CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-004

MEDICAL REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE DIRECTOR'S DECISIONAL MEMORANDUM

Date: Friday, October 20, 2006
NDA: 22-004
Sponsor: Altana Pharma
Proprietary Name: Omnaris (ciclesonide)
Author: Curtis J. Rosebraugh, MD, MPH, Deputy Director, ODE II

Planned Action: Approval (AP).

Summary: This is a first cycle review for ciclesonide which is a new chemical entity. Ciclesonide is a pro-drug corticosteroid that is enzymatically cleaved to an active metabolite, des-ciclesonide, and has been submitted for review in treating the symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). The signatory authority has been delegated to me by Dr. Robert J. Meyer, Director of ODE III. I would like to note that I have been involved in Dr. Badrul Chowdhury's divisional review by reading, editing and offering comments. We have had several discussions of the data and regulatory and precedence concepts applicable to this application and I agree with the content of his memorandum. This memorandum will be a brief summary serving to highlight some issues but I would refer the reader to Dr. Chowdhury's excellent Divisional Memorandum for a detailed review of this application.

This application was submitted as a 505(b)(1) on December 20, 2005 for the indication of SAR and PAR in patients 2 years of age and older. It should be noted that Sanofi-Aventis is also developing an inhalation aerosol formulation of ciclesonide for the treatment of asthma [redacted]

For this application, there were eleven clinical studies. Of these eleven studies, there was one 2-week SAR dose ranging study (CL-002), one 4-week SAR study (401-identified as pivotal by sponsor), and one 6-week PAR study (402-identified as pivotal by sponsor) and one 52-week study (404), all including patients 12 years of age and older. Pediatric studies included one 12-week study in PAR patients 6-11 years of age (403), and one 6 week study in PAR patients 2-5 years of age (405). Finally, there were three pharmacodynamic HPA-axis evaluation studies (CL-001, M1-408 and M1-409) and two environmental exposure chamber studies (M1-406 and M1-407).

The division's interpretation of the results of the studies were that efficacy and safety were demonstrated in patients 12 years and older for a dose of 200 mcg once daily, but efficacy was not demonstrated in patients 2-11 years of age. I agree with this interpretation. It is interesting

to note that the pediatric studies included dosing up to the adult dose of 200 mcg once daily, and yet efficacy, while trending in a direction possibly indicating dose related efficacy, was not statistically significant. As such, to obtain the SAR/PAR indication in this age group (6-11 year olds), the sponsor will need to conduct additional studies demonstrating efficacy.

The most common adverse effects were headache, nasopharyngitis, epistaxis and nasal passage irritation.

HPA axis evaluation demonstrated that there was a dose related decrease in urine and plasma cortisol in the 2-5 year old group, the possibility of urine cortisol suppression in the 6-11 year old group (the results were not consistent and the lack of efficacy in the study of this age group make conclusive judgments in this age group difficult) and the studies in adults were not adequately designed to make conclusive judgments regarding HPA effects. While HPA axis effects should be an expected effect with corticosteroid products, for labeling purposes and to allow physicians to make informed product choices, these effects need to be further explored. I do not think that this an approval issue, because as I stated these effects are expected and the labeling reflects this, but I do feel this needs further definition as a Phase 4 evaluation. Therefore, the sponsor will need to adequately assess possible HPA axis effects in adults.

Along those lines, the Agency believes that linear growth suppression in children is an important marker for systemic effect of corticosteroids that may not be characterized by, and is more sensitive than, HPA axis testing. As such, the sponsor will need to further characterize the safety of this product in children (which would include those in the 12-16 year age group included in this application) by conducting an adequately designed growth study with the nasal product or provide data from an adequate study with the inhaled product along with sufficient bridging data to support the inhalation study's relevance to the intranasal product.

Based on the unanimous recommendation of the various review disciplines and my own review of the data, I recommend approval of ciclesonide for ages 12 years old and above for the treatment of SAR and PAR.

CMC: I will highlight one CMC issues. [redacted]. The sponsor will therefore distribute the product in an aluminum pouch with an oxygen absorber. The expiration date of the product in the pouch will be [redacted] months with an out-of-pouch, 'in-use', recommended storage of four months. The product includes an adhesive sticker that allows for recording of when the product should be discarded after opening the pouch.

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/s/

Curtis Rosebraugh
10/20/2006 05:02:07 PM
MEDICAL OFFICER

DIVISION DIRECTOR'S MEMORANDUM

Date: October 20, 2006

To: NDA 22-004

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy products, CDER, FDA

Product: Omnaris (ciclesonide) Nasal Spray 50 mcg

Applicant: Altana Pharma

Administrative and Introduction

Altana Pharma submitted a 505(b)(1) new drug application (NDA 22-004) on December 20, 2005 (CDER stamp date) for use of ciclesonide nasal spray 50 mcg for the treatment of nasal symptoms of seasonal and perennial allergic rhinitis in patients 2 years of age and older. The PDUFA due date for this application is October 22, 2006. Sanofi-Aventis is developing an inhalation aerosol formulation of ciclesonide for the treatment of asthma [redacted] No other drug product containing the active moiety ciclesonide is marketed in the United States for any indication. Altana Pharma submitted the necessary CMC data, pre-clinical data, and clinical data that support approval of this application in patients 12 years of age and older, but not down to the age of 2 years.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug substances ciclesonide is a pro-drug with an ester moiety attached to the carbon position 21 that is enzymatically cleaved to a pharmacologically active metabolite C21-des-ciclesonide (also called RM1). Only the R-epimer of ciclesonide is present in the formulation. The formulation contains a hypotonic aqueous suspension of ciclesonide fine particles; microcrystalline cellulose, carboxymetehylcellulose, [redacted] and potassium sorbate and sodium edetate [redacted] The final drug product is the formulation contained in a [redacted] glass bottle with a plastic outer sleeve to minimize breakage, sealed with snap-cap metering plastic spray pump, and closed with a plastic cap. The final drug product is packaged in an aluminum foil pouch with added oxygen absorbent [redacted] The drug product has a specified out-of-pouch (i.e., patient use) storage time limit. Each actuation of the pump delivers 50 mcg of ciclesonide in 70 mcl. The commercial presentation is a 12.5 gram bottle that provides 120 actuations.

All DMFs associated with this application are acceptable. The drug substance and the final drug product are manufactured in Altana Pharma facilities in Germany. All the

manufacturing and testing facilities associated with this drug product have acceptable EER status with the exception of the [redacted] facility.

There were several CMC issues identified by the CMC review team early in the review period. Those were communicated to Altana Pharma in discipline review letters. Altana Pharma resolved these issues and the CMC team recommends an approval action. I concur with this recommendation. There is one CMC issue worth noting. Stability data submitted during review of the application showed that the level of [redacted] was higher than the originally proposed acceptance limit of [redacted]

[redacted]

Pharmacology and Toxicology

Altana Pharma submitted results from an abbreviated preclinical program with this submission. The program included studies where the animals were dosed with the drug product nasally in appropriate bridging studies to bridge nasal exposure to preclinical data submitted [redacted] for the ciclesonide inhalation formulation. The toxicology programs for ciclesonide are reviewed in detail in the PharmTox review of Dr. Hao. The PharmTox team has determined that the submitted studies are adequate and recommends an approval action. I concur with that recommendation. Brief comments on some key preclinical issues are made in the following paragraphs.

The nasal toxicology study showed some lymphoid tissue atrophy in the nose of dogs. The proposed human dosing has approximately 4-fold safety margin for this toxicity. Systemic toxicity findings with intranasal exposure were typical of corticosteroids. Early in development for the inhalation product there was a concern regarding the potential of testicular toxicity. The dog nasal toxicology study was reported to have found testicular atrophy in animals tested with ciclesonide. The proposed human nasal dose provides 30-fold safety margin for this toxicity. Additionally, "spermiogenic disturbance" was noted in a chronic dog study in which ciclesonide was administered by oral inhalation. On further review of the slides a panel of Pathologists convened by the company concluded that the earlier reading was an artifact. The PharmTox team accepts that conclusion. Studies addressing genotoxicity, carcinogenity, and reproductive toxicity did not show any unique finding for ciclesonide. All genotoxicity studies were negative except the in vivo mouse micronucleus test that was positive. Two-year carcinogenicity studies conducted in mice and rats with oral dosing and inhalation dosing, respectively, were negative. Reproductive toxicology studies with ciclesonide in rabbits showed some

known teratogenic effects of corticosteroids. There were no unique findings with ciclesonide. The pregnancy category for ciclesonide was determined to be C, which is the same category for many other corticosteroids.

Clinical Pharmacology

Altana Pharma submitted results from a fairly comprehensive clinical pharmacology program with this application and with [redacted] for the inhalation formulation of ciclesonide. The programs addressed the key pharmacokinetic issues, such as in vitro studies to assess protein binding and metabolism, pharmacokinetics after single and multiple does, in vitro and in vivo metabolism, effect of hepatic impairment, and drug-drug interaction. Studies in renal impaired patients were not conducted since renal excretion of ciclesonide and its active metabolite des-ciclesonide is a minor route of elimination. Clinical Pharmacology studies submitted to [redacted] were reviewed by Dr. Sandra Suarez, and the studied submitted to this application were reviewed by Dr. Al-Habet's. The Clinical Pharmacology team has determined the submitted clinical pharmacology studies are adequate and recommends an approval action. I concur with that recommendation.

Ciclesonide is a pro-drug that is hydrolyzed by esterases to a pharmacologically active metabolite des-ciclesonide, which is also a glucocorticoid. Des-ciclesonide has approximately a 120-fold greater affinity for the glucocorticoid receptor than ciclesonide. The esterases involved in the hydrolysis of ciclesonide to des-ciclesonide are not identified. Although des-ciclesonide appears to be the major metabolite after esterification, mass balance studies showed that only 20% of the total plasma radioactivity corresponds to ciclesonide or des-ciclesonide. It appears that the full range of potentially active metabolites of ciclesonide has not yet been characterized. Des-ciclesonide is predominately metabolized by CYP3A4 (about 83%), and to a lesser extend by CYP2D6 and CYP2C8. Both ciclesonide and des-ciclesonide are rapidly absorbed from the nasal cavity and lung. The relative bioavailability of ciclesonide+des-ciclesonide following inhalation of ciclesonide is about 41%. The absolute oral and inhaled bioavailability of ciclesonide and des-ciclesonide are 1.1% and 26%, respectively.

Blood levels for ciclesonide and des-ciclesonide after nasal administration were measured in studies CL-001, 403, and 405 (comments on these studies can be found in the following section). The lower limit of quantification of the assay was 25 pg/mL for ciclesonide and 10 pg/mL for des-ciclesonide. In these studies ciclesonide was essentially undetectable in the blood but des-ciclesonide was detectable in some subjects (Table 1). In adults at 200 mcg once daily dose des-ciclesonide was not detectable in any subject, but at 2 or 4 fold higher doses des-ciclesonide was detectable in more than half of the subjects (study CL-001). In children 2 to 11 years of age (studies 403 and 405) at 200 mcg once daily dose des-ciclesonide was detectable in approximately half of the study subjects. Compared to adults children had higher des-ciclesonide in blood with the same nominal dose. Presence of des-ciclesonide in the blood after nasal ciclesonide

administration appears to be related to the dose administered and the age of subjects. The latter is likely due to lower volume of distribution in younger subjects.

Table 1. Blood levels of des-ciclesonide after ciclesonide nasal spray treatment

Study	Subjects	n	Dose (mcg)	Days of Treatment	% subjects detectable	Cmax (pg/mL)	
						Median	Maximum
CL-001	Adult SAR	6	800	14	50	<12.9	16.3
	Adult Healthy	6	800	14	100	17.0	28.8
		6	400	14	67	11.5	29.1
		6	200	14	0	<10	<10
403	6-11 yr, PAR	16	200	84	50	<10.3	44.9
		20	100	84	5	<10	13.1
		19	25	84	0	<10	<10
405	2-5 yr, PAR	30	200	42	41	<10	39.1
		30	100	42	22	<10	36.1
		31	25	42	13	<10	64.5

HPA-axis function was assessed in adult studies 404, 408, 409, and CL-001, and in pediatric studies 403 and 405. Comments on these studies can be found in the following section.

Clinical and Statistical

Overview of the clinical program:

The clinical program for ciclesonide nasal spray was typical of a new molecular entity being developed for allergic rhinitis. The pivotal clinical studies submitted to support efficacy and safety of ciclesonide nasal spray in adults and adolescent patients 12 years and older with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) included one 2-week dose ranging study in SAR patients (study CL-002), one 4-week study in SAR patients (study 401), and one 6-week study in PAR patients (study 402). Pivotal clinical studies submitted to support efficacy and safety in pediatric patients included one 12-week study in PAR patients 6 to 11 years of age (study 403), and one 6-week study in PAR patients 2 to 5 years of age (study 405). Other pivotal clinical studies included one 52-week safety study (study 404), two onset-of-action environmental exposure unit (EEU) studies (studies 406 and 407), and three HPA-axis safety studies (studies CL-001, 408, and 409). Detailed review of the clinical program can be found in Dr. Bosken's medical review, Ms. Feng's statistical review, and in Dr. Gilbert-McClain's medical team leader memorandum. Altana Pharma's intent was to use the clinical program to support approval in patients 2 years and older. The clinical and statistical teams concluded that the submitted studies support efficacy and safety of ciclesonide nasal spray in patients 12 years and older, but not in patients 2 to 11 years of age. I concur with that conclusion.

The pivotal clinical studies mentioned above, which have direct bearing on the approvability decision of this application are briefly reviewed in the following sections.

The design and conduct of these studies are briefly described, followed by efficacy and safety findings and conclusions.

Design and conduct of the pivotal efficacy and safety studies:

Dose-ranging study (study CL-002):

Study CL-002 was double-blind, placebo-controlled, parallel group in design, conducted in 6 centers in Texas, United States, in patients 18 years of age and older with at least a two-year history of SAR. The study had a 1-week rescue medication only run in period, followed by 2-week double blinded treatment period. The treatment arms were ciclesonide nasal spray 200 mcg, ciclesonide nasal spray 100 mcg, ciclesonide nasal spray 50 mcg, ciclesonide nasal spray 25 mcg, and placebo nasal spray, all dosed in the morning. The primary efficacy variable was reflective patient scoring of four nasal symptoms, rTNSS, (rhinorrhea, nasal congestion, nasal itching, and sneezing) twice daily (AM and PM) on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). Other efficacy variables included patient and investigator global evaluation performed on day 7 and 14. The primary efficacy endpoint was the difference from placebo in the change from baseline of the sum of AM and PM rTNSS averaged over the 2-week treatment period. The study was designed to have 125 patients per treatment arm to give 80% power to detect a 0.9 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. Safety assessment included recording of adverse events, vital signs, physical examination, clinical laboratory measures, ECG, and eye examination including pen light examination and tonometry to measure intraocular pressure. A total of 726 patients were randomized approximately equally to the five treatment arms and 703 patients (96.8%) completed the study. There were no preferential discontinuations in any treatment arms.

Adult and adolescent efficacy and safety studies (studies 401 and 402):

Study 401 was double-blind, placebo-controlled, parallel group in design, conducted in 6 centers in Texas, United States, in patients 12 years of age and older with history of SAR and positive sensitivity to Mountain Cedar pollen by skin test. The study had 7-10 days no treatment run in period, followed by 4-weeks double blind treatment period. The treatment arms were ciclesonide nasal spray 200 mcg, and placebo nasal spray, both dosed in the morning. The intent of the study was to confirm the efficacy of 200 mcg dose seen in study CL-002. The primary efficacy variable was reflective patient scoring of four nasal symptoms, rTNSS, (rhinorrhea, nasal congestion, nasal itching, and sneezing) twice daily (AM and PM) on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). Other efficacy variables included instantaneous patient recording of the same symptoms, iTNSS, on the same scale, investigator overall assessment of efficacy, and Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ) assessment at weeks 2 and 4. The primary efficacy endpoint was the difference from placebo in the change from baseline of the average of AM + PM rTNSS averaged over the first 2 weeks of treatment. To assess the onset of action iTNSS was measured hourly (from 4 to 12 hours after the first dose) on the first day of treatment. The study was designed to have 151

patients per treatment arms to give 90% power to detect a 0.9 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. Safety assessment included recording of adverse events, vital signs, physical examination specifically looking for nasal findings, clinical laboratory measures, and ECG. A total of 327 patients were randomized approximately equally to the two treatment arms and 292 patients (89.3%) completed the study. There were no preferential discontinuations in any treatment arms.

Study 402 was double-blind, placebo-controlled, parallel group in design, conducted in 41 centers in the United States and Canada in patients 12 years of age and older with history of PAR and positive sensitivity test to relevant allergen by skin test. The study had 7 days no treatment run in period, followed by 6-weeks double blind treatment period. The treatment arms were ciclesonide nasal spray 200 mcg, and placebo nasal spray, both dosed in the morning. The intent of the study was to confirm the efficacy of 200 mcg dose seen in Study CL-002. Efficacy and safety variables were similar to Study 401 with the notable difference that the primary efficacy endpoint was assessed over the 6 weeks of treatment. The study was designed to have 209 patients per treatment arms to give 90% power to detect a 0.7 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. A total of 471 patients were randomized approximately equally to the two treatment arms and 409 patients (86.8%) completed the study. There were no preferential discontinuations in any treatment arms.

Pediatric efficacy and safety studies (studies 403 and 405):

Study 403 was double-blind, placebo-controlled, parallel group in design, conducted in 74 centers in the United States and Canada in patients 6 to 11 years of age and older with history of PAR and positive sensitivity to relevant allergen by skin test. The study had 7-10 days no treatment run in period, followed by 12-weeks double blind treatment period. The treatment arms were ciclesonide nasal spray 200 mcg, ciclesonide nasal spray 100 mcg, ciclesonide nasal spray 25 mcg, and placebo nasal spray, all dosed in the morning. The primary efficacy variable was reflective patient or care-provider scoring of four nasal symptoms, rTNSS, (rhinorrhea, nasal congestion, nasal itching, and sneezing) twice daily (AM and PM) on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). The other efficacy variable assessed was investigator assessment of efficacy. The primary efficacy endpoint was the difference from placebo in change from baseline of the average of AM + PM rTNSS averaged over the first 6 weeks of treatment. The study was designed to have 159 patients per treatment arms to give 80% power to detect a 0.6 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. Safety assessment included recording of adverse events, vital signs, physical examination, clinical laboratory measures, tonometry to measure intraocular pressure, and HPA axis assessment by single AM plasma cortisol and 24-hour urinary cortisol measurement in a subset of patients (n=320). Pharmacokinetic assessment was done in a subset of patients (n=80). A total of 665 patients were randomized approximately equally to the treatment arms and 586 patients (88.1%) completed the study. There were no preferential discontinuations in any treatment arms.

Study 405 was double-blind, placebo-controlled, parallel group in design, conducted in a single center in Little Rock, Arkansas, United States, in patients 2 to 5 years of age with at least 3-months history of PAR and positive sensitivity to relevant allergen. The study has 3-10 days no treatment run in period, followed by 6-weeks double blind treatment period. The treatment arms were ciclesonide nasal spray 200 mcg, ciclesonide nasal spray 100 mcg, ciclesonide nasal spray 25 mcg, and placebo nasal spray, all dosed in the morning. The primary objective of the study was to assess safety. Safety was assessed by recording of adverse events, vital signs, physical examination, clinical laboratory measures, ECG, eye examination including tonometry to measure intraocular pressure, and HPA axis assessment by single AM plasma cortisol and 24-hour urinary cortisol measurement. Efficacy assessment was secondary and was assessed by surrogate recording of rTNSS. A total of 133 patients were randomized approximately equally to the treatment arms and 129 patients (97.0%) completed the study. There were no preferential discontinuations in any treatment arms.

One-year safety study (study 404):

Study 404 was a double-blind, placebo-controlled, parallel group in design, conducted in 35 centers in the United States in patients 12 years of age and older with PAR. The study had a screening visit where eligibility was determined, followed by 12 months of double blind treatment with either ciclesonide nasal spray 200 mcg or placebo, dosed in the morning. Safety was assessed by recording of adverse events, vital signs, physical examination, clinical laboratory measures, HPA axis assessment in a subset of patients (n=286), and formal eye examination. HPA axis assessment included a single morning AM plasma sample and a 24-hour urine for cortisol with no specified criteria for adequacy of urine collection. Eye examination included tests for visual acuity, slit lamp examination, measurement of intraocular pressure, LOCS scoring for lens opacification. HPA axis assessment and eye examination was done at baseline, at 24 weeks, and at 48-52 weeks. Efficacy assessment was secondary and was assessed by recording of rTNSS. A total of 663 patients were randomized in a 2:1 ratio in the ciclesonide nasal spray and placebo nasal spray treatment arms and 474 patients (71.5%) completed the study. There were no preferential discontinuations in any treatment arms.

EEU onset-of-action studies (studies 406 and 407):

Studies 406 and 407 were double-blind, placebo-controlled, parallel group in design, conducted in single center in Canada (Study 406 was conducted in Mississauga, Ontario, and Study 407 was conducted in Kingston, Ontario) in patients 18 years of age and older with SAR with sensitivity to short ragweed. These studies were primarily designed to get pharmacodynamic onset of action data for ciclesonide nasal spray. Eligible patients were primed in the EEU for 1 to 5 days, and patients who met the eligibility criteria of a predefined minimum nasal symptom score were exposed to the allergen in the EEU on the test day and administered a single dose ciclesonide nasal spray 200 mcg or placebo nasal spray. Efficacy was assessed by frequent instantaneous patient scoring of four nasal symptoms, iTNSS, (rhinorrhea, nasal congestion, nasal itching, and sneezing) twice daily (AM and PM) on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe)

over 12 hours after dosing. In study 406 a total of 503 patients were randomized and 502 completed the study. In study 407 a total of 420 patients were randomized and 417 completed the study.

HPA-axis safety studies (studies CL-001, 408, and 409):

Study CL-001 was double-blind, placebo-controlled, sequential in design, conducted in a single center in the Netherlands, in adult healthy volunteers and symptomatic subjects with SAR. The objective of this study was to evaluate safety of daily escalating doses of ciclesonide nasal spray given for 14 days. A total of 48 subjects with mean age of 30 years were randomized into 6 cohorts of 8 subjects each with 6 subjects receiving ciclesonide nasal spray and 2 subjects receiving placebo nasal spray in each cohort. The doses of ciclesonide used in the study were 50 mcg once daily, 100 mcg once daily, 200 mcg once daily, 400 mcg once daily, and 400 mcg twice daily. Plasma samples were collected for ciclesonide assay on various study days. HPA axis function was assessed by plasma cortisol and urinary cortisol assessment by collection of samples over 24 hours on days 1 and 14.

Studies 408 and 409 were double-blind, placebo- and active-controlled, parallel design, conducted in single center in the United States (study 408 was conducted in San Antonio, Texas, and study 409 was conducted in Long Beach, California) in patients 18 years of age and older with PAR. These studies were designed to assess the additive effect of ciclesonide nasal spray on HPA-axis function over Qvar (beclomethasone) Inhalation Aerosol (study 408) or Advair (fluticasone proprionae and salmeterol) Diskus (study 409). The studies had a 10-day run in period, followed by 42 days double-blind treatment period. During the 10-day run-in period patients were treated with a placebo nasal spray plus Qvar 320 mcg twice-daily (study 408) or Advair Diskus 500/50 twice-daily (study 409). During the 42-day double-blind treatment period patients were randomized to receive ciclesonide nasal spray 200 mcg once daily or placebo while Qvar (study 408) or Advair Diskus (study 409) was continued at the same doses. On randomized treatment day 43 (day 53 of the study) all patients received 2 mg of dexamethasone orally in addition to the nasal spray and the inhalation products. The intention of the 10-day run-in period was to suppress the HPA-axis by the inhalation products; the intention of the 42-day double-blind treatment period was to assess the additive suppression of the HPA-axis by ciclesonide; and the intention of the final dexamethasoe treatment was to demonstrate that the HPA-axis of these patients were steroid responsive. HPA-axis function was assessed by plasma cortisol and urinary cortisol assessment by collection of samples over 24 hours on various treatment days. Efficacy was assessed by reflective patient scoring of four nasal symptoms, rTNSS, as in the pivotal efficacy studies. Plasma samples were not assessed for ciclesonide. In Study 408 a total of 111 patients were randomized approximately equally to the two treatment groups and 105 (94.5%) completed the study. In Study 409 a total of 150 patients were randomized equally to the two treatment groups and 132 (88.0%) completed the study. The design of these studies does not allow clear assessment of the effect of ciclesonide on HPA axis and is not endorsed by the Division for this purpose.

Efficacy findings and conclusion:
The submitted studies support efficacy of ciclesonide nasal spray at a dose of 200 mcg once daily in patients with SAR and PAR ages 12 years and older, but does not support efficacy in patients 2 to 11 years of age.

In the dose ranging study conducted in patients 12 years of age and older (study CL-002) a dose-related increase in efficacy trend was observed with only the 200 mcg once daily dose reaching statistical significance for the primary efficacy endpoint of rTNSS (Table 2). This study did not assess iTNSS, which is a measure of end-of-dosing interval efficacy that would support the dosing frequency. The 200 mcg once daily dose was further studies to confirm its efficacy in one SAR and one PAR study in patients 12 years of age and older (studies 401 and 402). In both of these studies 200 mcg dose was statistically superior to placebo in the primary efficacy endpoint of rTNSS, and also for iTNSS (Tables 3 and 4). The AM iTNSS supports this particular dose and the dosing frequency. Secondary endpoints were also generally supportive of efficacy. RQLQ scores did not separate from placebo; treatment differences were 0.18 (95% CI, -0.13, 0.24) and 0.28 (95% CI, 0.07, 0.50) favoring ciclesonide in studies 401 and 402, respectively. To get a support of onset of action, in both the studies iTNSS was assessed hourly on the first day of treatment. At no point in the first day ciclesonide nasal spray separated statistically from placebo nasal spray.

Supportive efficacy evidence of efficacy was seen in the one-year safety study (study 404). In that study, over the one-year treatment period, mean treatment difference between the ciclesonide nasal spray and the placebo nasal spray was 0.6 in rTNSS with 95% CI ranging from 0.3 and 0.9.

Table 2. Study CL-002, Change in reflective AM+PM TNSS over 2 weeks

Treatment	n	Baseline	Change from Baseline	Difference from Placebo		
				Estimate	95% CI	p-value
Ciclesonide 200 mcg	144	18.8	-5.73	-1.35	(-2.43, -0.28)	0.04
Ciclesonide 100 mcg	145	18.7	-5.26	-0.88	(-1.96, 0.19)	0.11
Ciclesonide 50 mcg	143	18.4	-4.82	-0.44	(-1.52, 0.63)	0.42
Ciclesonide 25 mcg	146	18.7	-4.74	-0.35	(-1.42, 0.71)	0.51
Placebo	148	17.8	-4.38			

Table 3. Studies 401 and 402, Change in reflective and instantaneous AM+PM TNSS over 4 weeks

Treatment	n	Baseline	Change from Baseline	Difference from Placebo		
				Estimate	95% CI	p-value
Study 401 (SAR) – Reflective TNSS, AM+PM score						
Ciclesonide 200 mcg	162	8.96	2.40	-0.90	(-1.36, -0.45)	<0.01
Placebo	162	8.83	1.50			
Study 401 (SAR) – Instantaneous TNSS, AM+PM score						
Ciclesonide 200 mcg	162	8.40	-2.15	-0.87	(-1.31, -0.44)	<0.01
Placebo	162	8.33	-1.28			
Study 401 (SAR) – Instantaneous TNSS, AM score						
Ciclesonide 200 mcg	162	8.45	-1.87	-0.84	(-1.30, -0.39)	<0.01
Placebo	162	8.33	-1.03			

Treatment	n	Baseline	Change from Baseline	Difference from Placebo		
				Estimate	95% CI	p-value
Study 402 (PAR) – Reflective TNSS, AM+PM score						
Ciclesonide 200 mcg	232	7.59	-2.51	-0.62	(-0.97, -0.28)	<0.01
Placebo	229	7.72	-1.89			
Study 402 (PAR) – Instantaneous TNSS, AM+PM score						
Ciclesonide 200 mcg	232	7.07	-2.21	-0.53	(-0.87, -0.20)	<0.01
Placebo	229	7.09	-1.68			
Study 402 (PAR) – Instantaneous TNSS, AM score						
Ciclesonide 200 mcg	232	7.05	-1.99	-0.53	(-0.90, -0.17)	<0.01
Placebo	229	7.05	-1.46			

Table 4. Study 403, Change in reflective AM+PM TNSS over 6 weeks

Treatment	n	Baseline	Change from Baseline	Difference from Placebo		
				Estimate	95% CI	p-value
Ciclesonide 200 mcg	165	6.6	-2.1	-0.31	(-0.75, 0.13)	0.166
Ciclesonide 100 mcg	165	6.7	-1.8	0.03	(-0.41, 0.46)	0.911
Ciclesonide 25 mcg	169	6.8	-1.7	0.09	(-0.35, 0.53)	0.681
Placebo	165	6.8	-1.8			

To support efficacy in patients 2 to 11 years of age results from two studies (studies 403 and 405) were submitted. Study 403 was a typical efficacy study conducted in patients 6 to 11 years of age. Study 405 was a small safety study in patients 2 to 5 years of age with efficacy assessed as a secondary measure. In both the studies the adult dose 200 mcg once daily and two lower doses 100 mcg once-daily and 25 mcg once-daily was tested. The intention of the pediatric program was to demonstrate efficacy in children 6 to 11 years of age, and support efficacy in children 2 to 5 year of age by demonstration of safety, extrapolation of efficacy from older patients, and with possibly some trends in efficacy. The expectation was that the adult dose 200 mcg once daily would be effective and possibly the lower dose of 100 mcg once daily may also be effective. However, results of study 403 did not show efficacy for any dose tested (Table 4). For the lower two doses there were even no trends of efficacy. Study 405 also did not show any evidence of efficacy. Given the findings of these two studies ciclesonide nasal spray cannot be recommended for use in children 2 to 11 years of age.

Results from two EEU studies (studies 406 and 407) in SAR patients were submitted to support a [redacted] For regulatory purpose, onset of action is defined as the first time point, replicated in two studies, where the difference between the active treatment and placebo in efficacy measure is statistically significant and the difference persists consistently after that time point. It is also expected that the difference would be clinically meaningful and the effect size pre-specified based on the effect size seen in pivotal phase 3 efficacy studies. In study 406 the difference between ciclesonide nasal spray 200 mcg once-daily and placebo nasal spray for iTNSS separated statistically at 1 hour time point (effect size was 0.5) and persisted consistently after that. At hour 9 the effect size reached 0.8, which was comparable to the effect size seen in the SAR study (study 401). In study 407 the difference between ciclesonide nasal spray 200 mcg once daily and placebo nasal spray

for iTNSS separated statistically only at hours 6 and 7 (effect size was 0.7 and 0.6, respectively), but did not persist after that. Therefore, onset of action could not be defined in this study. Without replication, no pharmacodynamic onset of action claim can be supported for ciclesonide nasal spray.

The efficacy of ciclesonide nasal spray was consistent across adult and adolescent patients in multiple-dose pivotal studies (studies CL-002, 401, and 402), but the efficacy finding overall did not seem robust. Studies in children lower than 12 years of age could not show efficacy even at the dose that showed efficacy in patients 12 years of age and older. EEU studies failed to show replicative pharmacodynamic onset of action. Based on the dose-ranging study (study CL-002) it appears that doses lower than 200 mcg would not be effective, although a lower dose was not investigated in the confirmatory SAR and PAR studies in patients 12 years of age and older. It appears that either the 200 mcg once daily dose in the true lowest effective dose or the efficacy of ciclesonide nasal spray is simply not robust. Nevertheless, the demonstration of efficacy at 200 mcg once daily is adequate to support approval in patients 12 years of age and older.

Safety findings and conclusion:
The submitted studies support safety of ciclesonide nasal spray at a dose of 200 mcg once daily in patients with SAR and PAR ages 6 years and older. Safety data for ages 2 to 5 years is scant and involves a total of 132 patients involved in a 6-week study. In this study 99 patients received ciclesonide in three active treatment arms of 33 patients each. Ciclesonide doses in the three treatment arms were 200 mcg, 100 mcg, and 25 mcg. The number of subjects treated is too small to make conclusions about general safety of ciclesonide in this very young age group.

Overall safety database for ciclesonide nasal spray includes 2612 subject ages 2 years of and older who received any dose of ciclesonide. In any clinical program placebo-controlled repeat-dose studies are generally more useful for safety assessment because these studies allow some ascertainment of drug effect. Such studies for the ciclesonide nasal spray program included three short-term efficacy and safety studies in patients 12 years of age an older (studies CL-002, 401, and 402), two short-term efficacy and safety studies in patients 2 to 11 years of age (studies 403 and 405), and one one-year safety study in patients 12 years of age and older (study 404). In these studies a total of 744 patients received ciclesonide nasal spray at the dose of 200 mcg once daily for duration of 2 to 12 weeks (144 in study CL-002, 164 in study 401, 238 in study 402, 165 in study 403, and 33 in study 405). In the one-year study (study 404) 441 patients received ciclesonide 200 mcg once-daily. These exposure numbers are reasonable for safety assessment in patients 6 years of age and older.

In the controlled clinical studies ciclesonide nasal spray was generally well tolerated. There were no deaths in any of the studies. Serious adverse events were not common and not of a type that could be ascribed to corticosteroid treatment. The common adverse events associated with ciclesonide were headache, nasopharyngitis, epistaxis, and nasal passage irritation. These are adverse events commonly seen with nasal corticosteroids.

Nasal physical examination, vital signs, clinical laboratory tests, and ECG did not show any safety signals of concern.

Ophthalmologic examination was done in the adult dose ranging study (study CL-002), pediatric short-term efficacy and safety studies (studies 403 and 405), and in the one-year safety study in adults and adolescents (study 404). Ophthalmologic examination was particularly extensive in study 404. In this program particular attention was paid to ocular safety because of concerns with lens opacification seen in one study with the ciclesonide inhalation formulation. With the ciclesonide nasal formulation no evidence of ophthalmologic adverse effect including lens opacification was seen.

Examination of HPA-axis in the ciclesonide nasal spray program was done in six studies. These were one small ascending dose study in adults (study CL-001), two pediatric studies (studies 403 and 405), one one-year study in adults and adolescents (study 404), and two studies in adults where ciclesonide was added to either Qvar (study 408) or Advair (study 409). HPA axis assessment in the ciclesonide clinical program was not extensive and some studies did not meet the methodological rigors that are required of such studies. The Division expects HPA axis studies involve at least 6 weeks of treatment with the study drug, include an active control that can demonstrate that the study could show an HPA axis effect if such an effect was present, assess HPA axis by plasma cortisol measure over 24 hours or urinary cortisol from a complete 24 hour collection or both, and assure compliance by plasma pharmacokinetic sampling of study drug or demonstration of efficacy or both. Of the six studies that examined HPA axis only the two pediatric studies (studies 405 and 403) could be considered as adequate. Brief comments on the six HPA axis studies are made in the following paragraphs.

The two pediatric studies (studies 403 and 405) were of adequate duration, included pharmacokinetic sampling of ciclesonide, and assessed HPA axis by 24 hour urinary cortisol. Urine collections in both the studies were adequate. Compliance could be reasonably assured because pharmacokinetic sampling showed detectable des-ciclesonide in some patients (Table 1), and study 403 had some trends towards efficacy for the 200 mcg dose (Table 4). Although the studies did not include a positive control arm, but the positive HPA results verify internal validity of the study (Table 5). In both the studies there were trends of HPA axis effect with ciclesonide. Dose ordered trend of HPA axis effect seen in study 405 is highly suggestive of an HPA suppressive effect in the 2 to 5 year age group.

Table 5. Decrease in 24-hour urine cortisol after treatment (mcg/day)

Study	Subjects	n	Dose (mcg)	Weeks of Treatment	LS mean Change from Baseline	Treatment Difference (95% CI)
403	6-11 yr, PAR	35	200	12	-1.69	-0.81 (-4.0, 2.4)
		44	100	12	-0.96	-0.08 (-3.1, 2.9)
		32	25	12	-2.99	-2.11 (-5.3, 1.1)
		33	Placebo	12	-0.90	
405	2-5 yr, PAR	22	200	6	-3.55	-2.04 (-4.4, 0.3)
		15	100	6	-3.47	-1.96 (-4.5, 0.6)
		16	25	6	-3.27	-1.76 (-4.3, 0.8)

Study	Subjects	n	Dose (mcg)	Weeks of Treatment	LS mean Change from Baseline	Treatment Difference (95% CI)
		18	Placebo	6	-1.51	

Study CL-001 was of limited value because only six subjects were assessed for each dose level and the duration of treatment was 2 weeks.

The one-year study in adults and adolescents (study 404) showed efficacy that could assure compliance, but this study had other problems that makes the results questionable. The assessment of HPA axis included a single morning blood sample and the 24-hour urine for cortisol had no criteria that could define adequate collection. Line listing shows that many samples had urine volumes less than 500 ml.

The six-week ciclesonide + Qvar study (study 408) and ciclesonide + Advair study (study 409) was not informative because of the design of the studies. The intent of these studies was to suppress HPA axis by the inhaled corticosteroids and then show additive effect, if any, of ciclesonide nasal spray. These studies showed fairly large decrease in plasma cortisol (study 408) and urinary cortisol (study 409) and no additive effect of ciclesonide. One cannot rule out a small effect on ciclesonide nasal spray because such an effect may not be easy to show in the backdrop of large effect with the inhaled corticosteroid. There was no assurance of compliance with ciclesonide in these two studies. Both the studies failed to show any efficacy for ciclesonide nasal spray. In study 408 the effect sizes for rTNSS for ciclesonide and placebo were identical; in study 408 the effect sizes of rTNSS favored placebo over ciclesonide. There were no pharmacokinetic sampling either that could assure compliance.

Data Quality, Integrity, and Financial Disclosure

DSI audited three sites during review of the application. These were routine inspections and the sites were recommended by the clinical review team based on the importance of the studies and large numbers of subjects enrolled at these sites. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements.

Of the three sites audited by DSI, one site was found to have multiple problems. The site located in Little Rock, Arkansas, was the single center that enrolled all patients in the single study submitted to support safety in patients 2 to 5 years of age. DSI inspected 69 of 133 patient records and identified three types of deficiencies. First, 10 of 69 patients were noted to be on prohibited medications at the screening visit. These included OTC antihistamine containing products in 5 patients, Singular in 4 patients, and Rhinocort in 1 patient. Second, many of the bottle weights were outside the protocol specified acceptance range. Bottle weight and information recorded in dairy data were measures of compliance.

[redacted] Altana Pharma responded to these identified deficiencies in a letter dated June 21, 2006, to the FDA Dallas District Office. Altana Pharma acknowledges the problems, but argues that these DSI findings should not affect the overall conclusions related to the safety findings of the study. The use of prohibited medications could affect efficacy, but not safety, and the use of these medication were actually discontinued 2 days prior to randomization. Bottle weight was one of the two measures of compliance and was meant to corroborate the information recorded on dairy. Diary recording did not show any problem. Discrepancy of the bottle counts is a problem, but the overall number of bottles involved is small. The Division acknowledges that the site had multiple problems, but these do not make the safety findings from this study invalid. The problems are likely to affect efficacy conclusion, but not safety. The primary intent of the study was to assess safety. Moreover, two other pieces of information suggest that patients were compliant rendering further support to the validity of the study. First, blood samples from a reasonable number of patients had measurable amount of des-ciclesonide (Table 1). Second, the data showed a measurable effect of ciclesonide on the HPA axis in the study subjects (Table 5). Demonstrate of a safety finding in the face of these study conduct issues makes the finding even more persuasive. The Division will accept the safety findings from this study and include the results in the product label.

Pediatric Considerations

Altana Pharma included children 2 years and older in the studies that were submitted with this application. The lower age bound is typical for a nasal corticosteroid and the Division has not asked that drugs of this class be studied in children younger than 2 years. The Division has historically taken the position that SAR occurs in children 2 years of age and older and PAR occurs in children 6 months of age and older. Although the lower age cut-off is somewhat arbitrary, there is literature support on the lower age bound (J Allergy Clin Immunol 2000, 106:832). For children younger than 2 years nasal corticosteroids is not an optimum choice because of possible nasal and systemic adverse effects. Such young patients are better treated with drugs of other classes such as antihistamines. Therefore, Altana Pharma's lower age cut off for the clinical program is appropriate.

Linear growth suppression in children is an important marker for systemic effect of corticosteroids including nasal corticosteroids. Altana Pharma has conducted a one-year growth study in pediatric patients 5 to 8.5 years of age with orally inhaled ciclesonide at doses 40 mcg and 160 mcg once-daily (study 343). Only a summary result of the growth study was submitted to this NDA without any datasets. This study may be adequate for the nasal formulation if the systemic exposure from the inhaled formulation is higher than the systemic exposure from the nasal formulation. [redacted]

Labeling

Altana Pharma submitted a label that generally conforms with labeling of other products of this class. The label was reviewed by various disciplines of this Division, and on consult by OSE and DDMAC. Various changes to different sections of the label were done to reflect the data accurately and truthfully and better communicate the findings to health care providers. Safety results for patients 2 to 11 years are presented in the label, and the label mentions that efficacy in this age group were not demonstrated. The Division and Altana Pharma have agreed to the final version of the label.

Product Name

Altana Pharma originally intended to use the tradename for this product. The Division and the OSE found that name unacceptable because of the suffix that is typical of drugs for asthma, such as Similarity of the names with the ' ' suffix, and similarity of the nasal spray pump and nasal metered dose inhaler dosage forms raised the concern that the name could result in medication error with unacceptable safety risk. This was communicated to Altana Pharma within the review period. Altana Pharma subsequently changed the tradename to Omnaris. This name was reviewed by the OSE and DDMAC and found to be acceptable.

Action

Altana Pharma has submitted adequate data to support approval of ciclesonide nasal spray for the treatment of nasal symptoms associated with SAR and PAR in adults and adolescents 12 years of age and older. Altana Pharma has not submitted adequate data to support approval in patients 2 to 11 years of age. The action on this application would be APPROVAL specific to the ages 12 years and above.

Phase 4 commitment studies:

1. HPA-axis effect of ciclesonide nasal spray was not adequately assessed in adults . Altana Pharma will be asked to conduct one adequate HPA axis safety study in patients 12 years of age and older with the labeled dose and with at lease one higher dose to define the HPA axis effect of ciclesonide nasal spray.
2. Altana Pharma will be asked to submit results of one one-year linear growth study in children with ciclesonide using a dose that is relevant to the proposed ciclesonide nasal spray dose in children. A linear growth study conducted with a formulation other than the nasal formulation may be adequate provided the systemic exposure from that formulation is higher than the systemic exposure from the nasal formulation.

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

/s/

Badrul Chowdhury
10/20/2006 11:08:19 AM
MEDICAL OFFICER
DD Summary Review

Curtis Rosebraugh
10/20/2006 11:55:04 AM
MEDICAL OFFICER
I concur with the content and recommendations contained in Dr. Chowdhury's

Medical Team Leader Memorandum

Date: September 22, 2006

To: NDA 22-004

From: Lydia I. Gilbert-McClain, MD, FCCP
Medical Team Leader, DPAP

Product: Ciclesonide nasal spray 200 mcg

Applicant ALTANA Pharma

Background/Administrative

A new drug application for ciclesonide nasal spray was submitted to the Agency on December 21 2005 under 505 (b)(1) of the Federal Food Drug and Cosmetic Act and 21 CFR 314.50. The application is to obtain marketing approval for ciclesonide nasal spray for the treatment of nasal symptoms with seasonal and perennial allergic rhinitis in adults and children 2 years of age and older. The proposed dose for adults and children [redacted] of age and older is 200 mcg once daily administered as 2 sprays (50 mcg/spray) in each nostril. [redacted] The application was filed on February 20, 2006 in accordance with 21 CFR 314.101(a). The review priority classification for this application is standard (s) and the PDUFA goal date is October 22, 2006.

The drug development program for ciclesonide nasal spray was carried out under IND 65,488 which was first opened on August 8, 2002. The Initial sponsor of the IND was Teijin America Inc., the U.S. counterpart of Teijin, a diversified Japanese company engaged in research and the development of health care and pharmaceutical products. On April 04, 2003, sponsorship of the IND was transferred to ALTANA Pharma. Teijin licensed the use of R-ciclesonide in allergic rhinitis from Byk Gulden the pharmaceutical division of ALTANA. Under a separate licensing agreement, Altana/Byk Gulden worked with Aventis Pharmaceuticals (U.S.A.) and with Teijin (Japan) to develop ciclesonide inhalation aerosol for the maintenance treatment of asthma. That development program was conducted under [redacted] which was first opened in [redacted] was submitted to the Agency on [redacted] for marketing approval of ciclesonide inhalation aerosol for the maintenance treatment of asthma in adults and [redacted] years of age and older. [redacted] The application was given an approvable action because of efficacy deficiencies. For the nasal spray application, the Applicant is using the clinical pharmacology studies submitted to [redacted] to provide the pharmacokinetic data on ciclesonide as well as supplemental pharmacodynamic and safety information. The Applicant has a letter of authorization from Aventis

Pharmaceuticals to allow ALTANA to access information in [redacted] in support of NDA 22-004.

ALTANA had several interactions with the Division during the development program for ciclesonide nasal spray that include a pre-IND meeting on February 22, 2002, an end-of-phase 2 (EOP2) meeting on October 1, 2003, and a pre-NDA meeting on June 7, 2005. At the EOP2 meeting, ALTANA questioned whether a growth study using ciclesonide nasal spray would be required given that they were conducting a 1-year growth study with the inhalation aerosol formulation. This growth study was being conducted using 40 mcg and 160 mcg of ciclesonide inhalation aerosol once daily. [redacted] The Division informed ALTANA that if they demonstrate that the systemic exposure from 200 mcg of ciclesonide nasal spray is significantly lower than 160 mcg of ciclesonide oral inhalation aerosol then it would be reasonable to use the data from the growth study with the oral inhalation formulation. ALTANA also asked the Division whether the ciclesonide data from the studies conducted under the asthma program along with the nasal spray studies would supply sufficient information to evaluate the effect of ciclesonide on the HPA-axis and the Division agreed.

Chemistry Manufacturing and Controls and Establishment Evaluation

Ciclesonide is a non-halogenated glucocorticoid with a molecular weight of 540.7. The molecular formula is $C_{32}H_{44}O_7$. It is insoluble in water but soluble in ethanol and acetone. The nasal spray is a hypotonic aqueous suspension containing microcrystalline cellulose, carrboxymethylcellulose, [redacted], and potassium sorbate and edetate sodium [redacted] The pH of the formulation is 4.5 achieved by the addition of hydrochloric acid. The nasal spray is supplied in an amber glass bottle with a manual metered pump for nasal delivery. Prior to initial use, the pump must be primed by actuating eight times. Once primed each actuation delivers 50 mcg ciclesonide in 70 mcL from the actuator.

The overall CMC development program was acceptable. Early in the development of the drug, ALTANA recognized that the levels of potassium sorbate, [redacted] However during stability testing (reported late in the review cycle) of the drug packaged in the pouch it was found [redacted] Limited stability data to date with out-of-pouch testing has led the CMC team to recommend that the bottle should be discarded after 4 months after removal from the foil pouch since the amount of [redacted] may increase to unacceptable levels when the bottle is left outside of the pouch for longer than 4 months. The CMC reviewer recommends that the current specifications for [redacted] for long-term stability testing be [redacted] with an expiration of 24 months. The pharmacology/toxicology team indicates that these specifications are acceptable and provide a large safety margin. Two manufacturing site inspections are still pending at the time of this writing. The ALTANA site in Germany that manufactures the final dosage form is scheduled for inspection October 13, 2006 one week prior to the PDUFA date. The inspection of the site that [redacted] the drug substance is scheduled after the PDUFA date. The CMC

team recommends that the application can be approved if the manufacturing site for the final dosage form passes inspection and the inspection of the other site can be addressed post approval. For additional details please refer to Dr. Arthur Shaw's excellent CMC review.

OVERVIEW OF CLINICAL PROGRAM

A total of eleven (11) completed clinical studies with ciclesonide nasal spray were submitted in the NDA application. These studies include 3 pharmacodynamic studies (CL-001, M1-408, and M1- 409), two environmental exposure chamber (EEC) studies (M1- 406 and M1- 407), one dose ranging study (CL-002), two pivotal efficacy and safety studies in adults and adolescents (M1- 401 and M1- 402), one 52-week safety study in adults and adolescents (M1- 404), and two pediatric studies as outlined in the table below.

Table 1: Table of clinical studies with ciclesonide Nasal Spray

Study	Primary Objective(s)	Treatment Duration	Population / number randomized (n)
CL-001	PK/PD	2 weeks	Healthy adult volunteers (40) and asymptomatic SAR subjects (8)
CL-002	Dose-ranging	2 weeks	Adults with SAR (n = 726)
M1-401	Pivotal efficacy	4 weeks	Adults with SAR (n =327)
M1-402	Pivotal efficacy	6 weeks	Adults with PAR (n = 471)
M1-404	Long-term safety	52 weeks	Adults with PAR (n =663)
M1-403	Pivotal efficacy	12 weeks	Children 6 -11 years with PAR (665)
M1-405	Safety, PK/PD	6 weeks	Children 2 -5 years with PAR
M1-406	Onset of action	1 day	Adults with SAR (n =503)
M1-407	Onset of action	1 day	Adults with SAR (n = 420)
M1-408	HPA axis	6 weeks	Adults with PAR (n =111)
M1-409	HPA axis	6 weeks	Adults with PAR (n =150)

EFFICACY

- **Dose-ranging**

Study CL-002 was the only dose ranging study conducted in adults. A total of 726 patients 18 - 65 years of age with SAR were enrolled in this study. Following a 7-day run-in period, they were randomized to treatment with ciclesonide 200 mcg, 100 mcg, 50 mcg, 25 mcg or placebo once daily in the morning for 14 days. Patients recorded the severity of four nasal symptoms (runny nose, itchy nose, sneezing, and nasal congestion) twice daily (AM and PM) in a diary based on a categorical severity scale of 0 to 3 [0 = none, 1 = mild, 2= moderate, 3 = severe] in a reflective (how they felt over the last 12 hours) and instantaneous (how they felt now) manner. The primary efficacy variable was the change from baseline in the average of the summed AM and PM reflective total nasal symptom score (r-TNSS) over the 14 days of treatment. Baseline was defined as the average of the summed AM and PM reflective TNSS over the 7-day screening period. Compared to placebo, patients treated with ciclesonide nasal spray 200 mcg had a statistically significant improvement in the r-TNSS however, neither the 100 mcg dose nor any of the other doses showed statistically significant superiority over placebo. Of note, when the Applicant conducted the analyses excluding the baseline values, both the 100 mcg and the 200 mcg doses were statistically superior to placebo. However, when the baseline values are incorporated into the analysis (as they should be), only the 200 mcg dose is effective. The findings of this dose ranging study indicate that the 200 mcg dose is not the most effective; however, the Applicant did not explore higher doses. The efficacy results for the dose-ranging study are shown in Table 2. Of note, the efficacy study conducted in children 6 to 11 years of age evaluated 200 mcg, 100 mcg, and 25 mcg and neither one of the doses was effective.

Table 2: Primary Efficacy Results Study CL-002

Treatment	Baseline mean	LS mean change from baseline	Treatment comparison vs. placebo	
			LS mean difference (95% CI)	p-value
Ciclesonide 200 mcg (n = 144)	18.8	-5.73	-1.35 (-2.43,-0.28)	0.04
Ciclesonide 100 mcg (n =145)	18.7	-5.26	-0.88 (-1.96,0.19)	0.11
Placebo (n =148)	17.80	-	---	

Data source: Re-analysis of the Applicant's data by Biostatistics reviewer Dr. Feng Zhou. The difference from placebo is calculated as placebo – ciclesonide so that superiority of ciclesonide is represented by a negative number.

- **Adults and adolescents 12 years of age and older**

Two randomized double-blind placebo-controlled studies - M1-401 [SAR patients] and M1-402 [PAR patients] comparing the efficacy and safety of ciclesonide nasal spray 200 mcg to placebo were conducted in adult and adolescents 12 years of age and older.

In study M1-401, patients who had a history of SAR for at least 2 years and a positive allergen skin test to mountain cedar pollen [all study sites were in South-Central Texas] were randomized to study treatment for 4 weeks. Patients in study M1- 402 had a history of PAR for at least 2 years. The majority (66%) of these patients had a positive skin test to mites while the remainder had a positive skin test to various allergens: cat dander (16%), molds (13%), dog (3%) and cockroach/cockroach products (2%). The demographic characteristics in both studies were similar. The majority of patients (86%) were Caucasian and most [patients] were between 18 and 64 years of age. Patients 65 years of age and older were markedly underrepresented making up only 6% of the study population in study M1-401 and even less (2%) in study M1-402. Subjects under 18 years of age made up 7% of the population in study M1-401 and 11% in study M1- 402.
In addition to the usual exclusion criteria in clinical trials, patients were excluded if they had nasal polyps or nasal malformations, nasal trauma or nasal surgery within 60 days, were non-vaccinated against chicken pox or measles and had been exposed to, or had an active infection within 21 days of screening, had active asthma, or used topical steroids in excess of 1% of hydrocortisone. Patients were prohibited from medications such as corticosteroids, other intranasal medications, and immunosuppressive therapies, short and long-acting antihistamines during the study, and needed to have discontinued these medications for a pre-defined period prior to study enrollment to allow for an adequate washout.

The studies were designed with a 7-day screening period during which, patients eligible for enrollment recorded the severity of four nasal symptoms (runny nose, itchy nose, sneezing, and nasal congestion) twice daily in a diary based on a categorical severity scale of 0 to 3 [0 = none, 1 – mild, 2= moderate, 3 = severe]. The total score of these nasal symptoms make up the Total Nasal symptom Score (TNSS) [maximum score = 12]. At the end of the screening period, patients with a reflective (AM or PM) score of at least 6 on at least 4 of the last 7 days of screening were randomized. They received treatment with ciclesonide nasal spray 200 mcg or placebo once daily in the morning. During the randomization period, patients recorded reflective and instantaneous nasal symptom scores twice daily (AM and PM). The AM instantaneous scores were recorded before the patients took their study medication. Patients in study M1-401 were randomized to 4 weeks of treatment, whereas, patients in study M1-402 were treated for 6 weeks. Compliance to treatment was assessed by the patient's diary data and by visual inspection of the medication bottle.

The primary efficacy endpoint was the mean change from baseline (the average reflective TNSS over the 7-day screening period) in the average of the AM and PM reflective total nasal symptom score (r-TNSS) over the first 14 days of treatment in study M1- 401 and over 42 days in study M1- 402. Secondary efficacy endpoints included:

- ✓ AM and PM instantaneous scores,
- ✓ Individual components of the TNSS
- ✓ Physician assessed nasal symptoms (PANS)
- ✓ Rhinioconjuntivitis quality of life questionnaire (RQLQ)

These endpoints were tested sequentially to correct for multiplicity. Of the 327 patients enrolled in study M1-401, the intent-to-treat (ITT) population consisted of 162 patients

treated with ciclesonide and 162 treated with placebo. Of the 471 patients enrolled in study M1-402, 232 treated with ciclesonide and 229 treated with placebo made up the ITT population.

Ciclesonide nasal spray 200 mcg once daily was statistically superior to placebo in improving the reflective TNSS (r-TNSS) in adults and adolescents 12 years of age and older with SAR and PAR. Both the sum of the AM and PM instantaneous scores, and the AM instantaneous scores (i-TNSS) were statistically superior to placebo. The results for the r-TNSS and the AM i-TNSS are displayed in the table below. The results of the AM i-TNSS confirm maintenance of effect throughout the 24-hour dosing interval (end-of-dosing interval efficacy) in both studies. The four individual nasal symptoms supported the primary efficacy endpoint in that each favored ciclesonide over placebo. Except for congestion, each individual symptom had statistical superiority over placebo. The other secondary efficacy measures PANS and RQLQ did not demonstrate statistical significance compared to placebo and the change in the RQLQ compared to placebo did not achieve the minimum clinically important change.

Table 3: Primary Efficacy Results Study 401 and 402

Treatment	Baseline mean (SD)	LS mean change from baseline (SE)	Treatment comparison vs. placebo		
			LS mean difference	95%CI	P-value
Study 401					
Reflective TNSS (r-TNSS)					
Ciclesonide (n =162)	8.96 (1.96)	-2.40 (0.16)	-0.90	(-1.36,-0.45,)	<0.01
Placebo (n =162)	8.83 (1.82)	-1.50 (0.16)	---		
AM Instantaneous TNSS (i-TNSS)					
Ciclesonide (n = 162)	8.45	-1.87	-.084	(-1.30, -0.39)	<0.01
Placebo (n = 162)	8.33	-1.03	----		
Study 402					
Reflective TNSS (r-TNSS)					
Ciclesonide (n = 232	7.59 (2.04)	-2.51 (0.12)	-0.63	(-0.97, -0.28)	<0.01
Placebo (n =229	7.71 (2.14)	-1.89 (0.13)	----		
AM Instantaneous TNSS (i-TNSS)					
Ciclesonide (n =232)	7.05	-1.99	-0.53	(-0.90, -0.17)	<0.01
Placebo (n =229)	7.05	-1.46			

Data Source: The r-TNSS is taken from the Applicant's data table 8 page 57 study protocol report BY9010/M1-401 and table 9 page 62 of study report BY9010/M1-402. The i-TNSS data are obtained from the biostatistics reviewer Dr. Feng Zhou's analysis of the Applicant's data. The difference from placebo is calculated as placebo – ciclesonide and superiority is represented by a negative number.

- **Pediatric studies**

➢ Children 6 to 11 years of age (Study M1-403)

Children in this study had physician-diagnosed PAR to a relevant allergen for at least 6 months. The design was similar to study M1- 401 and M1- 402 with a few exceptions namely:

- ✓ The diary data were recorded by either the patient or the caregiver
- ✓ Screening included assessment of intraocular pressure (IOP)
- ✓ Patients with an IOP of ≥ 21 mmHg were excluded
- ✓ The duration of treatment was 12 weeks
- ✓ The doses of ciclesonide were 200 mcg, 100 mcg, and 25 mcg
- ✓ Adrenal function was assessed with 24-hour urinary free cortisol and AM cortisol

A total of 665 patients (393 males, 272 females) were randomized in this study distributed relatively evenly among the treatment groups. Similar to the adult studies the majority of subjects (79%) were Caucasian, and 57% reacted positively to skin testing with house dust mites. The primary efficacy endpoint was the same as for the adult studies. A step-down approach was used for multiplicity adjustment. The analysis of ciclesonide 200 mcg compared to placebo was conducted first, with sequential analysis of the lower doses if the 200 mcg dose was statistically significant. Although the mean r-TNSS showed numerical improvement in all the ciclesonide treatment groups, the difference compared to placebo was not statistically significant. The treatment difference between ciclesonide 200 mcg and placebo was only 0.31 ($p = 0.16$).

➢ Children 2 to 5 years of age (Study M1-405)

Efficacy was assessed as a secondary objective using a Physician-assessed Nasal Symptom Score (PANSS). The primary objective of this study was safety. A total of 133 patients (75 males, 58 females) with PAR were randomized to 6 weeks of treatment with ciclesonide 200 mcg, 100 mcg, 25 mcg (n=33 per arm) or placebo (n =34). The study design was similar to that of study M1-403. One notable difference in this study population is that the majority of patients were Black: 70.5% compared to only 28% Caucasian. The race distribution was relatively even across the treatment groups except that all the Hispanic subjects (5.9%) were in the placebo group. All the subjects in this study came from a single U.S. study site in Little Rock, Arkansas which was the subject of a DSI audit (*see Data Integrity section*). All subjects were allergic to mites.

Onset of Action

Onset of action was evaluated in two environmental exposure chamber (EEC) studies (M1-406 and M1- 407) and in the clinical studies M1-401 and M1-402. The EEC studies were both conducted in Canada at 2 separate sites (M1-406 in Mississauga, Toronto, Canada and M1-407 in Kingston, Ontario). A total of 502 and 420 patients in study M1-406 and study M1-407 respectively, completed the study. In both studies, patients were treated with ciclesonide 200 mcg or placebo in a cross-over design. Following exposure to the appropriate allergen, they were evaluated for 12 hours in the EEC with serial assessments of the i-TNSS. An onset of action was determined based on the first time

point where there was a statistically significant separation of ciclesonide from placebo and the subsequent time points showing persistence of that separation. In study M1-406 a statistically significant separation of ciclesonide from placebo was demonstrated at the 1 hour time point (effect size 0.5) with persistence of effect throughout the 12 hour assessment period. However, study M1-407 failed to demonstrate an onset of action during the 12-hour assessment period. There was only one time point in that study (at 6 hrs) where there was statistical separation between ciclesonide and placebo. The Applicant pooled the results of these 2 studies to [redacted] pooling the results of these two studies is not acceptable since the patient characteristics were very different. The EEC data [redacted] because the results have not been replicated. In addition, the effect size seen in the EEC studies was smaller than the effect size seen in the clinical trials. In the clinical studies, patients recorded their nasal symptoms immediately preceding their dose of medication at the follow up visits. Four hours after recording their instantaneous scores patient began recording nasal symptom scores every hour for up to 12 hours. The first statistically significant separation of ciclesonide and placebo occurred at 9 hrs (study M1-402) and 12 hrs (study M1-401) with other statistically significant time points noted over the next 48 to 72 hours. Therefore, [redacted] accurately reflect these data would be an onset of action within 24 to 48 hours.

