CLINICAL REVIEW

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Review Completion Date	9/10/2014
Established Name	ciclesonide nasal aerosol
Trade Name	Zetonna
Therapeutic Class	intranasal corticosteroid
Applicant	Takeda/Sunovion
Formulation(s)	37 mcg ciclesonide per actuation
Dosing Regimen	1 actuation per nostril daily (74 mcg/day)
Indication(s)	Seasonal and perennial allergic rhinitis
Intended Population(s)	≥ 12 years of age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, the recommended regulatory action for this supplemental NDA is Approval. This sNDA adequately fulfills four of the postmarketing requirements (PMRs) issued at the time of approval, which required the Applicant to conduct three pediatric studies in patients 6 to 11 years of age and one long-term safety study of nasal and ocular effects in patients ≥ 12 years of age.

1.2 Risk Benefit Assessment

The application contains efficacy and safety data from two adequate and well-controlled trials, SEP060-305 and SEP060-306, in patients 6 to 11 years of age with seasonal and perennial allergic rhinitis (SAR and PAR). These two studies evaluated the effectiveness of ciclesonide nasal aerosol 37 mcg and 74 mcg once daily in reducing nasal symptoms of allergic rhinitis compared with placebo as measured by the reflective total nasal symptom score (rTNSS). While both doses of ciclesonide nasal aerosol demonstrated a similar degree of efficacy in PAR, neither dose of ciclesonide nasal aerosol demonstrated efficacy in SAR. The safety profile observed in the 6 to 11 year old population was consistent with the safety observed in clinical trials of adults and adolescents with SAR/PAR. The Applicant has not requested to extend the indication to patients under 12 years of age (b) (4) The lack of consistent efficacy results, regardless of the safety profile, does not support approval for use in pediatric patients 6 to11 years of age.

In addition to the PREA required studies in patients 6 to 11 years of age, the Applicant submitted results from Study SEP060-401, a PMR to further evaluate nasal and ocular safety due to the occurrence of two nasal septum perforations in the original clinical development program. The primary endpoint in this study was the number and percentage of patients ≥ 12 years of age experiencing nasal mucosal/septum disorders or nasal septum perforations as treatment-emergent adverse events (TEAEs) during a 6 month open-label treatment period with either ciclesonide nasal aerosol (Zetonna) or the related product, ciclesonide nasal spray (Omnaris). The extent of exposure in this study (737 patients total) was adequate to assess the risk of local toxicity. Local nasal treatment-emergent adverse events were consistent with those observed for other intranasal corticosteroid products and were balanced between Zetonna and Omnaris treatment groups. Importantly, there were no nasal septum perforations reported following treatment with either Zetonna or Omnaris. In addition, there were no significant differences in the frequency or types of ocular TEAEs reported between the two treatment groups, although 6 months is too short to definitively assess the risk of

corticosteroid-associated ocular toxicity. The lack of nasal septal perforations in Zetonna-treated patients previously observed in the Zetonna phase 3 program supports the conclusion that Zetonna has a similar local nasal safety profile as Omnaris and other intranasal corticosteroids.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for additional postmarketing risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

Studies SEP060-305 and SEP060-306 in SAR and PAR did not provide substantial evidence of efficacy for Zetonna in pediatric patients 6-11 years of age. As such, the Applicant does not intend to pursue an indication for Zetonna in pediatric patients under 12 years of age. For these reasons, the Applicant requested a partial waiver of the three PREA requirement studies in patients 2 to 5 years of age. Given the marginal efficacy observed in pediatric patients 6 to 11 years of age and that Zetonna provides no additional benefit over the many other intranasal corticosteroids approved for use in the pediatric age group, this reviewer believes granting the partial waiver is reasonable. Concurrence with this assessment was received from the Agency's Pediatric Review Committee (PeRC) on September 3, 2014.

2 Introduction and Regulatory Background

2.1 Product Information

Zetonna Nasal Aerosol was approved on January 20, 2012, for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. The active ingredient is ciclesonide, a non-halogenated glucocorticoid. Ciclesonide is a pro-drug that is enzymatically hydrolyzed to its pharmacologically active metabolite, des-ciclesonide, upon intranasal application. Des-ciclesonide demonstrates high affinity for the glucocorticoid receptor (120 times higher than the parent compound) and is primarily responsible for the drug's activity. In the Zetonna product, ciclesonide is in solution with (b) (4) dehydrated alcohol and (b) (4) (b) (4) HFA 134a propellant. Zetonna Nasal Aerosol is supplied as a (b) (4) pressurized aluminum canister containing ciclesonide (b) (4) and is delivered via a dose indicating nasal actuator. Each actuation delivers 37 mcg of ciclesonide from the nasal actuator. The recommended dosing is 74 mcg daily (37 mcg/1 actuation per nostril).

2.2 Table of Currently Available Treatments for Proposed Indications

There are currently 10 corticosteroids formulated for intranasal administration for the treatment of SAR and PAR, two of which have been approved for over-the-counter (OTC) use.

Table 1. Intranasal Corticosteroids Available for Treatment of Allergic Rhinitis

Drug	Trade Name	Formulation	Indication	Age Range (years)	OTC
Triamcinolone acetonide	Nasacort HFA Nasal Aerosol*	microcrystalline suspension in metered-dose aerosol	SAR PAR	≥ 6 ≥ 6	
	Nasacort Allergy 24HR	microcrystalline aqueous suspension in manual pump	SAR PAR	≥ 2 ≥ 2	X
Beclomethasone dipropionate	Beconase AQ	microcrystalline aqueous suspension in manual pump	SAR PAR	≥ 6 ≥ 6	
	QNASL	nonaqueous solution in metered-dose aerosol	SAR PAR	≥ 12 ≥ 12	
Fluticasone propionate	Flonase	microfine aqueous suspension in meterizing atomizing spray pump	SAR PAR	≥ 4 ≥ 4	X
Fluticasone furoate	Veramyst	Aqueous suspension in manual pump	SAR PAR	≥ 2 ≥ 2	
Mometasone	Nasonex	aqueous suspension in manual pump	SAR PAR	≥ 2 ≥ 2	
Budesonide	Rhinocort Aqua	microcrystalline aqueous suspension in manual pump	SAR PAR	≥ 6 ≥ 6	
Flunisolide	Nasarel**	aqueous solution in metered dose manual pump	SAR PAR	≥ 6 ≥ 6	
Ciclesonide	Omnaris	aqueous suspension in manual pump	SAR PAR	≥ 6 ≥ 12	
	Zetonna	metered-dose aerosol	SAR PAR	≥ 12 ≥ 12	

*Nasacort HFA Nasal Aerosol never marketed in US
**Nasarel brand name drug no longer marketed in US; generics available

2.3 Availability of Proposed Active Ingredient in the United States

Ciclesonide is present in two additional FDA-approved products. Omnaris (ciclesonide aqueous nasal spray) was approved for marketing on October 20, 2006, for SAR and PAR in adults and adolescents 12 years of age and older. On November 21, 2007, the SAR indication was expanded to include patients 6 to 11 years of age. Alvesco (ciclesonide HFA metered-dose inhaler) was approved for marketing on January 10, 2008, for the treatment of asthma in adults and adolescents 12 years of age and older. No major safety issues have arisen since their approvals.

2.4 Important Safety Issues With Consideration to Related Drugs

Ciclesonide and its metabolite des-ciclesonide have low systemic availability when delivered intranasally. However, des-ciclesonide is a potent glucocorticoid receptor agonist, and thus has the potential to lead to adverse events associated with corticosteroid administration such as HPA axis suppression, development of cataracts or glaucoma, and growth effects in children.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following is an abbreviated timeline of regulatory interactions related to the ciclesonide nasal aerosol pediatric development plan.

September 28, 2011:

- Dose-ranging trials are required in the 6-11 year old population.
- The lowest effective dose from dose-ranging trials in the 6-11 year old population should be applied to the 2-5 year old population.
- The Division strongly encouraged dose-ranging beyond 74 mcg and 37 mcg doses for the SAR and PAR studies in subjects 6-11 years of age due to data from PK and Scintigraphy studies which showed higher systemic exposure (~ 4-fold higher Cmax) and higher drug deposition in the nasal cavity than Omnaris.
- Nycomed proposed to conduct pediatric studies using the 37 mcg and 74 mcg doses (b) (4).
- If the 37 mcg dose is efficacious, lower doses may need to be explored.
- (b) (4)

January 20, 2012:

- Zetonna Nasal Aerosol 74 mcg was approved for the treatment of symptoms associated with SAR and PAR in adults and adolescents 12 years of age and older.
- The approval letter outlined six pediatric studies in children 2 through 11 years of age required under the Pediatric Research and Equity Act (PREA) (21 U.S.C. 355c), and one long-term study of nasal and ocular safety in adults and adolescents required under Section 505(o)(3) due to the relative imbalance in local nasal adverse events observed in the clinical development program.

  Completed studies

  - Conduct a 6-week double-blind, placebo-controlled HPA axis trial with ciclesonide nasal aerosol in patients with PAR 6 to 11 years of age (Study 060-308). This trial will evaluate the effect of ciclesonide nasal aerosol (74 mcg) compared to placebo on HPA axis as measured by serum cortisol over 6 weeks of treatment. Additionally, the steady-state PK profile after 6

weeks of treatment and the relationship between study drug exposure and change in cortisol exposure will be investigated.

- Conduct a 2-week double-blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with SAR 6 to 11 years of age (Study 060-305). The proposed adolescent and adult dose and at least one dose lower will be studied.
- Conduct a 12-week double-blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with PAR 6 to 11 years of age (Study 060-306). The primary endpoint will be evaluated after 6 weeks of treatment followed by collection of an additional 6 weeks of safety data. The proposed adolescent and adult dose and at least one lower dose will be studied.
- Conduct a randomized clinical trial in adolescent (age 12 years and older) and adult patients with perennial allergic rhinitis of a minimum of 6 months duration to evaluate the long term safety of ciclesonide nasal aerosol as measured by local nasal and ocular assessments. Include the active comparator OMNARIS (ciclesonide) Nasal Spray.

Outstanding studies

- A 2-week double-blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with SAR 2 to 5 years of age
- A 12-week double-blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with PAR 2 to 5 years of age. The primary efficacy endpoint will be evaluated after 6 weeks of treatment followed by collection of an additional 6 weeks of safety data.
- A 6-week double-blind, placebo-controlled HPA axis trial with ciclesonide nasal aerosol in patients with PAR 2 to 5 years of age. This trial will evaluate the effect of ciclesonide nasal aerosol compared to placebo on HPA axis as measured by serum cortisol over 6 weeks of treatment. Additionally steady-state PK after 6 weeks of treatment and the relationship between study drug exposure and change in cortisol exposure will be investigated.

2.6 Other Relevant Background Information

After filing, the clinical team held a teleconference with the Applicant on February 19, 2014, to discuss their decision to not pursue an indication for Zetonna in the 6 to 11 year old age group and to discuss a path forward for the pediatric program if they wished to do so. (b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA was submitted electronically and included complete study reports, appropriate case report forms, and proposed labeling. The submission was appropriately indexed and organized to permit clinical review. Review of the application did not raise any data integrity concerns, and there was no reason to suspect irregularities in the conduct of the trials. In addition, Zetonna Nasal Aerosol is already an approved product for the treatment of allergic rhinitis. For these reasons, the Division did not request an audit by the Division of Scientific Investigations (DSI) for this supplement.

3.2 Compliance with Good Clinical Practices

The Applicant stated that the clinical trials were conducted in compliance with Good Clinical Practices and submitted a statement certifying that no debarred individuals participated in the conduct of trials included in this NDA. Prior to trial initiation, the clinical study protocols and written informed consent forms were reviewed and approved by an IRB. For minors under 18 years of age who were legally unable to provide informed consent, the parent(s) or legal guardian provided informed consent for study participation. When appropriate or required by state or local law, an attempt was made for subjects <18 years of age to complete an informed assent prior to study participation.

3.3 Financial Disclosures

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. None of the principle investigators or sub-investigators who participated in the clinical trials referenced in this sNDA disclosed receiving significant financial compensation from Sunovion. The financial disclosure checklist is provided below. The disclosed financial interests raise no questions about the integrity of the data and do not affect the approvability of this application.

Table 2. Financial Disclosure Checklist

Covered clinical studies: SEP060-305, SEP060-306, SEP060-308, SEP060-401		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 97		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3454): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	N/A ☒
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	N/A ☒
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	N/A ☒

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Ciclesonide nasal aerosol (Zetonna) is an approved product; therefore, no new quality data was submitted or required.

4.2 Clinical Microbiology

Ciclesonide nasal aerosol (Zetonna) is an approved product; therefore, no new microbiology data was submitted or required.

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was included or required in this supplement.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

As described in previous reviews, ciclesonide is a non-halogenated glucocorticoid that is rapidly metabolized to des-ciclesonide (RM1). This metabolite has a high affinity for the glucocorticoid receptor and is primarily responsible for the drug's pharmacologic activity. By binding to the glucocorticoid receptor, ciclesonide acts as an anti-inflammatory agent. While the exact mechanism is not known, in the setting of allergic rhinitis, ciclesonide, like other intranasal corticosteroids, acts at the local level to inhibit release of inflammatory mediators, which in turn decreases nasal inflammation and symptoms associated with allergic rhinitis.

4.4.2 Pharmacodynamics

The Applicant conducted two studies in children 6 to 11 years of age using two doses (37 mcg and 74 mcg once daily). The studies are reviewed in detail in Section 6. Neither study demonstrated a dose response with respect to efficacy; however, lack of dose response is a commonly observed in intranasal corticosteroid development programs.

An assessment of the effect of ciclesonide nasal aerosol 74 mcg once daily for 6 weeks on the HPA axis in children 6 to 11 years of age was performed in study SEP060-308. This study demonstrated that there was no significant difference between ciclesonide nasal aerosol 74 mcg daily and placebo on HPA axis suppression based on changes in serum cortisol levels and 24-hour urinary free cortisol levels from pre-dose to the end of the 6-week treatment period. The study design and results are described in detail in Sections 5.3 and 7.4.5 of this review and in the Clinical Pharmacology review by Dr. Sheetal Agarwal.

4.4.3 Pharmacokinetics

The pharmacokinetics of ciclesonide and des-ciclesonide in patients 6 to 11 years of age was evaluated in study SEP060-308. Serum concentration-time profiles of ciclesonide and its active metabolite, des-ciclesonide, were measured after 6-weeks of treatment with ciclesonide nasal aerosol 74 mcg once daily. The mean peak serum concentrations (C_{max}) of ciclesonide and des-ciclesonide were 12 pg/mL and 29 pg/mL, respectively, which were achieved at a median of 1.00 and 1.98 hours, respectively. The median calculated half-life of des-ciclesonide was 9.59 hours.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical trials submitted in this supplement are presented below in Table 3. The remainder of the review will refer to the individual studies by the last three digits (study 305, study 306, etc.).

Table 3. Sources of Clinical Data

Study	Dates	Design	Age (yrs)	Population	Treatments*	Duration	Objective	Primary Endpoint
SEP060 -305	12/2011-03/2012	R, DB, PC, PG	6-11	SAR, US	Cic37: 282 Cic74: 282 PBO: 284	2 wks	Efficacy and safety	rTNSS
SEP060 -306	10/2011-01/2013	R, DB, PC, PG	6-11	PAR, US	Cic37: 282 Cic74: 283 PBO: 283	12 wks	Efficacy and safety	rTNSS
SEP060 -308	07/2011-11/2011	R, DB, PC, PG	6-11	PAR, US	Cic74: 47 PBO: 42	6 wks	HPA axis	serum cortisol
SEP060 -401	09/2012-07/2013	R, OL, AC, PG	≥12	PAR, US	Cic74: 368 OMN: 369	26 wks	Long-term safety	local nasal TEAEs

Abbreviations: R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel group, AC=active control, OL=open-label, SAR=seasonal allergic rhinitis, PAR=perennial allergic rhinitis, US=United States, Cic37=ciclesonide nasal aerosol 37 mcg/day, Cic74=ciclesonide nasal aerosol 74 mcg/day PBO=placebo, OMN=Omnaris® 200 mcg/day, rTNSS=reflective total nasal symptom score, TEAE=treatment-emergent adverse event
*Number of subjects randomized to each treatment group. Two subjects in study 305 and two subjects in study 306 were randomized, but discontinued prior to receiving study medication. One subject in study 401 was initially randomized to ciclesonide nasal aerosol, but received Omnaris.

5.2 Review Strategy

This clinical review will focus on the efficacy and safety trials in children 6 to 11 years of age (studies 305 and 306) and the long-term comparative safety trial (study 401). Review of the HPA axis study (308) was primarily focused on safety in terms of adverse events; a detailed review of the HPA axis effects may be found in the clinical pharmacology review by Dr. Sheetal Agarwal. The study designs are summarized in Section 5.3 with efficacy and safety results discussed in detail in Sections 6 and 7, respectively.

5.3 Discussion of Individual Studies/Clinical Trials

Studies 305 and 306
The Applicant conducted two pivotal trials (study 305 in SAR and study 306 in PAR) to assess efficacy and safety for ciclesonide nasal aerosol in subjects 6 to 11 years of age. Since the trials were similar in design, they are discussed jointly with differences noted where relevant.

Protocol #	SEP060-305
Title	A 2-week Randomized, Double-Blind Placebo-Controlled, Parallel-Group, Safety and Efficacy Study of Ciclesonide Nasal Aerosol in Subjects 6 to 11 Years with Seasonal Allergic Rhinitis
Study dates	Study initiated: December 1, 2011 Study completed: March 12, 2013 Final study report: October 30, 2013
Sites	62 clinical study sites in the U.S.
IRB	(b) (4)
Protocol #	**SEP060-306**
Title	A 12-week Randomized, Double-Blind Placebo-Controlled, Parallel-Group, Safety and Efficacy Study of Ciclesonide Nasal Aerosol in Subjects 6 to 11 Years with Perennial Allergic Rhinitis
Study dates	Study initiated: October 21, 2011 Study completed: January 2, 2013 Final study report: August 26, 2013
Sites	54 clinical study sites in the U.S.
IRB	(b) (4)

Amendments
There was one protocol amendment to study 305, dated August 3, 2012, that incorporated measures to enhance subject recruitment such as allowing afternoon clinic visits, enrollment of siblings once the first sibling completed the study, and screen failures to participate in study 306 if eligible. The amendment also clarified that the eye, ear, nose, and throat (EENT) exam must be conducted by a physician and that the reflective symptom scores on the morning of Visit 3 (randomization) were not included in the average score to qualify subjects for randomization.

There were no official protocol amendments to study 306; however, an administrative letter dated April 6, 2012, allowed for enrollment of siblings once the first sibling completed the study and for screen failures to participate in study 305 if eligible. The letter also clarified that the EENT exam must be conducted by a physician and that the reflective symptom scores on the morning of Visit 3 (randomization) were not included in the average score to qualify subjects for randomization.

Objectives
The objectives of the studies were to evaluate the efficacy, safety/tolerability, and quality of life after once daily dosing with ciclesonide nasal aerosol at doses of 37 mcg

and 74 mcg compared with placebo in pediatric subjects 6 to 11 years of age with SAR or PAR.

