

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202129Orig1s000

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 202129
Request for Ophthalmology Consultation

NDA 202129
SDN-29

Date of Document: 12/9/2011
Date of Consultation: 12/14/2011
Date of Review: 1/3/2012

Applicant:

Nycomed GMBH
c/o Sunovion Pharmaceuticals Inc.
84 Waterford Drive
Marlborough, MA 07152-7010

Drug:

ciclesonide nasal aerosol

Pharmacologic Category:

steroid

Proposed Indication:

treatment of seasonal allergic conjunctivitis
and treatment of perennial allergic
conjunctivitis

Consultation Comments/Special Instructions:

We are evaluating NDA 202129 for an HFA formulation of ciclesonide, a nasal steroid proposed for the treatment of seasonal and perennial allergic rhinitis. For this application, the sponsor did not conduct specific ocular safety studies, but made reference to studies from the Omnaris program (NDA 22004), an aqueous formulation of the same active moiety. However, the systemic and local exposure to the HFA product is greater than Omnaris. Also, two nasal septal perforations were observed in 2 week pivotal trials with the HFA formulation, raising concerns of local safety. As such, we are requiring a post-marketing safety study to assess for local toxicity, including ocular findings. The sponsor has submitted a study synopsis for the required study.

This submission is located in the EDR:

\\CDSESUB1\EVSPROD\NDA202129\202129.enx. eCTD sequence 0025.

Please provide comments on the adequacy of the proposed ocular assessments in the safety trial.

STUDY SEP060-401: A 6-Month Randomized, Open-Label, Parallel Group, Safety Study Of Ciclesonide Nasal Aerosol And Ciclesonide Nasal Spray (Omnaris®) In Subjects 12 Years And Older With Perennial Allergic Rhinitis

Reviewer's Comments: *Comments regarding this synopsis are limited to ophthalmic safety evaluations.*

Number of Subjects (planned): Approximately 600 subjects will be randomized in a 1:1 ratio to either ciclesonide nasal aerosol 74 mcg or ciclesonide aqueous nasal spray 200 mcg (approximately 300 subjects per treatment group).

Study Design: This is a 6-month, multicenter, randomized, open-label, parallel group, safety study of ciclesonide nasal aerosol and ciclesonide aqueous nasal spray administered once daily to male and female subjects 12 years and older diagnosed with PAR.

In order to limit observer bias, study medication will be dispensed and collected by personnel not otherwise involved in safety assessments. Access to treatment assignments will also be restricted from any personnel involved in data cleaning process. Nasal and ocular assessments conducted after randomization will be conducted by physicians who have no knowledge of treatment assignment.

This study will consist of the following periods/visits:

Screening (Visit 1): 3 to 30 days prior to Visit 2

Treatment period (Visit 2 through Visit 8): At Visit 2, subjects will be randomized to treatment with either ciclesonide nasal aerosol 74 mcg or ciclesonide nasal spray 200 mcg for 6 months of treatment. Visit 8 will be the end of study visit.

Subjects will undergo evaluations to confirm study eligibility, a physical examination (including vital sign measurements), serum pregnancy tests (all females). Subjects will undergo a nasal examination (5 to 10 minutes after decongestion with 0.05% oxymetazoline in each nostril) to evaluate the presence of infection, significant anatomic abnormality, ulceration of the mucosa, blood in the nose, or any other clinically relevant finding. The nasal examination will be conducted by a physician. Subjects will also undergo an ocular examination (slit lamp and assessment of intraocular pressure). The ocular examination will be conducted by a physician within 7 days prior to Visit 2. To qualify for randomization, subjects must have had significant symptoms for the last 12 months that would require treatment.

Subjects who meet the eligibility criteria will return to the clinic 3 to 30 days after Visit 1 to begin the **open-label treatment period (Visit 2)**. At Visit 2, subjects will undergo a nasal examination (5 to 10 minutes after decongestion with 0.05% oxymetazoline in each nostril) to evaluate the presence of infection, significant anatomic abnormality, ulceration of the mucosa, blood in the nose, or any other clinically relevant finding. The nasal examination will be conducted by a physician (or designee) blinded to treatment assignment; where possible, this should be the same person who conducted the Visit 1 exam. Clinic staff will access the IVR system to randomly assign subjects to treatment with either ciclesonide nasal aerosol 74 mcg or ciclesonide aqueous nasal spray 200 mcg. Randomization will be stratified by current findings of nasal mucosal or septal disorders.

Subjects will administer study medication once daily in the morning (1 actuation per nostril for ciclesonide nasal aerosol and 2 sprays per nostril for ciclesonide nasal spray) for 6 months. The date of time and dosing will be recorded in subject diaries. Study medication will be administered by the subject at home on non-clinic visit days. On clinic visit days, study medication will be administered by the subject at the clinic under supervision of clinic staff, and the investigator (or designee) will record the date and time of dosing in the electronic case report form (eCRF).

Subjects will have clinic visits once per month (ie, every 30 ± 7 days) during the study. Safety will be assessed throughout the study by monitoring AEs (including specific nasal AEs) and concomitant medication use. Subjects will have decongested nasal examinations at Visit 8, and an ocular examination (slit lamp and intraocular pressure assessment) at Visit 8. The nasal and ocular examinations will be conducted by a physician (or designee) blinded to treatment assignment; where possible, this should be the same person who conducted these exams at the prior visits.

Treatment compliance will be assessed throughout the study based on subject report of study medication administration date and time in subject diaries.

Duration of Treatment: The total duration of subject participation will be approximately 7 months (with a 3- to 30-day Screening period followed by a 6-month Treatment period).

Investigational Product, Dosage and Mode of Administration: Ciclesonide nasal aerosol is provided in a canister that delivers 37 mcg of ciclesonide per actuation. Ciclesonide nasal aerosol is to be administered once daily as 1 actuation in each nostril (for a total daily dose of 74 mcg). Each canister contains 60 actuations. The product uses the propellant hydrofluoroalkane-134a and includes ethanol (b) (4)

Reviewer's Comments: *Subjects may not have a history of ocular injury/surgery in the last 6 months (including LASIK eye surgery), bacterial or viral infection of the eyes or upper respiratory tract within 14 days of the Screening visit (Visit 1), current or history of glaucoma or ocular herpes simplex, current cataract or previous history of cataract surgery, use of chronic treatment with agents known to promote the development of cataracts (potassium-sparing diuretics and allopurinol). Acceptable.*

Table 1: Schedule of Assessments

Period	Screen	Treatment						
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Day	3-30 days prior to Visit 2	1	30±7	60±7	90±7	120±7	150±7	180±7
Informed Consent/Assent	X							
Inclusion/Exclusion Review	X							
Demography	X							
Register subject via IVRS	X							
Medical History	X							
Height and Weight	X							
Vital Sign Measurements	X							
Physical Examination (including vital signs)	X							
Blinded Nasal Examination ^a	X	X						X
Blinded Ocular Examination ^b		X						X
Serum Pregnancy Test ^c	X							
Randomization via IVRS		X						
Dispense Study Medication ^d		X	X	X	X	X	X	
Administer Study Medication ^d		X	X	X	X	X	X	X
Dispense Diary Card		X	X	X	X	X	X	
Collect/Review Diary Card			X	X	X	X	X	X
Collect Used/Unused Study Medications			X	X	X	X	X	X
Adverse event and Concomitant Medication Recording ^e	X	X	X	X	X	X	X	X
Schedule Next Visit ^f	X	X	X	X	X	X	X	

Abbreviations: EOS = End of Study; ET = Early Termination; IVRS = interactive voice 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.

^c Within 7 days prior to Visit 2. Slit lamp examination and measurement of intraocular pressure by a physician blinded to treatment assignment.

^e Subjects with a positive serum pregnancy test will not be allowed to continue in the study.

^d Preparation and administration of study medication is as follows for Visit 2:

- Investigator (or designee) will instruct the subject on proper administration of study medication.
- Investigator (or designee) will prime the ciclesonide nasal aerosol by depressing the canister 3 times in a well-ventilated area. Investigator will prime the ciclesonide nasal spray by depressing the canister 7 times in a well-ventilated area.
- Investigator (or designee) will observe subject administer the study medication at the study site at Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, and Visit 8, and record the date and time of dosing in the eCRF.

- Subject will administer study medication at home in the morning on non-clinic visit days, and record the date and time of dosing in the Subject Diary.

- Subject will be instructed to withhold study medication until subject arrives at the clinic at Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, and Visit 8.

- Investigator (or designee) will review study medication administration instructions with the subject at each clinic visit.

^e Adverse Event and concomitant medication information will be collected after subjects have signed informed consent.

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

Reviewer's Comments: *Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Use of corticosteroids may result in posterior subcapsular cataract formation. As proposed in the submitted synopsis, the SEP060-401 is not adequate to assess ocular toxicity.*

The protocol should specify that the ocular examinations will be performed by a physician with training in the use of a slit lamp.

Best Corrected Visual acuity should be assessed at each ophthalmic evaluation. Intraocular pressure should be assessed at Visit 1 (Baseline), Visit 5 (Day 90 ± 7), and end of the trial.

Cataract formation from the use of corticosteroids typically does not occur in the first six months of exposure. Intraocular steroids typically take 18-24 months to cause cataracts. The seven month exposure proposed in this study synopsis is not likely to definitively evaluate the potential for ciclesonide nasal aerosol to result in cataract formation. To definitively evaluate the potential for this drug product to cause cataract formation, a safety trial of at least 18 -24 months duration would be required.

The protocol should specify a standardized grading system for the evaluation of cataracts (e.g. Lens Opacities Classification System II or III) should it be necessary.

Recommendations/Conclusions:

1. As proposed in the submitted synopsis, SEP060-401 is not adequate to assess ocular toxicity.
2. The protocol should specify that the ocular examinations will be performed by a physician with training in the use of a slit lamp.
3. Best Corrected Visual acuity should be assessed at each ophthalmic evaluation. Intraocular pressure should be assessed at Visit 1 (Baseline), Visit 5 (Day 90 ± 7), and end of the trial.
4. Cataract formation from the use of corticosteroids typically does not occur in the first six months of exposure. Intraocular steroids typically take 18-24 months to cause cataracts. The seven month exposure proposed in this study synopsis is not likely to definitively evaluate the potential for ciclesonide nasal aerosol to result in cataract formation. To definitively evaluate the potential for this drug product to cause cataract formation, a safety trial of at least 18 -24 months duration would be required.
5. The protocol should specify a standardized grading system for the evaluation of cataracts (e.g. Lens Opacities Classification System II or III) should it be necessary.

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Products

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/s/

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01/04/2012

WILEY A CHAMBERS
01/09/2012

CLINICAL REVIEW

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Priority or Standard Standard

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Reviewer Name(s) Robert H. Lim, MD
Review Completion Date 12/16/2011

Established Name Ciclesonide
(Proposed) Trade Name
Therapeutic Class Nasal corticosteroid
Applicant Nycomed

Formulation(s) Nasal HFA
Dosing Regimen 74 mcg daily (37 mcg each nostril)
Indication(s) Treatment of symptoms associated with seasonal and perennial allergic rhinitis
Intended Population(s) Adults and adolescents 12 years of age and older

Template Version: [March 6, 2009](#)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended regulatory action, from a clinical prospective, is Approval of ciclesonide nasal HFA (CIC-HFA) for the treatment of symptoms associated with seasonal (SAR) and perennial allergic rhinitis (PAR) in the ≥ 12 year old population at a dose of 74 mcg once daily (37 mcg each nostril).

1.2 Risk Benefit Assessment

Two adequate and well controlled phase 3 trials demonstrated that CIC-HFA 74 mcg once daily (37 mcg each nostril) significantly improved symptoms associated with SAR. In these identically designed trials (060-622 and 060-634), a total of 463 patients with SAR received CIC-HFA 74 mcg once daily for 2 weeks and 455 received placebo. Key endpoints included change from baseline in reflective total nasal symptoms scores (rTNSS), reflective total ocular symptom scores (rTOSS), and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores. The rTNSS, rTOSS, and RQLQ endpoints are commonly used and accepted as valid in drug development programs for allergic rhinitis. Patients on CIC-HFA at 74 mcg daily demonstrated a statistically significant improvement from baseline in rTNSS compared to placebo. For both trials, difference from placebo in rTNSS was approximately 1 with p-values < 0.001 . Reflective total ocular symptom scores (rTOSS) were also improved in the CIC-HFA 74 mcg group compared to placebo, with a difference from placebo of approximately 0.5 ($p < 0.001$) in both trials. Patients who received CIC-HFA 74 mcg also demonstrated improvement in quality of life as measured by RQLQ. In both trials, clinically significant improvements in RQLQ scores were seen (0.6, $p < 0.001$). Based on this data, CIC-HFA at 74 mcg daily is clearly effective in the treatment of SAR.

Evidence for benefit with respect to PAR was taken from one adequate and well controlled phase 3 trial (060-633). Since the product demonstrated efficacy in SAR and the two disease entities are closely related, replicative studies in PAR are not required for approval. In the PAR trial, 298 patients with PAR received CIC-HFA 74 mcg once daily for 26 weeks and 307 received placebo. Key secondary endpoints included rTNSS and RQLQ. Patients on CIC-HFA 74 mcg once daily demonstrated a statistically significant improvement from baseline in rTNSS compared to placebo. The difference from placebo in rTNSS was 0.7 with a p-value < 0.001 . However, patients who received CIC-HFA 74 mcg once daily did not demonstrate clinically significant improvement in RQLQ, although statistical benefit was demonstrated. Ocular symptom scores were not measured in this trial. Based on this data, while CIC-HFA at 74 mcg daily is clearly

effective in the treatment of PAR symptoms, it did not demonstrate effectiveness in PAR with regard to quality of life.

In terms of risk, the most common adverse events (AEs) reported for CIC-HFA following short term exposure (2-6 weeks) were epistaxis, nasal discomfort/instillation site discomfort, headache, and URI. Of these, only epistaxis exhibited a dose response. After long-term exposure (6 months), the most common AEs were similar with the addition of nasopharyngitis. Most of the common AEs in the Respiratory, Thoracic, and Mediastinal disorders SOC demonstrated a dose response in the long-term exposure group. Local AEs, as a group, for both exposure periods also demonstrated a dose response. Additionally, there was a clear imbalance with regard to many individual local AEs and as a group when comparing patients who receive CIC-HFA versus placebo. This was most notable in the long-term exposure group. The most common local AEs that exhibited an imbalance were nasal discomfort/instillation site discomfort and nasal mucosal/septum disorders. However, the imbalance in local AEs is not surprising given the known local toxicities associated with nasal steroids. Overall, the common AEs observed in the CIC-HFA development program were generally consistent with comparable products.

With regard to rare AEs, there were two (2) nasal septal perforations reported in the CIC-HFA development program. This is of particular concern as septal perforations are very rare in clinical development programs for nasal steroids. Both nasal septal perforations were in patients with two week exposures (SAR dose ranging trial M1-602, and phase 3 trial 060-634) and at the lowest dose studied (74 mcg once daily). No septal perforations were noted in the long term study (060-633) or its 6 month extension (060-635). Nasal septal perforations are a known risk associated with nasal steroids; however, they are rarely seen in clinical development programs. Based on additional information provided by the sponsor, in one patient an outside ENT believed that the lesion may have pre-dated entry in the study and was likely missed on the screening exam. The other patient had had a previous history of nasal surgery (polyp resection) and a previous septal perforation. This patient should also not have been randomized as she was noted to have bilateral nasal erosions at the end of single blind placebo run in phase that immediately preceded the double blind treatment phase. Even with the sponsor's additional information, these 2 septal perforations are still of concern.

While the perforations are of concern, the potential benefits of this product outweigh the risk for the following reasons. First, there were no perforations in the higher dose groups or in the long term trials, suggesting that the perforations may not have been related to CIC-HFA exposure alone. Second, the common adverse event profile of CIC-HFA is generally consistent with comparable products. Third, in the clinical studies CIC-HFA had very robust efficacy demonstrating statistically and clinically significant improvements across multiple endpoints. Additionally, there are no other marketed HFA nasal steroid formulations. Due to the occurrence of nasal septal perforations, a post-marketing study is recommended to further characterize the potential risk CIC-HFA compared to an active control (Omnamis).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No formal Risk Evaluation and Mitigation Strategy (REMS) beyond information provided about local nasal safety in the product label is required for CIC-HFA. The product label will include the risk of nasal septal perforations prominently in the Warnings, along with specific data from the clinical trials. The label will also advise that health care practitioners (HCP) perform an ENT exam to assess for nasal pathology prior to medication initiation. Following initiation, HCPs will also be advised to perform exams periodically to assess for adverse local reactions. Were local reactions to be noted, it will be recommended that the HCP stop the medication. Finally, information for patients and the patient instructions for use mention nasal septal perforations and prominently instruct the patient not to spray the product directly on the nasal septum.

1.4 Recommendations for Postmarket Requirements and Commitments

The clinical review recommends a postmarketing requirement for trials to further characterize the safety profile (both local and ocular) of CIC-HFA compared to Omnaris. In addition, we recommend trials to assess for dose, safety, efficacy, and HPA axis effects in the 2-11 year old patient population.

Local nasal safety:

As with other products of this class, local toxicity is a safety issue. Although its local adverse event profile is in general similar to other nasal steroids, the occurrence of nasal septal perforations during the development program is rare. While the additional information regarding the two cases may in part explain the perforations and it is reassuring that no perforations were seen at higher exposure levels (duration and dose), an additional safety study is required. This study will be used to further characterize the safety profile of CIC-HFA and provide reasonable assurance that local TEAE rates are no higher in this product as compared to Omnaris. This safety trial will include 2 treatment arms (CIC-HFA 74 mcg once daily and Omnaris, 1:1 randomization), approximately 600 patients with PAR, and be approximately 6 months in duration. Additionally, patients with a history of nasal pathology will not be excluded to simulate 'real world' usage. This trial will also include both slit lamp examination and assessment of intraocular pressure.

Ocular safety:

At the pre-IND meeting, there was agreement that Nycomed did not have to collect ocular safety data for their CIC-HFA development program, and could reference the data from Alvesco and Omnaris. However, after review of the data in this NDA package, ocular safety data will be required following approval. From the clinical pharmacology data provided, it is clear that systemic exposure to ciclesonide's active metabolite (des-ciclesonide) is significantly higher in CIC-HFA compared to Omnaris. Additionally, a significantly higher percentage of ciclesonide remains in the nasal cavity in CIC-HFA

compared to Omnaris. As such, data from the Omnaris development program cannot be used to support ocular safety for CIC-HFA. The usage of the Alvesco's ocular safety data is also inappropriate as Alvesco is orally inhaled, and hence, would not account for ocular exposure via the naso-lacrimal duct. Ocular safety will be assessed in the post-marketing safety trial (see above).

Pediatrics:

To fulfill PREA requirements, we recommend evaluation of dose range, safety, efficacy, and HPA axis effects in patients 2-11 years of age. We recommend waiving studies in the <2 year old population since SAR does not exist in this patient population and other, safer alternatives (antihistamines) are available to treat PAR. At a Type C meeting that occurred following submission of this NDA, the Division met with Nycomed to discuss their pediatric development plan. At that meeting, there was agreement that studies assessing for HPA-axis effects, dose range, safety, and efficacy would be first performed in the ≥6 to <12 year old population. Once dose, safety, and efficacy are established in the older age group, safety studies should be pursued in the ≥2 to <6 year old population. While there was general agreement with their sequential approach, the Division recommended including an additional lower dose in their dose-ranging/safety/efficacy trials and consideration for a positive control in their HPA axis studies.

This application was presented at the Pediatric Review Committee meeting on 11/30/11. The committee agreed to a waiver of PREA requirements for age 0-2 and a deferral of trials in the 2-11 year old age group.

2 Introduction and Regulatory Background

2.1 Product Information

The active ingredient in the proposed product is ciclesonide. Ciclesonide is a non-halogenated glucocorticoid, which is rapidly metabolized to des-ciclesonide. This metabolite demonstrates a high affinity for the glucocorticoid receptor and is primarily responsible for this drug's activity. In the proposed product, ciclesonide will be in solution with (b)(4) dehydrated alcohol and (b)(4) HFA 134a as a propellant. This will be packaged into a (b)(4) canister (ciclesonide (b)(4)) and delivered via a dose indicating nasal actuator. Each actuation will deliver 37 mcg of medication.

The proposed indication is for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in the 12 and older patient population. Proposed dosing is 74 mcg daily (37 mcg/1 actuation each nostril).

The actuator used in the phase 2 and 3 clinical studies was determined to be equivalent to the to-be-marketed device actuator (based on sponsor CMC data, see section 4.1 and CMC review). In the phase 2 and 3 clinical studies, the product came in 3 strengths: (b) (4) which corresponded to ex-valve strengths of 50 mcg, 100 mcg, and 200 mcg per actuation. These ex-valve strengths corresponded to approximate ex-actuator doses of 40 mcg, 80, mcg, and 160 mcg, respectively. The final ex-actuator label claim for these strengths was determined to be 37 mcg, 74 mcg, and 141 mcg, respectively. However, in many of the phase 2 and 3 clinical trials, approximate values for these strengths were referenced. In this review, the final ex-actuator doses [i.e. 37, 74, 141 mcg per actuation; or 74, 148, and 282 mcg per day (1 actuation each nostril)] will be used when referencing this product. However, in some of the figures and tables taken directly from the sponsor, the ex-valve or approximate ex-actuator doses may be referred to.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently 8 corticosteroids formulated for intranasal administration for the treatment of both perennial and seasonal allergic rhinitis (Table 1). There are no marketed nasal corticosteroids that use an HFA as the propellant. Nasacort was approved as an HFA formulation, but has never been marketed in the US.

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

Drug	Trade Name	Formulation	Indication*	Age Range (years)
Triamcinolone	Nasacort HFA Nasal Aerosol	Microcrystalline suspension in metered-dose aerosol	SAR PAR	≥6 ≥6
	Nasacort AQ Nasal Spray	Microcrystalline aqueous suspension in manual pump	SAR PAR	≥2 ≥2
Beclomethasone	Beconase AQ	Microcrystalline aqueous suspension in manual pump	SAR PAR	≥6 ≥6
Fluticasone propionate	Flonase	Microfine aqueous suspension in metering atomizing spray pump	SAR PAR	≥4 ≥4
Fluticasone furoate	Veramyst	Aqueous suspension	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	Suspension in metered-dose aerosol	SAR PAR	≥6 ≥6
Ciclesonide	Omnaris	Suspension in manual pump	SAR PAR	≥6 ≥12

*SAR=seasonal allergic rhinitis, PAR=perennial allergic rhinitis

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in the proposed product, CIC-HFA, is present in two FDA approved locally acting medications. Omnaris (ciclesonide aqueous nasal spray) was approved for marketing in October 20, 2006 for SAR/PAR in adults and adolescents aged 12 years and older. In November 21, 2007, its SAR indication was expanded to cover children aged 6 to 12 years. Alvesco [ciclesonide HFA oral metered dose inhaler (MDI)] was approved for marketing January 10, 2008 for use in asthmatic patients aged 12 years and older. No major safety issues have arisen since their approval.

2.4 Important Safety Issues With Consideration to Related Drugs

Ciclesonide and its metabolite des-ciclesonide have low systemic availability when delivered intranasally. However, as des-ciclesonide is a potent glucocorticoid receptor agonist, it has the potential to produce the adverse events associated with corticosteroid administration. These adverse effects include adrenal suppression, the development of cataracts and glaucoma, and decreased growth velocity in children.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Prior to submission of this NDA, this product has been the subject of multiple regulatory proceedings (as IND 74,674), summarized below:

10/16/06: Pre-IND meeting:

- Agreement that no ECG or ocular safety data were required with this application

11/10/06: IND submission

12/15/08: EOP2 meeting. The major points of discussion were as follows:

- Agreement to carry forward the 74 mcg and 148 mcg doses for evaluation in phase 3, with the caveat that depending on the results of the phase 3 trials, lower doses may be required for evaluation in the pediatric population.
- 12 months of long-term safety data would be needed. A reasonable approach would be for the Sponsor to plan for a one-year study, but to examine the 6-month data, and if found acceptable, submit the NDA with plans to submit the one-year data at the time of the 4- month safety update. The Division also commented that a controlled safety study was preferred, and that in the absence of a control arm, all adverse events would be attributable to the proposed product.
- Agreement that the overall design of the proposed HPA axis study appeared adequate, but that patients 12 years and older should be included.

- Statement that the proposed HPA-axis study should include an assessment of efficacy, and, if feasible, PK measurements to assure compliance.
- Statement that the results of the HPA-axis study would ultimately be described (compared to placebo) in the clinical pharmacology section of a label, without statements regarding non-inferiority.
- Agreement that two SAR trials and one PAR trial would be sufficient to support efficacy provided that they all showed the desired result.

11/3/10: Pre-NDA meeting. The major points of discussion were as follows:

- Agreement that the likely effective dose was 74mcg/day, pending review of data.
- Agreement that the clinical development program (two phase 3 SAR studies, and one phase 3 PAR study) would be adequate to support review.
- Agreement that data from the two replicate SAR trials (060-622 and 060-634) could be pooled.
- Statement that the scintigraphy study appeared reasonable, but it was unlikely that the results would be included in the product label.
- Agreement that Alvesco (orally inhaled ciclesonide) growth study 343 (NDA 21658, SD#51) provided sufficient data for the proposed product such that no further growth studies were needed.

In addition, products containing the same active moiety were approved as below:

- 10/20/06: NDA 22,004 was approved for ciclesonide nasal spray (Omnaris) in 12 and older.
- 11/21/07: NDA 22,124 was approved for ciclesonide nasal spray (Omnaris) in 6 and older.
- 01/10/08: NDA 21,658 was approved for ciclesonide HFA inhalational solution (Alvesco).

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was appropriately indexed and complete to permit review. A DSI audit was requested for 2 sites that had patients with nasal septal perforations.

Contact information	Trial/Site#	Number of Subjects
Robert Lee Jacobs, MD Biogenics Research Institute 8233 Fredericksburg Road San Antonio, TX 78229 210-614-2564	060-622/003 060-634/003 060-633/014	124 100 39
Pinkus Goldberg, MD Clinical Research Center of Indiana 3266 N. Meridian St. Suite 900 Indianapolis, IN 46208	M1-602/5357 060-633/10	19 30

DSI review of these sites did not demonstrate any findings which bring into question data integrity. Only minor violations were reported. It should be noted that one of the violations at Dr. Pinkus' site involved the patient who developed the nasal septal perforation. This patient should not have been randomized as nasal erosions were observed following the single blind run in period.

3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in each clinical study report.

3.3 Financial Disclosures

The Applicant has submitted a statement certifying that no debarred individuals were used in the conduct of the trials included in this NDA. The Applicant had submitted the following financial arrangements with investigators:

- [REDACTED] (b) (6) Category 2: Significant payments >\$25,000.00. Dr. [REDACTED] (b) (6) enrolled [REDACTED] (b) (6) subjects into Study [REDACTED] (b) (6).
- [REDACTED] (b) (6) Category 4: Significant equity interest

>\$50,000.00. Dr. (b) (6) site enrolled (b) (6) subjects into Study (b) (6)

Dr. (b) (6) was only involved in the (b) (6) trial (b) (6). Therefore, it is unlikely that his financial interests would have significantly affected the results. Dr. (b) (6) site was audited (b) (6)

This analysis was confirmed by FDA biostatisticians. Because of the previous audits and evaluation (b) (6), further FDA audit of the site was deemed to be low yield.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The recommendation from the CMC review is Approval. Details of the CMC review can be found in Dr. Arthur Shaw's review. The drug substance is a white to yellowish white (b) (4) powder. For nasal delivery, ciclesonide is put in solution with (b) (4) dehydrated alcohol and (b) (4) HFA 134a propellant. This solution (b) (4) is packaged in a (b) (4) canister that is closed with a 50mL metering valve. Per actuation, 37 mcg of ciclesonide is delivered ex-actuator. The to-be-marketed product will come in 2 sizes; 30 and 60 actuations.

The to-be-marketed actuator, designated V2, is slightly different than that used in the phase 2 and 3 trials (V1 actuator). It was modified (b) (4). Due to the changes between the V1 and V2 actuator, the sponsor performed testing which demonstrated that the 2 actuators were equivalent (sponsor analysis). Determination of equivalence was based on actuator parameters (dimensions, spray pattern, and airflow resistance) and drug product parameters (spray content uniformity, particle size distribution, plume geometry, and deposition in system components).

The demonstration of equivalence was based on versions of the V1 and V2 actuators which dispensed (b) (4) actuations. However, as the to-be-marketed product will dispense 30 or 60 actuations, the actuator dose counter was modified. After modification, the dose counter performance was tested for count accuracy, drop test, Force to Count, Force to Expel, and Counter Actuation Stroke. Based on this testing, the 60 dose actuation (b) (4) was deemed by the sponsor to be comparable to the (b) (4) dose

actuation (b) (4) The changes to the actuator were discussed in the pre-NDA meeting (12/21/2010).

The sponsor's analysis determined that the actuators used in the clinical studies were equivalent to the to-be-marketed actuators.

During the review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) voiced concerns that patients may inhale the medication orally due to its similarity in appearance to orally dosed MDIs. In addition, due to the short nozzle on the actuator, there was also concern regarding accidental discharge into the eyes. The risk related to accidental oral inhalation is low. This medication is to be used symptomatically and systemic exposure following oral inhalation is extremely low. Also, the product is approved in a higher dose for oral inhalation (Alvesco). The level of risk relating to accidental exposure to the eyes is not clear. The risk associated with ocular exposure will be determined in the post-marketing trial. Additionally, the label will specifically instruct patients to avoid spraying into the eyes. However in the clinical development program, no mention was made of device misuse by the sponsor.

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

The recommendation from the Pharmacology/Toxicology review is approval. Details of the Pharmacology/Toxicology review can be found in Dr. Luqi Pei's review.

The sponsor did not submit any new preclinical data with this NDA and is relying on the preclinical data from the Omnaris and Alvesco NDAs/INDs. Both have the same active ingredient (b) (4) At the 10/16/06 meeting for this product's IND (74,974), DPARP and Nycomed were in agreement that no new preclinical testing was required.

Ciclesonide is a pro-drug of des-ciclesonide (RM1), which is the pharmacologically active metabolite. The oral bioavailability of ciclesonide is <6% in most species. In rats and mice ciclesonides half life is 1 hour. RM1's half life is 2.4-7 hours in rats, mice, rabbits and dogs. Once absorbed, ciclesonide is de-esterified to RM1. CYP3A4 further metabolizes RM1. These metabolites are considered inactive. The major elimination pathway is bile and feces.

Complete toxicology programs have been completed with ciclesonide to support its inhalational (Alvesco) and intranasal (Omnaris) routes. Notably, preclinical toxicology testing for Alvesco, (b) (4) did not

demonstrate any significant local toxicity when given to dogs via whole face inhalation. The systemic toxicologic profile for ciclesonide is typical for glucocorticoids.

Preclinical testing also demonstrated that ciclesonide was not a carcinogen (2 year testing), teratogen, or mutagen. It also did not impair fertility.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The recommendation from the Clinical Pharmacology (CP) review is Approval. Details of the CP review can be found in Dr. Ying Fan's review. Ciclesonide is a non-halogenated glucocorticoid that is rapidly metabolized to des-ciclesonide (RM1). This metabolite has a high affinity for the glucocorticoid receptor (GR) and is primarily responsible for this drug's pharmacologic activity. By binding GR, ciclesonide acts as an anti-inflammatory. While the exact mechanism is not known, in the setting of allergic rhinitis (AR), ciclesonide, like other nasal corticosteroids, acts at the local level to inhibit the release of inflammatory mediators which in turn decreases nasal inflammation/symptoms associated with AR. The sponsor also proposes that ciclesonide improves ocular symptoms associated with AR. The mechanism for this action is not known, but would likely be through local ocular effects as there is little systemic exposure. It is possible that reduced nasal inflammation results in decreased inflammatory mediators not only in the nasal mucosa, but also in adjacent areas affecting the eyes. Alternatively, reduction of nasal inflammation may improve drainage of fluid containing allergens/inflammatory mediators away from the eye via the nasolacrimal duct. It is also possible that inhaled nasal corticosteroids (INCS) modulate the naso-ocular neurogenic reflex. Regardless of the exact mechanism, this broader indication is not without precedent. Veramyst (fluticasone furoate) is indicated to treat nasal and ocular symptoms associated with AR.

4.4.2 Pharmacodynamics

The sponsor conducted one dose ranging trial (M1-602) using 3 doses [74, 148, and 282 mcg daily (37, 74, and 141 mcg each nostril daily)] and three phase 3 trials (060-622, 060-634, 060-633) using 2 doses [74 and 148 mcg daily (37 and 74 mcg each nostril daily)]. All the above studies are reviewed in detail in section 5.3. None of the studies demonstrated a dose response with respect to efficacy; however, this lack of dose response is similar to other nasal corticosteroid products. All doses demonstrated efficacy with regard to nasal symptoms.

The HPA axis was evaluated in subjects 12 years of age and older in trials FHP-017, M1-601, and 060-010. In trials FHP-017, serum cortisol levels were measured after 7

daily doses of CIC-HFA at 282 mcg (141 mcg each nostril). In trial M1-601, serum cortisol levels were measured after 14 daily doses at 148 mcg (74 mcg each nostril) or 282 mcg (141 mcg each nostril). In both trials, no significant differences were seen in the serum cortisol AUC_{0-24hr} for those exposed to CIC-HFA versus placebo. However, these were relatively short exposures to ciclesonide; therefore, Trial 060-010 was performed. This trial assessed HPA axis effects of CIC-HFA (serum cortisol AUC_{0-24hr}) after 6 weeks of exposure. Patients (12 years and older) were divided into 4 treatment groups which were as follows:

- 1) Placebo HFA daily + Dexamethasone (DEX) 6mg
- 2) Placebo HFA daily + Placebo DEX
- 3) CIC-HFA 148 mcg daily (74 mcg each nostril)
- 4) CIC-HFA 282 mcg daily (141 mcg each nostril)

For groups 1 and 2, the DEX (or placebo DEX) was started 4 days prior to the 2nd collection of 24 hour serum cortisol levels (end of treatment). Results are summarized in Table 2.