SAFETY

- Short-term safety

Short-term safety information in adults and adolescents 12 years of age and older are derived from 3 [M1-401, M1-402, and CL-002] controlled short-term (2 to 6 weeks) studies. In these studies, a total of 546 patients (360 females and 186 males) were exposed to ciclesonide nasal spray 200 mcg once daily. Overall, the adverse events were reported with a similar frequency by patients who received ciclesonide nasal spray and by those who received placebo. The most common adverse events (reported by > 2% of patients) were upper respiratory system events and headache (*see table below*). One patient, a 43-year old female in the ciclesonide-treated group in study M1-401 experienced a serious adverse event (epistaxis) on day 16 of treatment and was discontinued.

Table 4: Adverse events with > 2% incidence in controlled clinical trials of 2 to 6 weeks duration with ciclesonide nasal spray in patients with Seasonal or Perennial Allergic Rhinitis in Adults and Adolescents 12 years of age and older

Adverse Event n (%)	Ciclesonide 200 mcg N = 546	Placebo N = 542
Headache	33 (6%)	25 (4.6%)
Epistaxis	26 (4.7%)	16 (3%)
Nasal passage irritation	13 (2.4%)	14 (2.6%)
Nasopharyngitis	20 (3.6%)	18 (3.3%)
Pharyngitis	16 (3%)	19 (3.5%)
Upper respiratory tract infection NOS	10 (2%)	22 (4%)

Data source: -Applicant's table 20 page 54 protocol TBN-CL-002; table 23 page 83 protocol BY9010/M1-401; table 22 page 87 protocol BY9010/M1-402

- Long-term safety

Long term safety information is obtained from one 52-week study [M1-404] in adults and adolescents. In this study, 441 patients (149 males and 292 females) were exposed to ciclesonide nasal spray 200 mcg and 222 received placebo. A total of 202 (45.8%) patients were exposed to ciclesonide for 327 -347 days and 97 (22.0%) were exposed for ≥ 364 days. Adverse events were reported in similar frequency in the ciclesonide (75.1%) and the placebo-treated (74.3%) patients. The most common adverse events (> 2%) were upper respiratory system events (e.g. URTI, epistaxis, sinusitis, and bronchitis), headache, nausea, and urinary tract infection and the incidence was similar in the two treatment groups. Epistaxis was reported with a slightly higher frequency (10%) in the ciclesonide-treated patients compared to the placebo-treated (9%) patients.
Overall, the adverse event profile was similar to that seen in the short-term studies except for a few differences which are most likely due to the longer duration of exposure namely:

(a) Treatment-related events

Adverse events considered treatment-related occurred with a greater incidence in the ciclesonide group (17.0%) versus (10.8%) in the placebo group. Most of these events were in the upper respiratory system but there was one report of candidiasis and increase ocular pressure in the ciclesonide-treated group.

(b) Serious Adverse Events

Serious adverse events were reported with a slightly higher frequency in the ciclesonide-treated patients. A total of 16 (3.7%) patients treated with ciclesonide 200 mcg in the one-year safety study had a serious adverse event. Of these events, there were 3 cases of pneumonia, and 4 cases of suicidal ideation/depression. Two of the pneumonia cases had an underlying diagnosis of asthma and 3 of the 4 patients with suicidal ideation/depression were on chronic therapy for psychiatric disorders prior to enrollment in the studies. All the cases were reported as recovered in the study report and only one case of pneumonia resulted in discontinuation from the study. In contrast, 6 (2.7%) patients receiving placebo reported serious adverse events and there were no reports of pneumonia or suicidal ideation/depression in the placebo-treated patients. Long-term use of corticosteroids can increase susceptibility to infections and cause psychiatric disturbances (e.g. mood swings and psychosis); however, given the case histories it seems unlikely that these events are drug-related although the role of ciclesonide as a contributing factor cannot be entirely ruled out.

(c) Discontinuations due to adverse events

Adverse events resulting in discontinuation occurred in 4.3% of the ciclesonide-treated patients compared to 2.7% of the patients in the placebo group. Except for pneumonia, looking at the listing of events that resulted in discontinuation they do not appear to be drug-related.

There were no deaths reported in any of the studies. There were no gender or racial differences in the safety data in any of these studies.

- Ocular Safety

The Applicant conducted detailed ophthalmologic assessments in the one-year safety and the two pediatric studies. These assessments included slit lamp examinations, and measurement of intraocular pressure by a protocol designated board-certified ophthalmologist. This detailed assessment was conducted because in the asthma development program, lenticular opacities were reported in a 12-week controlled study in a higher frequency (5.1%) in patients treated with ciclesonide compared to patients on placebo (0.7%) or fluticasone propionate (1.4%). Although a one-year active controlled study showed similar percentages of these events in patients treated with ciclesonide or beclomethasone diproprionate HFA (QVAR), the Division asked the sponsor (Aventis Pharmaceuticals) to conduct a long-term study designed to evaluate ocular safety with ciclesonide inhalation aerosol. Therefore, with this background, this Applicant included a rigorous ophthalmologic evaluation in the nasal spray program. There were no significant differences in the ciclesonide nasal spray and placebo-treated patients. Nevertheless, since long-term use of corticosteroids have been associated with the development of glaucoma and/or cataracts, the PRECAUTIONS section of the package insert should include the appropriate class labeling language.

- Effect on Growth

The Applicant included the report of a growth study conducted in asthmatic patients with mild asthma. Patients received ciclesonide oral inhalation aerosol 40 mcg or 160 mcg once daily or placebo for one year. The Applicant did not submit data sets in the original NDA application with this study report to allow for a substantive review. The Applicant concluded that there was no effect on growth with ciclesonide. Even if these results can be verified, there is not enough information to decide whether this growth study will obviate the need for a growth study using ciclesonide nasal spray. As mentioned earlier, the Applicant was informed at the EOP-2 meeting that demonstration of a lower systemic exposure with ciclesonide nasal spray 200 mcg compared to ciclesonide oral inhalation solution 160 mcg would be necessary to use the data from this growth study. The Applicant has not provided these comparative data.

CLINICAL PHARMACOLOGY

The bulk of the pharmacokinetic information on ciclesonide is derived from the ciclesonide inhalation aerosol development program. The clinical pharmacology for ciclesonide was extensively reviewed by Dr. Sandra Suarez-Sharp under [redacted] and her review includes information on the mechanism of action, and pharmacokinetics (including Absorption, Distribution, Metabolism, and Elimination). As noted earlier, the Applicant has a right of reference to these data. In her review Dr. Suarez-Sharp points out that although the metabolite RM1 (des-ciclesonide) is purported to be the major active metabolite, this hypothesis is inconclusive since mass balance studies showed that only 20% of the total plasma radioactivity corresponds to RM1. In addition, another metabolite M9, whose pharmacological potency is unknown, was as abundant as RM1 in plasma samples. (*Executive Summary Clinical Pharmacology review Dr. Sandra Suarez-Sharp*). Ciclesonide and des-ciclesonide have low oral bioavailability (<1%) due to low

gastrointestinal absorption and high first-pass metabolism. For further details on the clinical pharmacology of ciclesonide refer to Dr. Suarez-Sharp's review.

Based on the systemic exposure seen with the ciclesonide aerosol inhalation formulation, the Applicant purports that the systemic exposure to ciclesonide after nasal inhalation is negligible. However, both ciclesonide and des-ciclesonide (RM1) have been detected in the plasma of patients after intranasal inhalation of ciclesonide. There are no direct comparison studies comparing the exposure of the two formulations in the same study. Cross-study comparisons cannot be relied upon to provide an accurate comparison of exposure between the two formulations. The nasal formulation is a suspension and as such its physical properties (viscosity) allow it to be retained in the nose which may result in more of the drug being absorbed systemically with the potential for increased systemic exposure because everything may get absorbed. Furthermore, both ciclesonide and des-ciclesonide (RM1) have been detected in the plasma of patients after intranasal inhalation of ciclesonide. In the safety and PK study CL-001, plasma samples were assayed for ciclesonide and des-ciclesonide. The bioanalytical assay has a lower limit of quantification of 25 pg/mL for ciclesonide and 10 pg/mL for des-ciclesonide. Forty (40) healthy subjects and 8 asymptomatic subjects with SAR, received ciclesonide in doses of 50 to 800 mcg daily or placebo for 14 days. Ciclesonide was detected in the plasma (46.2 pg/mL) of 1 subject treated with 400 mcg twice daily. The metabolite RM1 was detected in 4/6 healthy subjects treated with ciclesonide 400 mcg once daily and in 9/12 subjects (6/6 healthy subjects and 3/6 allergic rhinitis subjects) treated with ciclesonide 400 mcg twice daily.

Assessment of adrenal function and integrity of the hypothalamic-pituitary-adrenal (HPA) axis was not ideal. Although the Applicant completed 24-hour urinary free cortisol and AM cortisol measurements in 6 [CL-001, M1-404, 408, 409, 403 and 405] of the 11 clinical studies, the results from most of these studies are unsuitable to use in the assessment of adrenal function. Of note, none of the studies included a positive control. In study M1-404 there was no assessment of the adequacy of urine collection for the 24-hour urine cortisol measurement. In study CL-001 subjects were domiciled for the 24-hour urinary collection for urinary free cortisol. There were no appreciable differences between the ciclesonide and the placebo-treated groups in urinary free cortisol or morning plasma cortisol. Nevertheless, these findings cannot be used to conclude that there is no effect on adrenal function because of the limited number of subjects (6 per ciclesonide treatment arm) and the short duration of the study. Studies M1-408 and M1-409 were conducted in adults with PAR to evaluate the effect of ciclesonide on adrenal function in patients taking concomitant orally inhaled corticosteroids. Patients were first treated with orally inhaled corticosteroids (budesonide 320 mcg or fluticasone/salmeterol (Advair Diskus) 500/50 twice daily) during a 10-day run in period. At randomization patients continued on their inhaled corticosteroid, and in addition received ciclesonide or placebo for 6 weeks. The Applicant claimed that there is no effect on adrenal function with the concomitant use of ciclesonide and other inhaled corticosteroids. However, both the 24-hour urinary free cortisol and the plasma cortisol AUC_{0-24} decreased throughout the 6-week treatment period in the patients randomized to placebo nasal spray. This suggests that the adrenal axis was undergoing continued progressive suppression from the

orally inhaled corticosteroids. Therefore conclusions about the effect of concomitant use of other corticosteroids with ciclesonide nasal spray on adrenal function cannot be made. Secondly, an effect of ciclesonide itself on adrenal function would be masked with this study design.

Information on adrenal function that is reasonable enough for labeling is limited to the 2 pediatric studies M1-403 and M1- 405. Study M1-405 was conducted in 133 subjects with PAR randomized to 6 weeks of treatment with ciclesonide 25, 100, or 200 mcg (n=33 per arm) or placebo (n =34). Adrenal function was assessed with 24 hour urinary free cortisol and AM plasma cortisol levels prior to randomization and on day 43. Subjects were domiciled in the clinic for a 24-hour period to have urine collected for urine cortisol and urine creatinine measurements. Plasma samples were also analyzed for ciclesonide and the RM1 metabolite. The number of patients with adequate urine samples for analysis of urine free cortisol was 22, 15, 16, in the ciclesonide 200, 100 and 25 mcg groups respectively, and 18 in the placebo group. The difference from placebo in the LS mean change from baseline in the 24 hour urinary free cortisol decreased in all the treatment groups. As shown in the table below, the point estimates were small and the confidence intervals included zero. However the trend was dose-ordered and a similar finding was seen for the AM plasma cortisol. Using outlier analyses with various threshold values as the lower limit of normal (7, 5, and 3 mcg/day) the trend of a dose-dependent decrease in 24 hour urine cortisol was still present. For example, for the threshold of 7 mcg/day, there were 13, 10, and 7 patients in the ciclesonide 200, 100, and 25 mcg groups respectively, who had cortisol values below this threshold compared to 4 subjects in the placebo group.

The parent compound and the active metabolite M1 were assayed at the 0, 2, and 5 hour time point to encompass the trough and peak of the drug at the final study visit. The parent compound (ciclesonide) was detected in 3/285 plasma samples (one in each of the ciclesonide groups) while the M1 metabolite was detected in 38/285 (13.3%) plasma samples obtained from ciclesonide-treated patients. The number and the value of detectible levels increased with higher dosages of ciclesonide. A total of 21, 12, and 5 samples from the ciclesonide 200 mcg; 100 mcg, and 25 mcg treatment groups had detectible levels. The highest value of ciclesonide detected was 39.1 pg/mL in a ciclesonide 200 mcg-treated patient and the highest detectable level for des-ciclesonide was 64.49 pg/ml observed in one patient receiving ciclesonide 25 mcg. [*Data source pages 82 and 83 study report BY9010/M1-405]* From post-hoc analyses, there does not appear to be a correlation between urine cortisol change from baseline and the detection of ciclesonide and the RM1 metabolite in plasma (*Applicant's data table 14.3.6.2 study M1-405*). Nevertheless, these data indicate that ciclesonide nasal spray administered intranasally is systemically absorbed and therefore could have systemic effects.

Table 5: 24-hour Urinary Free Cortisol (mcg/day) and AM plasma cortisol (mcg/dl)

24-hour urinary free cortisol (mcg/day)				
	Ciclesonide			
	200 mcg N = 22	100 mcg N = 15	25 mcg N =16	**Placebo** N =18
Baseline	11.8 (10.2)	8.8 (4.4)	12.6 (8.6)	8.6 (3.7)

Mcg/day (SD)				
Endpoint (LS mean change)	-3.55	-3.47	-3.27	-1.51
Difference from Placebo (95% CI)	-2.04 (-4.4,0.3)	-1.96 (-4.5,0.6)	-1.76 (-4.3,0.8)	------
AM Plasma cortisol (mcg/dl)				
	N = 28	N = 27	N =28	N = 30
Baseline (SD)	9.7 (3.7)	9.6 (4.2)	10.3 (3.3)	10.5 (4.7)
Endpoint)LS mean change (mcg/dl)	-1.07	-0.39	-0.15	-0.03
Difference from Placebo (95% CI)	-1.04 (-2.7,0.7)	-0.36 (-2.1,1.4)	-0.12 (-1.8,1.6)	-----

Data source: Applicant's data table 14.3.4.1 and 14.3.4.1.1 Study protocol M1-405

In study 403, plasma cortisol and 24-hour urinary free cortisol were measured at baseline and after 12 weeks of treatment in pediatric patients 6 to 11 years of age with PAR treated with ciclesonide 200 mcg, 100 mcg, or 25 mcg and placebo. The adequacy of the urine collection was assessed with measurement of 24-hour urine creatinine but patients were not domiciled for the urine collections. The number of patients with adequate urine samples for analyses ranged form 32 - 44. The difference from placebo in the LS mean change from baseline to Endpoint in the 24 hour urinary free cortisol was -0.81, -0.08 and -2.11 in the ciclesonide 200 mcg, 100 mcg, and 25 mcg treatment groups respectively and for the morning plasma cortisol the difference was 0.35, 0.12 and -038 for the ciclesonide 200 mcg, 100 mcg and 25 mcg respectively.

Table 6: 24-hour Urinary Free Cortisol (mcg/day) and AM plasma cortisol (mcg/dl)

24-hour urinary free cortisol (mcg/day)				
	Ciclesonide			
	200 mcg N = 35	**100 mcg** N = 44	**25 mcg** N =32	**Placebo** N =33
Baseline Mcg/day (SD)	15.4 (7.56)	14.1 (5.81)	13.2 (6.11)	13.2(6.28)
Endpoint (LS mean change)	-1.69	-0.96	-2.99	-0.88
Difference from Placebo (95% CI)	-0.81(-4.0,2.4)	-0.08 (-3.1,2.9)	-2.11 (-5.3,1.1)	------
AM Plasma cortisol (mcg/dl)				
	N = 45	N = 61	N =51	N = 47
Baseline (SD)	10.2 (4.78)	9.6 (4.64)	10.1 (3.81)	10.8 (5.34)
Endpoint)LS mean change (mcg/dl)	0.74	0.51	0.01	0.39
Difference from Placebo (95% CI)	0.35 (-1.4,2.1))	0.12 (-1.5,1.7)	-0.38 (-2.1,1.3)	-----

Data source: Applicant's data table 14.3.4.5 Study protocol M1-403

In summary, data on the effect of ciclesonide nasal spray on adrenal function are limited to these 2 pediatric studies and even these data have limitations given the relatively small sample size, the lack of a positive control, and the variability in the data. Those caveats

aside, the results suggest that ciclesonide just like any other corticosteroid could have an effect on adrenal function.

There are no adequate studies in adults that could be used to assess adrenal function. Although several studies were conducted in the ciclesonide inhalation aerosol asthma program, there are several limitations with these studies. All the studies that assessed HPA axis used the low-dose (1 mcg) [redacted] test which is not standardized. In addition, [as mentioned earlier] no studies have been conducted to assess the comparative exposure of the ciclesonide nasal spray to ciclesonide inhalation aerosol and it is possible that systemic exposure with the nasal spray could be even higher than with the inhalation aerosol.

NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

The Applicant conducted 14- and 28-day intranasal toxicity studies in rats and dogs and a 6 –month nasal inhalation toxicity study in dogs to bridge the non-clinical pharmacology toxicology data from the ciclesonide oral inhalation program. The pre-clinical findings from the oral inhalation program were consistent with glucocorticoid effects. The intranasal studies identified one local toxicity - lymphoid tissue atrophy. The NOAEL was 1200 mcg/kg providing a 4.3-fold safety margin on a mg/cm^2 nasal surface basis for the proposed human dose of 200 mcg/day. For further information refer to Dr. Huiqing Hao's review.

PEDIATRIC CONSIDERATIONS

Although the Applicant conducted studies in pediatric patients 2 to 11 years of age, these studies do not support the efficacy of ciclesonide nasal spray in this age group and this information will be reflected in the labeling. The Applicant will need to conduct additional efficacy and safety studies if they wish to pursue an indication in pediatric patients under 12 years of age. Because there are safety concerns (local toxicity) with the use of intranasal corticosteroids in patients under 2 years of age, the Applicant should be granted a wavier under PREA (Pediatric Research Equity Act) for pediatric studies in children less than 2 years. Adequate growth data for the ciclesonide nasal spray formulation is lacking and the Applicant should be asked to provide this as a post marketing commitment (PMC).

ETHICS AND DATA INTEGRITY

The clinical studies were conducted in keeping with good clinical practice and in accordance with the appropriate regulations for human subjects' protection. A Division of Scientific Investigation (DSI) audit was requested from 3 study sites primarily because they enrolled a large number of patients but there were no data integrity signals that prompted the audit. One of the sites selected enrolled all the patients in study M1-405. The sites for the adult studies were found to be acceptable with only minor deficiencies noted at one site and the data from both sites were deemed acceptable by the DSI. For the pediatric study site, the DSI audit reported three deficiencies. The DSI report recommended that the data be excluded from the analysis. This reviewer disagrees with the DSI's conclusions for the following reasons:

1) The DSI report stated that in 10 of 69 patient files reviewed, patients were randomized while still on prohibited medications. However, review of the report reveals that the prohibited medications were discontinued prior to randomization. The medications cited were mainly leukotriene antagonists and antihistamines except for one patient who was on Rhincort nasal spray. These medications would not have affected the study given their relatively short half-lives and the fact that they were all discontinued prior to randomization. Rhinocort nasal spray was discontinued on the day of screening.
2) The report raised concerns about compliance because of discrepancies between the diary data and the actual bottle weights and reported that 60/69 patients had values outside the Applicant's pre-defined acceptable range. Bottle weights were meant to be a secondary assessment of compliance to help corroborate the diary data in terms of trends. It is unclear how accurately and efficiently these measurements were carried out. Furthermore, the active metabolite was detected in up to 38 plasma samples from patients treated with ciclesonide indicating that patients received the drug.
3) The third deficiency noted in the DSI report was that unused supplies of the study medication were not returned to the sponsor. This finding has no bearing on the study results. In conclusion, the data from study M1-405 are acceptable.

NOMENCLATURE

The Applicant does not have a trade name that is acceptable to the Agency at this time. The Applicant proposed the name [redacted] during the drug development program and this name was rejected by the Division of Marketing, Advertising, and Communications (DDMAC) (*See DDMAC memorandum December 27, 2005*). The Applicant submitted two other proposed names [redacted] and both names were deemed unsuitable by this Division and the Division of Medication Errors and Technical Support (DMETS). (*See DMETS consultation response September 13, 2006*) The Division finds the names [redacted] unsuitable because of similarity of the last part of the name [redacted] which could lead to medication errors. The Applicant's most recent trade name proposal OMNARIS is currently under review.

LABELING

[redacted]

[redacted]

SUMMARY

The Applicant has established efficacy of ciclesonide nasal spray 200 mcg once daily for the treatment of the nasal symptoms of seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. The applicant has not established efficacy in children less than 12 years of age. The reason for this observation is probably multifactorial. As noted earlier, the Applicant has not identified the most effective dose of ciclesonide nasal spray. Patients enrolled in the pediatric studies had a history of PAR – generally a more difficult disease to treat than SAR. In the pediatric studies, either the patient or the caregiver recorded the nasal symptoms in the diary and this could have affected the results. The data for the evaluation of adrenal function and HPA axis are not robust and come from 2 small pediatric studies which at best are not ideal. Neither of these studies included a positive control. Still, the dose-ordered trend of decreased urinary free cortisol and morning plasma cortisol in study 405, along with the observation of detectable levels of ciclesonide and des-ciclesonide in 3 studies support the conclusion that ciclesonide nasal spray is absorbed systemically, and like other corticosteroids could affect adrenal function.

RECOMMENDATION

I recommend that the Applicant receive marketing approval for ciclesonide nasal spray 200 mcg for the treatment of the nasal symptoms of SAR and PAR in adults and adolescents 12 years of age and older. [redacted]. The Applicant should provide data on the effect of ciclesonide nasal spray on growth as a post-marketing commitment. Ideally, the Applicant should also conduct a well-designed pharmacodynamic study in adults and adolescents to provide more robust data on adrenal function and HPA axis effects.

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/s/

Lydia McClain
9/22/2006 03:07:58 PM
MEDICAL OFFICER

PREAPPROVAL SAFETY CONFERENCE

Date: October 13, 2006

To: NDA 22-004

From: Lydia I. Gilbert-McClain, MD, FCCP
Medical Team Leader, DPAP

Product: Ciclesonide nasal spray 200 mcg

Applicant ALTANA Pharma

A new drug application for ciclesonide nasal spray was submitted to the Agency on December 21 2005 under 505 (b)(1) of the Federal Food Drug and Cosmetic Act and 21 CFR 314.50. The application is to obtain marketing approval for ciclesonide nasal spray for the treatment of nasal symptoms with seasonal and perennial allergic rhinitis in adults and children 2 years of age and older. The proposed dose for adults and children 6 years of age and older is 200 mcg once daily administered as 2 sprays (50 mcg/spray) in each nostril. [redacted] The application was filed on February 20, 2006 in accordance with 21 CFR 314.101(a). The review priority classification for this application is standard (s) and the PDUFA goal date is October 22, 2006.

During the review it was determined that efficacy was demonstrated only for patients 12 years of age and older and the clinical team recommends approval for children and adults 12 years of age and older. There were no safety issues identified that would have prevented approval.

Ciclesonide is a new molecular entity of the corticosteroid class of compounds. Since ciclesonide is a new molecular entity (NME) a pre-approval safety conference with the office of surveillance and epidemiology (OSE) 4 weeks before the PDUFA goal date is expected as per the Good Review Management Guidance (GRMP). During the review cycle, the review team determined that there were no unique safety issues or signals with this NME. Like every corticosteroid, the package insert will contain the standard Warnings and Precautions that all products of this class carry. The Applicant will be asked to commit to submitting data on growth effects of ciclesonide in prepubescent children as a post-marketing commitment. This is consistent with our request for all corticosteroid products. Additionally, standard language on the effect of corticosteroids on growth will be included in the package insert and the label will be updated with growth data from ciclesonide studies when those become available. Systemic exposure to corticosteroids may also impact the HPA axis and the label will carry the standard warnings and precautions for that. The Applicant will also be asked to conduct an adequate HPA axis study in adults since the ones they conducted were not ideal. The

safety review did not reveal any particular safety concern and the most common (>2%) adverse events noted were headache (6%), epistaxis (4.7%), and nasopharyngitis (3.6%) compared to 4.6%, 3%, and 3.3% in the placebo group. These events are similar to other adverse events seen with nasally inhaled products for allergic rhinitis.

The Division discussed the added value of the pre-approval safety conference for a corticosteroid product with a know safety profile and without any new safety signals identified during the review process. The Division determined that a separate pre-approval safety conference was not necessary; however the OSE staff was invited to attend the Division Wrap-up meeting. The DDRE in the OSE was notified that there were no safety issues with this application and that a separate pre-approval safety conference was not necessary.

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/s/

Lydia McClain
10/13/2006 12:24:33 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-004
Submission Code	s_000
Letter Date	December 21, 2005
Stamp Date	December 22, 2005
PDUFA Goal Date	October 20, 2006
Reviewer Name	Carol H. Bosken, M.D.
Review Completion Date	September 1, 2006
Established Name	Ciclesonide
(Proposed) Trade Name	Omnaris
Therapeutic Class	Corticosteroid
Applicant	Altana Pharma
Priority Designation	S
Formulation	Aqueous Nasal Spray
Dosing Regimen	100 or 200 mcg, once daily
Indication	Allergic Rhinitis
Intended Population	Subjects with seasonal and perennial allergic rhinitis age – years and above.

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ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
AERS	Adverse Event Reporting System
ANOVA	Analysis of Variance
AR	Allergic rhinitis
AUC	Area under the curve
BID	Twice a day
C_{max}	Maximal concentration
CI	Confidence Interval
CMC	Chemistry Manufacturing and Controls
CYP	Cytochrome P450 oxidase
DB	Double-blind
DSI	Division of Scientific Investigation
ECG	Electrocardiogram
EEC	Environmental Exposure Chamber
ENT	Ear Nose and Throat
EOP2	End of Phase Two
HFA	Hydrofluroalkane
HPA-axis	Hypothalamic-pituitary-adrenal
ICH	International Conference Harmonization
ICS	Inhlaed corticosteroids
IRB	Institutional Review Borad
ISS	Integrated Summary of Safety
ITT	Intention To Treat
i-TNSS	Instantaneous Total Nasal Symptom Score
LOS	Lens Opacification System
LS	Least square
M1	Primary metabolite of ciclesonide
MDI	Metered dose inhaler
MedDRA	Medical Distionary
NOAEL	No Observable Adverse Effect Level
PANS	Physicians Assessment of Overall Nasal Signs and Symptoms Severity
PAR	Perennial Allergic Rhinitis
PBMC	Peripheral Blood Mononuclear Cells
PK	Pharmacokinetic
PNSS	Overall Physician-Assessed Nasal Symptom Score
PD	Pharmacodynamic
QD	Every Day
RAST	RadilAllergoSorbent Test
RQLQ	Rhinitis Quality of Life Questionnaire

Abbreviation	Description
r-TNSS	Reflective Total Nasal Symptom Score
SAE	Serious adverse event
SAR	Seasonal Allergic Rhinitis
SOC	Organ system classification
TNSS	Total Nasal Symptom Score
VAI	Voluntary Action Indicated

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 and perennial allergic rhinitis in adults and adolescents 12 years of age and older. The recommendation is based on the results of well designed pivotal efficacy trials of appropriate length in subjects with both seasonal and perennial allergic rhinitis (SAR and PAR) as well as a year-long safety follow-up trial in adults with PAR. Safety of ciclesonide nasal spray was also demonstrated in all of these studies where adverse events were mild and infrequent.

The earliest onset of action that was seen in any of the studies in this submission was 24 hours in the adults with SAR. Consistent efficacy was not demonstrated until several days after the first dose in the adults with PAR. One environmental exposure chamber study designed to demonstrate the onset of action was positive and one was negative. In the negative study effectiveness could not be demonstrated during the 12 hours in which symptoms were assessed.

Studies in children less than 6 years of age failed to show efficacy of ciclesonide nasal spray. The single study in children 2-5 enrolled only 33 subjects per treatment group and was not designed to be used for statistical inference because the Applicant intended to extrapolate efficacy from the study in the 6 – 11 year-old subjects. The study in the 6 – 11 year-olds was adequately powered to demonstrate efficacy. However, the difference between ciclesonide treatment and placebo for the primary efficacy variable failed to reach statistical significance in any of the treatment groups. The largest difference for the reflective total nasal symptom score (r-TNSS) was a LS mean of 0.31 points in the children who were treated with 200 mcg. There was no safety signal in the pediatric population to suggest any adverse events that are not routinely included in corticosteroid class labeling. However, the conclusion is based on a small data set. This is particularly marked in the 2-5 year age group where the maximum exposure was 30 subjects for 30 days at the 200 mcg dose and another 30 subjects for 30 days at the 100 mcg dose. The database for the 2 to 5 year olds had other deficiencies: the subjects were required to have had a diagnosis of PAR for only 3 months, the range of the data was wide, including the demographic and baseline variables, and a DSI audit indicated that there were serious failures to follow the protocol in the single center when the trial was conducted. In sum, ciclesonide nasal spray is not recommended for approval in children < 6 years of age due to the failure to demonstrate efficacy and the limited exposure of subjects in this age-group.

1.2 Recommendation on Post-marketing Actions

No phase 4 studies are 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. The proposed indication is for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and children 2 years of age and older. The [redacted]. The basic adult and adolescent program included one 2-week dose-ranging study (Study CL-002), one pivotal 4-week trial in subjects with SAR (Study 401), and one pivotal 6-week trial in subjects with PAR (Study 402). There was, in addition, a 52-week safety study in adults with PAR (Study 404). The program also included two environmental exposure chamber (EEC) studies (Studies 406 and 407) in adults with SAR to determine onset of action, and biopharmacology studies to assess the effects of ciclesonide nasal spray on the HPA-axis (Studies CL-001, 408 and 409). The pediatric program included one 12-week safety and efficacy study in subjects 6 – 11 (Study 403) years of age with PAR and one 6-week safety study in subjects 2 – 5 years of age with PAR (Study 405).

In the dose-ranging study which explored doses ranging from 25 to 200 mcg, 726 subjects were enrolled of whom 144 received 200 mcg and 145 received 100 mcg ciclesonide daily; in the pivotal SAR trial 327 were enrolled of whom 162 received 200 mcg of ciclesonide daily; in the pivotal PAR trial 471 were enrolled of whom 238 received 200 mcg ciclesonide daily; and in the 52-week safety trial 663 were enrolled, 441of whom received 200 mcg ciclesonide daily. In the two EEC studies a total of 922 subjects were enrolled of whom 461 received a single dose of 200 mcg ciclesonide. The pediatric program enrolled a total of 665 subjects, age 6 – 11 years, of whom 165 received 200 mcg and 165 received 100 mcg ciclesonide daily. In the 2 – 5 age group a total of 133 were enrolled, of whom 33 were treated with 200 mcg and 33 were treated with 100 mcg ciclesonide daily.

The total number of subjects who received ciclesonide in the above described studies was 2612 (1777, 344, 143, and 348 received 200, 100, 50, and 25 mcg, respectively). Of the 1777 treated with 200 mcg, 461 received a single does in the EEC studies leaving 1316 who received multiple doses. Of these, 198 were <12 years of age and 1118 were 12 or older. There were 199 subjects <12 years of age who received multiple doses of 100 mcg ciclesonide daily and 145 subjects 12 year or older. The total duration of exposure to 200 mcg ciclesonide daily was greater than 364 days in 97 subjects and greater than 337 days in 152. A total of 346 were exposed for more than 182 days. All of the subjects who were exposed for 6 months or longer were 12 years of age or older. In the adult and adolescent age-group the total exposure is sufficient to assess safety. The total exposure of 97 subjects for one year is close enough to the ICH required 100, given the large number who were treated for at least 337 days, the lack of any safety signal of concern (see below), and the additional exposure to ciclesonide in ciclesonide MDI.

In the children 6 - <12 years of age the maximum exposure to 200 mcg was 99 days. The mean exposure was 80 days, and 149 received > 77 days of therapy. In the children 2 – 5 years of age the maximum exposure to both the 200 mcg and 100-mcg daily dose was 44 days. The mean exposure was 38.6 and 39.9 days in the 200 and 100 mcg groups, respectively, and 30 and 31 subjects were treated for >29 days.

1.3.2 Efficacy

1.3.2.1 Adults and Adolescents

All of the trials in this submission were randomized, double-blind, and placebo-controlled. The efficacy trials conducted in subjects >12 years of age enrolled subjects with SAR or PAR of at least 2 year's duration, all of the subjects were symptomatic at the time of enrollment, and all had positive skin tests or RAST tests for relevant antigens. Subjects 6 to 11 years of age with PAR were required to have been symptomatic for 6 months, and children 2 to 5 years of age with PAR were required to have been symptomatic for only 3 months prior to enrollment. The children <12 years of age all had skin tests positive for common perennial allergens.

In all of the adult and adolescent trials, the Total Nasal Symptom Score (TNSS) was the primary efficacy outcome variable. This score is the sum of four symptom scores (runny nose, itchy nose, sneezing, and nasal congestion) which were graded on a 4-point scale (Absent, Mild, Moderate, and Severe). The subjects recorded both immediate and reflective scores in daily diaries. The reflective scores required the subjects to recall their symptoms over either the prior 12 or 24 hours. In the dose-ranging study and the two pivotal trials the scores were obtained twice a day, in the morning prior to the dose of study medication and approximately 12 hours later. In the 1-year safety study the score was obtained once daily in the morning. The secondary outcomes included a physician's assessment of signs and symptoms (PANS) and a rhinitis quality of life questionnaire (RQLQ). The symptoms in the PANS were identical to those recorded by the subject for the TNSS. However, the PANS included 4 physical findings (discoloration, swelling, and presence of secretions in the nasal passages, and evidence of post-nasal drip). The final PANS was the average of the symptoms and signs scores.

The primary analysis compared the reflective TNSS at baseline to the scores obtain throughout the trial using a repeat measures ANOVA. The PANS, RQLQ, and analysis of other components of the TNSS (immediate TNSS, AM TNSS, PM TNSS, and individual symptom scores) were secondary efficacy outcomes. In the dose-ranging study the r-TNSS was measured in the morning and evening, and the analysis variable was the sum of the AM and PM scores. In the two pivotal trials the score was also measured twice daily, but the analysis variable was the mean of the AM and PM values. In the one year safety study, efficacy was a secondary outcome, however the r-TNSS was measured once daily and the mean of the values obtained during each week was the analysis variable. In the EEC onset of action studies the instantaneous TNSS was measured hourly after treatment and the

earliest time point of divergence between placebo and ciclesonide was defined as the onset of action. The study of 6 to 11 year-olds analyzed r-TNSS as the primary efficacy variable, however, either the subject or the care-giver could have filled out the diary. In addition, the key secondary outcome was the physician's assessment of symptoms alone (PNSS) in contrast to the physician's assessment of signs and symptoms (PANS) in the adults. In Study 405 (2 – 5 year olds) efficacy was a secondary outcome and the primary efficacy variable was the PANS. The RQLQ was not administered to any of the children < 12 years of age.

In the dose-ranging trial (Study CL-002), subjects 18 to 86 years of age with SAR were treated with ciclesonide 200, 100, 50, 25 mcg, or placebo for two weeks. Over the course of the trial, the 200 mcg ciclesonide daily dose resulted in the greatest improvement in r-TNSS. The TNSS decreased by an LS mean of 5.83, 5.33, 4.79, 4.81, and 4.19 units in the ciclesonide 200, 100, 50, 25, and placebo groups respectively. Compared to placebo the mean difference in r-TNSS during treatment with 200 mcg was 1.35 units (p=0.012) and the mean difference during treatment with 100 mcg was 0.88 units (0.099). The applicant decided, on the basis of this data, to conduct all further studies in adults and adolescents using the 200 mcg dose of ciclesonide alone.

Adults and adolescents, 12 years of age and older with SAR, were treated with ciclesonide 200 mcg once daily or placebo for 4 weeks (Study 401). The primary efficacy analysis was conducted with data obtained during the first two weeks of treatment so it would be comparable with the results of other SAR studies. The r-TNSS fell by a LS mean of 2.4 and 1.5 units in the ciclesonide and placebo subjects, respectively. The i-TNSS fell by a LS mean of 2.15 and 1.28 units, respectively. The mean difference between placebo and ciclesonide was, thus, 0.90 (p<0.001) for the r-TNSS and 0.88 (p<0.001) for the i-TNSS. The secondary efficacy variables were assessed at 28 days. The mean PANS improved to an equivalent degree in both treatment groups (LS mean of 1.98 and 1.99 units in the ciclesonide and placebo group, respectively), and the RQLQ decreased more in the ciclesonide-treated subjects, but the difference was not significant. The LS mean difference in RQLQ between placebo and ciclesonide-treated subjects was 0.18.

Adults and adolescents, 12 years of age and older with PAR, were treated with ciclesonide 200 mcg once daily or placebo for 6 weeks (Study 402). The r-TNSS fell by a LS mean of 2.5 and 1.9 units in the ciclesonide and placebo subjects, respectively. The i-TNSS fell by a LS mean of 2.2 and 1.7 units, respectively. The difference between placebo and ciclesonide was, thus, a mean of 0.63 (p<0.001) for the r-TNSS and 0.54 (p=0.001) for the i-TNSS. In the subjects with PAR the secondary efficacy variables also improved more in the ciclesonide than placebo-treated subjects. The difference between ciclesonide and placebo for the PANS was a LS mean of 0.38 and for the RQLQ it was 0.28 (0.07, 0.50). The difference of 0.28 for the RQLQ did not reach the commonly accepted clinically meaningful level of 0.5.

The one year safety trial in adults (Study 404) was also supportive of efficacy. The 24-hour r-TNSS fell by a LS mean of 2.3 units in the 435 subjects treated with 200 mcg

score = 0.8). However, no statistical analysis was performed on this outcome as required by the hierarchical analysis rule to limit the Type I error. In addition, it is noted that the physician's assessment required the subject/care-giver to recall symptoms over a week. Since the diary entires were made daily, every 12 hours, they would be expected to more accurately reflect the subject's clinical condition than responses that depended on recall over a week.

Only 33 children age 2 – <6 were included in each treatment group in study 405. While the responses favored ciclesonide, the range of the data was very broad. The study was not designed to demonstrate statistical significance. Rather, the intent was to extrapolate efficacy from the data obtained in the older children. Since efficacy was not demonstrated in the 6 to <12 year olds, efficacy can not be extrapolated to the younger age-group. In addition, a DSI audit indicated that there were substantial irregularities in the conduct of the trial at this single-center study, suggesting that the results might be unreliable.

1.3.3 Safety

The safety review is based on data obtained from a total of 2612 subjects exposed to ciclesonide nasal spray. Of the total, 1777 received multiple doses and 1316 received multiple doses of 200 mcg once daily. Of those who received the 200 mcg dose, 1118 were adults or adolescents and 198 were <12 years of age. Of the 344 subjects who received 100 mcg ciclesonide, 145 were adults or adolescents and 199 were less than 12 years of age. In those 12 years of age or older, 97 were treated with 200 mcg for at least 364 days and 152 were treated for at least 337. In the pediatric population, the maximum length of treatment was 106 days in children 6 to <12 years, and 149 were treated with ciclesonide 200 mcg for >77 days. In the 2 – 5 year olds the maximum length of treatment was 44 days and 30 received 200 mcg and 31 received 100 mcg for more than 30 days.

In general, ciclesonide was safe and well-tolerated. There were no deaths in any of the studies submitted with this NDA. Serious adverse events were not common and not of a type usually ascribed to corticosteroid therapy. Looking at the total data base, the incidence of SAEs was highest in the 200 mcg group (1.2, 1.2, 0.6, 0.4% in the 200, 100, 25, and placebo groups respectively). However, the subjects in this group were treated longer: 24.4% were enrolled in the 1-year safety follow-up study compared with 14.7% of the placebo subjects and none of those treated with the other doses of ciclesonide was treated for more than 6 months. In the 1-year follow-up, 3.6 and 2.7% of the ciclesonide and placebo subjects had serious adverse events. In the entire data base, withdrawal occurred in 11.6, 6.4, 2.8, 8.3, and 10.1% of the ciclesonide 200, 100, 50, 25, and placebo subjects, respectively, and adverse events were the reason for withdrawal in 2.4% of the ciclesonide 200 mcg subjects and 2.5% of the placebo subjects. Overall adverse events were reported in 53.6 and 49.0% of the ciclesonide and placebo-treated subjects, respectively. Headache (7.3% vs 6.2%), epistaxis (6.6% vs 4.7%), pharyngolaryngeal pain (4.0% vs 2.0%) sinusitis (3.6% vs 2.2%) and ear pain (2.0% vs 0.7%) were the only MedDRA preferred terms that were reported in the ciclesonide-treated subjects with a frequency of 1% greater than in the placebo-treated subjects.

Examination of the HPA-axis function was conducted prospectively in the 1-year safety trial in adults with PAR (#404) and in the two pediatric trials (#403 and #405). A smaller study was conducted in healthy adults and those with SAR (CL-002) using high doses of ciclesonide, and two studies were performed to assess the combined effect of ciclesonide nasal spray and an inhaled corticosteroid on cortisol production. In study 404, the plasma cortisol fell slightly more in the ciclesonide than the placebo subjects (LS mean difference (95% CI) -0.7 mcg/dL (-2.0, 0.60). After treatment for 2 weeks with 400 and 800 mcg ciclesonide daily the plasma cortisol fell less in the ciclesonide-treated subjects than after two weeks of treatment with placebo. After treatment of 6 – 11 year-olds for 12 weeks, the plasma cortisol increased more in those treated with 200 mcg (0.74 mcg/dL) and 100 mcg (0.51 mcg/dL) than in those treated with placebo (0.39 mcg/dL). In the children treated with 25 mcg ciclesonide the plasma cortisol increased only 0.01 mcg/dL. Thus in the adults and children down to 6 years of age there was no evidence of HPA-suppression as evidenced by the plasma cortisol. In the 2 – 5 year-olds, there was a dose-dependent, decrease in the plasma cortisol, although the differences between ciclesonide treatment and placebo were small, statistically and probably clinically insignificant (LS mean difference [95% CI] = -1.04 [-2.7, 0.7], -0.36 [-2.1, 1.4], and -0.12 [-1.8, 1.6] mcg/dL in the ciclesonide 200, 100, and 25 mcg groups, respectively). There were only 27 or 28 subjects per treatment group and the range in the response variable was wide. The data in the younger children would be insufficient to make a definitive conclusion about the effect of ciclesonide on the HPA-axis on the basis of the plasma cortisol levels even if the DSI audit had not thrown doubt on the accuracy of the reported patient adherence to the treatment regimen.

The results of the 24-hour urinary cortisol measurements were uninterpretable in the 1 year adult follow-up study because of failure to define a cortisol population (i.e. the samples that would be used for the cortisol measurements that met certain pre-defined criteria). There was no definition of an adequate urine sample and the line listings suggest that many samples were abnormally small (<500 ml). The 2-week study in normal adults also failed to define an acceptable urine collection. In the pediatric studies the normal predicted 24-hour urinary creatinine was used to determine the adequacy of the samples. This resulted in sample sizes of 32 to 47 children 6 to <12 years of age and 16 to 30 in the children 2 to 5 years of age. In the 6 to 11 year olds, the 24-hour urine cortisol levels fell more during ciclesonide treatment than during placebo treatment. However, the differences were not statistically significant and not dose ordered. The greatest decrease was seen in those treated with 25 mcg ciclesonide, a group in which no M1 ciclesonide metabolite was detected in the blood. In the 2-5 year olds the decrease in 24-hour urinary cortisol was greater than in adults and older children and was very slightly dose related. Again, the differences were relatively small (maximum difference between ciclesonide and placebo was in the 200 mcg ciclesonide group LS mean (95% CI = -2.04 [-4.4, 0.3]) and the range of the responses was too wide to rule out the null hypothesis. All in all there was very little evidence of HPA-axis suppression due to ciclesonide treatment in the adults or older children. The database in the 2 – 5 years-olds is too small to interpret.

Two studies were submitted (408 and 409) with the objective of demonstrating that there was no interaction between ciclesonide nasal spray and corticosteroids administered concomitantly as an inhalation aerosol as assessed by urinary and plasma cortisol levels. The studies included a 10-day run-in at which time the subjects were treated with either budesonide 320 mcg BID (study 408) of fluticasone/salmeterol 500/50 mcg BID (Study 409). Cortisol measurements were made at the end of the run-in and again after subjects had been treated with the inhalation aerosol for an additional 6 weeks plus either ciclesonide nasal spray or a placebo nasal spray. The results showed similar changes in cortisol levels in the ciclesonide and placebo treated subjects. However, there were relatively large decreases in the plasma cortisol (study 408) and 24-hour urinary cortisol measurements (study 409) during treatment with inhalation aerosol corticosteroid and placebo nasal spray. This suggests that the changes in cortisol metabolism were primarily related to the inhalation corticosteroid. One can not rule out a small effect from the nasal spray with the data presented.

Detailed ophthalmologic examinations were carried out in studies 404, 403, and 405. In the one year adult follow-up study intraocular pressure decreased by a LS mean of 1.0 mm Hg in the ciclesonide treated subjects and increased by 0.1 mm Hg in the placebo treated subjects. In both of the pediatric trials the IOP increased in the placebo-treated subjects and either decreased or increased less in all of the ciclesonide groups. Thus, there was no evidence of an adverse effect of ciclesonide treatment on intraocular pressure. Visual acuity was also measured in study 404 and did not change substantially in either group. Slit-lamp examination for an assessment of cataract development was carried out after one year of treatment with ciclesonide 200 mcg daily. Using the LOS III grading system, 23% of the ciclesonide subjects developed Class I findings compared to 18.7% of the placebo subjects. Class II and III abnormalities were seen in 1.5% and 0.8%, respectively, more often in the ciclesonide than the placebo-treated subjects. None of the differences was significant. In addition, the sub-classification of the cataracts showed that most were categorized as "nuclear opalescence" a change that is not characteristic of a corticosteroid effect. Posterior subcapsular cataract, the abnormality more typical of corticosteroid effect, was actually less common in the ciclesonide treated group (0.8% compare with 1.6% in the placebo group). In summary, there was no evidence of an adverse effect of ciclesonide treatment on the ophthalmologic tract.

An ENT examination with an emphasis on nasal pathology was performed at all clinic visits in all of the repeat dose studies. In the entire cohort two erosions were demonstrated in ciclesonide treated subjects and three in subjects treated with placebo. In all cases the erosions/ulcerations were seen at an interim visit and had resolved on treatment by the end of the study. Vital signs and ECG examinations were unremarkable. Routine laboratory tests provided no evidence for an adverse effect of ciclesonide treatment.

In summary, ciclesonide nasal spray, in the doses administered in these studies, was generally safe. Adverse events were mild and infrequent, and occurred in only a few percentage points more of the ciclesonide-treated than the placebo-treated subjects. Most events occurred in the upper airway and are similar to those seen with the administration of

other nasal corticosteroids. Examination of the HPA-axis and ophthalmologic systems showed no consistent corticosteroid effect. Nasal septal erosions and ulcerations were rare and were no more common in the ciclesonide-treated than the placebo-treated subjects.

1.3.4 Dosing Regimen and Administration

Approval of ciclesonide nasal spray in a dose of 200 mcg once daily (two activations in each nostril) is recommended for patients 12 years and older. Because of failure to demonstrate efficacy, ciclesonide nasal spray is not recommended for children less than 12 years of age.

1.3.5 Drug-Drug Interactions

Very little active drug is absorbed when ciclesonide is administered to adults via nasal inhalation. Therefore drug-drug interactions are not anticipated.

1.3.6 Special Populations

The efficacy of ciclesonide nasal spray in the pediatric population remains to be documented. Because of the low absorption of active drug when it is administered intra-nasally no special studies are required in subjects with renal or hepatic failure.

Appears This Way
On Original

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] Potassium Sorbate NF, Edetate Disodium USP, Hydrochloric Acid NF and Purified Water USP. The solution in 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 6 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 is approved for children as young as 4 years, and mometasone for children as young as 2 years. All are available as aqueous suspension 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	Flonase	Microfine aqueous suspension in metering atomizing spray pump	SAR PAR	 ≥4
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

Ciclesonide is not currently marketed in the United States.

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 Pre-submission Regulatory Activity

An [redacted] for the use of Ciclesonide MDI [redacted] in the maintenance treatment of asthma was submitted to the agency on December 22, 2003. That application was given an approvable action in September 2004 due to the failure to demonstrate efficacy in the doses and dosing regimens described in the application. There were additional CMC issues, however, the preclinical data submitted for ciclesonide was deemed to be adequate. An IND (65,488) for the nasal formulation was submitted in August of 2002, and the applicant came in for an EOP2 Meeting on October 1, 2003. During the EOP2 meeting the applicant expressed the intention to test only the 200 mcg QD dose in adults in the pivotal trials. The Agency suggested that the 100 mcg QD dose be included in the phase 3 trials to improve dose-ranging. The Agency also indicated that a dose ranging study would have to be performed in the pediatric subjects to determine the appropriate pediatric doses. Once the preferred dose was chosen, the pivotal trials would be expected to show statistical significance for efficacy in the 6 to 11 year-old subjects. However, if efficacy is documented in the 6 to 11 years olds, then the planned PD/PK study in 2 to 5 year-olds would be sufficient to support approval in the younger children, and studies in subjects less than two years of age would not be required. The Agency also agreed that environmental chamber exposures could be used to demonstrate an onset of action, with the proviso that a meaningful clinical response was pre-specified based on the effect size seen in the Phase 3 studies that support drug approval.

As to the safety evaluation, the Agency accepted the principal that the data from the MDI program could be cross referenced. This was raised specifically in terms of HPA-axis suppression, growth, and ophthalmologic toxicity. The agency said that it would take into consideration the results of the adult ophthalmologic toxicity study but that measurement of intra-ocular pressure in children in the nasal spray studies would also be required. The agency also agreed to accept the results of the MDI growth study as long as it could be

demonstrated that systemic exposure to ciclesonide was lower after exposure to the nasal spray than after exposure to the MDI.

The applicant came in for a pre-NDA meeting in May of 2005 with the program as described during the EOP2 meeting. Many of the same issues were raised. In addition, the Division suggested that there may be too few subjects in the 2 – 5 year age group to demonstrate safety for anything other than HPA-axis suppression, and the cortisol suppression assessment may be inadequate because background use of ICS was not controlled.

2.6 Other Relevant Background Information

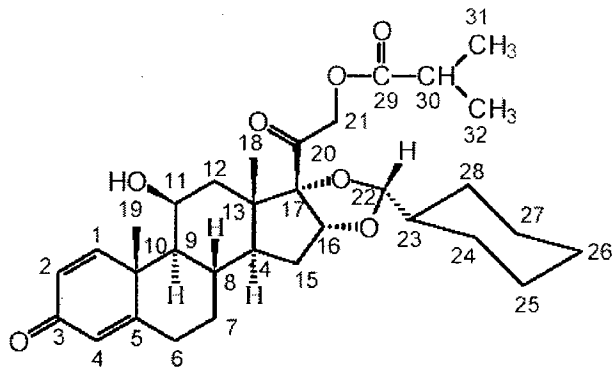
There is no other relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

Ciclesonide is a non-halogenated glucocorticoid, administered by nasal inhalation. The chemical name of ciclesonide is pregna-1,4-diene-3,20-dione,16,17[[®-cyclohexymethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-,(11β,16α). The molecular weight is 540.7 and the molecular formula is $C_{32}H_{44}O_7$.

Figure 1. Chemical Structure of Ciclesonide



The ester moiety attached to carbon position 21 of ciclesonide is enzymatically cleaved *in vitro* and *in vivo* to provide an active metabolite, des-ciclesonide (C21-desmethylpropionyl-ciclesonide or C21-desisobutyryl-ciclesonide [abbreviated as RM1]). Tradename ciclesonide contains only the R-epimer of ciclesonide because it is more active than the S-epimer. The manufacturing controls, stability, and spray content uniformity of ciclesonide have all been reviewed by the Agency chemists and found to be acceptable. The excipients are all compendial *(see Chemistry Review for details).*

1200 mcg/day. On a mcg/cm2 nasal surface area basis the NOAELs in the rat and dog provided at 6.2 and 4.3-fold safety margin, respectively when compared to the proposed adult dose of 200 mcg/day.

3.2.3 Mutagenicity, Genotoxicity, and Reproductive Toxicity

In previous reviews the FDA toxicology reviewers have agreed with the applicant that the results of mutagenicity, genotoxicity, and reproductive studies are consistent with the know risks associated with corticosteroids.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

4.1.1 General

The review of efficacy was based exclusively on the reports of the clinical trials submitted with the original NDA application. The review of safety was based on the clinical trials and the 120-Day safety update. Brief summaries of the reviews of the preclinical and pharmacokinetic data that were made for were incorporated in the appropriate sections of this review.

4.2 Tables of Clinical Studies

Table 2a. Pivotal Trials

Study	Design	Allergic Rhinitis	Age	Dosage (mcg)	Freq	Time**	N*	Outcome
144/2005 (405)	R, DB, PC*	Perennial	2-5 years	25 100 200	QD	6 w	133	PK, PD safety
149/2005 (403)	R, DB, PC	Perennial	6-11 years	25 100 200	QD	12 w	665	PK, PD, TNSS
76-2004 (CL-002)	R, DB, PC Dose-ranging	Seasonal	18-66 years	25 50 100 200	QD	2 w	726	TNSS
287/2004 (401)	R, DB, PC	Seasonal	12-86 years	200	QD	4 w	327	TNSS
363/2004 (402)	R, DB, PC	Perennial	12-75 years	200	QD	6w	471	TNSS
146/2005 (404)	R, DB, PC	Perennial	12-73 years	200	QD	52 w	663 (2:1)	AEs including ocular and ENT, PD

* N = safety population.

Table 2b. Supportive Trials

Study	Design		Disease	Time**	N	Outcome
143/2005 (406)	R, DB, PC*	Pollen exposure in an EEC	Seasonal	SD	503	Onset
145/2005 (407)	R, DB, PC	Pollen exposure in an EEC	Seasonal	SD	420	Onset
147/2005 (408)	R, DB, PC	Ciclesonide+ concomitant beclomethasone	Perennial	6 w	111	PD
148/2005 (409)	R, DB, PC	Ciclesonide + concomitant fluticasone	Perennial	6 w	150	PD
202/2003 (CL-001)	R, DB, PC	Ciclesonide nasal spray at 50, 100, 200, 400, 800 mcg	Normal volunteers	2 w	48	PD

* R=randomized, DB=double-blind, PC= placebo controlled. ** Time = duration of treatment, W = weeks, SD=single dose

Table 2c. Trials Submitted but Not Reviewed

Study	Age	Design	Disease	Time**	n	Outcome
[redacted]						

4.3 Review Strategy

4.3.1 General Approach

Study #401 and 402 were reviewed in detail as the pivotal efficacy trials for adults with allergic rhinitis. Study 401 was conducted in subjects with SAR and 402 in subjects with PAR. The two, together meet the requirement for replication of the efficacy results. In study 404 adults with PAR were treated with ciclesonide or placebo for 52 weeks. Enough of the subjects treated with ciclesonide completed the year of follow-up to meet the ICH requirements for a long-term safety evaluations. As agreed to with the applicant in EOP2 and pre-NDA meetings, the assessment of the efficacy of ciclesonide nasal spray in children age 6 to 11 was based on a review of the single efficacy trial conducted in that age-group (403). The assessment of efficacy in the children age 2 to 5 was based on an interpretation of the results of the trials in the older age groups, and safety was assessed through a detailed review of study (405).

[redacted] The 120-safety update was reviewed, but no separate search of the AERS data base was made because no form of ciclesonide is marketed in the United States.

4.3.2 Notation

The data and tables in the review were taken from the body of the study reports unless otherwise noted. Specific pages in the study report are referred to by page number, as printed on the page, (i.e. 34/30164). The other primary sources of data are the post-text tables and the SAS transport data files. The post-text tables are referred to by the table number and the printed page number. The data files are referred as "...\tabulations\SAS transportfile name" or ...\analyses\SAS transport file name". Table 3 outlines the path whereby the data files can be found. All of the files in this submission are labeled N022004\submission number\module number\section: the original NDA is N022004\000, the safety update is in N022004 [redacted] and the sponsor's response to the DSI audit is in N022004 [redacted] All of the clinical reports are found in module 5. Figures and tables constructed by the reviewer are printed in italics and titled "*Reviewer Figure*" and "*Reviewer Table*".

The applicant presents all of the efficacy results as the difference between placebo and ciclesonide. In all but study 76-2004 (CL-002) the ciclesonide score is subtracted from placebo score. Since improvement is represented by a negative (fall in score) the difference between placebo and ciclesonide is a positive number if ciclesonide is superior. Study 76-2004 was performed early in the development program and is the only study where this convention was not followed. In this study the placebo score was subtracted from the ciclesonide score so that a difference between placebo and ciclesonide that was negative indicated superiority of ciclesonide. The calculation was performed variably for the safety data depending upon whether improvement was represented by a fall or increase in the variable of interest. If improvement was represented by a low number (IOP) the ciclesonide was subtracted from placebo whereas if improvement was represented by a high or increasing value (cortisol) the placebo value was subtracted from the ciclesonide value. In this way superiority of ciclesonide was always represented by a positive value for the difference between placebo and ciclesonide.

Table 3. Map of File Locations

Outline of Path Leading to Clinical Trial Reports (76-2004, 143-2005, 145-2003, 146-2005, 149-2005, 287-2004, 363-2004)	Explanation
N022004\000	Original NDA
...\000\m5	All Clinical Studies
...\m5\53-clin-stud-rep	All Safety and Efficacy Studies
...\53-clin-stud-rep\535-rep-effic-safety-stud	
...\535-rep-effic-safety-stud\allergic rhinitis	
...\allergic rhinitis\5351-stud-rep-contr	Controlled Clinical Trials
...\5351-stud-rep-contr\Study name	**All reports for each study**
...\Study name\files and folders	
Examples	**Explanation**
...\146-2005\	Study name
...\146-2005\146-2005-report-body-2.pdf	Body of study report
...\146-2005\datasets\tabulations\define.pdf	Data definition for tabulated data
...\tabulations\ae.xpt*	Listing of adverse events
...\146-2005\datasets\analyses\define.pdf	Data definition for analyzed data
...\analyses\re.xpt*	Listing of weekly mean r-TNSS
Outline of Path Leading to PD Trial Reports (Studies 144-2005, 147-2005, 148-2005)	**Explanation**
N022004\000	Original NDA
...\000\m5	All Clinical Studies
...\m5\53-clin-stud-rep	
...\53-clin-stud-rep\534-rep-human-pd-stud	All PD Studies
...\535-rep-human-pd-stud\5342-patient-pd-stud-rep	
...\5342-patient-pd-stud-rep\Study name	PD trials in patients
...\Study name\files and folders	**All reports for each study**

* The reference that is used in the text of the review.

4.4 Data Quality and Integrity

There was no apparent problem with data integrity at any of the sites that could be discerned from reading the reports. Three sites were chosen for on-site auditing on the basis that they enrolled a large number, or a crucial type of subjects. The sites chosen were as follows:

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

Site 5202 (Study 287/2004)
Investigator: Daniel V. Freeland, MD
8501 North Mopac Expressway, Suite 200
Austin, Texas 78759

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

Site 5724 was deemed to be of particular importance because all of the 2-5 year-olds were enrolled there. The study report for this site described a high degree of subject compliance and high completion rates. However, the DSI audit, conducted on May 2 – 16, 2006 suggested that this data was not as complete as described, and the site was issued a 483 that described multiple deficiencies. Observation #1 included enrollment of subjects who were taking prohibited medication at the time of enrollment (10 of 69 subjects audited) and inaccurate compliance assessments. Compliance was assessed, in part of the basis of medication bottle weight. Review of the recorded bottle weights showed that only 9 of 69 audited records were within the Applicant's pre-specified range of acceptability although all of the subjects were recorded as having completed the trial in compliance with the protocol. Observation #2 stated that the study medication had not been adequately accounted for. Both active and rescue medications bottles were to have been returned to the clinic at the end of the study. Specifically, [redacted] bottles of study medication and [redacted] bottles of rescue medication were unaccounted for. Observation #3 states that unused medication was not returned to the sponsor.

The Applicant submitted a response to the audit on June 21, 2006. They admitted that the identified subjects who had taken prohibited medications were enrolled inappropriately. They stated, however, that the prohibition was intended to eliminate drugs that could confound the efficacy analysis. Therefore, the inclusion of these subjects should not interfere with the safety analysis which was the primary objective of the trial. The sponsor

also noted that all of the medications were stopped at least 2 days prior to randomization, so the effects had probably worn off.

Reviewer: At least one of the drugs taken inappropriately was Rhinocort which could have effected the cortisol evaluation.

In response to deficiency #1B the Applicant noted that bottle weights were only a secondary measure of compliance and that the FDA should accept the diary record as the primary and accurate measure of compliance. They also noted that the protocol for determining 80% use of the medication may not have been correct. They did institute changes in monitoring and training to address the deficiency.

