline to 1-12 weeks of treatment. Subject compliance was assessed with the diary and by weighing the medication bottle.

2.1.4 Study Population

Inclusion Criteria

- Male or female, 2 to 5 years of age
- Have at least a three-month history of PAR as assessed by a physician
- Positive skin test to an allergen known to induce PAR within 12 months of enrollment

Reviewer: the requirement for only 3 months of PAR prior to enrollment is very short.

Exclusion Criteria

The presence of any of the following required exclusion of the patient from the study:

- History or physical findings of nasal pathology: nasal polyps, malformations, recent nasal biopsy, nasal trauma, or surgery and atrophic rhinitis or rhinitis medicamentosa (within the last 60-d for all conditions of Screening Visit [B0])
- Planned participation in any investigational drug study within the 30-d preceding the Screening Visit (B0) or at any time during the study
- A known hypersensitivity to any corticosteroid or any of the excipients in the study drug formulation
- History of a respiratory infection or disorder (including, but not limited to bronchitis, pneumonia, the common cold, acute or chronic sinusitis, flu, severe acute respiratory syndrome [SARS]) within the 14-d preceding the Screening Visit (B0)
- History of a positive test for HIV, hepatitis B, or hepatitis C
- Active asthma requiring treatment with inhaled or systemic corticosteroids and/or routine use of ß-agonists and any controller drugs (e.g. theophylline, leukotriene antagonists, etc.); intermittent use (less than or equal to 3 uses per week) of inhaled short acting ß -agonists is acceptable
- Use of any prohibited concomitant medications within the prescribed (per-protocol) withdrawal periods prior to the Screening Visit (B0) (Refer to section 6.3 of the protocol)
- Use of antibiotic therapy for acute conditions within 14-d prior to the Screening Visit (B0) and thereafter. Low doses of antibiotics taken for prophylaxis was permitted if the therapy was started prior to the Screening Visit (B0) AND was expected to continue throughout the study duration

- Initiation or dose escalation of immunotherapy during the study period or within 90-d of Screening.
- Non-vaccinated exposure to, or active infection with, chickenpox or measles within the 21-d preceding the Screening Visit (B0)
- Exposure to systemic corticosteroids for any indication, chronic or intermittent (e.g. contact dermatitis), during the past 60-d prior to Screening Visit (B0), or presence of an underlying condition that could reasonably be expected to require treatment with corticosteroids during the course of the study
- Use of topical corticosteroids in concentrations in excess of 1% hydrocortisone or equivalent within 30-d prior to the Screening Visit (B0); use of topical hydrocortisone or equivalent in any concentration covering greater than 20% of the body surface; or presence of an underlying condition (as assessed by the investigator) that could reasonably be expected to require treatment with topical corticosteroids during the course of the study
- Use of antiepileptic drugs for epilepsy within 30-d of the Screening Visit (Visit B0) or anytime during the treatment period
- Initiation of pimecrolimus cream 1% or greater or tacrolimus ointment 0.03% or greater during the study period or planned dose escalation during the study period. However, initiation of these creams/ointments 30-d or more prior to the Screening Visit (B0) AND use of a stable (maintenance) dose during the study period could be considered for inclusion
- Previous participation in an intranasal ciclesonide study;
- Two patients in the same household.

Randomization Criteria

Only patients meeting the following criteria were randomized:

- Continued to be in general good health
- No adverse event that would result in failure to continue to meet inclusion and exclusion criteria
- No use of the prohibited concomitant medications (Refer to section 9.4.8.1)
- No respiratory infection during the Baseline Period;
- Completion the Allergic Rhinitis Assessment Diary during the Baseline Period (defined as completing all items on 70% or more of the days)

.

Withdrawal Criteria

There was no specific withdrawal criterion.