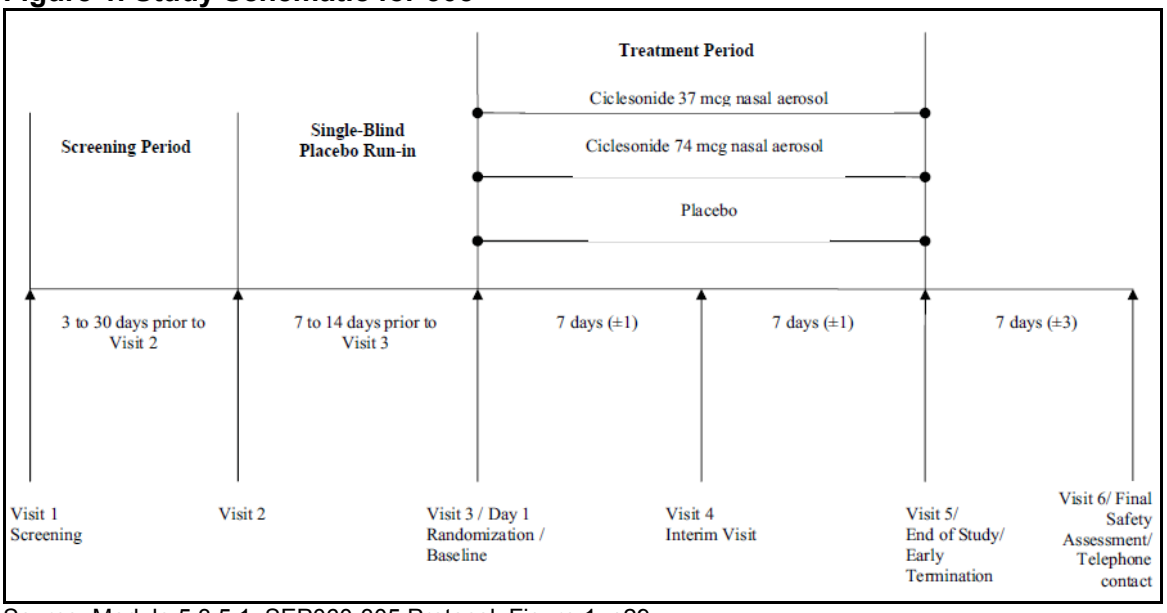
Study Design

Both studies 305 and 306 were randomized, double-blind, placebo-controlled, parallel group trials comparing the efficacy and safety of ciclesonide nasal aerosol (37 mcg and 74 mcg) once daily with placebo in children 6 to 11 years of age. Study 305 evaluated subjects with SAR and was 2 weeks in duration while study 306 evaluated subjects with PAR and was 12 weeks in duration. After screening (Visit 1) and a 7 to 14 day single-blind, placebo run-in period (Visit 2), subjects who met the specified symptom criteria[1] were randomized (Visit 3) to treatment with ciclesonide nasal aerosol 37 mcg (Cic37), ciclesonide nasal aerosol 74 mcg (Cic74), or vehicle placebo. In study 305, subjects returned to the study site for mid-treatment (Visit 4) and final safety evaluations (Visit 5). In study 306, subjects returned for clinical study visits every 2 weeks (Visits 4-9). Subjects who completed the end of study visit received follow-up phone contact 7 to 10 days later. Treatments were either self-administered or administered with the help of a caregiver once daily in the morning. The use of rescue medication was not allowed in study 305, while the use of loratadine syrup (1 mg/mL) was allowed only after week 6 (Visit 6) in study 306. The primary efficacy measure was the change from baseline over 2 or 6 weeks in mean daily reflective, total nasal symptom scores (rTNSS). Additional efficacy measures were changes from baseline in average morning (AM) and evening (PM) scores over the 2, 6, or 12 week treatment period in rTNSS, iTNSS, rTOSS, and iTOSS as well as time to maximal treatment effect. Quality of life was also assessed using the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ). All efficacy measures were based on subject or caregiver assessments. Instantaneous (within the last 10 minutes) and reflective (within the last 12 hours) nasal symptoms (sneezing, runny nose, itchy nose, nasal congestion) and ocular symptoms (itching, tearing, and redness) were assessed and recorded twice daily in the Allergic Rhinitis Assessment diary. Treatment compliance was assessed by report of study medication administration date and time in the diary. Safety measures included monitoring adverse events (AE), concomitant medication use, vital sign measurements, clinical laboratory tests, and EENT examinations. Study schematics and schedule of procedures are shown below in Figure 1 and Table 4 for study 305 and Figure 2 and Table 5 for study 306.

Reviewer Comment: Disallowing rescue medication is a little odd and may have affected their ability to recruit subjects or resulted in an increased number of dropouts.

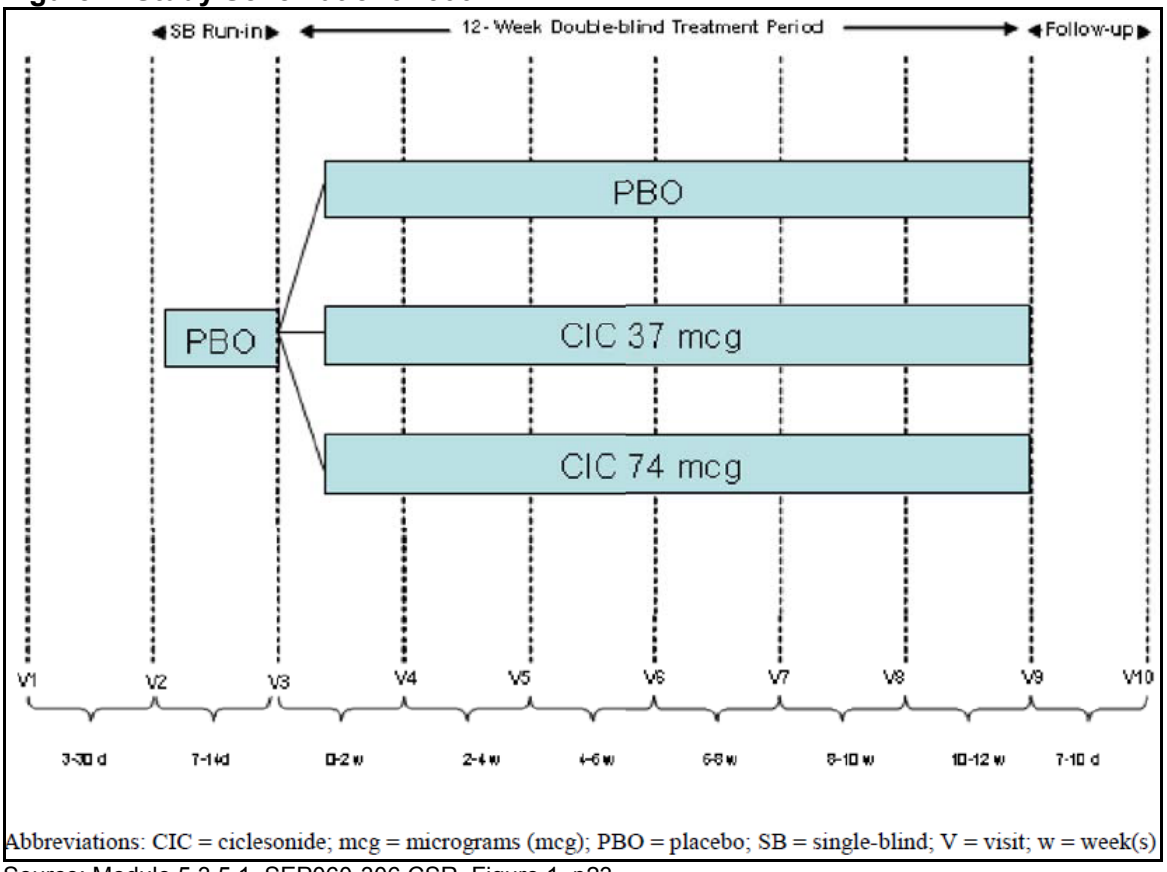
[1] Defined as an average AM and PM reflective total nasal symptom score (rTNSS) of ≥ 6 and an average AM and PM reflective score for runny nose or nasal congestion of ≥ 2 over any 4 of the last 7 days of the placebo run-in period.

Figure 1. Study Schematic for 305



Source: Module 5.3.5.1, SEP060-305 Protocol, Figure 1, p29

Figure 2. Study Schematic for 306



Source: Module 5.3.5.1, SEP060-306 CSR, Figure 1, p23

Table 4. Schedule of Procedures for Study 305

	Screening[a]	Single-blind Run-in	Double-blind Treatment			Follow-up Telephone Contact
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6[b]**
Day	**3-30 days prior to Visit 2**	**7-14 days prior to Visit 3**	**1**	**8±1**	**15±2 (EOS/ ET)**	**7-10 days after Visit 5**
Informed Consent/Assent	X					
Inclusion/Exclusion Review	X					
Demography	X					
Register subject via IVRS	X					
Review of Continuation Criteria		X				
Review of Randomization Criteria			X			
Medical History	X					
Height and Weight	X					
Vital Sign Measurements	X	X	X	X	X	
Physical Examination	X					
EENT Examination[c]	X	X	X	X	X	X[d]
Nasal Examination[e]	X	X				
Skin Prick Test for seasonal allergen[f]	X					
Clinical laboratory Tests (Hem/Chem/UA)	X					
Serum Pregnancy Test[g]	X					
Dispense Single-blind Placebo		X				
Administer Single-blind Placebo[h]		X				
Randomization via IVRS			X			
Administer PRQLQ[i]			X		X	
Administer P-CIQ[i]			X		X	
Dispense Double-blind Treatment			X			
Administer Double-blind Treatment[j]			X	X	X	
Dispense Allergic Rhinitis Assessment diary[k]		X	X	X		
Collect/Review Allergic Rhinitis Assessment diary			X	X	X	
Allow Subject Time to Self-report Nasal Symptom Scores and Ocular Symptom Scores in the Allergic Rhinitis Assessment Diary[l]			X	X	X	
Collect Used/Unused Study Medications			X		X	
Dispense MEC	X	X	X	X		

	Screening[a]	Single-blind Run-in	Double-blind Treatment			Follow-up Telephone Contact
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6[b]**
Day	**3-30 days prior to Visit 2**	**7-14 days prior to Visit 3**	**1**	**8±1**	**15±2 (EOS/ ET)**	**7-10 days after Visit 5**
Collect and Review MEC		X	X	X	X	
Adverse event and Concomitant Medication Recording[m]	X	X	X	X	X	X
Record Rain Fall Amounts	X	X	X	X	X	X
Record Pollen Counts	X	X	X	X	X	X
Administer Sponsor's Device Survey					X	
Schedule Next Visit[n]	X	X	X	X	X	

Abbreviations: AE = adverse event; Chem = serum chemistry; d = day; DB = double blind; EENT = eyes, ears, nose, throat; EOS = End of Study; ET = Early Termination; Hem = hematology; IVR = interactive voice response; MEC = Medical Event Calendar; P-CIQ = Pediatric Classroom Interference Questionnaire; PRQLQ = Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; TNSS = total nasal symptom score(s); TOSS = total ocular symptom score(s); UA = urinalysis.

Note: With the exception of Visit 3, which is to occur in the morning, study visits may occur in the morning or in the afternoon. Clinic Visit 3 should occur between 05:00 AM-12:00 PM.

[a] If a subject has a screening period longer than 30 days, subjects will be required to return to the study site to repeat certain procedures to determine study eligibility (physical examination, vital sign measurements, and EENT examination).

[b] This visit is a telephone contact, except for subjects who present with nasal pathology at Visit 5. These subjects will be required to come back to the clinic for Visit 6 assessments, which will include a concomitant medication review, AE monitoring, and an EENT examination. Likewise, subjects who present with nasal pathology at the phone screen (Visit 6) will also be required to come back to the clinic for and EENT, concomitant medication review, and AE monitoring.

[c] EENT examinations will be performed to assess signs of AR as well as known complications of intranasal corticosteroid use (ie, bleeding, perforation, and ulceration). Throat examinations will be conducted to evaluate for evidence of throat irritation, candidiasis, and postnasal drip.

[d] Only subjects presenting with nasal pathology at Visit 5 or subjects who present with nasal pathology at the phone screen (Visit 6) will be required to come back to the clinic for Visit 6 assessments, which will include a concomitant medication review, AE monitoring, and an EENT examination.

[e] Nasal examination to be conducted 5 to 10 minutes after subject is decongested with 0.05% oxymetazoline in each nostril. Subjects with evidence of infection, significant anatomic abnormality, ulceration of the mucosa, blood in the nose, or other clinically relevant finding on nasal examination at Visit 1 must not be enrolled. Subjects with evidence of infection, significant anatomic abnormality, ulceration of the mucosa, blood in the nose, or other clinically relevant finding on nasal examination at Visit 2 must not enter the single-blind run-in period.

[f] Only conducted for subjects without a positive skin-prick test within one year prior to Visit 1, to demonstrate sensitivity to a relevant dominant seasonal allergen, by standard skin prick test. A positive test is defined as a wheal diameter at least 3 mm larger than the negative control wheal for the skin-prick test. The positive allergen test must be consistent with the medical history of SAR, and the allergen must be present in the subject's environment throughout the study.

[g] Female subjects 8 to 11 years of age only. Subjects with a positive serum pregnancy test will not be allowed to continue in the study.

[h] Preparation and administration of single-blind placebo is as follows for Visit 2:

- Investigator (or designee) will instruct the subject or parent/guardian on proper administration of single-blind placebo.
- Investigator (or designee) will prime the single-blind placebo by depressing the canister 3 times in a well-ventilated area.

Source: Module 5.3.5.1, Sep060-305 Protocol, Table 3, p31

Table 5. Schedule of Procedures for Study 306

Study Period	Screening	Single-blind Placebo Run-in	Double-blind Treatment Period							Follow-up Phone Contact
Study Visit	1[a]	2[b]	3[b]	4[b]	5[b]	6[b]	7[b]	8[b]	9[b]	10[c]
Study Day/Week	3 to 30 days prior to Visit 2	7 to 14 days prior to Visit 3	Day 1	Week 2 (±3 d)	Week 4 (±3 d)	Week 6 (±3 d)	Week 8 (±3 d)	Week 10 (±3 d)	Week 12 (±3 d)	7 to 10 days after Visit 9
Procedure										
Informed Consent/Assent	X									
Review Inclusion/Exclusion Criteria	X									
Review Continuation Criteria		X								
Review Randomization Criteria			X							
Demographics	X									
Medical History	X									
Height and Weight	X									
Vital Sign Measurements	X	X	X	X	X	X	X	X	X	
Physical Examination	X									
EENT Examination[d]	X	X	X	X	X	X	X	X	X	X[c]
Nasal Examination[e]	X									
Skin-Prick Test to Relevant Allergen[f]	X									
Clinical Laboratory Tests (Hem/Chem/UA)	X								X	
Serum Pregnancy Test	X[g]									
Administer PRQLQ			X			X			X	
Dispense Single-blind Placebo		X								
Administer Single-blind Placebo[h]		X								
Randomize Subject via IVR System			X							
Dispense Rescue Medication						X				
Dispense Double-blind Treatment			X	X	X	X	X	X		
Administer Double-blind Treatment[i]			X	X	X	X	X	X	X	
Collect Used/Unused Study Medication			X	X	X	X	X	X	X	
Collect Rescue Medication									X	
Dispense MEC	X	X	X	X	X	X	X	X		
Collect and Review MEC		X	X	X	X	X	X	X	X	
Distribute Allergic Rhinitis Assessment Diary		X	X	X	X	X	X	X		

Study Period	Screening	Single-blind Placebo Run-in	Double-blind Treatment Period							Follow-up Phone Contact
Study Visit	1[a]	2[b]	3[b]	4[b]	5[b]	6[b]	7[b]	8[b]	9[b]	10[c]
Study Day/Week	3 to 30 days prior to Visit 2	7 to 14 days prior to Visit 3	Day 1	Week 2 (±3 d)	Week 4 (±3 d)	Week 6 (±3 d)	Week 8 (±3 d)	Week 10 (±3 d)	Week 12 (±3 d)	7 to 10 days after Visit 9
Procedure										
Instruct Subject on Self-report of Nasal Symptom Scores via Allergic Rhinitis Assessment Diary[j]		X	X	X	X	X	X	X		
Collect and Review Allergic Rhinitis Assessment Diary Nasal Symptom Scores and Medication Administration Date and Time			X	X	X	X	X	X	X	
Allow Subject Time to Self-report Nasal Symptom Scores and Study Medication Administration in the Allergic Rhinitis Assessment Diary[k]		X	X	X	X	X	X	X	X	
AE and Concomitant Medication Recording	X	X	X	X	X	X	X	X	X	X
Schedule Next Visit[l]	X	X	X	X	X	X	X	X	X	

Abbreviations: AE = adverse event; Chem = serum chemistry; d = days; EENT = eyes, ears, nose, throat; Hem = hematology; IVR = interactive voice response; MEC = Medical Event Calendar; PAR = perennial allergic rhinitis; PRQLQ = Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; UA = urinalysis.

[a] If a subject has a screening period longer than 30 days, subjects will be required to return to the study site to repeat certain procedures to determine study eligibility (physical examination, vital sign measurements, and EENT examination).

[b] Visit to occur between 05:00 AM and 12:00 PM (local time).

[c] This visit is a telephone contact, except for subjects who present with nasal pathology at Visit 9. These subjects will be required to come back to the clinic for Visit 10 assessments, which will include a concomitant medication review, AE monitoring, and an EENT examination. Likewise, subjects who present with nasal pathology at the telephone contact (Visit 10) will also be required to come back to the clinic for observation.

[d] All EENT examinations for each subject should be performed by the same person throughout the study.

[e] Nasal examination to be conducted 5 to 10 minutes after subject is decongested with 0.05% oxymetazoline in each nostril. Subjects with evidence of infection, significant anatomic abnormality, ulceration of the mucosa, blood in the nose, or other clinically relevant finding on nasal examination must not be enrolled. The screening nasal examination must be performed by a qualified person experienced in performing EENT examinations.

[f] Only conducted for subjects without a positive skin-prick test within 12 months prior to Visit 1, to demonstrate sensitivity to at least 1 allergen known to induce PAR (house dust mite, animal dander, cockroaches, and molds) by standard skin-prick test. A positive test is defined as a wheal diameter at least 3 mm larger than the negative control wheal for the skin-prick test. The positive allergen test must be consistent with the medical history of PAR, and the allergen must be present in the subject's environment throughout the study.

[g] Female subjects 8 to 11 years of age only. The sample will be collected at Visit 1 and the value will be reviewed and recorded at Visit 3. Subjects with a positive serum pregnancy test will not be randomly assigned to treatment.

[h] Preparation and administration of single-blind placebo is as follows for Visit 2:

- Investigator (or designee) will prime the single-blind placebo by depressing the canister 3 times in a well-ventilated area.

- Investigator (or designee) will observe subject or parent/legal guardian administer the dose of single-blind placebo at the study site at Visit 2, and record date and time of dosing in the electronic case report form.
- Subject or parent/legal guardian will administer single-blind placebo at home in the morning on nonclinic visit days, and record the date and time of dosing in the Allergic Rhinitis Assessment Diary.
- Subject or parent/legal guardian will be instructed to refrain from taking single-blind placebo on the morning of Visit 3.

[i] Preparation and administration of double-blind medication is as follows for Visits 3 through 9:

- Investigator (or designee) will prime the double-blind medication by depressing the canister 3 times in a well-ventilated area.
- Investigator (or designee) will observe subject or parent/legal guardian administer the dose of double-blind medication at the study site at Visits 3 through 9, and record date and time of dosing in the electronic case report form.
- Subject or parent/legal guardian will administer double-blind medication at home in the morning on nonclinic visit days, and record the date and time of dosing in the Allergic Rhinitis Assessment Diary, as well as any rescue medication taken.
- Subject or parent/legal guardian will be instructed to withhold double-blind medication until subject arrives at the clinic at Visits 4 through 9.