In response to deficiency #2 and 3, the Applicant provided a variety of explanations of what happened to the medication bottles that had not been accounted for. They also noted that the rescue medication was an over-the-counter product so lack of accountability would not affect patient safety any more "than what would be expected if the parent/caregiver chose to administer this medication to the child outside the confines of the clinical trial". To remedy the situation the responsible pharmacist was dismissed and additional training was provided for other clinic personnel.

Reviewer: The listed deficiencies show a serious lack of concern for following the protocol by the investigator at this site, and the Applicant's rejoinder suggests that they do not understand the importance of following the protocol.

At site 5202 minor omissions were described in 3 subjects and the observations that "diaries appeared to be pre-dated by staff, skin test results were read by a Cedra technician not by Dr. Freeland, patient randomization numbers were not allocated in sequential order" were made. The inspection was classified as VAI. The inspection of site 5203 revealed no irregularities and no FDA-483 was issued.

DSI reviewed the Applicant's response to the audit. In reference to site 5724 they noted that the Applicant's explanation for the errors and the plans to improve accounting in the future did not change the basic findings. The results of study #405 (Safety of Ciclesonide in 2 to 5 year olds with PAR) are based on subjects who were on prohibited medications after screening, bottle weights that were out of range suggesting non-compliance, and data that lacked quality control as shown by the failure to account for all of the medication dispensed. For these reasons, the conclusion of DSI was that "In general, the data appear unreliable at this site..

4.5 Compliance with Good Clinical Practices

On the title page of each clinical study there is a statement to the effect that the studies were conducted using Good Clinical Practices. In section 5.1 of each study there is the

statement that each study was approved by an appropriate IRB and was conducted according to the Helsinki Convention.

4.6 Financial Disclosures

The financial disclosure forms indicate that Teijin Pharma Ltd as well as ALTANA Pharma sponsored the clinical trials. All of the investigators signed forms indicating that they had no financial interest in ALTANA. However, Teijin Pharma Ltd was added as a sponsor later and the financial disclosure forms had to be signed a second time to include interests in Teijin. This second request for information failed to obtain a response from 8 investigators. Most of the failures were because the investigator had left the original institution. The investigators who could not be contacted participated in study 404 (n=4) and 402 (n=4). Each of the non-responding investigators was located at a different site except for 2 in study 402 who were located at the University of Wisconsin Medical School. While one of the investigators listed as not responding in study 404 enrolled 30 subjects and another enrolled 25, the number is still probably too low to affect the outcome of the studies. Study 404 enrolled 663 subjects at 35 sites in the United States. Teijin Pharma was not involved in the conduct of any of these studies.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The pharmacokinetics of oral, inhaled, and intravenously administered ciclesonide were extensively reviewed for . In brief, after oral inhalation of single doses of 360 mcg by normal volunteers, the C_{max} of ciclesonide and M1 (the active component) occurred at 0.25 and 1.1 hours respectively. The mean $AUC_{0-\infty}$ of M1 (1.72 ng•hr/ml) ranged from 2.5 to 3-fold higher than that observed for the parent drug. However, the C_{max} (0.3 ng/ml) was 3.5-fold lower than the parent drug. The mean C_{max} and $AUC_{0-\infty}$ of M1 following multiple doses of ciclesonide 360 mcg QD increase up to 26% compared to those after single administration. The T_{max} was similar to that after single dose administration and it is estimated that the time to reach steady-state would be within 2 – 3 days. The M1 half-life increased from 5.2 to 6.7 hours. Following multiple doses of ciclesonide (250 and 1000 mcg BID), C_{max} and AUC were both dose proportional.

Radioactive ciclesonide was predominantly excreted through the faeces, both after oral (77.9%) and IV (65.95%) administration. The biotransformation of ciclesonide is catalyzed by an esterase which has not been identified. M1 appears to be the major metabolite after esterification, however, mass balance studies showed that only 20% of the total plasma radioactivity corresponds to M1. M9, another metabolite whose pharmacologic potency is unknown, was found in plasma in concentrations equal to those of M1, so it appears that the full range of potentially active metabolites has not be characterized to date. M1 is esterified to form fatty acid conjugates in the lung when it is administered by inhalation.

The reaction is catalyzed by CYP3A4 (83%), CYP2D6 (~30%), and CYP2C8 (~11%), although the exact role of each enzyme had not been completely elucidated. M1 does not produce significant inhibition (<25%) of major cytochrome P450 enzymes. The systemic exposure to ciclesonide and M1 after a single inhaled dose of 800 mcg ciclesonide in healthy subjects did not change during co-administration with a single dose of erythromycin 500 mg

Blood levels were obtained for ciclesonide and the M1 metabolite after nasal inhalation in studies 405, 403, and CL-001 submitted in the current application. The parent compound was essentially undetectable in all of the studies. In healthy adults given doses of 2 and 4 times greater than the dose proposed for the rhinitis indication, blood levels were detectable in 67 and 83% of the subjects, respectively (Table 4). At the recommended dose of 200 mcg once daily, none of the adult subjects had detectable levels. Of note, the subject with SAR had M1 detectable less often (50%) than healthy volunteers (83%) given the same dose. In the children 6 – 11 years of age 50% of those who were treated with the recommended 200 mcg dose had M1 detected in the blood. The maximum level was 44.9 pcg/mL. The 2-5 year-olds had M1 detected in a minority of subjects when they inhaled 25 or 100 mcg ciclesonide. At the 200 mcg dose level 41% had detectable levels. The maximum level was 64.5 pcg/mL. The maximum levels are an order of magnitude lower than the maximum levels seen after inhalation therapy (See above).

Table 4. Blood levels of the primary metabolite (M1) of ciclesonide after nasal inhalation

Study	Subject	N	Dose (mcg)	Days	Percent with Detectable M1	Median* C_{max}	Max* C_{max}
CL-001	Adult SAR	8	800	14	50	<12.9	16.3
		8	800	14	83	17.0	28.8
	Healthy	8	400	14	67	11.5	29.1
	Adult	8	200	14	0	<10	<10
403		16	200	84	50	<10.3	44.9
	6-11 y o	20	100	84	5	<10	13.1
	PAR	19	25	84	0	<10	<10
405		30	200	42	41	<10	39.1
	2-5 y o	30	100	42	22	<10	36.1
	PAR	31	25	42	13	<10	64.5

* Cmax in pg/mL. The lower limit of detection is 10 pg/mL

5.2 Pharmacodynamics

The HPA-axis was evaluated in adults in study 404, 408, 409, and CL-001 and in both of the pediatric trials (405 and 403). In adults with PAR treated for one year, the fall in plasma cortisol was slightly (-1.1 mcg/day) but not statistically significantly greater than the fall after placebo treatment (-0.4 mcg/Day) (Table 5). In study CL-001 subjects were treated for only two weeks and there was no dose ordering of the change in plasma cortisol.

In the 8 normal volunteers treated with 800 mcg ciclesonide daily the urinary cortisol increased (0.4 mcg/Day) compared to a fall (-0.8 mcg/Day) in the placebo-treated subjects. On the other hand, the adult SAR subjects who were treated with 800 mcg had a greater fall (-1.0 mcg/day) despite the fact that fewer had ciclesonide detected in the blood than the normal volunteers that received the same dose (Table 4).

Table 5. LS Mean (SE) Change in Plasma Cortisol (mcg/dL) During Treatment with Ciclesonide Nasal Spray

Study	N* (Cicles/Plbo)	Age (years)	Duration (Weeks)	Dose mcg	Ciclesonide	Placebo	Treatment Difference (95% CI)
404	193/93	≥12	52	200	-1.1 (0.42)	-0.4 (0.60)	-0.7(-2.0, 0.60)
CL-001	8/8	≥ 18	2	800**	-1.0	1.3	-2.3
				800	0.4	-0.8	1.2
				400	-0.5		0.3
				200	0.9		1.8
				100	-3.6		-2.8
				50	0.9		1.7
405	45/47	6-11	12	200	0.74	0.39	0.35 (-1.4, 2.1)
	61/47			100	0.51		0.12 (-1.5, 1.7)
	51/47			25	0.01		-0.38 (-2.1, 1.3)
403	28/30	2-5	6	200	-1.07	-0.03	-1.04 (-2.7, 0.7)
	27/30			100	-0.39		-0.36 (-2.1, 1.4)
	28/30			25	-0.15		-0.12 (-1.8, 1.6)

* Number of ciclesonide/number of placebo subjects treated. ** Subjects with SAR. The others were normal volunteers

In the 6 to 11 year-olds, all of the mean plasma cortisol levels were elevated at the end of 12 weeks when compared to baseline, but none of the differences was statistically significant. By comparison, the plasma cortisol fell in a dose ordered manner in the 2 to 5-year olds. The differences were small (-1.04, -0.36, and -0.12 comparing placebo to 200, 100, and 25 mcg ciclesonide, respectively) and the range in values was quite broad.

Table 6. Twenty-four hour urine for cortisol (mcg/Day)

Study	N (Cicles/Plbo)	Age (years)	Duration (Weeks)	Dose mcg	LS mean Ciclesonide	Placebo	Treatment Difference (95% CI)
CL-001	8/8	≥ 18	2	800**	-2.5	-5.4	1.9
				800	-1.3	-1.2	-0.1
				400	-0.0		1.2
				200	-1.1		0.1
				100	1.2		2.4
				50	-0.6		0.5
403	35/47	6-11	12	200	-1.69	-0.9	-0.81 (-4.0, 2.4)
	44/47			100	-0.96		-0.08 (-3.1, 2.9)
	32/47			25	-2.99		-2.11 (-5.3, 1.1)
405	22/30	2-5	6	200	-3.55	-1.51	-2.04 (-4.4, 0.3)
	15/30			100	-3.47		-1.96 (-4.5, 0.6)
	16/30			25	-3.27		-1.76 (-4.3, 0.8)

** Subjects with SAR. The others were normal volunteers

The 24-hour urinary excretion of cortisol was measured in the 1-year adult PAR safety study. However, there was no assessment of the adequacy of the urine samples, so the results could not be interpreted. In the high-dose, 2-week study in adults (CL-001) the urinary cortisol fell to a relatively large degree in both placebo and ciclesonide 800 mcg-treated subjects with SAR with a smaller decrease in the ciclesonide-treated subjects (Table 6). In the remainder of the subjects the changes were small and there was no dose-ordering over a range of 50 to 800 mcg daily ciclesonide. As in the 1-year safety study, there was no assessment of the adequacy of the urine collection. However, the subjects stayed in the clinic for the 24 hours of the collection which should have improved the adequacy of the collection. On the other hand, the placebo subjects had a greater decrease than was seen in any other study in this submission which could be due to incomplete collections. At most, one can say that there is no evidence of adrenal suppression by these measures even at a dose that is four times that recommended for allergic rhinitis.

In both of the pediatric studies the adequacy of the urine collections was assessed with urinary creatinine measurement with minimal accepted values taken from the literature. In the 6 to 11 year-olds the 24-hour excretion decreased more in the ciclesonide- than placebo-treated subjects, although the differences were small between placebo and ciclesonide and not dose ordered. Unfortunately, 10.4% of the cortisol excretion values were abnormally low at baseline (4, 4, 2, and 5 in the ciclesonide 200, 100, 25, and placebo groups) despite the requirement for a normal urine volume. The Applicant took a value of 7 mcg/Day as the lower limit of normal for cortisol excretion. Using this cutoff 16.1, 17.5, 30.0, and 21.4% of the ciclesonide 200, 100, 25, and placebo subjects, respectively, who were normal at baseline were abnormal at the end of the study. While it is reassuring that the incidence of abnormality was not dose related, the overall high incidence suggests that the data are not reliable. In the 2 to 5 year-olds the fall in urinary cortisol was larger than in the older subjects and minimally dose ordered. Again, the range of values was wide in this very small sample (15 – 30 subjects per group). While the DSI audit has suggested that the data from study 405 (2-5 year olds) is not reliable, the urine samples were obtained while the subjects were domiciled in the clinic and inadequate samples were excluded. This may make them more reliable than the data obtained while the subjects were out-patients.

The applicant submitted two studies (408 and 409) in which ciclesonide or placebo was administered concomitantly with an inhaled corticosteroid: budesonide 320 mcg BID or fluticasone/salmeterol 500/50 mcg BID. In both studies the run-in, during which the subject inhaled the corticosteroid without concomitant nasal spray, was only 10 days long. In both studies the plasma cortisol AUC and 24-hour urinary cortisol fell during therapy with the inhalation aerosol (approximately 60 mcg•hr/dL in the plasma and 16 mcg/Day in the 24-hour urinary excretion). During randomized therapy with budesonide and concomitant ciclesonide or placebo nasal spray, the urinary excretion of cortisol decreased by 13.6 and 11.4 mcg/day, respectively. During randomized therapy with fluticasone/salmeterol and concomitant ciclesonide or placebo nasal spray, the plasma cortisol AUC decreased by 12.7 and 15.7 mcg•hr/dL, respectively. The Applicant has interpreted these findings as showing no effect of ciclesonide on the HPA-axis when

administered with budesonide or fluticasone/salmeterol inhalation aerosols. However, the decrease in urinary and plasma cortisol measures during the randomized treatment phase, in subjects randomized to placebo nasal spray suggests that the adrenal axis was undergoing continued, progressive suppression from the inhalation aerosol therapy. It is possible that a relatively weak effect of ciclesonide on the adrenal was masked with this study design. The studies were not adequately designed to demonstrate the combined inhalation and nasal corticosteroid effect as opposed to the nasal inhalation alone and not comment related to these studies should occur in the label.

5.3 Exposure-Response Relationships

Exposure-Response relationships were not formally addressed in this application. Exposure to ciclesonide and the M1 metabolite is very low, often undetectable, after intranasal exposure to ciclesonide nasal spray.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Tradename Nasal Spray is indicated for the treatment of [redacted] (b) (4) seasonal and [redacted] (b) (4) allergic rhinitis in [redacted] (b) (4) years of age and older.

6.1.1 Methods

Efficacy was assessed with randomized, placebo-controlled, double-blind clinical trials.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint in all of the studies of subjects older than 5 years was some form of the patient 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 and of symptoms recalled over various periods of time. In the adult dose-finding (CL-002) and pivotal trials (#401 and 402) the reflective TNSS (r-TNSS) was measured twice daily. For the analysis in the pivotal trials, the AM and PM 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 CL-002 (dose-finding) only, the AM and PM scores were summed. In the efficacy trial in 6 to 11 year-olds (#403) the average of the AM and PM 12-hour r-TNSS was also used as the primary efficacy outcome. However, the recordings could have been made by the subject or the care-giver, and there is no indication in that the reporter was consistent throughout the trial.. In the 1-year safety study in adults (#404) and the safety study in 2 to 5 year-olds (#405), efficacy was not the primary outcome, however the r-TNSS was recorded once daily. In both of these trials, the daily recordings were averaged weekly and

these weekly averages were compared to the recordings averaged over the 7 days prior to randomization.

Secondary efficacy measurements included the instantaneous TNSS (i-TNSS) and a Physicians Assessment of Overall Nasal Signs and Symptoms Severity (PANS). The instantaneous score was described as "an evaluation of the symptom severity at the time of the evaluation" in the pivotal efficacy trial, but this same score was used to record symptoms over a ten-minute period in the onset of action studies performed in the EEC. The PANS was made up of a Nasal Symptom Score which included the same 4 symptoms that were recorded by the subject in the diary and a Nasal Sign Score. The Nasal Sign Score consisted of 4 additional physician-assessments: discoloration of nasal passages, swollen nasal passages, presence of secretions, and evidence of post-nasal drip and/of throat irritation. The four components of the Signs and Symptoms Scores were summed individually and the two scores averaged for the final PANS. There is no indication as to the time frame of the physician's assessed symptom score except in study 403 (children 6-11 years of age) where it is stated that the subject/care-giver was asked to recall the symptoms over the prior week. The PANS was a key secondary outcome in the two pivotal adult trials and the 1-year adult safety follow-up. In the pivotal pediatric trials (#403, 405) only the Nasal Symptom Score (without nasal signs) was designated as the efficacy variable (primary in 405 and secondary in 403). In the adult trials a Rhinitis Quality of Life Questionnaire (RQLQ) was also administered.

6.1.3 Study Design

All of the trials in this submission were randomized, double-blind, and placebo controlled. The subjects had a diagnosis of seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR). In all of the SAR trials and in the PAR trials conducted in subjects ≥ 12 years of age, the minimum duration of symptoms was 2 years. In the children 6 - <12 years symptoms were required for a minimum of 6 months and for the subjects 2 to 5 years of age symptoms were required for only 3 months. All of the subjects in the efficacy trials were symptomatic and all of the subjects had evidence of allergies (positive skin tests or RAST) to appropriate antigens. There were two different types of SAR subjects. The adult dose-ranging and efficacy trial were performed in a restricted area in South Central Texas and all of the subjects were allergic to Mountain Cedar pollen. Ambient pollen counts were made throughout the study. The onset of action studies were conducted in two different environmental exposure chambers (EEC) in Canada, and all of the subjects were allergic to ragweed pollen. The level of ragweed pollen was controlled and monitored throughout the exposures. The PAR subjects were allergic to a wide variety of antigens, but the majority (>60%) were allergic to some form of mite. The trials were adequately powered to assess efficacy in the subjects age 6 and above: all enrolled >100 subjects in each treatment group and the follow-up and compliance were good. In one trial designed to support efficacy in subjects 2 – 5 years of age, only 33 subjects per dose were treated. While no statistical inference was performed on this data it was difficult to even make qualitative judgments because of the variability in the data.

In a preliminary dose-ranging study it was determined that 200 mcg once daily was the most effective dose in adults and 200 mcg was the only dose administered to adults in the subsequent trials. In children <12 years of age, 25 and 100 mcg were administered in addition to the 200 mcg dose.

The duration of the trials was adequate to demonstrate efficacy: At least two weeks for seasonal rhinitis and 6 weeks for perennial rhinitis. Some of the trials were carried out over longer periods of time, but the primary efficacy evaluation was performed at the two and six week time periods.

The onset of action was demonstrated using environmental exposure chambers. Subjects were primed prior to the test exposure. On the test day, the subjects were exposed continuously to a standard dose of pollen for two hours. At the two hour time point, they were treated with 200 mcg ciclesonide and the i-TNSS was recorded hourly for the subsequent 12 hours.

6.1.4 Efficacy Findings

6.1.4.1 Adults and Adolescents

In a single dose-finding study (CL-002), adults (> 18 years of age) with SAR were treated with 25, 50, 100, and 200 mcg ciclesonide nasal spray once daily for 2 weeks. The primary efficacy variable was the sum of the AM and PM, 12-hour reflective TNSS (r-TNSS). The improvement in r-TNSS was statistically significantly better after the 200 mcg dose of ciclesonide than after treatment with placebo nasal spray (Table 7).

Table 7. Reflective TNSS after 2 Weeks of Treatment with Ciclesonide Nasal Spray*

Ciclesonide Dose (mcg daily)	N	TNSS** Baseline	Difference from Placebo Estimate	95% Confidence Interval	p-value
200	144	18.8 (3.3)			
100	145	18.7 (3.4)			
Placebo	148	17.8 (3.4)			
		Change from Baseline			
200	144	-5.8 (4.6)	-1.35	-2.41, -0.23	0.012
100	145	-5.3 (5.1)	-0.88	-1.93, 0.17	0.099
Placebo	146	-4.2 (4.7)			

*The difference between ciclesonide and placebo is calculated as ciclesonide – placebo in contrast to the other efficacy studies where the difference was calculated as placebo-ciclesonide. In this study, only, a negative value for the difference indicates superiority of ciclesonide.
** LS mean (SD)

There were two pivotal trials in subjects 12 years of age and older, one in subjects with SAR (#401) and one in subjects with PAR (#402). In both, a statistically significantly greater decrease (improvement) in the mean of the AM and PM 12-hour reflective TNSS was shown comparing ciclesonide 200 mcg once daily to placebo. In the subjects with SAR the r-TNSS decreased by a LS mean (95% CI) of 0.9 (0.45, 1.36) points and the

immediate TNSS decreased by a LS mean (95% CI) of 0.88 (0.44, 1.31) points more in the ciclesonide than the placebo subjects. In the subjects with PAR the r-TNSS decreased by a LS mean (95% CI) of 0.63 (0.28, 0.97) points and the immediate TNSS decreased by a LS mean (95% CI) of 0.54 (0.21, 0.88) points more in the ciclesonide than the placebo subjects (Table 8). The individual components of the symptom scores showed changes of similar magnitude.

Table 8. Reflective TNSS after Treatment of Adults with Ciclesonide or Placebo

Subjects with SAR (Study 401)	Ciclesonide 200 mcg N = 162	Placebo N=162	Treatment Difference (95% CI)	p-value
Average AM and PM r-TNSS				
Baseline, Mean (SD)	8.96 (1.96)	8.83 (1.82)		
Change from Baseline (LS mean [SE])	-2.40 (0.16)	-1.50 (0.16)	0.90 (0.45, 1.36)	<0.001
Average AM and PM i-TNSS				
Baseline, Mean (SD)	8.40 (2.24)	8.33 (2.08)		
Change from Baseline (LS mean [SE])	-2.15 (0.16)	-1.28 (0.16)	0.88 (0.44, 1.31)	<0.001
Subjects with PAR (Study 402)	Ciclesonide 200 mcg N = 232	Placebo N=229	Treatment Difference (95% CI)	p-value
Average AM and PM r-TNSS				
Baseline, Mean (SD)	7.59 (2.04)	7.72 (2.14)		
Change from Baseline (LS mean [SE])	-2.51 (0.12)	-1.89 (0.13)	0.63 (0.28, 0.97)	<0.001
Average AM and PM i-TNSS				
Baseline, Mean (SD)	7.07 (2.25)	7.09 (2.27)		
Change from Baseline (LS mean [SE])	-2.22 (0.12)	-1.68 (0.12)	0.54 (0.21, 0.88)	0.001

Secondary outcomes in both of the pivotal trials included the physician's assessment (PANS) of signs and symptoms and the results of a rhinitis quality of life questionnaire (RQLQ). In the subjects with SAR the values of both variables were very similar in the two treatment groups (Table 9).

Table 9. Physician's Assessment and Quality of Life Assessment after Treatment of Adults

Subjects with SAR	Ciclesonide 200 mcg N = 151	Placebo N=152	Treatment Difference (95% CI)
PANS			
Baseline, Mean (SD)	7.97 (1.58)	8.07 (1.44)	
Change from Baseline (LS mean [SE])	-1.98 (0.16)	-1.99 (0.16)	-.01 (-0.13, 0.49)
Combined Adult and Adolescent RQLQ			
Baseline, Mean (SD)	3.96 (1.05)	3.78 (0.98)	
Change from Baseline (LS mean [SE])	-1.39 (0.11)	-1.21 (0.11)	0.18 (-0.13, 0.24)
Subjects with PAR	Ciclesonide 200 mcg N = 233	Placebo N=230	Treatment Difference (95% CI)
PANS			
Baseline, Mean (SD)	6.91 (1.98)	6.81 (2.05	
Change from Baseline (LS mean [SE])	-2.05 (0.15)	-1.67 (0.15)	0.38 (0, 0.76)
Combined Adult and Adolescent RQLQ	N=211	N=202	
Baseline, Mean (SD)	3.32 (1.08)	3.38 (1.10)	
Change from Baseline (LS mean [SE])	-1.30 (0.08)	-1.01 (0.08)	0.28 (0.07, 0.50)

In the subjects with PAR, the improvement was very slightly greater in the ciclesonide-treated subjects.

In the one-year safety study in subjects with PAR (#404) all of the efficacy variables were considered to be secondary. The results, however, were very similar to the results of the 6-week pivotal trial. The 24-hour r-TNSS, measured once daily, improved by a LS mean (95% CI) of 0.60 (0.3, 0.9) points more in the ciclesonide-treated subjects than in those who received placebo (Table 10). The physician's assessment showed similar changes in both treatment groups and the RQLQ was slightly more improved in the ciclesonide group.

Table 10. Response to Treatment of Adults with PAR for 52 Weeks with Ciclesonide

Variable	Ciclesonide 200 mcg N = 435	Placebo N=229	Treatment Difference (95% CI)
Average 24-hour r-TNSS			
Baseline, Mean (SD)	6.4 (2.9)	6.3 (2.9)	
Change from Baseline (LS mean [SE])	-2.3 (0.09)	-1.8 (0.13)	0.6 (0.3 0.9)
PANS	N = 438	N=220	
Baseline, Mean (SD)	5.85 (2.3)	5.80 (2.2)	
Change from Baseline (LS mean [SE])	-1.78 (0.11)	-1.76 (0.15)	0.01 (-0.33, 0.35)
Combined Adult and Adolescent RQLQ	N=395	N=202	
Baseline, Mean (SD)	2.87 (1.18)	2.81 (1.16)	
Change from Baseline (LS mean [SE])	-1.1 (0.06)	-0.88 (0.08)	0.19 (0.01, 0.36)

There is no quality of life claim in the label for either of the patient groups.

6.1.4.2 Onset of Action

Two studies with an identical design were conducted with the specific objective of determining the onset of action of ciclesonide nasal spray (#406, 407). In each, subjects with SAR were primed with Ragweed antigen, exposed to Ragweed pollen in an environmental exposure chamber (EEC), and then randomized to treatment with 200 mcg ciclesonide or placebo. The immediate (including 10 minutes prior to the evaluation) TNSS was recorded hourly after administration of the randomized treatment. In study 406 (251 subjects in each treatment group), the response was uniformly in favor of ciclesonide treatment with the difference in TNSS between 0.5 and 0.9 points (Table 11). All of the differences were statistically significant. Study 407 (210 subjects per treatment group) had an identical study design, however, the results showed almost no difference in the change in TNSS between the two treatment groups. Only a single value at 6 hours post-dose was statistically significant by the pre-set rules of the analysis. The two studies were identical in terms of inclusion criteria, however, they were performed at different sites and enrolled subjects with different ethnic backgrounds. The population in 406 was 61% Caucasian, 29% Black, and 12.4% Asian, while the population in 407 was 96% Caucasian. Over 10% of the population in 406 had participated in previous clinical trials of experimental medication for rhinitis as compared with none of the subjects in study 407. Thus variability in the two populations could be partly responsible for the variable results. On the other hand, the data from study 406 appeared to be somewhat less reliable (more large skin test

reaction to the control diluent and more out of range pollen measurements during the exposure) than those from study 407. In either event, the early onset of action was not replicated.

In the pivotal efficacy studies (#401, 402) the instantaneous TNSS was obtained hourly from 4 to 12 hours after the first dose of randomized medication and again 24 hours after the dose. In these studies no onset of action could be determined. In both studies there was a single time point when the difference between placebo and ciclesonide was statistically significant (Table 11). Since the definition of onset of action included a requirement for persistence of the effect, the onset of activity was not seen within the 12 hours of follow-up.

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Table 11. Change in Immediate TNSS after first dose of Ciclesonide 200 mcg or Placebo

	Environmental Exposure Chamber								Pivotal Efficacy Trials					
	Study 406 (SAR)				Study 407 (SAR)				Study 401 (SAR)			Study 402 (PAR)		
Time	Cicles[1]	Plbo[2]	Difference[3]	p-val[4]	Cicles[1]	Plbo[2]	Difference[3]	p-val[4]	Cicles[1]	Plbo[2]	p-val[5]	Cicles[1]	Plbo[2]	p-val[5]
Baseline	9.9 (1.9)	9.9 (1.9)			9.7 (1.7)	9.7 (1.6)			8.2	7.9		6.8	6.7	
Hour1	**-2.3 (0.15)**	**-1.8 (0.15)**	**0.5 (0.08, 0.93)**	**0.010**	-2.8 (0.17)	-2.7 (0.17)	0.1 (-0.38, 0.57)	0.35	---	---	---	---	---	---
Hour 2	**-2.1 (0.16)**	**-1.6 (0.16)**	**0.5 (0.03, 0.90)**	**0.018**	-3.7 (0.20)	-3.6 (0.16)	0.1 (-0.44, 0.68)	0.33	---	---	---	---	---	---
Hour 3	**-2.0 (0.17)**	**-1.5 (0.17)**	**0.5 (0.07, 1.00)**	**0.012**	-4.3 (0.20)	-3.9 (0.20)	0.4 (-0.19, 0.94)	0.098	---	---	---	---	---	---
Hour 4	**-2.0 (0.16)**	**-1.3 (0.16)**	**0.7 (0.21, 1.10)**	**0.002**	-4.0 (0.21)	-3.6 (0.21)	0.4 (-0.18, 1.02)	0.084	-1.8	-1.3	0.088	-1.3	-1.3	0.872
Hour 5	**-1.8 (0.16)**	**-1.2 (0.16)**	**0.6 (0.11, 1.02)**	**0.008**	-3.5 (0.22)	-3.2 (0.22)	0.4 (-0.22, 0.99)	0.11	-1.9	-1.8	0.671	-1.5	-1.4	0.712
Hour 6	**-1.8 (0.16)**	**-1.0 (0.16)**	**0.7 (0.27, 1.18)**	**<0.001**	**-3.8 (0.23)**	**-3.1 (0.23)**	**0.7 (0.06, 1.32)**	**0.016**	-2.3	-1.8	0.148	-1.7	-1.6	0.623
Hour 7	**-1.6 (0.16)**	**-1.1 (0.16)**	**0.5 (0.06, 0.97)**	**0.014**	-3.7 (0.23)	-3.1 (0.23)	0.6 (-0.00, 1.27)	0.025	-2.3	-2.1	0.554	-1.9	-1.7	0.371
Hour 8	**-1.6 (0.16)**	**-0.9 (0.16)**	**0.7 (0.23, 1.13)**	**0.001**	-3.3 (0.23)	-2.7 (0.23)	0.5 (-0.11, 1.17)	0.051	-2.3	-2.2	0.673	-1.9	-1.6	0.312
Hour 9	**-1.5 (0.16)**	**-0.7 (0.16)**	**0.8 (0.35, 1.22)**	**<0.001**	-3.1 (0.22)	-2.8 (0.22)	0.4 (-0.27, 0.98)	0.13	-2.1	-1.8	0.258	**-1.9**	**-1.4**	**0.034**
Hour 10	**-1.6 (0.16)**	**-0.7 (0.16)**	**0.9 (0.46, 1.36)**	**<0.001**	-2.9 (0.23)	-2.7 (0.23)	0.3 (-0.35, 0.93)	0.19	-2.2	-1.7	0.121	-1.8	-1.5	0.155
Hour 11	**-1.3 (0.16)**	**-0.5 (0.16)**	**0.8 (0.38, 1.28)**	**<0.001**	-2.9 (0.23)	-2.6 (0.23)	0.3 (-0.37, 0.90)	0.21	-2.1	-1.5	0.056	-1.8	-1.4	0.124
Hour 12	**-1.4 (0.17)**	**-0.5 (0.17)**	**0.9 (0.41, 1.34)**	**<0.001**	-2.9 (0.22)	-2.5 (0.17)	0.4 (-0.21, 1.04)	0.10	**-1.9**	**-1.2**	**0.022**	-1.7	-1.3	0.082
Hour 24	---	---	---	---	---	---	---	---	-0.7	-0.4	0.293	-0.7	-0.5	0.122

1 – Cicles = instantaneous TNSS during treatment with ciclesonide 200 mcg daily. Baseline is absolute score. All others are LS mean change from baseline.
2 – Plbo = instantaneous TNSS during treatment with placebo once daily. Baseline is absolute score. All others are LS mean change from baseline.
3- Difference in change from baseline comparing placebo and ciclesonide
4 – One-sided p-value of the difference between placebo and ciclesonide 5- Two-sided p-value for the difference

1 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Medical-*_____

The study in children 2 to 5 years of age was underpowered to demonstrate efficacy and the results are not helpful in an efficacy assessment. In addition, due to the DSI audit of the single site that enrolled 2 – 5 year-olds, there is a lack of confidence in the adequacy of follow-up and compliance with the medication regimen. Lastly, because efficacy was not demonstrated in 4 to 11 year-olds, it can not be extrapolated to the younger children.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The applicant performed an integrated analysis of the following 10 studies: CL-002, 401, 402, 403, 404, 405, 406, 407, 408, and 409. This pooling combines pediatric and adult populations and two studies (408 and 409) where inhaled corticosteroids were administered concomitantly with ciclesonide. For some of the assessments the 1-year safety study in adults (404) was omitted and in other summations the EEC, single-dose studies were omitted. In addition to adverse events, ENT examination, vital signs, and laboratory examinations were performed on all subjects. In some of the studies the HPA-axis was also assessed with plasma cortisol and urine 24-hour cortisol determinations (Reviewed in Section 5.2, pg 31 above).

7.1.1 Deaths

There were no deaths in any of the studies reviewed for this NDA.

7.1.2 Other Serious Adverse Events

There were a total of 31 serious adverse events (24 ciclesonide and 7 placebo) in the 11 trials that were reviewed. None was likely to have been related to drug treatment, and 22 of the 31 occurred in the one year safety follow-up. The one-year follow-up randomized subjects in a 2:1 ratio of ciclesonide:placebo and the pediatric trials used multiple doses of ciclesonide so the total number of subjects treated with ciclesonide was 2612 and the total treated with placebo was 1556. Thus the overall incidence of SAEs was 0.9% and 0.4% in the ciclesonide and placebo subjects, respectively. In the subjects who received 200 mcg of ciclesonide, the incidence was 1.2%. This seeming dose-response should be interpreted in light of the fact that 346/1316 (26.35%) of the subjects treated with ciclesonide 200 mcg and 169/1095 (15.4%) of the placebo subjects were treated for over 6 months, and treatment with the other doses was limited to 12 weeks for most of the subjects. Thus the small difference in incidence of SAEs could be explained by the increased exposure of the subjects who received 200 mcg daily. Most of the serious events occurred singly, but there were two cases of cholecystitis, two of abdominal pain, 3 pneumonias and 4 cases of depression/suicidal ideation/suicide attempt in the ciclesonide 200 mcg-group. The placebo subjects had two cases of coronary artery disease, two of traumatic fractures and single incidences of basal cell carcinoma, hypersensitivity and Brugada syndromes. None of these conditions other than pneumonia

are customarily thought to be associated with corticosteroid use, and two of the cases had associated asthma which could have been a predisposing factor. The incidence of 4 suicidal ideation/depression/suicide attempts in this otherwise healthy population seems high. However, three of the four subjects with this complaint were on chronic therapy for psychiatric disorders prior to enrollment in the studies.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The incidence of early withdrawal was similar in the ciclesonide 200 (11.6%) and placebo subjects (10.1%). The lower incidence in the ciclesonide 25 (8.3%), 50 (2.8%), and 100 groups (6.4%) is probably a reflection of the fact that these doses were only used in short term studies. Comparing the subjects who received 200 mcg ciclesonide to those who received placebo, the distribution of indications for early withdrawal was similar.

7.1.3.2 Adverse events associated with dropouts

Overall, the rate of withdrawal due to adverse events was the same in the placebo (2.4%) and 100 and 200 mcg ciclesonide groups (2.3% each). The lower rate in the ciclesonide 25 (1.4%) and 50 groups (0.7%) may reflect the shorter exposure to these doses (Table 19). In the ciclesonide 200 mcg subjects the most common adverse events resulting in withdrawal were asthma, epistaxis, upper respiratory infection, pregnancy, and sinusitis (0.2% each). In the placebo subjects the most frequent were asthma (0.4%), upper respiratory infection (0.2%) and sinusitis (0.2%). All other events occurred in less than 0.2% percent of subjects.

7.1.3.3 Other significant adverse events

No other significant adverse events were described in the application.

7.1.4 Other Search Strategies

No other search strategy was employed

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In section 3.2.1 of the ISS (pg 42/6837) the method for assessing adverse events is described as follows:

> "Patients were instructed to inform the investigator of any and all untoward effects felt during a study. In all repeat dose studies (Multidose AR Studies),

> patients (or caregivers) were instructed to record all medical problems on their diary cards, and these were reviewed by the investigator at clinic visits. *If these were considered to be adverse events* (AEs), these were recorded in the case report form (CRF). In addition, patients were queried during every clinic visit as to any adverse effects since the last visit. *Information that was considered an AE by site personnel was to be noted on the CRF.* Only AEs recorded in the CRF were used for assessing AEs during the trials....An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product." Emphasis added.

It is not specified how an event recorded in the diary would not be considered an adverse event.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

While compiling of the data, the applicant noted a variable description for what appeared to be the same entity. For that reason, they combined some of the preferred terms. Table 14 describes the combined terms.

Table 14. Applicant Grouping of Preferred Terms in ISS

Related Preferred Terms	Combined Term
Nasal passage irritation and Nasal discomfort	Nasal passage irritation
Pharyngitis and Pharyngolaryngeal pain	Pharyngitis
'Preferred term' and 'Preferred term' NOS (e.g. Urticaria and Urticaria NOS, Vomiting and Vomiting NOS, etc)	'Preferred term' (e.g Urticaria, Vomiting, etc)

Reviewer: It is unclear how the grouping was used because Table 18 (pg 66/6738) in the ISS (Reproduced as Table 17 in this review) uses both pharyngitis and pharyngolaryngeal pain and Upper respiratory tract infection and upper respiratory tract infection, NOS)

In addition, some of the preferred terms were coded to two different system organ categories (SOC). This dual listing (Table 15) was maintained for the following preferred terms and SOCs:

Table 15. Preferred Terms that are Included in More than One SOC

Preferred term	SOC
Contusion	Injury, poisoning, procedural complications Skin and subcutaneous tissue disorders
Dysgeusia	Gastrointestinal disorders Nervous system disorders
Facial pain	General disorders and admin site conditions Musculoskeletal and connective tissue disorders
Fall	General disorders and admin site conditions Injury, poisoning, procedural complications
Gastroenteritis viral NOS	Gastrointestinal disorders Infections and infestations
Nasopharyngitis	Infections and infestations Respiratory, thoracic and mediastinal disorders
Pharyngitis	Infections and infestations Respiratory, thoracic and mediastinal disorders
Urticaria NOS	Immune system disorders Skin and subcutaneous tissue disorders
Vertigo	Ear and labyrinth disorders Nervous system disorders

Tables that include SOC and the above preferred terms have the preferred term listed in both SOC.

7.1.5.3 Incidence of common adverse events

In general, the incidence of common adverse events increased with the duration of the trial. In study 405 the 2 – 5 year olds had a relatively low incidence, possibly because of incomplete reporting events in young children. The low incidence in study 408, a PD study comparing ciclesonide and placebo taken concomitantly with fluticasone/salmeterol is not easy to explain, but may be related to relief of non-nasal allergic manifestations from the inhaled combination product.

Table 16. Comparison of Adverse Events in Clinical Trials of Varying Duration

					Ciclesonide, mcg daily			
Study	Disease	Age, yrs	Trial Duration	Placebo	25	50	100	200
CL-002	SAR	16 - 66	2 w	20.9	24.7	27.3	26.2	22.2
401	SAR	12 - 86	4 w	39.3				40.2
402	PAR	12 – 75	6 w	47.2				42.9
404	PAR	12 – 74	52 w	74.3				75.1
406	SAR	18 – 75	1 d	14.3				7.2
407	SAR	18 – 71	1 d	7.6				8.1
403	PAR	5 - 11	12 w	66.1	66.9		69.3	70.3
405	PAR	2 – 5	6 w	26.5	21.2		24.2	18.2
407	SAR	18 – 57	6 w	60.0				57.1
408	SAR	18 – 57	6 w	22.7				26.7

In no instance were the events markedly more frequent in the ciclesonide 100 or 200 mcg groups.

The most common events were nasopharyngitis, headache, epistaxis, upper respiratory tract infection, and pharyngolarygeal pain. All were more frequent in the ciclesonide 200 mcg treated subjects than in the placebo group, but never by more than 1 or two percentage points.

7.1.5.4 Common adverse event tables

Table 17. Adverse events in >2% of subjects treated in multidose trials.

Preferred Term	Ciclesonide 200 mcg (N=1316)	Ciclesonide 100 mcg (N=344)	Ciclesonide 50 mcg (N=143)	Ciclesonide 25 mcg (N=348)	Placebo (N=1095)
Mean treatment exposure (days)	**124.0**	**49.2**	**14.7**	**47.7**	**90.8**
Patients with one or more treatment-emergent AEs	**705 (53.6%)**	**161 (46.8%)**	**39 (27.3%)**	**156 (44.8%)**	**537 (49.0%)**
Nasopharyngitis	104 (7.9%)	21 (6.1%)	0	19 (5.5%)	83 (7.6%)
Headache	96 (7.3%)	23 (6.7%)	6 (4.2%)	15 (4.3%)	68 (6.2%)
Epistaxis	87 (6.6%)	19 (5.5%)	3 (2.1%)	16 (4.6%)	52 (4.7%)
Upper respiratory tract infection	84 (6.4%)	21 (6.1%)	0	13 (3.7%)	60 (5.5%)
Pharyngolaryngeal pain	52 (4.0%)	15 (4.4%)	0	9 (2.6%)	22 (2.0%)
Sinusitis	47 (3.6%)	8 (2.3%)	0	3 (0.9%)	24 (2.2%)
Cough	44 (3.3%)	14 (4.1%)	1 (0.7%)	13 (3.7%)	33 (3.0%)
Nasal discomfort	27 (2.1%)	6 (1.7%)	0	8 (2.3%)	13 (1.2%)
Ear pain [1]	26 (2.0%)	4 (1.2%)	0	3 (0.9%)	8 (0.7%)
Influenza	23 (1.7%)	7 (2.0%)	0	3 (0.9%)	13 (1.2%)
Pharyngitis	23 (1.7%)	7 (2.0%)	1 (0.7%)	5 (1.4%)	28 (2.6%)
Vomiting	16 (1.2%)	11 (3.2%)	0	8 (2.3%)	10 (0.9%)
Asthma	14 (1.1%)	7 (2.0%)	0	3 (0.9%)	11 (1.0%)
Pyrexia	13 (1.0%)	14 (4.1%)	2 (1.4%)	7 (2.0%)	21 (1.9%)
Abdominal pain upper	12 (0.9%)	7 (2.0%)	0	1 (0.3%)	5 (0.5%)
Upper respiratory tract infection NOS	12 (0.9%)	2 (0.6%)	1 (0.7%)	0	23 (2.1%)
Intraocular pressure increased	8 (0.6%)	7 (2.0%)	6 (4.2%)	11 (3.2%)	7 (0.6%)

NOS = not otherwise specified
[1] Not included in Post-text Table 6.13 since incidence was 1.975%. As this has been rounded to 2.0% in Post-text Table 4.13, this AE has been added to this in-text table.
Data source: Post-text Table 6.13, Post-text Table 4.13 and Post-text Table 3.13

7.1.5.5 Identifying common and drug-related adverse events

The incidence of adverse events was so evenly distributed among the treatment groups that it is difficult to say that any were consistently drug related. Epistaxis, headache, Nasopharyngitis could be drug-related.

7.1.5.6 Additional analyses and explorations

No additional analyses were performed.

7.1.6 Less Common Adverse Events

No uncommon adverse event represented a safety signal of concern.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine safety hematology and chemistry blood tests were performed at baseline and at the end of the study in all of the trials other than 406, and 407, the EEC onset of action studies. The HPA-axis was evaluated in studies 403, 404, 405, 408, and 409, CL-001, and intra-ocular pressure was measured in studies CL-002, 403, 404, and 405.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

All of the studies were randomized and placebo controlled and all were reviewed for the laboratory results.

7.1.7.3 Standard analyses and explorations of laboratory data

There were no clinically meaningful changes in the mean values of any of the routine laboratory values. Laboratory values were reported rarely as adverse events and the incidence was no higher in the ciclesonide-treated subjects than in the placebo-treated subjects. There was an unusually high rate of abnormal chemistry values in some of the studies. The abnormalities were seen in all of the subjects and do not suggest a drug effect. However, it is hard to explain a 12.1 and 19.3% shift from normal to abnormal in the calcium values in the ciclesonide and placebo subjects. The abnormalities were not extreme, however, the analyses were performed at a central laboratory [redacted] and the results bring into question the accuracy of the laboratory procedures.

7.1.7.4 Additional analyses and explorations

There was no indication for further analyses.

7.1.7.5 Special assessments

A protocol specified ENT examination was performed routinely in all of the clinic visits. The intraocular pressure was measured in studies CL-002, 403, 404, and 405. In the 52 week adult trial, a slit lamp examination and a systematic examination for cataracts was performed, and the LOCS III evaluation was performed by ophthalmologists (See Section 7.1.12 Special Safety Studies). An HPA-axis evaluation was performed in selected studies (See 5.2 Pharmacodynamics [page 31, above]

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were recorded at baseline, follow-up, and end of study visits in all the trials.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

All of the studies were reviewed for overall drug-control comparisons,

7.1.8.3 Standard analyses and explorations of vital signs data

There was no evidence of a clinically meaningful effect of ciclesonide nasal spray on vital signs.

7.1.8.4 Additional analyses and explorations

No additional analyses were performed

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, I ncluding brief review of preclinical results

ECGs were performed in study CL-002 at baseline and at the end of the study and in study 404 at baseline, and after 6 months, and one year of treatment.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Study CL-002 and 404 were reviewed to assess the ECG results.

7.1.9.3 Standard analyses and explorations of ECG data

In study CL-002 one patient treated with ciclesonide 25 mcg had an abnormal baseline ECG and two subjects suffered a cardiac adverse event. One patient in the ciclesonide 25 group had an accelerated junctional nodal rhythm on day 12 of treatment and one ciclesonide 200 subject had a mild sinus tachycardia on day 13 of treatment. The nodal rhythm persisted to the end of the trial, but the tachycardia resolved. Both of the events were judged to be not drug related, and this reviewer concurs with this assessment.

In study 404 38.8% of the ECGs were abnormal at baseline. Of those that were normal at baseline 24.3% and 21.6% of the ciclesonide and placebo subjects had abnormalities after 1 year of treatment. None of the abnormalities was thought to be significant. Most were sinus arrhythmias, non-specific S-T changes, old ischemia, and common conduction abnormalities. None was reported as an adverse event.

7.1.9.4 Additional analyses and explorations

No additional analyses were performed. This is appropriate because corticosteroids have a low potential to effect cardiac rhythm or function.

7.1.10 Immunogenicity

Immunogenicity was not assessed in these studies. Corticosteroids are known to be immunosuppressive in high doses, and the issue will be addressed in the class labeling section of the label.

7.1.11 Human Carcinogenicity

Carcinogenicity was not assessed in these studies. In a prior NDA for ciclesonide inhalation aerosol ciclesonide was assessed as no more carcinogenic than other corticosteroids.

7.1.12 Special Safety Studies

7.1.12.1 ENT Examinations

An ENT examination that included protocol specified attributes was performed at all of the clinic visits in studies 401, 402, 404, 403, and 405. Most of the subjects showed evidence of active rhinitis throughout the studies. Only transient nasal septal erosions were seen and were as common in the placebo subjects as in the ciclesonide treated

subjects. In study 402, 1 placebo and 1 ciclesonide-treated subject had a septal erosion noted at 3 weeks that was not seen at 6 weeks of treatment. In the 1-year adult safety study one perforation and one ulceration were reported, both in placebo treated subjects. One ciclesonide 200 mcg subject in study 403 had an ulceration noted at the 2-month visit which had disappeared by the 3-month visit.

7.1.12.2 Ophthalmologic Examinations

The intraocular pressure was measured in studies CL-002, 403, 404, and 405. In study CL-002 a large number of abnormal values were reported, but the Applicant stated that the personnel performing the measurements had not been adequately trained. In the 52-week safety study in adults (#404) the mean pressure decreased in the ciclesonide treated subjects (-0.0 mm Hg) and increased slightly in the placebo subjects (0.1 mm Hg). In the 12-week trial in the 6 – 11 year olds the IOP increased by the largest amount in the placebo-treated subjects. Comparing baseline to the end of the study the changes were 0.58, 0.49, 0.26, and -0.02 in the placebo, and ciclesonide 200, 100, and 25 mcg groups. In the 2-5 year-olds (#405) the changes in IOP were also greatest in the placebo subjects and not dose related in the ciclesonide treated subjects.

In the 52 week adult trial, a slit lamp examination and a systematic examination for cataracts was performed. A slightly higher proportion of the ciclesonide-treated subjects had an increase in the Class (severity) of abnormality than those treated with placebo, but the differences were small and not statistically significant. Compared to baseline, 23% of the ciclesonide subjects developed Class I abnormalities compared with 18.7% of the placebo subjects; 9.5 and 8.0% developed Class II abnormalities, and 5.1 and 4.3% developed Class III abnormalities in the ciclesonide and placebo groups, respectively. However, the type of abnormality that increased the most was not a typical corticosteroid effect. The greatest disproportion (22% in the ciclesonide group and 16.6% in the placebo group) was in nuclear opalescence which is a non-specific finding. By comparison, posterior subcapsular opacity (typical of corticosteroid effect) increased less frequently (0.8%) in the ciclesonide treated than Placebo-treated subjects (1.6%). All in all there was no evidence that ciclesonide increased the risk of cataracts in this relatively young population. Visual acuity did not differ among the treatment groups or change during the course of treatment. These results were discussed with an FDA ophthalmologist who agreed that the findings did not represent a risk above and beyond that seen with other intranasally administered corticosteroids.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There was no evidence of drug abuse or dependence in these studies. Follow-up visits were conducted in studies 401, 402, 403, and 405. No evidence of withdrawal phenomena or rebound was described.

7.1.14 Human Reproduction and Pregnancy Data

During this development program 7 subjects treated with ciclesonide and two treated with placebo became pregnant. In the ciclesonide group 2 subjects had normal term deliveries, 2 had spontaneous abortions, 2 had voluntary abortions, and one subject was lost to follow-up. Of the placebo subjects, one had a normal term delivery and one was lost to follow-up.

7.1.15 Assessment of Effect on Growth

A single study comparing growth in children treated with ciclesonide inhalation aerosol and placebo was submitted, without supporting data sets, to the original application. The study was not referred to in the product label until the 120-Day safety update was submitted in June 2006. The revised label submitted in June included the results of the growth study. Because corticosteroids are known to have an effect on growth in high doses, this effect is included in class labeling for all inhaled corticosteroid products.

7.1.16 Overdose Experience

No overdose was reported in the clinical program.

7.1.17 Postmarketing Experience

The product is not marketed anywhere in the world.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Study 76-2004 (CL-002) was a two-week, randomized, double-blind, placebo-controlled dose-ranging trial in subjects 18 to 66 years of age with SAR. There were 144, 145, 143, 146, and 148 subjects who received 25, 50, 100, and 200 of ciclesonide or placebo, respectively. The safety assessment consisted of adverse events, routine safety laboratory examinations and intra-ocular pressure measurements.

Study 287-2004 (401) was a four-week, randomized, double-blind, placebo-controlled efficacy and safety trial in subjects 12 to 86 years of age with SAR. There were 163 and 164 subjects who received placebo and ciclesonide, respectively. The safety assessment consisted of adverse events, routine safety laboratory examinations and ear, nose, and throat examination.

Study 363-2004 (402) was a 12-week, randomized, double-blind, placebo-controlled efficacy and safety trial in subjects 12 to 75 years of age with PAR. There were 233 and 238 subjects who received placebo and ciclesonide, respectively. The safety assessment consisted of adverse events, routine safety laboratory examinations and ear, nose, and throat examination.

Study 146-2005 (404) was a 52-week, randomized, double-blind, placebo-controlled safety trial in subjects 12 to 73 years of age with PAR. There 222 and 441 subjects who received placebo and ciclesonide, respectively. The safety assessment consisted of adverse events, routine safety laboratory examinations and ear, nose, and throat examination. Ophthalmologic examination included slit lamp examination with LOCSIII grading by a qualified ophthalmologist, and HPA-axis evaluation included an AM plasma and 24-hour urine samples for cortisol.

Study 143-2005 (406) was a randomized, double-blind, placebo-controlled environmental exposure chamber trial in subjects 18 to 75 years of age with SAR. The subjects were treated with one dose of placebo or 200 mcg ciclesonide after exposure to an antigen to which they had been primed. The safety population consisted of 251 subjects each who received placebo and ciclesonide. The safety assessment consisted of adverse events, and ear, nose, and throat examination only.

Study 145-2005 (407) was a randomized, double-blind, placebo-controlled environmental exposure chamber trial in subjects 18 to 75 years of age with SAR. The subjects were treated with one dose of placebo or 200 mcg ciclesonide after exposure to an antigen to which they had been primed. The safety population consisted of 210 subjects each who received placebo and ciclesonide. The safety assessment consisted of adverse events, and ear, nose, and throat examination only.

Study 149-2005 (403) was a 12-week, randomized, double-blind, placebo-controlled efficacy and safety trial in subjects 6 to 11 years of age with PAR. There were 165, 169, 166, and 165 subjects who received placebo and 25, 100, and 200 mcg ciclesonide, respectively. The safety assessment consisted of adverse events, routine safety laboratory examinations and ear, nose, and throat examination and IOP. The HPA-axis evaluation included an AM plasma and 24-hour urine samples for cortisol.

Study 144-2005 (405) was a six-week, randomized, double-blind, placebo-controlled safety trial in subjects 2 to 5 years of age with PAR. There were 34, 33, 33, and 33 subjects who received placebo and 25, 100, and 200 mcg ciclesonide, respectively. The safety assessment consisted of adverse events, routine safety laboratory examinations and ear, nose, and throat examination and IOP. The HPA-axis evaluation included an AM plasma and 24-hour urine samples for cortisol.

Study 147-2005 (408) was a six-week, randomized, double-blind, placebo-controlled safety trial in subjects 18 to 57 years of age with PAR. The subjects were treated with

inhalation budesonide during a 10-day run-in period and were then randomized to concomitant placebo or 200 mcg ciclesonide for 6 additional weeks. The safety population consisted of 55 and 56 subjects who received placebo or 200 mcg ciclesonide in addition to budesonide. The safety assessment consisted of adverse events, routine safety laboratory examinations and ear, nose, and throat examination. The HPA-axis evaluation included a 24-hour urine sample for cortisol and plasma samples drawn over 24 hours for cortisol.

Study 148-2005 (409) was a randomized, double-blind, placebo-controlled safety trial in subjects 18 to 57 years of age with PAR. The subjects were treated with inhalation fluticasone/salmeterol DPI 500/50 mcg BID during a 10-day run-in period and were then randomized to concomitant placebo or 200 mcg ciclesonide for 6 additional weeks. The safety population consisted of 75 subjects each who received placebo or 200 mcg ciclesonide in addition to fluticasone/salmeterol. The safety assessment consisted of adverse events, routine safety laboratory examinations and ear, nose, and throat examination. The HPA-axis evaluation included a 24-hour urine sample for cortisol and plasma samples drawn over 24 hours for cortisol.

Study 202-2003 (CL-001) was a randomized, double-blind, placebo-controlled pharmcodynamic trial in subjects 18 to 55 years of age. Five treatment groups were made up of normal volunteers and one group treated with 400 mcg BID had SAR. The subjects were randomized to placebo or 50, 100, 200, 400 mcg ciclesonide once daily or 400 mcg BID for 6 additional weeks. The safety population consisted of 8 subjects in each treatment group. The safety assessment consisted of adverse events, and routine safety laboratory examinations. The HPA-axis evaluation included a 24-hour urine sample for cortisol and plasma samples drawn over 24 hours for cortisol. The results of adverse events and routine laboratory examinations are not included in the tables of pooled events.

7.2.1.2 Demographics

As seen in Table 18 the mean age of the treated subjects was between 20 and 40 years. The mean age was 33 and 31 years in the ciclesonide 200 and placebo-treated subjects. In the ciclesonide 200 group, 198 were less than 12 years of age, 91 were 12 to 17, and 24 were 65 years or older. The distribution was similar in the placebo group. In the ciclesonide 200 and placebo groups 60% were female, 79% were Caucasian, and 11% Black. Approximately 20% of the subjects described themselves as Hispanic.

Table 18. Demographics of Subjects Enrolled in Multi-dose Studies

Ciclesonide Dose (N)	200 mcg (1316)	100 mcg (344)	50 mcg (143)	25 mcg (348)	Placebo (1095)
Age					
Mean (SD)	33 (16)	20 (17)	40 (11)	21 (17)	31 (17)
Age Category (%)					
< 12 years	15.0	57.8	0	58.0	18.2
12-17 years	6.9	0	0	0	6.1

18-64 years	76.2	41.9	100	42.0	73.3
≥ 65 years	1.8	0.3	0	0	2.4
Gender (%)					
Male	39.8	50.0	26.6	43.1	40.3
Female	60.2	50.0	73.4	56.9	59.7
Race (%)					
Caucasian	78.7	81.7	95.8	80.5	79.6
Black	10.9	13.7	3.5	13.2	10.6
Other	10.4	4.6	0.7	6.3	9.8

7.2.1.3 Extent of exposure (dose/duration)

The data base contains a total of 2612 subjects who were exposed to ciclesonide. Of these, 1777 received multiple doses, 1316 received multiple doses of 200 mcg, and 344 received multiple doses of 100 mcg (Table 19). In the multiple dose studies, 97 subjects were exposed to ciclesonide 200 mcg for 364 days or greater and another 152 were exposed to 337 to 363 days.

Table 19. Summary Exposure to Ciclesonide in Multiple-Dose Studies

	Ciclesonide Dose				
Days of Exposure	200 mcg N=1316	100 mcg N=344	50 mcg N=143	25 mcg N=348	Placebo N=1096
Mean (SD)	124 (132.7)	49.2 (33.6)	14.7 (1.9)	47.7 (33.3)	90.8 (111.3)
Distribution					
1-28	331	152	143	159	323
29-182	639	192		189	603
183-365	346				169

Of note, no child less than 12 years of age was exposed for longer than 106 days and no child less than 6 was exposed for longer than 45 days (Table 20). Thus, at most, the 2-5 year-olds were exposed to half of the Guidance for Industry recommended duration of 3 months.

Table 20. Extent of Exposure in Subjects <12 Years of Age

	Ciclesonide 200 mcg		Ciclesonide 100 mcg		Ciclesonide 25 mcg		Placebo	
Age, yrs / Days	2 - <6	6 - <12	2 - <6	6 - <12	2 - <6	6 - <12	2 - <6	6 - <12
1-28	3	8	2	6	0	12	2	14
29-42(45)	30	1	31	3	32	6	32	2
43-77		7		6		9		12
>77		149		151		142		137
Mean Days	38.6	80.0	39.9	81.0	40.5	77.5	39.5	76.0
Maximum Days	44	99	44	106	44	104	45	105

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No other study was reviewed.

7.2.2.2 Postmarketing experience

Ciclesonide Nasal spray is not marketed in any country.

7.2.2.3 Literature

According to the applicant, there are no published reports of the use of ciclesonide nasal spray in humans.

7.2.3 Adequacy of Overall Clinical Experience

The study number, design, and duration are sufficient to assess the efficacy and safety of ciclesonide nasal spray in adults with SAR and PAR. All of the studies were double-blind, randomized, and placebo-controlled. All of the subjects had an appropriate diagnosis for at least 2 years with current evidence of allergy. All were symptomatic at the time or enrollment. The Total Nasal Symptom Score, an accepted instrument for measuring efficacy in allergic rhinitis was used as the primary efficacy variable. The statistical analysis was appropriate. The 52-week safety study included 97 subjects who were followed for >364 days and 152 who were followed for >353 days. This experience, in combination with other evidence of low systemic absorption and low toxicity, is sufficient to support safety in the adult population.

Efficacy and safety in the pediatric population was evaluated in a single 12-week trial in children 6 – 11 years of age and safety was evaluated in a single 6-week trial in children 2 to 5 years of age. The protocol does not specify who is to fill out the diary for the 6 to 11 year olds. In one place it says the subject and the care-giver should respond to the questions and in another place it says that it can be either/or the subject or the caregiver. If different parties were to fill out the diaries at different times, an unquantifiable degree on unnecessary variability could have been introduced into the results. Both trials were randomized, double-blind and placebo controlled. The 6 – 11 year-olds were required to have a diagnosis of PAR for 6 months, but the 2-5 year-olds were only required to have the diagnosis for 3 months. The Guidance to Industry for Allergic Rhinitis does not include a requirement for the duration of the diagnosis of PAR. However, three months is a short time to assess these non-specific symptoms in young children and could have resulted in misdiagnosis. The Guidance does call for at least 12 weeks of treatment for pediatric patients and the trial of the 2-5 year-olds did not meet this criterion. The study was designed to assess the safety of ciclesonide nasal spray in patients 2 to 5 years of age. Given that a maximum of only 30 subjects were exposed to the 200 mcg dose for a maximum of 45 days (mean 38.6 days) and the fact that there were suggestive dose

ordered reductions in 24-hour urine cortisol, this single trial is not sufficient to assess the safety in these subjects. For all of these reasons and the results of the DSI audit, the clinical experience with children 2 -5 years of age is inadequate to draw any conclusions about the safety ciclesonide nasal spray in this population.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed. The drug is a corticosteroid about which the basic mechanism of action and range of toxicities are known.