Table 2. Trial 060-610. Change from Baseline in Serum Cortisol AUC_(0-24hr) (mcg*hr/dL) in Per Protocol Population

	Placebo HFA+DEX	Placebo HFA +Placebo DEX	CIC-HFA Dose	
			148 mcg	282 mcg
Cortisol AUC _{0-24hr}				
N	18	57	60	50
Baseline (SD)	167.7 (36.3)	173.1 (53.5)	171.7 (40.1)	183.2 (61.9)
End of Treatment (SD)	13 (14.3)	169.9 (48.3)	170.6 (47.4)	178 (55.5)
Change from baseline (SD)	-154.4 (40)	-2.7 (41.1)	-1.5 (34.1)	-7.7 (33.7)
LS Mean Change from baseline (SE)		-5 (4.6)	-2.6 (4.6)	-4.6 (5)
Treatment difference vs. Pbo (95% CI)			-2.4 (-15.1, 10.2)	-0.5 (-13.9, 13)

Source: Trial 060-610 CSR, Table 13, pp102

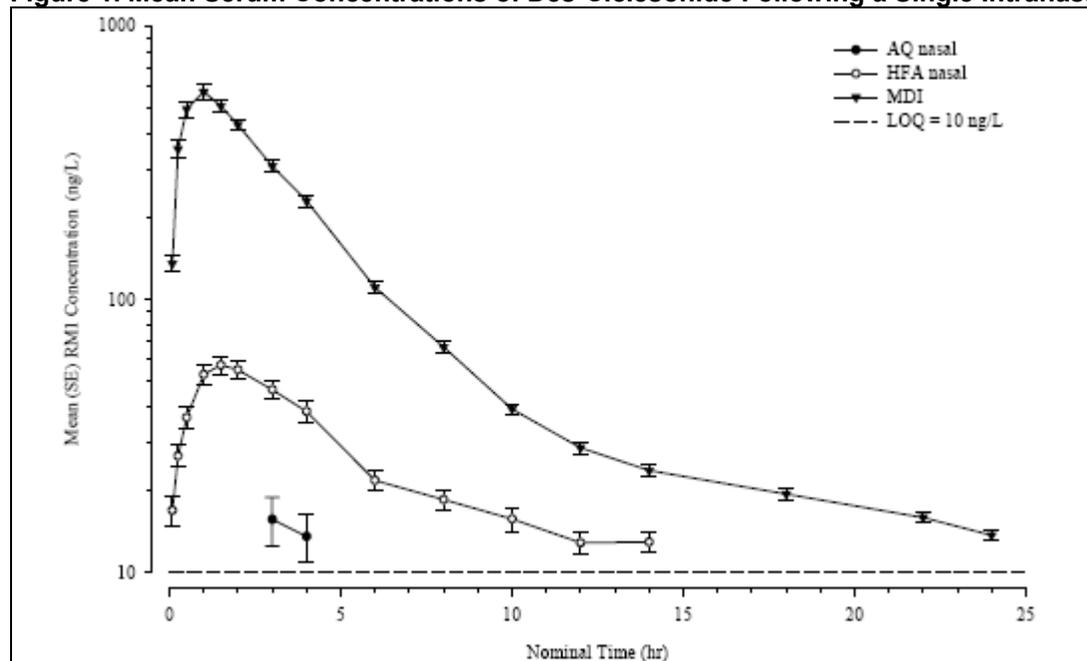
Numerically, the least squares (LS) mean changes from baseline for the CIC-HFA groups were similar to the placebo HFA+ Placebo DEX group. Statistically, the CIC-HFA groups demonstrated non-inferiority compared to the placebo HFA+Placebo DEX groups based on a pre-specified non-inferiority margin (upper limit of the 95% confidence interval for the LS mean difference from Placebo HFA+Placebo DEX <38 mcg*hr/dL). This non-inferiority margin was chosen as in the prior HPA axis studies using Omnaris, the baseline serum cortisol AUC_{0-24hr} were on average 190 mcg*hr/dL and the sponsor chose a 20% non-inferiority margin. Thus, 6 weeks of treatment at 2-4 times the proposed CIC-HFA dose did not suppress the HPA axis. However, it should be noted that based on the point estimate for LS mean change from baseline in serum cortisol levels, the 282 mcg treatment had greater suppression compared to the 148 mcg and placebo groups. This implies that at higher doses, CIC-HFA may cause subtle HPA axis suppression. The positive control (Placebo HFA+DEX) also demonstrated that

the assay would have been able to detect HPA axis suppression. The sponsor also collected nasal symptom data as a measure of efficacy and to assess for compliance.

4.4.3 Pharmacokinetics

This NDA included 3 new PK/PD studies, and also made reference to 13 other studies that were previously reported as part of the Omnaris and Alvesco NDAs. What follows is a brief summary. After inhalation, ciclesonide is rapidly converted to des-ciclesonide (RM1), which is primarily responsible for its activity. Following nasal inhalation of 282 mcg CIC-HFA, the elimination half life of RM1 is 3.38 hours, which is less than Alvesco (9.17 hours), but greater than Omnaris (2.75 hours). Ciclesonide nasal HFA elimination half life was based on data collected 3 hours after dosing, whereas ciclesonide oral inhalation (Alvesco) was based on data collected 9 hours after dosing. This difference may, in part, account for the differences seen between the 2 products. After a single nasal dose of the proposed product (282 mcg), the systemic exposure to RM1 based on peak plasma concentrations was 10 fold less than Alvesco (320 mcg) (Figure 1).

Figure 1. Mean Serum Concentrations of Des-Ciclesonide Following a Single Intranasal Dose



AQ Nasal= Omnaris 300mcg, HFA Nasal= Ciclesonide 282 mcg, MDI= Alvesco 320 mcg
Source: Summary of Clinical Pharmacology Studies (2.7.2), Figure 1, pp23

Based on $AUC_{(0-\infty)}$, the systemic exposure to RM1 was less than Alvesco by 6.8 fold. Similar to RM1 levels, a single dose of Alvesco resulted in much higher systemic exposure to ciclesonide compared to a single dose of the test product. Overall, systemic exposure to ciclesonide or RM1 was much higher when ciclesonide was given as an oral MDI as compared to nasal HFA inhaler. However, the nasal HFA inhaler does have

increased systemic exposure to both ciclesonide and RM1 as compared to the aqueous nasal spray (Omnaris).

Both ciclesonide and RM1 are predominantly bound to human serum proteins (~99%). Ciclesonide is primarily excreted through the feces. The clearance of RM1 was not significantly affected by body weight, age, race, asthma severity, gender, or hepatic function.

The sponsor also conducted a scintigraphy study (060-101) to evaluate the pulmonary and nasal deposition of CIC-HFA versus ciclesonide aqueous spray (Omnaris). In this study, after screening and baseline MRI, ten (10) healthy volunteers received ciclesonide HFA 148 mcg (74 mcg each nostril) labeled with ^{99m}Tc. Following administration, scintigraphy was performed to assess for deposition. After a wash-out period of ≥72 hours, radiolabeled ciclesonide aqueous 200 mcg (100 mcg each nostril) was administered followed by scintigraphy. Scintigraphy data was overlaid on MRI images to determine nasal and pulmonary deposition. For ciclesonide HFA, 98.36% of the delivered dose deposited in the nasal cavity, 1.42% in the lungs, 0.03% in nasal wipes, and 0.22% in the nasopharynx. For ciclesonide aqueous (Omnaris), 76.38% of the delivered dose deposited in the nasal cavity, 0.55% in the lungs, 22.74% in nasal wipes, and 0.34% in the nasopharynx. A much higher percentage of the delivered dose was retained in the nasal cavity for CIC-HFA versus Omnaris. This may have implications for both safety and efficacy, as both are primarily related to local delivery.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The sources of clinical data used in this review are summarized in Table 3.

Table 3. Sources of Clinical Data

Study	Objective	Design	Population	Treatment Arms	Status
Phase 2b					
M1-602	Dose range, safety, efficacy	MC, R, DB, PC	SAR patients ≥12 years old N=513	Ciclesonide HFA nasal: 74 mcg qDay x 2 weeks (N=22) 148 mcg qDay x 2 weeks (N=125) 282 mcg qDay x 2 weeks (N=136) Placebo HFA nasal	Completed
Phase 3					
060-622	Safety/efficacy in SAR	MC, R, DB, PC	SAR patients ≥12 years old N=707	Ciclesonide HFA nasal: 74 mcg qDay x 2 weeks (N=237) 148 mcg qDay x 2 weeks (N=235) Placebo HFA nasal	Completed
060-634	Safety/efficacy in SAR	MC, R, DB, PC	SAR patients ≥12 years old N=671	Ciclesonide HFA nasal: 74 mcg qDay x 2 weeks (N=226) 148 mcg qDay x 2 weeks (N=225) Placebo HFA nasal	Completed
060-633	Safety/efficacy in PAR	MC, R, DB, PC	PAR patients ≥2 years old N=1111	Ciclesonide HFA nasal: 74 mcg qDay x 6 weeks (N=298) 148 mcg qDay x 6 weeks (N=506) Placebo HFA nasal	Completed
060-635	Long-term safety (extension of 060-633)	OL	PAR patients ≥ 12 years old	Ciclesonide HFA nasal 148 mcg qDay x 26 weeks No Placebo group	Completed

R=randomized, DB=double-blind, PC=placebo controlled, MC=multi-center, OL=open label, CO=cross-over.

All treatment arms received 2 sprays to achieve dose (i.e. 74 mcg = 37 mcg each nostril, 148 mcg = 74 mcg each nostril, and 282 mcg = 141 mcg each nostril)

The phase 3 trials consisted of two replicated safety and efficacy trials in patients with SAR (060-622 and 060-634) and one safety and efficacy trial in PAR patients (060-633). Doses used in these studies were 74 mcg (37 mcg each nostril) and 148 mcg (74 mcg each nostril) daily, based on results from the dose ranging study (M1-602). Study 060-633 is being extended as an open label safety study (060-635) for an additional 6 months. These results will be reported in the 120 day safety update.

In addition to trials listed in Table 3, five (5) other phase 1 and 2 trials were conducted which assessed PK, PD, safety, lung deposition, and HPA axis effects. These are not the focus of this review, but trials FHP-017, M1-601, 060-010, M1-422, and 060-101 are discussed briefly in section 4.4.2 and 4.4.3.

5.2 Review Strategy

This clinical review will focus on dose ranging study M1-602, the Phase 3 SAR studies 060-622 and 060-634, and the Phase 3 PAR study 060-633. The long term safety trial to be submitted at the 120 day update will also be reviewed. The individual protocols, efficacy results, and safety results are discussed in detail in section 5.3 Discussion of Individual Studies/Clinical Trials. The efficacy results of all the listed trials will be summarized by indication in section 6 Review of Efficacy. The combined safety of the list trials will be presented in section 7 Review of Safety.

5.3 Discussion of Individual Studies/Clinical Trials

Note that for all trials, total daily dose is divided between each nostril (i.e. 74 mcg = 37 mcg each nostril, 148 mcg = 74 mcg each nostril, and 282 mcg = 141 mcg each nostril).

5.3.1 Trial M1-602

Administrative Information

- **Study title:** A Double-Blind, Randomized, Placebo- Controlled, Parallel Group, Multicenter, Dose- Ranging Study to Assess the Safety and Efficacy of Ciclesonide HFA Nasal Aerosol in Adult and Adolescent Patients 12 years and Older with Seasonal Allergic Rhinitis (SAR)
- **Study dates:** 4/10/2007-6/22/2007
- **Study sites:** 35 centers throughout the U.S. during the spring season
- **Relevant Allergens:** Tree/grasses
- **Study report date:** 10/12/2010

Objectives/Rationale

- Determine the optimal dose of ciclesonide HFA, applied as a nasal aerosol once daily, in patients 12 years and older with SAR.
- Evaluate the safety and tolerability of ciclesonide HFA nasal aerosol.
- Assess quality of life.

Study Design and Conduct

Overview

This was double-blind, randomized, placebo controlled, parallel group, multi-center, dose ranging efficacy and safety study in 513 SAR patients 12 years of age and older. This study consisted of a 1-3 week run-in period followed by a 2 week treatment period.

During the run-in period, patients self administered single-blind placebo every morning and assessed and recorded their 12 hour reflective and instantaneous nasal symptoms (Total Nasal Symptom Score, TNSS) twice daily and 24 hour non-nasal symptoms once daily.

Following the run-in period, patients were randomized via Interactive Voice Response System (IVRS) to 2 weeks of double-blind treatment with either CIC-HFA 74 mcg once daily, 148 mcg once daily, 282 mcg once daily, or placebo. Randomization was 1:1:1:1. During the treatment period, patients recorded their nasal and non-nasal symptoms as in the run-in period.

This study consisted of 3 visits. The initial screening visit (B0), the randomization visit (T0), and the end of study visit (T1/T_{end}). The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was to be completed by the patient on visits T0 and T1/T_{end}. During visit B0, T0, and T1/T_{end}, the investigator questioned the patients regarding their nasal symptom severity (Physician Assessed Total Nasal Symptom Score). The assessment schedule is summarized in Table 4:

Table 4. Trial M1-602. Assessment Schedule

Visit Day	B0 -7 to -14/21	T01	T1/T _{end} 14 + 2
Weeks	-1 to -2/3	0	2
Written informed consent/assent/HIPAA authorization at Screening (B0)	X		
Rhinoconjunctivitis Quality-of-Life (RQLQ)		X	X
Distribution of RQLQ booklet and review of instructions with the patient		X	
Medical history including concomitant medication history	X		
Physical exam (incl. Seated vital signs)	X		X
Ear, nose and throat exam (ENT)	X	X	X
Collection of urine for pregnancy test (if applicable)	X		X
Skin prick test for relevant seasonal allergen (pollen)	X	X	
Physician assessment of nasal symptom severity	X	X	X
Query and Evaluation of concomitant/prohibited drugs	X	X	X
Adverse event monitoring		X	X
Review of Inclusion/Exclusion Criteria	X		
Distribute and review instructions for proper use of HFA nasal aerosol	X		
Prime and dispense single-blind placebo	X		
Distribution of electronic diary instructions and review of instructions with the patient	X		
Administer single-blind placebo	X		
Review of electronic diary instructions with the patient		X	
Review of Randomization Criteria		X	
Electronic diary data review		X	
Randomization using Interactive Voice Response System (IVRS)		X	
Review of instructions for the proper use of HFA nasal aerosol with the patient		X	
Prime and dispense randomized double-blind study medication		X	
Administer randomized double-blind study drug		X	
Compliance check (study procedures and study medications)		X	X
Patient assessment and recording of 12-hour <i>reflective and instantaneous TNSS</i>	X		

Patient assessment and recording of 24-hour <i>non-nasal symptom severity</i>	X		
Call into IVRS to discontinue patient			X
Return all study medications, used and unused		X	X
Daily Pollen Counts	X		

Source: Module 5.3.5.1.1, Section 9.5.1, Table 3

Study Population:

This study included 513 patients 12 years of age and older with SAR. Patients were randomized using a central, computerized randomization system (Interactive Voice Response System, IVRS)

Key Inclusion Criteria

1. Male or female 12 years and older, as of the Screening Visit (B0).
2. General good health, and free of any concomitant conditions or treatment that could interfere with study conduct, influence the interpretation of study observations/results, or put the patient at increased risk during the trial.
3. A history of SAR to relevant seasonal allergen for a minimum of two years immediately preceding the study Screening Visit (B0). The SAR must have been of sufficient severity to have required treatment (either continuous or intermittent) in the past and in the investigator’s judgment is expected to require treatment throughout the entire study period.
4. A demonstrated sensitivity to grass or tree pollen known to induce SAR through a standard skin prick test. Documentation of a positive result 12 months prior to screening is acceptable.
5. If female and of childbearing potential (as judged by the investigator) and she must be currently using and will continue to use a medically reliable method of contraception for the entire study duration (e.g. oral, injectable, trans-cutaneous or implantable contraceptives or intrauterine devices or double-barrier protection). Females who are not sexually active must agree to use double-barrier protection should they become active during the course of the study. Women of childbearing potential, or less than 1 year postmenopausal, will require a negative urine pregnancy test at the Screening Visit (B0). Female subjects will be considered to be of non –childbearing potential and will not require a urine pregnancy test if at least one of the following apply:
 - before menarchy;
 - more than one year post-menopausal;
 - had a hysterectomy;
 - had bilateral ovariectomy or salpingectomy or tubal ligation;
 - has congenital sterility.

Key Exclusion Criteria

1. Pregnancy, nursing, or plans to become pregnant or donate gametes (ova or sperm) for *in vitro* fertilization during the study period or for 30 days following the subject’s last study related visit (for eligible patients only – if applicable). Eligible female

- patients unwilling to employ appropriate contraceptive measures to ensure that pregnancy will not occur during the study will be excluded.
2. History of physical findings of nasal pathology, including nasal polyps or other clinically significant respiratory tract malformations, recent nasal biopsy, nasal trauma, or surgery and atrophic rhinitis or rhinitis medicamentosa (all within the last 60 days prior to the B0 Visit).
 3. History of a respiratory infection or disorder [including, but not limited to bronchitis, pneumonia, chronic sinusitis, influenza, severe acute respiratory syndrome (SARS)] within the 14 days preceding the Screening Visit (B0), or development of a respiratory infection during the Run-in Period.
 4. History of alcohol or drug abuse within two years preceding the B0 Visit.
 5. History of a positive test for HIV, hepatitis B or hepatitis C.
 6. 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, etc.); intermittent use (less than or equal to 3 uses per week) of inhaled short acting beta-agonists is acceptable.
 7. Plans to travel outside the study area (the known pollen area for the investigative site) for 24 or more hours during the last 7 days of the Run-in period.
 8. Plans to travel outside the study area (the known pollen area for the investigative site) for 2 or more consecutive days OR 3 or more days total between Randomization Visit (T0) and the final Treatment Visit (T1).
 9. Use of any prohibited concomitant medications within the prescribed (per protocol) time since last dose period prior to the Screening Visit (B0) and during entire treatment duration.
 10. Use of antibiotic therapy for acute conditions within 14 days prior to the Screening Visit (B0). Low doses of antibiotics taken for prophylaxis are permitted if the therapy was started prior to the Screening Visit (B0) and is expected to continue throughout the trial.
 11. Initiation of immunotherapy during the study period or dose escalation during the study period. However, initiation of immunotherapy 90 days or more prior to the Screening Visit (B0) and use of a stable (maintenance) dose (30 days or more) may be considered for inclusion.
 12. Previous participation in an intranasal ciclesonide HFA nasal aerosol study.
 13. Non-vaccinated exposure to or active infection with, chickenpox or measles within the 21 days preceding the Screening Visit (B0).
 14. Use of topical corticosteroids in concentrations in excess of 1% hydrocortisone or equivalent within 30 days prior to the Screening Visit (B0); use of a topical hydrocortisone or equivalent in any concentration covering greater than 20% of the body surface; or presence of an underlying condition (as judged by the investigator) that can reasonably be expected to require treatment with such preparations during the course of the study. Initiation of pimecrolimus cream 1% or greater or tacrolimus ointment 0.03% or greater during the study period or planned dose escalation during the study period. However, initiation of these creams/ointments 30 days or more prior to the Screening Visit (B0) and use of a stable (maintenance) dose during the study period may be considered for inclusion.

15. Study participation by more than one patient from the same household at the same time. However, after the study completion by one patient another patient from the same household may be screened.
16. Have any of the following conditions that are judged by the investigator to be clinically significant and/or affect the subject's ability to participate in the clinical trial:
 - impaired hepatic function including alcohol-related liver disease or cirrhosis;
 - history of ocular disturbances e.g. glaucoma or posterior subcapsular cataracts;
 - any systemic infection;
 - hematological, hepatic, renal, endocrine (except for controlled diabetes mellitus or postmenopausal symptoms or hypothyroidism);
 - gastrointestinal disease;
 - malignancy (excluding basal cell carcinoma);
 - current neuropsychological condition with or without drug therapy.

Randomization Criteria

Only patients meeting the following criteria will be randomized (7-14/21 days after initial Screening Visit (B0):

1. Patient did not leave the study area (the known pollen area for the investigative site) for longer than 24 hours during the 7 days prior to the Randomization Visit (T0).
2. Patient continues to be in general good health, meeting the selection criteria.
3. Patient has not experienced an adverse event that would result in failure to continue to meet selection criteria.
4. Patient has a minimum *patient-assessed* reflective TNSS of an average of 6 (out of a possible 12) on the last 7 days during the Run-in Period.
5. The patient-assessed scores for rhinorrhea OR nasal congestion must be an average of 2 or greater during the last 7 days during the Run-in Period.
6. Each patient must have adequately completed the AR Assessment Diary (failure is defined as missing one or more of the entries on more than 2 calendar days during the last 7 days of the Run-in Period).
7. Each patient must have taken their single-blind medication during at least 80% of the entire Run-in Period.
8. Patient has not used any of the prohibited concomitant medications during the Run-in Period.
9. Patient has not suffered from the common cold or acute sinusitis within 7 days prior to the Randomization Visit (T0).

Reviewer Comment:

The inclusion, exclusion, and randomization criteria are appropriate. The patient population was appropriate and typical for a SAR clinical trial. This population was similar to the populations used in the Omnaris clinical development program.

Treatments

Treatment Groups:

Ciclesonide HFA nasal aerosol 74 mcg (37 mcg each nostril) daily
 Ciclesonide HFA nasal aerosol 148 mcg (74 mcg each nostril) daily
 Ciclesonide HFA nasal aerosol 282 mcg (141 mcg each nostril) daily
 Placebo HFA nasal inhaler (2 inhalations) daily

- Placebo HFA was identical in formulation to the ciclesonide HFA except for the absence of ciclesonide.

Concomitant Medications/Prohibited Medications

All medications taken by the patients were recorded in the CRF. If the patient was on a prohibited medication which could not be withdrawn, the patient was not allowed to enter the trial. In cases where the medication could be discontinued, it was not for the sole purpose of enrollment in the trial. The prohibited medications are summarized in Table 5.

Table 5. Trial M1-602. Prohibited Medications

Type of Medication	Time since last dose prior to T0 Visit	Time since last dose prior to B0 Visit
All Intranasal Corticosteroids except study drug	21 days	-
Topical/Oral/Nasal Decongestants	10 days	-
Short acting antihistamines including intranasal and ocular antihistamines (i.e., Azelastine)	10 days	-
Long acting antihistamines	10 days	-
Over-the-Counter cough and cold preparations or sleep aids containing antihistamines	10 days	-
Vasoconstrictors	-	3 days
Major tranquilizers	-	3 days
Airozan (OTC food supplement /diet to reduce leukotrienes)	-	7 days
Cromolyn, nedcromil, or Iodoxamide (intranasal, ocular, or oral)	14 days	-
Leukotriene or 5-LO inhibitors	14 days	-
Inhaled/Oral/Intranasal anticholinergics	14 days	-
Tricyclic antidepressants	-	14 days
Monoamine oxidase inhibitors	-	14 days
Any other investigational drug	-	30 days
Inhaled corticosteroids (oral)	-	30 days
Azoles, anti-fungals	-	30 days
Systemic corticosteroids (intermittent or chronic)	-	60 days
Anti IgE therapy	-	60 days
Immunosuppressive drugs	-	60 days

Source: Module 5.5.3.1.1, Section 9.4.8.1, Table 2

These above listed medications could be taken if sufficient time had elapsed between the last dose and visits T0 or B0. They were not to be taken during the study.

Efficacy

Primary Efficacy Endpoint:

- Change from baseline in the average AM and PM reflective Total Nasal Symptom Score (rTNSS).

Key Secondary Efficacy Endpoints:

Change from baseline in the following parameters

- The average AM and PM instantaneous TNSS over the 2 week period
- AM instantaneous TNSS over the 2 week period
- Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) of patients with impaired quality of life (RQLQ >3) at run-in period.
- AM reflective non-nasal symptom over the 2 week period

Other Endpoints

Change from baseline in the following parameters

- Patient-reported average AM and PM reflective and instantaneous TNSS for each day
- Patient-reported individual reflective and instantaneous nasal symptoms over the two-week Treatment Period
- Patient-reported AM reflective TNSS over the two-week Treatment Period and each day;
- Patient-reported AM instantaneous TNSS for each day;
- Patient-reported PM reflective and instantaneous TNSS over the two-week Treatment Period and each day;
- Patient-reported average AM and PM reflective TNSS averaged over the two week Treatment Period;
- Physician-assessed total nasal symptom score (PNSS) at T_{end} and individual physician-assessed nasal symptoms at T_{end};
- Individual domains of the RQLQ at T_{end} for patients with impaired quality of life at Baseline;
- RQLQ and individual domains at T_{end} for the ITT analysis;
- AM 24-hour patient-reported individual reflective non-nasal symptoms over the two-week Treatment Period.

Baseline assessments were made during the run-in period.

Reviewer comment:

The primary endpoint and key secondary endpoints were appropriate and typical for SAR studies. Positive findings for these endpoints would be supportive for the proposed indication. Some of the above listed endpoints are overlapping. In cases where this occurs, the results were only reported and reviewed once.

Efficacy Parameters

Total Nasal Symptom Score (TNSS).

This subject assessed score is comprised of 4 domains which are sneezing, running nose, itchy nose, and nasal congestion. Each domain is scored according to following scale:

0 = absent

1 = mild (clearly present, but minimal awareness; easily tolerated)

- 2 = moderate (definite awareness and is bothersome, but tolerable)
- 3 = severe (hard to tolerate and interferes with activities of daily living).

The reflective TNSS (rTNSS) represents perception of symptoms in the preceding 12 hours and the instantaneous TNSS (iTNSS) reflect symptoms in the past 10 minutes. During this study both the iTNSS and rTNSS were at least twice daily (AM and PM). The AM assessment was to occur prior to the morning dose of study medication, and before bathing, consumption of food or beverage, or strenuous activities. The PM assessment was to occur 12 hours after the AM assessment. These assessments were to be performed throughout the study period.

24 Hour non-nasal symptoms:

This subject assessed score is comprised of 4 domains which are itching/burning of the eyes, tearing/watering eyes, redness of the eyes, and itching of the ears and palate. These symptoms were to be scored similar to the TNSS. These were to be assessed at the same time as the AM TNSS, and throughout the study.

Rhinoconjunctivitis Quality of Life Questionnaire:

The RQLQ has 28 questions in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). Subjects recall their experiences during the previous week and to give their responses on a 7-point scale (0 = Not Troubled to 6 = Extremely Troubled). When required at a particular visit, this questionnaire was to be the first subject-completed activity of the visit.

The self-administered version of the RQLQ was to be completed by the subjects at the investigator site at study visits T0, T1, and Tend.

Physician Assessment of Nasal Symptom Severity:

This is a physician assessed score that grades symptoms in 4 domains: runny nose, itchy nose, congestion, and sneezing. Its grading scale is similar to the TNSS. This assessment was to be performed on visits B0, T0, T1 and Tend.

Compliance Parameters:

Treatment compliance was to be assessed by patient diary, and, at the end of the study, an accurate accounting was to be conducted of all the drug supplies returned to the sponsor. Patient diary data was to be provided by the patient using a telephone or web based system (Interactive Voice Response System/Interactive Web Response System, IVRS/IWRS).

Safety Parameters:

Patient safety assessments included AEs, ear nose throat (ENT) exams, physical exams, pregnancy test and seated vital signs. The ENT exam was to assess for signs of AR and complications associated with nasal steroids (i.e. epistaxis, septal perforation, septal erosion, septal ulceration), as well as throat irritation, candidiasis, and post-nasal drip. The ENT exam was to be performed at every study visit, and any changes in comparison to prior exam were noted. Findings not related to the SAR were not to be

reported as AEs. No clinical lab parameters were to be evaluated. These assessments were to be performed as per Table 4.

Ethics

An institutional review board (IRB) reviewed and approved this study protocol. No changes were made without the IRB's approval. The IRB was (b) (4)
The study was performed in accordance with the Declaration of Helsinki and ICH Good Clinical Practices.

Statistical Plan

Sample size

The sample size was calculated based on the results from ciclesonide AQ nasal spray 4 week efficacy study BY9010/M1-401. Based on this, it was estimated that 120 patients would provide 90% power to detect a difference between treatment groups of 0.9 in the change from baseline in TNSS with a 2 sided alpha of 0.05. Therefore, the sponsor planned to randomize 480 patients in a 1:1:1:1 for the 4 treatment groups.

Analysis populations:

The sponsor pre-defined several populations for analysis. These included intention to treat (ITT) population, per protocol (PP) population, and safety population. The ITT population was defined as those patients who were randomized, receive at least one dose of trial medication, had baseline values, and had at least one post-baseline value. The PP population consisted of patients in the ITT population without any major protocol deviations, and data obtained from other patients prior to the first major protocol deviation. The safety population was those patients who were randomized and received at least one dose of trial medication.

Efficacy Analysis

The primary efficacy variable to be analyzed was change from baseline in average AM/PM daily rTNSS over the 2 week treatment period in the ITT population. This variable was analyzed using repeated ANCOVA with covariate adjustment for baseline, day, treatment, and treatment by day interaction using the ITT analysis set. Baseline was defined as the average of rTNSS over the 7 days prior to randomization. No imputation for missing data was planned. The average AM and PM rTNSS was calculated from the PM rTNSS and the AM rTNSS from the following day. To control for type 1 error, doses were to be analyzed sequentially. If the p-value for the difference in treatment effect between the 282 mcg dose and placebo was greater than or equal to 0.05, then the 148 mcg vs. placebo would be analyzed. If that p-value was greater than or equal to 0.05, then the 74 mcg dose would be analyzed.

The key secondary efficacy variables were change from baseline in average AM and PM iTNSS, AM iTNSS, RQLQ for those with a baseline score >3, AM 24 hours iTNSS, and non-nasal symptoms scores. All endpoints, except for RQLQ, were to be analyzed as per the primary efficacy variable. The RQLQ was analyzed using ANCOVA with adjustments for baseline RQLQ, treatment, and pooled center. These endpoints were to

be analyzed in a sequential manner in order to minimize type 1 error. The analytical approach is summarized in Table 6:

Table 6. Trial M1-602. Order of Statistical Testing

Order of Testing for Determining Statistical Significance vs Placebo				
Start →	300 mcg	150 mcg	75 mcg	
Days 1-14 Reflective TNSS	↓ →	↓ →	↓	
Days 1-14 Instantaneous TNSS	↓ →	↓ →	↓	
AM Instantaneous TNSS	↓ →	↓ →	↓	
RQLQ in impaired patients	↓ →	↓ →	↓	
Non-nasal symptom score	→	→		
Note: Arrows indicate the order of testing, from left to right and from top to bottom				

**The listed doses correspond to the approximate ex-actuator dose. In this review final ex-actuator strengths for label claims will be/were used (i.e 300 mcg= 282 mcg, 150 mcg=148mcg, and 75 mcg= 74 mcg). Per sponsor, these are only differences in terminology, not in actual dosing.
 Source: Module 5.3.5.1.1, Section 11.5.2

Results:

Protocol Changes

The original protocol was amended once on 3/30/07, prior to study initiation. This amendment made several changes: 1) sponsor personnel were changed, 2) total number of sites increased (from 25 to 35). 3) to be considered of non-childbearing potential, women had to be more than 1 year post-menopausal (changed from 2 years post-menopausal), 4) a dose counter was no longer used to assess compliance, 5) over the counter cold medication wash out period was decreased from 14 days to 10 days, and 6) study visits were renamed for clarity.

Protocol Violations

A total of 513 patients were randomized, of these 50 had major protocol violations defined as violations that could impact the evaluation of efficacy. Overall, these were fairly evenly split between the treatment groups. The most common violation was use of prohibited concomitant medications. There were 60 minor protocol violations, defined as those that were unlikely to influence the evaluation of efficacy. The most common was an “out of window study visit.”

Reviewer comment:

Removal of the dose counter as a measure of compliance may reduce the sponsor’s ability to detect compliance, as they would be relying primarily on patient report in the daily diaries. With regard to the protocol violations, given that they were evenly distributed across all treatment arms, it does not likely indicate any systematic bias.

Patient Disposition

A total of 513 patients from 35 sites were randomized. Of these, 498 completed the study. The number of discontinuations in each treatment group was similar (2.5-3.1%).

The most common reason for discontinuation was adverse events. These will be described in more detail in the safety results. All randomized patients comprised the intent to treat population (ITT). The per protocol population (PP) consisted of the 463 patients who did not have major protocol deviations. Two patients received incorrect medication in this study. One patient randomized to receive placebo received CIC-HFA 74 mcg, and one patient randomized to receive CIC-HFA 282 mcg received placebo instead. This is reflected in the differences in the ITT population and safety population. The safety population was based on what dose the patient actually received (versus intended to receive as in the ITT). Patient disposition is summarized in Table 7.

Table 7. Trial M1-602. Patient Disposition

Category	Ciclesonide Dose			
	CIC-HFA 74 mcg N=122 (%)	CIC-HFA 148 mcg N=125 (%)	CIC-HFA 282 mcg N=136 (%)	Placebo N=130 (%)
ITT Analysis Set	122 (100)	125 (100)	136 (100)	130 (100)
Safety Analysis Set	123 (100.8)	125 (100)	135 (99.3)	130 (100)
PP Analysis Set	111 (91)	110 (88)	122 (89.7)	120 (92.3)
Completed Study	119 (97.5)	121 (96.8)	132 (97.1)	126 (96.9)
Prematurely Discontinued	3 (2.5)	4 (3.2)	4 (2.9)	4 (3.1)
Reason for Discontinuation				
Adverse Event	1 (0.8)	2 (1.6)	1 (0.7)	2 (1.5)
Lack of Compliance	1 (0.8)	0	0	0
Lost to follow-up	1 (0.8)	0	0	0
Patient request	0	1 (0.8)	1 (0.7)	1 (0.8)
Other	0	1 (0.8)	2 (1.5)	1 (0.8)

Source: Module 5.3.5.1.1, Section 10.1, Table 4

Demographics:

The ITT population was predominantly female (320, 62.4%), Caucasian (421, 82.1%), and ranged in age from 12-76 years. Across treatment groups and placebo, the gender, race, ethnicity, and age distribution were fairly even. Overall, 12.7% of the population were aged 12-17 and 1.9% were 65 years of age or older. More patients in the 74 mcg group had current skin prick tests (68.9%), as compared to the 148, 282 mcg and placebo groups (56.8%, 59.6%, and 62.3%, respectively). The demographics are summarized below in Table 8.