2.1.5 Study Procedures

Treatment

Ciclesonide nasal spray was provided in canisters containing 50 mcg ciclesonide per actuation. All subjects/caregivers were provided two bottles of blinded medication. They were instructed to take two sprays in each nostril from each bottle each AM. Compliance was assessed by

weighing the medication bottles after treatment. Rescue medication (chlorpheniramine maleate syrup, 5.0 mg was provided at the randomization visit.

Reviewer: The dose of rescue medication is double that used in Study 405

Prohibited medications were as listed in Table 19 (pg 32 of this review) except that topical decongestants and antihistamine were prohibited from the time of screening which could have been within 7 days of randomization. In study 417 these agents were prohibited for 14 days prior to randomization. Restricted medications were as listed for Study 417 (page 32) of this review.

Safety Evaluation

Safety was assessed with adverse events, vital signs, physical exam, routine laboratory examination and serum cortisol. In addition, a directed ENT examination was performed at each visit.

Efficacy Evaluation

Total Nasal Symptom Score was defined as the sum of the scores for four nasal symptoms consisting of runny nose, itchy nose, sneezing, and nasal congestion. Each symptom was rated on a severity scale of 0 to 3 (See pg). The scores were to be recorded by the parent/care-giver in the morning only. The maximum score was 12 (4 symptoms time maximum score of 3). Instantaneous TNSS was not recorded. The baseline value was the average of the scores obtained during the 7 days prior to randomization.

The investigator assessment of nasal symptoms (PNSS) consisted of a scoring (0 to 3) of 4 symptoms: runny nose, itchy nose, congestion, and sneezing. The baseline value was the score obtained at randomization.

Use of rescue medication was recorded in the Diary. The parent/caregivers were instructed to use the rescue medication only if the symptoms were unbearable.

2.1.6 Data Analysis

Sample Size

The sample size was taken to provide information on safety and tolerability of ciclesonide. A formal power analysis was not performed.

Study Populations

The primary analysis was performed on the intention-to-treat (ITT) population which included all subjects who were randomized and had at least one post-randomization efficacy evaluation. The per-protocol (PP) population included those who finished the study as planned and who underwent all of the planned procedures.

Efficacy Analysis

The primary efficacy variable was the change from baseline in the AM 24-hour r-TNSS. The baseline was taken as the mean of the AM scores obtained during the run-in period. Summaries of weekly averages were calculated for both the TNSS and the individual symptom scores. The change from baseline in the weekly average for each treatment group was compared for weeks 1 to 12 and treatment differences were assessed with a repeated measures analysis of covariance. The PNSS at 12 weeks/endpoint was compared to baseline. Rescue medication use was summarized by treatment group. Statistical inference was not applied to these observations.

For the safety analysis, the adverse events were tabulated by treatment group. Laboratory values were presented as means and medians and shifts in and out of the normal range for the aggregate values.

2.2 Results

2.2.2 Study Population

Disposition

There were 125 subjects randomized and 113 (90.4%) completed the trial: 83 were randomized to ciclesonide and 42 to placebo. The entire population was included in the safety analysis, but 123 were included in the ITT population. Two subjects randomized to ciclesonide failed to return for any efficacy evaluations. Lack of compliance was responsible for withdrawal in 2 (4.8%) of the placebo and 2 (2.4%) of the C200 subjects, although 3 (3.6%) of the C200 subjects were described as unwilling to continue compared to none of the placebo subjects.

Only 5 subjects were screened but not randomized. In 2 of these failure to comply with or understand the protocol was listed as the reason. Two subjects were not in good health during the run-in and 1 had PAR less than two years (pg 54/3861 of the study report).

Reviewer: The entry criteria state that PAR must have been present for a minimum of 90 days, so the failure to randomize due to a history of less than 2 years in unclear.