7.2.5 Adequacy of Routine Clinical Testing

Adverse events were collected daily and reviewed by the investigators at all clinic visits. Vital signs were collected at all clinic visits and routine laboratory testing was conducted in all the trials other than the onset of action trials (406 and 407) at baseline and at the end of the study. ECGs were performed in two of the trials. Given that ciclesonide is in a class (corticosteroid) about which there is extensive information and the fact that very little of the nasal formulation is absorbed systemically, this degree of safety monitoring is sufficient.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The absorption, distribution, metabolism, and clearance of ciclesonide when administered orally, intravenously, or by oral inhalation were reviewed extensively for
Very little is absorbed after nasal inhalation (at most half of the subjects had blood levels up to 10 times less than were seen after oral inhalation). A more detailed profile of clearance and metabolism of ciclesonide after nasal inhalation is not indicated due to the low absorption.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

In general, the clinical studies were adequate to assess the common corticosteroid adverse events. Given that absorption is very low, systemic toxicity at the proposed dose is not expected. Despite this, the HPA-axis was assessed in one early dose-ranging study and one 12- month safety study in adults. Both of the pediatric trials included measurements of plasma and urine cortisol. Urine creatinine was used to assess the adequacy of the urine collection. In addition, the 2-5 year-olds were kept in the clinic for the 24 hours of the collection to help improve on the completeness of the urine collection. Ophthalmologic examination for glaucoma (intra-ocular pressure measurements) was successfully performed in the one-year adult safety study (404) and in both of the pediatric pivotal trials (403 and 405). A detailed slit-lamp examination with quantitative

scoring of cataracts (LOCS III) was also performed in the 1-year safety study. In addition, a physical examination of the nose was performed in all of the efficacy trials.

7.2.8 Assessment of Quality and Completeness of Data

While the studies were well designed and adequately powered, the execution was less than optimal. The most glaring deficiency was in study 405 where a DSI audit of the site that enrolled all of the subjects (2-5 years of age) found significant irregularities in the site's procedures (see Section 4.4, pg 28 above). Review of study 406 (The successful onset of action study) showed that more than 15% of the subjects had skin test reactions of >3 mm to the control diluent and the pollen measurements during the exposures were much higher that specified on several days. An increase in intraocular pressure was reported as an adverse event in 3.4 to 6.8% of the subjects in the dose-ranging study (Cl-002), but the Applicant discounted the results saying that the study personnel were not trained to make the measurement. There were several instances were laboratory values were abnormal in all of the treatment groups to a degree that raises a question about the laboratory techniques and standardization procedures. An example of this is the rate of 28% of placebo subjects who reportedly had serum calcium levels that were normal at baseline and abnormal at the end of the study. In the same study 10.4% of the 24-hour urinary cortisol excretion rates were abnormal at baseline despite a requirement for an adequate urine sample. Of the subjects with normal baseline values, 16.1, 17.5, 30.0, and 21.4% of the ciclesonide 200, 100, 25, and placebo subjects had abnormal values at the end of the study. While it might be true, as the Applicant concludes, that there is no evidence of HPA-axis suppression due to ciclesonide, this number of abnormal values brings in to question the validity of the results.

The CRFs were referred to infrequently in this data set because adverse events were infrequent and were similar to what has been seen in this patient population in these types of clinical trials. A review of the CRFs submitted with the serious adverse events seen in adult 1-year safety study (#404) revealed them to be complete, well organized, and consistent with the study synopses included in the text of the study report.

7.2.9 Additional Submissions, Including Safety Update

The 120-day safety update contains limited information obtained from two ongoing clinical trials. The studies are still blinded so that only overall adverse events can be reported. Ciclesonide nasal spray is still not marketed so there is no post-marketing data.

7.2.9.1 Ongoing Clinical Trials with Ciclesonide Nasal Spray

Study M1-416 is a randomized, double-blind, placebo-controlled clinical trial designed to assess the safety and tolerability of ciclesonide 200 mcg once daily in subjects 2 – 5 years of age with PAR. Efficacy is a secondary objective. Children in the USA are being treated for 84 days following a 7 to 19 day run-in. The plan is to enroll 68 ciclesonide and 34 placebo subjects. In addition to adverse events a morning plasma cortisol will be

collected at screening and at the end of the treatment period. Efficacy is being assessed with a care-giver assessment of the TNSS.

Study TBN-15/008 has recently been completed in Japan. Adults (16 to 85 years of age) with PAR were randomized to receive 200, 400 mcg or placebo once daily or 200 mcg and placebo BID for 21 days. It was planned to enroll 44 subjects in each treatment group. Throughout the Baseline Period and the 21-day Treatment Period, patients recorded daily scores for the three primary symptoms of sneezing, nasal discharge and nasal congesting but noting the number of sneezing fits, number of nose blows, and severity of nasal congestion. Safety will be assessed with adverse events, IOP and plasma cortisol measurements.

No deaths of serious adverse events have been reported in either of the ongoing studies. In study M1-416 there have been 87 subjects enrolled (11 two-year olds, 24 three year-olds, 24 four year-olds, and 28 five year-olds). One 5-year old boy was withdrawn due to the onset of a severe headache and dizziness on the sixth day of treatment. The symptoms resolved. The study blind has not been broken. Study TBN-15/008 has completed enrollment of 220 subjects. The analysis is ongoing, but no notable adverse events were reported.

7.2.9.2 Post-marketing Reports for Ciclesonide Inhalation Aerosol

Ciclesonide HFA inhalation aerosol is marketed in 36 countries. The applicant states that "post-marketing reports for ciclesonide MDI have raised no concerns of relevance to the usage of ciclesonide nasal spray." The listing of serious events that was reported to the Applicant between October 1, 2005 and February 1, 2006 includes 37 events in 20 patients. Five of the patients were enrolled in clinical trials and the remainder represented spontaneous reports. In the spontaneous reports there were two cases of asthma and one of pneumothorax and respiratory failure. All other diagnoses occurred in only one individual. One case reported from Germany, was described in detail. A male patient (age unknown) was admitted to the hospital about 4-12 hours after inhalation of ciclesonide because he had developed swelling of the tongue and lips, as well as an itchy feeling around his lips. The only concomitant medication reported was salmeterol. There was a past medical history included *baboon syndrome [Reviewer: intertriginous allergic dermatitis], asthma bronchiale*, allergies against cortisone, triamcinolone, budesonide, ropivacaine and prilocaine (local anaesthetics). The subject was discharged from the hospital the same day after treatment with anti-histamines.

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

Common adverse events associated with corticosteroid use 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. In this submission Assessment of HPA-axis function was studied in adults and children as young as 2 years

of age. In adults there was no evidence of an effect of ciclesonide nasal spray on the HPA-axis as measured with plasma and 24-hour urinary cortisol measurements. In the 6 to 11 year-olds, plasma cortisol was not affected, but urinary cortisol was decreased in the ciclesonide-treated subjects. In the 2 to 5 year-olds, both the plasma and urinary cortisol levels decreased slightly in a dose-dependent manner after treatment with ciclesonide. However the treatment groups were small, especially in the 2 - 5 year-old group (15 – 22 per treatment). Ciclesonide administered as a nasal spray appears to have a minimal effect on the HPA-axis in adults and older children. However, the data are inadequate to definitively conclude that there was no effect on the HPA-axis in the 2 to 5 year old subjects.

The development of glaucoma was assessed in all of the age groups and was not found to be increased in the ciclesonide-treated subjects. The development of cataracts was assessed after 1 year of treatment of adults. A very small (not statistically significant) increase in nuclear opalescence (not typical of corticosteroid effect and not statistically significant) was the only abnormality that was noted more commonly in the ciclesonide-treated subjects. Osteoporosis and bone demineralization were not assessed in this development program. Development programs for corticosteroid nasal sprays do not typically assess for this because this adverse event is not expected with such low doses of corticosteroids and the duration of exposure.

The only common adverse events that were seen more frequently in the ciclesonide treated subjects were epistaxis and headache. In summary, there was no evidence of a systemic effect of ciclesonide nasal spray as would be expected from a drug with very low systemic bioavailability. Even adverse events that are routinely associated with corticosteroid used were seen infrequently. It is safe to conclude that ciclesonide nasal spray presents no greater risk than any other nasally inhaled corticosteroid preparation.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The efficacy and safety trials were of variable duration and enrolled subjects of variable ages and disease classification. No pooling of the data was attempted. The onset of action studies were of identical design, however, the nature of these studies make it imperative that the results are replicated in at least two populations. The applicant was informed at various times that the EEC studies would have to have robust

7.4.1.2 Combining data

No data was combined for inferential purposes.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Except in the pediatric trial and a two-week dose-response study in adults with SAR, the only dose tested for efficacy and safety was 200 mcg. There were too few 2-5 year-olds to draw any conclusions about dose dependency of adverse events, and the dose-ranging study was only 2 weeks in duration, making it difficult to draw safety conclusions on dose dependency from the results. That leaves only the 12-week study in the 6 to 11 year-olds to assess dose dependency. There was a trivial increase in the incidence of adverse events in the 100 and 200 mcg groups (69.3 and 70.3, respectfully) compared to the placebo and 25 mcg groups (66.1 and 66.8%, respectively). No single event or group of events was markedly higher in the higher dose groups.

7.4.2.2 Explorations for time dependency for adverse findings

More adverse events were reported in the 52-week safety trial than in the shorter efficacy trials. This is not unexpected as longer exposure generally results in more adverse events being reported.

7.4.2.3 Explorations for drug-demographic interactions

As described in the efficacy review, ciclesonide nasal spray did not demonstrate a statistically significant effect in children < 12years of age with PAR. Of the three pivotal adult efficacy and safety trials, less than 100 subjects out of 1461 enrolled were > 60 years of age, therefore, subset analyses on the efficacy and safety of ciclesonide nasal spray in the elderly would be unreliable.

The racial distributions within the studies in this application varied widely. While most of the adult pivotal studies enrolled 81 - 95% Caucasians, one of the EEC trials enrolled 60.0% Caucasian, and the study in 2-5 year-olds enrolled less than 30% Caucasian. Because the trials were conducted throughout the US and Canada, and they involved different age groups, different disease categories and used different testing methods, it is not possible to ascribe any difference in response to the racial distribution within the study populations. There were no apparent differences in the response of men and women.

7.4.2.4 Explorations for drug-disease interactions

The effect size was slightly larger in the subjects with SAR (0.9 points on the r-TNSS) than in those with PAR (0.6 points). This is consistent with what is typically seen in allergic rhinitis trials where the effect size is larger in the SAR population than in the PAR population. This is in keeping with the understanding that generally PAR is a more difficult manifestation of allergic rhinitis to treat.

7.4.2.5 Explorations for drug-drug interactions

In studies 408 and 409, subjects were treated with an inhaled corticosteroid or corticosteroid + long-acting beta agonist in addition to ciclesonide nasal spray or placebo. The rate of adverse events was not excessive and did not exceed the rate in the subjects treated with inhaled corticosteroid and placebo nasal spray, suggesting a lack of drug-drug interaction. Measurements of ciclesonide or the inhaled corticosteroid in the blood were not obtained so a PK interaction can not be ruled out.

7.4.3 Causality Determination

There were no unusual or rare adverse events that require a causality determination. All of the adverse events seen were those commonly seen in this class of drug, in this patient population and in this mode of administration.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Only the 200 mcg once daily dosing was evaluated in the adult pivotal studies and only this dose is recommended. This dose was found to be effective in subjects with SAR for two weeks and for subjects with PAR for up to one year. Although the Applicant proposes ciclesonide nasal spray for children and adults 2 years of age and older, ciclesonide nasal spray is not recommended for children < 12 years of age because of failure to demonstrate efficacy.

8.2 Drug-Drug Interactions

In the review of [redacted] it was noted that concomitant administration of erythromycin did not affect the metabolism of ciclesonide, but more potent inhibitors of CYP 3A4 have not been tested, and there is no information on co-administration of a CYP 3A4 inhibitor with ciclesonide nasal spray. The current application contains 2 reports of studies where subjects were concomitantly exposed to an inhalation aerosol corticosteroid and ciclesonide nasal spray. Plasma and urinary cortisol determinations showed no difference between those treated with ciclesonide and those treated with a placebo nasal spray. The Applicant stated in the proposed label that there was no interaction between these two forms of therapy on the basis of these two studies. However, the run-in was only 10 days and was not sufficient for the subjects to have reached a new steady state after initiation of the inhalation therapy. Urinary cortisol continued to fall over the period of inhalation aerosol plus placebo nasal spray treatment. While the fall was not greater in the subjects treated with the ciclesonide nasal spray, the results are subject to two interpretations. Either ciclesonide did not have an effect, or the effect was masked by the changes induced by the more potent inhalation treatment.

Therefore, the Applicant's interpretation of these study results cannot be included in the label.

8.3 Special Populations

The only special population that was addressed in this application was the pediatric population (See section 8.4 below). Very few subjects older than 65 were studied and no renal or liver failure patients were studied. This is acceptable because the subjects studied are appropriate for the disease. Special studies of renal or liver failure patients are not required because of the low bioavailability of ciclesonide and its primary metabolite after nasal inhalation.

8.4 Pediatrics

The treatment of children 2 to 12 years of age is covered in the body of the application. The applicant has requested a deferral of studies of subjects ages 6 months to 2 years of age and a waiver for those less than 6 months. The Division has had safety concerns (local) with the use of corticosteroids via nasal inhalation in children under 2 years of age. Additionally, there are more appropriate alternatives to corticosteroid nasal sprays for use in children under 2 years of age. For these reasons, it is appropriate to grant the Applicant a waiver for pediatric studies in children under 2 years of age.

8.5 Advisory Committee Meeting

No advisory meeting was held.

8.6 Literature Review

No literature review was submitted by the Applicant and none was performed by the reviewer.

8.7 Post-marketing Risk Management Plan

The applicant has not submitted a post-marketing risk management plan. A post-marketing risk management plan was not discussed with the Applicant at the pre-NDA meeting. At this time, other than appropriate language in the labeling, additional risk management strategies are not warranted.

8.8 Other Relevant Materials

No other material was reviewed.

9 OVERALL ASSESSMENT

9.1 Conclusions

The data submitted with this application supports the efficacy of ciclesonide 200 mcg daily to decrease nasal symptoms in adults and adolescents with seasonal and perennial rhinitis. The difference in the reflective TNSS between ciclesonide and placebo treatment was 0.9 in the SAR subjects and 0.6 in the PAR subjects. Adverse events were infrequent and mild. There was no safety signal that would suggest any label warnings other than those that are appropriate for corticosteroid class labeling.

While one study did show an early onset of action, a second identical study showed essentially no efficacy in the first 12 hours. In addition, the instantaneous TNSS measured after the first dose of medication administered in the efficacy trials also failed to demonstrate an onset of action in less than 24 hours. Ciclesonide is a pro-drug which must be taken up by the cells, and metabolized to its' active metabolite des-ciclesonide. *In vitro* studies have shown later translocation of the cortisol receptor into the nucleus after treatment with ciclesonide than after treatment with fluticasone and other directly acting corticosteroids.

The efficacy results in the children less than 12 years of age are not supportive of approval. The response of the reflective TNSS in the 6 to 11 year old patients was small (difference between placebo and ciclesonide 0.15 to 0.31) and not statistically significantly better than the response to placebo. The only evidence of efficacy was the physician's assessment (PANS) of nasal symptoms using the 200 mcg dose. Because this is a secondary outcome and the primary was not significant and because the primary outcome (TNSS) was measured daily and the PANS required recall of symptoms over a weeks time, the PANS is not sufficient to support efficacy in this trial. The symptom response was quantitatively larger in the 2 to 5 year olds, but there were so few in each treatment group (33) and the range in the data was so wide that the estimate of the response is not reliable. In addition, the response was better in those treated with 100 mcg daily than in those treated with 200 mcg daily. The efficacy assessment in the study with the 2 to5 year olds was not designed for statistical robustness. The plan for evaluation of efficacy in the 2 to 5 year olds was extrapolation from the results in the older children. Since efficacy was not demonstrated in the 6 – 11 year olds in study 403, it can not be extrapolated to the 2 to 5 year olds. Lastly, the results of the DSI audit of the single center that enrolled subjects into study 405 do not provide reassurance that the reported results are entirely accurate.

9.2 Recommendation on Regulatory Action

Approval of ciclesonide 200 mcg once daily for the treatment of the nasal symptoms of seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older is recommended.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No further risk management activity other than labeling is required.

9.3.2 Required Phase 4 Commitments

No phase 4 commitments are required.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

9.4 Labeling Review

[redacted]

9.5 Comments to Applicant

Pending detailed Label Review

10 APPENDICES

10.1 Review of Individual Study Reports

1 STUDY # 76/2004 (TBN-CL-002)

A Double-Blind, Randomized, Placebo-Controlled, Multicenter, Dose-Ranging Study to Assess the Safety and Efficacy of TBN-15 in Adult Patients with Seasonal Allergic Rhinitis

1.1 Protocol

1.1.1 Administrative

Study Dates: December 19, 2002 to February 21, 2003
Clinical Centers: 6 centers, all in Texas
Sponsor: Teijin America, Inc, Princeton, New Jersey
Medical Monitor: [redacted]

1.1.2 Objective/Rationale

The objectives of this study were to evaluate safety and efficacy of 25, 50, 100 and 200 μg doses of TBN-15 administered intra-nasally once daily for 14 days to adults with SAR.

1.1.3 Study Design

This was a randomized, double-blind, placebo-controlled, parallel study of approximately 145 subjects with SAR per treatment group.. After enrollment subjects were treated with Chlorpheniramine as rescue medication for one week. During that week they also completed the Allergic Rhinitis Assessment Diary twice a day. If they met enrollment criteria at the end of the week, they were randomized to one of the following treatment groups: 25, 50, 100, 200 mcg ciclesonide or placebo. Subjects self-medicated for two weeks and were seen by the investigators at weekly intervals. The primary efficacy outcome was the reflective Total Nasal Symptom Score (r-TNSS) which was calculated from the diary recordings of the 12-hour AM and 12-hour PM r-TNSS scores. Safety was assessed with adverse events, vital signs, and routine safety laboratory tests. Subject compliance was assessed with the diary and by inspection of the medication bottles.

1.1.4 Study Population

Inclusion Criteria

- Male or female, 18 to 65 years of age
- Have at least a two-year history of SAR as assessed by a physician and currently have a nasal symptom score (either the AM or PM score) of at least 8 (maximum of 12) for at least 3/7 days during the run-in.
- Positive skin test or RAST within 12 months of enrollment

Exclusion Criteria

- Evidence of bronchial, pulmonary, or respiratory tract infections within 14 days of screening
- Active asthma (requiring daily treatment with β-agonists)
- Planning travel outside of the area for >3 days of the active treatment period
- Change in immunotherapy injections within 30 days of screening
- Evidence of ocular herpes simplex, cataracts or glaucoma
- Positive for hepatitis B or C virus of human immunodeficiency virus
- Any significant physical abnormality including nasal polyps or nasal malformations.
- Inability to abide by medication restrictions.

Table 21. Prohibited medications

Forbidden Medication	Duration of Abstinence (Days)
Corticosteroids	
intranasal, inhaled or ocular corticosteroid	30
Oral except for oral contraceptives	42
Topical	42
Antihistamine	
Any prescription oral antihistamine other than loratadine/desloratadine	5
Any prescription intranasal antihistamine	3
Any non-prescription antihistamine excluding chlorpheniramine	3
Oral loratadine or desloratadine	10
Cromolyn, nedocromil or lodoxamide (by any route of administration)	14
Leukotriene 5-LO inhibitors	14
Inhaled anticholinergics	0.5
Oral anticholinergics	7
Decongestant	
Short-acting pseudoephedrine	0.17*
Any other	3

* Four hours

The protocol states that the subjects were randomized if they met enrollment criteria at the end of the run-in, but these criteria are not listed.

1.1.5 Study Procedures

Treatment

Ciclesonide nasal spray was provided in canisters containing 0, 12.5, 25, 50, and 100 mcg ciclesonide per actuation. The subjects were instructed to take one spray in each nostril each AM. All subjects were provided blister packs containing chlorpheniramine 4 mg each and instructed to take up to 24 mg/day if necessary for symptoms of rhinitis.

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 as follows:

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 scores were to be recorded in the morning and evening, approximately 12 hours apart. The maximum AM or PM score was 12 (4 symptoms times a maximum score of 3) and the maximum summed score was 24. At each time point, the subject recorded an instantaneous and a 12-hour reflective score for each symptom. In addition to grading each symptom, the subjects recorded the time of day the assessment was made and the number of tablets of rescue medication taken since the last diary entry.

Separate patient and investigator Global Evaluations were performed on Day 7 and 14. The evaluation consisted of a single response to a question regarding the treatment effect. The responses were graded on a five-point scale as follows:

1 = Complete relief (virtually no symptoms are present)
2 = Marked relief (symptoms are greatly improved and although present, are scarcely troublesome)
3 = Moderate relief (symptoms are present and may be troublesome but are noticeably improved)
4 = Slight relief (symptoms are present and only minimal improvement has been obtained)
5 = Treatment failure (no relief; symptoms are unchanged or worse than pretreatment baseline

Safety Evaluation

Safety was assessed with adverse event enumeration, vital signs, physical exam, ECG, routine laboratory examinations, and eye examinations. The ophthalmologic examinations consisted of pen light examination and tonometry to measure intraocular

pressure. A pressure of 20 mm Hg was taken as the upper limit of normal for reporting an adverse event.

1.1.6 Data Analysis

Sample Size

Assuming a standard deviation of 5.0 for the summed AM and PM r-TNSS (2.5 on the average AM and PM r-TNSS) it was estimated that a sample size of 125 subjects per treatment group would have 80% power to detect a difference of 1.8 units in the summed score (0.9 on the average score) with $\alpha = 0.05$. The standard deviation is based on previously conducted studies. To allow for a 10% dropout rate, the plan was to randomize at least 690 subjects.

Study Populations

The primary analysis was performed on the intention-to-treat (ITT) population which included all subjects who were randomized. The per-protocol (PP) population included subjects who finished the study as planned and who underwent all of the planned procedures. For the ITT population, a last observation carried forward (LOCF) procedure was used to account for missing data.

Efficacy Analysis

The primary efficacy variable was the change from baseline in the summed AM and PM 12-hour r-TNSS. The baseline was taken as the average of the summed AM and PM scores obtained during the screening period. The change from baseline for each treatment group was compared for the entire 14-day treatment period using a repeated measures ANOVA. Restricted maximum likelihood estimations for mixed effect models were obtained including treatment, day, and treatment-by-day as fixed effects and subject as a random effect. Placebo was compared to active treatment beginning with the highest dose of ciclesonide and proceeding to each lower dose. No correction for multiple outcomes was performed.

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. The repeated measures ANOVA was also used to determine the onset of action. The time to onset for each respective dose was assessed by a step-down procedure starting with all of the measurements. If significant, the test was repeated without the last measurement. If the test was again significant, the test was repeated without the last two measurements and so on. The onset of effect was then defined as the last day of the smallest group of days that was still statistically different from the placebo treatment group. The frequency of rescue medication use was compare using Fisher's exact test.

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

the aggregate values. Individual measurements and abnormal values were presented as listings.

1.2 Results

1.2.1 Study Population

Disposition

There were 726 subjects randomized and 703 (96.8%) completed the trial. One subject withdrew from the 200 mcg group compared with 6, 4, 6, and 6 in the 100mcg, 50 mcg, 25 mcg, and placebo groups respectively. There were no withdrawals for adverse events in the 200 mcg group compared with 3, 1, 1, and 2 in the 100mcg, 50 mcg, 25 mcg, and placebo groups respectively. Nine subjects were excluded from the per-protocol analysis due to significant protocol deviations: 3 subjects took the study drug BID, 2 did not meet entry criteria, 2 subjects tried to enroll at 2 study sites each, 2 subjects took prohibited medications, and 3 subjects took the study medication for less than 5 days.

Demographics

There were 214 males and 512 females. The mean age was between 38 and 41 years and >89% were Caucasian, (Table 22).

Table 22. Demographic variables

Ciclesonide (N)	200 mcg (144)	100 mcg (145)	50 mcg (143)	25 mcg (146)	Placebo (148)
Age, years Mean (SD)	41.8 (12.0)	37.8 (11.6)	40.7 (11.1)	40.4 (10.5)	38.7 (11.6)
Gender, %					
Male	27.8	34.5	26.6	28.8	29.7
Female	72.2	65.5	73.4	71.2	70.3
Race, %					
Caucasian	89.6	97.9	95.8	94.5	96.0
Black	8.3	2.1	3.5	3.4	2.0
Other	2.1	0	0.7	2.1	2.0
Skin test (mm) Mean (SD)					
Antigen	8.8 (3.9)	8.2 (3.6)	8.5 (3.7)	8.8 (3.7)	8.5 (4.0)
Control	0.3 (0.9)	0.3 (0.9)	0.4 (1.2)	0.3 (1.0)	0.4 (1.0)
Corticosteroid usage (%)	50	52.4	46.2	47.3	48.7

Approximately half of the subjects had used corticosteroids in the past. Skin tests were positive in all of the subjects and the size of the reactions were similar in the treatment groups. The antigen used for the skin tests was Mountain Cedar pollen.

Reviewer: The study report does not specify that the subjects who were previously treated with corticosteroids were treated with nasal corticosteroids. The allergen to which these subjects reacted is not included in the data set and there is no recording of

pollen counts. This study was performed in the same geographic area as study 401 (mid-central Texas) where all of the subjects were allergic to Mountain Cedar pollen. As in study 401 all enrollment occurred winter (January 3, 2003 to February 14, 2004)

1.2.2 Efficacy Results

Primary Efficacy Outcome

The primary efficacy variable was the sum of the AM and PM r-TNSS. The analysis was performed on the change from baseline over 14 days. The baseline values varied between 17.80 and 18.82 (maximum of 24) and were similar in all of the treatment groups. The LS mean scores fell in all of the treatment groups with statistically significant differences from placebo in the 200 (1.64 points, p=0.003) and 100 (1.14 points, p=0.040) mcg treatment groups (Table 23). The results were similar for the per-protocol population.

Table 23. Changes in r-TNSS During Treatment in Study CL-002 as Reported in the Application *

Ciclesonide Dose (mcg daily)	N	TNSS**	Difference from Placebo		
		Baseline	Estimate	95% Confidence Interval	p-value
200	144	18.8 (3.3)			
100	145	18.7 (3.4)			
50	143	18.4 (3.6)			
25	146	18.7 (3.5)			
Placebo	148	17.8 (3.4)			
		Change from Baseline			
200	144	-5.8 (4.6)	-1.64	-2.74, -0.55	0.003
100	145	-5.3 (5.1)	-1.14	-2.23, -0.53	0.040
50	142	-4.8 (4.9)	-0.60	-1.70, 0.50	0.284
25	145	-4.8 (4.4)	-0.62	-1.71, 0.47	0.265
Placebo	146	-4.2 (4.7)			

* The difference between placebo and ciclesonide is calculated as placebo – ciclesonide. Superiority of ciclesonide is represented by a negative value for the difference. This is in contrast to the other trials in this submission where the difference is calculated as ciclesonide – placebo and superiority of ciclesonide is represented by a positive value.
** LS mean (SD)

Reviewer: The above analysis was performed without the inclusion of the baseline TNSS as a covariate. This variable (baseline TNSS) was the single most important predictor of response in all of the efficacy analyses, and it was included as a covariate in the efficacy and safety studies. When the analysis was repeated with the inclusion of baseline TNSS the results showed statistical significance for only the 200 mcg dose. The resulting LS mean difference and p-values were 1.35 (p = 0.012) for the 200 mcg dose and 0.88 (p=0.099) for the 100 mcg dose. See Statistical Review for details.

Secondary efficacy outcome measures

For the most part the secondary efficacy outcome measures showed the same dose response relationships as the primary outcome. The AM r-TNSS decreased by 2.74, 2.46, 2.17, 2.18, and 1.98 points in the 200 mcg, 100 mcg, 50 mcg, 25 mcg and placebo groups

respectively. Likewise the PM r-TNSS decreased by 3.08, 2.78, 2.59, 2.57, 2.17 points respectively. The percent change in AM and PM r-TNSS was 32, 28, 25, 26, and 22% respectively. The AUC of the summed AM and PM scores fell by 35.4, 32.2, 29.0, 28.9, and 25.5 points in the 200 mcg, 100 mcg, 50 mcg, 25 mcg and placebo groups respectively. The sum of the instantaneous TNSS fell by 5.46, 4.82, 4.28, 4.42, and 3.75 points respectively.

Global evaluations of the change in symptoms were recorded by the subject and the investigator on day 7 and 14. For the subject-assigned scores, the percentage with marked or complete relief was approximately equal in the 200 and 100 mcg groups, with fewer good responses at doses less than 100 mcg (Table 24). All of the scores decreased (improved) with time including those in the placebo subjects. .

Table 24. Change in Self (Subject)-assigned Global Improvement

			Degree of Relief (Global Assessment Score)			
	Dose	N	Marked (1-2)	Moderate (3)	Slight or None (4-5)	Mean Score
Day 7	200	143	38 (26.6)	57 (39.9)	48 (33.5)	3.2
	100	145	47 (32.4)	37 (25.5)	61 (42.1)	3.2
	50	142	32 (22.5)	44 (31.0)	66 (46.5)	3.4
	25	146	29 (20.0)	44 (30.1)	73 (50)	3.4
	0	147	24 (16.3)	49 (33.3)	74 (50.3)	3.6
Day 14	200	144	56 (38.9)	44 (30.6)	44 (30.6)	2.9
	100	137	53 (38.7)	37 (27.0)	46 (33.6)	3.0
	50	140	48 (34.3)	32 (22.9)	60 (42.9)	3.2
	25	142	40 (28.2)	41 (28.9)	61 (43.0)	3.2
	0	143	45 (31.5)	39 (25.9)	59 (41.3)	3.2

The physician-assigned global scores were worse than the subject-assigned scores. They classified only 18.9% of the ciclesonide 200 subjects as markedly improved at 7 days and 30.6% on Day 14. By the end of two weeks 32.6, 39.4, 42.2, 46.5, and 42.0% of the ciclesonide 200, 100, 50, 25, and placebo subjects were classified by the physicians as minimally to not changed

Onset of Action

The onset of action was taken by the sponsor to be 3 days because there was a statistically significant difference between the LS mean r-TNSS comparing day 3 with day 2 for the subjects treated with 200 mcg. The improvement became significant for the 100 mcg group at day 4 (Table 25). The difference between placebo and active treatment did not change much during the second week of the study. (See Efficacy Analysis, pg 69, . for a description of the statistical analysis of onset of action.)

Table 25. Change in r-TNSS over the first six days of treatment.

Ciclesonide Dose (mcg daily)	N	TNSS*	Difference from Placebo	
		LS mean change (SD)	Estimate	95% Confidence Interval
Change From Day 2 to Day 3				
200	144	3.7 (4.7)	-1.17	-2.2, -0.12
100	144	-3.5 (5.1)	-0.97	-2.0, 0.08
Placebo	146	-2.5 (4.4)		
Change From Day 2 to Day 4				
200	144	-4.0 (4.6)	-1.27	-2.32, -0.22
100	145	-4.0 (5.1)	-1.21	-2.23, -0.17
Placebo	146	-2.7 (4.4)		
Change From Day 2 to Day 6				
200	144	-4.7 (4.5)	-1.69	-2.74, -0.63
100	145	-4.4 (5.1)	-1.41	-2.47, -0.37
Placebo	146	-3.0 (4.6)		

There was no difference in the use of rescue medication among the treatment groups: 39.6, 37.9, 41.6, and 40.8% in the ciclesonide 200, 100, 50, 25, and placebo groups, respectively.

1.2.3 Safety

Extent of exposure

The median exposure was 15.0 days. In the individual treatment groups the exposures means were 15.1 and 14.7 days for the 200 and 100 mcg groups, and 14.8 for the 50, 25, and 0 mcg groups.

Adverse Events

Overall, 176 (24.2%) of the subjects reported adverse events and the incidence was similar in all of the treatment groups: 32 (22.2%), 38 (26.2%), 39 (27.3%), 36 (24.7%), and 31 (20.9%) in the 200, 100, 50, 25, and 0 mcg groups respectively. Intraocular pressure increased in at least 3% of the subjects in each of the treatment groups including placebo (Table 26). Epistaxis was more common with active treatment, but pharyngitis was almost as common in the placebo groups.

Table 26. Study CL-200: Adverse Events Experienced by >2% of Subjects Enrolled

Preferred term	TBN-15 200 µg (N=144) n (%)	TBN-15 100 µg (N=145) n (%)	TBN-15 50 µg (N=143) n (%)	TBN-15 25 µg (N=146) n (%)	Placebo (N=148) n (%)
Intraocular press. increased	5 (3.5)	6 (4.1)	6 (4.2)	10 (6.8)	5 (3.4)
Dizziness	0	1 (0.7)	0	3 (2.1)	1 (0.7)
Headache	3 (2.1)	2 (1.4)	6 (4.2)	3 (2.1)	4 (2.7)
Epistaxis	2 (1.4)	3 (2.1)	3 (2.1)	1 (0.7)	0
Nasal passage irritation	3 (2.1)	1 (0.7)	2 (1.4)	0	2 (1.4)
Pharyngitis	2 (1.4)	5 (3.4)	1 (0.7)	4 (2.7)	4 (2.7)

There were 32 subjects reported as having increased IOP as an adverse event. However, the applicant noted that the IOP were not obtained by trained ophthalmologists, "but by study staff, who had minimal training or experience in measuring IOP." Twenty one patients were reported from one center where the protocol was misread and values that were not abnormal were reported as adverse events because they were higher than the baseline value. The remaining 11 subjects had values >20 mm Hg which was taken as the upper limit of normal. The highest value recorded was 26 mm Hg which was thought to be clinically non-significant. There was no dose ordering for the finding.

Reviewer: The ophthalmologic data is difficult to interpret. The actual values for the baseline IOPs are not recorded in the data listing (they are all reported as "normal"). The follow-up examinations irregularly include the actual numbers. In a two week study one would not expect much change in IOP even with a steroid with higher systemic exposure. This data is basically useless, and we will have to rely on the measurements made during the 52 week safety evaluation for any assessment of the IOP data. However, the Applicant's statement that an IOP of 26 mm Hg is clinically insignificant is not correct. A value of 20 mm Hg is routinely considered abnormal, and given the implications for vision, would be an important finding.

The distribution of adverse events into mild moderate and severe was not strikingly different among the treatment groups: 4.9, 5.5, 3.5, 2.7, and 3.4% severe in the 200, 100, 50, 25, and the 0 mcg groups.

Deaths and Serious Adverse Events and Events Leading to Withdrawal

There were no deaths. Serious adverse events occurred in two subjects treated with 100 mcg ciclesonide. One 25 year old female suffered multiple fractures in an automobile accident and a 44 year-old male suffered a bout of sigmoid diverticulitis. The drug was discontinued due to an adverse event in 7 subjects: 3 in the 100 mcg group, 1 each in the 50 and 25 mcg groups and 2 in the placebo group. In the 100 mcg group the female in the automobile accident was withdrawn from the study as well as a 23 year old female with bronchitis and a 39 year-old female with hives. The hives were judged to be possibly related to the study drug. The other early withdrawals were due to sinus infections and upper respiratory tract infections.

Pregnancy

Two subjects, both in the ciclesonide 100 mcg group, became pregnant during the trial. One pregnancy terminated in a spontaneous abortion at 14 weeks due to intrauterine strangulation of twins. The patient had had a negative pregnancy test at the screening visit which had become positive by the end-of-study visit. There was no family history of spontaneous abortion. The other pregnancy was terminated voluntarily.

Laboratory Results

There was a small but significant difference among the treatment groups for the fall in basophil % in the peripheral blood. The fall was a mean of -0.18% in the 200 mcg ciclesonide group compared with -0.03% in the placebo group. The intermediate dose-

groups had intermediate falls in mean basophil counts, ranging between -0.05 and -0.10%. (The range of all the values was -1.8 to 1.6%.)

Reviewer: The absolute cell counts were not provided by the sponsor. This reviewer took the absolute white blood cell count and multiplied it by the percentage of the individual cell count (e.g. 0.8% basophils) to arrive at the absolute individual cell counts. This calculation shows that the absolute basophil counts and the changes in the counts were small with a difference from placebo ranging between 1 and 6 cells/mm^3. There were no other differences in any of the other laboratory values, and the applicant is probably correct in ascribing the small change in basophile counts to random variation.

For ten (1.4%) of the 726 subjects, laboratory values were reported as adverse events. Four subjects had an elevated lipase (1 subject each in the 200 and 50 mcg group, and 2 in the 25 mcg group) and two subjects had elevated liver enzymes (1 each in the 25 and 50 mcg groups). Three women <42 years of age had blood detected in their urine, one 27 year old female had a total white count of 14.7 x 10^3 cells/mm^3, and one 33 year old female had minimally decreased albumin and total protein levels. Only one of the subjects, a 50 year old male in the 25 mcg group with elevated transaminases, was assessed as having an adverse event that was possibly related to the drug.

Reviewer: If the data from all the subjects is tallied, approximately 5 % of the lipase and liver function tests were elevated and the proportion did not differ among treatment groups. There were as many elevated values at baseline as at the end of the study. All of this suggests that the abnormal values are within the range of normal testing. There is no indication in the text or the patient listing as to why the elevations in liver function tests was thought to be possibly related to the study drug.

1.3 Summary and Discussion

In this two-week, randomized comparison of multiple doses of ciclesonide nasal spray to placebo, ciclesonide 200 mcg and 100 mcg once daily was superior to placebo when the drugs were compared using the sum of the AM and PM r-TNSS over the two week treatment period. The secondary efficacy variables supported the dose ordering seen in the analysis of the primary efficacy variable. Adverse events tended to be mild, infrequent, and similar among treatment groups. We agree with the applicant that the serious events were unlikely to be related to ciclesonide treatment. The attempt to assess ophthalmologic changes was not successful due, according to the applicant, to inadequate training of the study personnel.

2. STUDY # 287/2004 (BY9010/M1-401)

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Clinical Trial to Assess the safety and Efficacy of Ciclesonide (200 mcg Once Daily) Applied as a Nasal Spray in the Treatment of Seasonal Allergic Rhinitis (SAR) in Patients 12 Years and Older

2.1 Protocol

2.1.1 Administrative

Study Dates: December 15, 2003 to March 3, 2004
Clinical Centers: 6 Clinical Centers in the United States
Medical Officer: [redacted]

2.1.2 Objective/Rationale

The primary objective of this study was to demonstrate the efficacy of intranasal ciclesonide once daily in the treatment of SAR. The secondary objectives were to assess quality-of-life measures and the safety of administering ciclesonide intra-nasally.

2.1.3 Study Design

This was a 4-week randomized, double-blind, parallel-group placebo-controlled multi-center study conducted in adults and adolescents (151 per treatment group) with SAR. Subjects were screened 7 to 10 days prior to randomization. During the screening period subjects recorded their symptoms in a diary twice daily. If they had an appropriate level of symptoms at the end of the screening period they were randomized to receive either 200 mcg ciclesonide nasal spray, once daily, or placebo. After randomization they continued to record symptoms twice daily in the diary. In addition, on day one of treatment the subjects also recorded symptoms hourly from 4 to 12 hours after the dose. Patients were seen at screening, baseline, after 15 and 29 days of active treatment, and one follow-up visit approximately 7 days after the end of treatment. At all follow-up visits, the subjects had an ear, nose and throat (ENT) examination performed and daily pollen counts were obtained throughout the study. The primary efficacy variable was the mean of the AM and PM r-TNSS comparing baseline to the entire treatment period. Secondary outcomes included instantaneous TNSS, components of the TNSS, and the responses to a rhinoconjunctivitis quality-of-life questionnaire. Safety was assessed with adverse events, physical examination, and routine safety laboratory examinations. Treatment in this study continued for 28 days but the primary efficacy analysis was performed on the data obtained up to 14 days. Subject compliance was assessed with the diary and by visual inspection of the medication bottle.

2.1.4 Study Population

Inclusion Criteria

- Males and females ≥12 years of age
- History of SAR requiring treatment for a minimum of 2 years duration
- Positive skin prick to Mountain Cedar pollen within 12 months of enrollment
- Without any other significant medical disease

Exclusion Criteria

- Evidence of bronchial, pulmonary, or respiratory tract infections within 14 days of screening or development of an infection during the screening period
- Active asthma (requiring daily treatment with β-agonists)
- Planning travel outside of the area for ≥2 consecutive days of the active treatment period OR 5 days total
- Change in immunotherapy injections within 30 days of screening
- Evidence of ocular herpes simplex, cataracts or glaucoma
- Positive for hepatitis B or C virus of human immunodeficiency virus
- Any significant physical abnormality including nasal polyps or nasal malformations or nasal trauma or surgery within 60 days.
- Use of antibiotic therapy for acute conditions within 14 days of Screening except low-dose prophylaxis started prior to screening and expected to continue throughout the trial
- Pregnant, nursing, or planning to become pregnant
- Participation in an investigational trial within 30 days of screening
- History of alcohol abuse
- Hypersensitivity to corticosteroids
- Previous participation in an intranasal ciclesonide study
- Non-vaccinated exposure to or active infection with chickenpox or measles within 21 days of screening
- Use of topical steroids in excess of 1% hydrocortisone
- Inability to abide by medication restrictions listed in Table 27

Table 27. Table **Restricted Medications in Study 401**

Forbidden Medication	Duration of Abstinence (Days)
Any other investigational study medication	30
Corticosteroids	
Intranasal with the exception of the study medication	14
Inhaled	30
Systemic with the exception for oral contraceptives	60
Decongestants (oral, topical, or nasal)	B0
Antihistamines	
Short acting including intranasal antihistamines (Azelastine®)	B0
Long acting including loratadine/desloratadine cetirizine, fexofenadine	B0
Over-the-counter cough and cold preparations or sleep aids that contain antihistamines	B0
Cromolyn, nedocromil or lodoxamide (by any route of administration including intranasal, ocular and oral	7
Leukotriene 5-LO inhibitors	7
Inhaled intranasal or oral anticholinergics	7
Vasoconstrictors	3
Major tranquilizers	3
Antiepileptic medications	3
Tricyclic antidepressants	14
Monoamine oxidase inhibitors	14
Immunosuppressive medications	60
Anti-immunoglobulin E therapy	60
Airozan® (over-the-counter food supplement/diet to reduce leukotrienes)	7

Randomization Criteria

Subjects were required to have a single reflective TNSS (AM or PM) of at least 6 (maximum 12) on at least four of the last seven days of screening.

Continuation Criteria

There are no specific criteria for withdrawal. Adverse events, intercurrent illness, or subject request could result in withdrawal from the study. The following serious protocol violations could also result in withdrawal:

- Subjects inappropriately randomized
- <80% compliance with medication
- Use of forbidden concomitant medications
- Development of a co-morbid condition or procedural complication that might affect the validity of the assessment of the patient's clinical status to a degree deemed significant by the investigator
- Unblinding
- Other severe deviations from the study protocol considered to be relevant by the investigator and/or the sponsor

Reviewer: The use of the above listing of protocol violations is unclear because in the results section it is stated that there were 20 major violations, but the patient disposition table does not indicate that any subject was withdrawn for a protocol violation. (see below, Table 28, pg 82)

2.1.5 Study Procedures

Treatment

In addition to the blinded study medication, subjects were permitted to take the following medications with the indicated restrictions:

- Low-dose antibiotic therapy given prophylactically and started before the Screening Visit (B0) was permitted.
- Patients were permitted to receive immunotherapy injections during the study if they had received a stable maintenance regimen for at least 30 days before the Visit B0 and the dose did not change during the study.
- Intermittent use of β-agonists was acceptable for patients with asthma (daily use of β-agonists was not permitted).
- Aspirin (≤325 mg) given prophylactically and initiated before Visit B0 was permitted. No dosage adjustments were allowed during the study.
- Topical (dermatological) corticosteroids ≤1% hydrocortisone were allowed as needed.
- Other medications 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 as follows:

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 scores were to be recorded in the morning and evening, approximately 12 hours apart. The maximum AM or PM score was 12 (4 symptoms times a maximum score of 3). At each time point, the subject recorded an instantaneous and a 12-hour reflective score for each symptom. In addition to grading each symptom, the subjects recorded the time of day the assessment was made.

Secondary efficacy endpoints included the Physician Assessment of Overall Nasal Signs and Symptoms Severity (PANS). The scoring includes assessment of both signs and symptoms as follows:

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 scoring was between 0 and 3 for none, mild, moderate, and severe. The overall PANS was obtained by summing the signs and symptoms scores separately and then averaging the two summed scores. The signs were elicited at the time of the ENT exam, and were to be recorded prior to questioning the subjects about symptoms.

Subjects were to record 12-hour reflective scores for non-nasal symptoms. The symptoms included itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate. The symptoms were scored on the same 0 to 3 scale as the TNSS.

The Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ) was obtained at baseline and at 2 and 4 weeks. The adult questionnaire, containing 28 questions within seven domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional), was used. For the adolescents 12 to 17 years of age an adolescent RQLQ which contains 25 questions in six domains (activities, non-hay fever symptoms, practical problems, nasal symptoms, eye symptoms, and emotional) was used. Subjects were asked to recall their experiences during the week prior to questioning and to respond using a seven point scale (0=least severe to 6=most severe). The questionnaire has been validated in English and it was not administered to subjects who did not understand English.

Safety Evaluation

Safety was evaluated with adverse events, physical examination, vital signs, and ECGs. A physical examination specifically to look for nasal bleeding, perforation, and ulcerations was performed at each clinic visit.

2.1.6 Data Analysis

Sample Size

Assuming a common standard deviation of 2.4 for the average AM and PM TNSS it was estimated that a sample size of 151 subjects per treatment group would have 90% power to detect a difference of 0.9 units in the summed score (0.9 on the average score) with $\alpha = 0.05$. The standard deviation is based on previously conducted studies.

Study Populations

Analyses were based on the total set full analysis set, and valid cases set. The total set consisted of all subjects enrolled including those withdrawn prior to randomization and randomized patients who never took study medication. The full analysis set was used to describe the analysis set that was as complete as possible and as close as possible to the intention-to-treat ideal including all randomized patients. The documented failure to take at least one dose of the study medication after randomization led to excluding randomized patients from the full analysis set. The valid cases set consisted of all patients in the full analysis set without any major protocol violations. Major protocol violations were determined at a blinded Data Review Meeting.

Efficacy Analysis

The reflective total nasal symptom score (r-TNSS) was the sum of the reflective (over 12 hours) scores for nasal stuffiness/congestion, nasal itching, sneezing, and runny nose obtained in the morning before the first dose of medication and in the afternoon approximately 12 hours after the AM recording. The average r-TNSS was the average of the AM and PM scores. The primary efficacy variable was the change from Baseline in the average rTNSS recorded over days 1 – 14. The baseline was the average of the average scores obtained up to seven days prior to randomization. The analysis used a repeated-measures ANCOVA with baseline, treatment, day and treatment by day interactions included as covariates. A first order autoregressive structure was used to model intra-patient correlation. "No imputation of missing values was performed, as the extent of missing data was found to be low and the chosen analysis as a maximum likelihood method was valid for missing-at-random missingness." Outcome variables were analyzed sequentially starting with the mean r-TNSS or 14 days and proceeding to the iTNSS over 14 days and then the PANS. The procedure was stopped when a non-significant p-value was obtained.

Similar statistical procedures were used to analyze the secondary efficacy outcomes. These included changes in the individual components of the r-TNSS, the instantaneous TNSS, and the values obtained at the 28 day time point. Changes in the PANS and RQLQ were analyzed by univariate ANCOVA with baseline value, center, and treatment in the model.

Onset of Action

The onset of action was assessed with the instantaneous TNSS measured hourly on the first day of treatment. The onset of action was defined as the time from baseline until the two-sided p-value for the test of a difference in the average of patient-assessed i-TNSS

between intra-nasal ciclesonide and placebo was less than 0.05. An additional requirement was that the difference had to remain at least this large for one additional time point (hour). Baseline was defined as the zero hour on day 1. Treatment groups were compared on each day using ANCOVA with center, treatment and baseline entered as covariates.

Other Analytic Considerations

Pollen counts were obtained at each clinical center. A mean was derived from each respective patient's Day -7 values as well as for each successive day. Sub group analysis was performed for age (<18, 18-64, >64 years) gender (male, female), and race (Caucasian, Black, other).

2.2 Results

2.2.1 Study Population

Disposition

There were 327 subjects randomized and 292 (89.3%) completed the trial. Twenty-one subjects withdrew from the 200 mcg group compared with 14 in the placebo group (Table 28). The most common reason for withdrawal was adverse events, lack of compliance, and lack of efficacy. Adverse events and lack of efficacy were roughly equivalent in the two treatment groups while lack of compliance (2.4% vs 0.6%) and other (3% vs 0) were more frequent with ciclesonide treatment. The ITT population was made up of the 327 subjects who were randomized. Major protocol violations occurred in 41 subjects: 22 (13.4%) of the ciclesonide treated subjects and 19 (11.7%) of the placebo-treated subjects.

Table 28. Subject Disposition as percent of enrolled subjects

	Ciclesonide 200 mcg N=164	Placebo N=163
ITT analysis	100	100
PP analysis	90.9	95.1
Prematurely discontinued	12.8	8.6
Reason for discontinuation		
AE	2.4	3.1
Lack of Efficacy	2.4	3.1
Predefined criteria	1.2	1.2
Lost to follow-up*	7.2	1.8

* Lost to follow-up, compliance, patient request, and other

Reviewer: The data in Review Table 28 is taken directly from Table 3 (pg 50/18515) of the study report. Table 8, (pg 57/18516) of the study report indicates that no more than 163 ciclesonide-treated subjects and 162 placebo-treated subjects were included in any

of the efficacy analyses. The primary efficacy outcome is based on 162 subjects in each group, not 164 and 163 as suggested in the Disposition Table.

Demographics

There were 115 males and 212 females. The mean age was 35.2 years, >83.8% were Caucasian, and 65% were female (Table 29). Almost 70% were never smokers and all had a positive skin reaction to Cedar pollen. In the group as a whole, the mean response to antigen challenge was 9.7 mm with a mean control response of 0.9 mm and a mean response to histamine of 8.9 mm. The distribution and range of control and histamine responses was very similar in the two treatment groups.

Table 29. Baseline Demographics and Allergen Reactions

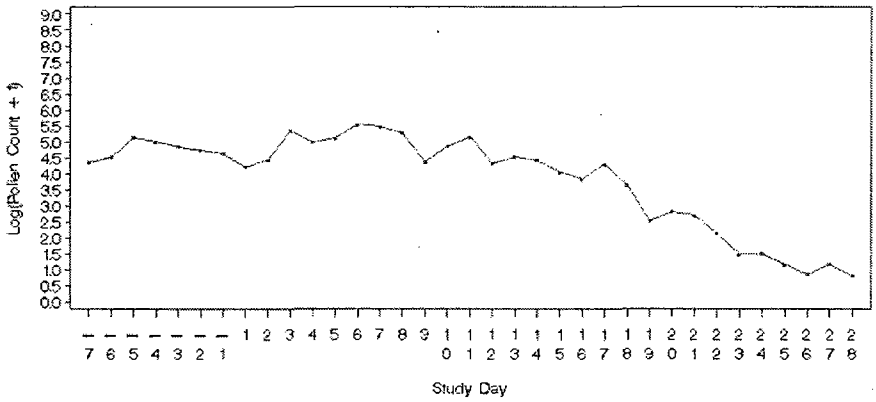
	Ciclesonide 200 mcg N=164	Placebo N=163	Total N=327
Age (years)			
Mean (SD)	39.1 (13.9)	40.8	40.0
Range	12 - 73	12 - 86	12 – 86
Gender (% Male)	35.4	35.0	35.2
Race (%)			
Caucasian	86	81.6	83.8
Black	6.1	7.4	6.7
Asian, native American	2.4	4.9	3.6
Other	5.5	6.1	5.8
Ethnicity (%)			
Hispanic	36	26.4	31.2
Non-Hispanic	64	73.6	68.8
Smoking History (%)			
Never	71.3	66.3	68.8
Former	18.3	21.5	19.9
Current	10.4	12.3	11.3
Antigen Challenge (mm)			
Mean (SD)	10.2 (5.1)	9.2 (3.4)	9.7 (4.4)
Range	3 - 35	4 - 23	3 - 35

Reviewer: All of the allergen testing was against Mountain Cedar Pollen. All of the subjects were enrolled between December 15, 2003 and March 10, 2004. Of note, 37(11.3%) of the diluent control skin tests were > 3mm.

Pollen Counts

The pollen counts were lower at the beginning and the end of the study period at all of the study sites when looked at by date. The tendency was most marked for site 5202, where it appeared, in addition, that the counts were lower at the end of the study than at the beginning. When the pollen counts were summarized by day on study, rather than date, there was a clear trend for the counts to be lower at the end of the treatment period than at the beginning in study 5202 (Figure 2).

Figure 2. Log of pollen counts, by study day, at site 5202



At site 5203 there was a very slight trend for lower counts at the end of the study, whereas, the counts were higher at the end of the study at site 3454 and 4820. None of the trends was as marked as that seen at site 5202.

Reviewer: Although all of the sites are located in South-central Texas, within 100 miles of each other, there was moderate variability in the pollen counts. When the counts were averaged by the study day, instead of the date they were obtained (to get an estimate of patient exposure during the treatment period) it was seen that subjects treated at Site 5202 were exposed to decreasing concentrations of pollen as the study progressed. This gradual change probably had little effect on the primary efficacy outcome since the changes were not dramatic during the first 14 days of treatment.

2.2.2 Efficacy Results

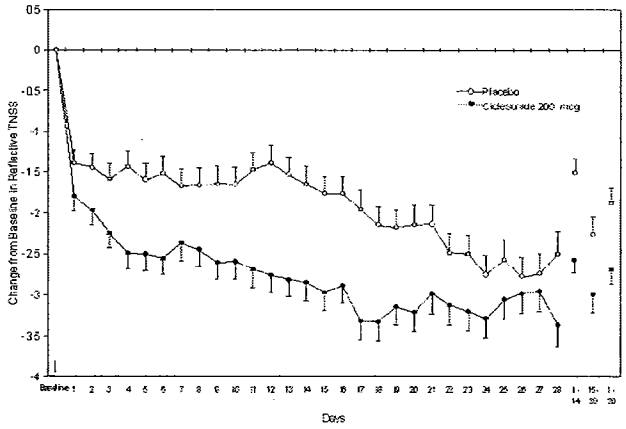
Efficacy Outcome

At baseline the mean of the AM and PM r-TNSS was 8.96 for the ciclesonide group and 8.83 for the placebo group. The baseline mean scores for the i-TNSS were very similar: 8.40 and 8.33 for the ciclesonide and placebo group respectively. The r-TNSS decreased by a LS mean of 2.4 points in the ciclesonide group and 1.50 in the placebo subjects. The treatment difference was 0.90 points which was significant with a p<0.001. The magnitude of the change and the statistical inferences are the same if the instantaneous scores were analyzed (Table 30). The changes in the r-TNSS are shown graphically in Figure 3.

Table 30. Changes in Symptom Scores During 14 Days of Treatment in Study 401

Variable	Ciclesonide N = 162	Placebo N=162	Treatment Difference (95% CI)	p-value
Average AM and PM r-TNSS				
Baseline, Mean (SD)	8.96 (1.96)	8.83 (1.82)		
Change from Baseline (LS mean [SE])	-2.40 (0.16)	-1.50 (0.16)	0.90 (0.45, 1.36)	<0.001
Average AM and PM i-TNSS				
Baseline, Mean (SD)	8.40 (2.24)	8.33 (2.08)		
Change from Baseline (LS mean [SE])	-2.15 (0.16)	-1.28 (0.16)	0.88 (0.44, 1.31)	<0.001

Figure 3. Changes in r-TNSS over 28 Days of Treatment



Reviewer: When the efficacy results are analyzed by site it can be seen that the results obtained at site 5202 were statistically significantly better than those obtained at the other sites. (See Biostats review for the statistical justification of this statement). It is of concern that this is same site where exposure to pollen decreased as the subjects remained in the study. However, while the scores fell in both the placebo and ciclesonide treated subjects, they fell by a statistically significantly greater amount in the ciclesonide-treated subjects. This suggests that ciclesonide was effective. The fact that the effect was greatest at the site with the lowest pollen counts may mean that ciclesonide is most effective when exposure to allergen is not high.

Secondary Efficacy Outcome Measures

The physician's assessment of signs and symptoms of rhinitis, as summarized in the PANS, showed no difference between the treatment groups (Table 31). The change from baseline was a LS mean of -1.98 for the ciclesonide group and -1.99 for the placebo-treated subjects. There was also no difference in the LS mean response to the RQLQ. At baseline the mean scores were 3.96 and 3.78 for the ciclesonide and placebo groups, and the scores decreased by a LS mean of 1.39 and 1.21 units in the ciclesonide and placebo groups, respectively.

Table 31. Changes in PAN and RQLQ over 28 days of Treatment

Variable	Ciclesonide N = 151	Placebo N=152	Treatment Difference (95% CI)
PANS			
Baseline, Mean (SD)	7.97 (1.58)	8.07 (1.44)	
Change from Baseline (LS mean [SE])	-1.98 (0.16)	-1.99 (0.16)	-.01 (-0.13, 0.49)
Combined Adult and Adolescent RQLQ			
Baseline, Mean (SD)	3.96 (1.05)	3.78 (0.98)	
Change from Baseline (LS mean [SE])	-1.39 (0.11)	-1.21 (0.11)	0.18 (-0.13, 0.24)

Other Efficacy Outcome Measures

The changes in the r-TNSS were less during the second half of the treatment period, but they remained greater for the ciclesonide than the placebo-treated subjects. The LS mean change from baseline between day 15 and 28 was -3.00 for the ciclesonide group and -2.25 for the placebo-treated subjects. The LS mean change from baseline to day 28 was -2.69 and -1.87 for the ciclesonide and placebo groups, respectively. The improvement in r-TNSS was 9.5% greater for the ciclesonide-treated subjects than for the placebo subjects over the fist 14 days of treatment. Over the first 14 days of treatment the magnitude of the change and the difference from placebo was similar for the AM and PM r-TNSS: For the AM scores the rTNSS fell by 0.89 more points in the ciclesonide group than in the placebo group, for the PM scores the difference was 0.90 points.

During the first 14 days of treatment, the scores for the individual symptom components of the r-TNSS all fell more in the ciclesonide group than in the placebo treated subjects and all fell to the same degree (the difference between ciclesonide and placebo was 0.20 to 0.26 points). During the second half of the study these trends continued.

The instantaneous TNSS also continued to decrease to a greater degree in the ciclesonide-treated subjects throughout the treatment period. The difference between ciclesonide and placebo for the LS mean change between baseline and day 28 was 0.80 points. The differences in the mean AM i-TNSS and PM i-TNSS were very similar to the changes in the r-TNSS, as were the differences in the changes in the individual symptom scores.

Onset of Action

At no point prior to 12 hours post-dose was the difference between ciclesonide and placebo statistically significant. The applicant noted that the first time point for the average of the AM and PM r-TNSS was on day 2.

The time to maximal effect was defined as the day in which the difference in the average AM and PM r-TNSS between ciclesonide and placebo was 90% of the maximum response. The maximum response was 1.37 (day 12) and 90% of this value (1.23) was reached on day 11. The PANS obtained on day 14 showed a LS mean difference between ciclesonide and placebo of 0.77 points although the difference had decreased to 0.03 by day 28. There was no significant difference between ciclesonide and placebo in the non-nasal symptom scores, although numerically the scores fell more in the ciclesonide group.

Subset analysis showed no difference in response comparing males and females at 14 days: mean (95% CI) difference between ciclesonide and placebo was 0.8 (0.0, 1.6) and 1.0 (0.4, 1.5) for men and women respectively. The estimate of the treatment effect appeared to be age dependent, but the small numbers of subjects < 18 (n=24) and >65 (n=21) make statistical comparisons inappropriate. The mean (95% CI) of the difference between ciclesonide and placebo was 0.3 (-1.0, 1.5), 0.9 (0.4, 1.4), and 2.2 (0.1, 4.3) in the <18, 18-65, and >65 age groups. Similarly, the infrequency of minority subjects make conclusion about racial differences in response imprecise. The mean (95% CI) of

the difference between ciclesonide and placebo at 14 days was 0.9 (0.4, 1.4), 0.9 (-0.4, 2.4), and 1.4 (-0.2, 3.1) in the Caucasian (N=271), Black (N= 22), and Other (N=31) subjects, respectively. At 28 days the differences from placebo were 0.7 (0.0, 1.3), 1.1 (-0.6, 2.7), and 1.7 (-0.0, 3.4) respectively.

Reviewer: The figures for the racial differences are taken from Table 14.2.2.7.3, pg 646/18516 in post-text tables.

2.2.3 Safety

Extent of Exposure

The mean (SD) number of days of study medication exposure was 26.4 (5.4) and 26.7 (5.1) in the ciclesonide and placebo groups respectively. Nine subjects in each treatment group received 14 days of treatment or less; 142 ciclesonide and 144 placebo treated subjects received 26 days of therapy.

Adverse Events

Adverse events were reported in 66 (40.2%) of ciclesonide and 64 (39.3%) of the placebo-treated subjects. One serious AE occurred in the ciclesonide group, and 4 (2.4%) and 5 (3.1%) of the ciclesonide and placebo subjects, respectively, were withdrawn due to adverse events. Adverse events occurring in ≥ 2% of subjects in either treatment group are tabulated in Table . The most frequent organ system affected in both treatment groups was the respiratory tract (30 [18.3%] and 29 [17.8%] of ciclesonide and placebo subjects, respectively), and the most commonly applied preferred terms in this organ system were nasal passage irritation (10 [6.1%] and 9 [5.5%] of the ciclesonide and placebo subjects, respectively) and Epistaxis (7 [4.3%] and 4 [2.5%] of the ciclesonide and placebo subjects, respectively). With the exception of infections and infestations (10 [6.1%] and 15 [9.2%] of the ciclesonide and placebo subjects, respectively) the frequency of AEs was equal or slightly higher (by no more than 3%) in the ciclesonide treated subjects

Listed by preferred term (Table 32) it can be seen that all events occurring in ≥2% of the subjects were slightly more common in the ciclesonide-treated subjects except for pharyngitis (5 [3.0%) and 6 [3.7%] of the ciclesonide and placebo-treated subjects, respectively) and upper respiratory tract infection (2 (1.2%) and 6 [3.7%] of the ciclesonide and placebo-treated subjects, respectively).