Table 8. Trial M1-602. Patient Demographics

Variable	Ciclesonide Dose			
	CIC-HFA 74 mcg N=122 (%)	CIC-HFA 148 mcg N=125 (%)	CIC-HFA 282 mcg N=136 (%)	Placebo N=130 (%)
Mean Age	36.87	36.15	39.63	37.95
Age category				
12-17 years	13 (10.7)	16 (12.8)	19 (14)	17 (13.1)

18-64 years	108 (88.5)	109 (87.2)	112 (82.4)	109 (83.8)
>=65 years	1 (0.8)	0	5 (3.7)	4 (3.1)
Sex				
Male	37 (30.3)	51 (40.8)	53 (39)	52 (40)
Female	85 (69.7)	74 (59.2)	83 (61)	78 (60)
Race				
Caucasian	96 (78.7)	102 (81.6)	111 (81.6)	112 (86.2)
Black	21 (17.2)	19 (15.2)	23 (16.9)	14 (10.8)
Asian	1 (0.8)	3 (2.4)	1 (0.7)	4 (3.1)
American Indian, Alaska Native	2 (1.6)	0	0	0
Pacific Island	1 (0.8)	0	0	1 (0.8)
Unknown	2 (1.6)	1 (0.8)	2 (1.5)	0
Ethnicity				
Hispanic	9 (7.4)	12 (9.6)	11 (8.1)	11 (8.5)
Non-Hispanic	113 (92.6)	113 (90.4)	125 (91.9)	119 (91.5)

Source: Module 5.3.5.1.1, Section 10.4.1, Table 7

Reviewer Comment:

Overall, the patient populations in each group are fairly well matched. The minor differences in demographics would not likely effect study results.

Efficacy

Compliance

Treatment compliance was based on information recorded by the patient in the electronic diary and supplies returned by patients at the end of study. Based on this measure, compliance was relatively high and similar across treatment groups and placebo (89.6%-92%). In the original protocol, compliance was also to be assessed using dose counters; however, this measure was removed in a protocol amendment.

Reviewer Comments:

Due to changes in the protocol, actual usage of the nasal spray was not directly measured, as dose counters were not used. The reported compliance may be an overestimate as usage of the nasal spray is only based on patient recorded data and returned supplies. However, assuming that true compliance was evenly distributed across groups, it is unlikely that this would exaggerate treatment effect. More likely, it would dilute the treatment effect.

Primary Endpoints

This study's primary endpoint was change from baseline in the average AM and PM rTNSS over the 2 week period. Analysis was performed on the ITT population. At baseline the average AM and PM rTNSS over the 2 week period was not significantly different between groups. Based on the pre-specified analysis plan, the 282 mcg dose was first compared to placebo. The 282 mcg dose demonstrated a significantly greater improvement from baseline as compared to placebo. As this was statistically significant, the 148 mcg dose was than compared to placebo, with similar results. The treatment

effect of the 74 mcg dose was then examined, and again showed statistically significant improvement compared to placebo. The treatment difference from placebo for the 74, 148, and 282 mcg doses were 0.66 (0.16, 1.16), 0.9 (0.4, 1.39), and 0.81 (0.32, 1.29), respectively. The values in parentheses are the 95% confidence intervals. There was no dose response, suggesting that the doses chosen were at the plateau of the dose response curve.

Key Secondary Endpoints

The key secondary efficacy variables included change from baseline in average AM and PM iTNSS, AM iTNSS, and AM 24 hour non-nasal symptom score over the 2 week treatment period. Change from baseline RQLQ at the end of study in those with an impaired quality of life (baseline RQLQ ≥ 3) at run-in was also assessed. These endpoints were analyzed sequentially in the manner described in Table 6. At baseline all key secondary efficacy parameters were similar between groups. For change from baseline in average AM and PM iTNSS and AM iTNSS over the 2 week treatment period, all doses showed significant improvement compared to placebo. As with the primary endpoint, there was no dose response. The results for the RQLQ demonstrated no effect of treatment at any dose. As this endpoint lacked statistical significance, per pre-specific analysis plan, no statistical analysis was performed on the AM 24 hour non-nasal symptom score endpoint.

Reviewer comment:

The key secondary endpoint of RQLQ at the end of study for those patients with a baseline RQLQ score ≥ 3 is an issue. Although this was pre-specified, usage of a patient subset is unacceptable as a key secondary endpoint used to support an indication.

Results for the primary and key secondary endpoints are summarized in the table below in Table 9:

Table 9. Trial M1-602. Results for Primary and Key Secondary Endpoints

	Ciclesonide Dose			
	CIC-HFA 74 mcg	CIC-HFA 148 mcg	CIC-HFA 282 mcg	Placebo
Average AM and PM rTNSS				
N	122	125	136	129
Change from baseline over the 2 week treatment period				
LS Mean (SE)	-1.98 (0.18)	-2.21 (0.18)	-2.12 (0.17)	-1.32 (0.18)
Treatment difference vs. Pbo (95% CI)	0.66 (0.16, 1.16)	0.90 (0.4, 1.39)	0.81 (0.32, 1.29)	
p-value vs. Pbo	0.01	<.0001	0.001	
Average AM and PM iTNSS				
N	122	125	136	129
Change from baseline over the 2 week treatment period				
LS Mean (SE)	-1.89 (0.18)	-2.00(0.18)	-1.89(0.17)	-1.14 (0.18)
Treatment difference vs. Pbo	0.75	0.86	0.75	

(95% CI)	(0.25, 1.25)	(0.36, 1.35)	(0.26, 1.23)	
p-value vs. Pbo	0.003	<0.001	0.002	
AM iTNSS				
N	122	125	136	129
Change from baseline over the 2 week treatment period				
LS Mean (SE)	-1.92 (0.19)	-2.06 (0.18)	-1.89 (0.18)	-1.03 (0.18)
Treatment difference vs. Pbo (95% CI)	0.88 (0.37, 1.39)	1.03 (0.52, 1.53)	0.86 (0.36, 1.35)	
p-value vs. Pbo	<0.001	<0.001	<0.001	
RQLQ (patients with baseline score ≥3)				
N	79	86	87	90
Change from baseline over the 2 week treatment period				
LS Mean (SE)	-1.56 (0.15)	-1.32 (0.15)	-1.50 (0.14)	-1.24 (0.14)
Treatment difference vs. Pbo (95% CI)	0.32 (-0.09, 0.72)	0.08 (-0.31, 0.48)	0.26 (-0.14, 0.65)	
p-value vs. Pbo	>0.05	>0.05	>0.05	
AM reflective non-nasal symptoms				
N	121	125	136	129
Change from baseline over the 2 week treatment period				
LS Mean (SE)	-1.54 (0.18)	-1.45 (0.18)	-1.51 (0.17)	-1.06 (0.17)
Treatment difference vs. Pbo (95% CI)	0.48 (-0.01, 0.97)	0.38 (-0.11, 0.87)	0.45 (-0.03, 0.92)	
p-value vs. Pbo	>0.05	>0.05	>0.05	

Source: Module 5.3.5.1.1, Section 11.2.1, Table 9

Reviewer Comment:

These results demonstrate that, at all doses, the test product improves nasal symptoms associated with SAR, and that it has little effect on non-nasal symptoms and quality of life. The lack of effect on non-nasal symptoms and quality of life is in distinction to the results for the ciclesonide 74 mcg dose in the phase 3 SAR trials. In the phase 3 trials, a modest effect was seen for ocular symptoms in one trial (060-622) and RQLQ in both trials (060-622/634). Similar to the phase 3 results, the 148 mcg dose demonstrated minimal to no effect.

The improvement seen in this trial for the nasal effect is modest, but similar in magnitude compared to Omnaris (ciclesonide aqueous nasal spray). The RQLQ results are also similar to the Omnaris data in the ≥ 12 age group; in that statistically/clinically significant improvements were not seen. It should be noted that the sponsor analysis only considered patients with a baseline RQLQ score of ≥3 for their RQLQ analysis. Usage of such a subset is problematic, as patients were not stratified based on RQLQ score, thus randomization may no longer be valid, and that population subset may no longer be representative of the total population. Based on the statistical plan, no statistical analysis should have been done on the AM reflective non-nasal symptoms;

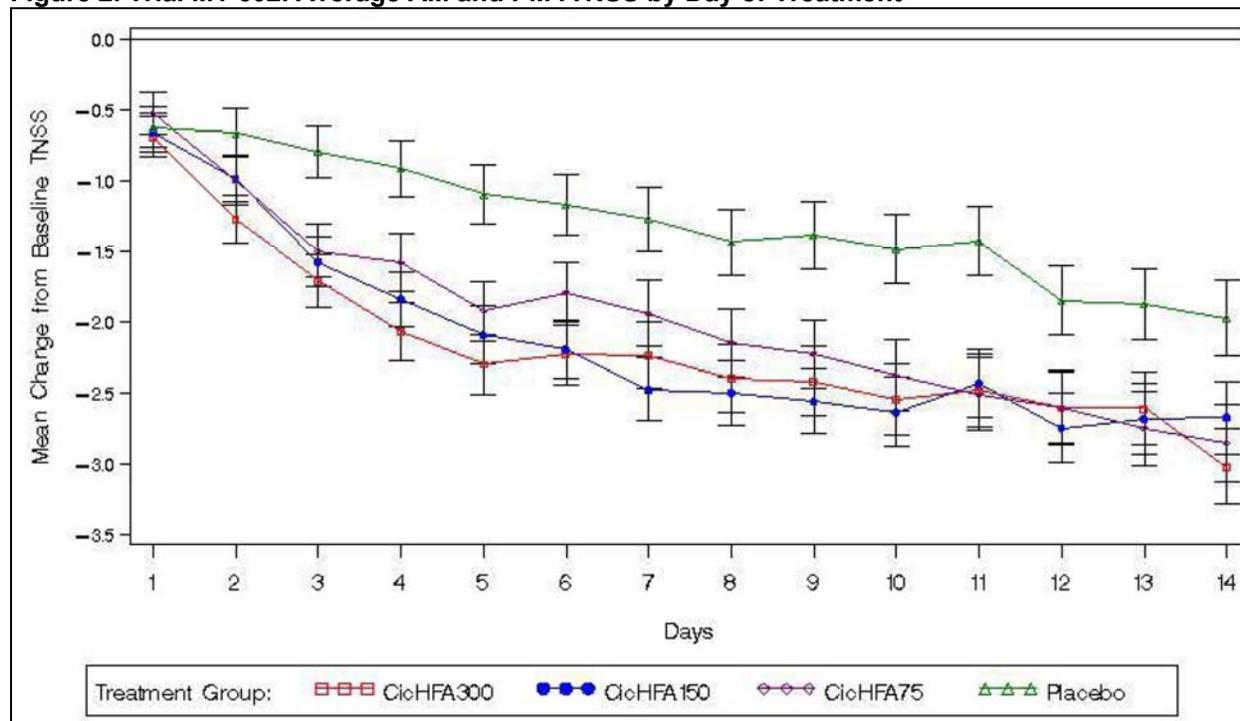
however, *p*-values were calculated. This does not affect interpretation of results as all *p*-values were >0.05.

Other Endpoints

In addition to primary and secondary endpoints, multiple other supportive endpoints were analyzed.

The average AM and PM rTNSS for each treatment day were reported and analyzed by comparing each treatment group to placebo for each day. For the 74 mcg group, statistically significant improvement compared to baseline was first noted on day 3 (*p*<0.05), and continued daily throughout the treatment period. For the 148 mcg dose group, statistically significant improvement was first noted on day 2 (*p*<0.05) and continued daily until the end of the treatment. The 282 mcg dose first showed an effect on day 3 (*p*<0.05), which lasted until day 13, however on day 14 there was no statistically significant difference (*p*=0.056). The largest treatment effect occurred on days 7, 5, and 11 for the 282, 148, and 74 mcg dose, respectively. Results are summarized in Figure 2. Note that the legend uses estimated ex-actuator dose, rather than final determined dose.

Figure 2. Trial M1-602. Average AM and PM rTNSS by Day of Treatment

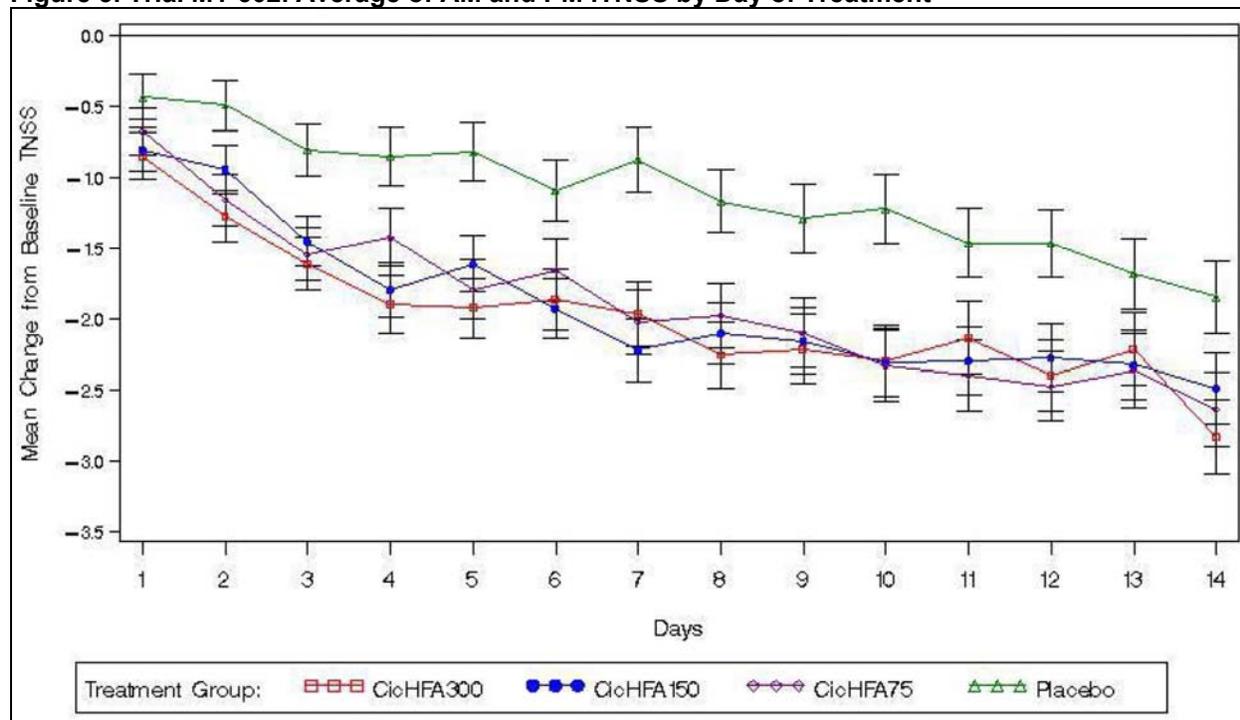


*CicHFA300= 282mcg dose, CicHFA150= 148 mcg dose, CicHFA75= 74mcg dose
 Source: Module 5, 5.3.5.1.1, Section 14, Figure 14.2.1.1.1

A similar analysis was also performed using average AM and PM iTNSS each treatment day comparing ciclesonide dose groups to placebo. For the 148 mcg group, a

statistically significant ($p < 0.05$) treatment effect was noted on days 2-10 and days 12-14 compared to placebo. For the 74 mcg group, days 2-5, days 7-12 and day 14 demonstrated statistically significant improvement from baseline. The 282 mcg group demonstrated statistically significant improvement on days 3-12. These results are summarized Figure 3:

Figure 3. Trial M1-602. Average of AM and PM iTNSS by Day of Treatment



*CicHFA300= 282mcg dose, CicHFA150= 148 mcg dose, CicHFA75= 74mcg dose
Source: Module 5, 5.3.5.1.1, Section 14, Figure 14.2.2.1.1

Reviewer comment:

In describing Figure 2 and Figure 3, the sponsor states that for the 282 mcg group, there was no statistical difference compared to placebo at day 14, however, this does not appear to be the case based on the figures. The reason for the discrepancies is not clear.

Change from baseline of the average AM and average PM rTNSS over the treatment period was also assessed. For both parameters and at every dose, ciclesonide showed statistically significant improvement compared to placebo. For the AM rTNSS, the improvement compared to placebo was 0.79, 0.87, and 0.64 for the 282, 148, and 74 mcg dose, respectively. For the PM rTNSS, the results were similar and the improvements were of similar magnitude.

Similar analysis was also performed on average AM and average PM iTNSS over the treatment period compared to baseline. Like the previous results, at each dose, CIC-

HFA showed statistically significant improvement in both parameters. These results are summarized in Table 10:

Table 10. Trial M1-602. Change from Baseline for Average AM and Average PM rTNSS and iTNSS over the 2 Week Treatment Period

	Ciclesonide Dose			
	CIC-HFA 74 mcg	CIC-HFA 148 mcg	CIC-HFA 282 mcg	Placebo
Average AM rTNSS				
N	122	125	136	129
Change from baseline over the 2 week treatment period				
LS Mean (SE)	-1.93 (0.19)	-2.16 (0.18)	-2.08 (0.18)	-1.29 (0.18)
Treatment difference vs. Pbo (95% CI)	0.64 (0.13, 1.15)	0.87 (0.37, 1.38)	0.79 (0.29, 1.28)	
p-value vs. Pbo	0.015	<.001	0.002	
Average PM rTNSS				
N	122	125	136	129
Change from baseline over the 2 week treatment period				
LS Mean (SE)	-2.01 (0.19)	-2.26 (0.18)	-2.17 (0.18)	-1.33 (0.18)
Treatment difference vs. Pbo (95% CI)	0.68 (0.17, 1.19)	0.93 (0.42, 1.44)	0.84 (0.35, 1.34)	
p-value vs. Pbo	0.009	<0.001	<0.001	
Average AM iTNSS				
N	122	125	136	129
Change from baseline over the 2 week treatment period				
LS Mean (SE)	-1.92 (0.19)	-2.06 (0.18)	-1.89 (0.18)	-1.18 (0.18)
Treatment difference vs. Pbo (95% CI)	0.88 (0.37, 1.39)	0.103 (0.52, 1.53)	0.86 (0.36, 1.35)	
p-value vs. Pbo	<0.001	<0.001	<0.001	
Average PM iTNSS				
N	122	125	136	129
Change from baseline over the 2 week treatment period				
LS Mean (SE)	-1.87 (0.19)	-1.94 (0.19)	-1.88 (0.18)	-1.18 (0.18)
Treatment difference vs. Pbo (95% CI)	0.68 (0.16, 1.2)	0.76 (0.24, 1.27)	0.70 (0.19, 1.2)	
p-value vs. Pbo	0.01	0.004	0.007	

Source: Module 5.3.5.1.1, Section 11.2.2, Table 10 & 12

Change from baseline in the average of AM and PM reflective individual nasal symptom scores over the treatment period was also assessed. At baseline, across each individual domain, the symptom scores were similar. Over the 2 week treatment period, for all doses, there was improvement across all domains compared to placebo. The improvements in each domain were comparable to each other. A similar analysis was performed for the average of AM and PM instantaneous individual nasal symptoms scores over the treatment period. The results were similar.

Change from baseline in the individual domains of the RQLQ was also analyzed. Much like the composite score, there was no treatment effect at any dose.

Change from baseline in AM 24 hour individual reflective non-nasal symptoms was also analyzed. Like the composite analysis, no differences between treatment groups and placebo were seen for the itching/burning and redness of eyes domains. However, there was significant improvement in the itching of the ears or palate and tearing/watering eyes domains for all ciclesonide doses compared to placebo.

In addition to analysis of patient assessed nasal symptom scores, analysis was also performed on physician assessed nasal symptom scores (PNSS). At baseline, PNSS were similar across all groups. Following 2 weeks of treatment, there significant improvement for all doses compared to placebo in the total score. When the individual domains were analyzed, only the domains “runny nose” and “itchy nose” demonstrated significant improvement from baseline. The “nasal congestion” and “sneezing” domain did not.

Change from baseline in daily AM and PM iTNSS and rTNSS was also analyzed. For these parameters there was generally significant improvement at all doses compared to baseline for the majority of the treatment period.

Subgroup analyses:

Subgroup analysis was performed based on age, sex, and race for the primary and key secondary measures. Patient age was divided in to 3 subgroups: 12-17, 18-64, and 65 and above. With regard to nasal symptoms, the results were similar to whole population. However, for the 65 year and older population, no treatment effect was seen for ciclesonide versus placebo. There were only 10 patients in the study who were 65 years or older in age. This small sample size likely accounts for the lack of effect seen in this age group. Subgroup analysis by sex and ethnicity yielded similar results to the whole population.

Reviewer Comment:

Based on these results, ciclesonide at doses from 74 - 282 mcg once daily is likely effective at improving the nasal symptoms associated with seasonal allergic rhinitis, though not non-nasal symptoms nor disease related quality of life. However, it should be noted that higher doses show no increased benefit with regard to efficacy. Therefore, it is possible that the lowest effective dose has yet to be identified.

Safety:

Exposure

Safety analysis was performed on all randomized patients who received at least one dose of study medication. A total of 513 patients were included in the safety data set. The mean exposure to CIC-HFA or placebo was between 15 - 15.1 days across groups. Four hundred ninety eight (498) patients completed the study.

Deaths/SAEs

There were no deaths or serious AEs in this study.

Treatment emergent adverse events (TEAEs)

There were similar numbers of TEAEs across all groups. The most common TEAE reported by System Organ Class (SOC) was Respiratory, Thoracic, or Mediastinal Disorders. The most common TEAE was headache. No dose effect was noted for any TEAEs. TEAEs that occurred in $\geq 2\%$ of the patients are summarized in Table 11.

Table 11. Trial M1-602. Summary of Adverse Events

	CIC-HFA 74 mcg	CIC-HFA 148 mcg	CIC-HFA 282 mcg	Placebo
N	123	125	135	130
Any SAE	0	0	0	0
Any TEAE	17 (13.8%)	12 (9.6%)	19 (14.1%)	14 (10.8%)
Discontinuation due to TEAEs	1 (0.8%)	2 (1.6%)	1 (0.7%)	2 (1.5%)
Common TEAEs ($\geq 2\%$ of Patients in any treatment group)				
Headache	6 (4.9%)	2 (1.6%)	3 (2.2%)	2 (1.5%)
Nasal Discomfort	1 (0.8%)	1 (0.8%)	3 (2.2%)	3 (2.3%)

Source: Module 5.3.5.1.1, Section 12.2.1, Table 19 and 20

Discontinuations due to TEAEs were similar across all groups. These results are summarized Table 11. Six (6) total patients discontinued due to TEAEs. One (1) patient receiving the 282 mcg dose discontinued due to a burning sensation in her nose that was deemed severe in intensity. The patient recovered after discontinuation of medication. At the 148 mcg dose, 2 patients discontinued due to TEAEs which were sinusitis and pharyngitis. Both were treated with antibiotics and recovered. In the 74 mcg group, one patient discontinued due to bronchitis and maxillary sinusitis. She was treated with antibiotics and recovered. Two (2) patients in the placebo group discontinued due to TEAEs which were migraine and insomnia.

Vitals/Physical Exam

Vital signs and physical exam findings were not significantly impacted by use of test article at any dose. There were only minimal changes in vital signs noted between visit B0 and T1/T_{end}. The same was true for physical exam findings.

Ear Nose Throat Examinations:

Ear, nose, throat exam results were notable for one nasal septum perforation. This was in 58 year old female patient (5357/80294) with SAR/PAR, mild asthma, and hypertension who was in the 74 mcg treatment arm. At the screening visit, she was noted to have inflammation of her nasal turbinates. At the end of the single blind run in period, she was noted to have bilateral septal erosions, and after the treatment period, a

septal perforation was recorded. It was mild in intensity and no action was taken. She had no other TEAEs. For the duration of the study, she reported moderate to severe nasal symptoms. Subsequent to the submission of the NDA, it was discovered that this patient had a significant history of nasal pathology. She had a history of nasal polyps which were surgically removed in 1993. In a clinic note from 1998, it was noted that she has a “septal perforation secondary to surgery in the past.” The location was not noted. She was also noted to have nasal polyps in 1999, however on that visit, no mention was made in the physical exam of a septum perforation.

Reviewer Comment:

Despite the fact that it was mild in intensity, the occurrence of the septal perforation is concerning as these are seldom seen in the setting of a clinical trial. Based on the patient narrative, it seems related to study drug, and it is at the proposed commercial dose. The perforation noted in this trial was likely a new occurrence as it was not noted at screening or at the 1999 physician’s visit where a recurrence of polyps was noted. However, it is also unlikely that a septal perforation would heal spontaneously without intervention, therefore it is also possible that nasal septal perforation was missed in the 1999 physician assessment and at the screening visit. The sponsor argues that this patient should not have been randomized based on her history of previous surgery, nasal polyps, and nasal septum perforation, and physical exam findings of nasal erosions at the end of the placebo run-in period. Regardless, the patient who developed a nasal perforation in this trial is typical of one that would be prescribed ciclesonide HFA, were it approved. Hence, this AE should still weigh into the risk/benefit analysis of this product.

Overall Reviewer Comment Trial M1-602

Based on the results from this trial, all doses of ciclesonide used improved patient nasal symptoms. There was no dose response. None of the doses had an effect of non-nasal symptoms or disease related quality of life. From these results, the sponsor decision to proceed with the 74 and 148 mcg dose in the pivotal trial is reasonable; however, the lack of dose response implies that lower doses may still be effective. When the sponsor pursues studies in the pediatric population, usage of lower doses may be indicated. With regard to adverse events, this product was fairly well tolerated. The nasal septum perforation is concerning, as perforations are generally rare occurrences.

5.3.2 Trial 060-622

Administrative Information

- **Study title:** A Randomized, Multicenter, Double-Blind, Placebo- Controlled, Parallel Group, Phase III Clinical Trial to Assess the Safety and Efficacy of Ciclesonide HFA Nasal Aerosol (148 mcg once daily and 74 mcg once daily) for the Treatment of Seasonal Allergic Rhinitis to Mountain Cedar in Subjects 12 years and Older
- **Study dates:** 11/15/2008-2/17/2009 (winter season)

- **Study sites:** 7 US centers (Texas)
- **Relevant Allergen:** Mountain Cedar
- **Study report date:** 12/01/2010

Objectives/Rationale

- To demonstrate the efficacy of ciclesonide HFA applied as a nasal aerosol (148 mcg and 74 mcg) once daily compared to placebo in subjects with SAR.
- Evaluate the safety and tolerability of ciclesonide HFA nasal aerosol once daily as compared to placebo in subjects with SAR.

Study Design and Conduct

Overview

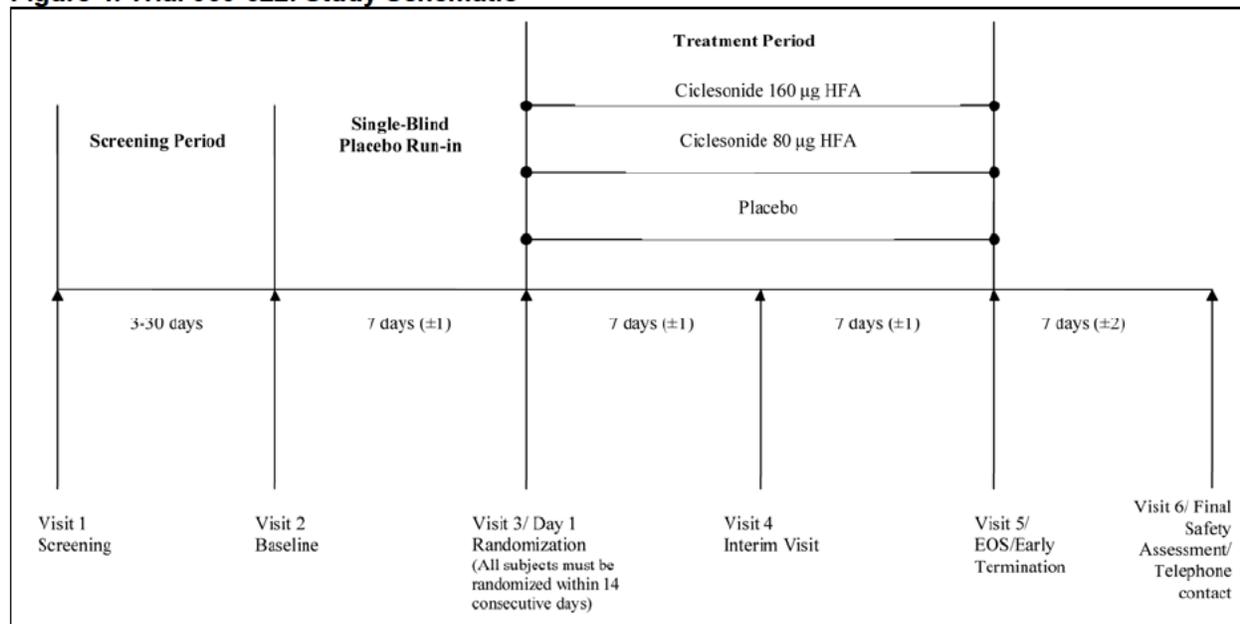
This was double-blind, randomized, placebo controlled, parallel group, multi-center, efficacy and safety study in 707 SAR patients 12 years of age and older. This study consisted of a 3 - 30 day screening period, a 1 week single-blind placebo run-in period, a 2 week double-blind treatment period, followed by a 7 day washout period.

The screening period began with visit 1 and ended prior to the single-blind placebo run-in visit (visit 2). During the screening period, patients signed the informed consent, underwent clinical laboratory evaluations, and skin prick tests to confirm seasonal allergy to Mountain Cedar.

The single blind run-in period began with visit 2. This was scheduled for all subjects when the pollen counts at the investigational sites had been elevated for at least 3 consecutive days at levels ≥ 50 grains/cubic meter. All subjects were randomized within 14 consecutive days in an attempt to maintain equivalent allergen exposure in all patients. During the single blind run-in period, patients self administered single blinded placebo every morning. Patients also assessed and recorded their reflective (rTNSS) and instantaneous (iTNSS) nasal symptoms (sneezing, running nose, itchy nose, and nasal congestion) twice daily (AM and PM). Reflective and instantaneous (rTOSS and iTOSS) ocular symptoms (itching, tearing, and redness) were also assessed twice daily. The symptoms were rated as in Trial M1-602. Further details regarding the TNSS/TOSS can be found under efficacy assessments.

Following the run-in period, at visit 3 patients were randomized to 2 weeks of double-blind treatment with either CIC-HFA 74 mcg once daily or 148 mcg once daily, or placebo. During the treatment period, patients recorded their TNSS/TOSS as in the run-in period. They returned for study visits after 7 days (visit 4) and 14 days (visit 5) of double-blind treatment. The final study visit occurred 7 days after the last dose (day 21, visit 6). The study schematic and assessment schedule are summarized in Figure 4 and Table 12, respectively.

Figure 4. Trial 060-622. Study Schematic



Source: Trial 060-622, Figure 9.1-1, pp30

Table 12. Trial 060-622. Assessment Schedule

Visit	1	2	3	4	5	6
	Screen	Run in	Randomization		End	
Day	-37 to -10	-7 ±1	1	8 ±2	15 ±2	22 ±2
Informed consent	X					
Inclusion/Exclusion Review	X	X	X			
Review of Randomization Criteria			X			
Rhinoconjunctivitis Quality-of-Life (RQLQ)			X		X	
Medical history	X					
Concomitant medication history	X	X	X	X	X	X
Physical exam (vital signs)	X				X	
Ear, nose and throat exam (ENT)	X		X		X	X
Serum pregnancy	X				X	
Clinical lab evaluation	X				X	
Skin test for Mountain Cedar	X					
Adverse event monitoring	X	X	X	X	X	X
Dispense single-blind placebo		X				
Collect and review diary			X	X	X	
Randomization			X			
Dispense double-blind study medication			X			
Instruct on recording/review of Reflective and instantaneous TNSS/TOSS		X	X	X	X	
Return all study medications, used and unused		X	X	X	X	
Dispense/Review Medical Event Calendar	X	X	X	X	X	
Daily Pollen Counts/rainfall	X	X	X	X	X	X

Source: Trial 060-622 CSR, Table 9.1-1, pp29

Study Population:

This study included 707 patients ages 12 years and older with SAR. In order to participate, the patients had to meet the following inclusion/exclusion criteria at screening, the continuation criteria at visit 2, and the randomization criteria at visit 3.

Key Inclusion Criteria

1. Subject must be in general good health (defined as the absence of any clinically relevant abnormalities as determined by the Investigator) based on screening physical examination, medical history, and clinical laboratory values (Hematology, Chemistries and Urinalysis).
2. A history of SAR to Mountain Cedar for a minimum of two years immediately preceding the study Screening Visit (Visit 1), and have required treatment in the past and in the Investigator's judgment (through exposure to allergen) is expected to require treatment throughout the entire study period.
3. A demonstrated sensitivity to Mountain Cedar known to induce SAR through a standard skin prick test administered at Visit 1 (screening).
4. If a female 65 years of age or younger, the patient must have a negative serum pregnancy test (performed at Visit 1) prior to randomization at Visit 2. Women of childbearing potential Females of childbearing potential must be instructed to and agree to avoid pregnancy during the study and must use an acceptable method of birth control:
 - a. An oral contraceptive, an intrauterine device (IUD), implantable contraceptive, transdermal or injectable contraceptive for at least 1 month prior to entering the study and will continue its use throughout the study and for thirty days following study participation.
 - b. Barrier method of contraception, e.g., condom and/or diaphragm with spermicide while participating in the study.
 - c. Abstinence.

Key Exclusion Criteria:

1. Female subject who is pregnant or lactating.
2. History of physical findings of nasal pathology, including nasal polyps or other clinically significant respiratory tract malformations; recent nasal biopsy; nasal trauma; nasal ulcers or perforations; or surgery and atrophic rhinitis or rhinitis medicamentosa (all within the last 60 days prior to the Screening Visit).
3. History of a respiratory infection or disorder [including, but not limited to bronchitis, pneumonia, chronic sinusitis, influenza, severe acute respiratory syndrome (SARS)] within the 14 days preceding the Screening Visit (Visit 1).