Major protocol violations were reported for 19.0 % of the placebo and 12.0% of the C200 subjects. The most common of these was taking prohibited medication which was reported in 14.3% of the placebo and 9.6% of the C200 subjects. Less than 60% compliance with study medication was also more common in the placebo subjects (4.8% compared to 1.2% in the C200 subjects). Minor violations were reported in 61.9% of the placebo and 55.4% of the C200 subjects. The most frequent minor violations were visits outside the window (38.1 and 30.1% of the placebo and C200 subjects, respectively) and taking of restricted medications (21.4 and 25.3% of the placebo and C200 subjects, respectively).

Demographics

There were 53 males and 70 females. The mean age was 4.2 years, and 57 (43.9%) were less than 4 years old. The majority were Caucasian (69.1%) and 10.6% were Black (Table 27).

Table 27. Demographics of Children 2 to 5 Years of Age in the ITT population

	Placebo N=42	C200 N=81	Total N=123
Age, n (%)			
2 years	7 (16.1)	14 (17.3)	21 (17.1)
3 years	12 (28.6)	21 (25.9)	33 (26.8)
4 years	9 (21.4)	24 (29.6)	33 (26.8)
5 years	14 (33.3)	22 (27.2)	36 (29.3)
Mean years (SD)	4.3 (1.2)	4.1 (1.1)	4.2 (1.1)
Gender (% Male)	50.0	39.5	43.1
Race (%)			
Caucasian	73.8	66.7	69.1
Black	11.9	9.9	10.6
Other	14.3	23.4	20.3
Hispanic (%)	40.5	48.1	45.5
Type of skin test (%)			
Current	47.6	59.3	55.3
Antigen Challenge (mm)			
Mean (SD)	5.5 (2.4)	5.1 (1.9)	5.2 (2.1)
Range	3 - 14	3 - 16	3 - 16
Control Challenge (mm)			
Mean (SD)	0	0	0

The mean (SD) response to antigen challenge was 6.3 (1.5) mm and the mean (SD) response to diluent control was 0.0 (0.0mm). The means did not vary among the treatment groups.

Mean compliance by diary or bottle weight was >90% in both treatment groups.

Reviewer: Prior medication ingestion was relatively uncommon (post-text Table 14.1.4.1 pg100/3861) in this young population. Eleven subjects (7 [8.4%] and 4 [9.5%] of the placebo and C200 subjects, respectively) had taken a nasal steroid prior to enrollment. A single C200 subject took pulmocort.

2.2.3 Efficacy Results

Efficacy Outcome

Efficacy was assessed using the 24 hour AM r-TNSS comparing baseline to the values obtained throughout the 12-week treatment period. The baseline values were 7.4 in the placebo group and 6.7 in the C200 group. The mean scores fell more with C200 treatment than placebo (Table 28). The differences in scores for the individual symptoms were most marked for nasal congestion and runny nose.

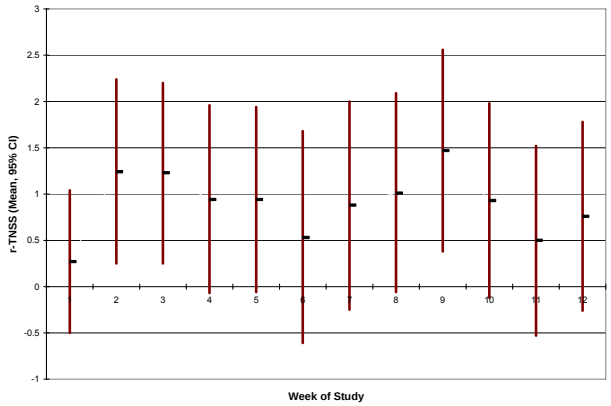
Table 28. Change in Symptom Scores After 12 Weeks of Treatment of 2-5 Year-Olds

24-hr r-TNSS	Placebo N=42	C200 N=81
Baseline, mean(SD)	7.4 (2.4)	6.7 (2.7)
Change from Baseline, LS mean (SE)	-1.5 (0.3)	-2.3 (0.2)
Treatment difference 95% CI		0.86 0.13, 1.60
PNSS	N=41	N=81
Baseline	7. (2.4)	7.2 (2.9)
Change from Baseline	-3.6 (0.5)	-3.3 (0.3)
Treatment difference 95% CI		-0.32 (-1.5, 0.81)

The PNSS also fell in both treatment groups, but the decrease was greater in the placebo than the C200 group. Rescue medication use was infrequent and similar in the two treatment groups. The C220 subjects took rescue medication on 6.1% of the treatment days and the placebo subjects on 5.2% of the days.