[j] Remind subject to record the morning instantaneous followed by reflective nasal symptoms between 5:00 AM and 12:00 PM and to record the evening instantaneous followed by reflective nasal symptoms between 4:00 PM and 11:30 PM. All subjects will be informed that failure to properly complete the daily diary may exclude them from the study.

[k] On clinic visit days, although dosing will occur at the study site, subjects can record their morning nasal symptom scores as well as study medication administration date and time at home or at the site. If the subject did not record symptom scores at home prior to coming to the site, allow subject adequate time to record nasal symptom scores and study medication administration date and time.

[l] The subjects will be called 1 to 2 days in advance of each study visit to remind them of their upcoming visit.

Source: Module 5.3.5.1, SEP060-306 Protocol, Table 3, p28

Study Population

In study 305, a total of 849 subjects were randomized: 282 subjects to Cic37, 283 subjects to Cic74, and 284 subjects to placebo. In study 306, a total of 848 subjects were randomized: 282 subjects to Cic37, 283 subjects to Cic74, and 283 subjects to placebo. Enrollment in each study was stratified by age group (6-8 years and 9-11 years) to ensure balance in treatment assignments.

Main Inclusion Criteria

1. Healthy male or premenarchal female ages 6 to 11 years old at screening (Visit 1)
2. History of SAR/PAR to any relevant dominant seasonal/perennial allergen for a minimum of one to two years immediately preceding study screening (Visit 1). The SAR/PAR must have been of sufficient severity to have required treatment in the past and expected to require treatment throughout the entire study period.
3. Positive skin prick test (wheal ≥3 mm larger than saline control) to at least one relevant dominant seasonal/perennial allergen either documented within 12 months prior to Visit 1 or performed at screening (Visit 1).

Main Exclusion Criteria

1. History of physical findings of nasal pathology, including nasal polyps or other clinically significant respiratory tract malformations; recent unhealed nasal biopsy; nasal trauma; or nasal ulcers or perforations. Surgery or atrophic rhinitis or rhinitis medicamentosa not permitted within 120 days prior to screening
2. Abnormal nasal examination at screening (i.e., evidence of infection, significant anatomic abnormality, ulceration of mucosa, blood in nose, or any other clinically relevant finding)
3. Nasal jewelry
4. Asthma requiring treatment with inhaled or systemic corticosteroids or routine use of beta-agonists and any controller drugs (Intermittent use [≤ 3 times/week] and use for exercise induced bronchospasm was allowed.)
5. Participation in investigational drug trial within 30 days of screening
6. Hypersensitivity to corticosteroid or ciclesonide nasal aerosol excipients
7. History of respiratory infection or disorder (e.g., bronchitis, pneumonia, influenza, SARS) within 14 days of screening

8. Initiation or dose escalation of immunotherapy during the study period
9. Nonvaccinated exposure to or activated infection with chickenpox or measles within 21 days prior to screening
10. Initiation or dose escalation of pimecrolimus cream 1% or tacrolimus ointment 0.03% during the study period.
11. Receipt of ciclesonide nasal aerosol in a previous clinical trial
12. Relative of any clinical investigator or site personnel
13. Any medical condition judged by the investigator to be clinically significant
14. Plans to travel outside the study area (study 305 only)
15. In the investigator's judgment, is or is likely to have a seasonal exacerbation at the time of screening or during the study (study 306 only)

Continuation Criteria
At Visit 2, subjects must have met the following criteria to enter the placebo run-in period:

- Continued general good health
- Continued to meet inclusion/exclusion criteria
- No common colds, acute sinusitis, or influenza infections within 14 days prior
- No antibiotic therapy for acute conditions within 14 days prior (study 306 only)
- Not expected to have a seasonal exacerbation during the placebo run-in period or during the first 6 weeks of the double-blind treatment (study 306 only)

Randomization Criteria
At Visit 3 (randomization visit), the subject must have met the following criteria:

- An average AM and PM rTNSS ≥ 6 over any 4 of the last 7 days of the single-blind placebo run-in period
- An average AM and PM reflective score for runny nose or nasal congestion of ≥ 2 over any 4 of the last 7 days of the single-blind placebo run-in period
- Negative serum pregnancy test from Visit 1 for female subjects 8 to 11 years of age
- Continued good health and meeting inclusion/exclusion criteria
- Adequately completed nasal symptom assessment during the run-in period in the Allergic Rhinitis Assessment Diary (missed no more than one calendar day entry)
- Took single-blind medication at least 6 out of the 7 days during the run-in period
- Did not use restricted concomitant medications during the run-in period
- No common cold, acute sinusitis, or influenza infections within 10 days prior
- No clinically significant laboratory abnormalities from Visit 1
- Agreed to continue in the trial
- Normal nasal examination 5-10 minutes after decongestion with 0.05% oxymetazoline [i.e., no evidence of infection, significant anatomic abnormality, ulceration of the mucosa, blood in the nose, or any other clinically relevant finding] (study 306 only)

- Did not leave the study area for longer than 24 hours during the placebo run-in period (study 305 only)

Withdrawal Criteria
Subjects were discontinued from study medication for any of the following reasons:

- Adverse event
- Lack of efficacy
- Pregnancy
- Other
- Violation of inclusion/exclusion criteria
- Lost to follow-up
- Withdrawal by subject

Study medication discontinuation required study participation termination. Subjects whose study participation was prematurely terminated were not replaced.

Prohibited Medications
A list of the prohibited medications along with the minimum time for withholding such medications is provided in the following table.

Table 6. Prohibited Medications in Studies 305 and 306

Medications Disallowed for Study Duration	Required Withholding Interval Prior to Visit 2
Short-acting antihistamines (nasal, ocular, oral)	5 days
Long-acting antihistamines (nasal, ocular, oral)	10 days
Ocular allergy preparations	10 days
Topical oral/nasal decongestants[a]	10 days
Over-the-counter cough and cold preparations or sleep aids containing antihistamines	10 days
Cromolyn, nedocromil, or lodoxamide (intranasal, ocular, or oral)	14 days
Leukotriene antagonists or 5-lipoxygenase inhibitors	14 days
Inhaled/oral/intranasal anticholinergics	14 days
Inhaled/systemic/intranasal/ocular corticosteroids	30 days
Azoles, anti-fungals	30 days
Immunosuppressive drugs	60 days

[a]Decongestant (0.05% oxymetazoline in each nostril was permitted for nasal examinations
Source: Module 5.3.5.1, Study SEP060-305 Protocol, Table 4 p39 and Study SEP060-306 Protocol, Table 4, p35

Treatments/Dose Rationale
The study included three treatments groups:

- Ciclesonide nasal aerosol 74 mcg (1 actuation per nostril of 37 mcg)
- Ciclesonide nasal aerosol 37 mcg (1 actuation per nostril of 18 mcg)
- Placebo nasal aerosol (1 actuation per nostril)

All study medication was provided by the Applicant. Each canister contained 60 actuations; a dose indicator was integrated into the actuator. The products used hydrofluoroalkane-134α as the propellant and ethanol (b) (4).

The 74 mcg dose was selected because it was the proposed dose to be marketed in adolescents and adults and was expected to be safe and effective in pediatric patients. A lower 37 mcg dose was evaluated for the pediatric population as well given that the systemic bioavailability of the ciclesonide nasal aerosol formulation was higher than that of the ciclesonide aqueous nasal spray.

Efficacy
The severity of allergic rhinitis symptoms, including sneezing, rhinorrhea, nasal congestion, and itchy nose, was assessed and recorded twice daily throughout the placebo run-in period and double-blind treatment period. Each symptom was scored according to a 4-point scale shown in Table 7 below. The total nasal symptom score (TNSS) was the sum of individual symptom scores; thus, the TNSS could range from 0 to 12 for the AM and PM scores, with higher scores indicating more severe symptoms. Subjects or their caregivers assessed both their instantaneous (within the last 10 minutes) and reflective (within the last 12 hours) symptoms once in the morning pre-dose ("AM") and once in the evening ("PM") approximately 12 hours after dosing.

Table 7. Symptom Severity Score

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])
Source: Module 5.3.5.1, SEP060-305 protocol, p44 and SEP060-306 protocol, p42	

The primary efficacy endpoint for studies 305 and 306 was the change from baseline in daily average rTNSS for the 2- or 6-week treatment period compared to placebo. Baseline was defined as the average of AM and PM responses obtained during the last 6 days of the single-blind placebo run-in period. The daily rTNSS was derived from the sum of the AM and PM rTNSS for each day (maximum score of 24).

Study 305 also evaluated efficacy for ocular symptoms associated with allergic rhinitis using the Total Ocular Symptom Score (TOSS). Similar to the TNSS, individual ocular

symptoms (itching, redness, and tearing) were assessed and recorded twice daily according to the same 4-point scale in Table 7. Both instantaneous and reflective scores were obtained; the maximum combined AM and PM TOSS was 18. In addition, both trials evaluated the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ). The PRQLQ has 23 questions in 5 domains (nose symptoms, eye symptoms, practical problems, activity limitation, and other symptoms). Each question is measured on a 7-point scale for a total possible score of 138 (higher score=greater impact on QOL). Subjects, rather than the parents/legal guardians, were instructed to independently complete the questionnaire at the randomization and end of study visits. In study 305 only, investigators administered the pediatric version of the Classroom Interference Questionnaire (P-CIQ) to measure school attendance, classroom productivity, and the impact of allergic rhinitis symptoms on daily activity during the previous 7 days. The P-CIQ was conducted at the randomization and end of study visits and was interviewer administered, with the first 3 questions answered by the parent/guardian and the last 2 questions answered independently by the subject.

Secondary efficacy endpoints included change from baseline in:

- Average daily rTOSS and iTOSS over 2 weeks (study 305)
- Average daily instantaneous TNSS (iTNSS) over 2 weeks (study 305) or 6 weeks (study 306)
- PRQLQ overall score at 2 weeks (study 305) or 6 and 12 weeks (study 306)
- Average weekly rTNSS and iTNSS over 12 weeks (study 306)
- AM iTNSS over 2 weeks (study 305) or 6 weeks (study 306)
- Time to maximal effect

Other efficacy endpoints included:

- Proportion of reflective nasal responders each day over 2 weeks (study 305) or at each week over 6 weeks (study 306)
- Change from baseline at end of 2 weeks in percentage of subject reported hours of classroom absenteeism due to allergies and impact of allergies on school productivity or daily activities score in past 7 days as measured by P-CIQ (study 305)
- Change from baseline in PRQLQ in individual item and domain scores at end of 2 weeks (study 305)
- Number and percentage of subjects responding to each question of the Sponsor's device survey

Efficacy analyses were performed on the intent-to-treat (ITT) population of all randomized subjects who received at least one dose of study medication. The treatment groups were compared using a repeat-measures linear model adjusted for baseline rTNSS (or rTOSS), week, age group (6-8 years and 9-11 years), treatment, and treatment-by-day/week interaction. The PRQLQ endpoint was analyzed using an analysis of covariance (ANCOVA) model adjusted for baseline, age group, and

treatment. If any of the component nasal symptom scores were missing for a particular time point, the TNSS score for that time point was also considered missing. If either the AM or PM TNSS was missing, then the average of AM and PM TNSS was set to the non-missing TNSS. For missing data associated with the PRQLQ score, the last post-baseline observation was carried forward for subjects terminating the study early. To control for type I error, a Bonferroni-based, tree-structured gatekeeping procedure was utilized.

Safety
The safety evaluation was based on reported adverse events (incidence, type, and severity), EENT examinations, clinical labs, physical exams, and vital sign assessments. The safety assessment was performed on all randomized subjects who received at least one dose of study medication (ITT population).

Study 308

Protocol #	SEP060-308
Title	A 6-Week Randomized, Double-Blind, Placebo-Controlled, Parallel Group Safety Study of the Potential Inhibitory Effects of Ciclesonide Nasal Aerosol on the Hypothalamic-Pituitary-Adrenal Axis in Subjects 6-11 years with Perennial Allergic Rhinitis
Study dates	Study initiated: July 12, 2011 Study completed: November 21, 2011 Final study report: August 28, 2012
Sites	7 clinical study sites in the U.S.
IRB	(b) (4)

Amendments
There were two protocol amendments dated June 29, 2011, and August 11, 2011. The revisions were primarily administrative changes or clarifications of the protocol to provide consistency across sites. There were no major changes to the study design or endpoints.

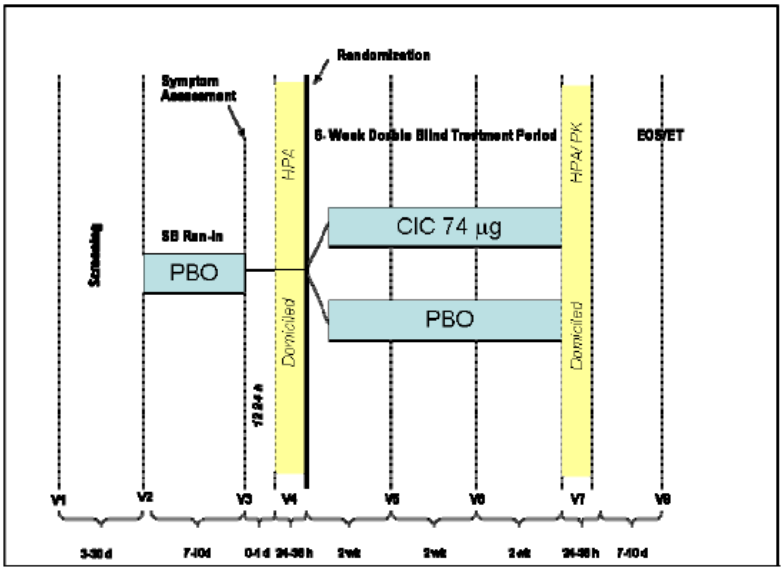
Objectives
Objectives of the study were to evaluate the effect of ciclesonide on the HPA axis as measured by serum cortisol area under the concentration-time curve (AUC) over 24 hours and by 24-hour urinary free cortisol when ciclesonide nasal aerosol 74 mcg was administered once daily to subjects 6 to 11 years of age with PAR compared with placebo. Additional objectives included an evaluation of the safety, tolerability, and efficacy of ciclesonide, an assessment of dose counter accuracy, and a characterization of the PK profile after 6 weeks of steady-state treatment.

Study Design
This was a 6-week multicenter, randomized, double-blind, placebo-controlled, parallel group study in subjects 6 to 11 years of age with PAR. The study schematic and schedule of assessments are shown in

Figure 3 and Table 8, respectively. At Visit 1 (3 to 30 days prior to Visit 2) subjects were screened for eligibility. At Visit 2, subjects entered a single-blind placebo run-in period for 7 to 10 days during which time AM and PM nasal symptoms were assessed to determine eligibility for randomization. At Visit 3 subject's baseline symptom scores from the placebo run-in period were determined. Subjects with normal morning serum cortisol levels at Visit 2 and the pre-specified symptom severity[2] during the placebo run-in period returned 12 to 24 hours later for Visit 4, a 24 to 36 hour domiciled period to obtain baseline 24-hour samples for serum and urinary cortisol measurements. Subjects who provided sufficient pre-treatment blood samples were then randomized in a 1:1 ratio to treatment with ciclesonide nasal aerosol 74 mcg or placebo nasal aerosol once daily for 6 weeks. Enrollment was stratified by age group (6-8 years and 9-11 years) to ensure balance in treatment assignments. Thereafter, subjects or their caregivers administered the study drug once every morning and recorded nasal symptom severity twice daily in a diary. Interim outpatient study visits occurred at 2-week intervals (Visits 5 and 6) with a second 24 to 36 hour domiciled period at week 6 (Visit 7) to collect serum and urinary free cortisol measurements and PK samples. Following the double-blind treatment period, subjects returned 7-10 days later for the end of study visit (Visit 8).

Figure 3. Study Schematic for 308

[2] Defined as an average AM and PM reflective total nasal symptom score (rTNSS) of ≥ 5 and an average AM and PM reflective score for runny nose or nasal congestion of ≥ 2 over any 4 of the last 7 days of the placebo run-in period (including the AM assessment at Visit 3)



Abbreviations: CIC = ciclesonide; d = days; EOS = end of study; ET = early termination; h = hours; HPA = hypothalamic-pituitary-adrenal; PBO = placebo; PK = pharmacokinetic; SB = single-blind; V = visit; wk = weeks.

Source: Module 5.3.5.1, SEP060-308 CSR, Figure 1, p24

Table 8. Schedule of Assessments for Study 308

Study Period	Screening	Single-blind Placebo Run-in	Symptom Baseline	Double-blind Treatment				End of Study/Early Termination
				Domiciled Period 1			Domiciled Period 2	
Visit	1	2[a]	3[a]	4	5[a]	6[a]	7	8
Day	3 to 30 days prior to Visit 2	7 to 10 days prior to Visit 3	–2 (12 to 24 hours prior to Visit 4)	–2 or –1 to 1 (24- to 36-hour inpatient)	15 (+ 3)	29 (+ 3)	41 or 42 to 43 (- 1 to + 3) (24- to 36-hour inpatient)	50 (- 1 to + 3)
Procedure								
Informed Consent/Assent	X							
Review Inclusion/Exclusion Criteria	X							
Review Continuation Criteria		X	X					
Review Randomization Criteria				X				
Demographics	X							
Medical History	X							
Height and Weight	X							
Vital Sign Measurements	X	X	X	X	X	X	X	X
Physical Examination	X							
EENT Examination	X	X	X	X	X	X	X	X
Nasal Examination[b]	X							
Skin-Prick Test to Relevant Allergen[c]	X							
Check in to Overnight Site				X			X	
Discharge from Overnight Site				X			X	
Clinical Laboratory Tests (Hem/Chem/UA)		X					X	
Serum Pregnancy Test[d]		X					X	
Single Sample for Serum Cortisol[e]		X						
24-Hour Sampling for Serum Cortisol[f]				X			X	
24-Hour Sampling for Urinary Free Cortisol and Urine Creatinine[g]				X			X	
Single Sample for Serum PK				X				
24-Hour Sampling for Serum PK[h]							X	
Indwelling Catheter Placement				X			X	
Distribute MEC	X	X	X	X	X	X	X	
Collect and Review MEC		X	X	X	X	X	X	X
Distribute Allergic Rhinitis Assessment Diary		X	X	X	X	X		
Procedure								
Instruct Subject on Self-report of Reflective and Instantaneous TNSS via Allergic Rhinitis Assessment Diary[i]		X	X	X	X	X		
Collect and Review Allergic Rhinitis Assessment Diary			X	X	X	X	X	
Dispense Single-blind Placebo		X						
Administer Single-blind Placebo[j]		X	X	X				
Randomization[k]				X				
Dispense Rescue Medication				X				
Dispense Double-blind Treatment				X	X	X		
Administer Double-blind Treatment[l]				X	X	X	X	
Record Dose Indicator Value[l,3]		X	X	X	X	X	X	
Collect Used Study Medications			X	X	X	X	X	
Collect Rescue Medication							X	
Administer Dose Indicator Survey					X	X	X	
Distribute Videophone[m]	X							
Call Center Videophone Viewing of Dosing[n]		X	X	X	X	X	X	
Collect Videophone							X	
AE and Concomitant Medication Recording	X	X	X	X	X	X	X	X
Schedule Next Visit	X	X	X	X	X	X	X	

Abbreviations: AE = adverse event; Chem = serum chemistry; EENT = eyes, ears, nose, throat; h = hour; Hem = hematology; HPA = hypothalamic-pituitary-adrenal; MEC = Medical Event Calendar; PAR = perennial allergic rhinitis; PK = pharmacokinetic; TNSS = total nasal symptom score(s); UA = urinalysis.

[a] Visit to occur between 06:00 AM and 12:00 PM (local time).