4. History of alcohol or drug abuse (or a positive urine drug screen at Visit 1) within two years preceding the Screening Visit.
5. Plans to travel outside the study area (the known pollen area for the investigative site) for more than 24 hours during the Run-in period or for 2 or more consecutive days between Randomization Visit (Visit 3) and the final Treatment Visit (Visit 5).
6. Active asthma requiring treatment with inhaled or systemic corticosteroids and/or routine use of beta-agonists and any controller drugs; intermittent use (less than or equal to 3 uses per week) of inhaled short acting beta-agonists is acceptable.
7. Use of any prohibited concomitant medications within the prescribed (per protocol) time period prior to the Screening Visit and expected use during treatment period (see Table 13)
8. Use of antibiotic therapy for acute conditions within 14 days prior to the Screening Visit. Low doses of antibiotics taken for prophylaxis are permitted if the therapy was started prior to the Screening Visit and is expected to continue throughout the trial.
9. Initiation of immunotherapy during the study period or dose escalation during the study period. However, initiation of immunotherapy 90 days or more prior to the Screening Visit and use of a stable (maintenance) dose (30 days or more) may be considered for inclusion.
10. Previous participation in an intranasal ciclesonide HFA nasal aerosol study.
11. Non-vaccinated exposure to or active infection with, chickenpox or measles within the 21 days preceding the Screening Visit.
12. Use of topical corticosteroids in concentrations in excess of 1% hydrocortisone or equivalent within 30 days prior to Visit 2; use of a topical hydrocortisone or equivalent in any concentration covering greater than 20% of the body surface; or presence of an underlying condition (as judged by the investigator) that can reasonably be expected to require treatment with such preparations during the course of the study.
13. Initiation of pimecrolimus cream 1% or greater or tacrolimus ointment 0.03% or greater during the study period or planned dose escalation during the study period. However, initiation of these creams/ointments 30 days or more prior to the Visit 1 and use of a stable (maintenance) dose during the study period may be considered for inclusion.
14. Have any of the following conditions that are judged by the investigator to be clinically significant and/or affect the subject's ability to participate in the clinical trial:
 - a. impaired hepatic function including alcohol-related liver disease or cirrhosis;

- b. history of ocular disturbances e.g. glaucoma or posterior subcapsular cataracts;
- c. any systemic infection
- d. hematological, hepatic, renal, or endocrine
- e. gastrointestinal disease
- f. malignancy
- g. current neuropsychological condition

Key Continuation Criteria:

1. Subject continues to meet the inclusion/exclusion criteria.
2. Subject has not experienced an adverse event that would result in failure to continue to meet inclusion/exclusion criteria.
3. Subject has not suffered from the common cold or acute sinusitis within the 14 days prior to the Single-blind Placebo Period (Visit 2).

Key Randomization Criteria:

1. Subject did not leave the study area (the known pollen area for the investigative site) for longer than 24 hours during the Single-blind Placebo Run-in Period.
2. Subject continues to meet the inclusion/exclusion criteria.
3. Subject has a minimum cumulative subject-assessed *reflective* TNSS of 47 (out of a possible 84) over any 3 of the last 4 days (including AM assessment at Visit 3) of the Single-Blind Placebo Run-in Period.
4. The cumulative subject-assessed *reflective* scores for runny nose OR nasal congestion must be at least 10 (out of a possible 21) during any 3 of the last 4 days for the single-blind placebo run-in period (which includes the AM assessment at Visit 3).
5. Each subject must have adequately completed the AR Assessment Diary. Failure is defined as not filling out the diary on more than 1 calendar day during the Single-Blind Placebo Run-in Period).
6. Each subject may not have missed more than 1 day of their single-blind medication during the entire Single-Blind Placebo Run-in Period.
7. Subject has not used any of the prohibited concomitant medications during the Single-Blind Placebo Run-in Period.
8. Subject has not suffered from the common cold or acute sinusitis within the 14 days prior to the Randomization Visit (Visit 3).

Reviewer Comment:

The study design is typical for a SAR study. The inclusion, exclusion, and randomization criteria are also appropriate. The patient population was appropriate and typical for a SAR clinical trial. This population was similar to the populations used in the Omnaris clinical development program.

Treatments

Treatment groups

Ciclesonide HFA nasal aerosol 74 mcg (37 mcg each nostril) daily
 Ciclesonide HFA nasal aerosol 148 mcg (74 mcg each nostril) daily
 Placebo HFA nasal inhaler (2 inhalations) daily

Concomitant Medications/Prohibited Medications

All medications taken by the patients were recorded in the CRF. If the patient was on a prohibited medication which could not be withdrawn, the patient was not allowed to enter the trial. In cases where the medication could be discontinued, it was not to be for the sole purpose of enrollment in the trial. The prohibited medications are summarized in the Table 13.

Table 13. Trial 060-622. Prohibited Medications

Medication Disallowed for the Study Duration	Required Withholding Interval Prior to Visit 2
Topical/Oral/Nasal Decongestants	10 days
Ocular allergy preparations	10 days
Short-acting antihistamines (nasal and ocular)	5 days
Long-acting antihistamines (nasal and ocular)	10 days
OTC cough and cold preparations or sleep medications	10 days
Airozan® (OTC food supplement/diet leukotrienes)	7 days
Cromolyn, nedcromil, or Iodoxamide (intranasal, ocular, or oral)	14 days
Leukotriene or 5-LO inhibitors	14 days
Inhaled/oral/intranasal anticholinergics	14 days
Tricyclic antidepressants	14 days
Monoamine oxidase inhibitors	14 days
Inhaled/systemic/intranasal corticosteroids	30 days
Azoles, anti-fungals	30 days
Immunosuppressive drugs	60 days

Source: Trial 060-622, Table 9.4.1-1, pp38

All the listed medications had to be discontinued at the given interval prior to visit 2 (single-blind placebo run-in period), and could not be taken during the remainder of the study. These restrictions were in addition to those outlined in the exclusion criteria. Any deviation with regard to medications was noted in the CRF. Aspirin (325mg/day or less) was allowed, however it had to be started prior to visit 1 and the dose has to remain stable for the duration of the study.

Efficacy Parameters

Primary Efficacy Endpoint:

- Change from baseline in the AM and PM reflective Total Nasal Symptom Score (rTNSS) averaged over the 2 week treatment period, where baseline was defined as the average of the responses obtained during the run-in period up to 6 days prior to randomization.

Key Secondary Efficacy Endpoints:

Change from baseline in the following parameters

- The average of AM and PM instantaneous TNSS over the 2 week treatment period
- The average of AM and PM rTOSS over the 2 week treatment period in patients with a baseline rTOSS ≥ 5.0

Other Secondary Endpoints

Change from baseline in the following parameters

- AM rTNSS, PM rTNSS, average AM and PM rTNSS at each day, averaged over each week, and averaged over the two-week treatment period (except two-week average of AM and PM rTNSS, which is the primary efficacy endpoint).
- AM iTNSS, PM iTNSS, average AM and PM iTNSS at each day, averaged over each week, and averaged over the two-week treatment period (except two-week average of AM and PM iTNSS, which is the first key secondary efficacy endpoint).
- AM rTOSS, PM rTOSS, average AM and PM rTOSS at each day, averaged over each week, and averaged over the two-week treatment period in subjects with baseline TOSS ≥ 5.0 (except two-week average of AM and PM iTOSS, which is the second key secondary efficacy endpoint).
- AM iTOSS, PM iTOSS, average AM and PM iTOSS at each day, averaged over each week, and averaged over the two-week treatment period in subjects with baseline TOSS ≥ 5.0 .
- Individual AM reflective nasal symptom score (NSS), individual PM rNSS, individual AM and PM rNSS at each day, averaged over each week, and averaged over the two-week treatment period.
- Individual AM iNSS, individual PM iNSS, individual AM and PM iNSS at each day, averaged over each week, and averaged over the two-week treatment period.

- Individual AM reflective ocular symptom score (OSS), individual PM rOSS, individual AM and PM rOSS at each day, averaged over each week, and averaged over the two-week treatment period in subjects with baseline TOSS ≥ 5.0 .
- Individual AM iOSS, individual PM iOSS, individual AM and PM iOSS at each day, averaged over each week, and averaged over the two-week treatment period in subjects with baseline TOSS ≥ 5.0 .
- Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities (RQLQ(S)) total and individual items at visit 5 in impaired patients (baseline RQLQ(S) score ≥ 3.0).

Baseline assessments were made during the single-blind placebo run-in period.

Onset of Action Endpoints

- Onset of nasal improvement, defined as the first assessment at which *instantaneous* TNSS for active treatment demonstrates an improvement over placebo from baseline with one-sided p-value of ≤ 0.025 . Additionally, the p-value of ≤ 0.025 for the test of a difference between treatments should be maintained for some period from this point forward. The active treatment and placebo group will be compared at each time point using ANCOVA with covariate adjustment for baseline, center, and treatment.
- Onset of ocular improvement, defined as the first assessment at which *instantaneous* TOSS for active treatment demonstrates an improvement over placebo from baseline with one-sided p-value of ≤ 0.025 in subjects with baseline TOSS ≥ 5.0 . Additionally, the p-value of ≤ 0.025 for the test of a difference between treatments should be maintained for some period from this point forward. The active treatment and placebo group will be compared at each time point using ANCOVA with covariate adjustment for baseline, treatment, and treatment.

Time to Maximal Effect Endpoint:

- The time to maximal effect is defined as the number of days until the first treatment day on which the estimated difference between CIC-HFA and placebo is at least 90% of the largest estimated difference. The change from baseline in the average of AM and PM patient-assessed reflective TNSS will be used to evaluate this measure. Estimated differences between treatment groups will be generated at each treatment day using ANCOVA with covariates adjustments for baseline, center, and treatment.

Efficacy Assessments:

Total Nasal Symptom Score (TNSS).

The symptoms and ratings used in the TNSS assessment were identical to study M1-602.

The reflective TNSS (rTNSS) represented perception of symptoms in the preceding 12 hours and the instantaneous TNSS (iTNSS) reflected symptoms in the past 10 minutes. During this study both the iTNSS and rTNSS were recorded at least twice daily (AM and PM). The AM assessment occurred prior to the morning dose of study medication, and before bathing, consumption of food or beverage, or strenuous activities. The PM assessment occurred 12 hours after.

Total Ocular Score (TOSS)

This subject assessed score was comprised of 3 domains which were ocular tearing, itching, and redness. It was scored similar to the TNSS. The reflective and instantaneous TOSS also assessed symptoms from the past 12 hours and 10 minute, respectively. The AM and PM timing of these assessments was the same as for the TNSS.

In addition to the AM and PM assessments for the TNSS/TOSS, on visit 2 (day 1 of the single-blind placebo run-in period), patients assessed their iTOSS and iTNSS at 4, 6, 8, and 10 hours post-dose. On day 2 of the run-in period, additional iTOSS and iTNSS assessments occurred 6 hours post dose. On days 3-7 of the run-in period AM and PM assessments were performed twice daily.

During the double-blind treatment period additional assessments also occurred. On visit 3 (day 1 of the treatment period), patients assessed their iTOSS and iTNSS at 4, 6, 8, and 10 hours post dose. On day 2 of the treatment period, an additional assessment of the iTOSS and iTNSS occurred at 6 hours post-dose. All other days had only the AM and PM assessments.

The order of assessments were iTOSS, iTNSS, rTOSS, and rTNSS for the AM and PM assessments.

Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities (RQLQ(S)):

The RQLQ(S) has 28 questions in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). Subjects recall their experiences during the previous week and to give their responses on a 7-point scale (0 = Not Troubled to 6 = Extremely Troubled). When required at a particular visit, this questionnaire is to be the first subject-completed activity of the visit. The self-administered version of the RQLQ(S) will be completed by the subjects at the investigator site at study Visits 3 and 5/End of Study visit.

Reviewer Comments:

The primary endpoints and efficacy assessments are typical for SAR trials. They are also similar to the endpoints used in the Omnaris trials. Positive results for the primary would be supportive of the proposed indication.

However, it should be noted that for all key secondary and secondary endpoints that involved ocular symptoms or RQLQ, only a subset of the patient population was analyzed. Both measures were only analyzed for those who were deemed symptomatic (i.e. TOSS \geq 5, RQLQ \geq 3). A similar tactic was employed in trial M1-602, and all subsequent trials. Analyzing only the subset is problematic, as it does not represent the whole SAR population, and patients were not randomized based on ocular symptoms or RQLQ. Efficacy conclusions for ocular symptoms and RQLQ cannot be based on these endpoints.

Safety Assessments:

- Spontaneous and elicited adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs
- Nasal AEs, including epistaxis, nasal ulceration, and nasal perforation
- Physical examinations, including ENT examinations. The ENT exams were to be performed and data recorded as in trial M1-602 (reviewed in section 5.3.1)
- Clinical laboratory evaluations
- Vital signs (blood pressure and pulse rate)

These assessments were performed as summarized in Table 12.

Compliance Assessment:

Compliance was measured based on patient/caregiver diary. Compliance was based on the number of doses expected to be taken. Percent compliance was calculated as follows:

$100 \times (\# \text{ days of compliance}) / (\# \text{ days during treatment period})$.

Ethics:

This study was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this study protocol. No changes were made without the IRB's approval.

Statistical Plan:

Sample Size

The sample size calculation was based on the primary efficacy endpoint. Based on study M1-401 (not reviewed), the standard deviation for the primary endpoint was assumed to be 2.1. From this standard deviation, 200 subjects per group were projected to provide at least 85% power to detect a difference between treatment groups of 0.7 in change from baseline with a 2-sided alpha of 0.025. Therefore, the sponsor planned to randomize approximately 660 patients (220 in each group).

Analysis populations:

The sponsor pre-defined several populations for analysis. These included the intention to treat (ITT) population, the per protocol (PP) population, and safety population. The ITT population was defined as those patients who were randomized, receive at least one dose of trial medication, and had at least one post-baseline value of efficacy. This population will be used for all efficacy measures. The PP population consisted of patients in the ITT population without any important protocol deviations, and data obtained from other patients prior to the first important protocol deviation. The PP will be used as supportive analyses for reflective and instantaneous TOSS/TNSS and RQLQ(S) in impaired subjects. The safety population consisted of those patients who were randomized and received at least one dose of trial medication.

Important Protocol Deviations:

Important protocol deviations (IPDs) were a subset of protocol deviations deemed important based on review of subject data by Sunovion personnel. This review was done prior to database lock. The deviations reviewed included, but were not limited to the following:

- Did not meet inclusion/exclusion criteria at Visit 1
- Did not meet continuation criteria at Visit 2
- Did not meet randomization criteria at Visit 3
- Received any disallowed concomitant medication for greater than 15% of their time during the double-blind treatment period (including medications in a disallowed drug class even if the medication was not specifically disallowed)
- Double-blind study medication compliance <80% or >120%
- Female subject with positive or missing pregnancy test result
- Other – further broken down if significant numbers in this group

If a large number of IPDs were categorized as “other,” this was further broken down.

Efficacy Analysis

The primary efficacy endpoint was the rTNSS averaged over the 2 week treatment period and analyzed in the ITT population. Treatment groups were compared using ANCOVA with factors of baseline TNSS, center, and treatment. In order to minimize type I error rates, a closed tree gatekeeping testing procedure based on the Bonferroni test was used. Doses were compared to placebo at the 0.025 significance level. No comparisons were made between doses. For calculation of averages, the PM measurements were averaged with the AM measurements on the following calendar days.

The key secondary endpoints were analyzed in a manner similar to the primary endpoint. Analyses of first key secondary endpoints were only performed when the primary endpoints achieved significance. Analyses of the second key secondary endpoint were only performed if the first key secondary endpoint achieved significance.

The other secondary endpoints were analyzed using the same ANCOVA model as the primary efficacy endpoint, using the appropriate baseline measure as the covariate. Only the primary and key secondary endpoints had p-values which were adjusted for multiple comparisons. For all other endpoints, no adjustment was made.

Onset of action was assessed by examining the change from baseline in the iTNSS at each time point during day 1 and day 2 of the double blind treatment period (see Efficacy Assessments for timepoints). Onset was defined as the first assessment when the iTNSS for CIC-HFA demonstrated an improvement over placebo from baseline with a one sided p-value of ≤ 0.025 , and the p-value was maintained for some period thereafter. Groups will be compared using ANCOVA. Onset of action for ocular symptoms was assessed based on change from baseline in iTOSS at each time point during day 1 and 2 of treatment. The analysis was similar to nasal symptom analysis, except that it was in only in patients with a baseline TOSS ≥ 5 .

The time to maximal effect was defined as the number of days until the first treatment day on which the estimated difference between test product and placebo is at least 90% of the largest estimated difference. The efficacy measure that was compared to determine time to maximal effect was the average of the AM and PM rTNSS. Differences between groups will be estimated for each day using ANCOVA.

Results:

Amendments:

The original protocol was submitted on 9/5/2008. An amendment was submitted on 12/3/08. This amendment added a device reaction survey to assess the patients' reaction to the new device. A change to the analysis plan was made on 2/10/09. This redefined the ITT population to include all randomized patients who received at least one dose of double blind study drug and removed the requirement for at least one post baseline value for efficacy (the same definition as the safety population). The safety population was removed, as it overlapped with the newly defined ITT population. The PP population was re-defined as all the ITT subjects without important protocol deviations, removing the inclusion of patient data obtain prior to the first major protocol deviation. All the above changes were made prior to data availability.

After the data became available, a minor change was made to age categories to follow the NIH categories. Two analyses were also added as exploratory endpoints. These were change from baseline in AM and PM rTNSS averaged over the 2 week treatment period excluding those who enrolled or attempted to enroll twice, and calculation of the percentage of responders with at least a 0.5 improvement from baseline values for rTNSS, iTNSS, and rTOSS averaged over the 2 week treatment period.

Reviewer comment:

It is unlikely that the changes made prior to data availability will impact study results or their interpretation. The changes made after data availability are also likely to have little impact, as the changes did not relate to primary or secondary endpoints.

Protocol Violations

Of the 707 patients randomized, 39 patients had important protocol deviations (IPD). Most IPDs were spread evenly across all groups. However, the most common IPD, usage of disallowed concomitant medications for >15% of the double blind treatment phase, occurred more frequently in the placebo and 74mcg groups (2.6% and 3%, respectively) compared to the 148 mcg group (0.9%).

Reviewer comment

The increased usage of disallowed concomitant medications in the placebo and 74 mcg dose group as compared to the 148 mcg group could be reflective of increased symptoms relief in the 148 mcg dose group. However, this disparity is unlikely to affect the results, given the small overall numbers. In addition, the primary and secondary endpoints analysis used the ITT population.

Patient Disposition

Of the 1096 patients screened, 912 patients enrolled, and 707 were randomized and received at least one dose of medication (ITT population). The primary reason for non-randomization was lack of symptoms. Six-hundred-sixty eight patients did not have important protocol deviations and were in the per protocol population. Of those that were randomized, 665 (94.1%) completed the study. Approximately twice as many patients on placebo (21, 8.9%) discontinued compared to the 74 (11, 4.6%) and 148 (10, 4.3%) mcg dose groups. The most common reason for discontinuation across all groups was “other.” Patient disposition is summarized in Table 14.

Table 14. Trial 060-622. Patient Disposition

Category	Ciclesonide Dose			
	CIC-HFA 74 mcg N=237 (%)	CIC-HFA 148 mcg N=235 (%)	Placebo N=235 (%)	Total N=707 (%)
ITT Analysis Set	237 (100)	235 (100)	235 (100)	707 (100)
PP Analysis Set	224 (94.5)	223 (94.9)	221 (94.0)	668 (94.5)
Completed Study	226 (95.4)	225 (95.7)	214 (91.1)	665 (94.1)
Prematurely Discontinued	11 (4.6)	10 (4.3)	21 (8.9)	42 (5.9)
Reason for Discontinuation				
Adverse Event	2 (0.8)	1 (0.4)	4 (1.7)	7 (1.0)
Protocol Violation	2 (0.8)	4 (1.7)	2 (0.9)	8 (1.1)
Withdrawal by Subject	2 (0.8)	0	6 (2.6)	8 (1.1)
Lost to follow-up	0	0	1 (0.4)	1 (0.1)
Other	5 (2.1)	5 (2.1)	8 (3.4)	18 (2.5)

Source: Trial 060-622 CSR, Table 10.1-1, pp67

Of those that discontinued for either “other” or “withdrawal by subject,” the most common specific reason was either lack of efficacy or enrollment/attempted enrollment

at 2 sites. For the 74 mcg, 148 mcg, and placebo groups, 3 (1.7%), 2 (0.8%), and 3 (1.2%) patients discontinued due to enrollment/attempted enrollment at 2 sites, respectively. For lack of efficacy, 2 (0.8%), 1(0.4%), and 7(3%) patients withdrew from the 74 mcg, 148 mcg, and placebo group respectively.

Reviewer Comments:

Overall discontinuations were higher in the placebo group compared to the ciclesonide groups, which is often the case for therapies that demonstrate efficacy. While this discrepancy could affect the results, given the overall small numbers of discontinuations, the effect is not likely to be significant.

Patient Demographics:

Trial patients were primarily 19 to less than 65 years of age (90.5%), female (66.3%), and white (93.1%). Across the treatment groups, the demographic characteristics were relatively balanced, although the placebo group did have somewhat more patients in the ≥65 year old age groups compared to the CIC-HFA groups. Demographic information is summarized on Table 15.

Table 15. Trial 060-622. Patient Demographics

Variable	Ciclesonide Dose			
	CIC-HFA 74 mcg N=237 (%)	CIC-HFA 148 mcg N=235 (%)	Placebo N=235 (%)	Total N=707 (%)
Mean Age	41.1	42.1	42.2	41.8
Age category				
≤18 years	11 (4.6)	8 (3.4)	12 (5.1)	31 (4.4)
19 to <65 years	220 (92.8)	217 (92.3)	203 (86.4)	640 (90.5)
≥65 years	6 (2.5)	10 (4.3)	20 (8.5)	36 (5.1)
Sex				
Male	78 (32.9)	80 (34)	80 (34)	238 (33.7)
Female	159 (67.1)	155 (66)	155 (66)	469 (66.3)
Race				
Caucasian	218 (92)	220 (93.6)	220 (93.6)	658 (93.1)
Black	13 (5.5)	8 (3.4)	14 (6)	35 (5)
Asian	4 (1.7)	3 (1.3)	1 (0.4)	8 (1.1)
American Indian, Alaska Native	0	2 (0.9)	0	2 (0.3)
Pacific Island	0	2 (0.9)	0	2 (0.3)
Multiple	2 (0.8)	0	0	2 (0.3)
Ethnicity				
Hispanic	109 (46)	102 (43.4)	109 (46.4)	320 (45.3)
Non-Hispanic	128 (54)	133 (56.6)	123 (53.3)	387 (54.7)

Source: Trial 060-622 CSR, Table 11.2-1, pp74

In addition to similar demographics between groups, the patients also have similar baseline AM and PM rTNSS, iTNSS, rTOSS, and iTOSS. The scores also indicated that they were symptomatic at baseline.

Compliance

Compliance was high across all groups at multiple time points. Overall study compliance was $\geq 80\%$ in $\geq 97.9\%$ of patients across all groups. When subdividing compliance by visits, compliance was lower. 93.6%, 97%, and 97.9% of the patients in the placebo, 74 mcg and 148 mcg groups, respectively, were $\geq 80\%$ compliant between visit 3 (double blind treatment day 1) and visit 4 (day 7 of treatment). Between visits 4 and 5 (treatment day 7-14), $\geq 80\%$ compliance was observed in 92.3%, 96.6%, and 97% of the patients in the placebo, 74 mcg, and 148 mcg groups, respectively.

Reviewer Comment:

Overall the patient demographics were similar between groups, and compliance was slightly decreased in the placebo group compared to CIC-HFA groups. This difference in compliance may lend circumstantial evidence for the efficacy of CIC-HFA, as lack of compliance in the placebo group may have been due to lack of observed effect by study participants.

Primary Endpoint

The primary endpoint was the average of the AM and PM rTNSS over the 2 week treatment period compared to baseline. For the ITT population, there was a statistically significant improvement in scores for the 74 mcg and 148 mcg groups compared to placebo. The treatment difference for the 74 and 148 mcg groups compared to placebo was 0.94 and 1.08 ($p < 0.001$), respectively. These results are summarized in Table 16.

Table 16. Trial 060-622. Results for Primary and Key Secondary Endpoints

	CIC-HFA 74 mcg	CIC-HFA 148 mcg	Placebo
Avg AM/PM rTNSS over the two week double blind period			
N	237	234	235
Change from baseline			
LS Mean (SE)	-1.45 (0.14)	-1.59 (0.14)	-0.51 (0.14)
Treatment difference vs. Pbo (95% CI)	0.94 (0.57, 1.32)	1.08 (0.7, 1.45)	
p-value vs. Pbo	<0.0001	<0.0001	
Avg AM/PM iTNSS over the two week double blind period			
N	237	234	235
Change from baseline			
LS Mean (SE)	-1.34 (0.13)	-1.47 (0.13)	-0.47 (0.13)
Treatment difference vs. Pbo (95% CI)	0.87 (0.5, 1.25)	1.00 (0.63, 1.37)	
p-value vs. Pbo	<0.0001	<0.0001	
Avg AM/PM rTOSS over the two week double blind period (baseline TOSS ≥ 5)			
N	164	160	148
Change from baseline			
LS Mean (SE)	-1.06 (0.12)	-1.05 (0.12)	-0.44 (0.12)
Treatment difference vs. Pbo (95% CI)	0.61 (0.28, 0.95)	0.60 (0.27, 0.94)	

p-value vs. Pbo	0.0007	0.0009	
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Source: Trial 060-622 CSR, Tables 11.4.1.1-1, 11.4.1.2-1, 11.4.1.2-3, pp79, 84, 89

Key Secondary Endpoints

The first key secondary endpoint assessed was change from baseline in AM and PM iTNSS averaged over the 2 week treatment period in the ITT population. For both doses, there was statistically significant improvement in symptom scores. Patients who received 74 mcg had a mean improvement of 0.87, and those receiving 148 mcg improved by 1.00 compared to placebo.

The second key secondary endpoint evaluated was change from baseline in AM and PM rTOSS averaged over the 2 week period in patients with a baseline rTOSS ≥ 5 . Similar to the TNSS results, improvement was seen in both the 74 and 148 mcg groups compared to placebo. The 74 and 148 mcg group treatment difference compared to placebo was 0.61 and 0.6, respectively. The results for the Key Secondary Endpoints are summarized in Table 16 (above).

Analysis of the AM and PM rTOSS in only the symptomatic patients (rTOSS ≥ 5) is problematic as it is not representative of the whole SAR population. Therefore, the data was reanalyzed for the whole patient population by FDA biostatisticians. These results are summarized in Table 17 .

Table 17. Trial 060-622. FDA Analysis of AM/PM rTOSS (Key Secondary Endpoint) in the Total Population

	CIC-HFA 74 mcg	CIC-HFA 148 mcg	Placebo
Avg AM/PM rTOSS over the two week double blind period (all patients)			
N	237	234	235
Treatment difference vs. Pbo (95% CI)	0.5 (0.30, 0.80)	0.5 (0.2, 0.8)	
p-value vs. Pbo	<0.001	<0.001	

p-values are significant at the 0.025 level based on Bonferroni correction

By analyzing the whole population, the effect size decreased and the unadjusted p-values were also less impressive. However, given the p-value and a CI that does not cross zero, the treatment effect may still be real. As with the sponsor analysis, there is no dose effect.

Per sponsor, there was very little missing data; therefore, no sensitivity analysis was performed for the primary endpoint, nor secondary endpoints.

Reviewer Comments:

Based on these results, CIC-HFA at either dose is efficacious in the treatment of nasal symptoms associated with SAR. With regard to ocular symptoms, CIC-HFA is likely efficacious based on this trial and FDA analysis of the total population. The treatment

effect is not significantly different between doses, and is similar to the treatment effect observed in the Omnaris studies (for nasal symptoms).

Other Secondary Endpoints

Only the primary and key secondary endpoints had p-values which were adjusted for multiple comparisons. For all other endpoints, no adjustments were made. For all endpoints involving TOSS or RQLQ, the sponsor only analyzed those with baseline symptoms (i.e. TOSS \geq 5.0, RQLQ \geq 3.0). For non-primary and non-key secondary endpoints, TOSS and RQLQ related endpoints were not reanalyzed for the entire population by FDA biostatisticians.

Change from baseline in AM and PM rTNSS averaged over each week was also assessed. When evaluating the average over week 1, both the 74 mcg and 148 mcg groups had significant improvement from baseline compared to placebo. The difference from placebo was 0.84 and 0.91 for the 74 mcg and 148 mcg groups, respectively. For the week 2 data, similar results were seen, though nominally greater in magnitude (1.05 and 1.21 for the 74 and 148mcg groups, respectively). Results summarized in Table 18.

Table 18. Trial 060-622. Change from Baseline for AM/PM rTNSS and iTNSS Averaged over Each Week

	CIC-HFA 74 mcg	CIC-HFA 148 mcg	Placebo
Avg AM/PM rTNSS over week 1 of the double blind period			
N	237	234	234
Change from baseline			
LS Mean (SE)	-1.18 (0.13)	-1.25 (0.13)	-0.34 (0.13)
Treatment difference vs. Pbo (95% CI)	0.84 (0.48, 1.21)	0.91 (0.55, 1.28)	
p-value vs. Pbo	<0.0001	<0.0001	
Avg AM/PM rTNSS over week 2 of the double blind period			
N	237	234	234
Change from baseline			
LS Mean (SE)	-1.79 (0.16)	-1.95 (0.16)	-0.74 (0.17)
Treatment difference vs. Pbo (95% CI)	1.05 (0.59, 1.5)	1.21 (0.76, 1.67)	
p-value vs. Pbo	<0.0001	<0.0001	
Avg AM/PM iTNSS over week 1 of the double blind period			
N	237	234	234
Change from baseline			
LS Mean (SE)	-1.11 (0.13)	-1.15 (0.13)	-0.33 (0.13)
Treatment difference vs. Pbo (95% CI)	0.79 (0.43, 1.15)	0.83 (0.46, 1.19)	
p-value vs. Pbo	<0.0001	<0.0001	
Avg AM/PM iTNSS over week 2 of the double blind period			
N	237	234	234
Change from baseline			
LS Mean (SE)	-1.63 (0.16)	-1.82 (0.16)	-0.68 (0.16)
Treatment difference vs. Pbo	0.95	1.14	

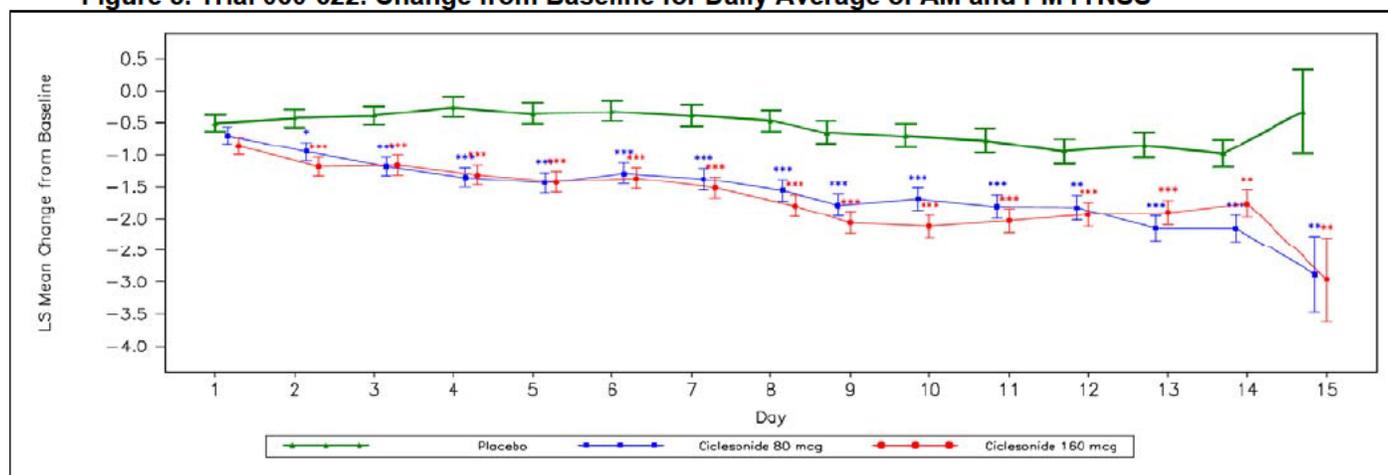
(95% CI)	(0.51, 1.4)	(0.7, 1.59)	
p-value vs. Pbo	<0.0001	<0.0001	

p-values not adjusted for multiple comparisons

Source: Trial 060-622, Tables: 11.4.1.3.1-1, 11.4.1.3.2-1, pp94, 96

The change from baseline for daily averages of AM and PM rTNSS was also assessed. For both the 74 and 148 mcg group, a statistically significant reduction relative to placebo was first noted on day 2, and persisted throughout the treatment period. These results are summarized in Figure 5. When analyzing AM and PM rTNSS scores separately similar results were seen.