The weekly averages and 95% confidence intervals for the r-TNSS are shown in Figure 5. The lower border of the confidence interval cleared zero on 3 of the 12 weeks in which it was measured.

Figure 5. Weekly Summary of 24-hour r-TNSS



2.2.3 Safety

Extent of exposure

The mean duration of exposure was 82 days in both treatment groups. On the other hand, only 88.1% of the placebo subjects received >80 days of treatment compared with 92.8% of the C200 subjects.

Adverse Events

Overall, 73 (58.4%) of the subjects reported adverse events (Table 29). The incidence was slightly higher in the C200 group (60.2%) compared with the placebo subjects (54.8%), but most of the events were reported in only 1 or 2 subjects. Pyrexia was the most common event and it was reported in 16.7 and 15.7% of the placebo and C200 subjects, respectively. The next most frequent events, in order, were upper respiratory tract infection, cough, otitis media, sinusitis, and influenza. Upper respiratory tract infection, otitis media, sinusitis, and influenza were more frequent in the C200 subjects while pyrexia and cough were more frequent in the placebo group. The vast majority of the events were mild and only 4.8 and 3.6% of the events were described as severe in the placebo and C200 groups respectively. Other than "Platelet count increased" the events are those commonly reported in this patient population.

Table 29. Adverse Events Experienced by >3% Subjects of either treatment group during 12 Weeks of Treatment

	Placebo N=42	C200 N=81	Total N=123
Subjects with one event, n (%)	23 (58.4)	50 (60.2)	73 (58.4)
Pyrexia	7 (16.7)	13 (15.7)	20
Upper respiratory tract infection	4 (9.5)	11 (13.3)	15
Cough	4 (9.5)	7 (8.4)	11
Otitis media	2 (4.8)	6 (7.2)	8
Sinusitis	1 (2.4)	6 (7.2)	7
Influenza	1 (2.4)	4 (4.8)	5
Platelet count increased	1 (2.4)	4 (4.8)	5
Increased systolic BP	0	3 (3.6)	3
Headache	0	3 (3.6)	3
Nasopharyngitis	1 (2.4)	3 (3.6)	4
Vomiting	2 (4.8)	3 (3.6)	5 (4.0)
Gastroenteritis	2 (4.8)	2 (2.4)	4
Alanine aminotransferase increased	2 (4.8)	1 (1.2)	3
Epistaxis	2 (4.8)	1 (1.2)	3
Pharyngolaryngeal pain	2 (4.8)	1 (1.2)	3
Rash	2 (4.8)	0	1

The elevated platelet counts were all reported from one center, however, the laboratory examinations, themselves, were performed at a single laboratory. See the section on Laboratory results, below, for more details.

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths or serious adverse events. Three subjects withdrew due to adverse events, two in the C200 group and one placebo subject. In one of the C200 subjects, a severe headache and dizziness were reported after taking the first dose and in the other subject, the report was of burning of the nose and eyes after taking the medication. In both cases the subject refused to continue the medication. The placebo subject was discontinued by the investigator due to a combination of worsening asthma and the development of a rash.

Laboratory Results

There were no notable changes in mean values for hematology or chemistry blood tests comparing baseline to the end of study values. Five out of the 40 abnormal platelet counts (>440 * 10^3 cells/mm^3) were reported as adverse events (see above) and one value of 601 * 10^3 cells/mm^3 was reported as an alert range laboratory abnormality in a placebo subject (see below).