[b] Nasal examination to be conducted after subject is decongested with 0.05% oxymetazoline in each nostril. Subjects with evidence of infection, significant anatomic abnormality, ulceration of the mucosa, blood in the nose, or other clinically relevant finding on nasal examination must not be enrolled.

[c] Only conducted for subjects without a positive skin-prick test within one year prior to Visit 1, to demonstrate sensitivity to at least one allergen known to induce PAR (house dust mite, animal dander, cockroaches, and molds) by standard skin-prick test. A positive test is defined as a wheal diameter at least 3 mm larger than the negative control wheal for the skin-prick test. The positive allergen test must be consistent with the medical history of PAR, and the allergen must be present in the subject's environment throughout the study.

[d] Female subjects 8 to 11 years of age only. The sample will be collected at Visit 2 and the value will be reviewed and recorded at Visit 3. Subjects with a positive serum pregnancy test will not be randomly assigned to treatment.

[e] To determine eligibility for randomization. Subjects with a morning serum cortisol value outside the laboratory's normal reference range will not be randomly assigned to treatment. The sample will be collected at Visit 2 and the value will be reviewed and recorded at Visit 3.

[f] Blood samples for serum cortisol measurement collected at Visit 4 (Day –1) to establish baseline values. Samples collected at 0 h (ie, immediately prior to administration of the last single-blind placebo dose) and at 2, 4, 8, 12, 16, and 24 h after the last single-blind placebo dose (but prior to the first double-blind treatment dose). Blood samples for serum cortisol measurement collected at Visit 7 (Day 42 [- 1 to + 3 days]) for assessment of HPA axis effects. Samples collected at 0 h (ie, immediately prior to administration of the last double-blind treatment dose) and 2, 4, 8, 12, 16, and 24 h after dosing. All sample collection time points will be relative to the first sample collected (ie, time 0 h). A window of ± 15 min will be allowed for all serum cortisol sample collection time points at Visit 4 and Visit 7.

[g] Urinary free cortisol samples collected at Visit 4 (Day –1) to establish baseline values. Urine samples collected and pooled over a 24-hour period. Urinary free cortisol samples collected at Visit 7 (Day 42 [- 1 to + 3 days]) for assessment of HPA axis effects. Urine samples collected prior to dosing and collected and pooled through 24 hours after dosing.

[h] Serial blood samples for serum PK evaluation collected at Visit 7 (Day 42 [- 1 to + 3 days]) only, immediately prior to administration of the last study medication dose (ie, at the same time as the predose cortisol sample) and at 30 min, 60 min, 90 min, 2 h, 4 h, 8 h, 12 h, 16 h, and 24 h after dosing. A window of ± 5 min will be allowed for sample collection for the predose and 30-, 60-, and 90-min postdose samples, and a window of ± 15 min will be allowed for the 2-, 4-, 8-, 12-, 16-, and 24-h postdose sample collections. The actual times of PK sample collection should be recorded.

[i] Subject or parent/legal guardian will record reflective and instantaneous TNSS twice daily (AM and PM [approximately 12 hours after the AM score]) in the Allergic Rhinitis Assessment Diary during each day of the Single-blind Run-in period and during each day of the Double-blind Treatment period.

[j] Preparation and administration of single-blind placebo is as follows for Visits 2, 3, and 4:

- Investigator (or designee) will prime the Visit 2 single-blind placebo by depressing the canister 3 times in a well-ventilated area that is separate from the area in which blood samples will be taken, then record value shown in dose indicator window. The number of priming shots will be recorded.
- At Visit 3 and Visit 4, study medication will be collected after dosing. At Visit 3, the investigator (or designee) will record value shown in dose indicator window, then actuate canister until next whole number is shown in center of dose indicator window and record number of actuations required to advance indicator to whole number.
- Investigator (or designee) will observe subject or parent/legal guardian administer the dose of single-blind placebo at the study site at Visits 2, 3, and 4, and record date and time of dosing.
- Subject or parent/legal guardian will administer single-blind placebo at home in the morning on nonclinic visit days and record the date and time of dosing in the Allergic Rhinitis diary card. A call center will contact the parent/legal guardian each morning on nonclinic dosing days to remind them to administer the dose of study medication. The call center will then observe the subject or parent/legal guardian administering the study medication dose via the videophone.
- Subject or parent/legal guardian will be instructed to withhold single-blind placebo until subject arrives at the clinic at Visit 3 and Visit 4.

[k] Random assignment to occur AFTER completion of 24-h sampling for serum cortisol measurement. The day of random assignment is defined as Day 1.

[l] Preparation and administration of double-blind medication is as follows for Visits 4, 5, 6, and 7:

- Investigator (or designee) will record value shown in dose indicator window prior to dispensing double-blind medication to subject or parent/legal guardian at Visit 4
- Investigator (or designee) will prime the double-blind medication by depressing the canister 3 times in a well-ventilated area that is separate from the area in which blood samples will be taken, then record value shown in dose indicator window at Visits 4, 5, 6, and 7. The number of priming shots will be recorded.
- At Visits 5, 6, and 7, investigator (or designee) will record value shown in dose indicator window, then actuate canister until next whole number is shown in center of dose indicator window and record number of actuations required to advance indicator to whole number.
- Investigator (or designee) will observe subject or parent/legal guardian administer the dose of double-blind medication at the study site at Visits 4, 5, 6, and 7, and record date and time of dosing in the electronic case report form.
- Subject or parent/legal guardian will administer double-blind medication at home in the morning on nonclinic visit days, and record the date and time of dosing in the Allergic Rhinitis diary card, as well as any rescue medication taken. A call center will contact the parent/legal guardian each morning on nonclinic dosing days to remind them to administer the dose of study medication. The call center will then observe the subject or parent/legal guardian administering the study medication dose via the videophone.
- Subject or parent/legal guardian will be instructed to withhold double-blind medication until subject arrives at the clinic at Visits 5, 6, and 7.

[m] A test call with the video call center should be completed by the subject or the subject's parent/legal guardian between Visit 1 and Visit 2. If necessary, the subject or the subject's parent/legal guardian will also be given a router along with the videophone.

[n] Videophone viewing will take place for nonclinic dosing only.

Source: Module 5.3.5.1, SEP060-308 protocol, Table 3, p34

Subjects

A total of 89 symptomatic PAR patients 6 to 11 years of age were randomized to study treatment for 6 weeks: 47 subjects to Cic74 and 42 subjects to placebo. Subjects were stratified by age to ensure balance between treatment assignments.

Main Inclusion Criteria

1. Male or premenarchal female 6 to 11 years old and ≥ 20 kg at Visit 1
2. In general good health based on screening physical examination and medical history
3. History of PAR to a relevant perennial allergen (e.g., house dust mites, cockroach, molds, animal dander) for a minimum of one year immediately preceding Visit 1. The PAR must have been of sufficient severity to have required intermittent or continuous treatment in the past and to require treatment throughout the entire study period
4. Sensitivity to at least one perennial allergen either by documented skin prick test result within one year prior to Visit 1 or by skin prick testing at screening (Visit 1). A positive test was defined as a wheal diameter of at least 3 mm larger than the negative control.

Main Exclusion Criteria

1. History of nasal pathology, including nasal polyps or other clinically significant respiratory tract malformations, recent nasal biopsy, nasal trauma, or nasal ulcers or perforations. Surgery, atrophic rhinitis, or rhinitis medicamentosa not permitted within 120 days prior to Visit 1

2. Evidence of infection, significant anatomic abnormality, ulceration of the mucosa, blood in the nose, or any other clinically significant finding on nasal examination at Visit 1
3. Nasal jewelry
4. Participation or planned participation in any investigational drug trial within 30 days prior to Visit 1 or during the study period, respectively
5. Hypersensitivity to any corticosteroid or excipients in ciclesonide
6. History of respiratory infection or disorder (e.g., bronchitis, pneumonia, influenza, SARS) within 14 days prior to Visit 1
7. History of adrenal insufficiency
8. Active asthma requiring treatment with inhaled or systemic corticosteroids and/or routine use of beta-agonists and any controller drugs (e.g., theophylline, leukotriene antagonists). Intermittent use (≤ 3 times/week) of inhaled short-acting beta-agonists or use for exercise-induced bronchospasm was acceptable.
9. Expecting to use any disallowed concomitant medications during the treatment period
10. Experiencing a seasonal exacerbation at Visit 1 (in the investigator's judgment)
11. Planning initiation or dose escalation of immunotherapy during the study period; initiation of immunotherapy 90 days prior to Visit 1 and use of a stable maintenance dose for ≥ 30 days was considered.
12. Nonvaccinated exposure to or active infection with chickenpox or measles within 21 days preceding Visit 1
13. Initiation or dose escalation of pimecrolimus cream 1% or tacrolimus ointment 0.03% during the study period
14. Significant blood loss within 60 days or loss of plasma within 72 hours prior to Visit 1 or intends to undergo elective surgery within 30 days following Visit 8
15. Relative of any clinical investigator or site personnel
16. Any condition judged by the investigator to be clinically significant

Continuation Criteria
Only subjects who met the following criteria were administered single-blind placebo beginning at Visit 2:

- Continued general good health
- Continued to meet inclusion/exclusion criteria
- No common colds, acute sinusitis, or influenza infections within 14 days prior
- No antibiotic therapy for acute conditions within 14 days prior
- Successfully completed a test call with the video call center

Only subjects who met the following criteria at Visit 3 were eligible to return for Visit 4:

- Continued general good health
- Continued to meet inclusion/exclusion criteria

- Clinical lab values (hematology, chemistry, urinalysis) from Visit 2 were within normal reference ranges or with deviations that were deemed not clinically significant by the investigator
- Negative serum pregnancy test from Visit 2 for females 8 to 11 years of age
- Had an average AM and PM rTNSS ≥ 5 and a reflective congestion or runny nose score of ≥ 2 on any 4 of the last 7 days
- Adequately completed nasal symptom assessment during the run-in period in the Allergic Rhinitis Assessment Diary (missed no more than one calendar day entry)
- Took single-blind medication at least 6 out of the 7 days during the run-in period
- Did not use restricted concomitant medications during the run-in period
- No common cold, acute sinusitis, or influenza infections within 10 days prior
- Morning serum cortisol value ≥ 2 mcg/dL from Visit 2 sample
- Agreed to continue in the trial

Randomization Criteria
Subjects who met the following criteria were eligible for random assignment at Visit 4:

- Continued to be in good general health
- Continued to meet the inclusion/exclusion criteria
- Successfully completed the overnight stay, including provision of required serum cortisol samples
- Agreed to continue in the trial

Prohibited Medications
The following table lists medications prohibited during the study along with the minimum time frame for withholding these medications.

Table 9. Prohibited Medications in Study 308

Medication Disallowed for Study Duration	Required Withholding Interval Prior to Visit 2
Topical/oral/nasal decongestants[a]	10 days
Ocular allergy preparations	10 days
Short-acting antihistamines (nasal, ocular, oral)	5 days
Long-acting antihistamines (nasal, ocular, oral)	10 days
Over-the-counter (OTC) cough and cold preparations or sleep aids containing antihistamines	10 days
Airozan® (OTC food supplement/diet leukotrienes)	7 days
Cromolyn, nedocromil, or lodoxamide (intranasal, ocular, or oral)	14 days
Leukotriene or 5-lipoxygenase inhibitors	14 days
Inhaled/oral/intranasal anticholinergics	14 days
Inhaled/systemic/intranasal/ocular corticosteroids	30 days
Azoles, antifungals	30 days
Immunosuppressive drugs	60 days

[a] Decongestant (0.05% oxymetazoline in each nostril) is permitted at Visit 1 ONLY for screening nasal examination.
Source: Module 5.3.5.1, SEP060-308 protocol, Table 4, p42

Stopping Criteria
Subjects could be discontinued from study medication for any of the following reasons. Subjects whose participation was prematurely terminated were not replaced.

- Adverse event
- Non-compliance with study drug
- Protocol violation
- Lost to follow-up
- Physician decision
- Pregnancy
- Other

Efficacy
As in studies 305 and 306, efficacy was assessed by subject or caregiver report of rTNSS in the Allergic Rhinitis Assessment Diary. Treatment efficacy was measured by the change from baseline in average daily subject-reported AM and PM rTNSS averaged over the 6 weeks of double-blind treatment. Treatment compliance was assessed by the efficacy endpoint, verification of study drug administration via videophone on non-clinic visit days, subject or caregiver daily diary report, and study drug canister weights.

Safety
The effects of ciclesonide on the HPA axis were assessed based on changes in serum cortisol levels and 24-hour urinary free cortisol levels from predose to the end of the 6-week treatment period. In addition, safety was assessed throughout the study by monitoring adverse events, concomitant medication use, vital sign measurements, EENT examinations, and clinical laboratory evaluations (hematology, chemistry, and urinalysis).

Study 401

Protocol #	**SEP060-401**
Title	A 6-Month Randomized, Open-Label, Parallel Group, Safety Study of Ciclesonide Nasal Aerosol (Zetonna) and Ciclesonide Nasal Spray (Omnaris) in Subjects 12 Years and Older with Perennial Allergic Rhinitis
Study dates	Study initiated: September 11, 2012 Study completed: July 2, 2013 Final study report: December 2, 2013
Sites	32 clinical study sites in the U.S.
IRB	(b) (4)

Amendments
The Sponsor submitted two protocol amendments dated July 17, 2012, and September 14, 2012, to incorporate recommendations from the Division and from an independent ophthalmology consultant. To improve the assessment of treatment compliance, Omnaris containers were to be weighed by a separate vendor before shipment to the clinical sites and after return; additionally, subject diaries were replaced by an interactive voice response (IVR) system that subjects called once daily to record the date and time of dosing. Based on feedback from the Division of Transplant and Ophthalmology Products, the Sponsor included an analysis of Snellen Vision acuity by conversion to logMAR and intraocular pressure in the statistical methods. The ocular exclusion criteria were also revised after consultation with an independent ophthalmologist employed by the Sponsor.

Objective
The objectives of this clinical trial were to evaluate the nasal safety, ocular safety, and overall safety of once daily dosing with ciclesonide nasal aerosol (Zetonna) and ciclesonide nasal spray (Omnaris) in subjects 12 years and older with PAR. The primary endpoint was the number and percentage of subjects experiencing Nasal Mucosal Disorders, Septum Disorders, or Nasal Septum Perforations as TEAEs. Secondary endpoints included number and percentage of nasal TEAEs, TEAEs, serious TEAEs, and TEAEs causing discontinuation as well as ocular safety as measured by development or worsening of lens opacities, increase in intraocular pressure (≥7 mmHg from baseline or ≥21 mmHg in either eye), and change in best corrected visual acuity.

Study Design
This was a 26-week, randomized, open-label, parallel group study in male and female subjects 12 years of age and older diagnosed with PAR. The study schematic and schedule of assessments are shown in Figure 4 and Table 10, respectively. Subjects were followed through 8 outpatient study visits over 6 months. The screening period (Visit 1) occurred 1 to 30 days prior to randomization and included baseline nasal and ocular examinations to confirm study eligibility. At Visit 2, subjects underwent a repeat nasal examination and were then randomized 1:1 to once-daily treatment with either Zetonna 74 mcg or Omnaris 200 mcg. Randomization was stratified by subjects at high risk of nasal adverse events (history of nasal surgery, presence of nasal jewelry, history of nasal ulcer, perforation, or polyps). Subjects self-administered the first dose of study medication under supervision at Visit 2, while the remaining doses were administered once daily at home for 6 months. Follow-up clinic visits occurred at Month 3 (Visit 5) and Month 6 (Visit 8) with interim phone contact at Months 1, 2, 4, and 5 (Visits 3, 4, 6, and 7). Subjects underwent nasal and ocular examinations at Visits 1, 2, 5, and 8 by physicians and ophthalmologists blinded to study treatment. The LOCS III was utilized to assess for lens opacities. Any abnormal findings on nasal exam warranted follow-up examinations by an ENT physician. Where possible, the same physician conducted serial follow-up examinations for an individual subject. Treatment compliance was

assessed by subject self-report, pharmacokinetic sampling, and number of actuations displayed by the device dose indicator (Zetonna) or returned canister weights (Omnaris).

Figure 4. Study Schematic for 401

Screening	Open-label Treatment Period						
Visit 1	Visit 2	Visit 3 (Telephone Contact)	Visit 4 (Telephone Contact)	Visit 5	Visit 6 (Telephone Contact)	Visit 7 (Telephone Contact)	Visit 8
1-30 days prior to Visit 2	Day 1	Day 30 (- 3 to + 7 d) Month 1	Day 60 (- 3 to + 7 d) Month 2	Day 90 (- 3 to + 7 d) Month 3	Day 120 (- 3 to + 7 d) Month 4	Day 150 (- 3 to + 7 d) Month 5	Day 180 (- 3 to + 7 d) Month 6
	Rand/ Baseline Nasal/Ocular Assessment Pre-dose PK			Nasal/Ocular Assessment PK			Nasal/Ocular Assessment EOS/ET PK

Abbreviations: d = Days; EOS = end of study; ET = early termination; PK = pharmacokinetics; Rand = randomization.

Source: Module 5.3.5.1, SEP060-401 Protocol, Figure 1, page 24

Table 10. Schedule of Assessments for Study 401

Period	Screen	Treatment						
Visit	Visit 1	Visit 2	Visit 3 (Telephone Contact)	Visit 4 (Telephone Contact)	Visit 5	Visit 6 (Telephone Contact)	Visit 7 (Telephone Contact)	Visit 8 EOS/ET
Day (Month)	1-30 days prior to Visit 2	1	30 (- 3 to + 7) (Month 1)	60 (- 3 to + 7) (Month 2)	90 (- 3 to + 7) (Month 3)	120 (- 3 to + 7) (Month 4)	150 (- 3 to + 7) (Month 5)	180 (- 3 to + 7) (Month 6)
Informed Consent/Assent	X							
Inclusion/Exclusion Review	X							
Ocular Exclusion Criteria Review		X						
Demography	X							
Register subject via IXR System	X							
Medical History	X							
Height and Weight	X							
Physical Examination (including vital signs)	X							
Blinded Nasal Examination[a]	X	X			X			X
Blinded Ocular Examination[b]		X			X			X
Serum Pregnancy Test[c]	X							
Urine Pregnancy Test								X
Randomization via IXR System		X						
Dispense Study Medication[d]		X			X			
Administer Study Medication[d]		X	X	X	X	X	X	
Subject Access IVR System[e]		X	X	X	X	X	X	X
Collect Used/Unused Study Medications					X			X
Pharmacokinetic Blood Sample Collection[f]		X			X			X
Adverse event and Concomitant Medication Recording[g]	X	X	X	X	X	X	X	X
Schedule Next Visit/Telephone Contact[h]	X	X	X	X	X	X	X	

Abbreviations: EOS = End of Study; ET = Early Termination; IVR = interactive voice response; IXR = Interactive web or phone response system.

[a] Nasal examination to be conducted by a physician blinded to treatment assignment 5 to 10 minutes after subject is decongested with 0.05% oxymetazoline in each nostril. If a subject has evidence of abnormal findings that do not exclude the subject from enrollment, a follow-up nasal examination is to be conducted by an ENT physician, and all further nasal examinations are to be conducted by the ENT physician.

[b] Screening ocular examination is to occur within 7 days prior to Visit 2. All ocular examinations will include measurement of intraocular pressure, dilated funduscopy and slit lamp examination, and best corrected visual acuity. All ocular examinations must be performed by a qualified ophthalmologist blinded to treatment assignment; where possible, this should be the same ophthalmologist who conducted the ocular examinations at the previous visit(s). The Lens Opacity Classification System (LOCS III) will be utilized to assess lens opacities. The ocular examinations at Visit 5 and Visit 8 are to be conducted at the same time of day (± 1 hour) as the baseline ocular examination.