Figure 5. Trial 060-622. Change from Baseline for Daily Average of AM and PM rTNSS



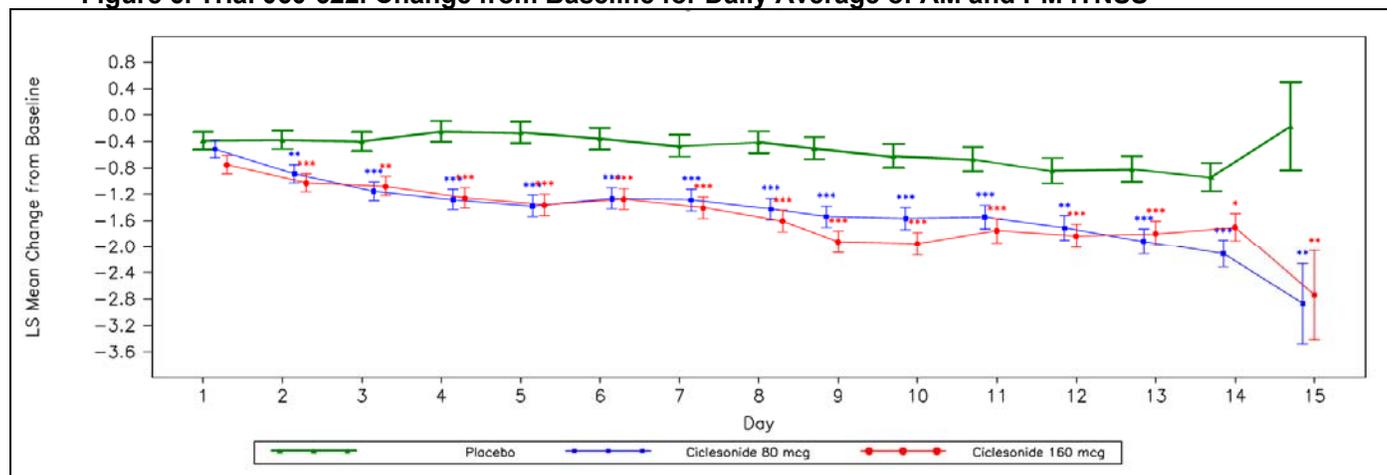
Ciclesonide 80 mcg= 74 mcg ex-actuator dose, Ciclesonide 160 mcg= 148 mcg ex-actuator dose

*p<0.05, **p<0.01, ***p<0.001, p-values unadjusted for multiplicity

Source: Trial 060-622, Figure 14.4.1

Change from baseline in AM and PM iTNSS at each day and average over each week was also evaluated. The analysis was similar as for the rTNSS data. The results were similar are summarized in Table 18 and Figure 6.

Figure 6. Trial 060-622. Change from Baseline for Daily Average of AM and PM iTNSS



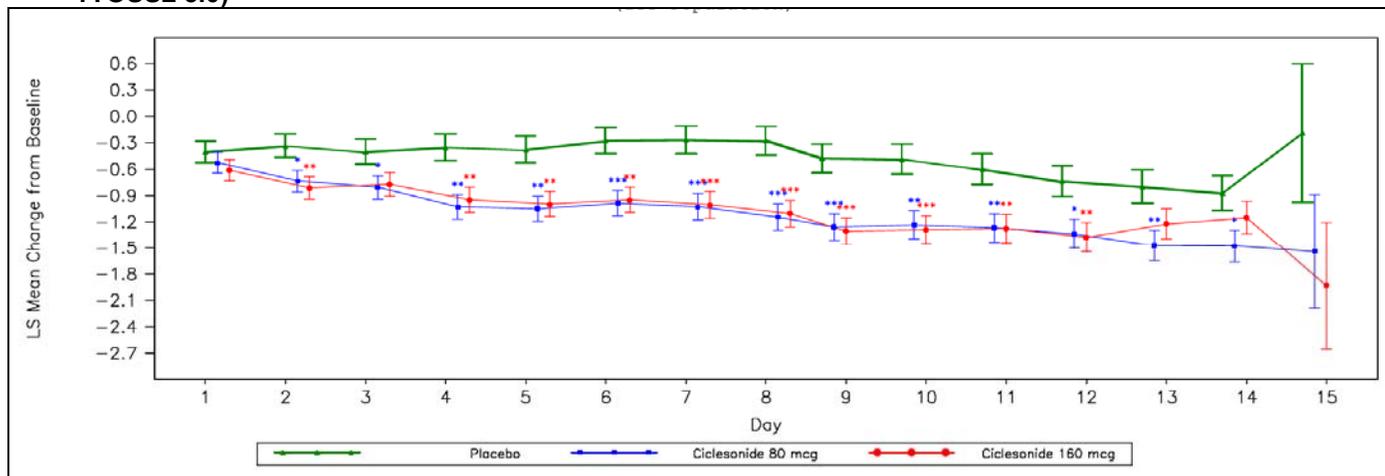
Ciclesonide 80 mcg= 74 mcg ex-actuator dose, Ciclesonide 160 mcg= 148 mcg ex-actuator dose
*p<0.05, **p<0.01, ***p<0.001, p-values unadjusted for multiplicity
Source: Trial 060-622 CSR, Figure 14.4.4

For both the 74 and 148 mcg group, a statistically significant reduction in the daily average of AM and PM iTNSS relative to placebo was first noted on day 2, and persisted throughout the treatment period (Figure 6). When analyzing AM and PM iTNSS scores separately similar results were seen.

In addition to analyzing the TNSS, the sponsor also analyzed results for individual nasal symptoms score (NSS). Consistent with the TNSS data, the reflective and instantaneous AM and PM NSS for each domain averaged over the 2 week treatment period showed significant improvement in ciclesonide groups compared to placebo. When analyzing the same data averaged over each week and daily (iNSS and rNSS), similar results were seen.

Change from baseline in *reflective* AM TOSS, PM TOSS, average AM and PM TOSS at each day, averaged over each week, and averaged over the two-week treatment period in subjects with baseline TOSS ≥ 5.0 was also analyzed. The results for change in baseline over each week and the 2 week period yielded similar results to the second key secondary endpoint. Both doses of ciclesonide resulted in statistically significant improvement in rTOSS over each week of treatment. The daily average of the AM and PM rTOSS was also consistent with the weekly score results, demonstrating improvement in scores starting day 2 (see Figure 7), though the effect waned somewhat near the end of the treatment period for the 148 mcg dose. When analyzing the daily AM and PM rTOSS separately similar improvement were seen.

Figure 7. Trial 060-622. Change from Baseline for Daily Average AM and PM rTOSS (baseline rTOSS \geq 5.0)



Ciclesonide 80 mcg= 74 mcg ex-actuator dose, Ciclesonide 160 mcg= 148 mcg ex-actuator dose
 *p<0.05, **p<0.01, ***p<0.001, p-values unadjusted for multiplicity
 Source: Trial 060-622 CSR, Figure 14.4.7

Change from baseline in *instantaneous* AM TOSS, PM TOSS, average AM and PM TOSS at each day, averaged over each week, and averaged over the two-week treatment period in subjects with baseline TOSS \geq 5.0 was also analyzed. Similar to the rTOSS data at the same time points, statistically significant improvement was seen for each week of treatment and at 2 weeks of treatment. With regard to daily averages of AM and PM iTOSS, significant improvement was seen first at day 3 for the 74 mcg group, and day 2 for the 148 mcg group. When daily PM assessments were analyzed separately, similar results were seen. However when the daily AM assessment were analyzed, improvement was not seen until day 5 and 6 for the 74 and 148 mcg group, respectively.

In addition to analyzing the TOSS, the sponsor also analyzed results for individual domains of the ocular symptoms score (OSS) in patients with baseline TOSS scores \geq 5. Consistent with the TOSS data, the reflective and instantaneous AM and PM OSS for each domain averaged over the 2 week treatment period showed significant improvement in ciclesonide groups compared to placebo. When analyzing the same data averaged over each week and daily (iOSS and rOSS), similar results were seen. Of note, the observed improvements in rOSS lagged 1-2 days behind the improvement seen in the nasal symptom scores.

Change from baseline in RQLQ(S) total and individual items at visit 5 in impaired (RQLQ(S) \geq 3.0) patients was also analyzed. After 2 weeks of treatment, statistically significant improvements in RQLQ(S) were seen in the 74 and 148 mcg groups compared to placebo. Least squares mean differences from placebo were 0.62 and 0.60 for the 74 and 148 mcg dose, respectively (p<0.0001). Statistically significant

improvement in the individual items were also seen in both ciclesonide groups compared to placebo after 2 weeks of treatment.

Reviewer Comment:

As with the TOSS related endpoints, the RQLQ endpoint was also only analyzed in a patient subset. Reanalysis of the RQLQ data for the whole patient population yielded similar results as that of the subset. Least squares mean differences from placebo were 0.60 and 0.6 for the 74 and 148 mcg dose, respectively (unadjusted $p < 0.001$).

Onset of Action/Improvement

Onset of action for nasal symptoms was defined as the first assessment at which iTNSS improved significantly (one-sided p -value ≤ 0.025) from baseline for the ciclesonide versus placebo, and the difference had to be maintained for “some period from this point forward.” For this endpoint, iTNSS was measured post first dose at hours 4, 6, 8, 10, and 30; in addition to the twice daily measurements. Based on this definition, the onset of action was first noted for both the 74 and 148 mcg groups at 36 hours post dose. The least square mean difference from placebo was 0.58 (95% CI= 0.12-1.03) and 0.82 (95% CI= 0.36-1.28) for the 74 and 148 mcg groups, respectively. This difference was maintained for the duration of the double-blind treatment period.

Onset of action for ocular symptoms was similarly defined, except used iTOSS in patients with baseline TOSS ≥ 5 . The onset of action for ocular symptoms was 36 hours post –dose for both the 74 and 148 mcg treatment groups. The least squares mean improvement compared to placebo was 0.62 (95% CI= 0.16-1.08) and 0.78 (95% CI=0.32-1.24) for the 74 and 148 mcg groups, respectively. This difference was maintained until day 12 for the 148 mcg group and until day 13 for the 74 mcg group.

Time to Maximal Effect

This endpoint was defined as the number of days until the first treatment day on which the difference between ciclesonide and placebo was at least 90% of the largest estimated difference. For the 74 mcg group, the time to maximal effect was 13 days, and for the 148 mcg group, it was 8 days.

Exploratory Endpoints

The sponsor also performed an *ad hoc* responder analysis for rTNSS, iTNSS, and rTOSS with improvement from baseline of at least 0.5 defined to represent a clinically meaningful change. These analyses were performed in the entire patient population. For rTNSS, a total of 47%, 59.9%, and 65% of subjects receiving placebo, 74 mcg, and 148 mcg had an improvement from baseline of at least 0.5. Similar results were seen for the iTNSS data (placebo:42.7%, 74 mcg: 59.1%, and 148 mcg: 65%). For the rTOSS data, fewer patients were responders. For those that received placebo, 74 mcg and 148 mcg, 40.6%, 52.7%, and 55.1% had improvement of at least 0.5, respectively.

Subgroup Analysis

For the primary and key secondary endpoints subgroup analysis was performed on the ITT population base on age, sex, and race. Gender had no effect. The effect of age and race was difficult to assess. In the ITT population, 90.5% of the population was 19 to <65 years of age and 93.1 % were Caucasian. The sample size of patients who were non-Caucasian or ≤18 years of age was too small to detect any differences.

In addition to subgroup analysis by demographic characteristics, analysis of the primary and key secondary endpoints was also performed based on baseline symptom severity (mild/moderate versus severe). Mild/moderate symptom severity was defined as a baseline symptom score less than the median baseline score. Severe symptom severity was defined as a baseline symptom score greater than the median baseline score.

The analysis based on severity mirrored the overall analysis of the primary and first key secondary endpoint. Whether or not baseline symptom scores were mild/moderate or severe, both doses of ciclesonide improved the average AM/PM rTNSS and AM/PM iTNSS over the 2 week double-blind treatment period. (Data not shown).

In contrast, when analyzing the change in baseline AM/PM rTOSS averaged over the 2 week treatment period by severity of baseline scores, the results did not mirror the results for the second key secondary endpoint. This subgroup analysis demonstrated that for those with mild/moderate symptoms scores at baseline, neither dose of ciclesonide improved symptoms scores. However, when analyzing those with severe symptoms scores at baseline, the results were consistent with the second key secondary endpoint. These results are summarized in Table 19.

Table 19. Trial 060-622. Change from Baseline for AM/PM rTOSS Averaged over the 2 Week Treatment Period in Patients with Baseline rTOSS ≥5 Based on Baseline Symptom Severity

Change from baseline in AM/PM rTOSS averaged over the double blind period	Mild/moderate			Severe		
	CIC-HFA 74 mcg (N=237)	CIC-HFA 148mcg (N=235)	Placebo (N=235)	CIC-HFA 74 mcg (N=237)	CIC-HFA 148mcg (N=235)	Placebo (N=235)
By Baseline iTNSS						
N	62	45	53	102	115	94
LS Mean (SE)	-1.03 (0.19)	-0.49 (0.21)	-0.56 (0.20)	-1.05 (0.15)	-1.24 (0.14)	-0.34 (0.16)
Treatment difference vs. Pbo (95% CI)	0.47 (-0.04, 0.99)	-0.07 (-0.63, 0.49)		0.7 (0.27, 1.14)	0.89 (0.48, 1.31)	
p-value vs. Pbo	0.0725	0.7982		0.0015	<0.0001	
By Baseline rTNSS						
N	52	50	62	112	110	85
LS Mean (SE)	-0.86 (0.2)	-0.53(0.2)	-0.39 (0.19)	-1.14 (0.15)	-1.30 (0.14)	-0.45 (0.16)
Treatment difference vs. Pbo (95% CI)	0.47 (-0.07, 1)	0.14 (-0.41,0.68)		0.69 (0.26, 1.12)	0.85 (0.42, 1.28)	
p-value vs. Pbo	0.0889	0.6157		0.0017	0.0001	
By Baseline iTOSS						
N	43	33	35	121	127	112

LS Mean (SE)	-1.07 (0.23)	-0.49 (0.26)	-0.64(0.25)	-1.04 (0.14)	-1.19 (0.14)	0.37 (0.15)
Treatment difference vs. Pbo (95% CI)	0.43 (-0.2, 1.07)	-0.15 (-0.85,0.54)		0.67 (0.27, 1.06)	0.82 (0.43, 1.21)	
p-value vs. Pbo	0.1795	0.6646		0.001	<0.0001	
By Baseline rTOSS						
N	41	64	68	123	126	109
LS Mean (SE)	-0.78 (0.24)	-0.54 (0.26)	-0.35 (0.25)	-1.13 (0.14)	-1.18 (0.13)	-0.45 (0.14)
Treatment difference vs. Pbo (95% CI)	0.43 (-0.24, 1.11)	0.19 (-0.52,0.91)		0.68 (0.29, 1.07)	0.72 (0.34, 1.11)	
p-value vs. Pbo	0.0405	0.5921		0.0007	0.0002	
By Baseline RQLQ(S)						
N	58	59	60	106	98	87
LS Mean (SE)	-1.24 (0.18)	-0.81 (0.18)	-0.7 (0.18)	-0.91 (0.15)	-1.2 (0.16)	-0.32 (0.17)
Treatment difference vs. Pbo (95% CI)	0.54 (0.02, 1.06)	0.11 (-0.39,0.62)		0.59 (0.14, 1.04)	0.88 (0.43, 1.33)	
p-value vs. Pbo	0.0405	0.6542		0.0104	0.0002	

Source: Trial 060-622 CSR, Tables 11.4.1.2-4, pp92

Reviewer Comment

The results for the non-key secondary endpoints support the efficacy of ciclesonide at both doses with regard to nasal symptoms in the entire study population. However, it is unclear if the non-key secondary endpoints are supportive with regard to ocular symptoms, as secondary analysis was limited to the subset of SAR patients with ocular symptoms (TOSS≥5.0). With regard to quality of life, based on FDA analysis of the total population, both doses of ciclesonide HFA appear to improve RQLQ scores. The onset of action at both doses is 36 hours, and time to maximal effect is sooner in the higher dosage group, based on the iTNSS data. The results from the subgroup analysis also demonstrate that no matter the baseline severity of symptoms, ciclesonide improves AM/PM rTNSS and iTNSS averaged over the treatment period compared to placebo. The subgroup analysis for rTOSS indicate that effect of ciclesonide on ocular symptoms was driven primarily by patients with more severe baseline symptoms. However, these results cannot be generalized to the entire patient population as the analysis of rTOSS was only performed in a subset of patients.

Safety:

Exposure

A total of 572 patients were exposed to CIC-HFA (237 in the 74 mcg group and 235 in the 148 mcg group), and 235 to placebo for a mean of 14.2-14.5 days.

Deaths/SAEs

There were no deaths in this study. There was one treatment emergent SAE. This occurred in a 48 year old female patient (060-622-007/S018) who was in the 148 mcg group. The SAE was gastroesophageal reflux disease (GERD) and occurred during the follow-up period. Six (6) days after the end of her double-blind treatment period, she

reported to an Emergency Department with chest pain. She was evaluated for cardiac disease and GERD. Her cardiac work up was negative, but she was admitted for observation and further testing. Testing was negative, and she was diagnosed with acute GERD and started on Prilosec. No other AEs were reported by this subject. In addition, one subject reported 2 SAEs (temporal bone fracture and subdural hematoma following go-cart accident), during the screening period.

TEAEs

Reported TEAEs were similar between ciclesonide groups, and slightly less compared to the placebo group. The most frequent TEAE reported was epistaxis, all of which resolved without intervention. Other frequent TEAEs included nasal discomfort, instillation site irritation, and nasal septum disorder (which included reports of nasal septum or turbinate irritation or abrasions). These results are summarized in Table 20.

Table 20. Trial 060-622. Treatment Emergent Adverse Events Occurring in ≥2% of Patients

System Organ Class/ Preferred term	CIC-HFA 74 mcg (N=237)		CIC-HFA 148 mcg (N=235)		Placebo (N=235)		Overall (N=707)	
	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n
Overall	51 (21.5)	69	44 (18.7)	59	58 (24.7)	87	153 (21.6)	215
General Disorders and Administration Site Conditions								
Instillation site irritation	6 (2.5)	6	8 (3.4)	8	11 (4.7)	13	25 (3.5)	27
Respiratory, Thoracic, and Mediastinal Disorders								
Epistaxis	22 (9.3)	27	16 (6.8)	20	26 (11.1)	31	64 (9.1)	78
Nasal discomfort	8 (3.4)	9	5 (2.1)	7	10 (4.3)	11	23 (3.3)	27
Nasal septum disorder	5 (2.1)	5	5 (2.1)	5	7 (3.0)	7	17 (2.4)	17
Nasal septum disorder	5 (2.1)	5	1 (0.4)	1	3 (1.3)	3	9 (1.3)	9

Source Trial 060-622 CSR, Table 12.2.3.1-1, pp114

A total of 7/707 patients withdrew due to TEAEs. This included 4 (1.7%) in the placebo group, and 2 (0.8%) and 1 (0.4%) in the 74 and 148 mcg groups, respectively. For the placebo group, the most common TEAEs leading to discontinuation were in the Infections and Infestation SOC, and included influenza, sinusitis, otitis media, and upper respiratory tract infection. For the 74 mcg group, the discontinuations were due to rash and bronchitis. For the 148 group, the discontinuation was due to insomnia.

Nasal AEs

Due to the concern for local adverse effect, nasal AEs were analyzed separately. Nasal AEs were identified during the blinded review of AE data prior to database lock. The nasal AEs are summarized in Table 21.

Table 21. Trial 060-622. Treatment Emergent Nasal Adverse Events by Preferred Term (ITT Population)

Preferred Term	CIC-HFA 74 mcg (N=237)		CIC-HFA 148 mcg (N=235)		Placebo (N=235)		Overall (N=707)	
	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N
Overall	31 (13.1)	36	26 (11.1)	30	31 (13.2)	41	88 (12.4)	107
Acute sinusitis	2 (0.8)	2	0	0	0	0	2 (0.3)	2
Epistaxis	8 (3.4)	9	5 (2.1)	7	10 (4.3)	11	23 (3.3)	27
Instillation site erythema	0	0	0	0	1 (0.4)	1	1 (0.1)	1
Instillation site irritation	5 (2.1)	5	3 (1.3)	3	2 (0.9)	2	10 (1.4)	10
Instillation site pain	0	0	1 (0.4)	1	0	0	1 (0.1)	1
Mucosal inflammation	0	0	0	0	1 (0.4)	1	1 (0.1)	1
Nasal congestion	0	0	1 (0.4)	1	0	0	1 (0.1)	1
Nasal discomfort	5 (2.1)	5	5 (2.1)	5	7 (3.0)	7	17 (2.4)	17
Nasal dryness	2 (0.8)	2	0	0	0	0	2 (0.3)	2
Nasal edema	0	0	0	0	1 (0.4)	1	1 (0.1)	1
Nasal septum disorder	5 (2.1)	5	1 (0.4)	1	3 (1.3)	3	9 (1.3)	9
Nasal septum ulceration	3 (1.3)	3	2 (0.9)	2	1 (0.4)	1	6 (0.8)	6
Nasopharyngitis	0	0	0	0	1 (0.4)	1	1 (0.1)	1
Parosmia	0	0	1 (0.4)	1	0	0	1 (0.1)	1
Rhinalgia	1 (0.4)	1	1 (0.4)	1	4 (1.7)	4	6 (0.8)	6
Rhinitis	0	0	0	0	1 (0.4)	1	1 (0.1)	1
Sinus headache	0	0	3 (1.3)	3	1 (0.4)	1	4 (0.6)	4
Sinusitis	4 (1.7)	4	4 (1.7)	4	4 (1.7)	4	12 (1.7)	12
Sneezing	0	0	1 (0.4)	1	0	0	1 (0.1)	1
Upper respiratory tract infection	0	0	0	0	2 (0.9)	2	2 (0.3)	2
Viral upper respiratory tract infection	0	0	0	0	1 (0.4)	1	1 (0.1)	1

Source: Trial 060-622 CSR, Table 12.2.3.4-1, pp118

No nasal AEs demonstrated a dose response. However, there were more reports of nasal septum ulceration in the 74 (3 patients) and 148 mcg (2 patients) groups compared to placebo (1 patient). All the ulcerations were mild or moderate in severity and resolved without treatment. The 74 mcg group also reported more nasal septum disorders compared to placebo and the 148 mcg group.

Reviewer Comment:

With regard to AEs, ciclesonide was relatively well tolerated. There were no deaths and no SAEs likely related to study drug. Overall, adverse events were similar between groups, but slightly higher in the placebo group. The AEs reported were typical of nasal corticosteroids. There were an increased number of nasal septum ulcerations in the 74 mcg groups compared to other groups which may be concern. While nasal septum ulcerations are always concerning, they were relatively rare, and were not restricted to the ciclesonide population. In the long term safety data, ulceration and perforations will

be specifically scrutinized. However, it is reassuring that they were all resolved without treatment.

Clinical Labs

Lab data was collected at screening (visit 1) and at the end of study visit (visit 5). Based on mean values, there were no significant changes in chemistry or hematology values between screening and end of treatment in any of the groups. Shift tables were used to detect differences in laboratory parameters from baseline to end of study. Shifts were similar between groups.

Although there were no significant changes when examining the mean values, on an individual level, several patients had significant changes in lab values. Subject 0002/S120 in the 148 mcg group was noted to have elevated ALT and AST levels on visit 5 (83 U/L and 58 U/L, respectively) compared to visit 1 (29 U/L and 27 U/L, respectively). These labs were followed for approximately 1 month. After a week off treatment, they continued to rise, however after a month off treatment they had begun to normalize. At the last unscheduled visit, however they were still not at baseline.

Two patients, one in the placebo group (0001/S130) and one in the 148 mcg group (003/S012) had increased serum glucoses between visit 1 and 5. Neither reported any other AEs.

Two patients (0001/S115 and 0001/S119) in the 148 mcg group also developed significant monocytosis (18% and 20%) between visit 1 and visit 5. For one patient, the AE of bronchitis was reported several days prior to the monocytosis, and for the other patient, a viral respiratory tract infection was reported concomitantly.

One patient in the placebo group developed a clinically significant leukocytosis and neutrophilia associated with a viral infection. Another patient in the (0004/S061) in the 74 mcg group developed a significant neutropenia. This was associated with a concomitant viral infection.

Reviewer Comment:

There were only a few abnormalities seen in clinical lab values in individuals. With regard to the elevated LFT's, given that they rose while on treatment and decreased after 1 month off treatment, the LFT elevations could have been drug related. However, were the elevations purely drug related, it is unlikely that they would have continued to rise after 1 week off treatment. The increases in serum glucose observed could potentially be related to systemic effects of glucocorticoids; however, this seems less likely as one of the patients was on placebo. With regard to the changes in hematology, all were associated with infection, which could account for the findings. Overall, the clinical lab findings are reassuring for the safety of the drug.

Vital Signs/Physical Exam

Mean vital signs between groups were similar across groups with regard to changes from baseline. Physical exams for the most part remained similar between visit 1 and visit 5. However a total of 3 patients in the placebo group, 2 patients in the 74 mcg group, and 1 subject in the 148 mcg group had changes that were described as worsening. Examples of worsening included rash, furuncle, cough, and swollen lymph nodes associated with a respiratory infection.

ENT exams

Clinically significant worsening based on ENT exam was noted in the 4 (1.7%), 4 (1.7%), and 2 (0.9%) subjects in the placebo, 74 mcg and 148 mcg groups, respectively. Most common findings were increased nasal edema and mucus.

Reviewer Comment:

The changes in general physical exam findings are not unexpected given the patient population. The changes noted on ENT examination are also not unexpected, as all the patients in the study were symptomatic with SAR.

Overall Reviewer Comment Trial 060-622

This trial is supportive of the proposed indication based on the positive results for the primary and key secondary endpoints. Like the dose ranging trial, there appears to be no benefit to higher doses of CIC-HFA. The treatment effect for nasal symptoms is similar to that seen in the Omnaris development program. The effect on the ocular symptoms in the total patient population was quite modest (least square mean difference from placebo -0.5), and less than that seen in the Veramyst program (-0.6), but was statistically significant (unadjusted p-value <0.001). The other TNSS related endpoints were also supportive of the proposed indication, though no conclusion could be made for the TOSS related supportive endpoints. The overall safety profile was also consistent with other inhaled nasal corticosteroids.

5.3.3 Trial 060-634

This trial was almost identical to 060-622 with regard to study design

Administrative Information

- **Study title:** A Randomized, Multicenter, Double-Blind, Placebo- Controlled, Parallel Group, Phase III Clinical Trial to Assess the Safety and Efficacy of Ciclesonide HFA Nasal Aerosol (148 mcg once daily and 74 mcg once daily) for the Treatment of Seasonal Allergic Rhinitis to Mountain Cedar in Subjects 12 years and Older
- **Study dates:** 12/01/09-2/10/10 (winter season)
- **Study sites:** 7 US centers (Texas)
- **Allergen:** Mountain Cedar
- **Study report date:** 10/05/10

Objectives/Rationale

- To demonstrate the efficacy of ciclesonide HFA applied as a nasal aerosol (148 mcg and 74 mcg) once daily compared to placebo in subjects with SAR.
- Evaluate the safety and tolerability of ciclesonide HFA nasal aerosol once daily as compared to placebo in subjects with SAR.

Study Design and Conduct.

Study Population

Treatments

Refer the review of trial 060-622 for the above study parameters.

Efficacy Parameters

The primary endpoint and key secondary endpoints are the same as for 060-622, with the addition of the following key secondary endpoint:

- Change from baseline in Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities (RQLQ(S)) total and individual items at visit 5 in impaired patients (baseline RQLQ(S) score ≥ 3.0).

In trial 060-634, the sponsor also changed the “Time to Maximal Effect Endpoint” to a secondary endpoint and removed the “Onset of Action Endpoints.”

Efficacy Assessments:

Safety Assessments:

Compliance Assessment:

Ethics:

Refer to review of trial 060-622 for the above study parameters

Statistical Plan:

The sample size was calculated based on the results of M1-602 and 060-622 with the assumption that the standard deviation for the primary endpoint was 2.1. Otherwise the statistical analysis was as in 060-622.

Results:

Protocol Amendments:

The original protocol was submitted on 9/3/2009. An amendment was submitted on 10/02/2009, which removed the requirement for urine drug testing as an exclusion criterion. Prior to data availability, a minor change was made to age categories to follow the NIH categories. Following availability of data, *ad hoc* analysis was added in an attempt to determine why the 148 mcg dose did not show a statistically significant treatment effect with respect to ocular symptoms.

Protocol Deviations:

There were a total of 41 (6.1%) important protocol deviations (IPDs). IPDs were noted more frequently in the placebo group [19, (8.6%)], as compared to the 74 and 148 mcg treatment groups [13 (5.8%) and 9 (4%), respectively]. The two most common categories of protocol deviations were “double-blind study medication compliance

<80%” and “other.” The placebo, 74 mcg and 148 mcg groups had 5 (2.3%), 4 (1.8%), and 2 (0.9%) individuals violate the protocol for medication compliance, respectively. The “other” group was subdivided into “dosing time deviation” and “out of visit window.” For dosing time deviation, the placebo, 74 mcg and 148 mcg groups reported 5 (2.3%), 3 (1.3%), and 1 (0.4%) patients, respectively, who violated the protocol. For the “out of window visit” the numbers were higher at 9 (4.1%), 6 (2.7%), and 7 (3.1%) for the placebo, 74 mcg and 148 mcg groups, respectively.

Reviewer Comment:

The protocol amendments were minor and did not likely affect the results. This trial reported a similar total number of IPDs as trial 060-622, though the distribution was different. In this trial the lack of compliance was the most common IPD, and it occurred in a dose dependent manner. This increased lack of compliance in the placebo groups compared to the CIC-HFA groups may be supportive of a treatment effect. The increased number of IPDs in the placebo group compared to the ciclesonide group will not likely affect study results, as the primary and key secondary endpoints were analyzed in the ITT population.

Patient Disposition

Of the 1096 patients screened, 836 patients enrolled, and 671 were randomized and received at least one dose of medication (ITT population). The primary reason for non-randomization was lack of sufficient nasal allergy symptoms. 630 patient did not have important protocol deviations and were in the per protocol population. Of those that were randomized, 647 (96.4%) completed the study. Approximately twice as many patients on placebo (13, 5.9%) discontinued compared to the 74 (8, 3.5%) and 148 (3, 1.3%) mcg dose groups. The most common reason for discontinuation across all groups was “adverse event.” This was most common in the 74 mcg group. The second most common reason was “withdrawal by subject.” This was most common in the placebo group. Patient disposition is summarized in Table 22.

Table 22. Trial 060-634. Patient Disposition

Category	Ciclesonide Dose			
	CIC-HFA 74 mcg N=226 (%)	CIC-HFA 148 mcg N=225 (%)	Placebo N=220 (%)	Total N=671 (%)
ITT Analysis Set	226 (100)	225 (100)	220 (100)	671 (100)
PP Analysis Set	213 (94.2)	216 (96)	201 (91.4)	630 (93.9)
Completed Study	218 (96.5)	222 (98.7)	207 (94.1)	647 (96.4)
Prematurely Discontinued	8 (3.5)	3 (1.3)	13 (5.9)	24 (3.6)
Reason for Discontinuation				
Adverse Event	4 (1.8)	2 (0.9)	3 (1.4)	9 (1.3)
Withdrawal by Subject	2 (0.9)	0	5 (2.3%)	7 (1.0)
Lost to follow-up	2 (0.9)	0	3 (1.4)	5 (0.7)
Other	0	1 (0.4)	2 (0.9)	3 (0.4)

Source: Trial 060-634 CSR, Table 6, pp67

In the placebo group, AEs leading to discontinuation were worsening SAR, worsening asthma, and nasopharyngitis. For the 74 mcg group, AEs leading to discontinuation were tonsillitis, pharyngitis, allergic reaction to allergy shot, and ear infection. For the 148 mcg groups AEs were flu and rash. Within the “withdrawal by subject,” the most common reason was lack of efficacy (2 in placebo and 1 in the 74 mcg group).

Reviewer Comment:

Overall, the percentage of patients that dropped out of the study was small. As the CIC-HFA dose increased from 0 (placebo) to 148 mcg, the rate of premature discontinuation decreased. This inverse relationship along with the reasons for discontinuation are supportive of a CIC-HFA treatment effect.

Patient Demographics:

Trial patients were primarily 19 to less than 65 years of age (88.5%), female (59.3%), and white (87.8%). Across the treatment groups, the demographic characteristics were relatively balanced. The placebo group had fewer pediatric patients compared to the ciclesonide groups, and the 148 mcg group had fewer Blacks compared to the placebo and 74 mcg groups. Demographic information is summarized in Table 23.

Table 23. Trial 060-634. Patient Demographics

Variable	Ciclesonide Dose			
	CIC-HFA 74 mcg N=226 (%)	CIC-HFA 148 mcg N=225 (%)	Placebo N=220 (%)	Total N=671 (%)
Mean Age	39.8	40.4	41	40.4
Age category				
≥12 to ≤18 years	21 (9.3)	20 (9.3)	10 (4.5)	51 (7.6)
19 to <65 years	194 (85.8)	198 (88)	202 (91.8)	594 (88.5)
≥65 years	11 (4.9)	7 (3.1)	8 (3.6)	26 (3.9)
Sex				
Male	86 (38.1)	96 (42.7)	91 (41.4)	273 (40.7)
Female	140 (61.9)	129 (57.3)	129 (58.6)	398 (59.3)
Race				
Caucasian	191 (84.5)	207 (92)	191 (86.8)	589 (87.8)
Black	26 (11.5)	13 (5.8)	23 (10.5)	62 (9.2)
Asian	7 (3.1)	3 (1.3)	5 (2.3)	15 (2.2)
American Indian, Alaska Native	0	0	1 (0.5)	1 (0.1)
Pacific Island	1 (0.4)	1 (0.1)	0	2 (0.3)
Other	0	1 (0.4)	0	1 (0.1)
Multiple	1 (0.4)	0	0	1 (0.1)
Ethnicity				
Hispanic	89 (39.4)	98 (43.6)	100 (45.5)	287 (42.8)
Non-Hispanic	137 (60.6)	127 (56.4)	120 (54.5)	384 (57.2)

Source: Trial 060-634 CSR, Table 9, pp73

In addition to above demographics, the patients also had similar baseline AM and PM rTNSS, iTNSS, rTOSS, and iTOSS. The scores also indicated that they were symptomatic at baseline.

Compliance

Compliance was high across all groups at multiple time points. Overall study compliance was ≥80% in ≥96.8% of patients across all groups. When subdividing compliance by visits, compliance was similar. In the placebo, 74 mcg and 148 mcg groups compliance was ≥80% between visit 3 (double blind treatment day 1) and visit 4 (day 7 of treatment) in 97.7%, 98.7%, and 99.6% of the patients, respectively. Between visit 4 and 5 (treatment day 7-14), ≥80% compliance was observed in 95%, 97.3%, and 97.8% of the patients in the placebo, 74 mcg, and 148 mcg groups, respectively.