Table 32. Adverse Events occurring in ≥2% of Subjects

Preferred Term	Ciclesonide 200 mcg (N=164) n (%)	Placebo (N=163) n (%)	Total (N=327) n (%)
Patients with one or more treatment-emergent AEs	**66 (40.2)**	**64 (39.3)**	**130 (39.8)**
Nasal passage irritation	10 (6.1)	9 (5.5)	19 (5.8)
Headache	9 (5.5)	4 (2.5)	13 (4.0)
Epistaxis	7 (4.3)	4 (2.5)	11 (3.4)
Ear pain	6 (3.7)	2 (1.2)	8 (2.4)
Nasopharyngitis	5 (3.0)	2 (1.2)	7 (2.1)
Pharyngitis	5 (3.0)	6 (3.7)	11 (3.4)
Tympanic membrane disorder NOS	4 (2.4)	1 (0.6)	5 (1.5)
Upper respiratory tract infection NOS	2 (1.2)	6 (3.7)	8 (2.4)

Data source: Section 14.3, post-text Table 14.3.1.2.

Of the 66 events reported in the ciclesonide group 13 (19.7%) were classified as severe, 33 (50.0%) moderate, and 20 (30.3%) mild. In the placebo group the distribution was 7 (10.9%) severe, 34 (46.9%) moderate, and 23 (35.9%) mild. The severe events were not aggregated in any one preferred term. According to the investigator's appraisal, 18 (11.0%) of the ciclesonide AEs and 16 (9.8%) could be attributed to the study drug.

Vital Signs

Four ciclesonide subjects had vital signs that were normal at randomization, but outside the protocol normal range at the end of the study. One subject had a systolic blood pressure of 78 mm Hg, two subjects had pulse rates that were > 30 bpm less than the value obtained at baseline, and one subject developed a rapid heart rate (discussed under serious Adverse Events below).

Ear Nose and Throat Examination

The study report (pg 96/18516) states that the ENT examinations were not clinically significant at baseline or at the end of the study. The shift table (Post-text Table 14.3.5.4 [pg 947/18516]) lists 89 (54.7%) of the examinations as abnormal in the ciclesonide subjects and 90 (55.9%) as abnormal in the placebo subjects at baseline. Of those with abnormal exams, 5.6% of the ciclesonide and 8.9% of the placebo subjects had normal exams at end of study. Of those who were normal at baseline, 5.4% of the ciclesonide subjects and 1.4% of the placebo subjects were abnormal at the end of the study.

Reviewer: Looking at the descriptions in the data sheets, it appears that abnormal in the above listing refers primarily to findings compatible with allergic rhinitis. It is not clear how the applicant is using the term clinically significant, since these physical findings are characteristic of the disease under treatment. It is noteworthy, that this assessment is compatible with the PANS in which the physician's assessment based on both physical findings and symptoms showed no difference between ciclesonide and placebo.

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths and only one serious AE. One 43 year-old female in the ciclesonide group discontinued study medication due to Epistaxis on day 16 of treatment. Seven days after discontinuing the medication, she developed tachycardia that resolved

after treatment with nitroglycerin. The event was classified as serious due to hospitalization, but unrelated to the study medication.

Four subjects in the ciclesonide group withdrew from the study due to adverse events. In addition to the subject with the serious AE (described above), one 34 year-old female developed an acute attack of asthma on day 11 of therapy, one 28 year-old female was diagnosed with acute, severe sinusitis on day 18, and one 49 year-old female was withdrawn on day 14 due to lack of efficacy. The subjects with sinusitis and lack of efficacy were treated with alternative intranasal corticosteroids (Nasonex and Rhinocort) with resolution of symptoms.

The five placebo subjects who were withdrawn reported the AE on day 1, 3, 6, 8, and 12 of therapy. A 13 year-old female developed tonsillitis and was withdrawn on day 12, one 32 year-old female was discontinued on day 8 due to lack of effectiveness, a 29 year-old female developed bronchitis on day 6 of therapy and was discontinued from the study on day 13, a 21 year-old female developed an upper respiratory infection on day 3, and a 52 year-old female developed night-time cough and throat irritation after one day of treatment and weight gain on day 6 of treatment. Medication was withdrawn on day nine.

Laboratory Results

There were no mean changes or differences from placebo to suggest that ciclesonide had an effect on the safety blood or urine tests. Shift tables showed infrequent changes from normal at baseline to abnormal at end of study and the abnormalities were equally distributed among the treatment groups. One ciclesonide subject and two placebo subjects had laboratory values that were reported as adverse events. None was categorized as serious and none required withdrawing the subjects from the study. The ciclesonide subject had a blood sugar that was elevated at baseline (153 mg/dL) and increased further to 240 mg/dL by the end of the trial. Both placebo subjects had abnormal liver enzymes. A 36 year-old female had slight increases in SGOT (40 U/L at baseline to 55 U/L at end) and SGPT (41 U/L at baseline to 46 U/L at end) and a 15 year-old female had moderate elevations. Her SGPT went from 12 U/L at baseline to 247 U/L at end of study and the SGOT went from 14 U/L to 105 U/L. At follow-up both values were returning to normal. This later subject is the only one for whom the investigator thought the changes might be related to the study drug.

2.3 Summary and Discussion

In this 4-week randomized double-blind trial, 300 subjects with documented SAR were randomized to receive ciclesonide 200 mcg or placebo daily. The primary outcome was analyzed at 2 weeks of therapy and consisted of patient reported symptom scores. The 24 hour reflective TNSS improved to a significantly greater degree in the ciclesonide subjects than in the placebo subjects. The instantaneous TNSS and individual symptom scores followed the same pattern of efficacy as the overall score. However, the physicians assigned improvement score and the results of the quality of life questionnaire

did not differ in the ciclesonide and placebo subjects. Adverse events were mild and infrequent. No evidence of nasal ulceration or perforation was described. The only caution with the interpretation of the efficacy data is the fact that the results obtained at one of the sites were substantially better than the results from the other sites. This was also the site with the lowest pollen counts as well as counts that appeared to decrease throughout the treatment period. On the positive side, the difference in the scores between the ciclesonide and placebo-treated subjects was maintained throughout the study period suggesting that ciclesonide was persistently effective. It is possible that the fixed dose of ciclesonide was less effective in geographic areas where exposure to relevant antigens is very high.

3. STUDY # 363/2004 (BY9010/M1-402)

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Clinical Trial to Assess the Safety and Efficacy of Ciclesonide (200 mcg once daily) Applied as a Nasal Spray in the Treatment of Perennial Allergic Rhinitis (PAR) in Patients 12 Years and Older

3.1 Protocol

3.1.1 Administrative

Study Dates: December 18, 2003 to May 12, 2003
Clinical Centers: 41 centers in the USA and Canada
Medical Officer: [redacted]
CRO: [redacted]

3.1.2 Objective/Rationale

The primary objective of this study was to demonstrate the efficacy of intranasal ciclesonide, 200 mcg administered once daily, in the treatment of PAR. Secondary objectives included assessment of quality of life measures and the safety of administering ciclesonide intra-nasally.

3.1.3 Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group study conducted in 400 adult and adolescent subjects with PAR. Eligible subjects recorded their symptoms in a diary for 7 days prior to randomization. Those who completed the diary correctly and who had an appropriate level of symptomatology were randomized to receive either ciclesonide 200 mcg daily (2 actuations in each nostril [50 mcg/actuation])

or placebo for 6 weeks. On the first day of drug administration the subjects recorded their instantaneous TNSS hourly from 4 to 12 hour after the dose. Starting on day 2 the subjects recorded their instantaneous and reflective TNSS twice daily: in the morning (AM TNSS) before taking the study drug and approximately 12 hours later (PM TNSS). Subjects were examined at Screening, randomization, at 3 and 6 weeks of active treatment and one week after stopping active treatment. At baseline and 3 and 6 weeks the rhinitis quality of life questionnaire (RQLQ) was administered prior to questioning the subject about symptoms and before the ENT examination. Blood and urine for safety hematology and chemistry was obtained at baseline and end of study. No ophthalmology exam was performed. Subject compliance was assessed with the diary and by visual inspection of the medication bottle.

3.1.4 Study Population

Inclusion Criteria

- Males and females ≥12 years of age
- PAR of at least 2 year's duration severe enough to require treatment
- A positive skin prick test to an allergen to which the subject is likely to be exposed during the study treatment period. The response to allergen must have been at least 3 mm greater than the response to control and the test had to have been performed within 12 months or screening.

Exclusion Criteria

- History or physical findings of nasal pathology, including nasal polyps, recent nasal biopsy, nasal trauma or surgery within 60 days of screening
- Atrophic rhinitis or rhinitis medicamentosa within 60 days of screening
- Subjects with seasonal allergies and seasonal exacerbations anticipated to occur during the study.
- History of respiratory infection within 14 days of screening
- Asthma requiring treatment with corticosteroids or routine beta agonists; intermittent use of beta agonists is acceptable.
- Use of antibiotic therapy within 14 days of screening (Low dose antibiotics used for prophylaxis are allowed)
- Initiation of immunotherapy or changing the dose of immunotherapy within 90 days of screening
- Non-vaccinated exposure to or active infection with chicken pox or measles within 21 days of screening
- Exposure to systemic corticosteroids within 2 months or topical corticosteroids in excess of 1% hydrocortisone with 1 month of screening
- History of positive test for HIV or hepatitis
- History of alcohol abuse
- Intention to become pregnant or refusal to employ birth control.
- Failure to withhold prohibited medications (for list see above, study 401, pg 78)

Randomization Criteria

- A minimum r-TNSS (either AM or PM) score of 6 (maximum of 12) on at least 4 of the 7 last days of the run-in
- Scores for rhinorrhea or nasal congestion 2 or greater on at least 4 of the 7 last days of the run-in
- Completion of all but 3 of the possible diary entries

Discontinuation Criteria

Subjects could be withdrawn due to an adverse event, intercurrent illness, or major protocol violations. Protocol violations severe enough to result in withdrawal of the subject included the following: inappropriate randomization, <60% compliance, use of forbidden medications, development of a co-morbid condition or procedural complication, unblinding, or any deviations that the investigator considered to be relevant.

3.1.5 Study Procedures

Efficacy Evaluation

The Total Nasal Symptom Score (TNSS) was calculated from the diary entries as described for study 401 (pg 79, above). The AM measurement before the first dose was included in the baseline measurement. The average AM and PM scores were calculated for each of the 42 days of treatment. The physician's assessment of nasal symptoms (PANS) and the adult and adolescent RQLQ were administered as in study 401 (pg 80). The onset of action was also calculated as in study 401: instantaneous TNSS was recorded hourly from 4 to 12 hours after the first dose of blinded medication.

Safety Evaluation

Safety was assessed with adverse events, routine safety labs and ENT examinations. The ENT exams were performed at every visit and were used to assess signs of AR and complications such as bleeding, perforation, and ulceration.

3.1.6 Data Analysis

Sample Size

It was assumed that the correlation between any two observations from the same patient would be 0.7 after adjusting for day. Assuming a standard deviation for a single observed change from baseline in the average of AM and PM TNSS would be 2.6, the standard deviation for the mean change from baseline over six weeks was estimated to be 2.2. With these assumptions, 209 patients per treatment groups would provide 90% power to detect a difference between treatment groups of 0.7 with an α of 0.05.

Primary Efficacy analysis

The primary efficacy variable was the change from baseline in the average of the AM and PM r-TNSS over days 1 to 42. Baseline was defined as the average scores obtained in

the seven days prior to randomization. The analysis relied on a repeated measures analysis of covariance with baseline score, treatment day and day by treatment interaction as covariates. Day was treated as an unordered categorical variable. A first order autoregressive structure in combination with treatment patients as a random effect was used to model intra-patient correlation.

Other analytic considerations

The onset of action was defined as the time from baseline until the two-sided p-value for the test of a difference in the average of i-TNSS between intranasal ciclesonide and placebo was ≤ 0.05 with the additional requirement that this observation be confirmed by an additional p-value of ≤ 0.05 at a subsequent time point.

3.2 Results

3.2.1 Study Population

Disposition

A total of 471 subjects were randomized and 409 (86.8%) completed the study. In all, 62 (13.2%) of the subjects failed to complete treatment: 32 (13.4%) in the ciclesonide group and 30 (12.9%) in the placebo group (Table 33). The most common reason for withdrawal was an adverse event, occurring in 4.6% of both treatment groups. There were a total of 79 major protocol violations: 41 (17.2%) in the ciclesonide group and 38 (16.3%) in the placebo group.

Table 33. Table Subject Disposition in Percentage of subjects enrolled.

	Ciclesonide 200 mcg N=238	Placebo N=233
ITT analysis	100	100
PP analysis	92.0	93.1
Prematurely discontinued	13.4	12.9
Reason for discontinuation		
AE	4.6	4.7
Lack of Efficacy	0	1.3
Predefined criteria	2.9	3.9
Lost to follow-up*	7.2	3.9

* Includes lost to follow-up, compliance, patient request, and other

Reviewer: The data in Review Table 33 is taken directly from Table 3 (pg 50/18515) of the study report. Table 9, (pg 62/22461) of the study report indicates that no more than 233 ciclesonide-treated subjects and 230 placebo-treated subjects were included in any of the efficacy analyses. The primary efficacy outcome is based on 232 and 229 subjects in the ciclesonide and placebo groups, respectively, not 238 and 233 as suggested in the Disposition table.

Demographics

The mean age of the population was 35.5 years, 35.2% were male and 87.5% Caucasian. Seven percent identified themselves as Hispanic in origin and 70% were never smokers (Table 34). The mean of the wheal from the positive skin test was 8.3 mm with a mean control of 0.33 mm and a mean response to histamine of 6.27 mm. All of these variables were distributed evenly between the treatment groups.

Table 34. Baseline Demographics for Subjects Enrolled in Study

	Ciclesonide 200 mcg N=238	Placebo N=233	Total N=471
Age (years)			
Mean (SD)	35.7 (14.2)	35.4	35.5
Range	12 - 75	12 - 73	12 – 75
Gender (% Male)	37	33.5	35.2
Race (%)			
Caucasian	85.7	89.3	87.5
Black	4.2	3.9	4.0
Asian, native American	7.3	2.6	4.4
Other	5.5	4.7	5.1
Ethnicity (%)			
Hispanic	7.1	6.9	7.0
Non-Hispanic	92.9	92.7	92.8
Smoking History (%)			
Never	71.0	69.5	70.3
Former	19.7	21.5	20.6
Current	9.2	9.0	9.1
Antigen Challenge (mm)			
Mean (SD)	8.4 (41)	8.3 (3.9)	8.3 (4.0)
Range	3 - 35	3 - 21	3 - 35

Reviewer: There were 102 separate allergens listed for the positive skin tests. However, the majority of subjects (312 [66.2%]) were allergic to some form of mite, while there were 77 subjects positive for cat/cat dander, 59 for molds, 15 for dog, and 8 for roach/roach products.(From datasheet:...363-2004\\datasheets\ tabulations\at.xpt). Of note, 14 (3.0%) of the diluent control skin tests were > 3 mm and 11 (2.3%) of the histamine skin tests were <3 mm in diameter.

3.2.2 Efficacy Results

Primary Efficacy Outcome

Compliance with the treatment regimen was 96.1% in the ciclesonide group and 97.2% in the placebo-treated subjects. At baseline the mean AM and PM reflective TNSS was 7.59 if the ciclesonide group and 7.72 in the placebo-treated subjects (Table 35). Over the course of the study the LS mean score fell by 2.51 and 1.89 points in the ciclesonide and placebo groups, respectively ($p < 0.001$ for the difference between ciclesonide and placebo). The median scores from day 1 to 42 were 4.96 and 5.56 in the ciclesonide and

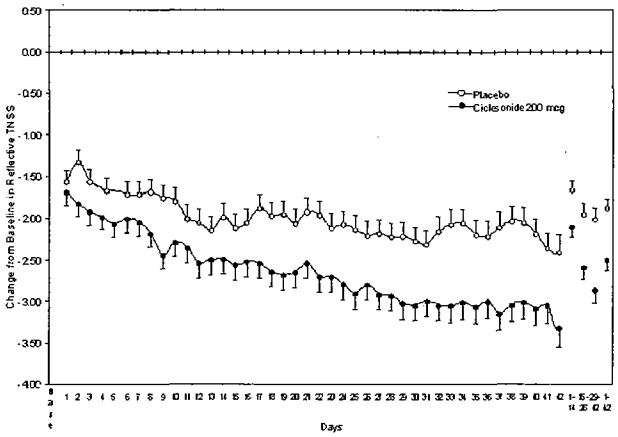
placebo groups respectively. (Day 1 median was 7.5 and 7.75 in the ciclesonide and placebo groups, respectively).

Table 35. Changes in r-TNSS During Six Weeks of Treatment in Study

Variable	Ciclesonide N = 232	Placebo N=229	Treatment Difference (95% CI)	p-value
Average AM and PM r-TNSS				
Baseline, Mean (SD)	7.59 (2.04)	7.72 (2.14)		
Change from Baseline (LS mean [SE])	-2.51 (0.12)	-1.89 (0.13)	0.63 (0.28, 0.97)	<0.001
Average AM and PM i-TNSS				
Baseline, Mean (SD)	7.07 (2.25)	7.09 (2.27)		
Change from Baseline (LS mean [SE])	-2.22 (0.12)	-1.68 (0.12)	0.54 (0.21, 0.88)	0.001

The baseline and change from placebo was similar for the instantaneous scores. The change in the r-TNSS scores is shown graphically in figure 4.

Figure 4. Reflective TNSS During Treatment with Ciclesonide 200 mcg or Placebo for 42 Days



Secondary Efficacy Measures

At baseline the physician Assessment of Nasal Symptoms (PANS) was 6.91 and 6.81 in the ciclesonide and placebo groups, respectively (Table 36). During treatment the score fell by a LS mean of 2.05 and 1.67 points, respectively. At baseline the RQLQ was 3.32 points in the ciclesonide-treated subjects and 3.38 in the placebo group. Both scores fell during treatment: LS mean of 1.30 and 1.01, respectively.

Table 36. Change in PANS and RQLQ After Six Weeks of Treatment

Variable	Ciclesonide N = 233	Placebo N=229	Treatment Difference (95% CI)
PANS			
Baseline, Mean (SD)	6.91 (1.98)	6.81 (2.05	
Change from Baseline (LS mean [SE])	-2.05 (0.15)	-1.67 (0.15)	0.38 (0, 0.76)
Combined Adult and Adolescent RQLQ	N=211	N=202	
Baseline, Mean (SD)	3.32 (1.08)	3.38 (1.10)	
Change from Baseline (LS mean [SE])	-1.30 (0.08)	-1.01 (0.08)	0.28 (0.07, 0.50)

The components of the rTNSS also improved to a greater extent in the ciclesonide than the placebo group. The mean scores for each week of treatment were better in the ciclesonide group, as were the values for percent change. The mean PM scores fell by more than the mean AM scores, although the difference between ciclesonide and placebo was greater for the AM score (Table 37). For all time points and for all analyses the mean scores fell more with ciclesonide than with placebo treatment.

Table 37. Changes in separate AM and PM r-TNSS

Variable	Ciclesonide N = 232	Placebo N=229	Treatment Difference (95% CI)
AM rTNSS			
Baseline, Mean (SD)	7.39 (2.31)	7.32 (2.41)	
Change from Baseline (LS mean [SE])	N=211	N=202	
Day 1-14	-1.93 (0.13)	-1.42 (0.13)	0.50 (0.15, 0.85)
Change from Baseline (LS mean [SE])			
Day 1-42	-2.40 (0.13)	-1.67 (0.13)	0.73 (0.36, 1.10)
PM rTNSS			
Baseline, Mean (SD)	7.78 (1.93)	8.11 (2.09)	
Change from Baseline (LS mean [SE])			
Day 1-14	-2.29 (0.31)	-1.95 (0.13)	0.34 (-0.02, 0.70)
Change from Baseline (LS mean [SE])			
Day 1-42	-2.63 (0.13)	-2.12 (0.13)	0.51 (0.15, 0.87)

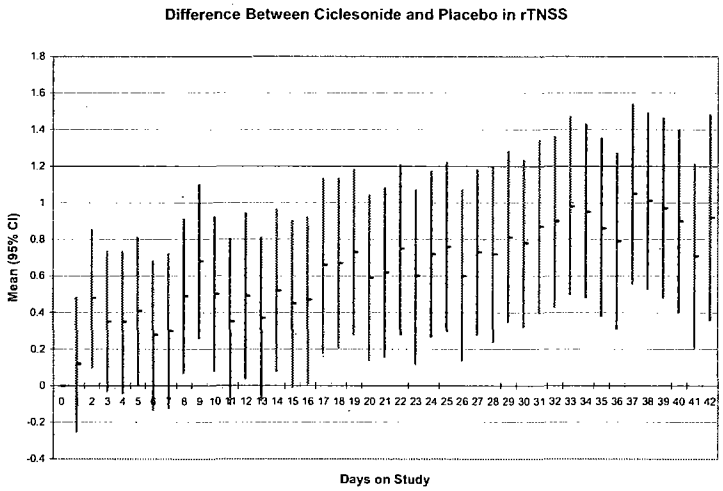
Analysis of the individual symptoms (nasal congestion, itching, sneezing, and rhinorrhea) at all time points showed more improvement during ciclesonide treatment than during treatment with placebo. The instantaneous TNSS followed a pattern that was similar to the rTNSS scores. Treatment with ciclesonide resulted in uniformly greater improvement that treatment with placebo.

Onset of Action

Only one time point showed a difference between ciclesonide and placebo that had a p-value of <0.05. Therefore, no onset of action could be assigned during the first 24 hours. The difference between placebo and ciclesonide ranged between 0.03 to 0.45 points.

Reviewer: The applicant wants to assign an onset of action of at least Day 2 due to the results of the r-TNSS (mean AM and PM values) because the difference between placebo and ciclesonide had a p-value of 0.05 on that day for the first time. However, the differences were not consistently significant until two weeks of treatment. Reviewer figure 1 (taken from Table 14.2.2.1.1 of post-text tables, pg233/22462) shows that the lower limit of the confidence interval was not consistently greater than zero until day 17.

Reviewer Figure 1.



Subset Analysis

There were no differences in the response to ciclesonide comparing males and females. The vast majority of subjects (87%) were between the ages of 18 and 64 years: 2% were less than 18 and 12% were > 64. Only 25 subjects between the ages of 12 and 17 were treated with ciclesonide. Therefore, statistical inference could not be applied to the age subgroups. However, there was no subgroup in which the placebo subjects improved more than the ciclesonide-treated subjects. Minorities were also poorly represented. Only 4% of the population was Black/African American and 10% was Asian/Other.

3.2.3 Safety

Extent of Exposure

Then mean days of exposure was 39.8 and 40.3 in the ciclesonide and placebo subjects, respectively (Table). Only 12 ciclesonide subjects and 10 placebo subjects received less than 15 days of therapy.

•

Adverse Events

One hundred and two (42.9%) subjects in the ciclesonide group and 110 (47.2%) in the Placebo group reported adverse events. Respiratory, thoracic, and mediastinal disorders were the most frequent in both groups (23.1 and 23.6% of the ciclesonide and placebo subjects, respectively). In the ciclesonide group the next most frequent events were in the nervous system (12.6%), infectious diseases (8.4%) gastrointestinal disorders (3.4%) ear disorders (2.9%), eye disorders (2.9%) and in the placebo group the order was infectious diseases (14.2%), nervous system disorders (9.9%) and gastrointestinal disorders (3.9%)

Comparing the treatment groups by adverse events that occurred in >2% of the subjects showed that headache, epistaxis, and sinus headache were slightly more frequent in the ciclesonide subjects (Table 38) whereas Nasopharyngitis, pharyngitis, upper respiratory

tract infection, nasal passage irritation, aggravation of asthma, and nausea were all more frequent in the placebo subjects. The differences in incidence were trivial except for upper respiratory tract infection which occurred in 8 (3.4%) of the ciclesonide subjects and 16 (6.9%) of the placebo subjects. Adverse events were classified as severe in 7.1 and 5.2% of the ciclesonide and placebo subjects, respectively. In the ciclesonide group 17.2% were moderate and 18.5% were mild, where as in the placebo group 21.0% were moderate and 21.0% were mild in intensity.

Table 38. Study M1-402: Adverse Events Occurring in >2% of Subjects

Preferred Term	Ciclesonide 200 mcg (N=238) n (%)	Placebo (N=233) n (%)	Total (N=471) n (%)
Patients with one or more treatment-emergent AEs	102 (42.9)	110 (47.2)	212 (45.0)
Headache	21 (8.8)	17 (7.3)	38 (8.1)
Epistaxis	18 (7.6)	12 (5.2)	30 (6.4)
Nasopharyngitis	15 (6.3)	16 (6.9)	31 (6.6)
Pharyngitis	9 (3.8)	9 (3.9)	18 (3.8)
Upper respiratory tract infection NOS	8 (3.4)	16 (6.9)	24 (5.1)
Cough	5 (2.1)	5 (2.1)	10 (2.1)
Sinus headache	5 (2.1)	2 (0.9)	7 (1.5)
Nasal passage irritation	3 (1.3)	5 (2.1)	8 (1.7)
Asthma aggravated	1 (0.4)	5 (2.1)	6 (1.3)
Nausea	1 (0.4)	5 (2.1)	6 (1.3)

Data source: Section 14.3, post-text Table 14.3.1.2

Physical Examination

Vital signs were normal at baseline but abnormal at the end of the study in 2 ciclesonide and 1 placebo subject. In the ciclesonide group, 1 subject had a pulse rate of 54 at baseline that increased to 90 bpm at Endpoint. Another subject had an increase in blood pressure from 100/60 to 150/110. One subject in the placebo group had a fall in systolic blood pressure from 178 to 128 mm Hg. None of these changes was assessed as severe and none was thought to be related to treatment.

An ENT examination was performed at each visit and revealed changes compatible with allergic rhinitis in most subjects. One subject each in the ciclesonide and placebo groups had erosion ("Septal erosion" and "Few erosion") listed in the physical examination data sheet (...\tabulations\pe.xpt). The erosions were present at week 3 and had resolved by week 6. Both cases were females in their twenties and both were seen at the same site.

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths and no serious adverse events. Eleven subjects in each group withdrew prematurely due to adverse events. In the ciclesonide group there were 3 upper respiratory infections, 2 sinus headaches, and one case each of asthma exacerbation, dental abscess, conjunctivitis, loss of appetite, snoring, and hives after application of an herbal lotion that resulted in withdrawal. In the placebo subjects there were 3 upper respiratory infections, 2 each asthma exacerbations, headaches, and rhinitis, and one each of sinusitis and urinary tract infection that resulted in withdrawal.

Laboratory Results

There were no clinically meaningful changes in the mean values for any of the laboratory tests. Shifts from normal to abnormal occurred in less than 5% of the subjects in each group except for several chemistries which tend to have variable values and fluctuate with the conditions of testing: Glucose increased in 6.6 and 8.2%, phosphate increased in 5.9 and 6.9%, and urate increased in 6.7 and 6.3% of the ciclesonide and placebo subjects, respectively.

Two ciclesonide and 4 placebo subjects had laboratory abnormalities defined as adverse events. None was serious and none resulted in early termination. In the ciclesonide group one 16 year-old female had persistent, mild abnormalities in alkaline phosphatase (low), calcium, albumin, and phosphate (high). A 25 year-old male had minimally elevated calcium at both determinations and liver enzymes that increased over the course of the trial. The ALT went from 33 to 127 U/L and the AST increased from 29 to 71. The abnormalities in the ciclesonide-treated subjects were judged to be likely due to the study drug. In the placebo group 2 subjects had normal glucose at baseline that was elevated at endpoint, one had a persistently low total white count (3,200 and 2,600 cells/mm^2) one had mildly elevated AST at baseline and endpoint, but an ALT that was high at baseline and decreased to normal at endpoint, and one subject had a normal lipase at baseline that was elevated at endpoint. None of the changes in the placebo subjects was thought to be due to the study drug.

3.3 Summary and Discussion

This was a 6-week, randomized, double blind comparison of ciclesonide 200 mcg daily to placebo for the treatment of PAR. The study was conducted at 41 sites widely distributed throughout Canada and the United States. Of the 471 subjects enrolled, 86.8% completed the trial and compliance with the treatment regimen was >90%. Thirty-five percent of the subjects were male, >85% were Caucasian, and the majority were between 18 and 64 years of age. All had positive skin tests to one of a variety of perennial antigens. The primary efficacy analysis showed that the r-TNSS decreased by a LS mean (95% CI) of 0.63 (0.28, 0.97) points more in the ciclesonide than in the placebo-treated subjects. The instantaneous TNSS and the components of the r-TNSS and i-TNSS also improved more in the ciclesonide group. The Physician Assessment of Nasal Symptoms improved by a LS mean (95% CI) of 0.38 (0, 0.76) points more in the ciclesonide-treated subjects, and the RQLQ improved by a LS mean (95% CI) of 0.28 (0.07, 0.50) more in the ciclesonide group. The onset of action as defined by the i-TNSS scores on day 1 of treatment failed to document an onset of action. Serial comparison of the r-TNSS showed consistently greater improvement in the ciclesonide-treated group only after 15 days of treatment. Adverse events were mild and infrequent. Two subjects had septal erosions on physical examinations, however, one of these subjects was treated with placebo. No specific ophthalmologic assessment was performed.

4. STUDY # 146/2005 (BY9010/M1-404)

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Clinical Trial to Assess the Long Term Safety of Ciclesonide Applied as a Nasal Spray (200 mcg once daily) in the Treatment of Perennial Allergic Rhinitis (PAR) in Patients 12 Years and Older

4.1 Protocol

4.1.1 Administrative

Study Dates: January 9, 2004 to April 29, 2005
Clinical Centers: 35 centers in the USA
Medical Officer: [redacted]

4.1.2 Objective/Rationale

The primary objective of this study was to demonstrate the long-term safety of ciclesonide, applied as a nasal spray once daily, in adults and adolescents with PAR. Secondary objectives included assessment of efficacy and quality of life measures in patients taking ciclesonide intra-nasally

4.1.3 Study Design

This was a 52-week, randomized, double-blind, placebo-controlled, parallel-group study conducted in adults and adolescents with PAR. Eligible subjects recorded their symptoms in a diary for 7-14 days prior to randomization. Those who completed the diary correctly during the run in were randomized (2:1 ciclesonide: placebo) at T0 to receive either ciclesonide 200 mcg daily (2 actuations in each nostril [50 mcg/actuation]) or placebo. Subjects were seen in the clinic at screening (B0), randomization (T0), and at 10 subsequent visits: at three (T1), six (T2), 12 (T4), 18 (T6), 24 (T8), 30 (T10), 36 (T12), 42 (T14), 48 (T16), and 52 (T18) weeks of follow-up. The trial was originally planned to continue for 48 weeks. However, to meet ICH guidelines for the exposure of at least 100 subjects for 52 weeks, the protocol was amended on October 18, 2004 to allow for a 4-week extension for subjects enrolled before March 31, 2004. Throughout the trial the subjects recorded an AM 24-hour reflective Total Nasal Symptom Score (r-TNSS) in a diary. In addition to patient-assessed nasal symptoms, the treating physicians assigned a signs and symptoms score (PANS), and ENT examination was performed at each follow-up visit. A rhinitis quality of life questionnaire, complete physical examination, 12-lead ECG, and an ophthalmologic examination (including IOP and slit lamp examination) were performed at baseline, 24 and 48/52 weeks. The HPA-axis was also assessed at baseline, 24, and 48/52 weeks in a subset of subjects (N=250) who were enrolled at pre-selected sties. The HPA-axis assessment included a 24-hour urine for free

cortisol and a single AM plasma determination of cortisol. Subject compliance was assessed with the diary and by visual inspection of the medication bottle.

4.1.4 Study Population

Inclusion Criteria

- Males and females ≥12 years of age
- PAR of at least 2 year's duration severe enough to require treatment
- A positive skin prick test to an allergen to which the subject was likely to be exposed during the study treatment period. The response to allergen must have been at least 3 mm greater than the response to control and the test had to have been performed within 12 months or screening.

Exclusion Criteria

- History of physical findings of nasal pathology, including nasal polyps, recent nasal biopsy, nasal trauma or surgery within 60 days of screening
- Atrophic rhinitis or rhinitis medicamentosa within 60 days of screening
- Subjects with seasonal allergies with seasonal exacerbation anticipated to occur during the study.
- History of respiratory infection within 14 days of screening
- Asthma requiring treatment with corticosteroids or routine beta agonists; intermittent use of beta agonists is acceptable.
- Use of antibiotic therapy within 14 days of screening (Low dose antibiotics used for prophylaxis are allowed).
- Initiation of immunotherapy or changing the dose of immunotherapy within 90 days of screening
- Non-vaccinated exposure to or active infection with chicken pox or measles within 21 days of screening
- Exposure to systemic corticosteroids within 2 months or topical corticosteroids in excess of 1% hydrocortisone with 1 month of screening
- History of positive test for HIV or hepatitis
- History of alcohol abuse
- Intention to become pregnant or refusal to employ birth control.
- Participation in any investigation drug trial within 30 days of screening.
- Chronic treatment with agents known to promote the development of cataracts (potassium-sparing diuretics, sulfonylurea hypoglycemic agents, allopurinol).
- History of eye disease
    - History of prior cataract surgery in either eye
    - Intraocular pressure >20 mm Hg at baseline
    - Inability to grade nuclear, cortical, or posterior subcapsular opacities in either eye with LOCS III at the baseline slit lamp examination
    - Inability to dilate pupils to at least 6.0 mm
    - Nuclear opalescence with a LOCS III grade ≥ 4 in either eye at the baseline slit lamp examination

  - Cortical lens opacities with a LOCS III grade ≥ 3 in either eye at the baseline slit lamp examination
  - Posterior subcapsular lens opacities with a LOCS III grade ≥ 2 in either eye at the baseline slit lamp examination
  - Glaucoma requiring treatment
  - Best corrected visual acuity worse than 20/30 (Snellen chart or equivalent) in either eye at baseline;
  - Refractive surgery within the past six months.
- Use of chemotherapeutic agents for malignancy within twelve months of screening

Randomization Criteria

- No adverse events during screening that would result in failure to meet screening criteria
- No use of prohibited medication during screening.
- Adequate completion of diary

Discontinuation Criteria

Subjects could be withdrawn due to an adverse event, intercurrent illness, or major protocol violations. Protocol violations severe enough to result in withdrawal of the subject included the following: inappropriate randomization, <80% compliance, use of forbidden medications, development of a co-morbid condition or procedural complication, unblinding, or any deviations that the investigator considered to be relevant.

4.1.5 Study Procedures

Treatment

The medications listed in Table 39 were forbidden throughout the trial and for the time prior to enrollment as specified in the table.

Table 39. Forbidden Medications

Type of Medication	Time since last dose
Any other investigational drug	30 days
All intranasal corticosteroids except study medication	30 days
Systemic corticosteroids (intermittent or chronic) except for oral contraceptives or hormone replacement therapy	60 days
Inhaled corticosteroids (oral or inhaled)	30 days
Immunosuppressive drugs	60 days
Anti IgE therapy	60 days

Permitted medications included low dose antibiotics, immunotherapy, intermittent beta-agonists for asthma, aspirin, and topical corticosteroids as described for study 401 (pg . above). No rescue medication was provided.

Efficacy Evaluation

Efficacy was designed as a secondary outcome in this trial. However The Total Nasal Symptom Score (TNSS) was calculated from the diary entries for sneezing, runny nose, nasal itching, and congestion. The symptoms were scored as described for study 401 (pg above) however, each entry was made only once daily. The diary was filled out in the morning before any medication or activity and represented the subject's recall of symptoms over the previous 24 hours. The physician's assessment of nasal signs and symptoms (PANS) and the adult and adolescent RQLQ were administered as in study 401. Compliance was assessed with the diary entries and by visual inspection of the medications bottles.

Safety Evaluation

Safety was assessed with adverse events, routine safety laboratory and ENT examinations. The ENT exams were performed at every visit and were used to assess signs of AR and complications such as bleeding, perforation, and ulceration. Additionally formal ophthalmologic evaluations were performed at baseline 24, and 48/52 weeks which included the following:

- Visual acuity (unrefracted and, as appropriate, refracted) by the standard technique (Snellen Chart or its equivalent) used by the ophthalmologist, using the same equipment for all examinations of an individual patient.
- Slit lamp examination
- Intraocular pressure
- Lens Grading (Lens Opacity Classification System Version III [LOCS III]):
    - Nuclear opalescence (NO)
    - Nuclear color (NC)
    - Cortical cataract(C)
    - Posterior subcapsular cataract (P)
- Lens opacities were evaluated at the end of each eye examination after pupil dilation to at least 6.0 mm.
- Overall ocular health

The 95% confidence interval for the average LOCS III grade treatment differences was compared to the thresholds defined for a Class I event (0.5 for nuclear opalescence or posterior subcapsular opacity and 0.8 for cortical opacity) in order to look for non-inferiority of ciclesonide to placebo.

The best-corrected visual acuity was defined as the refracted visual acuity for patients needing refraction and the un-refracted acuity otherwise. Visual acuity was measured using the Snellen fraction. If the ophthalmologist was unable to provide a Snellen fraction due to severe myopia, a Count Fingers (CF) was provided instead. CF values were categorized as worse than 20/200. Visual acuity was treated as a categorical variable as follows:

- 20/20 or better
- Worse than 20/20 to 20/50
- Worse than 20/50 to 20/100
- Worse than 20/100 to 20/200
- Worse than 20/200.

The analysis was performed on the value obtained from averaging the results from the two eyes.

The assessment of the HPA-axis included a single AM blood sample and a 24-hour urine for cortisol. There were no preset criteria for adequacy of the urine collection.

4.1.6 Data Analysis

Sample Size

The sample size was derived from the requirement to follow 100 subjects for 52 weeks and 300 for 24 weeks.

Primary Efficacy and Safety Analysis

The efficacy variables were defined as in study 401 (pg 79) except that a single 24-hour r-TNSS was obtained in the morning. The analysis was then performed on the mean weekly 24-hour r-TNSS. The comparison between placebo and ciclesonide was made on the scores obtained over the entire 48/52 weeks of treatment (the change from baseline in the average of the AM r-TNSS over days 2 to 365). Baseline was defined as the average scores obtained in the seven days prior to randomization. The analysis relied on a repeated measures analysis of covariance with baseline score, treatment, day and day by treatment interaction, and pooled center as covariates. A first order autoregressive correlation structure in combination with inclusion of patients as a random effect was used to model intra-patient correlation.

For the safety analysis of continuous variables, the randomization visit (T0) was taken as the baseline. For the urine and plasma cortisol determinations, changes from baseline were analyzed with an ANCOVA model with covariate adjustment for center, age, gender, baseline and treatment.

The ophthalmologic examinations were quantitated as follows:

- Class I: an increase in LOCS III grade of at least 0.5 for nuclear opalescence or posterior subcapsular opacity or 0.8 for cortical opacity in either eye, and/or cataract surgery.

- Class II: an increase in LOCS III grade of at least 0.9 for nuclear opalescence or posterior subcapsular opacity or 1.5 for cortical opacity in either eye.
- Class III: an increase in LOCS III grade of at least 0.9 for nuclear opalescence or posterior subcapsular opacity or 1.5 for cortical opacity in either eye and a LOCS III score of at least 2.0 for at least one type of opacity.

4.2 Results

4.2.1 Study Population

Disposition

A total of 663 subjects were randomized and 474 (71.5%) completed the study. In all, 189 (28.5%) of the subjects failed to complete treatment: 123 (27.9%) in the ciclesonide group and 66 (29.7%) in the placebo group (Table 40). The most common reason for withdrawal was lack of compliance which occurred in 11.0% of the subjects followed by loss to follow-up (7.5%). While lack of compliance was similar in the two treatment groups (10.9 and 11.3% in the ciclesonide and placebo groups, respectively) lost to follow-up was slightly more common in the placebo group (6.6 and 9.5% in the ciclesonide and placebo groups, respectively). There were a total of 91 major protocol violations: 63 (14.3%) in the ciclesonide group and 28 (12.6%) in the placebo group. All 663 subjects were included in the ITT and safety populations.

Table 40. Subject Disposition in percentage of subjects enrolled

	Ciclesonide 200 mcg N=441	Placebo N=222
ITT analysis	100	100
Prematurely discontinued	27.9	29.7
Reason for discontinuation		
AE	4.3	3.2
Lack of Efficacy	2.3	1.8
Predefined criteria	2.3	5.4
Lost to follow-up*	21.4	24.0

* Includes lost to follow-up, compliance, patient request, other

Demographics

The mean age of the population was 37.1 years, 34.2% were male, 81.4% Caucasian, and 13.3% identified themselves as Hispanic in origin (Table 41). The mean of the wheal from the positive skin test was 9.4 mm with a mean control of 0.76 mm and a mean response to histamine of 6.27 mm. All of these variables were distributed evenly between the treatment groups. The subjects were recruited from all over the United States, but the largest cohorts were recruited in Texas (181) and California (124). The remainder was recruited from 13 states, none of which enrolled more than 40 subjects.

Table 41. Baseline Demographics for Subjects Enrolled in Study

	Ciclesonide 200 mcg N=441	Placebo N=222	Total N=663
Age (years)			
Mean (SD)	37.4 (14.2)	36.7	37.1
Range	12 – 74	13 – 68	12 – 74
<18 (n)	52	26	78
>65 (n)	10	8	18
Gender (% Male)	33.8	35.1	34.2
Race (%)			
Caucasian	81.0	82.4	81.4
Black	10.9	9.5	10.4
Asian, native American	2.9	2.3	2.8
Other	5.4	6.3	5.7
Ethnicity (%)			
Hispanic	13.6	12.6	13.3
Non-Hispanic	86.4	87.4	86.7
Smoking History (%)			
Never	71.0	69.5	70.3
Former	19.7	21.5	20.6
Current	9.2	9.0	9.1
Antigen Challenge (mm)			
Mean (SD)	8.4 (41)	8.3 (3.9)	8.3 (4.0)
Range	3 - 35	3 - 21	3 - 35
Type of Skin Test			
Historical	33.1	33.3	33.2
Current	66.9	66.7	66.8

Reviewer: There were 94 separate allergens listed for the positive skin tests. However, the majority of subjects (414 [62.4%]) were allergic to some form of mite, while 105 were allergic to molds, 85 to cats, 24 to roaches, 14 to dogs, 13 to grasses/trees and the remainder to sundry, less common, antigens. (From datasheet:...146-2005\datasheet\tabulations\at.xpt). Of note, 48 (7.2%) of the Control skin tests were >3mm (Maximum response 19 mm) and 2 (<1%) of the Histamine tests were <3mm. A listing of medications taken prior to enrollment was taken from post-text table 14.1.4.1 (pg 164/30104. Nasal corticosteroids were taken by 31 (7%) of the ciclesonide and 10 (4.5%) of the placebo-treated subjects. The only other systemic corticosteroid treatment listed was one ciclesonide subject who had taken Advair and 1 placebo subject who had taken Pulmocort.

4.2.2 Efficacy Results

Primary Efficacy Outcome

Compliance with the treatment regimen was >95% in both treatment groups. At baseline the mean (SD) 24-hour reflective TNSS was 6.4 (2.9) in the ciclesonide group and 6.3 (2.9) in the placebo-treated subjects (Table 42). Over the course of the study the LS mean score fell by 2.3 and 1.8 points in the ciclesonide and placebo groups, respectively ($p < 0.001$ for the difference between ciclesonide and placebo). The percent change in the 24-hour r-TNSS was -31.2 in the ciclesonide group and -16.2 in the placebo subjects. There was thus a 15% difference between the two treatments. Ciclesonide treatment resulted in more improvement compared with placebo at all time points for both the

absolute and percent change. The scores for the individual symptoms also improved more with ciclesonide treatment.

Table 42. Changes in r-TNSS During Treatment with Ciclesonide for 52 Weeks

Variable	Ciclesonide N = 435	Placebo N=229	Treatment Difference (95% CI)	p-value
Average 24-hour rTNSS				
Baseline, Mean (SD)	6.4 (2.9)	6.3 (2.9)		
Change from Baseline (LS mean [SE])	-2.3 (0.09)	-1.8 (0.13)	0.6 (0.3 0.9)	<0.001
Percent Change in 24-hour rTNSS (LS mean [SE])	-31.2 (2.3)	-16.2 (3.2)	15.0 (7.3, 22.6)	<0.001

Secondary Efficacy Measures

At baseline the physician Assessment of Nasal Symptoms (PANS) was 5.85 and 5.80 in the ciclesonide and placebo groups, respectively. During treatment the score fell by a LS mean of 1.78 and 1.76 points, respectively (Table 43). At baseline the RQLQ was 2.87 points in the ciclesonide-treated subjects and 2.81 in the placebo group. The score fell by a LS mean of 1.1 and 0.88, respectively.

Table 43. Change in PANS and RQLQ During Treatment with Ciclesonide for 52 Weeks

Variable	Ciclesonide N = 438	Placebo N=220	Treatment Difference (95% CI)
PANS			
Baseline, Mean (SD)	5.85 (2.3)	5.80 (2.2)	
Change from Baseline (LS mean [SE])	-1.78 (0.11)	-1.76 (0.15)	0.01 (-0.33, 0.35)
Combined Adult and Adolescent RQLQ	N=395	N=202	
Baseline, Mean (SD)	2.87 (1.18)	2.81 (1.16)	
Change from Baseline (LS mean [SE])	-1.1 (0.06)	-0.88 (0.08)	0.19 (0.01, 0.36)

The Applicant claims statistical significance for the change in RQLQ. They further note that the overall scores were low so that there was not much room for improvement. A post hoc subset analysis showed an even larger difference between placebo and ciclesonide in the score (-0.49 [95% CI= 0.06, 0.93]) in the subset of subject with a baseline RQLQ score >3.5.

Reviewer: In no case did the difference between placebo and ciclesonide reach the clinically meaningful level of 0.5.

4.2.3 Safety

Extent of Exposure

The mean of the days of exposure was 287.9 and 286.5 in the ciclesonide and placebo subjects, respectively. Ninety-seven subjects were exposed to ciclesonide for ≥ 364 days. The majority of subjects (71.7%) were exposed to study drug for > 327 days.

Adverse Events

Three hundred thirty-one (75.1%) subjects in the ciclesonide group and 165 (74.32%) in the Placebo group reported adverse events. Upper respiratory tract infection, and nasopharyngitis were the most common events in both groups (Table 44) with epistaxis, nasopharyngeal pain, sinusitis, and headache the next most frequent. Upper respiratory tract infection and nasopharyngitis were slightly more common in the placebo subjects while epistaxis (10.0 vs 7.3%), pharyngolaryngeal pain (9.3 and 4.5%), sinusitis (9.3 vs 7.2%), and headache (7.5 vs 5.9%) were more common in the ciclesonide treated subjects. All other events occurred in less than 5% of subjects.

Table 44. Study M1-404: Adverse Events Occurring in > 2% of Subjects

Preferred Term	Ciclesonide 200 mcg (N=441)	Placebo (N=222)	Total (N=663)
Patients with one or more treatment-emergent AEs	**331 (75.1%)**	**165 (74.3%)**	**496 (74.8%)**
Upper respiratory tract infection	72 (16.3%)	39 (17.6%)	111 (16.7%)
Nasopharyngitis	58 (13.2%)	40 (18.0%)	98 (14.8%)
Epistaxis	44 (10.0%)	16 (7.2%)	60 (9.0%)
Pharyngolaryngeal pain	41 (9.3%)	10 (4.5%)	51 (7.7%)
Sinusitis	41 (9.3%)	16 (7.2%)	57 (8.6%)
Headache	33 (7.5%)	13 (5.9%)	46 (6.9%)
Nasal Discomfort	20 (4.5%)	9 (4.1%)	29 (4.4%)
Cough	19 (4.3%)	5 (2.3%)	24 (3.6%)
Bronchitis	18 (4.1%)	8 (3.6%)	26 (3.9%)
Influenza	17 (3.9%)	8 (3.6%)	25 (3.8%)
Acute sinusitis	13 (2.9%)	9 (4.1%)	22 (3.3%)
Back pain	13 (2.9%)	6 (2.7%)	19 (2.9%)
Sinus headache	12 (2.7%)	7 (3.2%)	19 (2.9%)
Urinary tract infection	12 (2.7%)	2 (0.9%)	14 (2.1%)
Nausea	10 (2.3%)	8 (3.6%)	18 (2.7%)
Ear pain	9 (2.0%)	3 (1.4%)	12 (1.8%)
Toothache	9 (2.0%)	5 (2.3%)	14 (2.1%)
Viral upper respiratory tract infection	8 (1.8%)	7 (3.2%)	15 (2.3%)

NOS = not otherwise specified
Data source: Section 14.3 and Post-text Table 14.3.1.2.1

In an assessment of severity, (13.4%) of ciclesonide-treated subjects had severe events and 44.7% had events that were classified as moderate. This compared with 11.7% of placebo subjects with severe events and 49.1% with moderate events. The applicant assessed 75 (17.0%) of the ciclesonide-treated subjects as having treatment related AEs and 24 (10.8%) of the placebo-treated subjects as having treatment related events. Of those assessed as treatment-related, the most common event in both treatment groups was epistaxis (8.4 and 6.3% in the ciclesonide and placebo groups, respectively).

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths. Sixteen subjects (3.6%) treated with ciclesonide had serious events: 3 pneumonia, 4 suicidal ideation/suicide attempt/depression, 2 cholecystitis, and one case each of multiple myeloma, stress incontinence, renal insufficiency, gastroesophageal reflux, spider bite, miscarriage and diaphragmatic hernia. The cases were judged serious due to the requirement for hospitalization. Of the three pneumonias two had a history of chronic asthma. Of those with suicidal ideation/depression, three were on medication for chronic emotional problems. Six subjects in the placebo group had serious adverse events. Two subjects were hospitalized with coronary artery disease, and there was one case each of basal cell carcinoma, acute allergic reaction (tomatoes), Brugada syndrome (a genetic abnormality in intra-ventricular conduction), and skull fracture.

Adverse events resulted in premature withdrawal in 19 (4.3%) of the ciclesonide subjects and 6 (2.7%) of the placebo-treated subjects (Table 45). In the ciclesonide group 2 subjects each withdrew with a diagnosis of asthma, bronchitis, and epistaxis. No other event occurred in more than a single subject in each treatment group. Six ciclesonide cases withdrew with respiratory or ENT complaints and the rest with a variety of organs involved. With the exception of the one case of asthma all of the cases that withdrew due to an AE in the placebo group were non-respiratory.

Table 45. Adverse events resulting in withdrawal.

	Ciclesonide 200 mcg N=441	Placebo N=222
Asthma/bronchitis	4	1
Epistaxis	2	0
Other respiratory	6	0
Other non-respiratory	7	6

Other Adverse Events

Three subjects developed cataracts during the trial: one in the ciclesonide group and 2 in the placebo group. For the prospective Ophthalmology Examination results, see below.

Six subjects became pregnant during the study: 4 in the ciclesonide group and 2 in the placebo group. Of the four ciclesonide subjects, one developed eclampsia (included in the SAE tabulation), one had a spontaneous abortion, and in two the outcome was unknown. Of the 2 pregnancies in the placebo group, one result is unknown and the other resulted in a normal delivery.

Physical Examination

Mean vital signs at baseline and end of study were similar for the two treatment groups. A 48 year-old male treated with ciclesonide had a normal BP at baseline but a value of 151/106 and 170/110 at follow-up.

An ENT examination was performed at each visit and revealed changes compatible with allergic rhinitis in most subjects. Two subjects, both in the placebo group, had evidence

of transient septal perforation/ulceration. One subject had a "small septal ulceration at 6 weeks that was not present at later follow-up. The other subject had a single observation of a septal ulcer at 18 weeks.

Reviewer: The description of the nasal perforation and ulceration is taken from the data sheet "datasets\tabulations\ pe.xpt". The ulceration, but not the perforation, was also listed as an adverse event.

Electrocardiograms

At baseline 59.5 % of the placebo and 63.0% of the ciclesonide subjects had normal ECGs at baseline. Of those with normal ECGs at baseline, and who attended the 6-month visit, 23.2% of the ciclesonide subjects and 23.6% of the placebo subjects had new abnormalities. Of those with normal ECGs at baseline, and who attended the 12-month visit, 24.3% of the ciclesonide subjects and 21.6% of the placebo subjects had new abnormalities. Most of the abnormalities were sinus arrhythmias, non-specific S-T changes, old ischemia, and common conduction abnormalities. Two subjects treated with ciclesonide had QTc prolongation noted at the end of treatment that was not seen at baseline, while three subjects treated with placebo had QTc prolongation on the baseline ECG that was not seen at follow-up. The exact duration of the prolongation is not reported. Two subjects in the placebo group had atrial fibrillation on the final ECG that was not present at baseline. In the ciclesonide group one subjects had atrial fibrillation on all three cardiograms and a 16 year-old male had a normal cardiogram at baseline, right bundle branch block diagnosed at 6 months and atrial fibrillation at 12 months. None of the abnormalities was thought to be significant and none resulted in withdrawal of the subject.

Reviewer: The percentage of abnormal ECGs reported in this review is taken from the datasheet "...tablations\eg.xpt". The percentages in the text of the study report (pg 107/30104) are taken from post-text table 14.3.6.5. This table is divided into two parts: one summarizes subjects who were tested at baseline and 6 months and the other lists subjects studied at baseline and at 12 months. It is, therefore, impossible to obtain the numbers or percentages of all the subjects at baseline. In addition, the percentage normal at baseline, 6 months and 12 months (77%) reported in the text of the study report is actually the percentage of those NORMAL AT BASELINE who were ALSO normal at 6 and 12 months. Finally, the number of subjects reported as having an abnormal ECG was highly site dependent (10 to 60% of all enrolled abnormal). This was independent of age and gender. In a logistic regression, site was a strong predictor of a positive finding and male gender was also predictive. Age, in this restricted population was not significant.

Ophthalmology Examinations

The results of the ophthalmologic examinations are summarized in Table 46. Intraocular pressure was measured in 577 of the subjects. The mean values were essentially the same in the two treatment groups at baseline and changed very little over the course of the study. At the end of the study 11 (2.8%) ciclesonide and 5 (2.7%) placebo subjects has

pressures >20 mm Hg, the pressure considered to be the upper limit of normal. The highest pressure recorded was 26 mm Hg in one ciclesonide-treated subject at the 6-month visit. The affected eye had a pressure of 20 mm Hg at baseline and again at the 12-month visit. Two subjects in the ciclesonide group had pressures of 24 mm Hg at the 6-month visit. One subject did not return for the 12-month visit and the other had a normal pressure at 12 months. One placebo subject had a pressure of 24 mm Hg at the end of the study, having entered with a pressure of 19 mm Hg. All of the other pressured were 22 mm Hg or less.

Table 46. Results of Ocular Examination During 52 Weeks of Treatment with Ciclesonide*

Variable	Ciclesonide N = 441	Placebo N=220	Treatment Difference (95% CI)
Intraocular pressure	390	187	
Baseline, Mean (SD)	15.2 (2.4)	15.1 (2.6)	
Change from Baseline (LS mean [SE])	-0.00 (0.12)	-0.1 (0.16)	-0.1 (-0.50, 0.3)
LOCS III			
Nuclear Color	N=389	N=187	
Baseline, Mean (SD)	1.07 (0.84)	1.04 (0.76)	
Change from Baseline (LS mean [SE])	0.14 (0.02)	0.14 (0.03)	0.00 (-0.06, 0.06)
Nuclear Opalescence			
Baseline, Mean (SD)	1.38 (0.83)	1.40 (0.78)	
Change from Baseline (LS mean [SE])	0.11 (0.02)	0.08 (0.03)	-0.03 (-0.09, 0.03)
Cortical Cataract			
Baseline, Mean (SD)	0.23 (0.32)	0.24 (0.31)	
Change from Baseline (LS mean [SE])	-0.01 (0.01)	0.00 (0.02)	0.01 (-0.02, 0.05)
Posterior Subcapsular Cataract			
Baseline, Mean (SD)	0.12 (0.11)	0.12 (0.13)	
Change from Baseline (LS mean [SE])	0.01 (0.01)	0.02 (0.01)	0.01 (-.01, 0.02)

* The standard deviation for the LOCS baseline measurements is taken from the post-text tables 14.3.7.3.2.1, 14.3.7.3.3.1, 14.3.7.3.4.1, and 14.3.7.3.5.1,

The LOCS III grading showed equivalent mean scores at baseline for all of the measurements and very small changes during the trial (Table 47). The cortical changes were also evaluated using the predetermined cutoffs for Class I, Class II, and Class III

Table 47. Change in LOCS III grade during 52 Weeks of Treatment*

Change at Endpoint	Ciclesonide 200 mcg (N=441)	Placebo (N=222)
No change	297 (76.2%)	152 (81.3%)
Class I	93 (23.8%)	35 (18.7%)
Class II	37 (9.5%)	15 (8.0%)
Class III*	20 (5.1%)	8 (4.3%)

* A LOCS III score ≥ 3.0 is required for at least 1 type of opacity.
Data source: Section 14.3, Post-text Table 14.3.7.3.1.1.

*The grading is progressive so that all subjects in Class II are also included in Class I and all subjects in Class III are included in Class II and Class I.

(see page 104 above for description). Although the changes were not statistically significant, there was a higher percentage of subjects in the Ciclesonide-treated group

who had changes into the abnormal range in each category (i.e. nuclear color, opalescence, cortical cataract, and posterior subcapsular cataract (Table 47).

The scoring in the LOCS III classification is based on the largest change in any one category. In other words, a change of 0.5 in the nuclear opalescence score results in a Class I designation regardless of what is happening to the scores in the other categories. When these categories are examined separately it is apparent that most of the abnormalities occurred in the nuclear opalescence category and, in addition, that the changes were worse in the ciclesonide group only in this category (Table 48).

Table 48. Incidence of abnormality in the individual components of the LOCS III

Overall and Components of Class I Events	Ciclesonide 200 mcg (N=441)	Placebo (N=222)
Class I Event	93 (23.8%)	35 (18.7%)
Nuclear Opalescence	86 (22.1%)	31 (16.6%)
Posterior Subcapsular Opacity	3 (0.8%)	3 (1.6%)
Cortical Opacity	8 (2.1%)	4 (2.1%)

Data source: Section 14.3. Post-text Table 14.3.7.3.1.5

Reviewer: The applicant states that the reason for the predominance of abnormalities in nuclear opalescence is because the standard deviation of the baseline value is higher for this category than for the others. However, the coefficient of variation, a better estimate of variability in the data, is actually the lowest in the nuclear opalescence category. Further, the standard deviation of the change is greater in the nuclear opalescence group but the standard error is almost identical in all of the categories. Even if the variability in the nuclear opalescence were greater than the variability in the other categories, that would not explain a preponderance of changes in the ciclesonide treatment group. Having said that, the applicant is correct in the assessment that posterior subcapsular cataracts are more important as an indicator of corticosteroid effect than the other components. These detailed studies may only be telling us what we already know, which is that corticosteroids even in low doses predispose to the development of cataracts. The ocular effects of corticosteroid use are noted in the package insert for corticosteroid products and the label for this product will contain similar language.

There was no apparent treatment effect from ciclesonide on visual acuity (Table 49)

Table 49. Changes in Visual Acuity During 52 Weeks of Treatment with Ciclesonide

Range	Ciclesonide 200 mcg (N = 441)		Placebo (N = 222)	
	Baseline	Endpoint	Baseline	Endpoint
20/20 or Better	127 (35.8)	134 (37.7)	63 (36.8)	61 (35.7)
>20/20 to 20/50	132 (37.2)	131 (36.9)	61 (35.7)	65 (38.0)
>20/50 to 20/100	31 (8.7)	32 (9.0)	17 (9.9)	18 (10.5)
>20/100 to 20/200	31 (8.7)	26 (7.3)	12 (7.0)	10 (5.8)
>20/200	34 (9.6)	32 (9.0)	18 (10.5)	17 (9.9)

Data source: Section 14.3, Post-text Table 14.3.7.2.1

Laboratory Results

There were no changes in the mean values for any of the safety laboratory values that represented a meaningful clinical change. Shifts from normal to abnormal occurred in less than 6% of the subjects in each group except for the calcium, glucose, and phosphate values. There was an unexplained shift from normal to abnormal in the serum calcium values in 12.1 and 19.3% of the ciclesonide and placebo subjects, respectively. The mean calcium values were 9.6 mg/dL in each group and the change from baseline was 0.2 mg/dL in both treatment groups. The maximum values at endpoint were 11 mg/dL (normal high = 10.2 mg/dL). The glucose values went from normal to abnormal in 8.5 and 7.8% of the ciclesonide and placebo subjects, respectively. The mean values at the endpoint were 93 mg in both treatment groups and the change during the trial was 3.8 and 4.9 mg/dL in the ciclesonide and placebo groups respectively. The maximum values at endpoint were 229 and 148 mg/dL in the ciclesonide and placebo groups respectively (normal high = 110 mg/dL). The phosphate values went from normal to abnormal in 6.0 and 11.1% of the ciclesonide and placebo subjects, respectively. As with the other two variables, the changes were small during the study. The maximum values at endpoint were 8 and 6 mg/dL in the ciclesonide and placebo subjects respectively (normal high = 4.5 mg/dL).