[c] Subjects with a positive serum pregnancy test will not be allowed to continue in the study.

[d] Preparation and administration of **ciclesonide nasal aerosol** is as follows for Visit 2 and Visit 5:

- Six (6) ciclesonide nasal aerosol devices will be dispensed to each subject at Visit 2 and Visit 5.
- Investigator (or designee) will instruct the subject on proper administration of study medication (see Zetonna full prescribing information for proper dosing instructions).
- Investigator (or designee) will prime the first ciclesonide nasal aerosol canister to be utilized by depressing the canister 3 times in a well-ventilated area (see Zetonna full prescribing information for priming instructions). The investigator (or designee) will instruct the subject on priming the additional ciclesonide nasal aerosol devices prior to use and to use each device until 25 of the 30 planned doses for a given month have been taken (ie, that device shows ≤ 10 in the dose indicator window).
- Investigator (or designee) will record value shown in dose indicator window in the eCRF (see Zetonna full prescribing information for description of the dose indicator and recording values). The number of priming shots will also be recorded in the eCRF. During telephone contacts, Investigator (or designee) will ask subject if they have completed dosing with 1 canister (ie, the subject has dosed for 30 days), and record whether a canister has been completed in the eCRF.
- Investigator (or designee) will observe subject administer the study medication at the study site at Visit 2 (only), and record the date and time of dosing in the eCRF (see Zetonna full prescribing information for proper dosing instructions).
- Subject will administer study medication once daily in the morning at home on all study days (except Visit 2), and access the IVR system to record the date and time of dosing as well as number of actuations.
- Investigator (or designee) will review study medication administration instructions as well as instructions for reporting damaged/dropped devices with the subject at each clinic visit (see Zetonna full prescribing information for proper dosing instructions).

Preparation and administration of **ciclesonide aqueous nasal spray** is as follows for Visit 2 and Visit 5:

- Six (6) ciclesonide nasal spray devices will be dispensed to each subject at Visit 2 and Visit 5.
- Investigator (or designee) will instruct the subject on proper administration of study medication (see Omnaris full prescribing information for proper dosing instructions).
- Investigator (or designee) will prime the ciclesonide nasal spray by depressing the canister 8 times in a well-ventilated area (see Omnaris full prescribing information for priming instructions). The investigator (or designee) will instruct the subject on priming the additional ciclesonide nasal spray devices prior to use.
- During telephone contacts, Investigator (or designee) will ask subject if they have completed dosing with 1 canister (ie, the subject has dosed for 30 days), and record whether a canister has been completed in eCRF.
- Investigator (or designee) will observe subject administer the study medication at the study site at Visit 2 (only), and record the date and time of dosing in the eCRF. See Omnaris full prescribing information for proper dosing instructions).
- Subject will administer study medication once daily in the morning at home on all study days (except Visit 2), and access the IVRS to record the date and time of dosing as well as number of actuations.
- Investigator (or designee) will review study medication administration instructions with the subject at each clinic visit (Omnaris full prescribing information for proper dosing instructions).

[e] After dosing, subject to access IVRS to record date and time of dosing as well as number of actuations.

[f] Blood samples will be collected from approximately half of all subjects randomized (approximately half of the subjects in each treatment group) at selected sites **only.** Collect sample prior to the first dose at Visit 2 (Day 1), and when the subject arrives at the clinical site at Visit 5 (Month 3) and Visit 8 (Month 6). Blood samples for pharmacokinetics are to be collected in a well-ventilated room, separate from the dosing area. Sample collection instructions are provided in Section 19, Appendix I.

[g] Adverse Event and concomitant medication information will be collected after subjects have signed informed consent.

[h] The subjects will be called 1 to 2 days in advance of Visit 5 and Visit 8 to remind them of their upcoming visit. Note: Subjects who discontinue study medication for any reason prior to Visit 8 will undergo nasal examination and an ocular examination at the time of study medication discontinuation (the nasal examination will be conducted by a physician blinded to treatment assignment, and the ocular examination will be conducted by a qualified ophthalmologist blinded to treatment assignment; where possible, these should be the same individuals who conducted the previous visit exam). Subjects who discontinue study medication prior to Visit 8 will be encouraged to remain in the study for collection of safety data for the full duration of the study. Subjects who discontinue the study prior to Visit 8 will undergo evaluations and procedures scheduled for Visit 8 at the time of discontinuation.

Source: Module 5.3.5.1, SEP060-401 Protocol, Table 3, pg 2

Subjects
A total of 737 PAR patients 12 years of age and older were randomized to receive treatment for 6 months: 368 subjects to Zetonna and 369 subjects to Omnaris. Subjects were stratified according to potential risk for nasal adverse events.

Main Inclusion Criteria

1. Male or female 12 years and older as of Visit 1
2. In generally good health
3. History of PAR to a relevant perennial allergen (e.g., house dust mites, cockroach, molds, animal dander) for a minimum of one year immediately preceding Visit 1. The PAR must have been of sufficient severity to have required either continuous or intermittent treatment in the past 12 months and require treatment throughout the entire study period
4. Female subjects ≤ 65 years of age and of child-bearing potential must have a negative serum pregnancy test at Visit 1 and must agree to use an acceptable method of birth control to avoid pregnancy during the study:
    a. An oral contraceptive, an intrauterine device, implantable contraceptive, transdermal or injectable contraceptive for at least 1 month prior to entering the study with continued use throughout the study and for 30 days following study participation
    b. Barrier method of contraception (e.g., condom and/or diaphragm with spermicide) while participating in the study
    c. Abstinence

Main Exclusion Criteria

1. Pregnancy or lactation
2. Current physical findings of nasal polyps, septal perforation, or nasal ulceration (Subjects showing significant progression of nasal pathology between Visit 1 and Visit 2 were excluded at the discretion of the investigator.)
3. Planned insertion of nasal septal jewelry during the study period.
4. Recent (within 30 days of Visit 1) nasal or sinus surgery, including biopsy, atrophic rhinitis, or rhinitis medicamentosa
5. Recent (within 30 days of Visit 1) or planned participation in any other investigational drug trial
6. Hypersensitivity to any corticosteroid or any of the excipients
7. History of respiratory infection or disorder (e.g., bronchitis, pneumonia, influenza, SARS) within 14 days of Visit 1
8. History of alcohol or drug abuse within 2 years of Visit 1
9. History of positive test for HIV, hepatitis B, or hepatitis C
10. Active asthma requiring treatment with inhaled or systemic corticosteroids
11. Chronic treatment with agents known to promote development of cataracts (e.g., potassium-sparing diuretics and allopurinol)

12. Non-vaccinated exposure to or active infection with chickenpox or measles within 21 days of Visit 1
13. Initiation of pimecrolimus cream 1% or tacrolimus ointment 0.03% or greater during the study period or planned dose escalation during the study period. Use of a stable maintenance dose for 30 days prior to Visit 1 and during the study period were considered for inclusion.
14. Use of nasal corticosteroids within 14 days or use of ocular, oral, or parental corticosteroids within 6 months of Visit 2
15. Conditions that are judged by the investigator to be clinically significant and/or affect the subject's ability to participate in the clinical trial (e.g., impaired hepatic function, diabetes mellitus, malignancy)

Ocular exclusion criteria (based on Visit 1 ophthalmic exam)

16. History of bacterial or viral infection of the eyes within 14 days of Visit 1 or current or history of ocular herpes simplex
17. Topical ocular corticosteroid use or intraocular or periocular corticosteroid injections within 6 months of Visit 1
18. Progressive retinal or optic nerve disease in either eye (including acute macular degeneration or unstable diabetic retinopathy)
19. Ocular injury or surgery in past 6 months
20. Any evidence of glaucomatous optic disc changes or vertical cup:disc ration > 0.8
21. Current or history of any glaucoma related diagnosis, including ocular hypertension, open-angle or closed-angle as well as secondary or congenital glaucoma
22. Occludable angles by slit lamp exam
23. Current PSC cataract or previous history of cataract surgery.
24. Current or history of congenital cataract or active/prior uveitis
25. Historical or current intraocular pressure of 22 mmHg or higher in either eye
26. Inability to complete ocular examination
    a. Inability to measure intraocular pressure
    b. Pupillary diameter < 6 mm upon dilation
    c. Significant media opacity in either eye that excluded adequate posterior segment exam
    d. Clinically significant corneal dystrophy, epithelial, or endothelial disease that precluded visualization or intraocular pressure measurement
    e. Corneal irregularities or scarring that would have impeded accurate intraocular pressure measurement or visualization of intraocular anatomy
    f. Unwillingness to remove contact lenses for ocular exam
    g. LOCS III grade NO>4.0, NC >4.0, and C>4.0 in either eye
27. Best-corrected visual acuity in either eye of 20/200 or worse
28. Planned or anticipated ocular surgery during next 6 months

Prohibited medications
The following list includes medications that were prohibited for the duration of the study and the time frame for which such medications must have been withheld prior to initiating study treatment.

- Hydrocortisone (> 1% concentration or equivalent) covering >20% of total body surface area without occlusion
- Nasal corticosteroids within 14 days of Visit 2
- Oral, ocular, or parenteral corticosteroids within 6 months of Visit 2
- Any medication known to alter intraocular pressure within 6 months of Visit 1 (systemic hypertensive medication at a stable dose excepted)
- Nasal products (except saline) within 7 days of Visit 1
- Agents known to promote development of cataracts (e.g., potassium-sparing diuretics, allopurinol)

Stopping criteria
Subject participation could have been terminated for any of the following reasons. Subjects who discontinued study medication prior to completion of the study underwent a nasal examination and complete ocular examination at the time of study medication discontinuation and were encouraged to remain in the study for collection of safety data.

- Adverse event
- Lack of efficacy
- Pregnancy
- Violation of inclusion/exclusion criteria
- Lost to follow-up
- Withdrawal by subject or investigator
- Other

Treatments
There were two treatment groups in the study. Treatments were provided by the Sponsor.

- Zetonna, ciclesonide nasal aerosol
  Mode of administration: topical/intranasal aerosol
  Dose: 74 mcg of ciclesonide, total daily dose
  Regimen: 1 actuation per nostril once daily
  Duration of Treatment: 6 months

- Omnaris, ciclesonide aqueous nasal spray
  Mode of administration: topical/intranasal spray
  Dose: 200 mcg ciclesonide, total daily dose
  Regimen: 2 sprays per nostril once daily
  Duration of Treatment: 6 months

Treatment compliance was assessed by subject self-report of study medication administration via IVR system, PK sampling in a subset of patients at Visits 2, 5, and 8, review of the Zetonna dose indicator value prior to priming and dispensing the canister and actuator to the subject, and measurement of Omnaris canister weights after return.

Efficacy
No efficacy measures were assessed in this study.

Safety
Safety was assessed throughout the study by monitoring AEs, concomitant medication use, blinded nasal examinations, blinded ocular examinations, and physical examinations including vital sign measurement.

6 Review of Efficacy

Efficacy Summary

This supplemental NDA submission contains adequate data to evaluate the efficacy of ciclesonide nasal aerosol 37 mcg and 74 mcg once daily for the relief of allergic rhinitis symptoms of PAR and SAR in patients 6 to 11 years of age. The primary efficacy endpoint was the difference from placebo in the change from baseline of the average of morning and evening reflective total nasal symptom scores (rTNSS) averaged over 2 weeks of treatment in SAR and over the first 6 weeks of treatment in PAR. In study 305 in patients with SAR, treatment with either dose of ciclesonide nasal aerosol failed to demonstrate efficacy compared to placebo. In study 306 in patients with PAR, both doses of ciclesonide nasal aerosol demonstrated significant improvement compared to placebo. Key secondary efficacy endpoints included the change from baseline in iTNSS, PRQLQ, and rTOSS over 2 or 6 weeks. None of the key secondary efficacy endpoints in study 305 suggested a significant treatment effect with either dose of ciclesonide nasal aerosol in SAR patients. By contrast, study 306 did demonstrate a statistically significant improvement in the iTNSS over 6 weeks in both ciclesonide dose treatment groups compared to placebo; however, the change in PRQLQ score was not statistically significant. While the reason ciclesonide nasal aerosol failed to demonstrate a significant treatment effect in SAR patients is not entirely clear, it is not uncommon for SAR studies to fail given the variability of pollen levels during a short 2-week trial, particularly with prolonged enrollment periods. Nonetheless, when taken together, the inconsistent results from studies 305 and 306 did not provide substantial evidence of efficacy in patients 6 to 11 years of age with allergic rhinitis.

The Applicant has submitted this supplement to fulfill the PREA requirement in children 6 to 11 years of age, but is not seeking to expand the indication to PAR or SAR patients in this age group.

6.1 Indication

This is a pediatric supplemental NDA for an approved drug product Zetonna Nasal Aerosol. Currently, the FDA-approved indication in the product labeling (Section 1.1) is "Zetonna (ciclesonide) Nasal Aerosol is indicated for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older". The Applicant submitted this supplement to comply with PREA regulations, but is not seeking to expand the indication to younger age groups.

6.1.1 Methods

See Section 5.3 for a description of the design and conduct of the two pivotal efficacy studies (305 and 306) in patients 6 to 11 years of age. The design and conduct of the studies were appropriate and consistent with the FDA guidance[3] for allergic rhinitis development programs.

6.1.2 Demographics

Table 11 summarizes the demographic data for ITT subject population in studies 305 and 306. Overall, the demographics and baseline characteristics of subjects who received Cic37, Cic74, or placebo were similar. In addition, the decongested nasal examinations performed at screening (data not shown) were similar across treatment groups in both studies. There were slightly more males than females in each treatment group in both studies.

[3] Draft Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products. April 2000

Table 11. Baseline Demographics and Characteristics: Studies 305 and 306

Study	Variable	PBO	Cic37	Cic74	Total
305 (SAR)	ITT population	283	282	282	847
	Age (Years)				
	Mean (SD)	8.6 (1.72)	8.5 (1.64)	8.7 (1.60)	8.6 (1.65)
	6-8 years – n(%)	132 (46.6)	132 (46.8)	131 (46.5)	395 (46.6)
	9-11 years – n(%)	151 (53.4)	150 (53.2)	151 (53.5)	452 (53.4)
	Sex – n(%)				
	Female	131 (46.3)	123 (43.6)	120 (42.6)	374 (44.2)
	Race – n(%)				
	White/Caucasian	209 (73.9)	220 (78.0)	226 (80.1)	655 (77.3)
	Black/African American	63 (22.3)	46 (16.3)	46 (16.3)	155 (18.3)
	Asian	5 (1.8)	7 (2.5)	3 (1.1)	15 (1.8)
	American Indian/Alaska Native	1 (0.4)	0	0	1 (0.1)
	Native Hawaiian / Other Pacific Islander	0	0	1 (0.4)	1 (0.1)
	Other	0	1 (0.4)	0	1 (0.1)
	Multiple	5 (1.8)	8 (2.8)	6 (2.1)	19 (2.2)
	Ethnicity – n(%)				
	Hispanic/Latino	102 (36.0)	115 (40.8)	134 (47.5)	351 (41.4)
	Skin Prick Allergy Test				
	Mountain Cedar	115 (40.6)	121 (42.9)	110 (39)	346 (40.9)
	Grasses	209 (73.9)	198 (70.2)	204 (72.3)	611 (72.1)
	Weeds	183 (64.7)	165 (58.5)	165 (58.5)	513 (60.6)
	Trees	230 (81.3)	236 (83.7)	224 (79.4)	690 (81.5)
306 (PAR)	ITT population	283	282	281	846
	Age (Years)				
	Mean (SD)	8.7 (1.67)	8.7 (1.61)	8.7 (1.71)	8.7 (1.66)
	6-8 years (%)	127 (44.9)	121 (42.9)	123 (43.8)	371 (43.9)
	9-11 years (%)	156 (55.1)	161 (57.1)	158 (56.2)	475 (56.1)
	Sex				
	Female – n(%)	120 (42.4)	113 (40.1)	130 (46.3)	363 (42.9)
	Race				
	White/Caucasian	224 (79.2)	216 (76.6)	216 (76.9)	656 (77.5)
	Black/African American	37 (13.1)	43 (15.2)	39 (13.9)	119 (14.1)
	Asian	5 (1.8)	2 (0.7)	7 (2.5)	14 (1.7)
	American Indian/Alaska Native	0	2 (0.7)	1 (0.4)	3 (0.4)
	Native Hawaiian / Other Pacific Islander	0	0	1 (0.4)	1 (0.1)
	Other	9 (3.2)	9 (3.2)	9 (3.2)	27 (3.2)
	Multiple	8 (2.8)	10 (3.5)	8 (2.8)	26 (3.1)
	Ethnicity – n(%)				
	Hispanic/Latino	89 (31.4)	101 (35.8)	91 (32.4)	281 (33.2)
	Skin Prick Allergy Test				
	House dust mite	216 (76.3)	220 (78.0)	215 (76.5)	651 (77.0)
	Animal dander	198 (70.0)	216 (76.6)	191 (68.0)	605 (71.5)
	Cockroach	91 (32.2)	92 (32.6)	89 (31.7)	272 (32.2)
	Mold	180 (63.6)	165 (58.5)	156 (55.5)	501 (59.2)

Abbreviations: PBO=placebo, Cic37=ciclesonide nasal aerosol 37 mcg once daily, Cic74=ciclesonide nasal aerosol 74 mcg once daily, SAR=seasonal allergic rhinitis, PAR=perennial allergic rhinitis, ITT=intent-to-treat
Source: Module 5.3.5.1, SEP060-305 CSR, Table 10, p74; SEP060-306 CSR, Table 11, p75

6.1.3 Subject Disposition

In study 305, a total of 1,444 subjects were screened, of whom 1,169 were enrolled into the placebo run-in period. In study 306, a total of 1,247 subjects were screened, of whom 1,088 were enrolled into the placebo run-in period. The majority of screening and randomization failure subjects were not eligible based on violation of inclusion or exclusion criteria or lack of sufficient symptom severity during the placebo run-in period. The table below displays the disposition for randomized patients in studies 305 and 306. The number of discontinuations across treatment groups was similar. The majority of discontinuations were due to "withdrawal by subject" or "other", most of which related to use of prohibited medications, difficulty in scheduling follow-up visits, and randomization errors. The discontinuations due to adverse events are described in greater detail in Section 7. Due to randomization errors, a few patients were discontinued prior to receiving double-blind study medication and therefore were not included in the ITT population. The Per Protocol (PP) population was not included in the original protocols, but was added to the studies prior to data availability; it was defined as all ITT subjects without important protocol deviations. Efficacy analyses in this review are based on the ITT population. The study completion rates were high overall and relatively balanced among treatment groups.