Primary Endpoint

The primary endpoint was the average of the AM and PM rTNSS over the 2 week treatment period compared to baseline. For the ITT population, there was a statistically significant improvement in scores for the 74 mcg and 148 mcg groups compared to placebo. The treatment difference for the 74 and 148 mcg groups compared to placebo was 1.04 and 1.02 (p<0.0001), respectively.

The sponsor also conducted sensitivity analysis to assess for the impact of missing data. Three models were used: worst case imputation, mixed effects of covariance model, and pattern mixture model. The worst case model assigns the best possible rTNSS score (0) on the day that the data is missing in the placebo groups and the worst value (12) for the ciclesonide groups. The proportion of patients with missing rTNSS on at least one day during the 6 week treatment period was 3%, 0.4% had intermittent missing data, and 2.6% were dropouts. The numbers were similar between groups. Sensitivity analysis using all three models yielded results similar to the primary analysis (*per sponsor*).

Key Secondary Endpoints

The first key secondary endpoint assessed was change from baseline in AM and PM iTNSS averaged over the 2 week treatment period in the ITT population. For both CIC-HFA doses, there was statistically significant improvement in symptom scores. Patients who received 74 mcg had a mean improvement of 0.90, and those receiving 148 mcg improved by 0.83 compared to placebo ($p < 0.0002$). The results for the primary are summarized in Table 24.

Table 24. Trial 060-634. Results for Primary and Key Secondary Endpoints

	CIC-HFA 74 mcg	CIC-HFA 148 mcg	Placebo
Avg AM/PM rTNSS over the two week double blind period			
N	226	225	220
Change from baseline			
LS Mean (SE)	-1.75 (0.15)	-1.74 (0.15)	-0.72 (0.16)
Treatment difference vs. Pbo (95% CI)	1.04 (0.61, 1.46)	1.02 (0.59, 1.45)	
p-value vs. Pbo	<0.0001	<0.0001	
Avg AM/PM iTNSS over the two week double blind period			
N	226	225	220
Change from baseline			
LS Mean (SE)	-1.58 (0.15)	-1.51 (0.15)	-0.68 (0.15)
Treatment difference vs. Pbo (95% CI)	0.90 (0.49, 1.32)	0.83 (0.42, 1.25)	
p-value vs. Pbo	<0.0001	0.0002	
Avg AM/PM rTOSS over the two week double blind period (baseline ≥5.0)			
N	159	161	165
Change from baseline over the 2 week treatment period			
LS Mean (SE)	-1.40 (0.13)	-1.21 (0.13)	-0.79 (0.13)
Treatment difference vs. Pbo (95% CI)	0.52 (0.15, 0.89)	0.34 (-0.03, 0.71)	
p-value vs. Pbo	0.0124	0.1444	
Overall RQLQ(S) at end of 2 week period (baseline ≥3.0)			
N	162	148	147
Change from baseline over the 2 week treatment period			
LS Mean (SE)	-1.44 (0.11)	-1.41 (0.12)	-0.88 (0.13)
Treatment difference vs. Pbo (95% CI)	0.64 (0.33, 0.95)	0.62 (0.3, 0.94)	
p-value vs. Pbo	0.0124	N/A	

Source: Trial 060-634 CSR, Tables 12, 14, 16, pp79, 87, 95

The second key secondary endpoint evaluated was change from baseline in AM and PM rTOSS averaged over the 2 week treatment period in patients with a baseline rTOSS ≥5. Improvement was seen in the 74 mcg group compared to placebo. The treatment difference compared to placebo was 0.52 (p<0.0124). For the 148 mcg treatment group, there was no significant improvement compared to placebo.

The third key secondary endpoint evaluated was change from baseline in RQLQ(S) overall score at the end of the 2 week treatment period in patients with a baseline score ≥3. Improvement was seen the 74 mcg group compared to placebo. The treatment difference compared to placebo was 0.64 (p<0.0124). For the 148 mcg treatment group, no analysis was done as the previous key secondary endpoint for the 148 mcg dose did not demonstrate significant improvement from baseline. These results are summarized in Table 24, above.

As with trial 060-622, this trial only analyzed the AM/PM rTOSS and RQLQ in only the symptomatic patients (baseline rTOSS \geq 5.0, RQLQ \geq 3.0). This is problematic as it is not representative of the whole SAR population. Therefore, the data was reanalyzed for the whole patient population by FDA biostatisticians. These results are summarized in Table 25.

Table 25. Trial 060-634. FDA Analysis for rTOSS and RQLQ Related Key Secondary Endpoints in the Total Population

	CIC-HFA 74 mcg	CIC-HFA 148 mcg	Placebo
Avg AM/PM rTOSS over the two week double blind period (all patients)			
N	226	225	220
Treatment difference vs. Pbo (95% CI)	0.4 (0.1, 0.7)	0.3 (0.0, 0.6)	
p-value vs. Pbo	0.024	0.055	
Overall RQLQ at the end the two week double blind period (all patients)			
N	226	225	220
Treatment difference vs. Pbo (95% CI)	0.5 (0.3, 0.8)	0.5 (0.3, 0.8)	
p-value vs. Pbo	<0.001	<0.001	

p-values are significant at the 0.025 level based on Bonferroni correction

Reviewer Comment:

Based on the primary and key secondary endpoints, both doses of ciclesonide improve nasal symptoms compared to placebo. The magnitude of improvement for nasal symptoms is similar to Trial 060-622 and M1-602. However, the magnitude of improvement of the ocular symptoms is less than 060-622. Interestingly, the treatment effect is more pronounced for the 74 mcg dose compared to the 148 mcg dose. The improvement seen in the 74 mcg dose group was modest with an unadjusted p-value of 0.024. Had the p-value been adjusted, statistical significance may have been lost. The 148 mcg dose had an even more modest nominal improvement with a non-significant unadjusted p-value. Based on this, CIC-HFA, at best, only modestly improves ocular symptoms. The treatment effect with regard to the RQLQ in the total population, however, is likely significant and similar between this trial and 060-622.

Other Secondary Endpoints

Only the primary and key secondary endpoints had p-values which were adjusted for multiple comparisons. For all other endpoints, no adjustment was made. Also note that for all secondary endpoints involving ocular symptoms (TOSS) or quality of life (RQLQ), the sponsor only analyzed data from a subset of the total population. For non-primary and non-key secondary endpoints, TOSS and RQLQ related endpoints were not reanalyzed for the entire population by FDA biostatisticians.

Change from baseline in AM and PM rTNSS over averaged over each week was also assessed. When evaluating the average over week 1, both the 74 mcg and 148 mcg

groups had significant improvement from baseline compared to placebo. The difference from placebo was 0.81 and 0.88 for the 74 mcg and 148 mcg groups. For the week 2 data, similar results were seen, though nominally greater in magnitude (1.28 and 1.17 for the 74 and 148 mcg groups, respectively). Results are summarized in Table 26.

The change from baseline in daily averages of AM and PM rTNSS was also assessed. These parameters were measured twice daily. For both the 74 and 148 mcg group, a statistically significant reduction relative to placebo was first noted on day 2, and persisted throughout the treatment period. These results are summarized in Figure 8. When analyzing AM and PM rTNSS scores separately similar results were seen.

Change from baseline in AM and PM iTNSS at each day and average over each week was also evaluated. The analysis was similar as for the rTNSS data. The results were similar and are summarized in Table 26 and Figure 9.

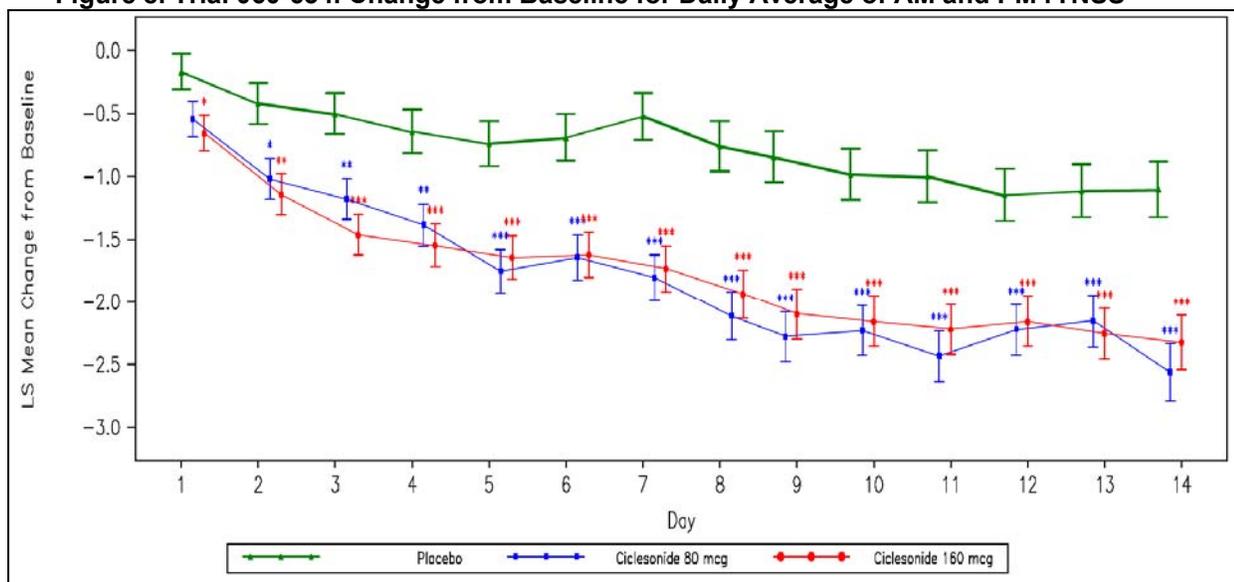
Table 26. Trial 060-634. Change from Baseline for the Average AM and PM rTNSS and iTNSS for each week

	CIC-HFA 74 mcg	CIC-HFA 148 mcg	Placebo
Avg AM/PM rTNSS over week 1 of the double blind period			
N	226	225	220
Change from baseline			
LS Mean (SE)	-1.31 (0.15)	-1.39 (0.15)	-0.51 (0.15)
Treatment difference vs. Pbo (95% CI)	0.81 (0.40, 1.21)	0.88 (0.47, 1.28)	
p-value vs. Pbo	0.0001	<0.0001	
Avg AM/PM rTNSS over week 2 of the double blind period			
N	237	234	234
Change from baseline			
LS Mean (SE)	-2.25 (0.18)	-2.13 (0.18)	-0.96 (0.19)
Treatment difference vs. Pbo (95% CI)	1.28 (0.88, 1.79)	1.17 (0.66, 1.68)	
p-value vs. Pbo	<0.0001	<0.0001	
Avg AM/PM iTNSS over week 1 of the double blind period			
N	226	225	220
Change from baseline			
LS Mean (SE)	-1.16(0.14)	-1.18 (0.14)	-0.50 (0.14)
Treatment difference vs. Pbo (95% CI)	0.66 (0.27, 1.05)	0.68 (0.29, 1.08)	
p-value vs. Pbo	0.001	0.0007	
Avg AM/PM iTNSS over week 2 of the double blind period			
N	226	225	220
Change from baseline			
LS Mean (SE)	-2.08 (1.07)	-1.82 (0.17)	-0.89 (0.18)
Treatment difference vs. Pbo (95% CI)	1.19 (0.7, 1.68)	1 (0.51, 1.49)	
p-value vs. Pbo	<0.0001	<0.0001	

p-values unadjusted for multiplicity

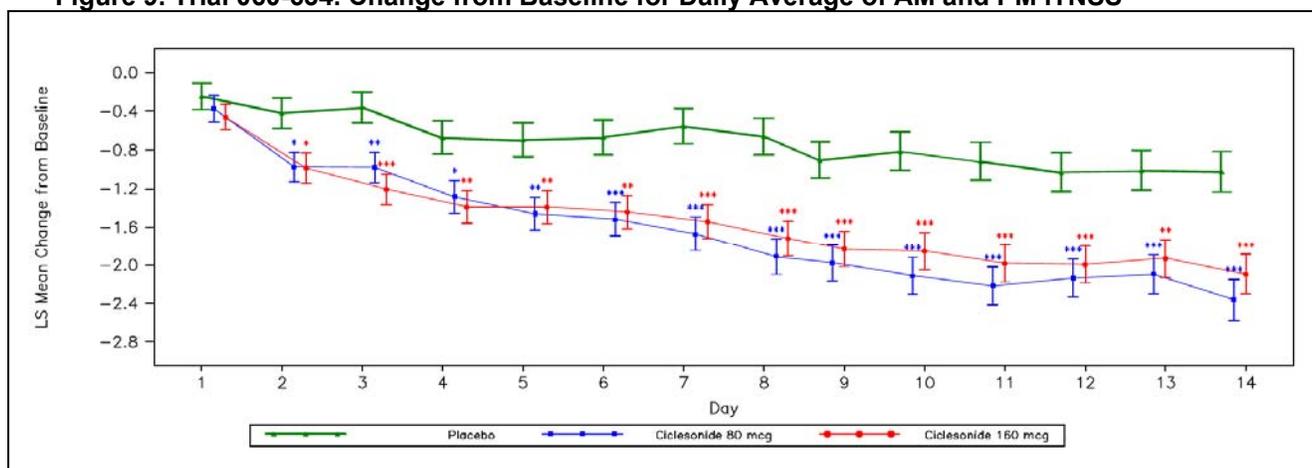
Source: Trial 060-634 CSR, Tables 19 and 20, pp 107 & 110

Figure 8. Trial 060-634. Change from Baseline for Daily Average of AM and PM rTNSS



Ciclesonide 80 mcg= 74 mcg ex-actuator dose, Ciclesonide 160 mcg= 148 mcg ex-actuator dose
 Source: Trial 060-634 CSR, Figure 6, pp106

Figure 9. Trial 060-634. Change from Baseline for Daily Average of AM and PM iTNSS



Ciclesonide 80 mcg= 74 mcg ex-actuator dose, Ciclesonide 160 mcg= 148 mcg ex-actuator dose
 Source: Trial 060-634 CSR, Figure 7, pp109

For both the 74 and 148 mcg group, a statistically significant reduction relative to placebo was first noted on day 2 for iTNSS (averaged AM and PM), and persisted throughout the treatment period. When analyzing AM and PM iTNSS scores separately, similar results were seen.

In addition to analyzing the TNSS, the sponsor also analyzed results for individual nasal symptoms score (NSS). Consistent with the TNSS data, the reflective and instantaneous AM and PM NSS for each domain averaged over the 2 week treatment period showed significant improvement in CIC-HFA groups compared to placebo. When

analyzing the same data averaged over each week and daily (iNSS and rNSS), similar results were seen. It should be noted that significance was based on p-values unadjusted for multiplicity.

For the following TOSS related endpoints, the total patient population was not analyzed by the sponsor, but rather only the subset with a baseline score ≥ 5 .

Change from baseline in reflective AM TOSS, PM TOSS, AM and PM TOSS at each day, averaged over each week, and averaged over the two-week treatment period in subjects with baseline rTOSS ≥ 5.0 was also analyzed. Only the 74 mcg dose of CIC-HFA resulted in statistically significant improvement (unadjusted p-values) in rTOSS over each individual week of treatment. The 148 mcg dose only showed improvement during week one, but not for week 2. The daily averages of the AM and PM rTOSS were also consistent with the weekly score results. When analyzing the daily AM and PM rTOSS separately, similar results to the weekly averages was seen.

Change from baseline in instantaneous AM TOSS, PM TOSS, AM and PM TOSS at each day, averaged over each week, and averaged over the two-week treatment period in subjects with baseline iTOSS ≥ 5.0 was also analyzed. Similar to the rTOSS data at the same time points, both doses of CIC-HFA demonstrated statistically significant improvement (unadjusted p-values) compared to placebo at week 1. However, for week 2, only the 74 mcg maintained statistically significant improvement compared to placebo. With regard to daily averages of AM and PM iTOSS, the results were similar to the weekly results.

In addition to analyzing the TOSS, the sponsor also analyzed results for individual ocular symptoms score (OSS) in patients with baseline TOSS scores ≥ 5 . Consistent with the TOSS data, the reflective and instantaneous AM and PM OSS for each domain averaged over the 2 week treatment period showed improvement in 74 mcg group compared to placebo. For the 148 mcg group for the 3 individual domains, improvement compared to placebo was marginal at best. When analyzing the same data averaged over each week and daily (iOSS and rOSS), similar results were seen.

Change from baseline in RQLQ(S) individual items at visit 5 in impaired (RQLQ(S) ≥ 3.0) patients was also analyzed. After 2 weeks of treatment, statistically significant improvements in RQLQ(S) were seen in the 74 and 148 mcg groups compared to placebo ($p < 0.05$ unadjusted for multiplicity).

Time to Maximal Effect

This endpoint was defined as the number of days until the first treatment day on which the difference between CIC-HFA and placebo was at least 90% of the largest estimated difference. For the 74 mcg group, the time to maximal effect was 8 days, and for the 148 mcg group, it was 7 days.

Reviewer Comment

The results for the other secondary endpoints support the efficacy of ciclesonide at both doses with regard to nasal symptoms. However, it is unclear if the non-key secondary endpoints are supportive with regard to ocular symptoms and quality of life, as secondary analysis was limited to the subset of SAR patients with baseline symptoms/impairment (TOSS \geq 5.0, RQLQ \geq 3.0). The onset of action, based on the twice daily iTNSS assessments, at both doses is 36 hours, and that time to maximal effect is sooner in the higher dosage group. The time to maximal effect for the 74 mcg groups is half that of what it was in trial 060-622. The reason for this discrepancy is not clear.

Exploratory Analyses
Device Use Survey

At visit 2 patients were asked “How did the spray feel?” and at visit 5 the question was repeated along with 7 additional questions relating to patient satisfaction. The questions and responses are summarized in Table 27.

Table 27. Trial 060-634. Device Survey

	CIC-HFA 74 mcg (N=226) N (%)	CIC-HFA 148 mcg (N=225) N (%)	Placebo (N=220) N (%)	Total (N=671) N (%)
Visit 2				
How did the spray feel?				
N	226	225	220	671
Very comfortable	59 (26.1)	59 (26.2)	61 (27.7)	179 (26.7)
Somewhat comfortable	60 (26.5)	64 (28.4)	58 (26.4)	182 (27.1)
Neither comfortable or uncomfortable	45 (19.9)	40 (17.8)	43 (19.5)	128 (19.1)
Somewhat uncomfortable	54 (23.9)	53 (23.6)	51 (23.3)	158 (23.5)
Very uncomfortable	8 (3.5)	9 (4.0)	7 (3.2)	24 (3.6)
Visit 5				
How did the spray feel?				
N	225	225	216	666
Very comfortable	43 (19.1)	38 (16.9)	32 (14.8)	113 (17.0)
Somewhat comfortable	64 (28.4)	58 (25.8)	60 (27.8)	182 (27.3)
Neither comfortable or uncomfortable	33 (14.7)	51 (22.7)	43 (19.9)	127 (19.1)
Somewhat uncomfortable	73 (32.4)	64 (28.4)	62 (28.7)	199 (29.9)
Very uncomfortable	12 (5.3)	14 (6.2)	19 (8.8)	45 (6.8)
Did spray run out of your nose?				
N	225	225	216	666
Yes	7 (3.1)	9 (4.0)	14 (6.5)	30 (4.5)
No	218 (96.9)	216 (96.0)	202 (93.5)	636 (95.5)
Did spray run down your throat?				
N	225	224	216	665
Yes	24 (10.7)	16 (7.1)	13 (6.0)	53 (8.0)
No	201 (89.3)	208 (92.9)	203 (94.0)	612 (92.0)
Did medication have an unpleasant taste?				
N	225	225	216	666
Yes	27 (12.0)	15 (6.7)	20 (9.3)	62 (9.3)
No	198 (88.0)	210 (93.3)	196 (90.7)	604 (90.7)

Did medication have an unpleasant scent?				
N	225	225	216	666
Yes	23 (10.2)	27 (12.0)	31 (14.4)	81 (12.2)
No	202 (89.8)	198 (88.0)	185 (85.6)	585 (87.8)
Was nasal spray device easy to use?				
N	225	225	216	666
Yes	216 (96.0)	211 (93.8)	211 (97.7)	638 (95.8)
No	9 (4.0)	14 (6.2)	5 (2.3)	28 (4.2)
How satisfied were you with the device?				
N	225	225	216	666
Very satisfied	110 (48.9)	115 (51.1)	107 (49.5)	332 (49.8)
Somewhat satisfied	73 (32.4)	68 (30.2)	66 (30.6)	207 (31.1)
Neither satisfied or dissatisfied	25 (11.0)	24 (10.7)	26 (12.0)	75 (11.3)
Somewhat dissatisfied	9 (4.0)	12 (5.3)	10 (4.6)	31 (4.7)
Very dissatisfied	8 (3.6)	6 (2.7)	7 (3.2)	21 (3.2)
How likely are you to continue to take this medication?				
N	193	196	190	579
Very likely	97 (50.3)	95 (48.5)	91 (47.9)	283 (48.9)
Somewhat likely	57 (29.5)	64 (32.7)	57 (30.0)	178 (30.7)
Neither likely or unlikely	17 (8.8)	15 (7.7)	21 (11.1)	53 (9.2)
Somewhat unlikely	13 (6.7)	13 (6.6)	14 (7.4)	40 (6.9)
Very unlikely	9 (4.7)	9 (4.6)	7 (3.7)	25 (4.3)

Source: Trial 060-634 CSR, Table 27, pp131-132

Between baseline and end of treatment more patients in each group found the device uncomfortable. Most patients also found the device easy to use.

Responder Analysis

The sponsor also performed an *ad hoc* responder analysis for rTNSS, iTNSS, and rTOSS with improvement from baseline of at least 0.5 defined to represent a clinically meaningful change. This was performed in the total patient population. For rTNSS, a total of 49.1%, 69%, and 64.4% of subjects receiving placebo, 74 mcg, and 148 mcg had an improvement from baseline of at least 0.5. Similar results were seen for the iTNSS data (placebo: 50%, 74 mcg: 69%, and 148 mcg: 64%). For the rTOSS data, fewer patients were responders. For those that received placebo, 74 mcg and 148 mcg, 48.6%, 54.4%, and 52% had improvement of at least 0.5, respectively.

Subgroup Analysis

For the primary and key secondary endpoints subgroup analysis was performed on the ITT population base on age, sex, and race. Gender had no effect. The effect of age and race was difficult to assess, as 90.5% of the ITT population was 19 to <65 years of age and 93.1 % were Caucasian. The sample size of patients who were non-Caucasian or ≤18 years of age was too small to detect any differences.

In addition to subgroup analysis by demographic characteristics, analysis of the primary and first two key secondary endpoints was also performed based on baseline symptom severity symptom severity was defined as in trial 060-622.

The analysis based on symptom severity mirrored the overall analysis of the primary and first key secondary endpoint. Whether or not baseline symptom scores were mild/moderate or severe, both doses of CIC-HFA improved the average AM/PM rTNSS and AM/PM iTNSS over the 2 week double-blind treatment period.

When analyzing the change in baseline AM/PM rTOSS averaged over the 2 week treatment period by severity of baseline scores, the results demonstrated that neither 74 mcg dose or 148 mcg dose consistently improved symptoms in patients with mild/moderate and severe baseline symptoms compared to placebo. These results are summarized in table Table 28.

Table 28. Trial 060-634. Change from Baseline for AM/PM rTOSS Averaged Over the Double-Blind Treatment Period by Baseline Severity

Change from baseline for AM/PM rTOSS averaged over the double blind period	Mild/moderate			Severe		
	CIC-HFA 74 mcg (N=226)	CIC-HFA 148mcg (N=225)	Placebo (N=220)	CIC-HFA 74 mcg (N=226)	CIC-HFA 148mcg (N=225)	Placebo (N=220)
By Baseline iTNSS						
N	57	67	56	102	94	108
LS Mean (SE)	-1.36 (0.23)	-1.11 (0.20)	-0.76 (0.22)	-1.57 (0.17)	-1.41 (0.18)	-1.02 (0.17)
Treatment difference vs. Pbo (95% CI)	0.59 (-0.02, 1.20)	0.35 (-0.24,0.93)		0.56 (0.09, 1.02)	0.39 (-0.09, 0.87)	
p-value vs. Pbo	0.0559	0.2417		0.0203	0.1093	
By Baseline rTNSS						
N	53	67	61	106	94	103
LS Mean (SE)	-1.38 (0.22)	-0.94 (0.19)	-0.45 (0.20)	-1.50 (0.17)	-1.51 (0.18)	-1.15 (0.17)
Treatment difference vs. Pbo (95% CI)	0.93 (0.35, 1.52)	0.49 (-0.06,1.03)		0.35 (-0.13, 0.82)	-0.35 (-0.14, 0.85)	
p-value vs. Pbo	0.0018	0.0780		0.1495	0.1572	
By Baseline iTOSS						
N	51	41	51	108	120	113
LS Mean (SE)	-1.61 (0.25)	-0.62 (0.28)	-0.67 (0.24)	-1.31 (0.16)	-1.50 (0.16)	-0.97 (0.16)
Treatment difference vs. Pbo (95% CI)	0.94 (0.27, 1.61)	-0.05 (0.77,0.6)		0.34 (-0.11, 0.79)	0.53 (0.09, 0.96)	
p-value vs. Pbo	0.0064	0.8803		0.1338	0.0172	
By Baseline rTOSS						
N	44	50	52	115	111	112
LS Mean (SE)	-1.19 (0.25)	-0.52 (0.23)	-0.65 (0.22)	-1.53 (0.16)	-1.58 (0.17)	-1.02 (0.17)
Treatment difference vs. Pbo (95% CI)	0.53 (-0.12, 1.19)	-0.13 (-0.77,0.50)		0.52 (0.07, 0.97)	0.56 (0.11, 1.01)	
p-value vs. Pbo	0.1100	0.6777		0.0242	0.0148	
By Baseline RQLQ(S)						
N	59	70	66	100	91	98
LS Mean (SE)	-1.31 (0.21)	-0.88 (0.19)	-0.90 (0.20)	-1.51 (0.18)	-1.51 (0.20)	-0.89 (0.19)
Treatment difference vs. Pbo (95% CI)	0.41 (-0.15, 0.97)	-0.02 (0.56,0.5)		0.62 (0.12, 1.12)	0.62 (0.10, 1.14)	
p-value vs. Pbo	0.1505	0.9401		0.0157	0.0192	

p-values unadjusted for multiplicity
 Source: Trial 060-634 CSR, Table 17, pp98-101

Reviewer Comment

The device survey indicated that device comfort decreased over time and that the device was easy to use. The survey did not assess for appropriate usage, which may be an issue due to the device design. The responder analysis was supportive of a treatment effect for CIC-HFA, as there were more responders in the CIC-HFA groups versus placebo. However, the sponsor did not provide sufficient justification for their

definition of a “clinically meaningful change” in the TNSS/TOSS scores. The subgroup analysis based on symptom severity was also consistent with the primary and first key secondary endpoint. The results for the ocular symptoms scores were much more variable in this trial as compared to trial 060-622 and less supportive of a treatment effect.

Safety

Exposure

A total of 551 patients were exposed to CIC-HFA (226 in the 74 mcg group and 225 in the 148 mcg group), and 220 to placebo for a mean of 14.6-14.8 days.

Deaths/SAEs

There were no deaths in this study. There were 2 SAEs reported. One occurred during the screening period (lung neoplasm) and one (chest pain) during the double-blind placebo phase.

TEAEs

A total of 107 patients reported 153 TEAEs. Reported TEAEs were similar between all groups. The most frequent TEAE reported was epistaxis (1.9%), followed by nasal septum disorder (1%). Other frequent TEAEs included nasal mucosal disorder and oropharyngeal pain. AEs in the Respiratory, Thoracic, and Mediastinal Disorder SOC (MedDRA v.12.1) exhibited a dose response. The other commonly occurring AEs (≥1%) were also more frequent in the CIC-HFA groups compared to placebo. These results are summarized in Table 29.

Table 29. Trial 060-634. Treatment Emergent Adverse Events Occurring in ≥1% of Patients

System Organ Class/ Preferred term	CIC-HFA 74 mcg (N=226)		CIC-HFA 148 mcg (N=225)		Placebo (N=220)		Overall (N=671)	
	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N
Overall	33 (14.6)	45	39 (17.3)	57	35 (15.9)	52	107 (15.9)	154
Respiratory, Thoracic, and Mediastinal Disorders	10 (4.4)	13	16 (7.1)	20	10 (4.5)	11	36 (5.4)	44
Epistaxis	3 (1.3)	3	6 (2.7)	6	4 (1.8)	4	13 (1.9)	13
Nasal mucosal disorder	1 (0.4)	1	4 (1.8)	4	0	0	5 (0.7)	5
Nasal septum disorder	3 (1.3)	4	3 (1.3)	4	1 (0.5)	1	7 (1.0)	9
Oropharyngeal pain	3 (1.3)	3	2 (0.9)	2	1 (0.5)	1	6 (0.9)	6

Source: Trial 060-634 CSR, Table 30, pp145

Only 9/671 patients discontinued due to adverse events. This included 3 in the placebo group, 4 in the 74 mcg group, and 2 in the 148 mcg group. The SOC most commonly leading to discontinuation across all groups was Infections and Infestations. In the placebo group, AEs leading to discontinuation were nasopharyngitis, asthma, and seasonal rhinitis. In the 74 mcg group, AEs leading to discontinuation consisted of drug hypersensitivity, ear infection, pharyngitis (streptococcal), and tonsillitis. The report of

drug hypersensitivity, was an allergic reaction to an allergy shot. For the 148 mcg group, AEs leading to discontinuation were influenza and rash. The rash developed after 3 days of treatment and was distributed over the patients face, neck, and arms. The patient was discontinued from the trial after 6 days of treatment. This AE was assessed by the investigator to be unrelated to drug.

Nasal AEs

Overall 33 (4.9%) patients reported 39 treatment emergent nasal AEs. The 148 mcg group had the most nasal AEs. The most common nasal AE was epistaxis, followed by nasal septum disorder. The 74 and 148 mcg ciclesonide groups had increased numbers of nasal septum disorders (3 and 3, respectively) compared to placebo (1). Nasal septum disorders included all non-ulcerative lesions (i.e. erythema, irritation, erosion) of the septum. Non-ulcerative lesions not located on the septum were classed as nasal mucosal disorders. Nasal mucosal disorders were the 3rd most common nasal AE, and were dose dependent. No nasal ulcers were reported.

One nasal septum perforation was reported. This occurred in a 34 year old female (0003/S150) with history of SAR, sinus headaches, anxiety and depression who was randomized to receive 74 mcg of CIC-HFA daily. At screening the ENT exam was normal, and at completion of the study a perforation was visualized. Per investigator, it appeared well healed. This patient also had reported AEs of headache and vomiting that had resolved by the time the perforation was reported. No epistaxis was reported. This lesion was assessed by an independent ENT physician who felt that based on the well healed appearance and lack of symptoms (i.e. epistaxis) the lesion pre-dated entry into the clinical study. Of note, this assessment took place on [REDACTED] (b)(4) and the nasal septum perforation was recorded by the site investigator (Dr. Frank Jacobs) on [REDACTED] (b)(6) (day 13 of treatment). The site investigator viewed pictures taken by the ENT and confirmed that it had not changed in appearance since he had initially noted it. Nasal AE results are summarized in Table 30.

Table 30. Trial 060-634. Treatment Emergent Nasal Adverse Events by Preferred Term (ITT Population)

Preferred Term	CIC-HFA 74 mcg (N=226)		CIC-HFA 148 mcg (N=225)		Placebo (N=220)		Overall (N=671)	
	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N
Overall	9 (4.0)	12	14 (6.2)	17	10 (4.5)	10	33 (4.9)	39
Epistaxis	3 (1.3)	3	6 (2.7)	6	4 (1.8)	4	13 (1.9)	13
Installation site discomfort	1 (0.4)	1	1 (0.4)	1	1 (0.5)	1	3 (0.4)	3
Instillation site dryness	0	0	1 (0.4)	1	0	0	1 (0.1)	1
Installation site irritation	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Nasal mucosal disorder	1 (0.4)	1	4 (1.8)	4	0	0	5 (0.7)	5
Nasal septum disorder	3 (1.3)	4	3 (1.3)	4	1 (0.5)	1	7 (1.0)	9
Nasal septum perforation	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Nasopharyngitis	0	0	0	0	1 (0.5)	1	1 (0.1)	1
Rhinitis seasonal	0	0	0	0	1 (0.5)	1	1 (0.1)	1
Sinusitis	0	0	0	0	1 (0.5)	1	1 (0.1)	1
Sneezing	0	0	1 (0.4)	1	1 (0.5)	1	2 (0.3)	2
Upper respiratory tract infection	1 (0.4)	1	0	0	0	0	1 (0.1)	1

Source: Trial 060-634, Table 32, pp148

Reviewer Comment:

With regard to AEs, CIC-HFA was well tolerated. There were no deaths nor SAEs related to study medication. Overall, adverse events were similar between groups, but slightly higher in the placebo group. The AEs reported were typical of nasal corticosteroids. However, as in trial M1-602, there was one nasal septum perforation. Although the sponsor argued that the perforation was likely present prior to study entry, no abnormality was noted on screening ENT exam. Occurrence of a perforation is concerning, as these are generally extremely rare in clinical trials. Overall, this trial had fewer AEs compared to trial 060-622 (total and nasal). The reason for this is not clear.

Clinical Labs

Lab data was collected at screening (visit 1) and at the end of study visit (visit 5). Based on mean values, there were no significant changes in chemistry or hematology values between screening and end of treatment in any of the groups. Shift tables were used to detect differences in laboratory parameters from baseline to end of study. Shifts were similar between groups.

Although there were no significant changes when examining the mean values, on an individual level, several patients had significant changes in lab values. In the 74 mcg group, one patient had urinalysis findings consistent with a urinary tract infection. In the 148 mcg group one patient had urinalysis consistent with urinary tract infection. Two patients receiving 148 mcg daily had elevated serum glucose (0001/S193 and

003/S110), one of which was associated with glucosuria. Neither patient had a history of diabetes. Proteinuria was also noted in a patient in the 148 mcg group.

Vital Signs/Physical Exam

Mean vital signs between groups were similar across groups with regard to changes from baseline. Any changes in physical exam were reported as adverse events and results are summarized in the safety section.