Reviewer: There was an extraordinarily high incidence of abnormal laboratory values at baseline in this study. Of 19 chemistry variables, more than 5% of the subjects were abnormal at baseline for 8 anylates in the C200 subjects and for 5 in the placebo subjects. Abnormal baseline values were particularly prominent for the determination of BUN (13.4% of subjects abnormal), CK (13.4% abnormal), Calcium (22.7% abnormal), and phosphorous (15.9%).

Table 30 ***Abnormal Blood Tests at Baseline***

Test	*Normal Value*	*Placebo N=40*	*C200 N=79*	*Total % Abnormal N=119*
BUN, % Hi		*7.5 %*	*16.5 %*	*13.4 %*
Range (mmol/L)	*1.4 – 5.7*	*6.1*	*(6.1 -7.5)*	
CK, % Hi		*7.5 %*	*16.5 %*	*13.4 %*
Range (U/L)	*2 - 167*	*(182 – 406)*	*(173 -361)*	
Calcium, % Hi		*17.5 %*	*22.8*	*22.7 %*
Range (mmol/L)	*2.14 – 2.62*	*(2.67 – 2.79)*	*(2.64 – 2.77)*	
Glucose, % Hi		*---*	*1.3%*	*2.1 %*
% Lo	*3.9 – 7.8*	*7.5%*	*10.1%*	*9.2 %*
Range (mmol/L)		*(3.3 – 3.8)*	*(3.1 – 3.8)*	
Lipase, % Hi		*5.0%*	*8.9%*	*7.6 %*
Range (U/L)	*3 – 32*	*(37 – 42)*	*(34 -45)*	
Phosphorous, % Hi		*17.5%*	*15.2%*	*15.9 %*
Range (mmol/L)	*1 – 1.78*	*(1.81 – 2.2)*	*(1.81 – 2.07)*	
		N=40	*N=76*	*N=116*
Eosinophils, % Hi		*12.5*	*18.4*	*16.4 %*
Range (%)	*0 – 4*	*(0 - 11)*	*(0 - 15)*	
Hemoglobin, % Hi		*10.0*	*14.5*	*12.9%*
Range (g/dL)	*105 – 151*	*(112 – 151)*	*(119 – 153)*	
Lymphocytes, % Hi		*27.5*	*18.4*	*20.7%*
% Lo	*13 – 53*	*2.5*	*1.3*	*1.7%*
Range		*(12 – 64)*	*(12 – 76)*	
Neutrophils, % Lo		*7.5*	*7.9*	*7.8%*
	31 – 78	*(24 – 74)*	*(16 – 79)*	
Platelets, % Hi		*10.0*	*18.4*	*15.5%*
Range (k/mm3)	*200 - 440*	*(203 – 571)*	*(220 – 619)*	

The percentage abnormal for the hematology anylates ranged from a low of 5.2% for the white count to a high of 20.7% for an elevation of the percentage of lymphocytes in the differential. In most cases the elevations were not extreme and a visual inspection of the distribution of values suggested that the laboratory normal values had been incorrectly determined (A smooth single peak that is shifted relative to normal range). On the other hand, some of the distributions show

a cutoff at the upper limit of normal. Finally, the mean changes over the six weeks of treatment were trivial, although between 12 and 25% of the C200 subjects had an increase from normal in the values for Calcium, CK, Phosphate, and Urea. In the placebo group 12% (4/32) of those who started out normal had an abnormal Calcium at the end of the study, and 8.3% (3/36) had abnormal BUNs. However, all other values increased in less than 3%.

Laboratory values that exceeded predetermined upper limits for alert values were reported for 4 Placebo (one each, Platelets>444 * 10^3 cells/mm^3, Potassium > 5.3 mEQ/L, and 2 ALT > 30 U/L) and 5 C200 subjects (Potassium > 5.3 mEQ/L in 2 subjects, and one each, WBC count > 12.0 * 10^3 cells/mm^3, ALT > 30 U/L, and Eosinophils >4%). There were no sequelae from these events and no subject was withdrawn as a consequence.