Table 12. Patient Disposition: Studies 305 and 306

Study		PBO	Cic37	Cic74	Total
305 (SAR)	Randomized	284	282	283	849
	ITT population	283 (99.6)	282 (100)	282 (99.6)	847 (99.8)
	PP population	274 (96.8)	268 (95.0)	272 (96.5)	814 (96.1)
	Completed Study	269 (95.1)	269 (95.4)	273 (96.8)	811 (95.7)
	Early Discontinuation	14 (4.9)	13 (4.6)	9 (3.2)	36 (4.3)
	Adverse Event	3 (1.1)	5 (1.8)	1 (0.4)	9 (1.1)
	Lost to Follow-up	3 (1.1)	2 (0.7)	1 (0.4)	6 (0.7)
	Withdrawal by Subject	3 (1.1)	1 (0.4)*	1 (0.4)	5 (0.6)
	Other	5 (1.8)	5 (1.8)	2 (0.7)	12 (1.4)
306 (PAR)	Randomized	283	282	283	848
	ITT population	283 (100)	282 (100)	281 (99.3)	846 (99.8)
	PP population	265 (93.6)	267 (94.7)	267 (95.0)	799 (94.4)
	Completed Week 6	263 (92.9)	264 (93.6)	261 (92.9)	788 (93.1)
	Completed Study	247 (87.3)	257 (91.1)	254 (90.4)	758 (89.6)
	Early Discontinuation	36 (12.7)	25 (8.9)	27 (9.6)	88 (10.4)
	Adverse Event	4(1.4)	3 (1.1)	6 (2.1)	13 (1.5)
	Lack of Efficacy	2 (0.7)	0	0	2 (0.2)
	Lost to Follow-up	4 (1.4)	4 (1.4)	7 (2.5)	15 (1.8)
	Withdrawal by Subject	15 (5.3)	8 (2.8)	6 (2.1)	29 (3.4)
	Other	11 (3.9)	10 (3.5)	8 (2.8)	29 (3.4)

Abbreviations: PBO=placebo, Cic37=ciclesonide nasal aerosol 37 mcg once daily, Cic74=ciclesonide nasal aerosol 74 mcg once daily, SAR=seasonal allergic rhinitis, PAR=perennial allergic rhinitis, ITT=intent-to-treat, PP=Per Protocol
*One subject discontinuation recategorized as "adverse event" in this review
Sources: Module 5.3.5.1, SEP060-305 CSR, Table 8, p70; SEP060-306 CSR, Table 8, p68; Data Analysis Datasets, ADSL.xpt

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for study 305 and study 306 was similar: change from baseline in the daily subject-reported AM and PM rTNSS averaged over the 2- or 6-week double-blind treatment period. As discussed in Section 5.3.1, the rTNSS was the sum of four individual symptom scores (runny nose, itchy nose, sneezing, and nasal congestion) which were graded on a 0 to 3 point scale, with higher scores indicating greater symptom severity. The rTNSS score reflected symptoms over the past 12 hours. Baseline was defined as the average of AM and PM rTNSS responses obtained during the last 6 days of the single-blind placebo run-in period. Analyses were performed on the ITT population. The baseline rTNSS scores were not significantly different between groups in either study. Based on the pre-specified analysis plan for each study, Cic74 was first compared to placebo for the primary endpoint. If this was statistically significant ($p \leq 0.05$), then Cic37 and Cic74 were compared to placebo in two parallel branches at the 0.025 level of significance. The primary endpoint analysis was followed by testing of the secondary endpoints in a hierarchical sequence. See the Biometrics Review by Dr. Robert Abugov for additional details regarding the statistical analyses.

The results of the primary endpoint analyses are shown in Table 13. Reductions indicate greater symptom improvement in the rTNSS. For study 305 in pediatric patients with SAR, neither Cic37 or Cic74 demonstrated a statistically significant improvement in the average daily rTNSS over the 2-week treatment period compared with placebo. In study 306, both Cic37 and Cic74 demonstrated a statistically significant improvement in the average daily rTNSS averaged weekly in pediatric patients with PAR over the first 6 weeks of treatment compared with placebo ($p<0.011$). There were no differences between the two ciclesonide treatment groups (data not shown).

Table 13. Reflective TNSS Change from Baseline: Studies 305 and 306

	Study 305 (SAR – 2 wks)			Study 306 (PAR – 6 wks)		
	PBO	Cic37	Cic74	PBO	Cic37	Cic74
Mean baseline rTNSS (SD)	8.44 (1.78)	8.57 (1.92)	8.61 (1.69)	8.14 (1.73)	8.04 (1.80)	8.25 (1.78)
ΔrTNSS	-1.63	-1.73	-1.61	-1.51	-2.10	-1.98
*Difference from placebo (95% CI)		-0.10 (-0.46, 0.27)	0.02 (-0.35, 0.39)		-0.59 (-0.95, -0.23)	-0.47 (-0.83, -0.11)
p value		0.607	0.914		0.001	0.011

Abbreviations: PBO=placebo, Cic37=ciclesonide nasal aerosol 37 mcg once daily, Cic74=ciclesonide nasal aerosol 74 mcg once daily, SAR=seasonal allergic rhinitis, PAR=perennial allergic rhinitis, rTNSS=reflective total nasal symptom score
*Treatment difference calculated as ciclesonide minus placebo and represented as least squares means.
Analysis based on ITT population
Source: Biometrics Review by Dr. Robert Abugov

6.1.5 Analysis of Secondary Endpoints(s)

Both studies had multiple secondary endpoints which were divided into "key secondary endpoints" and "other secondary endpoints". Studies 305 and 306 had two common key endpoints. These were change from baseline in the following parameters:

- Average AM and PM iTNSS over 2 or 6 weeks
- PRQLQ overall score at 2 or 6 weeks

Study 305 also included change from baseline in daily average AM and PM rTOSS as a key secondary endpoint. Key secondary endpoints were only analyzed if the primary endpoint at that dose demonstrated a statistically significant difference from placebo. The key secondary endpoints were then analyzed in a hierarchical fashion in the following order: ΔiTNSS, ΔPRQLQ, ΔrTOSS.

Like the the primary endpoint analysis in study 305, none of the key secondary efficacy endpoints in study 305 suggested a significant treatment effect with either dose of ciclesonide nasal aerosol in SAR patients. By contrast, study 306 did demonstrate a statistically significant improvement in the iTNSS over 6 weeks in both ciclesonide treatment groups compared to placebo; however, the change in PRQLQ score was not statistically significant. Results from the key secondary efficacy endpoints are shown in the table below.

Table 14. Key Secondary Endpoints: Studies 305 and 306

	Study 305 (SAR – 2 wks)			Study 306 (PAR – 6 wks)		
	PBO	**Cic37**	**Cic74**	**PBO**	**Cic37**	**Cic74**
ΔiTNSS	-1.32	-1.48	-1.35	-1.29	-1.77	-1.72
*Difference from placebo (95% CI)		-0.16 (-0.50, 0.19)	-0.03 (-0.38, 0.32)		-0.47 (-0.81, -0.14)	-0.43 (-0.77, -0.09)
p-value		0.38	0.87		0.006	0.014
ΔPRQLQ	-0.41	-0.43	-0.51	-0.39	-0.51	-0.30
*Difference from placebo (95% CI)		-0.02 (-0.17, 0.14)	-0.10 (-0.25, 0.05)		-0.12 (-0.27, 0.03)	0.09 (-0.06, 0.24)
p-value		0.83	0.20		0.10	0.23
ΔrTOSS	-0.84	-0.69	-0.79	--	--	--
*Difference from placebo (95% CI)		0.15 (-0.10, 0.40)	0.06 (-0.19, 0.31)		--	--
p-value		0.25	0.66		--	--

Abbreviations: PBO=placebo, Cic37=ciclesonide nasal aerosol 37 mcg once daily, Cic74=ciclesonide nasal aerosol 74 mcg once daily, SAR=seasonal allergic rhinitis, PAR=perennial allergic rhinitis, iTNSS=instantaneous total nasal symptom score, PRQLQ=Pediatric Rhinoconjunctivitis Quality of Life Questionnaire, rTOSS=reflective total ocular symptom score
*Treatment difference calculated as ciclesonide minus placebo and represented as least squares means.
Analysis based on ITT population
Source: Biometrics Review by Dr. Robert Abugov

Other secondary endpoints included change from baseline in AM iTNSS over 2 or 6 weeks, daily iTNSS at 12 weeks, daily rTNSS at 12 weeks, iTOSS at 2 weeks, PRQLQ overall score at 12 weeks, and time to maximal effect. As these were not key secondary endpoints, these were not reanalyzed by the FDA. Overall, the secondary endpoints in study 306 were generally supportive of a positive treatment effect in PAR for both ciclesonide nasal aerosol dose groups compared to placebo.

6.1.6 Other Endpoints

Although the Applicant analyzed additional efficacy endpoints (see Section 5.3.1), these were not reviewed in detail given the lack of statistical significance of the primary endpoint in study 305 and the Applicant's decision to seek no further indication (b) (4)

6.1.7 Subpopulations

Subgroup analyses by race and age group (6-8 years, 9-11 years) did not detect any significant subgroup effect on efficacy. A nominally significant effect of sex on treatment benefit was observed in study 305 (p=0.048), but not in study 306 (p=0.445). Compared to placebo, treatment with either dose of ciclesonide in study 305 was associated with a numerically detrimental effect in females and a numerically beneficial effect in males; however, the clinical significance of this finding is uncertain. See the Biometrics Review by Dr. Robert Abugov for additional details.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The studies conducted in children 6 to 11 years of age with SAR and PAR were performed using 2 doses: the 74 mcg/day approved dose and a lower 37 mcg/day dose. Results from the trials were mixed, but indicated that either this drug has a flat dose response or that both doses were on the flat portion of the dose response curve. Although the Applicant does not wish to expand the indication to younger age groups, the results suggest that the 37 mcg dose was equivalent to the 74 mcg dose in terms of efficacy in PAR patients 6 to 11 years of age.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Tolerance effects have not been previously shown with Zetonna Nasal Aerosol and were not noted in studies 305 or 306.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

This sNDA submission contains adequate data to support the safety of ciclesonide nasal aerosol 37 mcg and 74 mcg once daily for the treatment of SAR and PAR symptoms in patients 6 to 11 years of age. The evidence for safety in this age group is based on the three PREA required studies: 305 (2-week trial in SAR), 306 (12-week trial in PAR), and 308 (6-week HPA axis study). In addition, the submission includes a postmarketing requirement study (401) that has adequately evaluated the long-term local nasal effects of Zetonna compared to the related product, Omnaris.

In the three pediatric studies of patients 6 to 11 years of age with allergic rhinitis, there were no deaths reported, and nonfatal serious adverse events (SAEs) were rare and unlikely related to ciclesonide nasal aerosol. Both treatment discontinuations due to AEs and local nasal-related AEs occurred with similar frequency among treatment groups with no clear dose response in this age group. In addition, none of the pediatric patients experienced a nasal septum perforation. Overall, the number and type of AEs reported in the 6 to 11 year old age group were consistent with those observed in the development program for the approved population of adolescents and adults.

Study 401 was issued as a postmarketing requirement to further evaluate local nasal effects in patients ≥12 years of age because of the two nasal septum perforations noted in the 2-week trials from the Zetonna development program for adults and adolescents. Therefore, local nasal toxicity was the primary focus of this review. In this 6-month open-label, active-comparator, safety study, no deaths or nasal septum perforations were reported. Nonfatal SAEs were rare and appeared unlikely related to Zetonna or Omnaris use. Nasal mucosal or septum disorders, including erosions, ulcerations, and non-ulcerative lesions of the nose, occurred infrequently with the number and percentage of patients with nasal-related TEAEs balanced between Zetonna and Omnaris treatment groups. Although the 6-month safety study included ophthalmic examinations (slit-lamp, intraocular pressure and visual acuity assessments), the study duration was insufficient to definitively evaluate corticosteroid-associated ocular toxicity such as cataract development. Even so, there were no significant differences between the two treatment groups regarding ocular safety findings.

The most common AEs for both the 6-11 year old pediatric population and the 12 year and older “nasal safety study” population were cough, epistaxis, and headache which are consistent with adverse reactions described in the prescribing information for Zetonna and other intranasal corticosteroids. Overall, no new safety signals were identified in this review of the pediatric or long-term safety studies.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical trials used to evaluate safety are described in Table 3 in Section 5.1 and include studies 305, 306, and 308 for overall safety in the pediatric 6 to 11 year age group and study 401 for local nasal and ocular effects in adolescents and adults. Study 308 was an HPA axis study and is summarized in Sections 7.3.5 and 4.4.2.

7.1.2 Categorization of Adverse Events

Adverse events (AE) were defined as any new, untoward medical occurrence or worsening of a preexisting medical condition that occurred during study participation, whether or not the event was considered drug-related. Adverse events were collected from the time of informed consent to the end of the study. An AE was considered serious if it resulted in any of the following outcomes: death, persistent or significant disability/incapacity, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a congenital birth anomaly/defect, or an important medical event. Serious adverse events were collected from the time of informed consent to 30 days after the last dose of study drug and followed until resolution or until the subject was lost to follow-up. Treatment emergent adverse events (TEAE), defined as AEs that occurred after the patient received at least one dose of study drug, were the focus of this review.

Adverse events were coded using MedDRA, version 12.1 for studies 305, 306, and 308 and version 13.1 for study 401. Overall, the Applicant's categorization of AEs appears adequate. As in the original NDA, the Applicant grouped specific local nasal TEAEs in order to minimize splitting of similar preferred terms (PT). The following PTs were combined into a single group called "nasal mucosal/septum disorders": nasal septum disorder, nasal mucosal disorder, nasal ulcer, and nasal septum ulceration. The nasal mucosal/septum disorders group was further subdivided into "non-ulcerative lesions" (e.g., irritation, abrasions, excoriations, scabs) and "erosions and ulcerations". This review took a similar approach, but also including additional related PTs where relevant.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Due to the dissimilar nature of the clinical studies submitted to this application, pooling of data across trials was not appropriate, and instead, safety findings are discussed individually for each study.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 15 shows the overall exposure to ciclesonide nasal aerosol by age group, sex, and race, while Table 16 shows the overall exposure by dose, duration of exposure, and completion rates across the 4 studies. The total exposure was adequate to evaluate the safety of ciclesonide nasal aerosol in patients 6 to 11 years of age with allergic rhinitis and to evaluate the risk of local nasal effects in allergic rhinitis patients 12 years of age and older. To adequately assess the risk of corticosteroid-associated ocular toxicity, a study duration of 18-24 months is required.

Table 15. Demographics of Overall Exposure

Category	Study 305	Study 306	Study 308	Study 401
Total	847	846	89	737[a]
Age group				
6-8 years	396 (46.4)	371 (43.9)	37 (41.6)	0
9-11 years	452 (53.4)	475 (56.1)	52 (58.4)	0
12-18 years	0	0	0	73 (9.9)
18-64 years	0	0	0	653 (88.6)
> 64 years	0	0	0	11 (1.5)
Sex				
Female	374 (44.2)	363 (42.9)	44 (49.4)	482 (65.4)
Race				
White/Caucasian	655 (77.3)	656 (77.5)	64 (71.9)	561 (76.1)
Black/African American	155 (18.3)	119 (14.1)	19 (21.3)	127 (17.2)
Asian	15 (1.8)	14 (1.7)	4 (4.5)	26 (3.5)
American Indian/Alaska Native	1 (0.1)	3 (0.4)	0	3 (0.4)
Native Hawaiian/Pacific Islander	1 (0.1)	1 (0.1)	0	3 (0.4)
Other	1 (0.1)	27 (3.2)	0	6 (0.8)
Multiple	19 (2.2)	26 (3.1)	2 (2.2)	11 (1.5)

[a] ITT population
Source: Module 5.3.5.1, SEP060-305 CSR Table 10, p74; SEP060-306 CSR Table 11, p75; SEP060-401 CSR Table 7, p65; Module 5.3.5.4, SEP060-308 CSR Table 9, p77

Table 16. Extent of Exposure

	Cic37	Cic74	Placebo	OMN 200
Study 305				
ITT	282	282	283	--
Completed 2 wks (%)	269 (95.4)	273 (96.8)	269 (95.1)	--
Mean exposure in days (SD)	15 (2.4)	14.9 (2.4)	14.9 (2.6)	--
Study 306				
ITT	282	281	283	--
Completed 6 wks (%)	264 (93.6)	261 (92.9)	263 (92.9)	--
Completed 12 wks (%)	257 (91.1)	254 (90.4)	247 (87.3)	--
Mean exposure in days (SD)	80.5 (16.2)	79.5 (18.0)	79.4 (18.1)	--
Study 308				
ITT	--	47	42	--
Completed 6 wks	--	47 (100)	41 (97.6)	--
Mean exposure in days (SD)	--	43.1 (1.6)	42.1 (5.9)	--
Study 401				
ITT[a]	--	368	--	369
Safety[b]	--	367	--	370
Completed 26 wks	--	324 (88.0)	--	331 (89.7)
Mean exposure in days (SD)	--	166.7 (43.7)	--	168.8 (40.1)

Abbreviations: Cic37=ciclesonide nasal aerosol 37 mcg daily, Cic74=ciclesonide nasal aerosol 74 mcg daily, OMN 200=Omnaris 200 mcg daily, ITT=intent-to-treat population, SD=standard deviation
[a.] ITT population defined as any randomized subject who received at least 1 dose of double-blind study medication. Percentages based on number of ITT subjects.
[b.] Safety population based on actual treatment received. One subject randomized to Zetonna but received Omnaris.
Source: Module 5.3.5.1, SEP060-305 CSR Tables 8 and 19, p70, 95; SEP060-306 CSR Tables 8 and 22, p68, 113; SEP060-401 CSR Tables 5 and 13, p61, 74; Module 5.3.5.4, SEP060-308 CSR Tables 7 and 10, p73, 81

7.2.2 Explorations for Dose Response

Studies 305 and 306 in subjects 6 to 11 years of age evaluated the 74 mcg daily dose that is currently approved for adolescents and adults and a lower 37 mcg daily dose. Neither study revealed an appreciable dose response in terms of efficacy or safety.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was submitted as part of this application.

7.2.4 Routine Clinical Testing

The safety evaluation included monitoring of adverse events, vital signs, physical exam, clinical laboratory tests (hematology, chemistry, urinalysis), and nasal examinations throughout the studies. The methods used and the frequency of assessments provided an adequate assessment of the safety of ciclesonide nasal aerosol in the treatment of

allergic rhinitis. In addition, study 401 performed ocular examinations to assess lens opacity, intraocular pressure, and visual acuity; however, the duration of the study (6 months) was not long enough to adequately evaluate the risk of developing cataracts.

7.2.5 Metabolic, Clearance, and Interaction Workup

Appropriate studies to assess the absorption, distribution, metabolism, and clearance of ciclesonide nasal aerosol were submitted by the Applicant in support of the original NDA for the use of ciclesonide nasal aerosol to treat adult and adolescent patients 12 years of age and older with SAR and PAR. Additional pharmacokinetic information was submitted for this pediatric supplement (see Section 4.4.3, Clinical Pharmacology and the Clinical Pharmacology review by Dr. Sheetal Agarwal).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The major safety concern with intranasal corticosteroids is local nasal effects, particularly risk of mucosal erosion/ulceration and nasal septum perforation. The Applicant conducted post-marketing requirement study 401 to specifically address this safety concern; nasal examinations were performed at regular intervals in the study with treatment-emergent nasal-related adverse events as the primary outcome.

7.3 Major Safety Results

7.3.1 Deaths

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

7.3.2 Nonfatal Serious Adverse Events

The number of nonfatal serious adverse events (SAEs) was low overall and relatively balanced among treatment groups in each study. None of the SAEs appeared to be treatment-related. A summary of nonfatal SAEs by PT is provided in the table below followed by brief narratives of each event by study and treatment group.