Reviewer: These abnormalities are difficult to explain, but probably do not represent a safety concern. None of the abnormal values was very high and it is possible that there is a problem with laboratory standardization as the chemistry tests were performed at a central laboratory.

Abnormal laboratory values were reported as adverse events in 6 ciclesonide-treated and 2 placebo-treated subjects. Three of the ciclesonide-treated subjects had low blood counts (Hct 31%, 32%, and RBC count 3.77 x10^6 cells/mm^3) In each case the subject had a low-normal value at baseline. One subject had an elevated alkaline phosphatase at baseline that increased over the year of follow-up. One subject had an elevated white count (17.1 x 10^3 cells/mm^3), and one subject had a single elevated ALT (63 U/L; normal high = 43 U/L) at the 6-month visit that returned to normal by the next visit. One

placebo-treated subject had a white count of 1.0 x 10^3 cells/mm^3 which had returned to the baseline level of 1.6 x 10^3 cells/mm^3 by the end of the study (Normal low = 1.9 x 10^3 cells/mm^3), and one had an ALT of 50.0 U/L at the end of the trial.

HPA-axis Evaluation

The AM plasma cortisol was measured in 286 subjects. The baseline plasma cortisol was 14.3 and 14.5 mcg/dL in the ciclesonide and placebo subjects, respectively (Table 50). The values fell by a LS mean of 1.1 and 0.4 mcg/dL in the ciclesonide and placebo subjects, respectively. Urinary free cortisol was assessed with a 24-hour urine collection from which a measurement of the cortisol was obtained and the mcg/day was calculated as the concentration of cortisol multiplied by the urine volume. The reported results show no suppression of urinary cortisol in the ciclesonide-treated subjects. However, there without an assessment of the adequacy of the urine collection the results are not reliable.

Table 50. HPA-axis Evaluation After 52 Weeks of Treatment

Variable	Ciclesonide N = 441	Placebo N=220	Treatment Difference (95% CI)
Plasma Cortisol, mcg/dL	193	93	
Baseline, Mean (SD)	14.3 (7.3)	14.5 (7.3)	
Change from Baseline (LS mean [SE])	-1.1 (0.42)	-0.4 (0.60)	0.7 (-0.60, 2.0)
Uncorrected Urinary Cortisol, mcg/day	N=174	N=92	
Baseline, Mean (SD)	26.3 (14.5)	37.8 (14.7)	
Change from Baseline (LS mean [SE])	2.3 (1.93)	1.2 (2.5)	-1.00 (-6.7, 4.7)

Reviewer: No criterion for an adequate collection was provided in the protocol. However, the listing indicates that many of the samples were less than a liter and the smallest volumes were 300 mls. This indicates that some of the collections were incomplete. In addition, there is no mention of limiting the cortisol population on the basis of protocol violations. In addition to the subjects who took nasal corticosteroids prior to enrollment (7 and 4.5% of the ciclesonide and placebo subjects) approximately 7% took some form of corticosteroid during the trial including 19 who took prednisone (12 ciclesonide and 7 placebo. Without additional data, these results are unreliable and can not be used to support a claim in the label.

4.3 Summary and Discussion

This was a 52-week, randomized, double blind comparison of the safety of ciclesonide 200 mcg daily compared to placebo in patients with PAR. The study was conducted at 35 sites distributed throughout the United States. Of the 663 subjects enrolled, 71.5% completed the trial and compliance with the treatment regimen was >95%. As in the other adult trials in this submission the majority of the subjects were female, Caucasian, and between 18 and 64 years of age. All had positive skin tests to one of a variety of perennial antigens. The primary objective of the study was to evaluate long-term safety. To meet the requirements for long term exposure, 315 subjects were treated with

ciclesonide for over 300 days and 97 were treated for >364. During the year of exposure 75% of the subjects experienced adverse events. These occurred in a frequency and severity commonly seen in studies of intranasal corticosteroids used for the treatment of allergic rhinitis. The only events that occurred more frequently in the ciclesonide-treated subjects were epistaxis pharyngolaryngeal pain, sinusitis, and headache. Upper respiratory infection and Nasopharyngitis were more common in the placebo-treated subjects. There were no deaths reported, serious adverse events were uncommon and none was likely to be related to drug ingestion. Two subjects withdrew from the ciclesonide group due to epistaxis and this was probably related to drug ingestion.

Systematic examination was performed of the upper airway and of the eye. Other than signs of allergic rhinitis, one transient septal ulcer and one transient septal perforation were seen in two placebo-treated subjects. Both resolved spontaneously. The results of the ophthalmologic examinations showed no treatment effect on visual acuity or intraocular pressure. The LOCS III examination showed a small, statistically insignificant, increase in the frequency of Class I changes in the ciclesonide-treated subjects. This was predominantly in the category of Nuclear opalescence, and in the absence of an increased incidence of posterior subcapsular cataracts, may not be related to corticosteroid ingestion. Since the class labeling for nasal corticosteroid already includes a precaution about the development of cataracts, there is nothing additional that needs to be added for this product. However, the frequency of changes in both the treated and control populations suggests that ophthalmologic examination should be performed in all long-term trials of corticosteroids.

The evaluation of the HPA-axis was not optimal. Only a single AM blood measurement was obtained and there were no criteria established for the adequacy of the urine collections. Given the low systemic exposure when ciclesonide is administered intra-nasally, these negative findings are probably sufficiently reassuring in the adult population.

Efficacy was assessed as a secondary objective. The analysis showed that the r-TNSS decreased by a mean (95% CI) of 0.60 (0.3, 0.9) points more in the ciclesonide than in the placebo-treated subjects. This value is very similar to the results obtained in study 401, the 12-week efficacy trial for the treatment of PAR and suggests that the drug is effective when taken up to one year.

5. STUDY # 143/2005 (BY9010/M1-406)

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Using the Environmental Exposure Chamber (EEC) to Assess the Onset of Action of Ciclesonide as a Nasal Spray (200 mcg once daily) in the Treatment of Seasonal Allergic Rhinitis (SAR) in Patients 18 Years and Older

5.1 Protocol

5.1.1 Administrative

Study Dates: November 22, 2004 to February 12, 2005
Clinical Centers: [redacted]

Medical Officer: [redacted]
CRO: [redacted]

5.1.2 Objective/Rationale

The primary objective of this study was to determine the time to onset of action of intranasal ciclesonide, 200 mcg administered once daily, in patients with SAR.

5.1.3 Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group single-center study conducted in 503 adults with SAR. At the screening visit (B0) subjects had a skin prick test for short ragweed in addition to a history and physical examination. Eligible subjects then returned for 1 to 5 priming visits. At each priming visit the subject was exposed to 3500 ± 500 grains/m^3 of ragweed pollen in the environmental exposure chamber (EEC). Symptoms were assessed at 30 minute intervals from 0.5 to 3 hours after exposure. A successful priming visit was defined as a patient-assessed instantaneous Total Nasal Symptom Score (i-TNSS) of 6 or greater and a score of 2 or greater for rhinorrhea or nasal congestion at 1.5 hours after exposure. For the purposes of this evaluation, instantaneous included the 10 minutes prior to the evaluation. The TNSS was the sum of sneezing, nasal itching, rhinorrhea, and nasal congestion, as described in study 401 (pg 79, above). If priming was not successful after 5 attempts, the subject was not enrolled.

On a single treatment day (T0), 1 to 11 days after priming, subjects were exposed to pollen and a symptom score obtained 30 minutes, 1 hour and 1.5 hours after exposure. At 2 hours post exposure they were treated with ciclesonide nasal spray 200 mcg or placebo. Nasal symptoms were then recorded hourly for 12 hours. On both the priming

and treatment days the pollen counts were measured for 30 seconds every 30 minutes to assure a constant exposure as long as the subject remained in the chamber.

5.1.4 Study Population

Inclusion Criteria

- Males and females ≥18 years of age
- SAR to short ragweed pollen for at least 2 year's duration severe enough to require treatment
- A positive skin prick test to short ragweed pollen. The response to allergen must have been at least 3 mm greater than the response to control and the test had to have been performed within 12 months or screening.

Exclusion Criteria

- History of physical findings of nasal pathology, including nasal polyps causing > 50% obstruction or recent nasal biopsy, nasal trauma or surgery within 60 days of screening
- Atrophic rhinitis or rhinitis medicamentosa within 60 days of screening
- Subjects with seasonal allergies with seasonal exacerbation anticipated to occur during the study
- History of respiratory infection within 14 days of screening
- Asthma requiring treatment with corticosteroids or routine beta agonists; intermittent use of beta agonists is acceptable.
- Use of antibiotic therapy within 14 days of screening (Low dose antibiotics used for prophylaxis are allowed)
- Initiation of immunotherapy or changing the dose of immunotherapy within 90 days of screening
- Non-vaccinated exposure to or active infection with chicken pox or measles within 21 days of screening
- Exposure to systemic corticosteroids within 2 months or topical corticosteroids in excess of 1% hydrocortisone with 1 month of screening
- History of positive test for HIV or hepatitis
- History of alcohol abuse
- Intention to become pregnant or refusal to employ birth control.

Randomization Criteria

- A minimum of 1 or maximum of 2 successful priming visits.
- A minimum i-TNSS of 6 with at least 2 for rhinorrhea or nasal congestion at 1.5 hours after pollen exposure on the treatment day.
- No cold or sinusitis within the 7 days preceding the first priming visit or thereafter.

Discontinuation Criteria

Subjects could be withdrawn due to an adverse event, intercurrent illness, or major protocol violations. Subjects could also be withdrawn due to inappropriate randomization, improper administration of study medication, use of prohibited medications, or other severe protocol deviations.

5.1.5 Study Procedures and Data Analysis

Exposure

The exposure chamber had an area of [redacted] and was supplied with 100% HEPA (High Efficiency Particle Arresting) filtered air. Air was not recirculated. Pollen counts were monitored with [redacted] Rotational Impaction Samplers. Subjects were studied in 8 cohorts of 35 to 89 subjects each.

Treatment

The study treatments were self-administered after written and verbal instruction. Treatment was either ciclesonide (2 x 50 mcg sprays to each nostril) or placebo. Prohibited and permitted concomitant medications were as listed in study 401 (pg) with the exception that antihistamines had to be discontinued 7 days and decongestants 2 days prior to the first priming visit.

Efficacy Evaluation

The Total Nasal Symptom Score (TNSS) was calculated from the diary entries for sneezing, nasal itching, rhinorrhea, and congestion as described for study 401 (pg 79, above). Only instantaneous (incorporating the ten minutes prior to the evaluation) assessments were made. The onset of action was the primary outcome variable, and was measured as the difference in the mean i-TNSS comparing ciclesonide and placebo-treated subjects. Baseline was taken as the last pre-treatment value on the treatment day. The onset of action was defined as the time from baseline until the one-sided p-value for the test of difference between the ciclesonide and placebo-treated subjects for the i-TNSS was < 0.025. Additionally, the one-sided p-value for the test of a difference between treatment-groups was required to be less than 0.025 for a time point after the first significant time point. The two treatment groups were compared at each time point using ANCOVA with covariate adjustment for baseline and treatment.

A subject assessed categorical response to therapy was also calculated. To have a good to excellent response no symptom could be greater than mild in severity. The percentage of subjects in each treatment group with a good to excellent response and an odds ratio for a good response was calculated. Individual symptom scores were treated as secondary outcomes.

Safety Evaluation

Safety was assessed with adverse events and physical examination. No laboratory examinations were performed.

Sample Size

Assuming a standard deviation for a single observed change from baseline in i-TNSS is 2.7, then 241 patients per treatment groups will provide 90% power to detect a difference between treatment groups of 0.8 with a one-sided α of 0.025.

5.2 Results

5.2.1 Study Population

Disposition

A total of 503 subjects were randomized and 502 completed the study. One subject was randomized to receive placebo but developed a nose bleed prior to receiving study medication and was withdrawn. This left 251 subjects in each treatment group. The per protocol analysis included 250 ciclesonide and 242 placebo-treated subjects. There were 11 subjects with major protocol violations: 1 ciclesonide and 10 placebo-treated subjects. Use of prohibited medication by 2 placebo-treated subjects was the only protocol violation that occurred in more than a single subject. Minor protocol violations occurred in 2.8% of the ciclesonide and 2.0% of the placebo-treated subjects.

Demographics

The mean age of the population was 37.0 years and 45.5% were male. Only 60.6% of the population was Caucasian while 29.3% was Black and 14.4% was Asian. Seven percent identified themselves as Hispanic in origin with slightly more of the placebo subjects (9.6%) describing themselves as Hispanic. Never smokers predominated, but 14.1% were active smokers (Table 51). The mean of the wheal from the positive skin test was 11.3 mm with a mean control of 2.39 mm and a mean response to histamine of 6.1 mm. The skin test variables were distributed evenly between the treatment groups.

Table 51. Baseline Demographics for Subjects Enrolled in Study

	Ciclesonide 200 mcg N=251	Placebo N=251	Total N=502
Age (years)			
Mean (SD)	36.6 (11.3)	37.5 (11.9)	37.0 (11.6)
Range	18 - 75	18 - 74	18 – 75
Gender (% Male)	47.0	43.8	45.4
Race (%)			
Caucasian	59.8	61.4	60.6
Black	29.5	29.1	29.3
Asian, native American	15.9	12.4	14.4
Other	1.6	2.0	1.8
Ethnicity (%)			
Hispanic	5.6	9.6	7.6
Non-Hispanic	94.4	90.4	92.4
Smoking History (%)			
Never	64.5	61.4	62.9
Former	21.1	24.7	22.9

Current	14.3	13.9	14.1
Type of skin test (%)			
Historical	56.2	62.2	59.2
Current	43.8	37.8	40.8
Antigen Challenge (mm)			
Mean (SD)	11.4 (5.4)	11.2 (6.5)	11.3 (5.9)
Range	3 - 35	3 - 70	3 – 70

Reviewer: There are substantially more men and non-Caucasians in this population than in any of the other studies, and there are more current smokers. There is also a tremendous range in the antigen challenge reactions in the placebo subjects. Of note, 75 (14.8%) of the diluent control skin tests were > 3 mm and 11 (2.2%) of the histamine skin tests were <3 mm.

According to the text of the study report, the most frequently reported pre-enrollment medications included Tylenol (6%), an investigational nasal spray other than ciclesonide (4.2%), Advil (4.0%), and multivitamins (4.0%).

Reviewer: The above categorization of concomitant medications is taken directly from post-text Table 14.1.4.1. However, medications were not grouped by active ingredient For instance, Tylenol is reported at the top of the list (n=30 [6%]), then Tylenol W/Codeine (3 [0.6%]) somewhat further down the list. Each of the subsequent listings includes very few subjects because each medication is listed by its proprietary name. If the drugs are grouped by active ingredient, it appears that 45 (9.0%) received drugs containing acetaminophen, 23 (4.6%) ibuprofen and no less than 50 (10.0%) received experimental drugs other than ciclesonide. Of those who received other investigational drugs, 6 reported only "investigational medication", and one subject received an experimental calcium channel blocker. Of interest, relatively few subjects received prior treatment for symptoms that might be associated with allergic diseases. Less than one percent (n=3 [0.6%]) had previously been treated with a nasal corticosteroid and only 9 (1.8%) reported self medication with over the counter cold and cough medications. Antihistamine use was reported in 13 (2.6%) and antibiotics for any indication was reported by <1.0%. This compares with 65 (12.9%) who received hormone treatment, mostly for birth control, 11 (2.2%) who received drugs to lower serum lipids, 13 (2.6%) who received psychoactive drugs, 21 (4.2%) who received medication to lower blood pressure.

5.2.2 Efficacy Results

Primary Efficacy Outcome

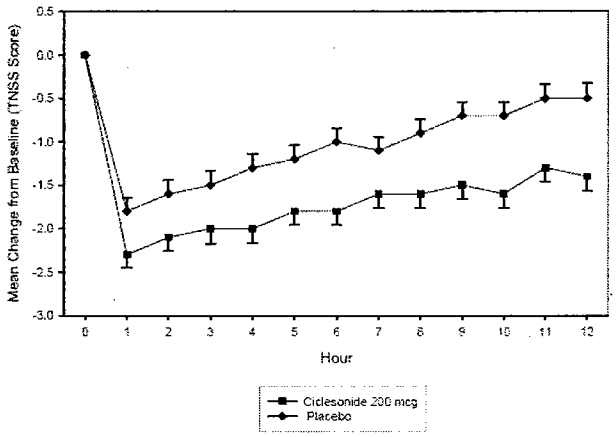
At baseline the mean i-TNSS was 9.9 in both treatment groups (Table 52). By one hour the score had fallen by a LS mean of 2.3 and 1.8 points in the ciclesonide and placebo treatment groups, respectively. This difference (LS mean difference = 0.5) and that found at all subsequent time points was statistically significant showing a greater improvement with ciclesonide treatment.

Table 52. Changes in i-TNSS After Ragweed Challenge in an Environmental Chamber (Study 406)

Variable	Ciclesonide N = 251	Placebo N=251	Treatment Difference (95% CI)	1-sided p-value
Baseline iTNSS Baseline, Mean (SD)	9.9 (1.9)	9.9 (1.9)		
Hour 1 Change from Baseline (LS mean [SE])	-2.3 (0.15)	-1.8 (0.15)	0.5 (0.08, 0.93)	0.010
Hour 2 Change from Baseline (LS mean [SE])	-2.1 (0.16)	-1.6 (0.16)	0.5 (0.03, 0.90)	0.018
Hour 3 Change from Baseline (LS mean [SE])	-2.0 (0.17)	-1.5 (0.17)	0.5 (0.07, 1.00)	0.012
Hour 4 Change from Baseline (LS mean [SE])	-2.0 (0.16)	-1.3 (0.16)	0.7 (0.21, 1.10)	0.002
Hour 5 Change from Baseline (LS mean [SE])	-1.8 (0.16)	-1.2 (0.16)	0.6 (0.11, 1.02)	0.008
Hour 6 Change from Baseline (LS mean [SE])	-1.8 (0.16)	-1.0 (0.16)	0.7 (0.27, 1.18)	<0.001
Hour 7 Change from Baseline (LS mean [SE])	-1.6 (0.16)	-1.1 (0.16)	0.5 (0.06, 0.97)	0.014
Hour 8 Change from Baseline (LS mean [SE])	-1.6 (0.16)	-0.9 (0.16)	0.7 (0.23, 1.13)	0.001
Hour 9 Change from Baseline (LS mean [SE])	-1.5 (0.16)	-0.7 (0.16)	0.8 (0.35, 1.22)	<0.001
Hour 10 Change from Baseline (LS mean [SE])	-1.6 (0.16)	-0.7 (0.16)	0.9 (0.46, 1.36)	<0.001
Hour 11 Change from Baseline (LS mean [SE])	-1.3 (0.16)	-0.5 (0.16)	0.8 (0.38, 1.28)	<0.001
Hour 12 Change from Baseline (LS mean [SE])	-1.4 (0.17)	-0.5 (0.17)	0.9 (0.41, 1.34)	<0.001

Calculation of the time of onset using the PP population resulted in the same conclusions. In the PP analysis the difference between ciclesonide and placebo groups was 0.5 (95% CI 0.07, 0.93) at one hour. The changes in the scores are shown graphically in figure 5.

Figure 5. Instantaneous TNSS after Exposure to Allergen



Secondary Efficacy Measures

In the patient satisfaction analysis, ciclesonide was favored at all time points other than hour 3. However, the 95% confidence interval crossed one at 1, 2, 3, and 5 hours (Table 53).

Table 53. Patient-Assessed Response to Allergen Challenge

Time after Dose	Percentage of Subjects with a Good/Excellent Response			
	Ciclesonide N = 251	Placebo N=251	Odds Ratio	(95% CI)
Hour 1	12.4	8.0	1.7	0.9, 3.1
Hour 2	9.2	8.0	1.2	0.6, 2.2
Hour 3	8.0	8.4	0.9	0.5, 1.8
Hour 4	10.4	5.6	2.1	1.0, 4.2
Hour 5	11.6	7.2	1.7	0.9, 3.3
Hour 6	10.4	5.6	2.0	1.0, 4.0
Hour 7	10.8	4.8	2.5	1.2, 5.2
Hour 8	10.0	5.6	1.9	1.0, 3.9
Hour 9	10.8	3.2	3.9	1.7, 9.0
Hour 10	10.8	3.6	3.4	1.5, 7.5
Hour 11	9.2	3.6	2.8	1.2, 6.2
Hour 12	13.1	3.2	4.9	2.2, 11.0

The components of the rTNSS also improved to a greater extent in the ciclesonide than the placebo group for all four symptoms and for each time point except for sneezing at one hour. At that one time point the difference between ciclesonide and placebo was only 0.1 point,

Subset Analysis

Only 13 subjects were older than 65 years so no analysis based on age was performed. The mean baseline and change values were similar in males and females. The racial categories were analyzed as "Caucasian", "Black", and "Other" with all subjects claiming a mixed heritage in the "Other" category. Using these definitions the baseline symptom scores were higher in the Black and Other categories (10.2 and 10.3, respectively) than in the Caucasian subjects (9.7), and the fall with treatment with ciclesonide was greater in the "Other" category than for the other subjects. The difference between placebo and ciclesonide at one hour was 0.20 for the Caucasians, 0.60 for the Blacks, and 1.30 for the Other category.

Reviewer: In a linear regression the change in i-TNSS was highly dependent upon the baseline score with greater changes in subjects with high scores at baseline. This was true even when the analysis was adjusted for treatment and race. Treatment was a significant factor in the relationship only if the "Other" racial group was included. If the "Other" subjects (N=45) were excluded, treatment was no longer a significant factor.

Pollen Counts

The mean pollen count for all of the time points on all of the treatment days was 3369 with a standard deviation of 1167. However, the range of the counts was 312 to 25,116. Examination of the individual study days showed that all of the extremely high values occurred on the second study day (the second cohort), December 11, 2004. The mean of the pollen counts excluding Session 2 was 3294 with a standard deviation of 683. The range was 312 to 7402. There were 89 subjects treated during Session 2.

5.2.3 Safety

Extent of Exposure

The subjects received a single dose of ciclesonide of 200 mcg.

Adverse Events

There were no deaths or serious AEs. Fifty four (10.8%) subjects reported an adverse event: 18 (7.2%) in the ciclesonide group and 36 (14.3%) in the Placebo group. Headache was the most common complaint, occurring in 5 (2.0%) of ciclesonide and 10 (4.0%) of placebo subjects. Increased blood pressure occurred in 2 (0.8%) and 6 (2.4%) of the ciclesonide and placebo subjects, respectively. No other event occurred at a frequency of >2%. No event was graded as severe and only 2 (0.8%) of the events in the ciclesonide subjects were reported as moderate. All others were mild.

Physical Examination

Vital signs were normal at baseline but abnormal at the end of the study in 3 (1.2%) ciclesonide and 18 (7.2%) of placebo subjects. The most common abnormality was an elevated blood pressure that occurred in 11 placebo and 2 ciclesonide subjects. The third ciclesonide subject had a low pulse and the other placebo subjects had low pulse (3), high pulse (2) and low blood pressure (2). None of the abnormalities was marked.

An ENT examination was performed at baseline and at the end of treatment. One ciclesonide and 2 placebo subjects were described as normal at baseline and abnormal at the end of treatment. All others were normal at both time points.

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths and no serious adverse events. One subject randomized to receive placebo developed epistaxis prior to dosing and was withdrawn.

Laboratory Results

No safety laboratory examinations were obtained.

5.3 Summary and Discussion

This was a single dose, randomized, double blind environmental exposure chamber challenge with ragweed pollen to determine the onset of action of ciclesonide 200 mcg.

The study was conducted at a single site in Canada, and the subject population contained fewer Caucasians than the other studies in this submission that were conducted in Texas or at several sites throughout the US and Canada. The population was also dissimilar to the others in the submission because 14% were active smokers.

The i-TNSS fell in both treatment groups but it fell to a significantly greater degree after ciclesonide treatment at all time points measured. Since one hour was the first time point this was determined to be the onset of action. However, only 10% of the ciclesonide subjects reported a good/excellent response. Adverse events were infrequent and mild in this single dose study. There was more abnormality in vital signs in the placebo subjects which could be explained as a response to the pollen challenge without medication.

6. STUDY # 145/2005 (BY9010/M1-407)

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Using the Environmental Exposure Chamber (EEC) to Assess the Onset of Action of Ciclesonide as a Nasal Spray (200 mcg once daily) in the Treatment of Seasonal Allergic Rhinitis (SAR) in Patients 18 Years and Older

6.1 Protocol

6.1.1 Administrative

Study Dates: February 8, 2005 to April 16, 2005
Clinical Centers: [redacted]
Medical Officer: [redacted]

6.1.2 Objective/Rationale

The primary objective of this study was to determine the time to onset of action of intranasal ciclesonide, 200 mcg administered once daily, in patients with SAR.

6.1.3 Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group single-center study conducted in 503 adults with SAR. At the screening visit (B0) subjects had a skin prick test for short ragweed in addition to a history and physical examination. Eligible subjects then returned for 1 to 5 priming visits. At each priming visit the subject was exposed to 3500 ± 500 grains/m^3 of ragweed pollen in the environmental exposure chamber (EEC). Symptoms were assessed at 30 minute intervals from 0.5 to 3 hours after exposure. A successful priming visit was defined as a patient-assessed instantaneous Total Nasal Symptom Score (i-TNSS) of 6 or greater and a score of 2 or

greater for rhinorrhea or nasal congestion at 1.5 hours after exposure. For the purposes of this evaluation, instantaneous included the 10 minutes prior to the evaluation. The TNSS was the sum of sneezing, nasal itching, rhinorrhea, and nasal congestion, as described in study 401 (pg , above). If priming was not successful after 5 attempts, the subject was not enrolled.

On a single treatment day (T0), 1 to 11 days after priming, subjects were exposed to pollen and a symptom score obtained 30 minutes, 1 hour and 1.5 hours after exposure. At 2 hours post exposure they were treated with ciclesonide nasal spray 200 mcg or placebo. Nasal symptoms were then recorded hourly for 12 hours. On both the priming and treatment days the pollen counts were measured for 30 seconds every 30 minutes to assure a constant exposure as long as the subject remained in the chamber. Subjects were enrolled in 4 cohorts of 101 to 109 subjects each.

6.1.4 Study Population

Inclusion Criteria

- Males and females ≥18 years of age
- SAR to short ragweed pollen for at least 2 year's duration severe enough to require treatment
- A positive skin prick test to short ragweed pollen. The response to allergen must have been at least 3 mm greater than the response to control and the test had to have been performed within 12 months or screening.

Exclusion Criteria

- History of physical findings of nasal pathology, including nasal polyps causing > 50% obstruction or recent nasal biopsy, nasal trauma or surgery within 60 days of screening
- Atrophic rhinitis or rhinitis medicamentosa within 60 days of screening
- Subjects with seasonal allergies with seasonal exacerbation anticipated to occur during the study.
- History of respiratory infection within 14 days of screening
- Asthma requiring treatment with corticosteroids or routine beta agonists; intermittent use of beta agonists is acceptable.
- Use of antibiotic therapy within 14 days of screening (Low dose antibiotics used for prophylaxis are allowed)
- Initiation of immunotherapy or changing the dose of immunotherapy within 90 days of screening
- Non-vaccinated exposure to or active infection with chicken pox or measles within 21 days of screening
- Exposure to systemic corticosteroids within 2 months or topical corticosteroids in excess of 1% hydrocortisone with 1 month of screening
- History of positive test for HIV or hepatitis
- History of alcohol abuse

- Intention to become pregnant or refusal to employ birth control.

Randomization Criteria

- A minimum of 1 or maximum of 2 successful priming visits.
- A minimum i-TNSS of 6 with at least 2 for rhinorrhea or nasal congestion at 1.5 hours after pollen exposure on the treatment day.
- No cold or sinusitis within the 7 days preceding the first priming visit or thereafter.

Discontinuation Criteria

Subjects could be withdrawn due to an adverse event, intercurrent illness, or major protocol violations. Subjects could also be withdrawn due to inappropriate randomization, improper administration of study medication, use of prohibited medications, or other severe protocol deviations.

6.1.5 Study Procedures and Data Analysis

Exposure Chamber

The exposure chamber at [redacted] can accommodate up to 160 subjects at a time. For this study 4 cohorts ranging between 101 and 109 subjects each were studied. The chamber was [redacted] and it contained grouped fans that generated a counterclockwise airflow. Ragweed pollen was dispersed into the airflow from a feeder located on the right side of the room and propelled by directional fans over the participant seating area. The EEC used a dedicated ventilation system which drew 100% fresh outdoor air, passed it through several filters and vented it back to the outdoors. The filtered air entered the chamber at a rate of 6 room changes per hour. The temperature was maintained between 21° and 24° C and the humidity between 40 and 60%. [redacted] rotorods were used to monitor the pollen throughout the exposure.

Treatment

The study treatments were self-administered after written and verbal instruction. Treatment was either ciclesonide (2 x 50 mcg sprays to each nostril) or placebo. Prohibited and permitted concomitant medications were as listed in study 401 (pg) with the exception that antihistamines had to be discontinued 7 days and decongestants 2 days prior to the first priming visit.

Efficacy Evaluation

The Total Nasal Symptom Score (TNSS) was calculated from the diary entries for sneezing, nasal itching, rhinorrhea, and congestion as described for study 401 (pg 79, above). Only instantaneous (incorporating the ten minutes prior to the evaluation) assessments were made. The onset of action was the primary outcome variable, and was measured as the difference in the mean i-TNSS comparing ciclesonide and placebo-treated subjects. Baseline was taken as the last pre-treatment value on the treatment day. The onset of action was defined as the time from baseline until the one-sided p-value for the test of difference between the ciclesonide and placebo-treated subjects for the i-TNSS

was < 0.025. Additionally, the one-sided p-value for the test of a difference between treatment-groups was required to be less than 0.025 for a time point after the first significant time point. The two treatment groups were compared at each time point using ANCOVA with covariate adjustment for baseline and treatment.

A subject assessed categorical response to therapy was also calculated. To have a good to excellent response no symptom could be greater than mild in severity. The percentage of subjects in each treatment group with a good to excellent response and an odds ratio for a good response was calculated. Individual symptom scores were treated as secondary outcomes.

Safety Evaluation

Safety was assessed with adverse events and physical examination. No laboratory examinations were performed.

Sample Size

Assuming a standard deviation for a single observed change from baseline in i-TNSS is 2.7, then 206 patients per treatment groups will provide 85% power to detect a difference between treatment groups of 0.8 with a one-sided α of 0.025. A difference between ciclesonide and placebo of 0.5 was thought to be clinically meaningful.

6.2 Results

6.2.1 Study Population

Disposition

A total of 420 subjects were randomized, all received randomized medication, and 417 completed the study. Two ciclesonide and 1 placebo subject were discontinued prematurely due to an adverse event. The per-protocol analysis included 204 ciclesonide and 206 placebo-treated subjects. There were 10 subjects with major protocol violations: 6 (2.9%) in the ciclesonide group and 4 (1.9%) in the placebo-treated subjects. An inappropriate medical history was the only major violation that occurred in more than one subject.

Demographics

The mean age of the population was 32.9 years, and 42.4% were male, and 96.2% were Caucasian. Never smokers predominated, but 15.7% were active smokers (Table 54). The mean of the wheal from the positive skin test was 9.9 mm with a mean control of 0.36 mm and a mean response to histamine of 3.8 mm. The skin test variables were distributed evenly between the treatment groups.

Table 54. Baseline Demographics for Subjects Enrolled in Study

	Ciclesonide 200 mcg N=210	Placebo N=210	Total N=420
Age (years)			
Mean (SD)	32.4 (11.3)	33.4 (11.9)	32.9 (11.8)
Range	18 - 71	18 - 70	18 – 71
Gender (% Male)	41.9	42.9	42.4
Race (%)			
Caucasian	96.7	95.7	96.2
Black	1.0	1.0	1.0
Asian, native American	2.0	4.8	3.3
Other	2.9	1.4	2.1
Ethnicity (%)			
Hispanic	0.5	0.5	0.5
Non-Hispanic	99.5	99.5	99.5
Smoking History (%)			
Never	61.9	62.4	62.1
Former	20.0	24.3	22.1
Current	18.1	13.3	15.7
Type of skin test (%)			
Historical	31.0	28.1	29.5
Current	69.0	71.9	70.5
Antigen Challenge (mm)			
Mean (SD)	10.1 (4.5)	9.7(4.5)	9.9 (4.5)
Range	3 - 29	3 - 26	3 - 29

Reviewer: This subject population is almost exclusively Caucasian which compares to the 56% Caucasians in the other onset of action study. Of note, no diluent control skin test was >3 mm and 19 (4.5%) of the histamine skin tests were <3mm.

According to the text of the study report, the most frequently reported pre-enrollment medications (n[%]) included Advil (78 [18.6%]), Tylenol Extra-Strength (77 [18.3%]), multivitamins (66 [15.7%]), and ibuprofen (48 [11.4%])

Reviewer: As in Study 406 the above figures are taken directly from post-text table 14.1.4.1 listing concomitant medications. Again, if the pre-enrollment medications are grouped by active ingredient it appears that 158 (37.6%) received ibuprofen, 151 (35.9%) acetaminophen, and 165 (39.3%) multivitamins. As in study 406, relatively few subjects received prior treatment for symptoms that might be associated with allergic diseases, although the incidence was higher in study 407 than in study 406. Almost one percent (n=5 [0.99%]) had previously been treated with a nasal corticosteroid and 27 (6.4%) reported self medication with over the counter cold and cough medications. Antihistamine use was reported in 35 (8.3%) and antibiotics for any indication had been taken by 27 (5.4%) o the subjects. In addition 3 subjects had been treated with inhaled corticosteroids and 4 had received immunotherapy. None had received experimental therapy. Treatment for common non-allergic manifestations included 117 (23.3%) who received hormone treatment, mostly for birth control, 10 (2.0%) who received drugs to

lower serum lipids, 35 (8.3%) who received psychoactive drugs, 11 (2.6%) who received medication to lower blood pressure.

6.2.2 Efficacy Results

Primary Efficacy Outcome

At baseline the mean i-TNSS was 9.7 in both treatment groups (Table 55). At one hour the score had fallen by a LS mean of 2.8 and 2.7 points in the ciclesonide and placebo treatment groups, respectively. This difference (LS mean difference = 0.1) was not significant. In the 12 hours of follow-up the difference was significant (p<0.025) at only one time point 6 hours post dose. Since only one time point showed a significant response no onset of action could be defined. An analysis using the PP population resulted in similar conclusions.

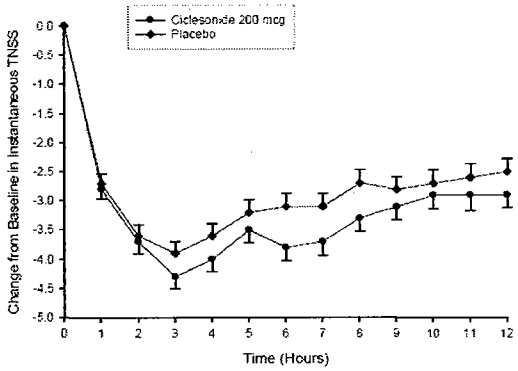
Table 55. Changes in i-TNSS After Ragweed Challenge in an Environmental Chamber (Study 407)

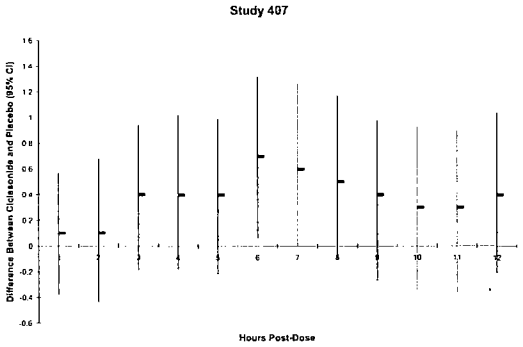
Variable	Ciclesonide N = 210	Placebo N=210	Treatment Difference (95% CI)	1-sided p-value
Baseline iTNSS Baseline, Mean (SD)	9.7 (1.7)	9.7 (1.6)		
Hour 1 Change from Baseline (LS mean [SE])	-2.8 (0.17)	-2.7 (0.17)	0.1 (-0.38, 0.57)	0.35
Hour 2 Change from Baseline (LS mean [SE])	-3.7 (0.20)	-3.6 (0.16)	0.1 (-0.44, 0.68)	0.33
Hour 3 Change from Baseline (LS mean [SE])	-4.3 (0.20)	-3.9 (0.20)	0.4 (-0.19, 0.94)	0.098
Hour 4 Change from Baseline (LS mean [SE])	-4.0 (0.21)	-3.6 (0.21)	0.4 (-0.18, 1.02)	0.084
Hour 5 Change from Baseline (LS mean [SE])	-3.5 (0.22)	-3.2 (0.22)	0.4 (-0.22, 0.99)	0.11
Hour 6 Change from Baseline (LS mean [SE])	-3.8 (0.23)	-3.1 (0.23)	0.7 (0.06, 1.32)	0.016
Hour 7 Change from Baseline (LS mean [SE])	-3.7 (0.23)	-3.1 (0.23)	0.6 (-0.00, 1.27)	0.025
Hour 8 Change from Baseline (LS mean [SE])	-3.3 (0.23)	-2.7 (0.23)	0.5 (-0.11, 1.17)	0.051
Hour 9 Change from Baseline (LS mean [SE])	-3.1 (0.22)	-2.8 (0.22)	0.4 (-0.27, 0.98)	0.13
Hour 10 Change from Baseline (LS mean [SE])	-2.9 (0.23)	-2.7 (0.23)	0.3 (-0.35, 0.93)	0.19
Hour 11 Change from Baseline (LS mean [SE])	-2.9 (0.23)	-2.6 (0.23)	0.3 (-0.37, 0.90)	0.21
Hour 12 Change from Baseline (LS mean [SE])	-2.9 (0.22)	-2.5 (0.17)	0.4 (-0.21, 1.04)	0.10

The changes in the scores are shown graphically in figure 6a and b. In a, the change in the score for the two treatment groups are shown and in b the difference between the treatment groups and the 95% confidence interval are plotted. (Figure 6b was constructed by the reviewer from the data in table *14.2.1.1, pg 146/6306)*

Figure 6 a. Instantaneous TNSS **6b. *Difference between Ciclesonide***

and Placebo in Instantaneous TNSS*





**Constructed from post-text table 14.2.1.1, pg 146/6306*

Secondary Efficacy Measures

In the patient satisfaction analysis, ciclesonide was favored at all time points. However, the 95% confidence interval crossed one at 1, 2, 4,5, and 10 hours (Table 56).

Table 56. Patient Satisfaction with Treatment After Exposure to Ragweed

Time after Dose	Percentage of Subjects with a Good/Excellent Response			
	Ciclesonide N = 232	Placebo N=229	Odds Ratio	(95% CI)
Hour 1	15.7	11.0	1.5	0.8, 2.6
Hour 2	25.2	22.9	1.1	0.7, 1.8
Hour 3	35.7	26.7	1.5	1.0, 2.3
Hour 4	30.5	24.8	1.3	0.8, 2.0
Hour 5	26.2	22.0	1.2	0.8, 2.0
Hour 6	31.0	21.5	1.6	1.0, 2.5
Hour 7	30.6	22.5	1.5	1.0, 2.3
Hour 8	27.8	17.7	1.8	1.1, 2.8
Hour 9	26.3	16.7	1.8	1.1, 2.8
Hour 10	25.4	18.7	1.5	0.9, 2.3
Hour 11	24.0	16.7	1.6	1.0, 2.5
Hour 12	25.5	16.7	1.7	1.0, 2.7

The components of the i-TNSS also improved to a greater extent in the ciclesonide than the placebo group, however many of the comparisons showed only small differences (all were between 0 and 0.2).

Subset Analysis

There were too few elderly subjects or non-Caucasians to draw any conclusions about variability due to age or race. Only 13 subjects were older than 65 years so no analysis based on age was performed.

Pollen Counts

The mean pollen count for all of the treatment days was 3414 with a standard deviation of 934. The range was 0 to 5924. In contrast to study 406 a baseline value of 0 to 80 was recorded for each treatment day. Similar counts were recorded in all of the sessions and there were no outliers.

6.2.3 Safety

Extent of Exposure

The subjects received a single dose of ciclesonide of 200 mcg.

Adverse Events

Thirty two (18.7%) subjects reported an adverse event: 17 (8.1%) in the ciclesonide group and 16 (7.6%) in the Placebo group. Headache was the most common complaint, occurring in 5 (2.4%) of ciclesonide and 3 (1.4%) of placebo subjects. Epistaxis occurred in 3 (1.4%) of ciclesonide and 4 (1.9%) of the placebo subjects. No other event occurred at a frequency of >2%. Nine of the events were reported as severe: four (1.9%) in the ciclesonide subjects (2 headaches, and 1 each hypoaesthesia and earache) and 7 events in 5 (2.4%) in the placebo subjects (2 headaches and one each eyelid erythema, back pain, feeling hot, and throat pain).

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths and no serious adverse events. During treatment, 2 ciclesonide subjects (1 each nausea and hypoesthesia) and one (pharyngolaryngeal pain) were withdrawn from treatment due to the adverse event. None of these events was thought to be related to the medication by the investigators.

Physical Examination

Mean values for vital signs were normal at baseline and changed very little during treatment. The mean change in systolic blood pressure was 3.4 and 3.7 mm Hg for the ciclesonide and placebo subjects. The changes in diastolic pressure were 1.6 and 1.4 mm Hg, respectively. No subject had a value that was outside of the protocol determined normal range.

An ENT examination was performed at baseline and at the end of treatment. Of the 182 ciclesonide-treated subjects who were normal at baseline, 138 (75.8%) were abnormal at the end of the exposure. This compares to 133 (76.9%) of the 173 placebo subjects who were normal at baseline.

Laboratory Results

No safety laboratory examinations were obtained.

6.3 Summary and Discussion

This was a single dose, randomized, double blind environmental exposure chamber challenge with ragweed pollen to determine the onset of action of ciclesonide 200 mcg. The study was conducted at a single site in Canada. Compared with study 406, the duplicate pollen challenge study, the current population was almost entirely Caucasian, more had current than historical allergen skin testing, and the overall skin test reactivity was relatively low. The population in this study had received more and a wider range of pre-enrollment medications except for experimental medication. On the other hand, treatment for hypertension and diabetes, conditions which would be expected to be high in a minority population, was reported more frequently in study 406. These differences could be due to reporting bias. However, another explanation is that the population in 406 had less access to medical treatment, especially optional treatments, and that they were more experienced as experimental subjects. (See Appendix I for a summary of demographic variables and medication history.) Lastly, the experimental set-up was not identical. Study 407 was conducted in a different province, at a different site with a larger environmental chamber where the study cohorts were larger. The distribution of pollen was more erratic in study 406 and may have resulted in a lower exposure. This is suggested by the fact that only 3 subjects in the entire study had an abnormal physical examination of the nose at the end of study 406, while >75% (271) of the subjects developed abnormal physical examinations of the nose at the end of the exposure in study in study 407. The important point is that this study failed to replicate the results of study 406 in that the study failed to show an onset of action.

7 STUDY # 149/2005 (BY9010/M1-403)

A Double-Blind, Placebo-Controlled, Randomized, Parallel-Group Phase 3 Clinical Trial Designed to Assess the Efficacy and Safety of Ciclesonide Applied as a Nasal Spray at Three Dose Levels (200 mcg, 100 mcg, or 25 mcg, once daily) in the Treatment of Perennial Allergic Rhinitis (PAR) in Patients 6 – 11 years of age.

7.1 Protocol

7.1.1 Administrative

Study Dates: June 4, 2004 to July 1, 2005
Clinical Centers: 74 Centers in the US and Canada. Enrollment at each center ranged between <5 (15 sites) to a maximum of 38.

Coordinating Investigator: [redacted] s,

7.1.2 Objective/Rationale

The objective of this study was to demonstrate the efficacy of 25, 100 and 200 μg doses of ciclesonide nasal spray administered intra-nasally once daily in the treatment of PAR in patients 6 to 11 years of age. A secondary objective was to demonstrate the safety of intra-nasally delivered ciclesonide in this population.

7.1.3 Study Design

This was a double-blind, placebo-controlled, parallel study of 665 subjects with PAR randomized into four treatment groups and treated for 12 weeks. Subjects were screened 7 to 10 days prior to randomization at which time they had a skin test in addition to the history and physical examination. During the screening period subjects/caregivers recorded the subject's symptoms in a diary twice daily. If the subject had an appropriate level of symptoms at the end of the screening period they were randomized to receive either 200 mcg, 100 mcg, or 25 mcg ciclesonide nasal spray once daily or placebo. After randomization they continued to record symptoms twice daily in the diary as well as any adverse events. Patients were seen at screening, baseline, and after 22, 43, 64, and 85, days of active treatment, and one follow-up visit approximately 7 days after the end of treatment. At all follow-up visits, the subjects had an ear, nose and throat (ENT) examination performed and a physician assessment of rhinitis signs and symptoms (PANS). At baseline, 43 days and 85 days they also had intraocular pressure (IOP) measured. The primary efficacy variable was the mean of the AM and PM r-TNSS comparing baseline to 1-6 weeks of treatment. Secondary outcomes included the r-TNSS over 1 – 12 weeks and the PANS. Safety was assessed with adverse events, physical examination, and routine safety laboratory examinations. A sub-set of the subjects (n=320) had an assessment of the HPA-axis consisting of AM plasma cortisol and a 24-hour urine free cortisol determination. Urine was collected at baseline, 43, and 85 days and blood was collected at baseline and end-of- treatment (85 days). Another sub-set (n=80 subjects) of subjects had pharmacokinetic measurements at day 43. Each of these subjects had 3 blood draws for ciclesonide levels at pre-dose and 2 and 5 hours post-dose. Subject compliance was assessed with the diary and by visual inspection of the medication bottle.

7.1.4 Study Population

Inclusion Criteria

- Male or female, 6 to 11 years of age
- A history of physician-diagnosed PAR to a relevant perennial allergen for 6 months prior to enrollment. The PAR must have been of sufficient severity to require treatment and be expected to require therapy in the future.

- Positive skin test to an allergen known to induce PAR within 12 months of enrollment

Exclusion Criteria

- Evidence of bronchial, pulmonary, or respiratory tract infections within 14 days of screening
- Active asthma (requiring daily treatment with β-agonists)
- Had change in immunotherapy injections within 30 days of screening
- Evidence of ocular herpes simplex, cataracts
- Positive for hepatitis B or C virus of human immunodeficiency virus
- Any significant physical abnormality including nasal polyps or nasal malformations.
- An IOP ≥ 21 mm Hg or glaucoma requiring treatment
- Inability to abide by medication restrictions as listed for study 401 (pg 78, above).

Randomization Criteria

- No respiratory infection during the run-in
- Adequate recording of symptoms in the diary (failure was defined as missing one or more of the entries on more than 3 days during run-in)
- A minimum TNSS (either AM or PM) of at least 5 for at least 4 of the last 7 days during the run-in.
- One symptom of the TNSS was of moderate severity (minimum score = 2) for 4 of the last 7 days of the run-in

7.1.5 Study Procedures

Treatment

Ciclesonide nasal spray was provided in canisters containing 0, 12.5, and 50 mcg ciclesonide per actuation. The subjects were instructed to take one spray in each nostril each AM. Each subject received two blinded bottles of medication and took one dose from each so that the delivered dose could range between 0 and 200 mcg daily. Rescue medication (chlorpheniramine maleate syrup, 2 or 2.5 mg every 4 – 6 hours) was allowed only after day 43.

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 Study 401, pg 79).

The scores were to be recorded in the morning and evening, approximately 12 hours apart. The maximum AM or PM score was 12 (4 symptoms times a maximum score of 3). At each time point, the subject recorded and instantaneous and a 12-hour reflective score for each symptom.

The investigator assessment (PANS) consisted of a scoring (0 to 3) of 4 symptoms and 4 signs (See study 401, pg 80). The total of the symptom and total of the sign scores were averaged for the final overall score. The assessment of allergic rhinitis signs was completed prior to querying the subjects/caregivers about symptoms. Symptoms within the week prior to the examination were included. A separate investigator assessment of nasal symptoms only was also calculated.

Other secondary efficacy measurements included the average of the AM and TM r-TNSS measured over the twelve weeks of treatment, individual symptom scores. i-TNSS, time to maximal effect, onset of action and percent change in TNSS.

Safety Evaluation

Safety was assessed with adverse events, vital signs, physical examination, ECG, routine laboratory examination, and eye examinations. Tonometry to measure intraocular pressure was performed on all subjects at baseline and follow-up. A pressure of 20 mm Hg was taken as the upper limit of normal for reporting an adverse event. Caregivers were instructed to restrict the child's activity for one hour prior to the measurement to avoid spurious elevations of pressure. For those who underwent HPA-axis assessment, a 24-hour urine was collected at baseline, 43 and 85 days. The adequacy of the urine collection was assessed with a 24-hour creatinine measurement. A value of <0.1 mmol/kg/day was taken as an indication of an inadequate specimen.

7.1.6 Data Analysis

Sample Size

It was assumed that the correlation between any 2 observations from the same patient was 0.7 after adjusting for day. It was further assumed that the standard deviation for a single observed change from baseline in the average of the AM and PM TNSS was 2.3 and the standard deviation for the mean change from baseline over 6 weeks was estimated to be 1.9. With these assumptions it was estimated that a sample size of 159 subjects per treatment group would have 80% power to detect a difference of 0.6 units in the average score with $\alpha = 0.05$.

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 finished the study as planned and who underwent all of the planned procedures. For the ITT population, a last observation carried forward (LOCF) procedure was used to account for missing data.

Efficacy Analysis

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. Individual measurements and abnormal values were presented in the listings only.

7.2 Results

7.2.1 Study Population

Disposition

There were 665 subjects randomized and 586 (88.1%) completed the trial. One subject in the ciclesonide 100 mcg group was not included in the ITT population. Premature discontinuation was more common in the placebo-treated (26 [15.8%]) and the low-dose ciclesonide subjects (22 [13.0%]) than in the high-dose ciclesonide subjects (16 [9.7%] and 15 [9.0%] in the ciclesonide 200 and ciclesonide 100 groups, respectively). Withdrawal due to adverse events was also more common in the placebo subjects (11 [6.7%]) than in the ciclesonide treated subjects (3 [1.8%], 5 [3.0%], and 4 [2.4%] in the

ciclesonide 200, ciclesonide 100, and ciclesonide 25 mcg groups, respectively). There were more major protocol violations in the placebo group (57 [34.5%]) than in the ciclesonide-treated subjects (49 [29.7%], 48 [28.9%], and 47 [27.8%] in the ciclesonide 200, ciclesonide 100, and ciclesonide 25 mcg groups, respectively). The per-protocol population consisted of 137 (83.0%), 135 (81.3%), 141 (83.4%), and 133 (80.6%) of the ciclesonide 200, ciclesonide 100, ciclesonide 25 mcg and placebo groups, respectively

Demographics

There were 393 males and 271 females. The mean age was 8.8 years, and 169 (25.5%) were less than 8 years old. The majority were Caucasian (79.7%) with 12.3% Black/African-Americans and 9.9% Asian and other (Table 57).

Table 57. Baseline Demographics of ITT population in Study 403

	Ciclesonide 200 mcg N=165	Ciclesonide 100 mcg N=165	Ciclesonide 25 mcg N=169	Placebo N=165	Total N=664
Age (years)					
Mean (SD)	9.0 (1.6)	8.8 (1.7)	8.8 (1.8)	8.7 (1.8)	8.8 (1.7)
Range	6- 11	5 - 11	6 - 11	6 - 11	5 –
Gender (% Male)	63.6	61.8	52.7	58.8	59.2
Race (%)					
Caucasian	79.4	80.6	79.3	79.4	79.7
Black	12.7	11.5	10.7	14.5	12.3
Asian, native American	0	4.8	5.3	3.0	3.6
Other	7.3	5.5	5.9	6.7	6.3
Ethnicity (%)					
Hispanic	14.5	14.5	16.0	13.9	14.8
Type of skin test (%)					
Historical	31.5	31.5	31.4	28.5	30.7
Current	68.5	68.5	68.6	71.5	69.3
Antigen Challenge (mm)					
Mean (SD)	7.2 (3.8)	8.2 (5.4)	7.2 (4.1)	7.3 (4.2)	7.4 (4.4)
Range	3 - 25	3 - 41	3 - 27	3 - 25	3 - 41
Control Challenge (mm)					
Mean (SD)	0.09 (0.38)	0.25 (1.1)	0.34 (0.9)	0.18 (0.6)	0.21 (0.8)
Range	0 - 3	0 - 11	0 - 4	0 - 4	0 - 11

The mean (SD) response to antigen challenge was 7.4 (4.4) mm and the mean (SD) response to diluent control was 0.21 (0.8mm). The means did not vary among the treatment groups, however there were some outliers. The majority of the control reactions were zero mm and only 7 were greater than 3 mm (five control reactions = 4 mm, and one each 5 mm and 11mm). Similarly, most of the responses to antigen were < 30 mm.

Reviewer: In the total subject population 13 individuals had a response to histamine <3mm with a plurality in the ciclesonide 100 mcg group (placebo = 3, ciclesonide 25 = 2, ciclesonide 100 = 6, and ciclesonide 200 = 2). Seven subjects had a diluent control skin test of >3 mm (placebo = 1, ciclesonide 25 mcg = 2, and ciclesonide 100 =4,

ciclesonide 200 = 0). Thus half of the subjects with aberrant skin tests were treated in the ciclesonide 100 mcg group. A summary of the antigens to which the subjects reacted was obtained from the transport data file at.xtp. A total of 168 individual antigens was listed. House dust mite was the most frequent antigen sited (380 [57.1%]) with cat/dog (144) and various molds (101) as the next most frequent. Only 27 reacted to cockroach antigens, 13 to more than one of the above and 2 individuals reacted to horse antigens and 1 to grasses.

A summary of prior medications was taken from 14.1.4.1 (pg 156/15460 of the study report). Of all those enrolled, 171 (25.7%) had taken some form of corticosteroid prior to enrollment, 146 (21.9%) of whom had taken a nasal corticosteroid. The distribution of prior nasal steroid use was generally similar across the treatment groups, although it was slightly lower in the subjects who were treated with 100 mcg: 22.4, 18.7, 24.8, and 21.8% in the ciclesonide 200, 100, 25, and placebo groups respectively

7.2.2 Efficacy Results

1 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 2

7.2.3 Safety

Extent of exposure

The mean duration of exposure was 78.6 days. In the individual treatment groups the exposures means were 80.0, 81.0, 77.5, and 76.0 days for the 200, 100, 25, and 0 mcg ciclesonide groups, respectively.

Adverse Events

Overall, 453 (68.1%) of the subjects reported adverse events. The incidence was slightly higher in the high dose ciclesonide groups (70.3 and 69.3% in the ciclesonide 200 and 100 groups) than in the ciclesonide 25 (66.9%) and the placebo (66.1%) groups. Specific adverse events, listed by preferred term, were more common in the higher dose ciclesonide groups, but there was not a consistent dose association overall because many events were more common in the placebo subjects than in the ciclesonide 25 – treated subjects (Table). The most common complaints overall were Nasopharyngitis (11.6%) and headache (11.0%). While the distribution among the treatment groups did not differ greatly, these symptoms were slightly more common in the high-dose ciclesonide groups. On the other hand, epistaxis and cough were more common in the placebo-treated subjects, and upper respiratory tract infection was high (>12%) in the placebo and ciclesonide 100 mcg group. Other events that occurred in more than 5% of subjects included pharyngolaryngeal pain, vomiting, nasal discomfort and pyrexia. Slightly more of the ciclesonide 100 subjects had increased rates of pharyngolaryngeal pain and vomiting than the other groups (Table 60). In general the types of events were typical of children with allergic diseases.

Table 60. Adverse Events Experienced by >2% of Subjects Enrolled

Preferred Term[1]	Ciclesonide 200 mcg N=165 n (%)	Ciclesonide 100 mcg N=166 n (%)	Ciclesonide 25 mcg N=169 n (%)	Placebo N=165 n (%)	Total N=665 n (%)
Any Treatment-Related, Treatment-Emergent AE	**116 (70.3%)**	**115 (69.3%)**	**113 (66.9%)**	**109 (66.1%)**	**453 (68.1%)**
Headache	23 (13.9%)	21 (12.7%)	12 (7.1%)	17 (10.3%)	73 (11.0%)
Nasopharyngitis	23 (13.9%)	19 (11.4%)	16 (9.5%)	19 (11.5%)	77 (11.6%)
Epistaxis	14 (8.5%)	15 (9.0%)	13 (7.7%)	16 (9.7%)	58 (8.7%)
Cough	13 (7.9%)	13 (7.8%)	12 (7.1%)	18 (10.9%)	56 (8.4%)
Upper respiratory tract infection	11 (6.7%)	21 (12.7%)	13 (7.7%)	20 (12.1%)	65 (9.8%)
Pharyngolaryngeal pain	11 (6.7%)	15 (9.0%)	9 (5.3%)	10 (6.1%)	45 (6.8%)
Vomiting	9 (5.5%)	11 (6.6%)	8 (4.7%)	8 (4.8%)	36 (5.4%)
Nasal discomfort	7 (4.2%)	6 (3.6%)	8 (4.7%)	3 (1.8%)	24 (3.6%)
Pyrexia	7 (4.2%)	12 (7.2%)	5 (3.0%)	13 (7.9%)	37 (5.6%)
Asthma	6 (3.6%)	7 (4.2%)	3 (1.8%)	8 (4.8%)	24 (3.6%)
Nasal disorder	6 (3.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	7 (1.1%)
Blood potassium increased	5 (3.0%)	2 (1.2%)	1 (0.6%)	0 (0.0%)	8 (1.2%)
Nasal congestion	5 (3.0%)	2 (1.2%)	1 (0.6%)	2 (1.2%)	10 (1.5%)
Rhinitis allergic	5 (3.0%)	1 (0.6%)	5 (3.0%)	2 (1.2%)	13 (2.0%)
Sinusitis	5 (3.0%)	8 (4.8%)	3 (1.8%)	7 (4.2%)	23 (3.5%)
Abdominal pain upper	4 (2.4%)	6 (3.6%)	1 (0.6%)	2 (1.2%)	13 (2.0%)
Ear pain	4 (2.4%)	4 (2.4%)	2 (1.2%)	2 (1.2%)	12 (1.8%)
Hypersensitivity	4 (2.4%)	2 (1.2%)	4 (2.4%)	3 (1.8%)	13 (2.0%)
Influenza	4 (2.4%)	5 (3.0%)	2 (1.2%)	2 (1.2%)	13 (2.0%)
Ear infection	3 (1.8%)	3 (1.8%)	4 (2.4%)	3 (1.8%)	13 (2.0%)
Gastroenteritis viral	3 (1.8%)	3 (1.8%)	5 (3.0%)	3 (1.8%)	14 (2.1%)
Pharyngitis streptococcal	3 (1.8%)	2 (1.2%)	3 (1.8%)	4 (2.4%)	12 (1.8%)
Acute sinusitis	2 (1.2%)	4 (2.4%)	2 (1.2%)	1 (0.6%)	9 (1.4%)
Otitis media	2 (1.2%)	5 (3.0%)	3 (1.8%)	3 (1.8%)	13 (2.0%)
Rash	2 (1.2%)	4 (2.4%)	1 (0.6%)	2 (1.2%)	9 (1.4%)
Urticaria	2 (1.2%)	1 (0.6%)	4 (2.4%)	0 (0.0%)	7 (1.1%)
Gastroenteritis	1 (0.6%)	0 (0.0%)	1 (0.6%)	4 (2.4%)	6 (0.9%)
Nausea	1 (0.6%)	2 (1.2%)	2 (1.2%)	4 (2.4%)	9 (1.4%)
Rhinorrhoea	1 (0.6%)	3 (1.8%)	1 (0.6%)	4 (2.4%)	9 (1.4%)

[1] Preferred Term counts: a patient was counted only once within each Preferred Term.
Data Source: Section 14.3, post-text Table 14.3.1.2.

The distribution of adverse events into mild moderate and severe was not strikingly different among the treatment groups: 7.9, 7.2, 4.7, and 7.3% severe in the 200, 100, 25, and the 0 mcg groups.

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths. Serious adverse events occurred in two subjects treated with 200 mcg ciclesonide (hospitalization for asthma and abdominal pain) and 1 placebo-treated subject (skull fracture after a fall). Overall 3.3% subjects were withdrawn from the study due to adverse events (1.8, 3.0, 2.4, and 6.1% of the ciclesonide 200, ciclesonide 100, ciclesonide 25, and placebo respectively). The most frequent events resulting in withdrawal were asthma (1.5%) and epistaxis (0.6%). Somewhat more subjects in the placebo group (6 [3.6%]) were withdrawn due to asthma than in the ciclesonide arms (2 [1.2%], 1 [0.6%], and 1 [0.6%] in the 200, 100, and 25 mcg groups).