HPA-Axis Evaluation

Blood samples for cortisol were obtained from 40 and 79 of the placebo and C200 subjects, respectively. The samples were all obtained before 9:30 AM and only three were obtained between 9:00 and 9:30. The LS mean plasma cortisol increased in both treatment groups over the course of the study (Table 31). The increase was greater in the placebo-treated subjects, but the difference did not reach statistical significance.

Table 31. HPA-axis Evaluation in subjects 2 to 5 years of age

Serum cortisol (mcg/dL) comparing baseline to 1-12 week average	Placebo N=40	C200 N=79
Baseline, mean(SD)	9.85 (3.8)	9.83 (3.9)
Change from Baseline, LS mean (SE)	1.94 (0.7)	0.99 (0.5)
Treatment Difference 95% CI	0.95 -0.72, 2.63	

Reviewer: The cortisol data suffers from the same deficiency as the other laboratory data. All of the distributions are shifted rightward resulting in many values above the normal limit at baseline as well as at the endpoint in both groups. As with the CK, phosphate, and Calcium determinations the baseline levels started out relatively high and increased further during the trial.

In response to the FDA query about the laboratory normal values [redacted] the Applicant noted that the reported cortisol normal values were incorrect. Instead of a normal range of 2.5 to 12.2 mcg/dL the correct range was 5.0 to 25.0 mcg/dL. When the baseline values were assessed after this correction, 3 subjects (2 C200 and 1 placebo) had a low baseline value and one C200 subject had a baseline value of 26.3 mcg/dL. The Applicant comment about the other laboratory values was that they were not far from the normal range and that possibly some of the children were dehydrated.

Physical Examination including ENT

The general physical examinations and vital signs were normal throughout the study for most subjects. The nasal examination was recorded as abnormal in 88 and 90% of the placebo and

C200 subjects, respectively. At the end of the study the percentages were unchanged. There were no reported perforations.

2.3 Summary and Discussion

This 12-week, randomized comparison of ciclesonide nasal spray 200 mcg once daily to placebo was designed to demonstrate the safety of ciclesonide nasal spray in the treatment of 2 to 5 year-olds with PAR. Demonstrating efficacy was a secondary objective, although, the 24 hour-reflective TNSS improved more in the C200 group than in placebo. The physician's assessment of nasal symptoms actually suggested that the placebo subjects fared better during the trial. These two outcomes can be reconciled if it is remembered that the r-TNSS was analyzed with a repeated measures ANOVA that includes all of the 12-weekly averages in the analysis, while the physician's assessment compared baseline to end of study score only. If an analysis had been performed on the baseline TNSS compared to the endpoint, the results would have been similar to those of the PNSS because the difference between placebo and C200 was not statistically different on the last three weeks of the trial. Finally, it should be noted that the 100 mcg dose of ciclesonide was not administered in this study, so the study provides no support for the proposed recommended dose of 100 mcg once daily.

The safety analysis showed a spectrum of adverse events that was similar to that seen in other studies in the subject group. Events were uncommon and mild. The ENT examination failed to show any evidence of septal ulceration or perforation. The mild abnormalities in the routine safety blood tests are probably artifacts. However, as in previous studies submitted to support approval of this product, the results suggest a general laxity in supervision of the laboratories. After the new normal values were used to assess the changes in plasma cortisol there were no apparent abnormalities induced by ciclesonide treatment. However, a single AM plasma measurement is not adequate to assess HPA-axis function.

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/s/

Carol Bosken
10/11/2007 04:43:57 PM
MEDICAL OFFICER

Lydia McClain
10/12/2007 10:02:35 AM
MEDICAL OFFICER
I concur with the recommendation for approval of Omnaris 200 mcg once daily for treatment of SAR symptoms in children 6 to 11 years