ENT exams

Clinical significant worsening based on ENT exam was rare and occurred in a minority (0.7%-1.3%) of patients in each treatment group. One nasal septum perforation was noted as discussed above. No ulcerations were reported.

Reviewer Comment

Overall the clinical lab findings are reassuring to the safety of the drug. The elevated serum glucoses in the 2 patients who received 148 mcg of CIC-HFA is of some concern as this could potentially represent systemic effects of this medication. However, as it was in so few patients and a patient in the placebo group was also found to have elevated serum glucose, these findings may not be indicative of a drug effect. Aside from the nasal septal perforation, the changes noted on ENT examination are also not unexpected, as all the patients in the study were symptomatic with SAR.

Overall Reviewer Comment Trial 060-634

This trial is supportive of the proposed indication with regard to nasal symptoms. The treatment effect for nasal symptoms is similar to that seen in trial M1-602 and 060-622, and the Omnaris development program. With regard to ocular symptoms, this trial is less supportive. In the FDA analysis of the key secondary endpoint related to ocular symptoms, the effect of CIC-HFA at both doses was marginal (LS mean difference from placebo was ≤ 0.4 for both doses), with a marginal to insignificant non-adjusted p-values. With regard to RQLQ, the effect was marginal with a difference from placebo of 0.5 for both doses (MCID 0.5), but statistically significant (unadjusted p-value <0.001 for both doses). The other endpoints related to nasal symptoms were consistent with primary and key secondary endpoints. They were also supportive of persistence of effect over the 2 week treatment period. However, it is unclear if the other end points were supportive with regard to ocular symptoms and quality of life, as analysis of these endpoints was limited to the subset of SAR patients with baseline symptoms/impairment (TOSS ≥ 5.0 , RQLQ ≥ 3.0). The overall safety profile was also consistent with other inhaled nasal corticosteroids. However, as in M1-602, a nasal septum perforation was noted. The occurrence of 2 nasal septum perforations in the clinical development program is especially concerning. However, in this case, based on ENT evaluation, this lesion may have pre-dated entry into the trial.

5.3.4 Trial 060-633

Administrative Information

- **Study title:** A 6-Month Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Efficacy and Safety Study of Once Daily Ciclesonide HFA Nasal Aerosol (74 and 148 mcg) in The Treatment of Perennial Allergic Rhinitis (PAR) in Subjects 12 Years and Older
- **Study dates:** 9/1/2009-5/18/2010
- **Study sites:** 46 U.S. centers
- **Relevant Allergens:** Perennial Allergens (dust mite, cockroach, molds, animal dander)
- **Study report date:** 12/01/2010

Objectives/Rationale

- To demonstrate the efficacy of ciclesonide HFA applied as a nasal aerosol (148 mcg and 74 mcg) once daily compared to placebo in subjects with PAR over 6 weeks.
- Evaluate the safety and tolerability of ciclesonide HFA nasal aerosol once daily as compared to placebo in subjects with PAR over 6 weeks and 6 months.

Trial Design and Conduct

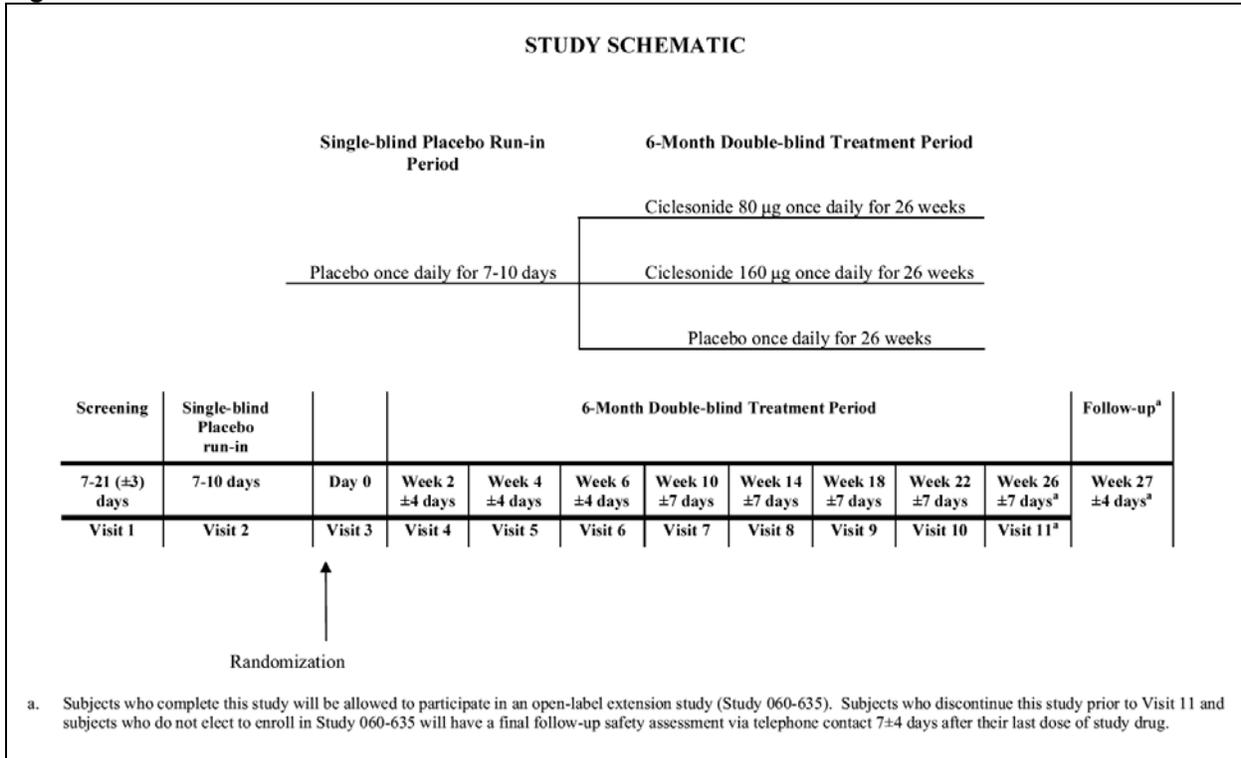
This was a 6 month multi-center, randomized, double-blind placebo controlled, parallel group efficacy and safety trial of CIC-HFA in patients 12 years and older with PAR. Patients were given either placebo or CIC-HFA (74 mcg or 148 mcg once daily) following randomization. This trial consisted of a screening period (7-21 days) from visit 1 to 2, followed by a single blind run in period (7-10 days) from visit 2 to 3. The double blind treatment period lasted 26 weeks beginning at visit 3 (randomization), and consisted of clinic visits at week 2, 4, 6, 10, 14, 18, 22, and 26. Patients were required to have positive skin prick test to a relevant perennial allergen (e.g. house dust mite, cockroach, molds, and animal dander), and have had a diagnosis of PAR for 2 years. Patients had to be sufficiently symptomatic to be randomized. At the end of this study, patients were allowed to continue in a 6 month open label extension (060-635).

During the single blind run-in period, patients self administered single-blind placebo every morning. Patients also assessed and recorded their reflective (rTNSS) and instantaneous (iTNSS) nasal symptoms (sneezing, running nose, itchy nose, and nasal congestion) twice daily (AM and PM). Their instantaneous and reflective ocular symptoms (rTOSS/iTOSS) were also recorded twice daily.

Following the run-in period, at visit 3, patients were randomized to double-blind treatment with either CIC-HFA 74 mcg once daily or 148 mcg once daily, or placebo. During the treatment period, patients recorded their TNSS/TOSS as in the run-in period.

In addition, the RQLQ(S) will be administered at visit 3, 6, and 11. The study schematic and assessment schedule are summarized in Figure 10 and Table 31.

Figure 10. Trial 060-633. Trial Schematic



Source: Trial 060-633 CSR, Figure 1, pp27

Table 31. Trial 060-633. Assessment Schedule

	Screen	Run in	6-month Double-Blind Treatment Period									
Visit	1	2	3	4	5	6	7	8	9	10	11	FU
Week			1	2	4	6	10	14	18	22	26	27
Day			0	14 ±4	28 ±4	42 ±4	70 ±7	98 ±7	126 ±7	154 ±7	182 ±7	189 ±4
Informed consent	X											
Inclusion/Exclusion Review	X	X										
Review of Randomization Criteria			X									
Rhinoconjunctivitis Quality-of-Life (RQLQ)			X			X					X	
Medical history	X					X					X	
Concomitant medication history	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (including ENT)	X					X					X	
Ear, nose and throat exam (ENT)		X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	
Serum pregnancy	X					X					X	
Clinical lab evaluation	X		X			X					X	
Skin Prick Testing for relevant allergen	X											
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X
Dispense single-blind placebo		X										
Review ePRO symptom scores and study medication administration		X	X	X	X	X	X	X	X	X	X	
Randomization			X									
Dispense double-blind study medication			X			X	X	X	X	X		
Collect and clean double-blind study medication					X							
Dispense/Review Medical Event Calendar	X	X	X	X	X	X	X	X	X	X	X	

Source: Trial 060-633 CSR, Table 2, pp24

Study Population

This study included 1111 patients ages 12 years and older with PAR. In order to participate, the patients had to conform the following inclusion/exclusion criteria at screening, the continuation criteria at visit 2, and the randomization criteria at visit 3.

Key Inclusion Criteria

The inclusion criteria were similar to trials 060-622 and 060-634, except that history of SAR to Mountain Cedar or skin test positivity to Mountain Cedar was not required (criteria 2 and 3). In addition, trial 060-633 required the following:

1. History of PAR to a relevant perennial allergen (e.g. house dust mite, cockroach, molds, animal dander) for a minimum of 2 years preceding visit 1. The PAR must have been of sufficient severity to have required treatment.
2. At visit 1, the patient had to demonstrate skin prick sensitivity to at least one relevant perennial allergen.
3. Based on the patient's medical history, in the investigator's judgment, the subject was unlikely to have an exacerbation of SAR during the first 6 weeks of the study.

Key Exclusion Criteria

The exclusion criteria were similar to trials 060-622 and 060-634.

Key Continuation Criteria:

1. Subject continues to meet the inclusion/exclusion criteria.
2. Subject has not experienced an adverse event that would result in failure to continue to meet inclusion/exclusion criteria.
3. Subject has not suffered from the common cold or acute sinusitis within the 14 days prior to the Single-blind Placebo Period (Visit 2).
4. Use of antibiotic therapy for acute conditions within 14 days prior to the Visit 2. Low doses of antibiotics taken for prophylaxis are permitted if the therapy was started prior to the Screening Visit and is expected to continue throughout the trial.
5. Subject is not expected to have an exacerbation of SAR during the single-blind run in period and first 6 weeks of double-blind treatment.

Key Randomization Criteria

1. Subject continues to meet the inclusion/exclusion criteria.
2. Subject has a minimum cumulative subject-assessed *reflective* TNSS of 54 (out of a possible 108) over any combination of AM and PM scores during 4 days of the last 6 days of the Single-Blind Placebo Run-in Period.
3. The cumulative subject-assessed *reflective* scores for runny nose OR nasal congestion must be at least 14 (out of a possible 27) over any combination of AM and PM scores during 4 days of the last 6 days of the Single-Blind Placebo Run-in Period.
4. Each subject must have adequately completed the symptom assessment via the ePRO system. Failure is defined as missing >20% of the symptom score entries during the Single-Blind Placebo Run-in Period.
5. Each subject may not have missed more than 1 day of their single-blind medication during the entire Single-Blind Placebo Run-in Period.
6. Subject has not used any of the prohibited concomitant medications during the Single-Blind Placebo Run-in Period.
7. Subject has not suffered from the common cold or acute sinusitis within the 14 days prior to the Randomization Visit (Visit 3).

Treatments

Treatment groups

Ciclesonide HFA nasal aerosol 74 mcg (37 mcg each nostril) daily
Ciclesonide HFA nasal aerosol 148 mcg (74 mcg each nostril) daily
Placebo HFA nasal inhaler (2 inhalations) daily

Concomitant Medications/Prohibited Medications

All medications taken by the patients were recorded in the CRF. If the patient was on a prohibited medication which could not be withdrawn, the patient was not allowed to enter the trial. In cases where the medication could be discontinued, it was not for the

sole purpose of enrollment in the trial. The disallowed and restricted medications are summarized in Table 32 and Table 33.

Table 32. Trial 060-633. Disallowed Medications

Medication	Required Withholding Interval Prior to Visit 2
Cromolyn, nedcromil, or Iodoxamide (intranasal, ocular, or oral)	14 days
Leukotriene antagonists or 5-LO inhibitors	14 days
Inhaled/Oral/Intranasal anticholinergics	14 days
Tricyclic antidepressants	14 days
Monoamine oxidase inhibitors	14 days
Inhaled/systemic/intranasal ocular corticosteroids	30 days
Azoles, anti-fungals	30 days
Immunosuppressive drugs	60 days

Source: Trial 060-633 CSR, Table 4, pp35

Table 33. Trial 060-633. Restricted Medications

Medication	Required Withholding Interval Prior to Visit 2	Required Withholding Interval during Treatment
Topical/Oral/Nasal Decongestants	10 days	Visit 2 through Visit 6
Short-acting antihistamines (nasal and ocular)	5 days	Visit 2 through Visit 6
Long-acting antihistamines (nasal and ocular)	10 days	Visit 2 through Visit 6
Over-the-Counter cough and cough medications or sleep aids containing antihistamines	10 days	Visit 2 through Visit 6
Airozan	7 days	Visit 2 through Visit 6

Source: Trial 060-633 CSR, Table 5, pp36

Reviewer Comment:

The study design and patient population are typical for PAR studies and similar to the Omnaris PAR study. The dosing and treatment groups are reasonable. The disallowed and restricted medications are also generally reasonable. It should be noted that allowing the usage of nasal decongestants and antihistamines after 6 weeks of double blind treatment (visit 6), may make interpretation of efficacy endpoints at later timepoints more difficult (see next section, exploratory endpoints).

Efficacy

Primary Efficacy Endpoint:

- Change from baseline in daily subject-reported AM and PM reflective TNSS averaged over the first 6 weeks of double-blind treatment.

Key Secondary Efficacy Endpoint:

- Change from baseline in daily subject-reported AM and PM instantaneous TNSS averaged over the first 6 weeks of double-blind treatment.

Other Secondary Efficacy Endpoints:

- Change from baseline in daily subject-reported AM reflective TNSS, PM reflective TNSS, AM and PM reflective TNSS, averaged over each week (Weeks 1-6), and averaged over the first 6 weeks of double-blind treatment (except AM and PM reflective TNSS averaged over the first 6 weeks)
- Change from baseline in daily subject-reported AM instantaneous TNSS, PM instantaneous TNSS, AM and PM instantaneous TNSS, averaged over each week (Weeks 1-6), and averaged over the first 6 weeks of double-blind treatment (except AM and PM instantaneous TNSS averaged over the first 6 weeks)
- Change from baseline in daily subject-reported individual AM reflective nasal symptom scores (NSS), individual PM reflective NSS, individual AM and PM reflective NSS, averaged over each week (Weeks 1-6), and averaged over the first 6 weeks of double-blind treatment
- Change from baseline in daily subject-reported individual AM instantaneous NSS, individual PM instantaneous NSS, individual AM and PM instantaneous NSS, averaged over each week (Weeks 1-6), and averaged over the first 6 weeks of double-blind treatment
- Change from baseline to Week 6 in RQLQ(S) overall score in impaired patients (baseline RQLQ(S) score ≥ 3.0)
- Change from baseline to Month 6 (Week 26) in RQLQ(S) overall score in impaired patients (baseline RQLQ(S) score ≥ 3.0)

Exploratory Efficacy Endpoints:

- Change from baseline in daily subject-reported AM reflective TNSS, PM reflective TNSS, AM and PM reflective TNSS averaged every two weeks during the 6-month double-blind treatment period (Weeks 1-26), and averaged over the 6-month double-blind treatment period (Weeks 1-26).
- Change from baseline in daily subject-reported AM instantaneous TNSS, PM instantaneous TNSS, AM and PM instantaneous TNSS, averaged every two weeks during the 6-month double-blind treatment period (Weeks 1-26), and averaged over the 6-month double-blind treatment period (Weeks 1-26).
- Change from baseline in daily subject-reported individual AM reflective nasal symptom scores (NSS), individual PM reflective NSS, individual AM and PM reflective NSS averaged every two weeks during the 6-month double-blind treatment period (Weeks 1-26), and averaged over the 6-month double-blind treatment period (Weeks 1-26).

- Change from baseline in daily subject-reported individual AM instantaneous NSS, individual PM instantaneous NSS, individual AM and PM instantaneous NSS averaged every two weeks during the 6-month double-blind treatment period (Weeks 1-26), and averaged over the 6-month double-blind treatment period (Weeks 1-26).
- Change from baseline to Week 6 in Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities (RQLQ(S)) domain scores, and individual item scores in impaired patients (baseline RQLQ(S) score ≥ 3.0).
- Change from baseline to Month 6 (Week 26) in RQLQ(S) domain scores, and individual item scores in impaired patients (baseline RQLQ(S) score ≥ 3.0).
- Time to maximal effect over the first 6 weeks of double-blind treatment. The time to maximal effect is defined as the number of days until the first treatment day on which the estimated difference between Ciclesonide HFA and placebo is at least 90% of the largest estimated difference in AM and PM reflective TNSS.
- Number and percentage of responders in each treatment group and overall at each week and averaged over the first 6 weeks of double-blind treatment, where response to treatment is defined as an improvement of at least 0.5 in the change from baseline in reflective AM and PM TNSS.
- Number and percentage of subjects responding to each category per question of the Sponsor's study medication device use survey.

Reviewer comment:

TOSS endpoints were not measured in this trial.

Efficacy Assessments:

Total Nasal Symptom Score (TNSS).

The reflective TNSS (rTNSS) represents perception of symptoms in the preceding 12 hours and the instantaneous TNSS (iTNSS) reflect symptoms in the past 10 minutes. During this study both the iTNSS and rTNSS were at least twice daily (AM and PM). The AM assessment occurred prior to the morning dose of study medication, and before bathing, consumption of food or beverage, or strenuous activities. The PM assessment occurred 12 hours after.

The order of assessments were iTNSS, and rTNSS for the AM and PM assessments. The TNSS was scored as in trial 060-622 and 060-633.

Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities (RQLQ(S)):

The RQLQ(S) has 28 questions in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). Subjects recall their experiences during the previous week and to give their responses on a 7-point scale (0 = Not Troubled to 6 = Extremely Troubled). When required at a particular visit, this questionnaire is to be the first subject-completed activity of the visit. Only patients with a baseline score ≥ 3.0 were included in the analysis.

Safety Assessments:

- Spontaneous and elicited adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs.
- Nasal AEs, including epistaxis, nasal ulceration, and nasal perforation.
- Physical examinations, including ENT examinations;
- Clinical laboratory evaluations;
- Vital signs (blood pressure and pulse rate).

Compliance Assessment:

Patients self-recorded date and time of study medication administration into the electronic Patient Reported Outcome (ePRO) system. This was done daily. The ePRO system also notified the investigator if patients did not take the study medication in real time. When notification was given, the investigator was required to contact the patient to determine the reason for lack of compliance.

Reviewer Comment:

The primary and key secondary endpoints are appropriate and will support the proposed indication if a positive result is found. The efficacy assessments (TNSS and RQLQ) are also appropriate and similar to those used in other PAR/SAR studies. It should be noted that as in Trials 060-622/634, for RQLQ, the sponsor only analyzed the subgroup of patients with a baseline score ≥ 3.0 , rather than the entire study population. This endpoint will be reanalyzed in the total population by FDA biostatisticians. The assessments for compliance and safety are also reasonable. As alluded to in the previous reviewer comment, interpretation of the endpoints that occur after 6 weeks of treatment is difficult, as the patients were permitted to take nasal decongestants and antihistamines. Usage of these medications will likely decrease the apparent treatment effect, as it is more likely that those in the placebo group will take these types of medications. However, evaluation of efficacy will not be based on the exploratory endpoints, and so it is unlikely to affect the conclusions of this review. Further, by allowing usage of these medications, patient drop out may decrease providing a larger safety population.

Ethics:

This study was conducted according to Good Clinical Practice, FDA, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this study protocol. No changes were made without the IRBs' approval.

Statistical Plan:

Sample Size

The sample size calculation was based on the primary efficacy endpoint. Based on study M1-402 (not reviewed), the standard deviation of the change from baseline in the AM/PM rTNSS averaged over the first 6 weeks of treatment was assumed to be 2.1. Using this assumed standard deviation, 300 subjects per group were projected to provide at least 90% power to detect a difference between treatment groups of 0.6 in change from baseline with a 2-sided alpha of 0.025. The sponsor assumed a 70% completion rate, and planned for 500 patients in the 148 mcg group, and 300 patients in the 74 mcg and placebo groups. Therefore, the sponsor planned to randomized approximately 1100 patients.

Analysis populations:

The sponsor pre-defined several populations for analysis. These included the enrolled population, the intention to treat (ITT) population, and the per protocol (PP) population. The enrolled population included all subjects enrolled, including those who withdrew prior to randomization, and those randomized patients who did not receive study medication. The ITT population was defined as those patients who were randomized, receive at least one dose of trial medication. This population was used for all efficacy and safety analysis. The PP population consisted of patients in the ITT population without any important protocol deviations (IPDs). IPDs were defined as in trial 060-622 and 060-634.

Efficacy Analysis

The primary efficacy endpoint was change in baseline in AM and PM rTNSS averaged over the 6 week treatment period and analyzed in the ITT population. Treatment groups were to be compared using ANCOVA with factors of baseline TNSS, center, and treatment. In order to minimize type I error rates, a closed tree gatekeeping testing procedure based on the Bonferroni test was used. Doses were compared to placebo at the 0.025 significance level. If any component of the rTNSS was missing for a time point, then the rTNSS score for that time point was considered missing.

The key secondary endpoint was the change from baseline in AM and PM iTNSS averaged over the first 6 weeks of the treatment period. This endpoint was analyzed in a manner similar to the primary endpoint.

The other secondary endpoints were analyzed using the same ANCOVA model as the primary and key secondary efficacy endpoints, using the appropriate baseline measure as the covariate. Except the primary and key secondary endpoint, p-values were not adjusted for multiple comparisons.

With the exception of time to maximal effect and the medication device survey, the exploratory endpoints were analyzed in a manner similar to the primary endpoints.

The time to maximal effect was defined as the number of days until the first treatment day on which the estimated difference between test product and placebo is at least 90% of the largest estimated difference. The efficacy measure that was compared to determine time to maximal effect was the average of the AM and PM rTNSS. Differences between groups were estimated for each day using ANCOVA.

Safety analysis was summarized by treatment group using description statistics. The results were reported separately for the first 6 weeks of double-blind treatment and the overall 6 months of double-blind treatment.

Results

Amendments:

The original protocol was submitted on July 15, 2009. The protocol was amended on October 22, 2009. The changes made were as follows:

1. Instructions for cleaning the nasal actuator were provided in the appendix.
2. The randomization criteria was changed from stating that AM and/or PM nasal symptoms scored could be used to determine if randomization criteria was met to stating that both AM and PM scores were required to meet randomization criteria.
3. Definition of patient failure to record symptoms scores was change from $\geq 20\%$ missing entries to $>20\%$.
4. All inhaled/systemic/intranasal corticosteroids were disallowed.

Prior to data availability, the age groups for the subgroup analysis were modified to be 12 to ≤ 18 years old, 19 to <65 years old, <65 years old, and >65 years old. In addition, an audit of site 0037 (Dr. Somerville) noted deficiencies in study conduct, protocol compliance, and investigator oversight. Corrective action was taken, and additional analysis was performed excluding the ITT patients from this site.

Following data availability, additional subgroup analysis was added based on baseline symptom severity.

Reviewer Comment:

Overall, it is unlikely that the changes made to the protocol significantly affected the study results. The finding of deficiencies during the audit of site 0037 is concerning, however, per report, corrective action was taken and additional analysis was performed excluding patients from this site. Given the small number of patients from this site (29/1100), it is unlikely that results from this site would skew the overall results. FDA biostatistics have re-analyze the data with and without this site to confirm this.

Protocol Violations:

Of the 1110 patients in the ITT population, 322 patients had important protocol deviations (IPDs) during the 6 week double-blind treatment period. During the 6 month double-blind treatment period, 445 patients had IPDs. IPDs during the first 6 weeks of double-blind treatment were more common in the placebo group compared to the

ciclesonide groups [placebo=104 (33.9%), 74 mcg=80 (26.8%), and 148 mcg=138 (27.3%)]. After the 6 months of treatment, the difference was maintained. The 2 most common IPDs at the 6 week and 6 month time point were usage of disallowed concomitant medications for >15% of the double blind treatment phase, and compliance <80% or >120%. These results are summarized in Table 34.

Table 34. Trial 060-633. Important Protocol Deviations in the ITT Population

	CIC-HFA 74 mcg N= 298 (%)	CIC-HFA 148 mcg N=505 (%)	Placebo N=307 (%)	Total N=1110(%)
Violation				
	6 Week Double-Blind Treatment Period (Visit 3-6)			
Total	80 (26.8)	138 (27.3)	104 (33.9)	322 (29.0)
Did not meet inclusion/ exclusion criteria at Visit 1	3 (1.0)	3 (0.6)	2 (0.7)	8 (0.7)
Did not meet continuation criteria at Visit 2	7 (2.3)	20 (4.0)	11 (3.6)	38 (3.4)
Did not meet randomization criteria at Visit 3	8 (2.7)	17 (3.4)	17 (5.5)	42 (3.8)
Received any disallowed medication for > 15% of their time during the 6-week double-blind treatment period	39 (13.1)	73 (14.5)	49 (16.0)	161 (14.5)
6-week double-blind study medication compliance < 80% or > 120%	39 (13.1)	56 (11.1)	45 (14.7)	140 (12.6)
< 80%	39 (13.1)	56 (11.1)	45 (14.7)	140 (12.6)
> 120%	0	0	0	0
Female subject ≤ 65 years of age with positive or missing pregnancy test result during the 6-week treatment period	1 (0.3)	4 (0.8)	6 (2.0)	11 (1.0)
	6 Month Double-Blind Treatment Period (Visit 3-11)			
Total	109 (36.6)	197 (39.0)	139 (45.3)	445 (40.1)
Did not meet inclusion/ exclusion criteria at Visit 1	3 (1.0)	3 (0.6)	2 (0.7)	8 (0.7)
Did not meet continuation criteria at Visit 2	7 (2.3)	20 (4.0)	11 (3.6)	38 (3.4)
Did not meet randomization criteria at Visit 3	8 (2.7)	17 (3.4)	17 (5.5)	42 (3.8)
Received any disallowed medication for > 15% of their time during the 6-month double-blind treatment period	39 (13.1)	80 (15.8)	53 (17.3)	172 (15.5)
6-month double-blind study medication compliance < 80% or > 120%	71 (23.8)	120 (23.8)	83 (27.0)	274 (24.7)
< 80%	71 (23.8)	120 (23.8)	83 (27.0)	274 (24.7)
> 120%	0	0	0	0
Female subject ≤ 65 years of age with positive or missing pregnancy test result during the 6-month treatment period	5 (1.7)	8 (1.6)	10 (3.3)	23 (2.1)

Source: Trial 060-633 CSR, Table 8, pp76

Reviewer Comment:

As compared to the SAR trials, this trial had a higher percentage of patients with IPDs. This may be partially due to the duration of the study. The increased number of IPDs seen in the placebo group compared to the CIC-HFA groups is primarily related to lack compliance and use of disallowed medications. This may imply that those in the placebo

group had increased PAR symptoms compared to the CIC-HFA groups leading them to either stop study medication or start disallowed medications.

Patient Disposition

Of the 1866 patients screened, 1551 were enrolled. Of the enrolled patients, 1111 patients were randomized. One patient was randomized despite not having sufficient allergy symptoms, and was removed prior to receiving double-blind medication. Therefore the ITT population was 1110. The most common reason for randomization failure was lack of sufficient allergy symptoms. A total of 1059 patients completed 6 weeks of the study and 965 patients completed all 6 months. A total of 145 patients withdrew prematurely. The most frequent reason for discontinuation was withdrawal of consent, followed by adverse events. These results are summarized in Table 35.

Table 35. Trial 060-633. Patient Disposition

Category	Ciclesonide Dose			
	CIC-HFA 74 mcg N=298 (%)	CIC-HFA 148 mcg N=505 (%)	Placebo N=307 (%)	Total N=1111 (%)
ITT Analysis Set	298	505	307	1110
PP Analysis Set (6 month)	189 (63.4)	308 (61.0)	168 (54.7)	665 (59.9)
PP Analysis Set (6 week)	218 (73.2)	367 (72.7)	203 (66.1)	788 (71.0)
Completed 6 week	283 (95.0)	485 (96.0)	291 (94.8)	1059 (95.4)
Completed 6 month	261 (87.6)	439 (86.9)	265 (86.3)	965 (86.9)
Prematurely Discontinued	37 (12.4)	66 (13.1)	42 (13.7)	145 (13.1)
Reason for Discontinuation				
Adverse Event	8 (2.7)	16 (3.2)	6 (2.0)	30 (2.7)
Protocol Violation	2 (0.7)	8 (1.6)	4 (1.3)	14 (1.3)
Withdrawal by Subject	13 (4.4)	15 (3.0)	12 (3.9)	40 (3.6)
Lost to follow-up	8 (2.7)	9 (1.8)	4 (1.3)	21 (1.9)
Physician Decision	2 (0.7)	7 (1.4)	3 (1.0)	12 (1.1)
Other	4 (1.3)	11 (2.2)	13 (4.2)	28 (2.5)

Source: Trial 060-633 CSR, Table 7, pp73

Nasal related AEs leading to discontinuation were similar in frequency between ciclesonide groups, but higher compared to the placebo group [74 mcg=2/8 (25%), 148 mcg 5/16 (31%), placebo 1/6 (17%)]. “Other” reasons leading to discontinuation were similar across groups and consisted primarily of pregnancy, non-compliance, or patient relocation. Physician decisions leading to discontinuation were primarily due to lack of compliance. Withdrawal by subjects was primarily related to inconvenience and patient relocation.

Reviewer Comment:

The percentage of patient drop out was greater compared to the SAR trials, however this is not surprising given the increased length of this study. Although higher, the overall rate of drop out was relatively low (13.1%) and evenly split between groups. When analyzing the specific reasons for discontinuation related to “other,” “physician decision,” and “withdrawal by subject,” the reasons were similar and evenly split

between groups. There did seem to be a dose effect related to AEs and nasal AEs leading to discontinuation. This was not seen in the previously reviewed trials. This finding is likely due to the increased drug exposure in this trial. Overall the pattern of discontinuation does not reveal any indication of systemic bias. The frequency of discontinuation is also similar to the Omnaris PAR study.

Patient Demographics:

Trial patients were primarily 19 to less than 65 years of age (90.2%), female (64.5%), and white (83.1%). Across the treatment groups, the demographic characteristics were relatively balanced. Demographic information is summarized on Table 36.

Table 36. Trial 060-633. Patient Demographics

Variable	Ciclesonide Dose			
	CIC-HFA 74 mcg N=298 (%)	CIC-HFA 148 mcg N=505 (%)	Placebo N=307 (%)	Total N=1110 (%)
Mean Age	37.5 (14.3)	36.5 (13.2)	38.0 (13.1)	37.2 (13.5)
Age category				
≥12 to ≤18 years	27 (9.1)	44 (8.7)	17 (5.5)	88 (7.9)
19 to <65 years	264 (88.6)	455 (90.1)	282 (91.9)	1001 (90.2)
≥65 years	7 (2.3)	6 (1.2)	8 (2.6)	21 (1.9)
Sex				
Male	102 (34.2)	195 (38.6)	97 (31.6)	394 (35.5)
Female	196 (65.8)	310 (61.4)	210 (68.4)	716 (64.5)
Race				
Caucasian	249 (83.6)	420 (83.2)	253 (82.4)	922 (83.1)
Black	40 (13.4)	65 (12.9)	41 (13.4)	146 (13.2)
Asian	3 (1.0)	5 (1.0)	10 (3.3)	18 (1.6)
American Indian, Alaska Native	2 (0.7)	0	0	2 (0.2)
Pacific Island	0	4 (0.8)	0	4 (0.4)
Other	3 (1.0)	6 (1.2)	3 (1.0)	12 (1.1)
Multiple	1 (0.3)	5 (1.0)	0	6 (0.5)
Ethnicity				
Hispanic	62 (20.8)	94 (18.6)	60 (19.5)	216 (19.5)
Non-Hispanic	236 (79.2)	411 (81.4)	247 (80.5)	894 (80.5)
Skin Prick Allergy Test				
Positive	298 (100.0)	505 (100.0)	307 (100.0)	1110 (100.0)
House dust mite	243 (81.5)	416 (82.4)	255 (83.1)	914 (82.3)
Animal dander	166 (55.7)	310 (61.4)	210 (68.4)	686 (61.8)
Cockroach	87 (29.2)	154 (30.5)	102 (33.2)	343 (30.9)
Mold	142 (47.7)	260 (51.5)	147 (47.9)	549 (49.5)

Source: Trial 060-633 CSR, Table 11, pp81

Overall, skin test positivity to perennial allergens was also similar between groups. The only notable difference between groups was for animal dander, which was highest in the

placebo group, followed by the 148 mcg group. The 74 mcg group was least frequently positive for animal dander.

Compliance:

Overall study compliance during the first 6 weeks of treatment (visits 3-6) was $\geq 80\%$ in 82.7 to 87.7% of patients across all groups. Compliance was lowest in the placebo group (82.7%) and highest in the CIC-HFA groups. For the whole 6 month treatment period (visit 3-11), compliance was lower. Compliance was $\geq 80\%$ in 70.4%-72.1% of patients across groups.

Efficacy:

Primary Endpoint:

The primary endpoint of this trial was change from baseline in AM and PM rTNSS averaged over the first 6 weeks of treatment in the ITT population. Both doses of CIC-HFA demonstrated significant improvement from baseline compared to placebo. The treatment difference compared to placebo for the 74 mcg group was 0.69 ($p=0.0001$); and for the 148 mcg groups was 0.54 ($p=0.001$). Due to irregularities at site 0037, the sponsor also performed analysis removing the data from this site. The results were similar (74 mcg= 0.63, 148 mcg=0.51, $p<0.0022$). These results are summarized in Table 37.