Laboratory Results

There were no notable changes in mean values for hematology or chemistry blood tests comparing baseline to the midpoint or end of study values. In addition, the percentage of subjects with shifts in values from normal to abnormal was similar in all of the treatment groups. Alert values for blood chemistries were reported for 7 ciclesonide 200, 4 ciclesonide 100, and 6 ciclesonide 25 mcg subjects. Nine of the 17 ciclesonide subjects with alert values had mildly elevated potassium levels (5, 3, 1, and 0 had elevated potassium in the ciclesonide 200, 100, 25 and placebo subjects). In three of these cases the investigator attributed the abnormality to poor blood drawing technique resulting in hemolysis.

Reviewer: It is true that the distribution of abnormal values was similar across the treatment groups. However the percentage of abnormalities listed in Text Table 24/25 are very high. According to this table 28% of the subjects treated with placebo had calcium values that increased from normal to abnormal. Looking at the dataset "tabulations\lb.xpt" some of these elevations (close to 3 mmol/L) are not trivial. Lastly, hemolysis, as indicated by the investigators for three of the elevated potassium levels, is a reasonable explanation for elevated potassium in blood. However it is curious that the elevated potassium levels were so clearly dose related.

HPA-Axis Evaluation

Blood samples for cortisol were obtained from 45, 61, 51, and 47 of the ciclesonide 200, 100, 25, and placebo subjects, respectively. The plasma cortisol increased in all of the treatment groups over the course of the study. The changes were small and similar in all of the treatment groups (Table). One placebo subject had decreased plasma and free urinary cortisol listed as an adverse event. The event was ongoing at the end of the study.

Urine samples were considered adequate for analysis of free cortisol levels in 35, 44, 32, and 33 of the ciclesonide 200, 100, 25, and placebo subjects, respectively. Twenty-four hour excretion fell slightly in all of the treatment groups (Table 61). The changes were

Table 61. HPA-axis Evaluation After 12 Weeks of Treatment with Ciclesonide

				LS Mean Change from Baseline		Treatment Difference (95% CI)
	Dose	N	Baseline (mcg/dL/mcg/Day)	Ciclesonide	Placebo*	Treatment Difference (95% CI)**
Plasma cortisol Outcome at Week 1 - 12	200	45	10.2 (4.8)	0.74	0.39	0.35 (-1.4, 2.1)
	100	61	9.6 (4.6)	0.51		0.12 (-1.5, 1.7)
	25	51	10.1 (3.8)	0.01		-0.38 (-2.1, 1.3)
Urine free cortisol Outcome at Week 1 - 12	200	35	15.4 (7.6)	-1.69	-0.9	-0.81 (-4.0, 2.4)
	100	44	14.1 (5.8)	-0.96		-0.08 (-3.1, 2.9)
	25	32	13.2 (6.1)	-2.99		-2.11 (-5.3, 1.1)

*Mean (SD) baseline placebo plasma cortisol = 10.8 (5.3) mcg/dL (N=47); Mean (SD) baseline placebo urine cortisol = 13.2 (6.3) mcg/Day (N=33)
** Note that the difference = ciclesonide - placebo

small and the confidence interval for the difference between ciclesonide and placebo treatment included zero in all cases. Low urinary cortisol was reported as an adverse event in 1, 0, 3, and 2 subjects in the ciclesonide 200, 100, 25, and placebo groups. The changes were not dose-related: more placebo and ciclesonide 25 subjects had more low values (<7 mcg/Day) than did subjects treated with the higher doses of ciclesonide (23.2%, 19.7%, 34.5%, 37.5%, in the ciclesonide 200, 100, and 25, and placebo groups respectively). Shift tables are not provided for this variable.

Reviewer: The values quoted in the study report for low cortisol (<7 mcg/Day) refer to the entire study population. If only the Cortisol population (subjects with adequate urine collections) is considered the values are 14.3, 22.7, 28.1, and 27.3% for the ciclesonide 200, 100, 25, and 0 groups, respectively. If only subjects with normal values at baseline are considered the percentages are 16.1, 17.5, 30.0, and 21.4 for the ciclesonide 200, 100, 25, and 0 mcg groups. The LS mean (median) decrease in urinary cortisol was 0.72 (0.74), 2.99 (1.98), 0.99 (0.89), and 3.22 (3.96) mcg/Day in the ciclesonide 200, 100, 25, and 0 mcg subjects who were in the cortisol population and who had normal urinary cortisol at baseline. The fact that 15/144 (10.4%) subjects (4,4,2, and 5 in the ciclesonide 200, 100, 25, and placebo groups) had abnormal values at baseline despite a requirement to analyze only specimens that were determined to be adequate using prospectively defined criteria, highlights the difficulty in obtaining adequate samples for this determination in the pediatric population.

Physical Examination including ENT

The general physical examinations and vital signs were normal throughout the study for most subjects. Sixty-three percent of the ENT examinations were abnormal at baseline and the transition to normal was dose related (26.8%, 21.8%, 18.7%, and 17.6% in the ciclesonide 200, 100, 25, and placebo groups, respectively). Thirty-seven percent of the ENT examinations showed signs of rhinitis. Of the subjects with a normal examination at baseline 14.8% were abnormal at the end of the study. The incidence of transition to abnormal was slightly less in the ciclesonide 25 group than the others (17.2%, 15.3%, 11.4%, and 16.1% in the ciclesonide 200, 100, 25, and placebo groups respectively). One mild nasal ulceration was reported in the ciclesonide 200 mcg group on the right outer mucosa of the left septum at visit 9 (64 days). It had disappeared by visit 12 (84 days) despite continued ingestion of the study medication. The investigator did not consider it serious enough to report as an adverse event.

Intraocular pressure

Baseline mean intraocular (IOP) ranged between 15.3 and 15.7 mm Hg. The changes were quantitatively small during the 12 weeks of follow-up. The pressure increased less in the ciclesonide than the placebo treated subjects, especially in the ciclesonide 25 group (Table .) Elevation in IOP was reported as an adverse event in one subject in each treatment group. The incidence with which subjects with normal pressure at baseline Increase to abnormal (>20 mm Hg) was infrequent and not dose dependent (8.9%, 6.9%, 5.7%, and 8.2% of the ciclesonide 200, 100, 25, and placebo subjects, respectively). A pressure of 25 mm Hg was reached in 0.6%, 1.3%, 0.6%, and 1.9% of the ciclesonide

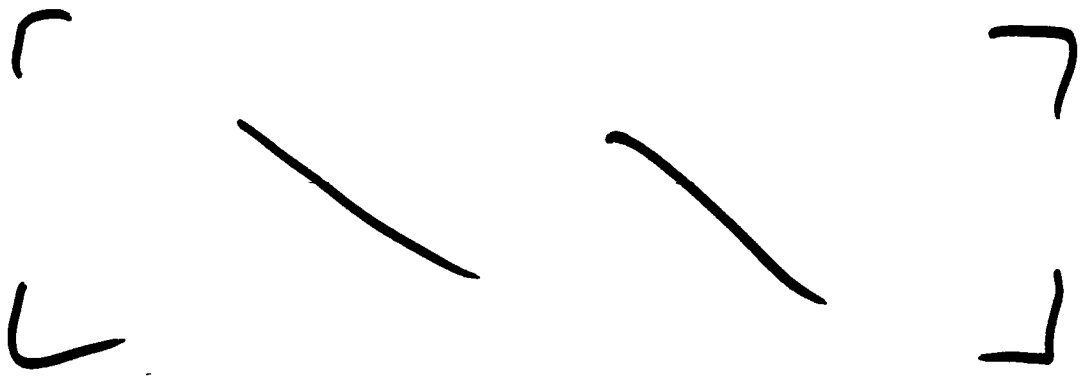
200, 100, 25, and placebo subjects, respectively). Two subjects in the ciclesonide 200 and one each in the ciclesonide 100 and ciclesonide 25 treatment groups had an IOP of >20 mm Hg at baseline. The pressure in all of these subjects decreased during treatment.

Table 62. Changes in Intraocular Pressure After Treatment of 6 to 11 year-olds with Ciclesonide or Placebo for 12 weeks

			LS Mean IOP Change from Baseline		Treatment Difference (95% CI)
Dose	N	Baseline IOP (mm Hg)	Ciclesonide	Placebo*	Treatment Difference (95% CI)
200	165	15.4 (3.1)	0.49	0.58	0.08 (-0.62, 0.78)
100	166	15.3 (2.9)	0.26		0.32 (-0.38, 0.62)
25	168	15.7 (2.9)	-0.20		0.79 (0.09, 1.5)

* Mean (SD) Placebo Baseline = 15.4 (3.21), n=165

7.3 Summary and Discussion



The safety data from this study are difficult to interpret. The adverse events were not excessive or severe and were distributed evenly across the treatment groups. The laboratory abnormalities were also distributed evenly across the treatment groups, however, there was an unusually high incidence of abnormalities in all of the subgroups. The most extreme case was in the serum calcium where almost 30% of all of the subjects (28% of them placebo) had abnormal values by the end of the study. These results throw doubt on either the laboratory methods or the means for standardization. Urine samples were assessed as adequate for analysis of cortisol excretion in a minority of the subjects. However, of those meeting the requirements for an acceptable specimen, >10% (15/144) of the subjects had abnormally low cortisol excretion at baseline. This also throws doubt on the reliability of the HPA-axis assessment. The IOP measurements provided a somewhat similar problem. There was a slight shift upward in all of the subgroups other than the ciclesonide 25 group. The results do not suggest a drug effect, but the technique for obtaining the IOP measurements might have been faulty. There were no major abnormalities found in the ENT examination, although one Ciclesonide 200 subject had a single transient nasal ulceration which resolved with continuation of study treatment. In

summary, while this study has not identified a safety concern,

8 STUDY # 144/2005 (BY9010/M1-405)

A Double-Blind, Placebo-Controlled, Randomized, Parallel-Group Clinical Trial Designed to Assess the Safety of Ciclesonide, Applied as a Nasal Spray at Three Dose Levels, 200 mcg, 100 mcg, or 25 mcg, once daily) for six weeks, in the Treatment of Perennial Allergic Rhinitis (PAR) in Patients 2 – 5 years of age.

8.1 Protocol

8.1.1 Administrative

Study Dates: September 10, 2004 to April 25, 2005
Clinical Centers: A single US site
Coordinating Investigator:

8.1.2 Objective/Rationale

The objective of this study was to demonstrate the safety of 25, 100 and 200 μg doses of ciclesonide nasal spray administered intra-nasally once daily in the treatment of PAR in patients 2 to 5 years of age. A secondary objective was to measure serum concentrations of ciclesonide and its active metabolite at three time points corresponding to peak and trough exposures

8.1.3 Study Design

This was a, double-blind, placebo-controlled, parallel study of 120 subjects with PAR randomized into four treatment groups and treated for 6 weeks. Subjects were screened 3 to 10 days prior to randomization at which time they had a skin test in addition to the history and physical examination. During the screening period subjects/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 (1:1:1:1) to receive either 200 mcg, 100 mcg, or 25 mcg ciclesonide nasal spray once daily or placebo. The subjects stayed in the clinic for 24 hours on the day of randomization to collect a 24-hour urine sample for cortisol. After randomization they continued to record symptoms in the morning as well as any adverse events. Patients were seen at screening, baseline, and after 22 and 43 days of active treatment, and at one follow-up visit approximately 7 days after the end of treatment. On day 43 they again remained in the clinic for 24 hours for a follow-up urine collection. Plasma for cortisol was also collected at baseline and end of study. At all visits at and after randomization, the subjects had an ear, nose and throat

(ENT) examination performed and a physician assessment of rhinitis signs and symptoms (Physician-Assessed Nasal Symptom Scores (PNSS). At baseline, 21, and 43 days they also had intraocular pressure (IOP) measured. Blood was also drawn on day 43 for ciclesonide levels at pre-dose and 2 and 5 hours post dose. The primary outcome was safety as measured by adverse events, ENT examination, IOP, and cortisol measurements. Efficacy was assessed with the PNSS and the AM 24-hour r-TNSS comparing baseline to 1-6 weeks of treatment. Subject compliance was assessed with the diary and by weighing the medication bottle.

8.1.4 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

- Evidence of bronchial, pulmonary, or respiratory tract infections within 14 days of screening
- Active asthma (requiring daily treatment with β-agonists)
- Change in immunotherapy injections within 30 days of screening
- Evidence of ocular herpes simplex, cataracts
- Positive for hepatitis B or C virus of human immunodeficiency virus
- Any significant physical abnormality including nasal polyps or nasal malformations.
- An IOP ≥ 21 mm Hg or glaucoma requiring treatment
- Received an antibiotic for any acute condition within 14 days of screening
- Initiation of immunotherapy or change in dose within 90 days of screening
- Non-vaccinated exposure to or active infection with chickenpox or measles within three weeks of screening
- Glaucoma requiring treatment
- Initiation of pimecrolimus or tacrolimus ointment 0.1% within 30 days of screening
- Inability to abide by medication restrictions specified in the protocol (See study 401, above. Pg 78)

Randomization Criteria

- No respiratory infection during the run-in
- Adequate recording of symptoms in the diary (failure was defined as missing one or more of the entries on more than 3 days during run-in)

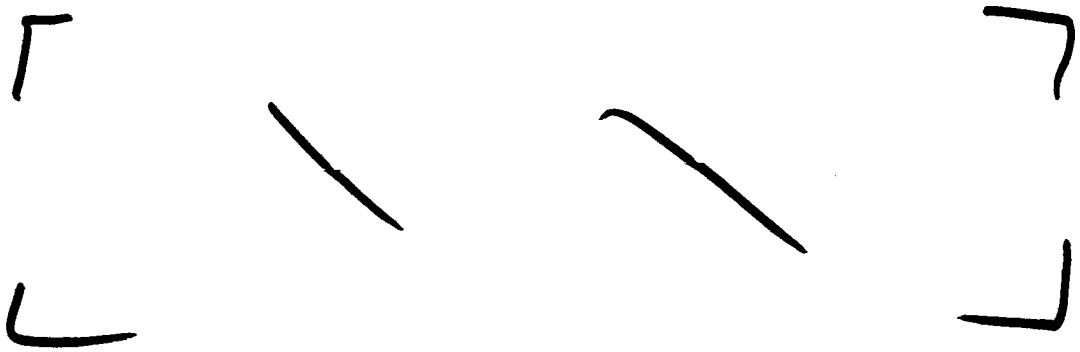
- Had not taken any prohibited medications

8.1.5 Study Procedures

Treatment

Ciclesonide nasal spray was provided in canisters containing 0, 12.5, and 50 mcg ciclesonide per actuation. All subjects/caregivers were provided two bottles of blinded medication. They were instructed to take one spray in each nostril from each bottle each AM. The contents of the bottles determined the dose delivered (0, 25, 100, or 200 mcg daily). Rescue medication (chlorpheniramine maleate syrup, 2 or 2.5 mg every 4 – 6 hours only after day 43.

Efficacy Evaluation



Safety Evaluation

Safety was assessed with adverse events, vital signs, physical exam ECG, routine laboratory examination and eye examinations. In addition, tonometry to measure intraocular pressure was performed on all subjects at baseline and follow-up. Caregivers were instructed to restrict the child's activity for one hour prior to the measurement to avoid spurious elevations of pressure. The HPA-axis assessment consisted of a 24-hour urine collected at baseline and on Day 43. The adequacy of the urine collection was assessed with a 24-hour creatinine measurement. A value of <0.05 mmol/kg/day was taken as an indication of an inadequate specimen.

8.1.6 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

[redacted]

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. The IOP measurements were performed by a single board-certified ophthalmologist.

Compliance was assessed by history, from the diary recordings, and from medication bottle weights.

8.2 Results

8.2.1 DSI Audit

This single-center study was included in the routine audit of clinical sites. The results revealed multiple deficiencies including failure to exclude subjects on prohibited medications (10 of 69 audited records); listing subjects as being fully compliant when their medication bottle weights were out of the sponsor's pre-specified range for compliance (only 9 of 69 audited were in range at all visits); and failure to collect unused medication at the end of the study. The final conclusion of the DSI auditors was that the data were unreliable.

8.2.2 Study Population

Disposition

There were 133 subjects randomized and 129 (97.0%) completed the trial. One subject in the 25 mcg ciclesonide group was not included in the ITT population. At least 97% of the subjects in each of the treatment groups completed the trial. One subject in each group was lost to follow-up. There were more major protocol violations in the ciclesonide-treated subjects (7 [21.2%], 7 [21.2%], and 4 [12.1%] in the ciclesonide 200, 100, and 25 groups, respectively) than in the placebo-treated subjects (3 [8.9%]). Prohibited medication was the reason for the violation in 14 of the 21 instances and were more than three times more common in the ciclesonide 200 group (18.2%) than in the placebo subjects (5.9%) and twice as common in the ciclesonide 100 group (12.1%).

Demographics

There were 74 males and 58 females. The mean age was 3.5 years, and 68 (25.5%) were less than 4 years old. The majority were Black/African-American (70.5%) with most of the remainder Caucasian (Table 63).

Table 63. Demographics of Children 2 to 5 Years of Age in the ITT population

	Ciclesonide 200 mcg N=33	Ciclesonide 100 mcg N=33	Ciclesonide 25 mcg N=33	Placebo N=34	Total N=132
Age (years)					
Mean (SD)	3.6 (1.1)	3.5 (1.0)	3.3 (1.0)	3.6 (1.3)	3.5 (1.1)
Range	2 - 5	2 - 5	2 - 5	2 - 5	2 - 5
Gender (% Male)	54.5	60.6	56.3	52.9	56.1
Race (%)					
Caucasian	30.3	27.3	31.3	23.5	28.0
Black	69.7	72.7	68.8	70.6	70.5
Other	0	0	0	2.5	1.5
Hispanic (%)	0	0	0	5.9	1.5
Type of skin test (%)					
Current	100	100	100	100	100
Antigen Challenge (mm)					
Mean (SD)	6.0 (1.6)	6.4 (1.6)	6.2 (1.8)	6.4 (1.4)	6.3 (1.5)
Range	3 - 8	4 - 10	4 - 13	4 - 10	3 - 13
Control Challenge (mm)					
Mean (SD)	0.24 (0.61)	0.15 (0.6)	0.41 (0.9)	0.24 (0.6)	0.26 (0.7)
Range	0 - 2	0 - 3	0 - 3	0 - 2	0 - 3

The mean (SD) response to antigen challenge was 6.3 (1.5) mm and the mean (SD) response to diluent control was 0.26 (0.7mm). The means did not vary among the treatment groups.

Reviewer: All of the subjects were allergic to mites and no histamine control was applied.

Prior medication ingestion was relatively uncommon (post-text Table 14.1.4.1 pg106/3227) in this young population. Approximately 40% of the subjects had taken benadryl. However, only 4 subjects (2 each, in the placebo and ciclesonide 200 groups) had taken a nasal steroid. An additional two subjects, each, in the 200 and 100 mcg group and 1 in the 25 mcg group took an inhalation corticosteroid prior to enrollment.

8.2.3 Efficacy Results

Efficacy Outcome

1 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 3

8.2.4 Safety

Extent of exposure

The mean duration of exposure was 40.9 days. In the individual treatment groups the exposures means were 38.6, 39.9, 40.5, and 39.5 days for the 200, 100, 25, and 0 mcg ciclesonide groups, respectively.

Adverse Events

Overall, 30 (22.6%) of the subjects reported adverse events (Table 66). The incidence was slightly higher in the placebo group (26.5%) than in the ciclesonide-treated subjects (18.2%, 24.2%, and 21.2% in the ciclesonide 200, 100, and 25 groups, respectively). Only Nasopharyngitis (4.5%), cough (3%), epistaxis (3%), and pyrexia (2.3%) occurred in more than 2% of the subjects. No predominance in any one treatment group was seen.

Table 66. Adverse Events Experienced by >2% Subjects after 6 Weeks of Treatment

Preferred Term[a]	Ciclesonide 200 mcg N=33	Ciclesonide 100 mcg N=33	Ciclesonide 25 mcg N=33	Placebo N=34	Total N=133
	n (%)	n (%)	n (%)	n (%)	n (%)
Patients With at Least 1 TEAE	**6 (18.2)**	**8 (24.2)**	**7 (21.2)**	**9 (26.5)**	**30 (22.6)**
Nasopharyngitis	1 (3.0)	2 (6.1)	1 (3.0)	2 (5.9)	6 (4.5)
Cough	0	1 (3.0)	1 (3.0)	2 (5.9)	4 (3.0)
Epistaxis	1 (3.0)	1 (3.0)	2 (6.1)	0	4 (3.0)
Pyrexia	1 (3.0)	0	1 (3.0)	1 (2.9)	3 (2.3)
Gastroenteritis Viral	0	0	0	2 (5.9)	2 (1.5)
Upper Respiratory Infection	0	1 (3.0)	0	1 (2.9)	2 (1.5)
Increased Alkaline Phosphatase	1 (3.0)	1 (3.0)	0	0	2 (1.5)
Increased Body Temperature	0	1 (3.0)	1 (3.0)	0	2 (1.5)
Headache	1 (3.0)	0	0	1 (2.9)	2 (1.5)
Rhinitis	0	1 (3.0)	1 (3.0)	0	2 (1.5)

The only event that was described as severe occurred in a subject taking ciclesonide 25 mcg. This 2 year-old male developed fever and swollen glands 4 weeks after completing the protocol. This event was also characterized as serious due to hospitalization.

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths. The only serious adverse event occurred in the subject treated with 25 mcg ciclesonide described above. The subject was lost to follow-up after discharge from the hospital.

Laboratory Results

There were no notable changes in mean values for hematology or chemistry blood tests comparing baseline to the end of study values. In addition, the percentage of subjects with shifts in values from normal to abnormal was low and similar in all of the treatment groups. Two subjects had a report of a laboratory based adverse event. One subject in

both the ciclesonide 200 and ciclesonide 100 groups had substantial increases in alkaline phosphatase during the trial. In the subject in the ciclesonide 200 group the value went from 274 U/L to 1577 U/L at six weeks. Follow-up determinations were 488 and 321 U/L. In the subject taking 100 mcg ciclesonide the value went from 235 U/L to 2264 U/L at 6 weeks and 462 and 278 U/L at follow-up. These events were not considered serious. Alert values for blood hematology or chemistries were reported for 5 (15%) ciclesonide 200, 12 (36.3%) ciclesonide 25, and 8 (23.5%) of the placebo subjects. Of the 25 alerts, 17 were elevated platelet counts and 6 were for elevated potassium levels.

Reviewer: The shift tables are difficult to interpret due to the small number of subjects in each treatment group. For instance 16.7% of the ciclesonide subjects that entered the trial with normal alkaline phosphatase values were abnormal at 6-weeks. However, 16.7% is only 4 individuals. On the other hand, there does seem to be a trend toward abnormal values which are more frequent at the end than the beginning of the trial. The elevated potassium is easier to explain with sample handling than the platelet count. It is also curious that except for two of the platelet count pairs all of the values increased over the treatment period.

HPA-Axis Evaluation

Blood samples for cortisol were obtained from 28, 27, 28, and 30 of the ciclesonide 200, 100, 25, and placebo subjects, respectively. The plasma cortisol decreased in all of the treatment groups over the course of the study. The changes were small and similar in all of the treatment groups (Table 67) although there was a suggestion of a dose relationship.

Table 67. HPA-axis Evaluation in subjects 2 to 5 years of age

				LS Mean Change from Baseline		Treatment Difference (95% CI)**
	Dose	N	Baseline (mcg/dL/mcg/D)	Ciclesonide	Placebo*	Treatment Difference (95% CI)
	200	28	9.7 (3.7)	-1.07		-1.04 (-2.7, 0.7)
Plasma cortisol	100	27	9.6 (4.2)	-0.39	-0.03	-0.36 (-2.1, 1.4)
Outcome at Week 1 - 12	25	28	10.3 (3.3)	-0.15		-0.12 (-1.8, 1.6)
Urine free cortisol	200	22	11.8 (10.2)	-3.55		-2.04 (-4.4, 0.3)
Outcome at Week 1 - 12	100	15	8.8 (4.4)	-3.47	-1.51	-1.96 (-4.5, 0.6)
	25	16	12.6 (8.6)	-3.27		-1.76 (-4.3, 0.8)

* Mean (SD) baseline placebo plasma cortisol = 10.5 (4.7) mcg/dL (N=30); Mean (SD) baseline placebo urine cortisol = 8.6 (3.7) mcg/D (N=18)
** Note that the difference = ciclesonide - placebo

Urine samples were considered adequate for analysis of free cortisol levels in 22, 15, 16, and 18 of the ciclesonide 200, 100, 25, and placebo subjects, respectively. Twenty-four hour excretion fell in all of the treatment groups (Table 67). The changes were larger than seen in the other studies in this submission, and they fell by twice as much in the active treatment groups as in the placebo-treated subjects. However, the confidence

interval for the difference between ciclesonide and placebo treatment included zero in all cases, at least in part due to the small number of determinations.

Reviewer: The applicant defined a normal urine sample as one that contained at least 0.5 mmol of creatinine. A lower limit for normal cortisol was not provided, but a reference to the literature is given. There is, however, no comment abut limiting the population to those who had not been exposed to corticosteroids within the prohibited time prior to enrollment or during the trial.

Physical Examination including ENT

The general physical examinations and vital signs were normal throughout the study for most subjects. The ENT examination was recorded as abnormal in 100% of the subjects at baseline. At the end of the study the percentage was 3%, 0%, 6.3% and 9.1% in the ciclesonide 200, 100, 25, and placebo groups, respectively.

Intraocular pressure

Baseline mean intraocular (IOP) ranged between 13.7 and 15.3 mm Hg. The changes during treatment were quantitatively small during the 6 weeks of follow-up. The pressure increased less in the ciclesonide than the placebo treated subjects, especially in the ciclesonide 200 group (Table 68). Two subjects had pressures of ≥ 25 mm Hg at the end of the study. One subject in the ciclesonide 100 group had values of OD 28 and OS 26 mm Hg. And a subject in the ciclesonide 25 group had a value of OD 29.

Table 68. Change in Intraocular Pressure in Children 2 to 5 Years of Age After Six Weeks of Treatment with Ciclesonide Nasal Spray

	Ciclesonide Subjects		Baseline (mm Hg)	LS Mean Change from Baseline		LS mean (95% CI) Treatment Difference
	Dose	N		Ciclesonide	Placebo*	
IOP	200	33	14.1 (4.1)	-072	-0.46	0.30 (-1.7, 2.2)
	100	32	15.3 (3.3)	1.34		-1.8 (-3.8, 0.2)
	25	33	13.7 (4.2)	0.34		-0.8 (-2.8, 1.2)

* Mean (SD) Placebo baseline = 13.4, N=34

Reviewer: As with the other quantitative data in this study, the values were not normally distributed and the ANOVA is therefore not an appropriate model to use in this data analysis. The two high values in the 100 and 25 mcg groups are outliers and are probably exerting an undue influence on the mean The use of the ANOVA in this analysis is, therefore, not appropriate.

8.3 Summary and Discussion

This six-week, randomized comparison of multiple doses of ciclesonide nasal spray 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. Unfortunately, the small number of subjects in each treatment group makes it

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 not severe. The ENT examination failed to show any evidence of septal ulceration or perforation, and the change in IOP did not differ among the treatment groups. There did appear to be a dose related decrease in both plasma and uncorrected urinary cortisol measurements, although the differences were not statistically significant. Ciclesonide was detected in the blood as the active metabolite in a dose dependent manner. Over 37% of the subjects taking the 200 mcg dose of ciclesonide had detectable levels of the metabolite at 2 hours, but the maximum levels were one tenth of those seen in subjects taking inhaled ciclesonide for asthma. The interpretation of all of these data is complicated by the DSI audit finding that compliance was not confirmed by weighing the medication bottles. However, the blood levels indicate that at least some of the subjects received substantial doses of ciclesonide. the study support the conclusion that this study is not adequate to provide safety information of ciclesonide nasal spray in this age-group.

9. STUDY # 147/2005 (408)

Investigation of Potential Additive Inhibitory Effects on HPA-Axis of Ciclesonide Nasal Spray when Administered Concomitantly with Orally Inhaled Beclomethasone Dipropionate (BDP-HFA) in Patients (18-60 Years) with Perennial Allergic Rhinitis (PAR)

9.1 Protocol

9.1.1 Administrative

Study Dates: December 27, 2004 to April 18, 2005
Clinical Centers:
Medical Monitor:
CRO:

9.1.2 Objective/Rationale

The primary objective of this study was to demonstrate that there were no clinically relevant additive inhibitory effects on the HPA-axis when ciclesonide nasal spray was concomitantly administered with orally inhaled HFA-BDP. A secondary objective was to evaluate the safety and tolerability of the combined regimen.

9.1.3 Study Design

This was a randomized, double-blind, placebo and active-controlled, parallel study of approximately 55 subjects with PAR per treatment group. After enrollment subjects were treated for 10 days with BDP-HFA 320 mcg BID and a nasal spray placebo, at which time they maintained a diary with nasal symptom scores. At the end of the run-in eligible subjects were randomized to receive ciclesonide 200 mcg once daily or placebo while continuing to inhale BDP-HFA twice daily. There was one follow-up visit on day 21 of randomized treatment and the subject returned on day 42 for final evaluation. Subjects stayed in the clinic for 24 hours on the day before the run-in, at the end of the run-in and before starting ciclesonide nasal spray. At the end of treatment they stayed in for 48 hours. Both urinary and plasma cortisol was measured over the 24-hour period (two serial collections on day 52 and 53). On Day 43 (Day 53 of the study) all subjects received 2 mg dexamethasone orally in addition to the daily dose of BDP-HFA and nasal spray. Plasma for cortisol was colleted for the following 24 hours. The last dose of BDP-HFA was taken on Day 54. A diagram of the study design is reproduced in Figure 7. Safety was assessed with adverse events, ENT examination, vital signs and clinical laboratory examinations as well as the cortisol measurements. Physical and ENT examinations were performed at the beginning and end of the trial and before each medication change. Safety laboratory examinations were conducted at the beginning and end of the study. Subject compliance was assessed with the diary and by weighing the medication bottle.

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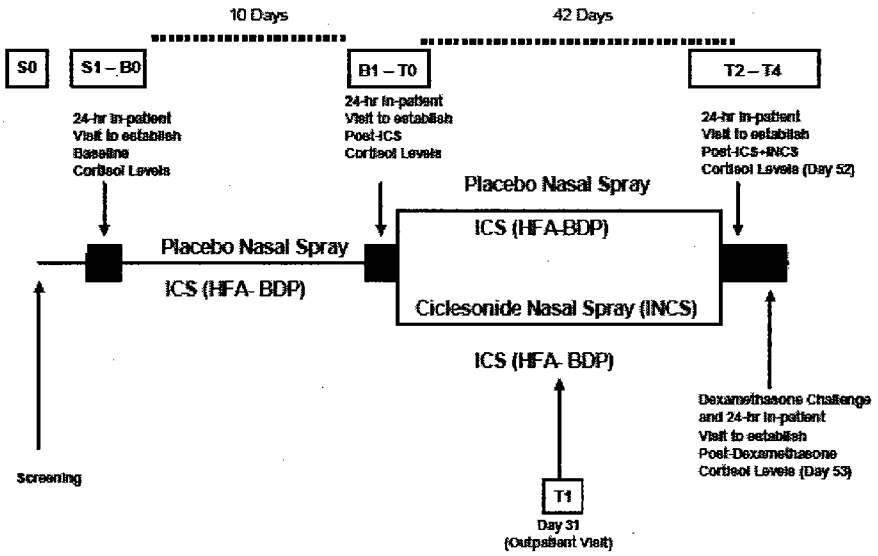
Figure 7. Schema of Study Design



9.1.4 Study Population

Inclusion Criteria

- Male or female, 18 to 60 years of age
- A history of PAR to relevant allergen for a minimum of 1 year immediately preceding the Screening Visit. The PAR must have been of sufficient severity to require treatment in the past, and, in the investigator's judgment, would be expected to require treatment throughout the study period.
- Positive skin test within 12 months of enrollment
- BMI between 18 and 31

Exclusion Criteria

- Exposure to corticosteroids for any indication, chronic or intermittent (e.g.: asthma, contact dermatitis), during the past 2 months, 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 the equivalent of 1% hydrocortisone for dermatological conditions during the past 1 month, or presence of an underlying condition that could reasonably be expected to require treatment with such preparations during the course of the study
- History or physical findings of nasal pathology, including nasal polyps (within the last 60 days) or other clinically significant respiratory tract malformations, recent nasal biopsy (within the last 60 days), nasal trauma, or surgery and atrophic rhinitis or rhinitis medicamentosa (within the last 60 days).
- Evidence of bronchial, pulmonary, or respiratory tract infections or use of an antibiotic for any indication within 14 days of screening
- Active asthma (requiring daily treatment with β-agonists)

- Change in immunotherapy injections within 90 days of screening
- Evidence of ocular herpes simplex, cataracts or glaucoma
- Positive for hepatitis B or C virus of human immunodeficiency virus
- Vegetarian or any other dietary restriction that would prevent participation in standardized meals.
- Absence of regular sleep patterns
- Inability to abide by medication restrictions outlined in the protocol

Randomization Criteria

24-hour r-TNSS 4 or greater on 5/7 days of the run-in period
Completion of all but 3 of the possible diary entries
Took at least 80% of the study medication during the run-in
No intercurrent illness or ingestion of prohibited medications

9.1.5 Study Procedures

Treatment

Ciclesonide nasal spray was provided in canisters containing 50 mcg ciclesonide per actuation. The subjects were instructed to take two sprays in each nostril each AM. No rescue medication was provided. Compliance was assessed with the diary entries and also by weighing the study medication bottles.

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 as follows:

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 scores were to be recorded in the morning. The maximum score was 12 (4 symptoms times a maximum score of 3). In addition to grading each symptom, the subjects recorded the time of day the assessment was made.

Safety Evaluation

Safety was assessed with adverse event enumeration, vital signs, physical exam, ECG, routine laboratory examinations. A 24-hour evaluation of plasma cortisol was performed 1) prior to run-in, 2) at the end of run-in 3) after the penultimate dose of study medication, and 4) on the last treatment day after all of the study medication and 2 mg dexamethasone. During each 24-hour period urine was also collected for cortisol

measurement. Plasma for cortisol was obtained at baseline and after 3, 6, 8, 10, 12, 14, 16, 18, 21, 22, and 24 hours after the start of the test or after the first dose of medication (BDP-HFA at the end of run-in, BDP-HFA and study nasal spray at the end of active treatment.

9.1.6 Data Analysis

Sample Size

In a previous study the standard deviation for the change from baseline in the weighted average of cortisol (0, 24) was 1.62 mcg/dL. That translated into an AUC of 38.8 mcg•hr/dL. The standard deviation of the treatment difference in a parallel group setting was 54.9 mcg•hr/dL. From the same prior study it was determined that bioequivalence bounds of a 20% difference would be reasonable. Thus the delta was taken as 27.2 mcg•hr/dL or 20% of 136.1 mcg•hr/dL. This calculation is based on the finding of a mean 24-hour AUC for cortisol in placebo treated subjects of 181.4 mcg•hr/dL, and BDP-HFA was predicted to reduce cortisol by 25%. It was therefore estimated that the $AUC_{0\text{-}24h}$ at the end of the run-in would be 136.1 mcg•hr/dL. Using these assumptions, a sample size of 45 evaluable subjects would provide a 90% power with a one-sided alpha of 0.025.

Study Populations

In addition to the intention-to-treat (ITT) population a per-protocol (PP) population was defined for the HPA-axis evaluation. For analyses of urine cortisol, only subjects with samples deemed to be complete were included. To meet this criterion, the total creatinine value was required to be greater than 60% of the lower limit of the normal range for total creatinine.

Analysis

The primary efficacy variable was the change from baseline in the 24-hour r-TNSS averaged over each week. The baseline was taken as the average of the average score obtained during the last 7 days of the screening period. The change from baseline for each treatment group was compared at each week using a repeated measures ANOVA.

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

9.2 Results

9.2.1 Study Population

Disposition

There were 111 subjects randomized and 105 (94.5%) completed the trial. Five subjects withdrew from the ciclesonide and 1 from the placebo group. Two subjects withdrew

from the ciclesonide and 1 in the placebo group due to adverse events, and the same numbers withdrew upon their request. All subjects were included in the ITT population

Demographics

There were 55 males and 56 females, the mean age was 33.6 years, and >92% were Caucasian (Table 69). The mean skin test reaction to allergen was 9.3 mm and the mean response to the control was 0 mm. These demographic variables were distributed evenly across the treatment groups. Seventy-one and 62 % of the ciclesonide and placebo subjects were non-smokers, and 20 and 24% were active smokers, respectively. No subjects had taken a corticosteroid prior to enrollment.

Table 69. Baseline Demographics for Subjects Enrolled in Study 408

	Ciclesonide 200 mcg N=56	Placebo N=55	Total N=111
Age (years)			
Mean (SD)	33.5 (11.3)	33.8 (12.2)	33.6 (11.7)
Range	18 - 56	18 - 57	18 – 57
Gender (% Male)	48.2	50.9	49.5
Race (%)			
Caucasian	92.9	94.5	93.7
Black	5.4	5.5	5.4
Asian, native American	1.8	0	0.9
Hispanic Ethnicity (%)	53.6	41.8	47.7
Antigen Challenge (mm)			
Mean (SD)	8.8 (4.1)	9.8 (4.8)	9.3 (4.4)
Range	5 - 20	5 - 21	5 - 21

Protocol Deviations

Five of the ciclesonide and 1 placebo subject were considered major protocol violators. Three subjects in the ciclesonide group and one placebo subjects were less than 60% compliant with at least one study medication. In the ciclesonide group one subject was pregnant and one had upper airway pathology.

9.2.2 Efficacy Results

Primary Efficacy Outcome

The primary efficacy variable was the 24-hour AM r-TNSS. The analysis was performed on the change from baseline over the 6 weeks of randomized (ciclesonide vs placebo) therapy. The baseline values were 7.9 and 7.7 in the ciclesonide and placebo groups, respectively. The mean scores fell to the same degree in both treatment groups (-0.20). The results were similar for the per-protocol population (Table 70).

Table 70. Changes in r-TNSS During Treatment in Study 408

Variable	Ciclesonide N = 56	Placebo N=55	Treatment Difference (95% CI)
Average 24-hr r-TNSS			
Baseline, Mean (SD)	7.90 (2.22)	7.71 (1.99)	
Change from Baseline (LS mean [SE])	-0.20 (0.23)	-0.20 (0.23)	0 (-0.66, 1.60)

9.2.3 Safety

Extent of exposure

The mean exposure was 41.4 days in the ciclesonide group and 42.7 in the placebo subjects.

Adverse Events

Overall, 65 (58.6%) of the subjects reported adverse events: 57.1% of the ciclesonide and 60.0% of the placebo subjects. None was characterized as serious, but 2 in the ciclesonide group resulted in withdrawal of the subject (Table 71). The most common events in both treatment groups were increased systolic (12.6%) and diastolic blood pressure (8.1%) and sinus bradycardia (9.0%), and these events occurred with approximately the same incidence in the two treatment groups. On the other hand bradycardia, NOS occurred in 7.1% of the ciclesonide as opposed to 1.8% of the placebo subjects. Cough, dizziness, dysmenorrhea, heart rate decreased, pharyngitis, and sinusitis were all more common in the ciclesonide group while headache and nasopharyngitis were more frequent in the placebo subjects (Table 71).

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Table 71. Study 408: Adverse Events Experienced by >2% of Subjects Enrolled

Preferred Term	Ciclesonide 200 mcg (N=56)	Placebo (N=55)	Total (N=111)
Patients with one or more treatment-emergent AEs	32 (57.1%)	33 (60.0%)	65 (58.6%)
Systolic blood pressure increased	7 (12.5%)	7 (12.7%)	14 (12.6%)
Diastolic blood pressure increased	5 (8.9%)	4 (7.3%)	9 (8.1%)
Sinus bradycardia	5 (8.9%)	5 (9.1%)	10 (9.0%)
Bradycardia NOS	4 (7.1%)	1 (1.8%)	5 (4.5%)
Cough	3 (5.4%)	1 (1.8%)	4 (3.6%)
Sinus headache	3 (5.4%)	2 (3.6%)	5 (4.5%)
Dizziness	2 (3.6%)	1 (1.8%)	3 (2.7%)
Dysmenorrhea	2 (3.6%)	0 (0.0%)	2 (1.8%)
Headache	2 (3.6%)	6 (10.9%)	8 (7.2%)
Heart rate decreased	2 (3.6%)	0 (0.0%)	2 (1.8%)
Nasopharyngitis	2 (3.6%)	4 (7.3%)	6 (5.4%)
Pharyngitis	2 (3.6%)	1 (1.8%)	3 (2.7%)
Sinusitis NOS	2 (3.6%)	1 (1.8%)	3 (2.7%)
Aggravated allergy	1 (1.8%)	2 (3.6%)	3 (2.7%)
Epistaxis	1 (1.8%)	2 (3.6%)	3 (2.7%)
Insomnia	0 (0.0%)	2 (3.6%)	2 (1.8%)

NOS = not otherwise specified

Data source: Section 14.3, post-text Table 14.3.1.2

Serious Adverse Events and Events Leading to Withdrawal

There were no deaths or serious adverse events. Two subjects in the ciclesonide group were withdrawn with influenza and influenza-like syndrome. Both events were described as moderate in intensity. One ciclesonide subject and 3 placebo subject had events that were described as severe. The ciclesonide subject had atopic dermatitis, and in the placebo group the severe events were labeled "Allergy aggravated", "Oral Candidiasis, and "Sinus headache".

Vital Signs

The mean values for systolic and diastolic blood pressure and for pulse remained within the normal limits for the entire study. Vital signs exceeded the alert values for 10 ciclesonide and 20 placebo subjects. All of the abnormal values were for change in pulse except two measurements of systolic pressure (142 and 174 mm Hg) in two placebo subjects at the end of the randomized treatment period, but prior to dexamethasone treatment. One ciclesonide subject had an "alert" pulse of 131 and a blood pressure of 147/101 at screening. The pulse ranged between 52 and 91 during follow-up, but the blood pressure remained elevated with a maximal value of 166/105 at the end of randomized treatment.

Reviewer: The alert values for high systolic blood pressure were 170 mm Hg or a 40 mm increase, for high diastolic blood pressure were >105 mm Hg, and the alert values for

pulse were >120 and <50 bpm. Many of the blood pressure values were above those conventionally considered to be healthy (>150 systolic and 90 diastolic), but there was no difference between the two groups and there was no trend over time. The reason for the relatively large number of blood pressure and pulse readings that were recorded as adverse events is hard to explain, but conceivably could be related to budesonide. The mean pre and post budesonide values were as follows: Systolic BP 120.1 and 122.2 (p=0.014); Diastolic BP 75.3 and 76.0 (p=0.26); pulse 77.4 and 74.7 (p=0.002). None of the differences was clinically significant

Laboratory Results

Mean changes in the laboratory values were small over the course of the study and were approximately the same in the two treatment groups. If a categorical analysis is performed, the most common values to increase from normal to abnormally high in the subjects who completed the study were the total white cell (WBC) and neutrophil counts. The changes occurred slightly more frequently in the ciclesonide treated group than the placebo group (Total WBC 40% and 22% and total neutrophil counts 22.4% and 5.8% of the ciclesonide and placebo groups, respectively). However, the mean change was very small in both groups: the WBC increased by a mean of 3.04 and 3.01 x 10^9 cells/L and the mean total neutrophil count increased by 2.22 and 2.08 x 10^9 cells/L in the ciclesonide and placebo groups respectively. The mean values for the clinical chemistry values showed sporadic, small increases in both treatment groups.

Individual abnormalities that exceeded the alert level were rare. In the Ciclesonide group one subject had an increase in the WBC count from 8.2 to 16.6 x 10^9 cells/L and one subject had an increase in lipase from 30 to 348 U/L. Three subjects in the placebo group had an increase in WBC count into the alert range (>13.5 x 10^9 cells/L). The changes over the course of the study were as follows: 12.8 to 19.5, 6.9 to 18.9 and 8.4 to 17.2 x 10^9 cells/L). An additional placebo subject had elevated glucose levels at baseline and at the end of the study: 14.7 and 12.3 mmol/L (upper limit of normal 5.8 mmol/L).

HPA-axis Evaluations

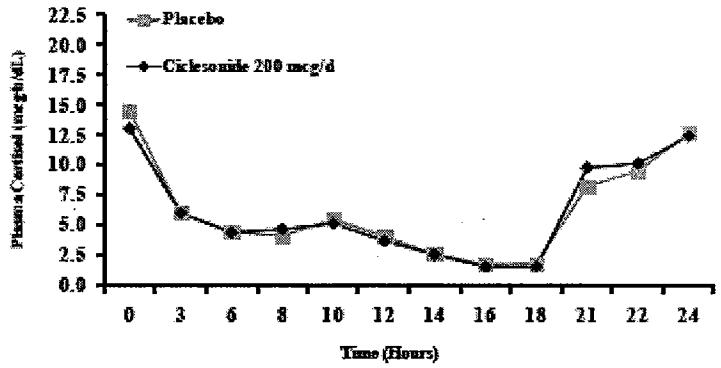
The mean baseline plasma cortisol AUC_{0-24} were similar in the two treatment groups (197.4 and 202.8 mcg•hr/dL in the ciclesonide and placebo groups, respectively) and the decrease with budesonide treatment during the Run-in period was also equivalent (-70.0 and -65.6 mcg•hr/dL in the ciclesonide and placebo groups, respectively). The addition of ciclesonide nasal spray resulted in no additional decrease in the mean plasma cortisol AUC_{0-24} (Table 72). The values after 6 weeks of treatment were 135.0 and 135.5 mcg•hr/dL in the ciclesonide and placebo groups, respectively. This represented a mean increase of 8.2 and 1.0 mcg•hr/dL during randomized treatment in the ciclesonide and placebo groups, respectively. After dexamethasone treatment the mean plasma cortisol AUC_{0-24} values were 68.1 and 72.1 mcg•hr/dL in the ciclesonide and placebo groups, respectively. This represented a decrease of 67.5 and 62.7 mcg•hr/dL in the ciclesonide and placebo groups, respectively. Over the course of the study, the plasma cortisol fell by 129.6 and 138.5 mcg•hr/dL (66.0% in both treatment groups) in the ciclesonide and placebo treated subjects, respectively.

Table 72. HPA-axis Assessment after Treatment with Budesonide Inhalation Aerosol and Ciclesonide Nasal Spray for 6 Weeks

Variable	Ciclesonide	Placebo	Treatment Difference (95% CI)
Plasma Cortisol AUC_{0-24}, mcg•hr/dL	N=50	N=47	
Baseline, Mean (SD)	197.4 (62.0)	202.8 (53.7)	
Plasma Cortisol, mcg, Change from Baseline (LS mean [SE])			
At end of Run-in (BDP alone)	-70.0 (5.5)	-65.6 (5.7)	4.4 (-11.4, 20.1)
After Ciclesonide Treatment	8.2 (6.9)	1.0 (7.0)	-7.5 (-27.2, 12.1)
After Dexamethasone	-67.5 (5.2)	-62.7 (5.3)	4.8 (-6.6, 16.1)
Urinary Cortisol, mcg/day	N=46	N=52	
Baseline, Mean (SD)	47.0 (22.9)	57.1 (33.5)	
Urinary Cortisol, mcg/Day, Change from Baseline (LS mean [SE])	N=174	N=92	
At end of Run-in (BDP alone)	-18.5 (2.0)	-20.58 (1.9)	-2.11 (-7.6, 3.3)
After Ciclesonide Treatment	-13.6 (2.2)	-11.43 (2.0)	2.16 (-3.3, 8.0)
After Dexamethasone	-4.6 (1.4)	-6.6 (1.3)	-0.92 (-4.9, 3.1)

The results of the plasma cortisol determinations after randomized treatment with ciclesonide or placebo nasal spray are shown in Figure .

Figure 8 . Plasma Cortisol after treatment with Budesonide Aerosol Inhaler + Ciclesonide Nasal Spray or Budesonide + Placebo Nasal Spray.



For patients to be include in the urine cortisol analysis they were required to have a complete sample as determined by urine creatinine values being above 60% of the lower limit of the normal range or by indication of a complete collection in the CRF. Eight patients were excluded due to inadequate samples, 2 in the placebo group and 6 ciclesonide-treated subjects (Table). The mean baseline 24-hour excretion of free cortisol was 47.0 and 57.1 mcg/D in the ciclesonide and placebo subjects, respectively. The values fell to an equal degree during budesonide treatment (-18.5 and -20.6 mcg/D, respectively). In contrast to the plasma cortisol, the urinary cortisol decreased further during randomized treatment with ciclesonide or placebo: -13.6 and -11.4 mcg/D, respectively. After dexamethasone treatment there was a small further fall in both groups (-4.6 and -6.6 mcg/D in the ciclesonide and placebo groups, respectively). Over the

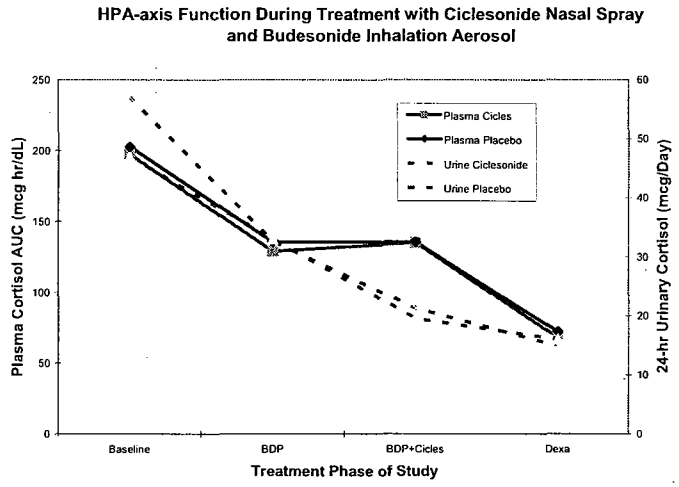
course of the study the urinary cortisol fell 30.9 and 42.2 mcg/Day (65.7 and 73.9%) in the ciclesonide and placebo treated subjects, respectively.

Reviewer: The fact that the urinary cortisol decreased during treatment with placebo nasal spray suggests that the progressive suppression of adrenal function seen during the period of randomized treatment was due to residual effects of the budesonide treatment. It would be expected that any effect of ciclesonide would be quantitatively less than that of inhaled budesonide. Therefore, this study does not rule out an effect of ciclesonide which could have been masked by the ongoing response to budesonide.

9.3 Summary and Discussion

This pharmacodynamic study evaluated the effects of ciclesonide nasal spray on the HPA-axis when it was taken concomitantly with Budesonide (BDP) by aerosol inhalation. After a 10 day run-in when all subjects inhaled BDP 320 mcg BID both the plasma and 24-hour urinary cortisol values decreased substantially. After an additional 6 weeks during which subjects were randomized to receive ciclesonide or placebo nasal spray, the plasma cortisol did not change significantly, but the urinary excretion fell further. As a positive control, all subjects were given 2 mg of dexamethasone by mouth on the last day of the study. This resulted in an additional decrease in the plasma cortisol and a lesser decrease in the urinary excretion. The change in the urinary and plasma cortisol is depicted graphically in Reviewer Figure 1 below The changes were virtually indistinguishable in the ciclesonide and placebo nasal spray groups.

Figure 9



However, the fact that the urinary cortisol decreased during placebo treatment suggests that the effects of budesonide inhalation had not stabilized prior to initiation of the randomized nasal spray.

The distribution of adverse events was somewhat different from that seen in the efficacy trials. The most common events were changes in blood pressure and pulse. Similarly there were more frequent increases in the total white count and neutrophil count than in the long-term efficacy trials. Both of these events can probably be ascribed to the concomitant treatment with budesonide.

10. STUDY # 148/2005 (409)

Investigation of Potential Additive Inhibitory Effects on HPA-Axis of Ciclesonide Nasal Spray when Administered Concomitantly with Orally Inhaled Fluticasone Propionate/Salmeterol (FP/SAL) in Patients (18-60 Years) with Perennial Allergic Rhinitis (PAR)

10.1 Protocol

10.1.1 Administrative

Study Dates: January 29, 2005 to August 29, 2005
Clinical Centers: [redacted]
Medical Monitor: [redacted]
CRO:

10.1.2 Objective/Rationale

The primary objective of this study was to demonstrate that there were no clinically relevant additive inhibitory effects on the HPA-axis when ciclesonide nasal spray was concomitantly administered with orally inhaled FP/Sal. A secondary objective was to evaluate the safety and tolerability of the combined regimen.

10.1.3 Study Design

This was a randomized, double-blind, placebo and active-controlled, parallel study of approximately 75 subjects with PAR per treatment group. After enrollment subjects were treated for 10 days with FP/SAL DPI (Advair Diskus) 500/50 mcg BID and a nasal spray placebo, at which time they maintained a diary with nasal symptom scores. At the end of the run-in eligible subjects were randomized to receive ciclesonide 200 mcg once daily or placebo while continuing on FP/SAL. There was one follow-up visit on day 21 of randomized treatment and the subject returned on day 42 for final evaluation. Subjects stayed in the clinic for 24 hours on the day before the run-in, at the end of the run-in and before starting ciclesonide nasal spray. At the end of treatment they remained in the clinic for 48 hours. Both urinary and plasma cortisol was measured over the 24-hour period (two serial 24 hour-collections at the end of the study). On randomized treatment Day 43 (Day 53 of the study) all subjects received 2 mg dexamethasone orally in addition

to the daily dose of FP/SAL and nasal spray. Plasma for cortisol was collected for the following 24 hours. The last dose of FP-SAL was taken on Day 54. (For a diagram of the study design see Study 408, above. Pg 156.) Safety was assessed with adverse events, ENT examination, vital signs and clinical laboratory examinations as well as the cortisol measurements. Physical and ENT examinations were performed at the beginning and end of the trial and before each medication change. Safety laboratory examinations were conducted at the beginning and end of the study. Subject compliance was assessed with the symptom diary and by weighing the medication bottle.

10.1.4 Study Population

Inclusion Criteria

- Male or female, 18 to 60 years of age
- A history of PAR to relevant allergen for a minimum of 1 year immediately preceding the Screening Visit. The PAR must have been of sufficient severity to require treatment in the past, and, in the investigator's judgment, would be expected to require treatment throughout the study period.
- Positive skin test within 12 months of enrollment
- BMI between 18 and 31

Exclusion Criteria

- Exposure to corticosteroids for any indication, chronic or intermittent (e.g.: asthma, contact dermatitis), during the past 2 months, 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 the equivalent of 1% hydrocortisone for dermatological conditions during the past 1 month, or presence of an underlying condition that could reasonably be expected to require treatment with such preparations during the course of the study.
- History or physical findings of nasal pathology, including nasal polyps (within the last 60 days) or other clinically significant respiratory tract malformations, recent nasal biopsy (within the last 60 days), nasal trauma, or surgery and atrophic rhinitis or rhinitis medicamentosa (within the last 60 days).
- Evidence of bronchial, pulmonary, or respiratory tract infections or use of an antibiotic for any indication within 14 days of screening
- Active asthma (requiring daily treatment with β-agonists)
- Change in immunotherapy injections within 90 days of screening
- Evidence of ocular herpes simplex, cataracts or glaucoma
- Positive for hepatitis B or C virus of human immunodeficiency virus
- Vegetarian or any other dietary restriction that would prevent participation in standardized meals.
- Absence of regular sleep patterns
- Inability to abide by medication restrictions listed in the protocol.

Randomization Criteria

24-hour r-TNSS 4 or greater on 5/7 days of the run-in period
Completion of all but 3 of the possible diary entries
Took at least 80% of the study medication during the run-in
No intercurrent illness or ingestion of prohibited medications

10.1.5 Study Procedures

Treatment

Ciclesonide nasal spray was provided in canisters containing 50 mcg ciclesonide per actuation. The subjects were instructed to take two sprays in each nostril each AM. No rescue medication was provided. Compliance was assessed with the diary entries and also by weighing the study medication bottles.

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 as follows:

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 scores were to be recorded in the morning. The maximum score was 12 (4 symptoms times a maximum score of 3). In addition to grading each symptom, the subjects recorded the time of day the assessment was made.

Safety Evaluation

Safety was assessed with adverse events (diary recorded and elicited during clinic visits), vital signs, physical exam, ECG, routine laboratory examinations. A 24-hour evaluation of plasma cortisol was performed 1) prior to run-in, 2) at the end of run-in 3) after the penultimate dose of study medication, and 4) on the last treatment day after all of the study medication and 2 mg dexamethasone. During each 24-hour period urine was also collected for cortisol measurement. Plasma for cortisol was obtained at baseline and after 3, 6, 8, 10, 12, 14, 16, 18, 21, 22, and 24 hours after the start of the test or after the first dose of medication (HFA-BDP at the end of run-in, BDP-HFA and study nasal spray at the end of active treatment.

10.1.6 Data Analysis

Sample Size

In a previous study the standard deviation for the change from baseline in the weighted average of cortisol (0, 24) was 1.62 mcg/dL. That translated into an AUC of 38.8 mcg•hr/dL. The standard deviation of the treatment difference in a parallel group setting was 54.9 mcg•hr/dL. From the same prior study it was determined that bioequivalence bounds of a 20% difference would be reasonable. Thus the delta was taken as 27.2 mcg•hr/dL or 20% of 136.1 mcg•hr/dL. This calculation is based on the finding of a mean 24-hour AUC for cortisol in placebo treated subjects of 181.4 mcg•hr/dL, and HFA-BDP was predicted to reduce cortisol by 25%. It was therefore estimated that the AUC0-24 at the end of the run-in would be 136.1 mcg•hr/dL. Using these assumptions, a sample size of 45 evaluable subjects would provide a 90% power with a one-sided alpha of 0.025. Because a standard deviation of 49.2 mcg•hr/dL was observed in study 408, the sample size was increased to 60 per treatment group to maintain the 20% delta and alpha of 0.05. To account for drop-outs, 75 were enrolled.

Study Populations

In addition to the intention-to-treat (ITT) population a per-protocol (PP) population was defined for the HPA-axis evaluation. For analyses of urine cortisol, only subjects with samples deemed to be complete were included. To meet this criterion, the total creatinine value was required to be greater than 60% of the lower limit of the normal range for total creatinine.

Analysis

The primary efficacy variable was the change from baseline in the 24-hour r-TNSS averaged over each week. The baseline was taken as the average of the average score obtained during the last 7 days of the screening period. The change from baseline for each treatment group was compared at each week using a repeated measures ANOVA.

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

10.2 Results

10.2.1 Study Population

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Disposition

There were 150 subjects randomized and 132 (88.0%) completed the trial. Six (8.0%) of the ciclesonide and 12 (16%) of the placebo subjects withdrew prematurely. The most frequent indication for premature withdrawal was "Patient request" in 1 ciclesonide and 5 placebo subjects. One ciclesonide and 2 placebo subjects withdrew due to adverse events. All subjects were included in the ITT population. All of the protocol requirements were met for at least a portion of the study by 139 (69 [92.0%] of the ciclesonide group and 70 [93.3%] of the placebo group) subjects, and these were included in the PP cortisol analysis.

Demographics

There were 80 males and 70 females, and the mean age was 30.8 years (Table 73). A plurality of the subjects (40.0%) classified their race as other. Only 23.3% were Caucasian while 24% were Black and 12% were Asian/Native American. Thirty-seven percent described themselves as Hispanic. The majority were never smokers (72.7%) while 12.0% were former smokers and 15.3% were current smokers. The mean skin test reaction to allergen was 7.8 mm with a mean response to control of 0.06 mm and a mean response to histamine of 9.6 mm. These demographic variables were distributed evenly across the treatment groups. According to post-text Table 14.1.4.1 (pg 111 of 5734) one ciclesonide subject had been treated with prednisone prior to enrollment and one placebo subjects was treated with hydrocortisone.

Table 73. Baseline Demographics for Subjects Enrolled in Study 409

	Ciclesonide 200 mcg N=75	Placebo N=75	Total N=150
Age (years)			
Mean (SD)	30.8 (10.5)	30.7 (9.8)	30.8 (10.)
Range	18 - 57	18 - 57	18 – 57
Gender (% Male)	52.0	54.7	53.3
Race (%)			
Caucasian	21.3	25.3	23.3
Black	22.7	26.7	24.7
Asian, native American	14.7	9.3	12.0
Other	41.3	38.6	40.0
Hispanic Ethnicity (%)	37.3	36.0	36.7
Antigen Challenge (mm)			
Mean (SD)	7.6 (4.8)	8.0 (5.3)	7.8 (5.0)
Range	3 - 38	3 - 35	3 - 38

Reviewer: The large number of "Other" races probably represents mixtures because American Indian, Alaska Native, Asian Black or African American, Caucasian, Native Hawaiian, and Other Pacific Islander were all specified.

Protocol Deviations

Six of the ciclesonide and 5 placebo subject were considered major protocol violators. Four subjects in each treatment group had <60% compliance with randomized study medication. Two ciclesonide and three placebo subjects had <60% diary compliance with FP/SAL. One ciclesonide subject took prohibited concomitant medication and one subject in each treatment group was "misrandomized".

Reviewer: Concomitant medications are listed for 1 ciclesonide subject as a major protocol violation and for 2 placebo subjects as minor violations. From the study design it is not clear how the distinction between minor and major violation was determined. This could be important because only major protocol violations were a criterion for

exclusion from the PP population and the cortisol analysis. However, it is stated that the determination was made blindly prior to unblinding.