Table 17. Nonfatal Serious Adverse Events

	Cic37		Cic74		PBO		OMN	
	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n
Overall	2 (0.4)	2	7 (0.8)	7	1 (0.2)	2	5 (1.4)	7
Study 305 (n)	282		282		283		--	
Appendicitis	1 (0.4)	1	0	0	0	0	--	--
Study 306 (n)	282		281		283		--	
Neutropenia	1 (0.4)	1	0	0	0	0	--	--
Appendicitis	0	0	1 (0.4)	1	0	0	--	--
Herpes zoster	0	0	1 (0.4)	1	0	0	--	--
Influenza	0	0	0	0	1 (0.4)	1	--	--
Pneumonia viral	0	0	0	0	1 (0.4)	1	--	--
Study 401 (n)	--		367		--		370	
Angina pectoris	--	--	0	0	--	--	1 (0.3)	1
Coronary artery disease	--	--	0	0	--	--	1 (0.3)	1
Bile duct stenosis	--	--	0	0	--	--	1 (0.3)	1
Appendicitis	--	--	0	0	--	--	1 (0.3)	1
Facial bones fracture	--	--	0	0	--	--	1 (0.3)	1
Limb injury	--	--	1 (0.3)	1	--	--	0	0
Blood pressure increased	--	--	0	0	--	--	1 (0.3)	1
Lacunar infarction	--	--	1 (0.3)	1	--	--	0	0
Migraine	--	--	1 (0.3)	1	--	--	0	0
Postmenopausal hemorrhage	--	--	0	0	--	--	1 (0.3)	1
Abortion spontaneous	--	--	1 (0.3)	1	--	--	0	0
Pulmonary embolism	--	--	1 (0.3)	1	--	--	0	0

Abbreviations: Cic37=ciclesonide nasal aerosol 37 mcg daily, Cic74=ciclesonide nasal aerosol 74 mcg daily, OMN 200=Omnaris 200 mcg daily
n=ITT population in studies 305 and 306 and safety population in study 401
Sources: Module 5.3.5.1, Data Analysis Data, Analysis Dataset Legacy, ADAE.xpt for each study; SEP060-305 CSR p102, SEP060-306 CSR p124, SEP060-308 CSR p91, SEP060-401 CSR p93

A brief narrative for each nonfatal SAE, organized by study and active treatment, is provided below:

Study 305

Subject 5066/S003 (Cic37): This was a 9 year old white female with a history of SAR, PAR, and asthma. Eleven days following her first dose of study medication, she complained of abdominal pain and was diagnosed with non-perforated appendicitis by her pediatrician. She was hospitalized and underwent a laparoscopic-assisted appendectomy 2 days later. She was discharged from the hospital the day after her appendectomy at which point the event had resolved. She continued on study

medication and completed the study. The SAE was assessed by the investigator as severe and unrelated to study medication.

Study 306

Subject 6046/S010 (Cic37): This was a 10-year-old black male with a history of PAR, SAR, intermittent and exercise-induced asthma, and eczema. On Day 76 of study medication, he experienced non-serious AEs of fever and abdominal pain which resolved the following day without treatment. On Day 79, he was hospitalized for fever, neutropenia (1900/mm^3), and lymphadenopathy. He was treated with cefipime, although blood cultures returned negative. A bone marrow aspirate and biopsy were normal. On Day 81, the fever resolved, and he was discharged home in stable condition. The neutropenia resolved on Day 85, and the subjected completed the study.

Subject 6005/S012 (Cic74): This was an 11-year-old white female with a history of PAR, SAR, allergic conjunctivitis, asthma, eczema, and heart murmur. On Day 22, she experienced a non-serious AE of viral gastroenteritis which self-resolved 2 days later. On Day 25, she developed a rash on the right shoulder which was confirmed to be herpes zoster by biopsy. She reported having chickenpox at age 2 or 3 years. The herpes zoster resolved on Day 37 following treatment with valcyclovir. She discontinued study treatment due to this event.

Subject 6010/S010 (Cic74): This was a 6-year-old Hispanic female with PAR and history of headaches. On Day 41, she was hospitalized with acute appendicitis. She underwent an appendectomy and was discharged on Day 48, fully recovered. She discontinued the study due to this event; her last dose of study medication was on Day 47.

Subject 6058/S004 (Cic74): This was a 10-year-old white male with a history of PAR, asthma, headaches, and urticaria. Ten days after completion of the 12-week study, he experienced an acute asthma exacerbation which had started with wheezing at school 3 days prior. He was transported to the emergency department after continued hypoxia (pulse oximetry 86%) despite treatment with albuterol nebulization, oxygen, and epinephrine. He was observed in the intensive care unit and discharged 2 days later with symptoms resolved.

Study 401

Subject 1006/S030 (Zetonna): This was a 47-year-old white female with SAR and PAR. On Day 4 of study medication, she was bitten by her dog on her right thumb while trying to break up a dog fight. She was transported to the emergency room and hospitalized for surgery and pain control. She was discharged the following day, and the event completely resolved. She completed the study, and the Investigator considered the event unrelated to study medication.

Subject 1010/S018 (Zetonna): This was a 62-year-old white female with a history of PAR, ankylosing spondylitis, asthma, and multiple other medical problems. She reported being hospitalized on Day 3 of study medication for a lacunar stroke in multiple areas of the brain, and withdrew her consent due to this event. She was discharged from the hospital 5 days later. Follow-up with the study investigator did not reveal any clear evidence of recent infarction either in the medical records or by neurological exam; the subject was noted to be scattered, anxious, and an unreliable historian.

Subject 1024/S018 (Zetonna): This was a 39-year-old white female with history of PAR, SAR, asthma, dysmenorrhea, and depression. She discontinued study medication on Day 103 due to increased intraocular pressure of moderate severity which began on Day 99; however, she remained in the study for safety assessments. Sixty-six days after discontinuation of study drug, she experienced a miscarriage, but did not seek medical treatment. She was later found to have a positive urine pregnancy test at Visit 8, and was instructed to follow-up with her OB/Gyn to ensure that no products of conception remained. A repeat pregnancy test 14 days later was negative.

Subject 1025/S026 (Zetonna): This was a 49-year-old white female with SAR, PAR, obesity, and postmenopausal syndrome on hormone replacement therapy (HRT). On Day 19 of study medication, she was hospitalized with multiple pulmonary emboli of the right middle and lower lung lobes. She was found to have a deep vein thrombosis in her leg. She discontinued study medication and HRT as a result of this event, but remained in the study for safety assessments. The pulmonary emboli event was resolving at the subject's final visit.

Subject 1026/S019 (Zetonna): This was a 41-year-old black female with history of PAR, SAR, headaches, and recurrent sinusitis. On Day 17, she experienced a headache that was not relieved with her regular migraine medications (acetaminophen with aspirin and sumatriptan). She was admitted to the hospital for pain control and discharged two days later with symptoms resolved. She continued dosing with study medication during her hospitalization and completed the study.

Subject 1004/S019 (Omnaris): This was a 56-year-old white female with history of PAR, postmenopausal bleeding, and depression. On Day 163, she was hospitalized for an elective hysterectomy due to her pre-existing history of moderate post-menopausal bleeding. She completed the study.

Subject 1005/S026 (Omnaris): This was a 60-year-old white female with history of PAR, hypertension, GERD, and headaches. On Day 153 of study medication, she was admitted to the hospital for an acute appendicitis without abscess. She underwent a laparoscopic appendectomy and was discharged the following day. She continued study medication and completed the study.

Subject 1008/S004 (Omnaris): This was a 57-year-old white female with a history of PAR, SAR, migraines, osteoarthritis, and multiple other medical problems. On Day 30, she was hospitalized for several of week of non-exertional chest pain, new onset shortness of breath, and elevated blood pressure with T-wave inversion on EKG with normal cardiac enzymes. A nuclear stress test and coronary artery angiography revealed severe single vessel (LAD) coronary artery disease. She experienced no complications following angioplasty and stent placement and was discharged after initiating medical management of her coronary artery disease with clopidogrel, metoprolol, and glyceryl trinitrate prn. She discontinued the study due to these events.

Subject 1015/S031 (Omnaris): This was a 27-year-old white male with PAR and SAR. On Day 153, he experienced a broken nose and mandible after a direct hit with a batted softball. He was hospitalized for a closed LaFort I fracture repair with internal maxillary fixation. He withdrew from the study due to this event.

Subject 1027/S021 (Omnaris): This was a 30-year-old-white female with a history of PAR, SAR, eczema, sinus headaches, and goiter. On Day 62, she experienced a bile duct stricture secondary to pancreatitis. She was not hospitalized for this event which was considered medically significant by the investigator. After consulting with a surgeon for ongoing symptoms, she had an elective cholecystectomy on Day 180 with a pathology report confirming the diagnosis of bile duct stricture/stenosis. She completed the study with her last dose of study medication on Day 183.

7.3.3 Dropouts and/or Discontinuations

The number of subjects who discontinued study medication early and the subset of early discontinuations due to adverse events are displayed in the table below. The number of adverse drop-outs differs slightly from those provided by the Applicant because one dropout from study 305 (withdrawal by subject) and one dropout from study 401 (other) actually reported AEs leading to discontinuation. The remainder of early discontinuations are not enumerated in Table 18, but were primarily due to "lost to follow-up", "withdrawal by subject", and "other".

Table 18. Subject Disposition by Study and Treatment Group

	Cic37	Cic74	Placebo	Omnaris	Total
Study 305 – n(%)[a]	282	282	283	--	847
Discontinued early	13 (4.6)	9 (3.2)	14 (4.9)	--	36 (4.3)
Adverse drop-outs	5 (1.8)	1 (0.4)	3 (1.1)	--	9 (1.1)
Application site pain	1[c]	1	0	--	2
Hypersensitivity	1	0	0	--	1
Pharyngitis streptococcal	1	0	0	--	1
Allergic respiratory symptom	0	0	1	--	1
Asthma	2	0	1	--	3
Rhinitis seasonal	0	0	1	--	1

	Cic37	Cic74	Placebo	Omnaris	Total
Study 306 – n(%)[a]	282	282	283	--	846
Discontinued early	25 (8.9)	27 (9.6)	36 (12.7)	--	88 (10.4)
Adverse drop-outs	3 (1.1)	6 (2.1)	4 (1.4)	--	13 (1.5)
Appendicitis	0	1	0	--	1
Herpes zoster	0	1	0	--	1
Influenza	0	0	1	--	1
Pneumonia viral	0	0	1	--	1
Sinusitis	1	0	0	--	1
Tonsillitis streptococcal	1	0	0	--	1
Upper respiratory tract infection	0	0	1	--	1
Headache	0	1	0	--	1
Sinus headache	0	1	0	--	1
Tic	1	0	0	--	1
Asthma	0	0	2	--	2
Epistaxis	0	2	0	--	2
Study 308 – n (%)[a]	--	47	42	--	89
Discontinued early	--	0	1 (2.4)	--	1 (1.1)
Adverse drop-outs	--	0	0	--	0
Study 401 – n(%)[b]	--	367	--	370	737
Discontinued early	--	50 (13.6)	--	45 (12.2)	95 (12.9)
Adverse drop-outs	--	13 (3.5)	--	13 (3.5)	26 (3.5)
Angina pectoris	--	0	--	1	1
Coronary artery disease	--	0	--	1	1
Ear pain	--	1	--	0	1
Tinnitus	--	0	--	1	1
Vision blurred	--	1	--	0	1
Bronchitis	--	1	--	0	1
Pelvic inflammatory disease	--	1	--	0	1
Upper respiratory tract infection	--	1	--	1	2
Facial bones fracture	--	0	--	1	1
Mucosal excoriation	--	0	--	1	1
Blood pressure increased	--	0	--	1	1
Intraocular pressure increased	--	1	--	0	1
Dizziness	--	0	--	1	1
Headache	--	2	--	1	3
Lacunar infarction	--	1	--	0	1
Nerve compression	--	1	--	0	1
Asthma	--	2	--	1	3
Epistaxis	--	1	--	3	4
Nasal congestion	--	0	--	1	1
Nasal discomfort	--	2	--	2[d]	3
Pulmonary embolism	--	1	--	0	1
Sneezing	--	1	--	0	1
Urticaria	--	0	--	1	1
Hematoma	--	0	--	1	1

Some patients experienced more than one AE leading to discontinuation; therefore, the number of PTs under adverse drop-outs may be greater than the total number of adverse drop-outs.
[a]n=ITT population in studies 305, 306, and 308
[b]n=safety population in study 401
[c]One additional adverse drop-out originally categorized by Applicant as "withdrawal by subject"
[d]One additional adverse drop-out originally categorized by Applicant as "other"
Sources: Module 5.3.5.1, Data Analysis Data, Analysis Dataset Legacy, ADAE.xpt for each study; SEP060-305 CSR Table 24, p103; SEP060-306 CSR Table 28, p124; SEP060-308 CSR p91; SEP060-401 CSR, Table 20, p85

7.3.4 Significant Adverse Events

The majority of AEs were mild to moderate in severity. Most severe AEs were single events, and none were related to local nasal or ocular toxicity. Serious AEs, AEs leading to treatment discontinuation, and local AEs are discussed in Sections 7.3.2, 7.3.3, and 7.3.5, respectively.

7.3.5 Submission Specific Primary Safety Concerns

Due to the local action of ciclesonide nasal aerosol and the occurrence of two nasal septum perforations in the Zetonna development program for adolescents and adults, local nasal-related TEAEs were the primary safety concern in this submission. Each study included EENT examinations by the site investigator, or if warranted by an otolaryngologist, at regular intervals throughout the duration of the study to detect nasal-related AEs. Patients with abnormal nasal examinations at screening were excluded from the studies, and study 401 stratified patients by risk for nasal-related AEs. As in the original NDA, the Applicant analyzed specific local TEAEs post-hoc by grouping similar PTs to minimize splitting. The Applicant included the following PTs under the umbrella category of "Nasal Mucosal/Septum Disorders": nasal mucosal disorders, nasal septum disorders, nasal septum ulceration, nasal ulcers, and nasal septum perforation. This review analyzed nasal-related TEAEs in a similar fashion, but included the additional PTs mucosal excoriation, mucosal erosion, scab, and scratch, where relevant. Overall, there was no apparent dose response relationship with respect to nasal-related TEAEs. Although more local TEAEs occurred in the Cic74 group in study 306, the incidence was approximately equal to that in the placebo group. Furthermore, the opposite pattern was observed in study 305, in which more local TEAEs occurred in the Cic37 group. In study 401, the incidence of nasal-related TEAEs, with the exception of nasal discomfort/application site pain, was balanced between the Zetonna and Omnaris treatment groups over a 6-month treatment period. The most frequent nasal-related TEAE was epistaxis. The occurrence of erosive or ulcerative nasal lesions was low across all studies, and there were no reports of nasal septum perforations in any study. The table below summarizes the incidence of nasal-related TEAEs by treatment group in each study.

Table 19. Nasal-related TEAEs by Study and Treatment Group

	Study 305			Study 306			Study 308		Study 401	
	Cic37	Cic74	Placebo	Cic37	Cic74	Placebo	Cic74	Placebo	Cic74	Omn200
N (%)	282	282	283	282	281	283	47	42	367	370
Epistaxis	13 (5)	6 (2)	10 (4)	20 (7)	27 (10)	26 (9)	2 (4)	2 (5)	22 (6)	26 (7)
Nasal discomfort, application site pain	9 (3)	3 (1)	4 (1)	7 (2)	10 (4)	9 (3)	1 (2)	1 (2)	13 (4)	4 (1)
Nasal Mucosal / Septum Disorders										
Erosions / ulcerations	0	1 (0.4)	0	1 (0.4)	2 (0.7)	1 (0.4)	0	2 (5)	3 (0.8)	4 (1)
Non - ulcerative lesions	2 (0.7)	0	2 (0.7)	1 (0.4)	5 (2)	6 (2)	0	0	1 (0.3)	2 (0.5)

Abbreviations: Cic37=ciclesonide nasal aerosol 37 mcg once daily, Cic74=ciclesonide nasal aerosol 74 mcg once daily, Omn200=Omnaris nasal spray 200 mcg once daily
N=ITT populations for studies 305, 306, and 308 and safety population for study 401
Epistaxis category includes the following MedDRA PTs: epistaxis, mucosal hemorrhage
Nasal discomfort/application site pain category includes the following MedDRA PTs: application site burn, application site discomfort, application site pain, application site paraesthesia, application site pruritis, nasal discomfort, rhinalgia
Nasal Mucosal/Septum Disorders category includes the following MedDRA PTs: mucosal excoriation, mucosal erosion, nasal mucosal disorder, nasal septum disorder, nasal septum ulceration, nasal ulcer, nasal septum perforation, scab, scratch
Non-ulcerative lesions include adverse events such as abrasions, excoriations, scabs, scratches, and irritation.
Source: Reviewer analysis of ADAE.xpt datasets for SEP060-305, SEP060-306, SEP060-308, and SEP060-401

Study 401 was designed to assess the long-term risk for local nasal and ocular effects with Zetonna as compared to Omnaris. The primary endpoint of the study was the number and percentage of subjects experiencing Nasal Mucosal/Septum Disorders, as defined above, or Nasal Septum Perforations as TEAEs. As displayed in Table 19 and Table 20, the combined incidence of Nasal Mucosal Disorders, Nasal Septum Disorders, and Nasal Septum Perforations was low overall and balanced between Zetonna and Omnaris treatment groups.

Although the primary objective of study 401 was to assess local nasal toxicity, ocular examinations (slit lamp examination, assessment of intraocular pressure, and best corrected visual acuity) were also performed at screening/baseline and at months 3 and 6 by an ophthalmologist blinded to treatment assignment. The PMR included an evaluation of ocular toxicity given that prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation. However, cataract formation resulting from the use of corticosteroids typically does not occur in the first 6 months of exposure; consequently, a safety trial of at least 18-24 months duration would be required to definitively evaluate the potential for a drug to cause cataract formation. In addition, study 401 could not fully evaluate the potential to cause defects in fields of vision related to glaucoma because visual fields were not assessed and the study duration was too short. Nonetheless, this study was of sufficient duration to adequately monitor the risk for increased intraocular pressure.

The LOCS III grading system was used to assess lens opacities. Class I events were defined as an increase in lens opacity from baseline of ≥0.5 in nuclear opalescence,

≥0.8 in cortical, ≥0.5 in posterior subcapsular, or cataract surgery. Increased intraocular pressure was defined as an increase of ≥7 mmHg from baseline or a change to > 21 mmHg. For the assessment of best corrected visual acuity, the Snellen visual acuity chart was converted to logMAR as recommended by the Agency. The protocol defined a worsening of best-corrected visual acuity as an increase in logMAR of ≥ 0.2.

Baseline values for lens opacities, intraocular pressure, and visual acuity were similar between treatment groups (data not shown). Although there was a numerical difference in the incidence of increased intraocular pressure events, in general, the number of protocol-defined ocular safety events was similar between Zetonna and Omnaris treated patients over the 6-month treatment period. A summary of the overall incidence of nasal and ocular safety TEAEs from study 401 is provided in the table below.

Table 20. Nasal and Ocular TEAEs: Study 401

	Zetonna 74 mcg (N=367)	Omnaris 200 mcg (N=370)
Nasal TEAEs		
Nasal mucosal disorder	2 (0.5)[d]	0
Nasal septum disorder	0	0
Nasal septum ulceration	1 (0.3)	4 (1.1)
Nasal ulcer	0	0
Nasal septum perforation	0	0
Any nasal TEAE	54 (14.4)	44 (11.9)
Ocular safety endpoints		
Developing/worsening lens opacities[a]	51 (13.9)	53 (14.3)
Increased intraocular pressure[b]	9 (2.5)	6 (1.6)
Worsening visual acuity[c]	1 (0.3)	2 (0.5)

[a] A LOCS III positive Class I lens event was defined as an increase from baseline in any of the following events in either eye: LOCS III grade of ≥0.5 (nuclear opalescence), LOCS III grade of ≥ 0.8 (cortical), LOCS III grade of ≥ 0.5 (posterior subcapsular)
[b] Defined as increase of ≥7 mmHg from baseline in intraocular pressure or a change to > 21 mm Hg in either eye
[c] Defined as a logMAR increase of ≥0.2
[d] Both events were nasal mucosal ulcerations coded as preferred term nasal mucosal disorder
Source: Module 5.3.5.1, SEP060-401 CSR, Tables 14 and 24, p76 and 96

There was one report of cataracts development during the study. Subject 1010/S024, a 20-year-old male in the Zetonna treatment group developed a posterior subcapsular cataract in the left eye, which was identified at the final ocular examination on Day 188. His subcapsular LOCS III grade was 0.1 at baseline and throughout the study, but increased to 0.8 in the left eye only at the final visit, representing a positive Class I lens event. The cataract was graded as mild in severity and required no treatment. The event was ongoing at the time of final contact with the subject.