10.2.2 Efficacy Results

Primary Efficacy Outcome

The primary efficacy variable was the 24-hour AM r-TNSS. The analysis was performed on the change from baseline over the six weeks of randomized (ciclesonide vs placebo) treatment. The baseline values were 7.6 and 7.8 in the ciclesonide and placebo groups, respectively (Table 74). The mean scores fell to approximately the same degree in both treatment groups (-0.40 and -0.6 in the ciclesonide and placebo groups, respectively). The results were similar for the per-protocol population and for the individual symptoms.

Table 74. Changes in r-TNSS During Treatment in Study 409

Variable	Ciclesonide N = 75	Placebo N=74	Treatment Difference (95% CI)
Average 24-hr r-TNSS			
Baseline, Mean (SD)	7.61 (1.97)	7.76 (1.99)	
Change from Baseline (LS mean [SE])	-0.40 (0.23)	-0.60 (0.23)	-0.2 (-0.63, 0.33)

10.2.3 Safety

Extent of exposure

The mean exposure was 40.6 days in the ciclesonide group and 39.9 days in the placebo subjects.

Adverse Events

Overall, 37 (24.7%) of the subjects reported adverse events: 26.7% of the ciclesonide and 22.7% of the placebo subjects. None was characterized as serious, but 3 (1 ciclesonide and 2 placebo subjects) resulted in premature withdrawal of the subject (Table 75). The most common event in both treatment groups was headache 6.7% (5.3% and 8.0% in the ciclesonide and placebo subjects, respectively). In the ciclesonide group there were 3 reports of increased white blood cell counts and 2 reports of elevated blood glucose in four subjects. One subject had both an elevated WBC and elevated glucose level. In the placebo group 2 subjects each complained of epistaxis and pharyngolarygeal pain.

Table 75. Study 409: Adverse Events Experienced by >2% of Subjects Enrolled

Preferred Term	Ciclesonide 200 mcg (N=75)	Placebo (N=75)	Total (N=150
Patients with one or more treatment-emergent AEs	**20 (26.7%)**	**17 (22.7%)**	**37 (24.7%)**
Headache	4 (5.3%)	6 (8.0%)	10 (6.7%)
White blood cell count increased	3 (4.0%)	0	3 (2.0%)
Blood glucose increased	2 (2.7%)	0	2 (1.3%)
Epistaxis	0	2 (2.7%)	2 (2.3%)
Pharyngolaryngeal pain	0	2 (2.7%)	2 (1.3%)

Data source: Section 14.3, post-text Table 14.3.1.2

Serious Adverse Events and Events Leading to Withdrawal

There were no serious events or deaths. One ciclesonide subject was withdrawn due to sinusitis, and one subject each in the placebo group was withdrawn due to bronchitis and dental caries. None of the events leading to premature withdrawal was thought to be drug-related. Most of the events were mild to moderate, however, one severe event was recorded in each treatment group. In the ciclesonide group one 46 year old Asian male had a normal AST (24 U/L) but an elevated ALT level (63 U/L, normal 8 – 45 U/L) at baseline. At the end of the study the AST was 18 U/L, but the ALT was 85 U/L. A follow-up sample taken one week after medication discontinuation revealed an AST of 174 U/L and ALT of 488 U/L. The bilirubin and alkaline phosphatase were normal. The subject failed to return for further follow-up. In the placebo group the dental caries were classified as a severe event.

Vital Signs

The mean values for systolic and diastolic blood pressure and for pulse remained within the normal limits for the entire study. Vital signs exceeded the alert values for 16 ciclesonide and 14 placebo subjects. All of the abnormal values were for change in pulse except three measurements of blood pressure in the ciclesonide-treated subjects. One had a consistently low systolic pressure (105-121 mm Hg), and one had a low systolic pressure at screening (83 mm Hg) which was then repeated at 154 mm Hg at the end of the study. The last value was recorded as abnormal because the pressure had increased > 40 mm Hg. A third subject had a systolic pressure of 122 mm Hg at the beginning of the randomized treatment period which increased to 158 mm Hg at the end of the randomized treatment period. Presumably the last measurement was 40 mm greater than one of the screening measurements. The highest abnormal pulse was 107 bpm and the lowest was 44 bpm. High and low values were distributed approximately evenly between the treatment groups.

Reviewer: The alert values for high systolic blood pressure were 170 mm Hg or a 40 mm increase, for high diastolic blood pressure were >105 mm Hg, and the alert values for pulse were >120 and <50 bpm.

Laboratory Results

Mean changes in the laboratory values were small over the course of the study and were approximately the same in the two treatment groups. If a categorical analysis is performed, the most common values to increase from normal to abnormally high in the subjects who completed the study were the total white cell (WBC) and neutrophil counts. The changes occurred slightly more frequently in the ciclesonide treated group than the placebo group (Total WBC 41.5% and 34.4% and total neutrophil counts 29.9% and 26.2% of the ciclesonide and placebo groups, respectively). However, the mean change was very small in both groups: the WBC increased by a mean of 3.54 and 3.09 x 10^9 cells/L and the mean total neutrophil count increased by 2.69 and 2.22 x 10^9 cells/L in the ciclesonide and placebo groups respectively. The glucose increased from normal at baseline to abnormal at the end of the study in 42.6% of ciclesonide and 36.2% of placebo-treated subjects. The mean increase was 22.6 and 16.1 mg/dL in the ciclesonide and placebo-treated subjects, respectively. The maximum increase was 164 and 101 mg/dL, respectively. The calcium values also increased in greater than 10% of the subjects: 12.3% of the ciclesonide and 16.0% of the placebo-treated subjects. The mean change in calcium was 0 in both groups and the maximum change was 1.0 and 0.9 mg/dL in the ciclesonide and placebo groups, respectively. At the end of treatment the lipase was abnormal in 5 (7.5%) of the ciclesonide subjects and in 1 (1.6% see below) of the placebo subjects.

Individual abnormalities that exceeded the alert level were reported for 8 ciclesonide and 1 placebo subject. In the Ciclesonide group three subjects had an increase in the WBC count (16.4, 18.9, and 16.7 x 10^9 cells/L) and three subjects had abnormal liver enzymes (ALT = 488, 142, and 179 U/L) The abnormal liver enzymes were not accompanied by elevations in bilirubin or alkaline phosphatase. However, the highest ALT measured was the last one recorded in each case and there is no clinical follow-up. There was no clinical illness in the subjects with elevated white counts. One subject with elevated ALT and one with elevated WBC also had an elevated glucose at the end of the study (265 and 261 mg/dL). One additional ciclesonide subject had an elevated sodium (151 mmol/L) at the last follow-up visit and on e subject was pregnant (Quantitative HCG of 4 – 5 IU/L). One placebo subject had a lipase of 308 at the end of the study in comparison with a baseline value of 61 (normal 0 to 59 IU)

HPA-axis Evaluations

The mean baseline plasma cortisol AUC_{0-24} was similar in the two treatment groups (193.3 and 188.0 mcg•hr/dL in the ciclesonide and placebo groups, respectively), but the decrease with FP/SAL treatment during the Run-in period was significantly greater in the group that was subsequently treated with ciclesonide (-63.0 and -44.4 mcg•hr/dL in he ciclesonide and placebo groups, respectively). The addition of ciclesonide nasal spray produced a small further decrease in the mean plasma cortisol AUC_{0-24} (Table 76). The values after 6 weeks of treatment were 118.0 and 124.8 mcg•hr/dL in the ciclesonide and placebo groups, respectively. This represented a mean decrease of 12.7 and 15.7 mcg•hr/dL during randomized treatment in the ciclesonide and placebo groups, respectively. After dexamethasone treatment the mean plasma cortisol AUC_{0-24} values

were 48.6 and 48.1 mcg•hr/dL in the ciclesonide and placebo groups, respectively. This represented a decrease of 71.7 and 74.8 mcg•hr/dL in the ciclesonide and placebo groups, respectively.

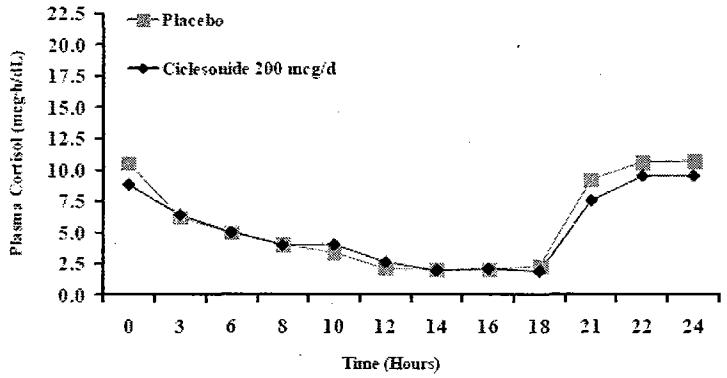
Table 76. HPA-axis Assessment after Treatment with Advair Diskus and Ciclesonide Nasal Spray for 6 Weeks

Variable	Ciclesonide N = 69	Placebo N=70	Treatment Difference (95% CI)
Plasma Cortisol AUC_{0-24}, mcg•hr/dL			
Baseline, Mean (SD)	193.3 (60.2)	188.0 (61.0)	
Plasma Cortisol, mcg, Change from Baseline (LS mean [SE])			
At end of Run-in (FP/SAL only)	-63.0 (5.0)	-44.0 (5.0)	18.6 (4.6, 32.6)
After Randomized Treatment	-12.7 (6.9)	-15.7 (7.1)*	-2.9 (-22.6, 16.8)
After Dexamethasone	-71.7 (2.8)	-74.8 (3.0)*	-3.1 (-11.2, 5.0)
Urinary Cortisol, mcg/day	N=54	N=54	
Baseline, Mean (SD)	40.1 (29.4)	39.0 (24.2)	
Urinary Cortisol, mcg/day, Change from Baseline (LS mean [SE])	N=54	N=54**	
At end of Run-in (FP/SAL only)	-12.5 (2.1)	-12.8 (2.2)	-0.39 (-6.4, 5.7)
After Randomized Treatment	-4.3 (2.2)	-5.9 (2.3)	-1.6 (-7.9, 4.7)
After Dexamethasone	-8.1 (0.9)	-10.7 (0.94)	-2.62 (-5.6, 0.03)

* These determinations were performed on 62 subjects, **For the end of randomized treatment there were only 49 determinations.

The results of the plasma cortisol determinations after randomized treatment with ciclesonide or placebo nasal spray are shown in Figure 10 .

Figure 10. Plasma Cortisol after treatment with Advair Diskus and Ciclesonide Nasal Spray or Advair Diskus alone.



For patients to be include in the urine cortisol analysis they were required to have a complete sample as determined by urine creatinine values being above 60% of the lower limit of the normal range or by indication of a complete collection in the CRF. The mean baseline 24-hour excretion of free cortisol was 40.1 and 39.0 mcg/D in the

ciclesonide and placebo subjects, respectively. The values fell to an equal degree during FP/SAL treatment (-12.5 and -12.8 mcg/D, respectively). The urinary cortisol decreased further during randomized treatment with ciclesonide or placebo: -4.3 and -5.9 mcg/D, respectively. After dexamethasone treatment there was a small further fall in both groups (-8.1 and -10.7 mcg/D in the ciclesonide and placebo groups, respectively). At none of the time points was the difference between ciclesonide and placebo significant.

10.3 Summary and Discussion

This pharmacodynamic study assessed the effects of ciclesonide nasal spray on the HPA-axis when it was ingested concomitantly with Fluticasone/Salmeterol DPI (Advair Diskus) by aerosol inhalation. After a 10 day run-in when all subjects inhaled FP/SAL 500/50 mcg BID both the plasma and 24-hour urinary cortisol values decreased substantially. After an additional 6 weeks during which subjects were randomized to receive ciclesonide or placebo nasal spray, the plasma and urinary cortisol levels fell further. That the combined treatment did not profoundly suppress adrenal function was documented by the further profound fall in plasma cortisol after 2 mg of dexamethasone was added to the prior medications. However, the fall in plasma cortisol during placebo treatment in the randomized phase suggests, as in study 408, that the ten-day run-in was too short to allow for stabilization of HPA-axis function after initiation of Advair therapy.

There were few adverse events and only one in each treatment group was categorized as severe. And the two severe reactions (dental caries and sinusitis) were unlikely to be related to any of the treatments administered in the study. Although not extreme, the incidence of abnormal liver function was greater in the ciclesonide subjects than either the placebo subjects in this trial or in the ciclesonide-treated subjects in the other studies in this submission. The follow-up was limited and did not elucidate the etiology of the changes.

11 STUDY # 202/2003 (CL-001)

A Phase I, Single-Center, Randomized, Placebo-Controlled, Double-Blinded, Modified Sequential Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Multiple Doses of TBN-15 (ciclesonide Nasal Spray) Administered Intranasally in Healthy Volunteers And Asymptomatic Subjects with Seasonal Allergic Rhinitis (SAR)

11.1 Protocol

11.1.1 Administrative

Study Dates: February 11, 2002 to April 25, 2002

Clinical Centers: [redacted]
Sponsor: Teijin America, Inc, Princeton, NJ

11.1.2 Objective/Rationale

The objectives of this study was to evaluate safety and tolerability of repeated escalating doses of TBN-15 (50-800 mcg/day) given for 14 days to healthy volunteers and symptomatic patients with SAR as measured by adverse events and to determine the pharmacokinetics profile of TBN-15 administered intranasally and to evaluate the influence of TBN-15 on endogenous cortisol concentrations.

11.1.3 Study Design

Forty-eight subjects were randomized into 6 cohorts of 8 subjects each (6 ciclesonide and 2 placebo). Eligible subjects were randomized to one of the following regimens:

- Normal Subjects - Ciclesonide 50 mcg QD
- Normal Subjects - Ciclesonide 100 mcg QD
- Normal Subjects - Ciclesonide 200 mcg QD
- Normal Subjects - Ciclesonide 400 mcg QD
- Normal Subjects - Ciclesonide 400 mcg BID
- SAR - Ciclesonide 400 mcg BID

Subjects who were treated once daily stayed in the clinic for two days at the beginning and end of the trial. Subjects who were treated twice daily stayed in the clinic for the entire treatment period. Additional follow-up visits and examinations occurred on day 21 and 28 after 3 and 4 weeks off of study drug, respectively. An ENT examination was performed on day 1 and 14. Serum cortisol was measured at baseline and at 1, 2, 4, 7, 10, 12, 14, and 22 hours after the dose on day 1 and 14, and prior to the morning dose on days 3, 7, 11, 12, and 13. Blood was also obtained for ciclesonide levels at the time of sampling for cortisol. Urine was collected for 24 hours prior to medication administration son days 1, 7, and 14.

11.1.4 Study Population

The subjects included 40 normal volunteers and 8 subjects with a history of SAR and a positive skin test to grasses and weeds. Other than for a history of SAR, all were healthy and between the ages of 18 and 55 and had a normal body weight. Exclusion criteria included any serious medical condition or abnormal laboratory value, allergic rhinitis in the normal volunteers, or asthma or the requirement for corticosteroid therapy in all of the subjects. Smoking was not permitted within 6 months of enrollment. Subjects were allowed to take only oral contraceptives, acetaminophen or topical, non-steroidal medication for 14 days prior to enrollment and throughout the treatment period.

11.1.5 Study Procedures

Ciclesonide nasal spray was provided in canisters containing 25, 50, and 100 mcg ciclesonide per actuation. It was manufactured at Teijin's facility in Japan.

Safety was assessed with adverse events, vital signs, physical exam, ECG, routine laboratory examinations and ENT examination.

There was no sample size determination and inferential statistical evaluation was not performed.

11.2 Results

11.2.1 Study Population

There were 48 subjects randomized and all completed the trial. There were 34 males and 14 females, and the mean age was 30 years. The racial distribution is not included.

11.2.2 Pharmacokinetic Analysis

The limits of the assay used were 25 pg/mL for the parent compound and 10 pg/mL for the M1 metabolite. At this sensitivity, one of the 12 subjects (6 volunteers and 6 SAR patients) who received 800 mcg daily had detectable ciclesonide (46.2 mcg/dL) detectable at one time point. The metabolite was detected in 4 of 6 subjects treated with 400 mcg daily and in 9 of the 12 subjects treated with 800 mcg. Of those treated with 800 mcg, 6 of 6 normal subjects and 3 of 6 subjects with SAR had detectable levels. The levels ranged between 10.4 and 25.9 pg/mL

11.2.3 Safety

Adverse Events

Overall, 134 treatment-related adverse events were reported. The number of events was similar across the treatment groups (19 on average), but with fewer in the 50 mcg dose-group (9) and a slight excess in the placebo group (32). Among the healthy subjects the most frequent events were headache, fatigue, rhinitis, nose congestion, and pharyngitis. Among the allergic subjects the most frequently reported events were paraesthesia, pain, and nasal congestion. There were no deaths or serious adverse events.

Laboratory Results

Six ciclesonide treated subjects were reported to have had abnormal laboratory values. Three subjects had abnormal C-reactive protein values on day 7 that had resolved by day 14. Two in the 50 mcg group had elevated bilirubin levels on day 7. Both had resolved by follow-up. The gamma GTT was elevated in one further subject. This was not resolved on the follow-up visit.

HPA-axis Evaluations

Only descriptive statistics are provided for the serum cortisol measurements. The summary statistics are shown in Table 77. The Day 14 values for AUC were lower than the Day 1 values for all of the doses above 50 mcg. However the differences were trivial and not greater than seen in the placebo subjects.

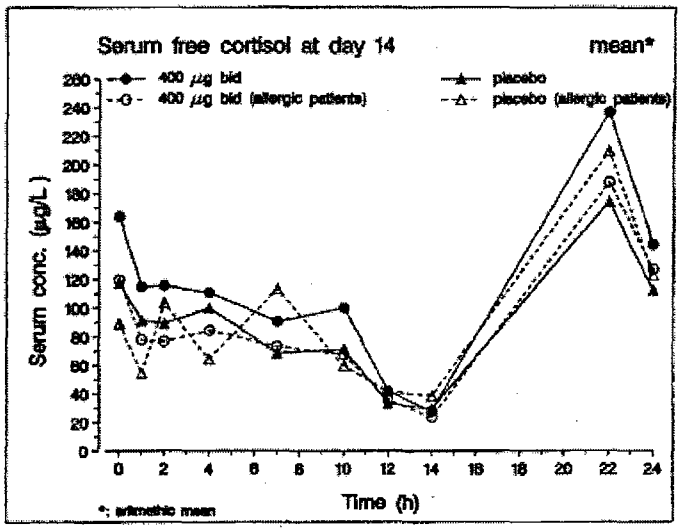
Table 77. Mean (SD) of Serum Free Cortisol After 14 Days of Treatment with Ciclesonide or Placebo.

Treatment	Cohort	E_{max} (µg/L)		$AUEC_{0-24}$ (µg.h/L)	
		Day 1	Day 14	Day 1	Day 14
50 µg od	I	189 (37)	198 (38)	2151 (403)	2208 (527)
100 µg od	II	229 (106)	193 (45)	2678 (1271)	2223 (544)
200 µg od	III	172 (25)	172 (43)	1952 (316)	1942 (316)
400 µg od	IV	196 (58)	191 (26)	2295 (636)	2228 (427)
400 µg bid	V	235 (92)	239 (87)	2643 (852)	2637 (765)
400 µg bid*	VI	201 (33)	191 (54)	2318 (493)	2108 (410)
Placebo	I-V	191 (53)	183 (43)	2175 (746)	2132 (658)
Placebo*	VI	197 (58)	210 (32)	2462 (965)	2349 (532)

* allergic patients

The results are shown graphically in Figure 11.

Figure 11. Serum Free Cortisol*



* Time 0 is between 9 and 11 AM

The summary statistics for 24-hour urinary cortisol are shown in Table 78. Only descriptive statistics are provided for this data. However, it appears that both 800 mcg groups had decreases in urinary cortisol on day 7 and 14. The normal volunteers who received 400 mcg once daily had a decrease on day 7 than had returned to baseline by

day 14. However, the 200 mcg group also appeared to have small decreases on day 7 and 14.

Table 78. Mean 24-hour urinary free cortisol excretion, mcg (mean [SD])

Treatment	Cohort	Day 1	Day 7	Day 14	Follow-up
50 µg od	I	115 (55.1)	109 (85.6)	83.1 (32.8)	61.8 (24.5)
100 µg od	II	53.8 (21.4)	58.3 (37.1)	65.3 (29.2)	53.8 (25.1)
200 µg od	III	69.0 (37.7)	58.1 (26.9)	57.9 (30.6)	70.7 (35.3)
400 µg od	IV	87.4 (33.6)	68.2 (38.6)	87.2 (43.9)	99.1 (70.6)
400 µg bid	V	63.3 (23.8)	52.6 (9.80)	49.7 (6.65)	50.6 (17.6)
400 µg bid*	VI	79.6 (23.1)	53.7 (9.27)	54.6 (10.6)	66.7 (35.7)
Placebo	I-V	94.3 (87.6)	72.1 (37.0)	82.0 (44.1)	66.9 (28.0)
Placebo*	VI	123 (24.1)	98.3 (83.2)	69.0 (6.91)	138 (30.8)

* allergic patients

11.3 Summary and Discussion

This phase I safety and PD trial demonstrated that at doses to be marketed (100 and 200 mcg), there was only a very small decrease in the urinary and serum cortisol measured in the 12 subjects who were treated. However, at the 400 and 800 mcg daily doses there was a definite decrease in the 24-hour urinary cortisol. This suggests that ciclesonide nasal spray could have an effect on the HPA-axis if it is taken in high enough doses. As in the other studies, the toxicity profile was benign and very little of the parent compound or metabolite could be measured in the blood.

10.2 LINE-BY-LINE LABELING REVIEW

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/s/

Carol Bosken
9/5/2006 11:35:02 AM
MEDICAL OFFICER

Lydia McClain
9/5/2006 05:19:15 PM
MEDICAL OFFICER
I concur

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE:	March 2, 2006
FROM:	Carol H. Bosken, MD
	Division of Pulmonary and Allergy Drug Products, HFD(570)
THROUGH:	Lydia I Gilbert-McClain, MD
	Team Leader, Division of Pulmonary and Allergy Drug Products, HFD(570)
TO:	Ele Ibarra-Pratt
	Division of Scientific Investigations
SUBJECT:	NDA 22,004 Audit

NDA 22-004: Ciclesonide Nasal Spray, submitted by Altana on December 22, 2006.

We would like to audit sites that participated in 2 of the pivotal efficacy studies.

144/2005 (405) – Single-center US dose-ranging study in children 2 – 5 years of age with perennial rhinitis
287/2004 (401) – Multicenter US (Adult and adolescent with seasonal rhinitis)

We are requesting an audit of the following sites:

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

Site 5202 (Study 287/2004)
Investigator: Daniel V. Freeland, MD
8501 North Mopac Expressway, Suite 200
Austin, Texas 78759

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

We would like a general survey of the trial conduct, IRB approval processes, and conduct of internal auditing by the sponsor at these three sites. We are submitting tables with selected laboratory values and adverse events taken from the SAS transport files submitted in this NDA. We would like you to check these data against the original data sources.

We are particularly interested in site 5724 because the investigators at this site enrolled all of the subjects age 2 to 5 years. Approval of the drug for this age range is, therefore, dependent wholly on the data obtained at this site. Because of the difficulty in obtaining reliable symptom scores in children this age, the efficacy determination will be made primarily on the basis of extrapolation from the results obtained from the studies in older subjects. The results of study 144/2005 are therefore of primary importance for interpreting safety: this includes adverse events, results of the ophthalmologic examinations, and laboratory analysis as well as pharmacodynamic measurements. Blood and 14-hour urine samples were obtained for cortisol determinations. The location of the data in the study report is under a Listing and a list of observations of particular interest will be found in the appendices at the end of this memo (Table 1).

Table 1. Location of the relevant listings

	Listing in Study Report	Observations of particular interest
Adverse Events	16.2.7.1	Appendix I
Ophthalmologic Exam	16.2.7.5	Appendix II
Serum Chemistry	16.2.7.5	Appendix III
Platelet Count	16.2.8.1	Appendix III
Cortisol (Urine and Blood)	16.2.8.2	Appendix III
PK	16.1.13*	Random Sample Requested

*These results are found in table 10 of the Bioanalytic Report (16.1.13) it begins on page 27/57 of the Bioanalytic Report (page 711/3226 of the study report).

Study 287/2004 was conducted in adults with seasonal allergic rhinitis. There were only six sites involved in this study and therefore, each site was responsible for a relatively large proportion of the total enrollment. The two sites that we have included in the audit request enrolled a large number of subjects. In addition, Site 5202 had efficacy results that were significantly better than the other sites, and also had a large number of moderate to severe adverse events. At Site 5203 the efficacy results were better than average, but not so much so that they affected the overall means. However, at this site, also, the number of moderate to severe adverse events was high for a 2-week study in a population with no other disease than rhinitis. We are submitting a list of adverse events to audit. For the efficacy endpoint we are submitting a list of subject IDs for those subjects who had better than expected results. We would appreciate it if the auditors would check a random selection of the diary entries for these subjects. Lastly, we would like the pollen counts audited for each of these sites. The pollen count consists of one value per day per site.

Pollen counts (Listing 16.2.4.10) Site 5202 Dec 15, 2003 through February 26, 2004 and site 5203 December 17, 2003 through February 29, 2004.

Symptom scores: (Listing 16.2.6.3) The scoring is divided into "Nasal" and "Non-nasal" areas and the nasal scores include itching, stuffiness/congestion, runny nose, and sneezing. Each subject has a score (0 to 3) recorded in the morning and evening and there is an instantaneous and reflective score at each time-point. The primary endpoint for the study was an average of the two reflective nasal score, so we would like to audit these. Appendix V includes the IDs for subjects of particular interest. Please audit these and a random sample of as many additional subjects as you think appropriate to make up an adequate sample.

Adverse Events: (Listing 16.2.7.1) Appendix IV of audit request.

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APPENDIX I

Adverse Events in Study 405(144/2005)

	Adverse Event	Start Date	End Date	Severity	id	DSI Comment
7.	Ear infection NOS	2004-10-27	2004-11-06	Moderate	5024	
9.	Varicella	2004-10-13	2004-11-05	Moderate	5031	
10.	Pneumonia NOS	2005-01-15	2005-01-24	Moderate	5045	
15.	Cough	2004-12-27	2004-12-27	Mild	5052	
16.	Body temperature increased	2005-01-01	2005-01-02	Mild	5052	
17.	Otitis media NOS	2005-01-01	2005-01-10	Moderate	5052	
18.	Headache	2004-12-29	2004-12-30	Mild	5054	
19.	Headache	2005-01-11	2005-01-12	Mild	5054	
20.	Nasopharyngitis	2005-01-09	2005-01-17	Moderate	5054	
26.	Epistaxis	2005-03-24	2005-03-24	Mild	5093	
27.	Abdominal pain NOS	2005-04-27		Severe	5093	
28.	Lymphadenopathy	2005-04-27		Severe	5093	
29.	Cough	2005-02-16	2005-02-18	Moderate	5098	
30.	Cough	2005-03-01	2005-03-07	Moderate	5098	
31.	Pyrexia	2005-03-06	2005-03-06	Moderate	5098	
35.	Viral infection NOS	2005-03-29	2005-04-15	Moderate	5104	
39.	Cough	2005-04-05	2005-04-10	Moderate	5118	
40.	Pharyngitis	2005-04-05	2005-04-10	Mild	5118	
41.	Upper respiratory tract infection NOS	2005-03-18	2005-04-11	Mild	5118	
45.	Pharyngitis streptococcal	2005-04-02	2005-04-07	Moderate	5126	
47.	Blood alkaline phosphatase NOS increased	2005-04-11		Moderate	5131	

APPENDIX II

Ophthalmologic Results: Study 405 (144/2005)

	id	result	Eye	Date/Visit/Time	DSI Comment
29.	5005	12	OD	2004-09-10T07:50	
30.	5005	15	OS	2004-09-10T07:50	
31.	5005	15	OD	2004-10-08T08:59	
32.	5005	14	OS	2004-10-08T08:59	
33.	5005	9	OD	2004-10-29T08:14	
34.	5005	10	OS	2004-10-29T08:14	
205.	5033	16	OD	2004-09-24T07:20	
206.	5033	14	OS	2004-09-24T07:20	
207.	5033	14	OD	2004-10-22T07:40	
208.	5033	14	OS	2004-10-22T07:40	
209.	5033	18	OD	2004-11-12T07:47	
210.	5033	18	OS	2004-11-12T07:47	
319.	5052	18	OD	2004-12-06T08:30	
320.	5052	18	OS	2004-12-06T08:30	
321.	5052	20	OD	2005-01-03T07:30	
322.	5052	18	OS	2005-01-03T07:30	
323.	5052	18	OD	2005-01-24T07:32	
324.	5052	18	OS	2005-01-24T07:32	
355.	5058	20	OD	2005-01-03T07:43	
356.	5058	20	OS	2005-01-03T07:43	
357.	5058	14	OD	2005-01-31T07:10	
358.	5058	10	OS	2005-01-31T07:10	
359.	5058	21	OD	2005-02-21T07:30	
360.	5058	18	OS	2005-02-21T07:30	
519.	5087	16	OD	2005-01-31T07:47	
520.	5087	14	OS	2005-01-31T07:47	
521.	5087	13	OD	2005-02-28T07:45	
522.	5087	15	OS	2005-02-28T07:45	
523.	5087	28	OD	2005-03-21T07:35	
524.	5087	26	OS	2005-03-21T07:35	
551.	5092	4	OD	2005-01-31T07:32	
552.	5092	6	OS	2005-01-31T07:32	
553.	5092	13	OD	2005-03-07T07:10	

554.	5092	8	OS	2005-03-07T07:10
555.	5092	6	OD	2005-03-28T07:15
556.	5092	8	OS	2005-03-28T07:15
701.	5117	14	OD	2005-02-21T07:57
702.	5117	14	OS	2005-02-21T07:57
703.	5117	17	OD	2005-03-24T07:30
704.	5117	15	OS	2005-03-24T07:30
705.	5117	15	OD	2005-04-13T07:25
706.	5117	15	OS	2005-04-13T07:25
725.	5121	12	OD	2005-02-21T08:19
726.	5121	6	OS	2005-02-21T08:19
727.	5121	12	OD	2005-03-21T07:20
728.	5121	12	OS	2005-03-21T07:20
729.	5121	26	OD	2005-04-11T07:18
730.	5121	24	OS	2005-04-11T07:18
813.	5134	17	OD	2005-03-03T07:30
814.	5134	15	OS	2005-03-03T07:30
815.	5134	8	OD	2005-03-28T07:45
816.	5134	10	OS	2005-03-28T07:45
817.	5134	12	OD	2005-04-18T07:30
818.	5134	18	OS	2005-04-18T07:30

APPENDIX III

Chemistry, cortisol and hematology values of interest from study 405(144(2005)

	id	result	Date/Visit/time	tmtgp*	Test	DSI Comment
264.	5087	368	2005-03-21T08:30	1	Platelet Count	
471.	5058	474	2005-02-21T08:30	1	Platelet Count	
814.	5005	329	2004-09-10T09:20	1	Platelet Count	
909.	5052	363	2005-01-24T08:59	1	Platelet Count	
1133.	5087	355	2005-01-31T09:20	1	Platelet Count	
1414.	5058	417	2005-01-03T08:08	1	Platelet Count	
1471.	5052	344	2004-12-06T09:28	1	Platelet Count	
1560.	5005	339	2004-10-29T00:00	1	Platelet Count	
1998.	5092	405	2005-02-07T08:27	2	Platelet Count	
3391.	5092	502	2005-03-28T09:00	2	Platelet Count	
3643.	5121	433	2005-04-11T09:07	3	Platelet Count	
3925.	5134	454	2005-04-18T09:18	3	Platelet Count	
4244.	5121	479	2005-02-21T09:00	3	Platelet Count	
4252.	5134	322	2005-03-03T08:30	3	Platelet Count	
5692.	5117	418	2005-04-13T08:15	4	Platelet Count	
6411.	5117	480	2005-02-21T08:50	4	Platelet Count	
6713.	5033	378	2004-11-12T09:04	4	Platelet Count	
6742.	5033	649	2004-09-24T08:15	4	Platelet Count	
259.	5005	716	2004-10-29T00:00	1	Cortisol-AM	
263.	5005	695	2004-09-10T09:20	1	Cortisol-AM	
1636.	5033	260	2004-09-24T08:15	4	Cortisol-AM	
1669.	5033	474	2004-11-12T09:04	4	Cortisol-AM	
2626.	5052	516	2004-12-06T09:28	1	Cortisol-AM	
2647.	5052	378	2005-01-24T08:59	1	Cortisol-AM	
2946.	5058	217	2005-01-03T08:08	1	Cortisol-AM	
2965.	5058	179	2005-02-21T08:30	1	Cortisol-AM	
4406.	5087	288	2005-01-31T09:20	1	Cortisol-AM	
4432.	5087	420	2005-03-21T08:30	1	Cortisol-AM	
4725.	5092	424	2005-02-07T08:27	2	Cortisol-AM	
4728.	5092	253	2005-03-28T09:00	2	Cortisol-AM	

6043.	5117	393	2005-02-21T08:50	4	Cortisol-AM
6056.	5117	318	2005-04-13T08:15	4	Cortisol-AM
6253.	5121	243	2005-02-21T09:00	3	Cortisol-AM
6260.	5121	207	2005-04-11T09:07	3	Cortisol-AM
7032.	5134	395	2005-03-03T08:30	3	Cortisol-AM
7052.	5134	326	2005-04-18T09:18	3	Cortisol-AM
235.	5005	1	2004-10-29T00:00	1	Urinary Creatinine
264.	5005	1.77	2004-09-17T09:00	1	Urinary Creatinine
1642.	5033	1.1	2004-11-12T09:04	4	Urinary Creatinine
2638.	5052	1.5	2005-01-24T08:59	1	Urinary Creatinine
2651.	5052	1.1	2004-12-13T00:00	1	Urinary Creatinine
2919.	5058	2.8	2005-01-10T00:00	1	Urinary Creatinine
2971.	5058	1	2005-02-21T08:30	1	Urinary Creatinine
4409.	5087	1.2	2005-02-07T00:00	1	Urinary Creatinine
4438.	5087	.	2005-03-21T08:30	1	Urinary Creatinine
4707.	5092	1	2005-02-14T00:00	2	Urinary Creatinine
4731.	5092	2.5	2005-03-28T09:00	2	Urinary Creatinine
6038.	5117	.	2005-04-13T08:15	4	Urinary Creatinine
6087.	5117	.	2005-02-28T00:00	4	Urinary Creatinine
6265.	5121	1.6	2005-02-28T00:00	3	Urinary Creatinine
6274.	5121	2	2005-04-11T09:07	3	Urinary Creatinine
7040.	5134	9.3	2005-04-18T09:18	3	Urinary Creatinine
7044.	5134	1.1	2005-03-07T00:00	3	Urinary Creatinine
2612.	5052	12	2005-01-24T08:59	1	24 Hr Urine Cortisol
2649.	5052	9	2004-12-13T00:00	1	24 Hr Urine Cortisol
4694.	5092	15	2005-03-28T09:00	2	24 Hr Urine Cortisol
4708.	5092	5	2005-02-14T00:00	2	24 Hr Urine Cortisol
6262.	5121	37	2005-02-28T00:00	3	24 Ht Urine Cortisol
6290.	5121	21	2005-04-11T09:07	3	24 Hr Urine Cortisol
7017.	5134	11	2005-03-07T00:00	3	24 Hr Urine Cortisol
7042.	5134	20	2005-04-18T09:18	3	24 Hr Urine Cortisol

* tmtgp = treatment group: 1 = ciclesonide 100 mcg, 2 = 200 ciclesonide 200 mcg, 3 = ciclesonide 25 mg, and 4 = placebo

APPENDIX IV
Adverse Events in Study 401 (287/2004)

Site 5202

	Adverse Event	id	Severity	Start Date	Stop Date	DSI Comment
68.	Lower respiratory tract infection NOS	1003	Mild	2004-02-02	2004-02-11	
69.	Urticaria NOS	1006	Mild	2004-01-06	2004-02-12	
70.	Gastroenteritis viral NOS	1006	Moderate	2004-02-10	2004-02-14	
71.	Headache	1009	Mild	2004-01-06	2004-01-06	
72.	Headache	1009	Mild	2004-01-13	2004-01-13	
73.	Anxiety	1009	Moderate	2004-01-29		
74.	Intraocular pressure	1017	Moderate	2004-01-09	2004-01-10	
75.	Skin chapped	1017	Moderate	2004-01-09	2004-01-09	
76.	Dry eye NOS	1017	Severe	2004-01-10	2004-01-13	
77.	Skin chapped	1017	Moderate	2004-01-21	2004-01-21	
78.	Dry eye NOS	1017	Moderate	2004-01-15	2004-01-15	
79.	Eye swelling	1024	Mild	2004-02-03	2004-02-07	
80.	Chapped lips	1030	Severe	2004-01-16	2004-02-12	
81.	Nasal dryness	1030	Mild	2004-01-21	2004-01-23	
82.	Contusion	1036	Mild	2004-01-18	2004-01-18	
83.	Nausea	1041	Severe	2004-01-09	2004-01-10	
84.	Hypersensitivity NOS	1041	Severe	2004-01-10	2004-01-21	
85.	Influenza like illness	1041	Severe	2004-01-18	2004-01-21	
86.	Nasopharyngitis	1044	Mild	2004-02-08	2004-02-09	
87.	Gastroenteritis viral NOS	1047	Moderate	2004-01-11	2004-01-11	
88.	Corneal infection NOS	1047	Severe	2004-02-08	2004-02-13	
89.	Dizziness	1389	Severe	2004-01-15	2004-01-15	
90.	Vomiting NOS	1391	Mild	2004-02-02	2004-02-02	
91.	Conjunctival hyperaemia	1406	Severe	2004-02-12	2004-02-19	
92.	Conjunctival hyperaemia	1407	Moderate	2004-02-17	2004-02-26	
93.	Headache	1418	Severe	2004-02-01	2004-02-18	
94.	Insomnia	1418	Severe	2004-02-02	2004-02-02	
95.	Nasopharyngitis	1421	Moderate	2004-01-17	2004-01-19	
96.	Post procedural pain	1421	Severe	2004-01-12	2004-01-16	
97.	Sinusitis NOS	1425	Moderate	2004-02-18	2004-03-03	
98.	Gastroenteritis viral NOS	1425	Severe	2004-02-13	2004-02-15	

	Adverse Event	id	Severity	Start Date	Stop Date	DSI Comment
99.	Limb injury NOS	1427	Moderate	2004-02-13	2004-02-18	
100.	Contusion	1427	Moderate	2004-02-13	2004-02-18	
101.	Nasopharyngitis	1479	Severe	2004-02-14	2004-02-17	
102.	Conjunctival hyperaemia	1479	Severe	2004-02-17	2004-02-24	
103.	Food poisoning NOS	1484	Moderate	2004-02-02	2004-02-03	

Site 5203

	Adverse Event	id	Severity	Start Date	Stop Date	DSI Comment
104.	Cough	1051	Moderate	2003-12-17	2003-12-24	
105.	Throat irritation	1051	Moderate	2003-12-17	2003-12-24	
106.	Cough	1051	Moderate	2003-12-28	2003-12-28	
107.	Limb injury NOS	1051	Moderate	2004-01-01	2004-01-08	
108.	Cough	1051	Moderate	2004-01-01	2004-01-26	
109.	Fatigue	1051	Moderate	2004-01-07	2004-01-09	
110.	Ear pain	1051	Moderate	2004-01-15	2004-01-16	
111.	Arthralgia	1051	Severe	2004-01-10		
112.	Pruritus	1051	Mild	2004-01-19	2004-01-19	
113.	Dysgeusia	1054	Mild	2003-12-24	2003-12-26	
114.	Headache	1054	Severe	2003-12-26	2004-01-09	
115.	Abdominal pain NOS	1054	Moderate	2004-01-02	2004-01-10	
116.	Nasal passage irritation	1054	Mild	2004-01-07	2004-01-14	
117.	Myalgia	1054	Moderate	2004-01-05	2004-01-05	
118.	Ear pain	1054	Moderate	2004-01-05	2004-01-05	
119.	Tympanic membrane disorder NOS	1054	Mild	2004-01-07		
120.	Nasal passage irritation	1055	Moderate	2003-12-24		
121.	Insomnia	1056	Mild	2004-01-01	2004-01-03	
122.	Headache	1057	Moderate	2004-01-14	2004-01-14	
123.	Tympanic membrane disorder NOS	1058	Mild	2004-01-06	2004-01-20	
124.	Pharyngitis	1060	Mild	2004-01-03	2004-02-10	
125.	Dizziness	1060	Moderate	2004-01-05	2004-02-10	
126.	Upper respiratory tract infection NOS	1060	Moderate	2004-01-21	2004-02-10	
127.	Cough	1061	Mild	2003-12-26	2003-12-26	
128.	Herpes simplex	1061	Mild	2004-01-09	2004-01-22	
129.	Tympanic membrane disorder NOS	1061	Mild	2004-01-27		
130.	Tympanic membrane disorder NOS	1066	Mild	2003-12-30	2004-02-03	
131.	Blood pressure increased	1066	Moderate	2004-01-27	2004-02-03	

132.	Nasal passage irritation	1067	Mild	2003-12-29	2003-12-29
133.	Nausea	1067	Moderate	2004-01-21	2004-01-22
134.	Nasal passage irritation	1073	Mild	2004-01-13	2004-01-28
135.	Tympanic membrane disorder NOS	1074	Moderate	2004-01-15	2004-01-29
136.	Rhinorrhoea	1076	Mild	2003-12-24	2003-12-24
137.	Bronchitis NOS	1076	Moderate	2004-01-05	2004-01-19
138.	Rhinorrhoea	1078	Mild	2004-01-07	2004-01-08
139.	Arthralgia	1078	Moderate	2004-01-24	2004-02-05
140.	Herpes simplex	1080	Moderate	2004-01-11	2004-01-15
141.	Nasal passage irritation	1080	Mild	2004-01-28	2004-02-04
142.	Pharyngeal erythema	1081	Mild	2003-12-30	2004-01-14
143.	Sneezing	1081	Moderate	2003-12-30	2004-01-27
144.	Skin test NOS positive	1083	Moderate	2003-12-23	2003-12-25
145.	Arthralgia	1083	Moderate	2004-01-07	2004-01-15
146.	Cough	1083	Moderate	2004-01-05	2004-01-06
147.	Pharyngitis	1083	Mild	2004-01-05	2004-01-06
148.	Musculoskeletal stiffness	1083	Mild	2004-01-26	2004-02-02
149.	Neck pain	1085	Moderate	2004-01-02	2004-01-02
150.	Ear pain	1085	Moderate	2004-01-04	2004-01-06
151.	Nausea	1085	Mild	2004-01-06	2004-01-06
152.	Nausea	1085	Mild	2004-01-25	2004-01-25
153.	Pain NOS	1086	Moderate	2004-01-02	2004-01-02
154.	Vomiting NOS	1086	Moderate	2004-01-02	2004-01-02
155.	Diarrhoea NOS	1086	Moderate	2004-01-02	2004-01-02
156.	Pruritus	1086	Moderate	2004-01-15	
157.	Cerumen impaction	1087	Mild	2003-12-31	
158.	Tympanic membrane disorder NOS	1088	Mild	2003-12-30	2004-01-27
159.	Nasal passage irritation	1091	Moderate	2003-12-30	2004-01-24
160.	Influenza	1092	Severe	2003-12-27	2003-12-30
161.	Ear pain	1095	Moderate	2004-01-13	2004-01-20
162.	Tympanic membrane disorder NOS	1095	Mild	2004-01-15	2004-01-29
163.	Upper respiratory tract infection NOS	1095	Severe	2004-01-30	2004-02-13
164.	Insomnia	1097	Moderate	2004-01-07	2004-01-08
165.	Back pain	1097	Severe	2004-01-11	2004-01-13
166.	Nasal passage irritation	1097	Moderate	2004-01-15	2004-01-29
167.	Insomnia	1097	Severe	2004-01-26	2004-01-27
168.	Hoarseness	1098	Moderate	2003-12-27	2003-12-29

169.	Cough	1098	Moderate	2003-12-28	2004-02-06
170.	Joint sprain	1100	Moderate	2004-01-30	2004-02-16
171.	Herpes simplex	1301	Severe	2004-01-03	2004-01-18
172.	Blood glucose increased	1303	Moderate	2004-02-03	
173.	Nasal disorder NOS	1304	Mild	2004-01-08	2004-01-15
174.	Rhinorrhoea	1304	Mild	2004-01-09	2004-01-09
175.	Unevaluable reaction	1304	Mild	2004-01-29	2004-01-29
176.	Epistaxis	1307	Mild	2004-01-21	2004-01-21
177.	Upper respiratory tract infection NOS	1307	Moderate	2004-02-06	2004-02-18
178.	Alanine aminotransferase increased	1307	Moderate	2004-02-05	2004-03-03
179.	Aspartate aminotransferase increased	1307	Mild	2004-02-05	2004-03-03
180.	Nasal passage irritation	1310	Mild	2004-01-09	2004-02-04
181.	Nasopharyngitis	1310	Moderate	2004-02-04	2004-02-13
182.	Upper respiratory tract infection NOS	1311	Moderate	2004-01-28	2004-02-04
183.	Toothache	1312	Moderate	2004-02-06	2004-02-08
184.	Somnolence	1313	Moderate	2004-01-09	2004-01-12
185.	Nasal passage irritation	1313	Moderate	2004-01-09	2004-01-12
186.	Nasopharyngitis	1313	Moderate	2004-02-05	2004-02-13
187.	Sinusitis NOS	1316	Severe	2004-01-04	2004-01-14
188.	Pharyngitis	1317	Mild	2004-01-28	2004-01-29
189.	Ear pain	1317	Moderate	2004-01-29	2004-01-31
190.	Rhinorrhoea	1317	Mild	2004-01-28	2004-02-01
191.	Nausea	1319	Moderate	2004-01-16	2004-02-02
192.	Epistaxis	1386	Mild	2004-01-14	2004-01-14
193.	Asthma aggravated	1386	Severe	2004-01-31	2004-02-10
194.	Upper respiratory tract infection NOS	1387	Mild	2004-02-06	2004-02-09
195.	Upper respiratory tract infection NOS	1393	Moderate	2004-02-17	2004-02-21
196.	Vaginosis fungal NOS	1503	Mild	2004-02-10	2004-02-13
197.	Urinary tract infection NOS	1503	Moderate	2004-02-10	2004-02-21
198.	Nasal passage irritation	1504	Mild	2004-02-04	2004-02-18
199.	Nasal passage irritation	1505	Mild	2004-02-04	2004-02-18

APPENDIX V
Efficacy in Study 401 (287/2004)

Subjects to be included in Efficacy (Symptom Score) Audit from Study 5202

	id
75.	1416
582.	1390
588.	1044
595.	1413
602.	1014
644.	1406
663.	1030
686.	1421
759.	1394
841.	1028

Subjects to be included in Efficacy (Symptom Score) Audit from Study 5203

	id
82.	1098
544.	1306
640.	1313
784.	1095
873.	1306

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

/s/

Carol Bosken
3/14/2006 12:09:33 PM
MEDICAL OFFICER

Lydia McClain
3/15/2006 09:04:04 AM
MEDICAL OFFICER
I concur

MEDICAL OFFICER 45-DAY Filing REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA # 22,004	TRADE NAME:	N/A
APPLICANT/SPONSOR:	Altana	USAN NAME:	Ciclesonide
MEDICAL OFFICER:	Carol H. Bosken, MD		
TEAM LEADER:	Lydia Gilbert-McClain, MD	CATEGORY:	Corticosteroid
DUE DATE:	February 24, 2006	ROUTE:	Nasal Inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
December 21 , 2005	Electronic	000	Original NDA

RELATED APPLICATIONS

Stamp Date	Application #	Product	Application Type	Approval Date
	IND 65,488	Nasal spray	Original IND	

REVIEW SUMMARY: This NDA is submitted to support the approval of ciclesonide nasal spray for the treatment of symptoms or allergic rhinitis in subjects 2 years of age and older. The adult and adolescent pivotal trials include one 4-week trial in subjects with SAR, one 6-week trial in subjects with PAR, and one 52-week safety study in subjects with PAR. All three used ciclesonide nasal spray 200 mcg as the active treatment, and all three were randomized, placebo controlled, and double-blind. Supportive studies in the adult population included two onset of action studies performed in an environmental exposure chamber. The pediatric trials consisted of one 12-week study in subjects 5 to 11 years of age with PAR and one dose-ranging, PK, and safety trial in subjects 2 to 5 years of age. The total exposure to ciclesonide in these studies is sufficient to support filing the NDA.

OUTSTANDING ISSUES: A preliminary review of the results indicates that the documentation of efficacy in the pediatric population will be a review issue, as well as the demonstration of onset of action. However, the data is sufficient to support filing the application. An appropriate number of subjects have been treated in well designed randomized trials and the administrative data is in order.

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	____	SAFE TO PROCEED	____	CLINICAL HOLD		
NDA/SUPPLEMENTS:	X	FILEABLE	____	NOT FILEABLE		
	____	APPROVAL	____	APPROVABLE	____	NOT APPROVABLE
OTHER ACTION:						

I. General Information

Ciclesonide is a poorly absorbed, non-halogenated corticosteroid that has a low affinity for the glucocorticoid receptor. It is metabolized in the body to a biologically active metabolite (RM1) with an affinity for the glucocorticoid receptor that is 120-fold greater than the parent compound. Because of the low affinity of the parent compound, it is hypothesized by the applicant that systemic toxicity will be lower than with the administration of currently available corticosteroids. Ciclesonide is, also, under development as an HFA MDI for the inhalation treatment of asthma. For the treatment of allergic rhinitis via nasal delivery, a hypotonic aqueous suspension was found to increase retention and uptake of the drug. The current NDA is submitted to support the use of ciclesonide nasal spray for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and children 2 years of age and older.

II. Regulatory and Foreign Marketing History

A. Regulatory History

An [redacted] for the use of Ciclesonide MDI [redacted] in the maintenance treatment of asthma was submitted to the agency on December 22, 2003. That application was given an approvable rating in September 2004 due to the failure to demonstrate efficacy in the doses and dosing regimens described in the application. There were additional CMC issues, however, the preclinical data submitted for ciclesonide was deemed to be adequate. An IND (65,488) for the nasal formulation was submitted in August of 2002, and the applicant came in for an EOP2 Meeting on October 1, 2003. During the EOP2 meeting the applicant expressed the intention to test only the 200 mcg QD dose in adults in the pivotal trials. The Agency suggested that the 100 mcg QD dose be included in the phase 3 trials to improve dose-ranging. The Agency also indicated that lower doses of ciclesonide would have to be administered in the pediatric studies so that the lowest effective dose could be established. While the Agency would have preferred the inclusion of doses of 50, 100, and 200 mcg daily, they agreed that doses of 25, 100, and 200 mcg would be acceptable. Once the preferred dose was chosen, the pivotal trials would be expected to show statistical significance for efficacy in the 4 to 11 year-old subjects. However, if efficacy is documented in the 4 to 11 years olds, [redacted]

The Agency also agreed that environmental chamber exposures could be used to demonstrate an onset of action, with the proviso that a meaningful clinical response was pre-specified based on the effect size seen in the Phase 3 studies that support drug approval.

As to the safety evaluation, the Agency accepted the principal that the data from the MDI program could be cross referenced. This was raised specifically in terms of HPA-axis suppression, growth, and ophthalmologic toxicity. The agency said that they would take into consideration the results of the adult ophthalmologic toxicity study but that measurement of intra-ocular pressure in children in the nasal spray studies would also be required. The agency also agreed to accept the results of the MDI growth study as long as it could be

demonstrated that systemic exposure to ciclesonide was lower after exposure to the nasal spray than after exposure to the MDI.

The applicant came in for a pre-NDA meeting in May of 2005 with the program as described during the EOP2 meeting. Many of the same issues were raised. In addition, the Division suggested that there may be too few subjects in the 2 – 5 year age group to demonstrate safety for anything other than HPA-axis suppression, and the cortisol suppression assessment may be inadequate because background use of ICS was not controlled. For the studies described as supportive, the applicant proposed to submit only study report texts and/or summaries. The Agency responded that they should submit CRFs for subjects who experienced SAEs or death in the studies performed in Japan, even if they only submit the study report text and no data. On the other hand, the applicant said that they would not submit CRFs for the safety studies (this includes the 52-week growth study in children) and the Agency appeared to agree with the plan. (Question 2.3.4 and answer in the EOP2 meeting.) Similarly, the applicant stated that they would probably not have the final study report for the adult ophthalmology toxicity study so they would cross reference it. The Agency accepted this plan. There was also a somewhat confusing discussion of the ISS and ISE at the pre-NDA meeting. In question 2.3.7 the Agency stated and the applicant agreed than there would be an ISS and ISE in module 5. However, in question 2.4.1 the applicant stated that there would be no ISE and the statistical reviewer appeared to accept this approach.

B. Foreign Marketing History

The product has not been marketed.

III. Items Required for Filing and Reviewer Comments

A. Reviewer Comments

1. Format

This is an electronic NDA submission in eCTD format. The format appears to follow the guideline and the electronic links are functional. There is no overall table of contents, but each module has a table of contents. The submission does not contain an Integrated Summary of Efficacy. Instead, the clinical studies are summarized separately in Module 2, Clinical Summary.

2. Financial disclosure

The financial disclosure forms indicate that Teijin Pharma Ltd as well as ALTANA Pharma sponsored the clinical trials. All of the investigators signed forms indicating that they had no financial interest in ALTANA. However, Teijin Pharma Ltd was apparently added as a sponsor later because the financial disclosure forms had to be signed a second time to include interests in Teijin. This second request for information failed to obtain a response from 8 investigators. Most of the failures were because the investigator had left the original institution. The investigators who could not be contacted participated in study 404 (n=4) and 402 (n=4). Each of the non-responding investigators was located at a different site except for

2 in study 402 who were located at the [redacted] While one of the investigators listed as not responding in study 404 enrolled 30 subjects and another enrolled 25, the number is still probably too low to affect the outcome of the studies. Study 404 enrolled 663 subjects at 35 sites in the United States. Teijin Pharma was not involved in the conduct of any of these studies. However, some of the non-reporting sites from study 404 will be subjected to auditing.

3. Indexes and references

References are included under each heading as required by the eCTD format:

Clinical overview	...\m2\25-clin-over\clinical-overview.pdf
Clinical summary	...\m2\27–clin-sum\literature-references.pdf
Clinical study reports	...\m5\54-lit-ref\(This folder contains individual published articles as well as FDA meeting minutes and responses to questions.)

There are no indexes.

4. Debarment

The applicant has certified that no person participant in the study has been debarred.

B. Necessary Elements (21 CFR 314.50)

Table 1 lists the required elements for filing an NDA and their location in the eCTD. Table 2 provides more detail and indicates the type of data available (folder, summary, dataset) for the pivotal trials. Table 3 summarizes the data for the supportive biopharmacology trials, and Table 4 summarizes the data for the other trials. Of note, the files for the trials listed in Table 4 are not accompanied by datasets and many of them do not have case report forms.

4 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Administrative- 4

IV. Clinical Studies

The primary support for approval of ciclesonide nasal spray consists of one phase I, one phase II, and nine phase III studies. In the phase II trial (CL-002) 726 adults with seasonal allergic rhinitis were treated with 25, 50, 100, or 200 mcg QD for two weeks. Despite finding efficacy with both the 100 and 200 mcg doses, the applicant decided to proceed with testing in the phase III program of only the 200 mcg dose in adults.

The adult pivotal trials include one 4-week trial in subjects with SAR (401) and one 6-week study in subjects with PAR (402). Additionally, a 52-week safety study was conducted in subjects with PAR (404). All three of these studies were randomized, double-blind, and placebo-controlled (Table 5). All enrolled subjects 12 years of age and older, and all administered 200 mcg ciclesonide nasal spray (2 activations, 50 mcg/activation, in each nostril) as the active treatment. The efficacy trials both used the reflective total nasal symptom score (TNSS) as the primary outcome variable. The long term follow-up study tabulated adverse events, including the results of systematic nasal and ophthalmologic examinations. The adult program also included two single-dose, onset of action studies (Table 6) conducted after exposure to pollen in an environmental exposure chamber (406, 407), and two studies to assess the pharmacodynamics of exposure to both ciclesonide and an additional ICS (408, 409).

Table 5. Pivotal Phase II/III Studies (All double blind, randomized, placebo-controlled)

Study	Design	Allergic Rhinitis	Age	Dosage (mcg)	Freq	Time	N*	Outcome
144/2005 (405)	R, DB, PC	Perennial	2-5 years	25 100 200	QD	6 w	133	PK, PD safety
149/2005 (403)	R, DB, PC	Perennial	5-11 years	25 100 200	QD	12 w	665	PK, TNSS
76-2004 (CL-002)	R, DB, PC Dose-ranging	Seasonal	18-66 years	25 50 100 200	QD	2 w	726	TNSS
287/2004 (401)	R, DB, PC	Seasonal	12-86 years	200	QD	4 w	327	TNSS
363/2004 (402)	R, DB, PC	Perennial	12-75 years	200	QD	6w	471	TNSS
146/2005 (404)	R, DB, PC	Perennial	12-73 years	200	QD	52 w	663* 441 (360/97)	AEs including ocular and ENT

* Total #randomized to receive ciclesonide (# followed 6 months/ completed the study)

Table 6. Summary of Primary Supporting Studies (All subjects ≥ 18 years of age and treated with 200 mcg ciclesonide QD or single dose)

Study	Design		Rhinitis	Time	n	Outcome
143/2005 (406)	R, DB, PC	Pollen exposure in an EEC	Seasonal	SD	503	Onset
145/2005 (407)	R, DB, PC	Pollen exposure in an EEC	Seasonal	SD	420	Onset
147/2005 (408)	R, DB, PC	Ciclesonide+ concomitant beclomethasone	Perenial	6 w	111	PD
148/2005 (409)	R, DB, PC	Ciclesonide + concomitant fluticasone	N/D	6 w	150	PD

The pediatric program consisted of one phase II dose-ranging, PK/PD, and safety study in subjects 2 to 5 years of age (405) and one PK and safety and efficacy study in subjects 5 to 11 years if age (Table 5). The applicant plans to extrapolate efficacy from the results obtained in the 4 to 11 year olds to the 2 to 5 year-olds.

Summaries of additional trials (Table 7) were submitted to support safety by showing a lack of effect of ciclesonide on the HPA-axis and on growth in children.

Table 7. Additional Studies (all R, DB, PC)

[redacted]

Table 8. Summary of Exposure

Type of Study	# Trials	# Total Enrolled	# and Duration of Exposure to 200 mcg Ciclesonide				
Duration of Exposure			2 w	4 w	6 w	6 m	12 m
Phase I							
Adult Phase II/III							
Phase II	1	726	144				
Phase III (S & E)	2	798	392	356	203		
Phase III (Long term follow-up)	1	663	430	430	420	360	97
Total Adults Exposed			966	786	623	360	97
Children Phase II/III							
Phase II (age 2-5 years)	1	133	32	30	22		
(≥ 100 mcg QD)			64	61	49		
Phase III (age 5-11)	1	665	162	159	156		
Total Children < 12 years			226	220	205		

V. Pediatric Administrative

The current application contains studies in subjects as young as 2 years of age. The applicant has requested a deferral for subjects 6 months to 2 years of age until December 2008. The deferral is requested "due to availability of data in patients 2 years and above

The applicant is requesting a waiver for subjects less than 6 months of age on the basis of the low disease prevalence and difficulty in the diagnosis of allergic rhinitis in this age group. The applicant notes that the Written Response to the pre NDA meeting package and pre-NDA meeting minutes indicated FDA concurrence with this plan.

C. Decision

The application is Fileable. Whether there is enough information provided for the pediatric population will be a review issue. The data submitted for the 2 – 5 year olds comes from a single center, and the results are based on exposure of less than 30 subjects to the highest recommended dose of ciclesonide. There is no long-term safety data on subjects <12 years of age, and this will be another review issue.

VI. DSI Review/ Audit Decision

DSI will be consulted to perform an audit on Daniel V. Freeland, Austin, Texas and Dr. Jerry Herron, Little Rock, Arkansas. The efficacy results obtained by Dr. Freeland (Investigator # 5202) were statistically significantly more favorable that those obtained in the other centers in study 401. There were no obvious problems at the center in Little Rock. However, Dr. Herron enrolled all of the subjects aged 2 to 5 years of age, which were included in this application. It is prudent to be sure that there has been no possibility of irregularity at this

site. One additional site will be chosen from one of the investigators who enrolled subjects into study 404 and who did not sign the disclaimer for financial investment in Teijin Pharma.

VII. Timeline for Review

Table 2. Timeline for Review

Milestone	Target Date for Completion
Stamp Date	December 21, 2005
Filing Meeting	February 13, 2006
Studies 002, 401, 402, 404	March 30, 2006
Studies 403, 405	April 15, 2006
Studies 406, 407, 408, 409	April 30, 2006
Mid-cycle Review	May 9, 2006
Integrated Efficacy Summary	May 30, 2006
Integrated Safety Summary	June 21, 2006
Draft Review (to TL)	July 22, 2006
Review Due Date	August 22, 2006
Wrap-up Meeting	August 29, 2006
Label Review	September 5, 2006
PDUFA Date	October 20, 2006