Additionally, there was one report of an increased intraocular pressure TEAE. Subject 1024/S018, a 39-year-old female in the Zetonna treatment group experienced an increase in intraocular pressure in her right eye on Day 99. At baseline, her intraocular pressure was 14 mmHg (right eye) and 16 mmHg (left eye). At Visit 5 (Day 99), her intraocular pressure was 19 mmHg (right) and 16 mmHg (left). The increase of 5 mmHg in the right eye was recorded as an AE of moderate severity and probably related to study medication. She was consequently discontinued from treatment due to the TEAE, but remained in the study for safety assessments. Repeat measurements were 20 mmHg (right) and 17 mmHg (left) on Day 113 and 16 mmHg (right) and 15 mmHg (left) on Day 134, at which time the AE was considered resolved.

Because a 6-month study is not of sufficient duration to definitively assess corticosteroid-related ocular toxicity, the Zetonna prescribing information will retain the class labeling Warnings and Precautions statement for glaucoma and cataracts.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse events reported across the four studies were headache, epistaxis, and cough. This is similar to the frequent adverse events observed in the Zetonna development program for adolescents and adults and with other intranasal corticosteroids. Table 21 displays common TEAEs reported in ≥2% of subjects in studies 305, 306, and 401 and in ≥3% of subjects in study 308.

Table 21. Common TEAEs by Study and Treatment Group

System Organ Class / Preferred Term	Study 305			Study 306			Study 308		Study 401	
	Cic37 (N=282)	Cic74 (N=282)	PBO (N=283)	Cic37 (N=282)	Cic74 (N=281)	PBO (N=283)	Cic74 (N=47)	PBO (N=42)	Cic74 (N=367)	Omn (N=370)
Overall – any TEAE	67 (23.8)	51 (18.1)	59 (20.8)	115 (40.8)	108 (38.4)	115 (40.6)	20 (42.6)	19 (45.2)	121 (33)	114 (30.8)
Ear and Labyrinth Disorders										
Ear Pain	4 (1.4)	0	1 (0.4)	3 (1.1)	4 (1.4)	8 (2.8)	0	0	2 (0.5)	0
Gastrointestinal Disorders										
Abdominal discomfort	0	0	0	0	0	0	1 (2.1)	0	0	0
Abdominal pain upper	4 (1.4)	5 (1.8)	1 (0.4)	6 (2.1)	13 (4.6)	12 (4.2)	1 (2.1)	2 (4.8)	0	1 (0.3)
Diarrhea	0	0	1 (0.4)	3 (1.1)	6 (2.1)	3 (1.1)	0	0	0	0
Vomiting	5 (1.8)	2 (0.7)	3 (1.1)	8 (2.8)	6 (2.1)	4 (1.4)	2 (4.3)	0	1 (0.3)	0
General Disorders and Administration Site Conditions										
Pyrexia	5 (1.8)	7 (2.5)	4 (1.4)	18 (6.4)	17 (6.0)	12 (4.2)	2 (4.3)	1 (2.4)	1 (0.3)	1 (0.3)
Infections and Infestations										
Gastroenteritis viral	3 (1.1)	2 (0.7)	0	5 (1.8)	5 (1.8)	6 (2.1)	0	0	6 (1.6)	0
Influenza	1 (0.4)	2 (0.7)	0	0	0	6 (2.1)	0	0	7 (1.9)	3 (0.8)
Nasopharyngitis	1 (0.4)	1 (0.4)	0	9 (3.2)	13 (4.6)	10 (3.5)	0	0	12 (3.3)	11 (3.0)
Pharyngitis streptococcal	1 (0.4)	2 (0.7)	1 (0.4)	11 (3.9)	8 (2.8)	11 (3.9)	1 (2.1)	1 (2.4)	1 (0.3)	1 (0.3)
Sinusitis	1 (0.4)	1 (0.4)	0	6 (2.1)	4 (1.4)	5 (1.8)	0	0	10 (2.7)	7 (1.9)
(Viral) Upper respiratory tract infection	1 (0.4)	0	3 (1.1)	24 (8.5)	25 (8.9)	18 (6.4)	1 (2.1)	2 (4.8)	17 (4.6)	13 (3.5)
Injury, Poisoning, and Procedural Complications										
Excoriation	0	2 (0.7)	0	0	0	0	0	2 (4.8)	2 (0.5)	0
Nervous System Disorders										
Headache	14 (5)	10 (3.5)	9 (3.2)	31 (11)	25 (8.9)	25 (8.8)	3 (6.4)	1 (2.4)	4 (1.1)	9 (2.4)
Respiratory, Thoracic, Mediastinal Disorders										
Cough	4 (1.4)	4 (1.4)	6 (2.1)	21 (7.4)	15 (5.3)	19 (6.7)	2 (4.3)	1 (2.4)	4 (1.1)	2 (0.5)
Epistaxis	12 (4.3)	6 (2.1)	10 (3.5)	20 (7.1)	26 (9.3)	26 (9.2)	1 (2.1)	2 (4.8)	22 (6.0)	26 (7.0)
Nasal discomfort	5 (1.8)	0	0	4 (1.4)	8 (2.8)	6 (2.1)	1 (2.1)	1 (2.4)	6 (1.6)	4 (1.1)
Oropharyngeal pain	4 (1.4)	0	2 (0.7)	15 (5.3)	10 (3.6)	17 (6.0)	0	4 (9.5)	3 (0.8)	3 (0.8)
Sneezing	0	1 (0.4)	0	1 (0.4)	0	7 (2.5)	0	0	6 (1.6)	0
Skin and Subcutaneous Tissue Disorders										
Rash	0	0	1 (0.4)	6 (2.1)	2 (0.7)	5 (1.8)	2 (4.3)	1 (2.4)	0	1 (0.3)
Urticaria	2 (0.7)	1 (0.4)	1 (0.4)	2 (0.7)	7 (2.5)	1 (0.4)	0	0	1 (0.3)	1 (0.3)

Abbreviations: Cic37=ciclesonide nasal aerosol 37 mcg once daily, Cic74=ciclesonide nasal aerosol 74 mcg once daily, PBO=placebo, Omn=Omnaris 200 mcg once daily
N=ITT population (studies 305, 306, 308) or safety population (study 401)
Table displays TEAEs reported in ≥2% of subjects (studies 305, 306, 401) or in ≥3% of subjects (study 308)
Sources: Module 5.3.5.1, SEP060-305 CSR, Table 14.3.1.1; SEP060-306 CSR Table 14.3.1.7; SEP060-308 CSR Table 14.3.1.1; SEP060- 401 Table 14.3.1.2

7.4.2 Laboratory Findings

Clinical laboratory measures included serum chemistry, hematology and urinalysis. Baseline measurements were collected in studies 305, 306, and 308; however, end of study measurements were only collected in studies 306 and 308 at 12 and 6 weeks, respectively. Clinical significance was determined by the Investigator, who reported

clinically significant lab abnormalities as TEAEs. There was no pattern or safety signal identified from the treatment-emergent laboratory findings.

7.4.3 Vital Signs

Vital sign measures included heart rate, blood pressure, respiratory rate, and body temperature. Vital signs were obtained at each visit in studies 305, 306, and 308 and at screening only in study 401. Changes from baseline in mean and median values were minimal and similar across treatment groups with no apparent trends or safety concerns.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed in any of the studies.

7.4.5 Special Safety Studies/Clinical Trials

EENT exams
Due to concern for local toxicity, ear, eye, nose, and throat (EENT) exams were performed at all clinic visits in each study. In general, abnormal findings were similar between groups. The percentage of patients with worsening clinical exams was low and similar between groups. Clinically significant findings were reported as adverse events which have already been discussed.

Assessments for HPA axis suppression
An evaluation of the effects of ciclesonide nasal aerosol 74 mcg once daily on the HPA axis in children 6-11 years of age was performed in study 308. Subjects were randomly assigned in a 1:1 ratio to double-blind treatment with either ciclesonide nasal aerosol 74 mcg once daily or placebo nasal aerosol once daily for 6 weeks. The effects of ciclesonide nasal aerosol on the HPA axis were assessed primarily based on changes in serum cortisol levels from predose to the end of the 6-week treatment period. Additionally, the effects of ciclesonide on the HPA axis were assessed based on changes in 24-hour urinary free cortisol levels from pre-dose to the end of the 6-week treatment period.

At Visit 4 (pre-dose), a single blood sample was collected approximately 30 minutes before the first double-blind treatment dose was administered, which served as a stable drug-free control sample for all subjects. At Visit 7 (last dose), serial blood samples for steady-state serum concentrations of ciclesonide and des-ciclesonide were collected starting in the morning of Day 42 (- 1 to + 3) immediately prior to administration of the last study medication dose (i.e., at the same time as the predose cortisol sample), and after dosing at 30, 60, 90 minutes and 2, 4, 8, 12, 16, and 24 hours. Systemic levels of ciclesonide and desciclesonide were quantified by a validated bioanalytical method

employing a sensitive assay with an LLOQ of 1.0 pg/mL for both ciclesonide and des-ciclesonide.

At the end of the 6-week treatment period, the LS means (SE) change from baseline in serum cortisol $AUC_{(0-24)}$ was 5.9 (5.6) mcg•hour/dL and 1.7 (5.2) mcg•hour/dL for placebo and ciclesonide nasal aerosol, respectively. The LS mean difference in serum cortisol $AUC_{(0-24)}$ change from baseline for the PP population was 7.6 mcg•hour/dL (95% CI: -7.4, 22.6) for ciclesonide nasal aerosol 74 mcg vs placebo. Change from baseline (Visit 4) to end of study (Visit 7) in serum cortisol $AUC_{(0-24)}$ is summarized by treatment group in Table 22, and serum cortisol concentrations by treatment group are displayed for the PP population in Figure 5. In addition, change from baseline in 24-hour urinary free cortisol excretion, corrected for urine creatinine, is summarized in Table 23. In sum, the data from this study indicate that the HPA axis effects following 6 weeks of treatment with ciclesonide nasal aerosol 74 mcg daily were not significantly different from placebo.

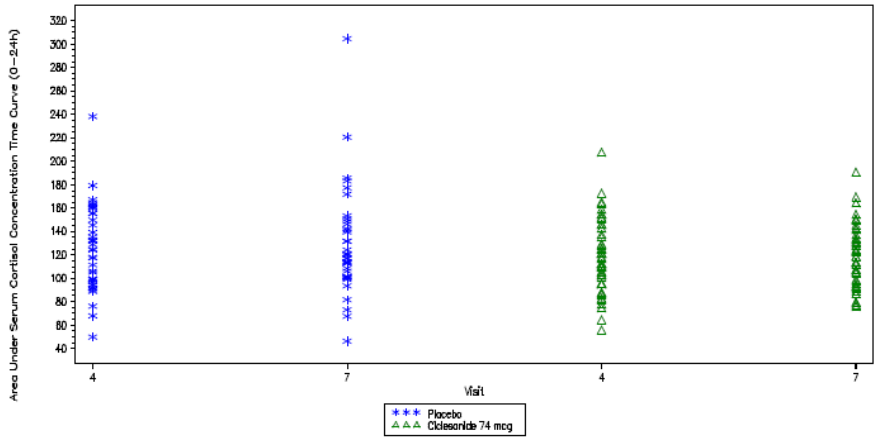
Table 22, Change from Baseline in Serum Cortisol $AUC_{(0-24)}$: Study 308

	Placebo (N = 39)		Ciclesonide 74 mcg (N = 46)	
	Value	Change from baseline	Value	Change from baseline
Baseline (Visit 4)				
n	39		46	
Mean (SD)	125.6 (36.6)		118.5 (31.2)	
Median	124.6		114.3	
Min, Max	50, 238		56, 208	
25^{th}, 75^{th} percentiles	96.9, 155.5		95.7, 142.4	
10^{th}, 90^{th} percentiles	88.7, 164.4		81.7, 158.7	
End of Treatment (Visit 7)				
n	39	39	46	46
Mean (SD)	127.9 (44.9)	2.3 (51.7)	118.9 (26.2)	0.4 (29.7)
Median	117.2	-2.3	118.5	2.7
Min, Max	46, 304	-115, 229	76, 191	-68, 64
25^{th}, 75^{th} percentiles	101.3, 146.1	-17.8, 12.7	97.7, 134.3	-19.9, 18.4
10^{th}, 90^{th} percentiles	81.5, 183.0	-46.9, 47.3	86.7, 150.5	-42.1, 37.6
LS Mean (SE)		5.9 (5.6)		-1.7 (5.2)
Diff Placebo LS Mean (SE)				7.6 (7.5)
95% CI				(-7.4, 22.6)

Abbreviations: SD = standard deviation; SE = standard error; LS Mean = least squares means;
Diff Placebo LS Mean = Difference from placebo in LS Mean.
Note: Difference was calculated as placebo – ciclesonide. The change from baseline in serum cortisol $AUC_{(0-24)}$ was analyzed using an ANCOVA model with baseline AUC value as a covariate and center, treatment, and age group as fixed effects, where baseline values for serum cortisol were collected at Visit 4 (Day -1).

AUC represented as mcg●hour/dL
N=Per Protocol population
Source: Module 5.3.5.1, SEP060-308 CSR, Table 11, p82

Figure 5. Vertical Scatter Plot of Serum Cortisol $AUC_{(0-24)}$: Study 308



AUC represented as mcg●hour/dL
N=Per Protocol population
Source: Module 5.3.5.1, SEP060-308 CSR, Figure 2, p83

Table 23. Change from Baseline in Urinary Free Cortisol*: Study 308

	Placebo (N = 39)		Ciclesonide Nasal Aerosol 74 mcg (N = 46)	
	Value	**Change from baseline**	**Value**	**Change from baseline**
Baseline (Visit 4)				
n	39		45	
Mean (SD)	27.6 (17.4)		26.1 (13.10)	
Median	21.0		22.0	
Min, Max	11, 103		8, 62	
25^{th}, 75^{th} percentiles	16.9, 35.1		16.6, 32.7	
10^{th}, 90^{th} percentiles	13.1, 51.0		10.5, 41.9	
End of Treatment (Visit 7)				
n	39	39	46	45
Mean (SD)	27.3 (11.5)	-0.3 (17.0)	28.1 (25.8)	2.2 (20.5)
Median	25.7	1.9	20.6	-1.8
Min, Max	11, 65	-75, 31	8, 179	-16, 120
25^{th}, 75^{th} percentiles	19.7, 33.6	-4.2, 6.2	16.4, 30.8	-4.5, 4.5
10^{th}, 90^{th} percentiles	14.8, 43.9	-23.7, 17.4	12.9, 42.9	-13.3, 13.5
LS Mean (SE)		1.4 (2.9)		3.3 (2.7)
Diff Placebo LSM (SE)				-1.9 (3.9)
95% CI				(-9.6, 5.9)

Note: Difference was calculated as Placebo – ciclesonide. LS Mean = Least Squares Means; SE = standard error; Diff Placebo LSM = Difference from Placebo in Least Squares Means. The change from baseline in urinary free cortisol (corrected for urine creatinine) was analyzed using an ANCOVA model with baseline value as a covariate and center, treatment, and age groups as factors where baseline was the urinary free cortisol-corrected for urine creatinine at Visit 4.

*Urinary free cortisol corrected for urine creatinine and represented as mcg/g.
N=Per Protocol population
Source: Module 5.3.5.1, SEP060-308 CSR, Table 11, p84

7.4.6 Immunogenicity

Immunogenicity was not specifically addressed as ciclesonide is a small molecular entity with no known immunogenic potential.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The clinical trial data in adolescents and adults demonstrated a clear dose response for nasal-related AEs; however, in studies 305 and 306, the same degree of dose dependency for adverse events is not present. Interestingly, in study 305, more patients from the lower 37 mcg dose group experienced local nasal toxicity such as epistaxis, application site pain/discomfort, and nasal mucosal/septum disorders. By contrast, the frequency of nasal toxicity AEs in study 306 was relatively balanced between both ciclesonide dose groups.

7.5.2 Time Dependency for Adverse Events

There was no apparent time dependency for the most commonly observed TEAEs or local TEAEs.

7.5.3 Drug-Demographic Interactions

There were no apparent drug-demographic interactions based on subgroup analyses.

7.5.4 Drug-Disease Interactions

There was no assessment of drug-disease interactions in this submission.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were included in this submission.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No carcinogenicity studies were included in this submission. Ciclesonide has demonstrated no carcinogenic potential in nonclinical studies.

7.6.2 Human Reproduction and Pregnancy Data

The use of ciclesonide nasal aerosol during pregnancy and lactation has not been evaluated. There were no pregnancies in the pediatric clinical studies in patients 6 to 11 years of age. During study 401, two pregnancies were reported in Zetonna-treated patients. One subject had a positive pregnancy test at the end of the 6 month study; the outcome of the pregnancy is unknown. One subject experienced a miscarriage 2 months after the last dose of study medication; a brief narrative of this event is provided in Section 7.3.2 Nonfatal Serious Adverse Events.

7.6.3 Pediatrics and Assessment of Effects on Growth

The growth effects of ciclesonide in pediatric patients were previously studied in the Alvesco development program, which demonstrated no differences in growth velocity in prepubescent children treated with Alvesco versus placebo. No additional growth studies were included in this submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are no data on the effects of acute or chronic overdosage with ciclesonide nasal aerosol. Overdosage and abuse or dependence potentials of ciclesonide nasal aerosol were not evaluated in pediatric clinical studies. However, no cases of overdose were reported and drug abuse potential, withdrawal, and rebound are not anticipated due to the low systemic bioavailability and nature of the drug.

7.7 Additional Submissions / Safety Issues

The Applicant submitted an Annual Report on March 14, 2014 along with Periodic Safety Update Reports (PSUR) on January 31, May 8, and August 13, 2014. The nature and distribution of the adverse events were consistent with current labeling and with the safety data in this submission. No new safety signals were identified.

8 Postmarket Experience

Based on PSURs and annual reports for Zetonna submitted to the NDA since approval in 2012, the postmarketing safety profile is similar to the safety profile observed in clinical trials with no new safety issues identified.

9 Appendices

9.1 Literature Review/References

The Applicant provided 17 literature references in this submission; however, none were specifically related to the safety or efficacy of ciclesonide nasal aerosol. A PubMed search using the term “ciclesonide nasal aerosol” retrieved 11 articles, none of which changed the risk-benefit profile of this drug.

9.2 Labeling Recommendations

At the time of this review, labeling discussions between the Applicant and the Agency were ongoing. Major labeling recommendations include the revision of Sections 5 and 6, Warnings and Precautions and Adverse Reactions to include results from study 401 and Sections 8.4 and 12.2 to include efficacy and safety data for pediatric patients 6 to 11 years of age.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was not held for this supplemental NDA. Zetonna Nasal Aerosol is already approved for the treatment of SAR and PAR in patients 12 years of age and older. The Applicant is not seeking to expand the indication, and no new safety concerns were identified in this supplement. Therefore, an AC discussion was not warranted.

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/s/

STACY J CHIN
09/10/2014

ANTHONY G DURMOWICZ
09/10/2014