Table 37. Trial 060-633. Results for Primary and Key Secondary Efficacy Endpoints

	CIC-HFA 74 mcg	CIC-HFA 148mcg	Placebo
Avg AM/PM rTNSS over the first 6 weeks of treatment			
N	298	504	305
Change from baseline			
LS Mean (SE)	-1.98 (0.13)	-1.82 (0.10)	-1.28 (0.13)
Treatment difference vs. Pbo (95% CI)	0.69 (0.35, 1.04)	0.54 (0.24, .84)	
p-value vs. Pbo	0.0001	0.001	
Avg AM/PM iTNSS over the first 6 weeks of treatment			
N	298	504	305
Change from baseline			
LS Mean (SE)	-1.76 (0.12)	-1.60 (0.10)	-1.18 (0.12)
Treatment difference vs. Pbo (95% CI)	0.58 (0.25, 0.92)	0.42 (0.12, 0.72)	
p-value vs. Pbo	0.0014	0.0122	

Source: Trial 060-633 CSR, Tables 14 and 15, pp88 & 92

The sponsor also conducted sensitivity analysis to assess the impact of missing data. Three models were used: worst case imputation, mixed random effects model, and pattern mixture model. The worst case model assigns the best possible rTNSS score (0) on the day that the data is missing in the placebo groups and the worst value (12) for the CIC-HFA groups. The proportion of patients with missing rTNSS on at least one day

during the 6 week treatment period was 26%, 22% had intermittent missing data, and 4% were dropouts. The worst case scenario model demonstrated only a nominal improvement for the CIC-HFA groups compared to placebo; however, the other two models (mixed random effects and pattern mixture) had results similar to the primary analysis.

Key Secondary Endpoints

Change from baseline in AM and PM iTNSS averaged over the first 6 weeks of treatment was the key secondary endpoint. Both doses of CIC-HFA demonstrated a statistically significant improvement from baseline compared to placebo. The treatment difference compared to placebo for the 74 mcg group was 0.74 and for the 148 mcg groups was 0.42 ($p \leq 0.0122$). This analysis was repeated removing site 0037 and the results were similar. These results are summarized in Table 37 above.

Reviewer Comment:

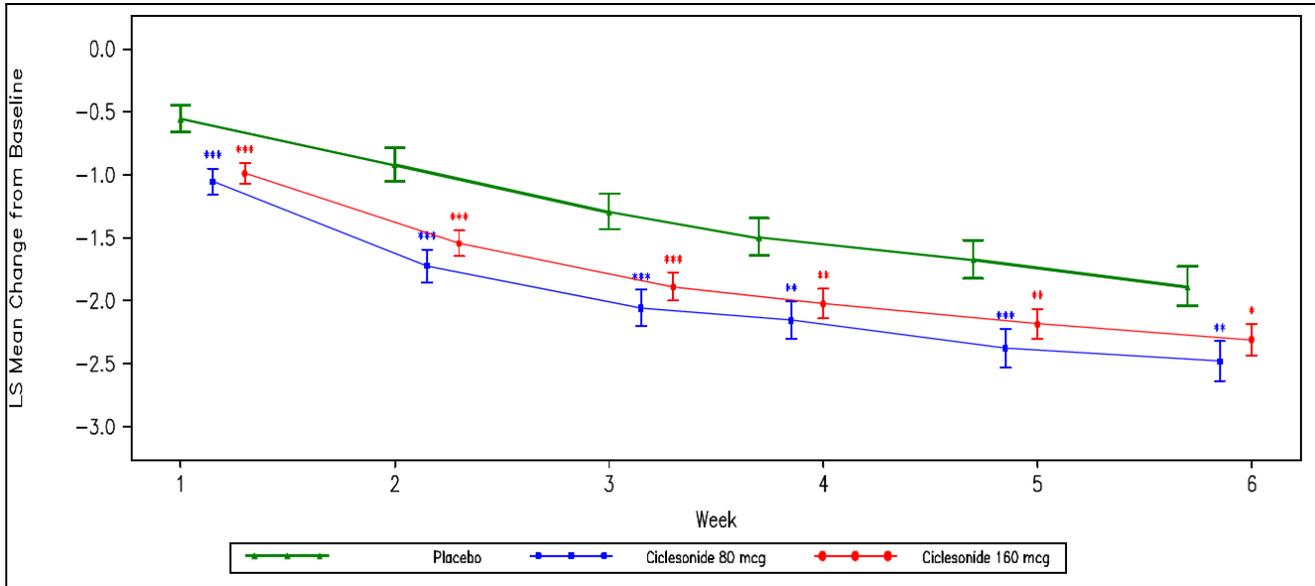
The results for the primary and key secondary endpoints are supportive for the proposed indication. The sensitivity testing used for the missing data analysis for the most part agreed with the primary analysis, except when using the worst case scenario model. The loss of significance using this model does not change my overall interpretation of efficacy, as the values used to fill the missing data likely do not realistically estimate what these values would have been. The treatment effect is modest, but similar to the Omnaris development program.

Other Secondary Endpoints

P-values reported for these endpoints did not adjust for multiplicity. Also note that for all secondary endpoints involving quality of life (RQLQ), the sponsor only analyzed data from a subset of the total population (baseline RQLQ ≥ 3.0). For the RQLQ related endpoints pertinent to label claims, the data was reanalyzed for the entire population by FDA biostatisticians.

Change from baseline in daily reflective and instantaneous AM TNSS, PM TNSS, AM and PM TNSS, averaged over each week (1-6) and averaged over the 1st 6 weeks of treatment was assessed (Figure 11). With regard to reflective TNSS, all parameters for both doses of CIC-HFA demonstrated statistically significant improvement compared to placebo.

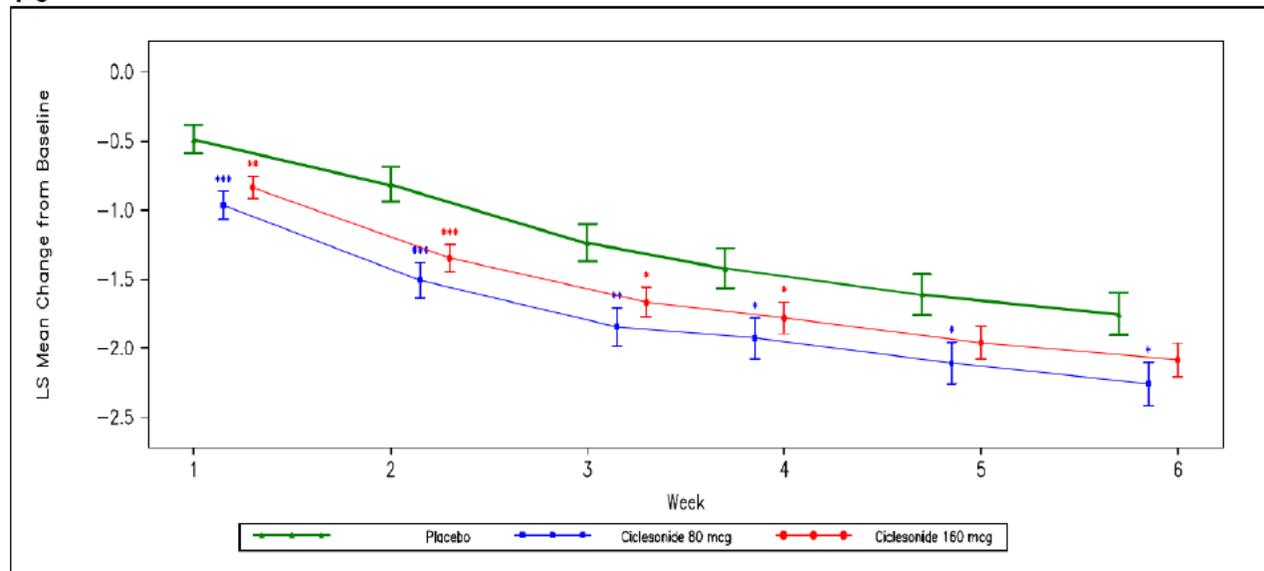
Figure 11. Trial 060-633. Change from Baseline for Weekly Average of AM and PM rTNSS for week 1-6



Ciclesonide 80 mcg= 74 mcg ex-actuator dose, Ciclesonide 160 mcg= 148 mcg ex-actuator dose
 *p<0.05, **p<0.01, ***p<0.001 vs placebo, p-values not adjusted for multiple comparisons
 Source: Trial 060-633 CSR, Figure 4, pp96

With regard to instantaneous scores, the results were not as consistent. When analyzing the change from baseline in AM and PM iTNSS averaged over each week of treatment, both doses demonstrated statistically significant improvement compared to placebo until week 5. At week 5, while the 74 mcg groups continued to have significant improvement, the 148 mcg group lost significance. These results are summarized graphically in Figure 12. Results when analyzing AM iTNSS and PM iTNSS over each week and for the 1st 6 weeks yielded similar results as the combined AM and PM iTNSS. The change from baseline in the average AM iTNSS over the 1st 6 weeks of treatment was significantly greater in the CIC-HFA groups versus placebo (Table 38).

Figure 12. Trial 060-633. Change from Baseline for Weekly Average of AM and PM iTNSS for week 1-6



Ciclesonide 80 mcg= 74 mcg ex-actuator dose, Ciclesonide 160 mcg= 148 mcg ex-actuator dose
 *p<0.05, **p<0.01, ***p<0.001 vs placebo, p-values not adjusted for multiple comparisons
 Source: Trial 060-633 CSR, Figure 5, pp99

Table 38. Trial 060-633. Change from Baseline for Average AM iTNSS over the First 6 Weeks of Treatment

	CIC-HFA 74 mcg	CIC-HFA 148mcg	Placebo
Avg AM iTNSS over the first 6 weeks of treatment			
N	297	503	304
Change from baseline			
LS Mean (SE)	-1.78 (0.12)	-1.67 (0.1)	-1.23 (0.12)
Treatment difference vs. Pbo (95% CI)	0.54 (0.21, 0.88)	0.44 (0.14, 0.74)	
p-value vs. Pbo	0.0016	0.004	

p-values unadjusted for multiple comparisons
 Source: Trial 060-633 CSR, Table 14.2.4.1.1

Change from baseline in the individual domains of the instantaneous and reflective TNSS was also analyzed in a manner similar to the total scores. In general, these results mirrored the total score results.

Change from baseline in RQLQ(S) for patients with a baseline score ≥ 3.0 at week 6 was also analyzed. For both CIC-HFA doses there was statistically significant improvement compared to placebo. However, for the 148 mcg dose, the difference from placebo was < 0.5 , the minimal clinically important difference (MCID). The difference compared to placebo for the 74 and 148 mcg groups were 0.55 and 0.37, respectively. This same endpoint was assessed at the 6 month time point. Again, both demonstrated statistically

significant improvement compared to baseline (p-values unadjusted for multiplicity). However, neither dose had improvement greater than the MCID. The difference compared to placebo for the 74 and 148 mcg groups were 0.40 and 0.37, respectively. The results are summarized in Table 39.

Table 39. Trial 060-633. Change from Baseline for RQLQ(S) after 6 weeks and 6 months of Treatment in Patients with Baseline RQLQ ≥ 3.0

	CIC-HFA 74 mcg	CIC-HFA 148mcg	Placebo
RQLQ(S) over the first 6 weeks of treatment			
N	152	252	160
Change from baseline			
LS Mean (SE)	-1.57 (0.11)	-1.39 (0.09)	-1.02 (0.11)
Treatment difference vs. Pbo (95% CI)	0.55 (0.26, 0.84)	0.37 (0.12, 0.63)	
p-value vs. Pbo	0.0002	0.0039	
RQLQ(S) over the first 6 months of treatment			
N	146	256	156
Change from baseline			
LS Mean (SE)	-1.67 (0.11)	-1.64 (0.09)	-1.27 (0.11)
Treatment difference vs. Pbo (95% CI)	0.4 (0.11, 0.69)	0.37 (0.11, 0.62)	
p-value vs. Pbo	0.0069	0.0052	

p-values unadjusted for multiplicity

Source: Trial 060-633 CSR, Table 19 and 20, pp107 &109

As with trial 060-622 and 060-634, this trial only analyzed RQLQ in impaired patients (RQLQ ≥ 3.0). This is problematic as it is not representative of the whole SAR population. Therefore, the 6 week data was reanalyzed for the whole patient population by FDA biostatisticians. These results demonstrate that at both doses CIC-HFA did not have a significant impact on RQLQ scores in the total patient population. These results are summarized in Table 40.

Table 40. Trial 060-633. FDA Analysis for RQLQ Related Secondary Endpoint in Total Population

	CIC-HFA 74 mcg	CIC-HFA 148 mcg	Placebo
Overall RQLQ at the end the 6 weeks of treatment (all patients)			
N	298	505	305
Treatment difference vs. Pbo (95% CI)	0.3 (0.1, 0.5)	0.3 (0.1, 0.4)	
p-value vs. Pbo	0.002	0.002	

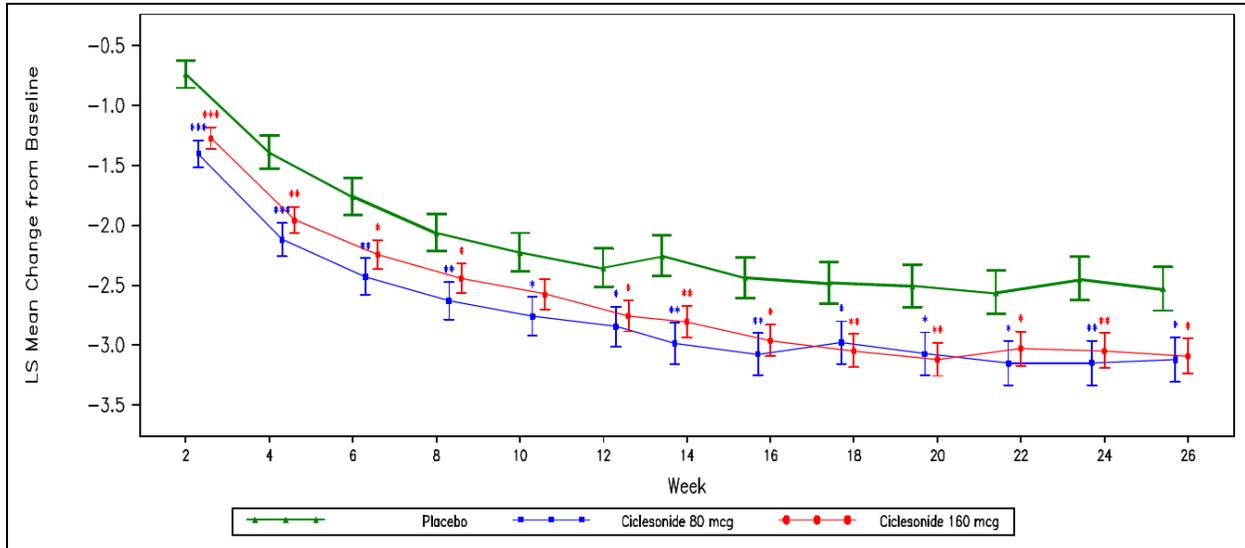
p-values are significant at the 0.025 level based on Bonferroni correction

Exploratory Endpoints

In addition to analyzing the TNSS data for the 1st six weeks of treatment, the sponsor also analyzed TNSS data for the entire 26 week study. The change from baseline in the AM and PM rTNSS at 26 week compared to placebo was 0.65 and 0.52 for the 74 and

148 mcg doses, respectively ($p \leq 0.0034$ unadjusted for multiplicity). The change from baseline in the AM and PM rTNSS averaged every 2 weeks over the 26 week period was also analyzed. The results demonstrated that either dose of ciclesonide generally had an improvement from baseline compared to placebo. This is summarized in Figure 13.

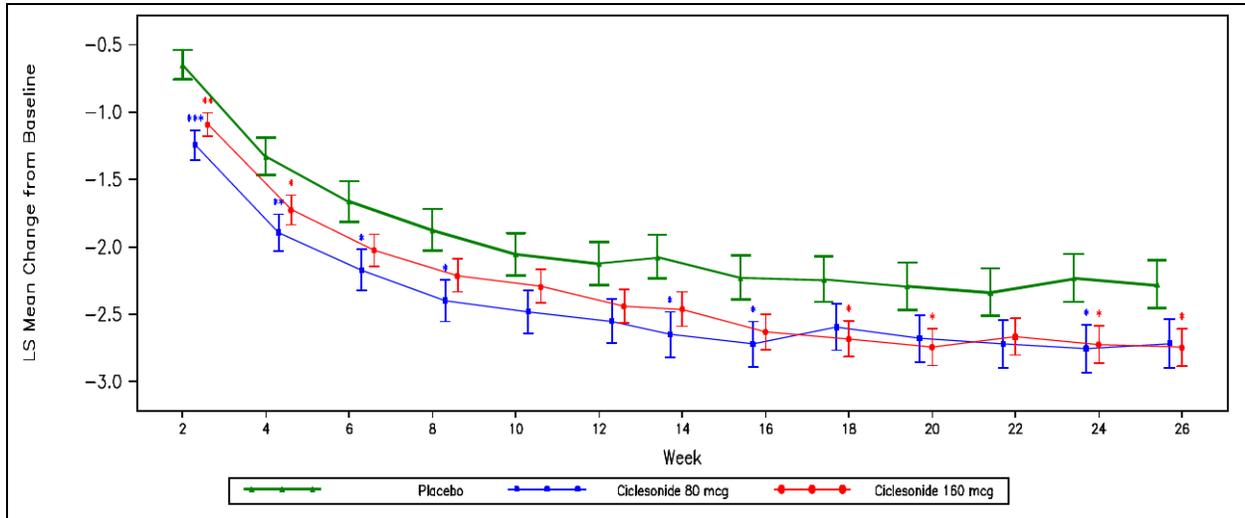
Figure 13. Trial 060-633. Change from Baseline for Biweekly Average of AM and PM rTNSS from weeks 1-26



Ciclesonide 80 mcg= 74 mcg ex-actuator dose, Ciclesonide 160 mcg= 148 mcg ex-actuator dose
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs placebo, p-values not adjusted for multiple comparisons
Source: Trial 060-633 CSR, Figure 8, pp111

A similar analysis was performed for iTNSS. Both the 74 and 148 mcg groups had a improvement in the AM and PM iTNSS averaged over the 6 month treatment period compared to placebo (74 mcg= 0.51 and 148 mcg= 0.42, $p \leq 0.0168$ unadjusted for multiple comparisons). The change from baseline in the AM and PM iTNSS averaged every 2 weeks over the 26 week period was also analyzed. The results demonstrated that either dose of CIC-HFA generally improved these scores from baseline compared to placebo. This is summarized in Figure 14.

Figure 14. Trial 060-633. Change from Baseline for Biweekly Average of AM and PM iTNSS from weeks 1-26



Ciclesonide 80 mcg= 74 mcg ex-actuator dose, Ciclesonide 160 mcg= 148 mcg ex-actuator dose
*p<0.05, **p<0.01, ***p<0.001 vs placebo, p-values not adjusted for multiple comparisons
Source: Trial 060-633 CSR, Figure 9, pp112

The treatment effect on the biweekly average of the AM and PM iTNSS was less consistent compared to the similar rTNSS results.

Change from baseline in the individual domains of the instantaneous and reflective TNSS was also analyzed in a manner similar to the total scores. In general, these results mirrored the total score results.

Similar to the SAR trials, the sponsor also determined time to maximal effect, defined as the time to reach 90% of the greatest effect. For the 74 mcg group, time to maximal effect was 11 days, and for the 148 mcg group, the time to maximal effect was 41 days. The reason for this large difference is unclear.

Device Use Survey

At visit 2 patients were asked “How did the spray feel?” and at visit 6 the question was repeated along with 7 additional questions relating to patient satisfaction. The questions and responses are summarized in Table 41.

Table 41. Trial 060-633. Device Survey

	CIC-HFA 74 mcg (N=298)	CIC-HFA 148 mcg (N=505)	Placebo (N=307)	Total (N=1110)
	N (%)	N (%)	N (%)	N (%)
Visit 2				
How did the spray feel?				
N	297	505	307	1109
Very comfortable	70 (23.6)	121 (24.0)	71 (23.1)	262 (23.6)
Somewhat comfortable	71 (23.9)	120 (23.8)	79 (25.7)	270 (24.3)
Neither comfortable or uncomfortable	77 (25.9)	120 (23.8)	72 (23.5)	269 (24.3)
Somewhat uncomfortable	68 (22.9)	125 (24.8)	73 (23.8)	266 (24.0)
Very uncomfortable	11 (3.7)	19 (3.8)	12 (3.9)	42 (3.8)
Visit 6				
How did the spray feel?				
N	282	485	292	1059
Very comfortable	38 (13.5)	70 (14.4)	40 (13.7)	148 (14.0)
Somewhat comfortable	61 (21.6)	89 (18.4)	52 (17.8)	201 (19.0)
Neither comfortable or uncomfortable	60 (21.3)	116 (23.9)	68 (23.3)	244 (23.0)
Somewhat uncomfortable	103 (36.5)	177 (36.5)	116 (39.7)	396 (37.4)
Very uncomfortable	20 (7.1)	34 (7.0)	16 (5.5)	70 (6.6)
Did spray run out of your nose?				
N	282	485	292	1059
Yes	20 (7.1)	26 (5.4)	17 (5.8)	63 (5.9)
No	262 (92.9)	459 (94.6)	275 (94.2)	996 (94.1)
Did spray run down your throat?				
N	282	485	292	1059
Yes	23 (8.2)	56 (11.5)	40 (13.7)	119 (11.2)
No	259 (91.8)	429 (88.5)	252 (86.3)	940 (88.8)
Did medication have an unpleasant taste?				
N	282	485	292	1059
Yes	37 (13.1)	81 (16.7)	53 (18.2)	171 (16.1)
No	245 (86.9)	404 (83.3)	239 (81.8)	888 (83.9)
Did medication have an unpleasant scent?				
N	282	485	292	1059
Yes	38 (13.5)	70 (14.4)	55 (18.8)	163 (15.4)
No	244 (86.5)	415 (85.6)	237 (81.2)	896 (84.6)
Was nasal spray device easy to use?				
N	282	485	292	1059
Yes	261 (92.6)	452 (93.2)	270 (92.5)	983 (92.8)
No	21 (7.4)	33 (6.8)	22 (7.5)	76 (7.2)
How satisfied were you with the device?				
N	282	485	292	1059
Very satisfied	126 (44.7)	221 (45.6)	122 (41.8)	469 (44.3)

Somewhat satisfied	90 (31.9)	144 (29.7)	100 (34.2)	334 (31.5)
Neither satisfied or dissatisfied	45 (16.0)	82 (16.9)	43 (14.7)	170 (16.1)
Somewhat dissatisfied	16 (5.7)	30 (6.2)	17 (5.8)	63 (5.9)
Very dissatisfied	5 (1.8)	8 (1.6)	10 (3.4)	23 (2.2)
How likely are you to continue to take this medication?				
N	282	485	292	1059
Very likely	147 (52.1)	241 (49.7)	137 (46.9)	525 (49.6)
Somewhat likely	82 (29.1)	174 (35.9)	103 (35.3)	359 (33.9)
Neither likely or unlikely	28 (9.9)	31 (6.4)	24 (8.2)	83 (7.8)
Somewhat unlikely	17 (6.0)	25 (5.2)	16 (5.5)	58 (5.5)
Very unlikely	8 (2.8)	14 (2.9)	12 (4.1)	34 (3.2)

Source: Trial 060-633 CSR, Table 23, pp121-122

Compared to baseline, after 6 weeks of treatment, an increased number of patients in all groups found the device uncomfortable. This is consistent with the device survey results in trial 060-634, though greater in magnitude in 060-633. This may be due to the additional 4 weeks of treatment in trial 060-633. Also, only approximately 55% of patients were satisfied with this device, and compared to ~80% in trial 060-634.

Reviewer Comment:

The results of the other secondary endpoints and exploratory endpoints are in general consistent with the primary and key secondary endpoints. Although the p-values reported were unadjusted for multiplicity, these results are supportive of a continued treatment effect at the 6 month time point, with regard to nasal symptoms. The results for the FDA analysis of the RQLQ(S) data demonstrated that there was no significant improvement at either dose after 6 weeks of treatment. The results for the time to maximal effect were inconsistent between doses. It is unclear why the lower dose had a shorter time to maximal effect compared to the higher dose. The results of the device survey are similar to trial 060-634, though overall satisfaction and comfort were scored lower. This may be due to the increased time on the device in trial 060-633.

Subgroup Analysis

For the primary and key secondary endpoints subgroup analysis was performed on the ITT population base on age, sex, and race. Gender had no effect, although the treatment effect was more pronounced in females compared to males. Both doses of CIC-HFA also improved TNSS in Black subjects. The effect of age was difficult to assess, as 90.2% of the ITT population was 19 to <65 years of age. For patients 19 to <65 years of age, the results were similar to the ITT analysis.

In addition to subgroup analysis by demographic characteristics, analysis of the primary and the key secondary endpoints was also performed based on baseline symptom severity. Symptom severity was defined as in trial 060-622. The analysis based on symptom severity mirrored the overall analysis of the primary and the key secondary

endpoint. Whether or not baseline symptom scores were mild/moderate or severe, both doses of CIC-HFA improved the average AM/PM rTNSS and AM/PM iTNSS over the 6 week double-blind treatment period.

Reviewer Comment

The subgroup analysis did not identify any differences in treatment effect base on race, gender, age, and symptom severity.

Safety:

Exposure

The ITT population was used for safety analysis. The mean duration of exposure was similar between all groups and ranged from 168.8-170.2 days. Approximately 50-56% of the ITT population received medication for the entire 6 month period.

Deaths/SAEs

There were no deaths during this trial. There were a total of 5 patients with 7 SAEs during the first 6 weeks of treatment. There were similar numbers of patients with SAEs in the placebo, 74 mcg and 148 mcg groups [1 (0.3%), 2 (0.7%), and 2 (0.4%), respectively]. In the 148 mcg group, one patient developed a breast cancer and one had a diverticular perforation. In the 74 mcg group, one patient had suicidal ideation and another an ovarian cyst. In the placebo group, one patient had hypertension and AV block.

Pregnancy-related

In this trial, there were a total of 14 pregnancies. Two (2) failed screening, four (4) were in the placebo group, four (4) were in the 74 mcg group, and four (4) were in the 148 mcg group. Of those in the 74 mcg group, one was lost to follow up, one resulted in spontaneous abortion, and two resulted in normal births. Of those in the 148 mcg group, one resulted in a preterm infant with congenital anomalies (VSD, PFO, PDA), two resulted in voluntary abortions, and one resulted in abortion where it was unknown if it was voluntary or spontaneous.

As expected there were more SAEs at the 6 month time point compared to the 6 week timepoint. There were a total of 20 patients with 28 SAEs. This included the SAEs reported at 6 weeks. The SAEs were relatively evenly spread between groups. The placebo, 74 and 148 mcg group had 6 (2%), 6 (2%), and 8 (1.6%) patients with SAEs, respectively. The SAEs for the 6 month period are summarized in Table 42.

Table 42. Trial 060-633. Serious Adverse Events During the 6 Month Double-Blind Treatment Period

System Organ Class/ Preferred Term	CIC-HFA 74 mcg (N=298)		CIC-HFA 148 mcg (N=505)		Placebo (N=307)		Overall (N=1110)	
	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N
Overall	6 (2.0)	7	8 (1.6)	13	6 (2.0)	8	20 (1.8)	28
Blood and Lymphatic System Disorders	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Thrombocytopenia	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Cardiac Disorders	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Atrioventricular block second degree	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Gastrointestinal Disorders	0	0	2 (0.4)	4	2 (0.7)	2	4 (0.4)	6
Colonic atony	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Diverticular perforation	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Megacolon	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Pancreatitis	0	0	0	0	2 (0.7)	2	2 (0.2)	2
Vomiting	0	0	1 (0.2)	1	0	0	1 (0.1)	1
General Disorders and Administration Site Conditions	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Hernia obstructive	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Infections and Infestations	2 (0.7)	2	0	0	0	0	2 (0.2)	2
Appendicitis	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Pneumonia	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Musculoskeletal and Connective Tissue Disorders	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Scleroderma	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Neoplasms Benign, Malignant and Unspecified	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Breast Cancer	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Nervous System Disorders	0	0	2 (0.4)	2	0	0	2 (0.2)	2
Embolic cerebral infarction	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Mononeuropathy multiplex	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Pregnancy, Puerperium and Perinatal Conditions	1 (0.3)	1	1 (0.2)	1	1 (0.3)	1	3 (0.3)	3
Abortion	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Abortion spontaneous	1 (0.3)	1	0	0	1 (0.3)	1	2 (0.2)	2
Psychiatric Disorders	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Suicidal ideation	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Reproductive System and Breast Disorders	2 (0.7)	3	1 (0.2)	2	1 (0.3)	1	4 (0.4)	6
Cystocele	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Menorrhagia	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Ovarian cyst	1 (0.3)	1	0	0	1 (0.3)	1	2 (0.2)	2
Pelvic adhesions	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Rectocele	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Respiratory, Thoracic, and Mediastinal Disorders	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Respiratory failure	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Social Circumstances	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Imprisonment	0	0	1 (0.2)	1	0	0	1 (0.1)	1

Vascular Disorders	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Hypertension	0	0	0	0	1 (0.3)	1	1 (0.1)	1

Source: Trial 060-633 CSR, Table 31, pp141-142

Reviewer Comment:

Overall, the SAEs at 6 weeks and 6 months were evenly split between groups. Only a small number of SAEs occurred only in the ciclesonide groups. Of those, it is unlikely that they were related to study drug.

TEAEs (6 Weeks)

After the 1st 6 weeks of double-blind treatment, 413 patients reported 711 TEAEs. The overall numbers were relatively evenly split between groups. The most commonly reported TEAE was epistaxis, which occurred more frequently in the CIC-HFA groups compared to placebo. Other TEAEs more frequent in the CIC-HFA groups included: upper respiratory tract infection, pyrexia, nausea, bronchitis, gastroenteritis, influenza, muscle strain, back pain, muscle spasm, headache, cough, nasal discomfort, and instillation site discomfort. The most common TEAEs at the 6 week time points are summarized in Table 43.

Table 43. Trial 060-633. Treatment Emergent Adverse Events Occurring in ≥1% of Patients During the First 6 weeks of Double-Blind Treatment

System Organ Class/ Preferred Term	CIC-HFA 74 mcg (N=298)		CIC-HFA 148 mcg (N=505)		Placebo (N=307)		Overall (N=1110)	
	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N
Overall	119 (39.9)	220	186 (36.8)	324	108 (35.2)	167	413 (37.2)	711
Gastrointestinal Disorders	12 (4.0)	17	21 (4.2)	25	10 (3.3)	10	43 (3.9)	52
Abdominal pain upper	2 (0.7)	2	5 (1.0)	6	3 (1.0)	3	10 (0.9)	11
Diarrhea	2 (0.7)	4	4 (0.8)	4	3 (1.0)	3	9 (0.8)	11
Nausea	6 (2.0)	6	3 (0.6)	3	0	0	9 (0.8)	9
General Disorders and Administration Site Conditions	15 (5.0)	16	22 (4.4)	25	6 (2.0)	6	43 (3.9)	47
Instillation site discomfort	8 (2.7)	9	8 (1.6)	10	0	0	16 (1.4)	19
Pyrexia	4 (1.3)	4	4 (0.8)	4	1 (0.3)	1	9 (0.8)	9
Infections and Infestations	51 (17.1)	57	78 (15.4)	86	50 (16.3)	58	179 (16.1)	201
Bronchitis	5 (1.7)	5	4 (0.8)	4	2 (0.7)	2	11 (1.0)	11
Gastroenteritis	3 (1.0)	3	1 (0.2)	1	0	0	4 (0.4)	4
Gastroenteritis viral	1 (0.3)	1	0	0	3 (1.0)	3	4 (0.4)	4
Influenza	5 (1.7)	5	7 (1.4)	8	1 (0.3)	1	13 (1.2)	14
Nasopharyngitis	3 (1.0)	3	10 (2.0)	10	10 (3.3)	11	23 (2.1)	24
Sinusitis	2 (0.7)	2	6 (1.2)	6	6 (2.0)	6	14 (1.3)	14
Upper respiratory tract infection	14 (4.7)	14	21 (4.2)	21	5 (1.6)	7	40 (3.6)	42
Urinary tract infection	9 (3.0)	9	9 (1.8)	9	7 (2.3)	7	25 (2.3)	25
Viral infection	0	0	5 (1.0)	5	2 (0.7)	2	7 (0.6)	7
Viral upper respiratory tract infection	5 (1.7)	6	3 (0.6)	3	3 (1.0)	4	11 (1.0)	13
Vulvovaginal mycotic	2 (1.0)	2	0	0	0	0	2 (0.3)	2

infection								
Injury, Poisoning and Procedural Complications	12 (4.0)	12	15 (3.0)	22	9 (2.9)	12	36 (3.2)	46
Muscle strain	3 (1.0)	3	3 (0.6)	4	0	0	6 (0.5)	7
Musculoskeletal and Connective Tissue Disorders	6 (2.0)	7	18 (3.6)	21	8 (2.6)	8	32 (2.9)	36
Back pain	3 (1.0)	3	5 (1.0)	5	1 (0.3)	1	9 (0.8)	9
Muscle spasms	3 (1.0)	3	2 (0.4)	2	0	0	5 (0.5)	5
Musculoskeletal pain	0	0	1 (0.2)	1	4 (1.3)	4	5 (0.5)	5
Nervous System Disorders	22 (7.4)	31	19 (3.8)	23	14 (4.6)	18	55 (5.0)	72
Headache	18 (6.0)	21	11 (2.2)	11	5 (1.6)	6	34 (3.1)	38
Sinus Headache	3 (1.0)	4	3 (0.6)	5	6 (2.0)	7	12 (1.1)	16
Reproductive System and Breast Disorders	3 (1.0)	4	3 (0.6)	3	2 (0.7)	2	8 (0.7)	9
Benign prostatic hyperplasia	1 (1.0)	1	0	0	0	0	1 (0.3)	1
Respiratory, Thoracic and Mediastinal Disorders	38 (12.8)	55	51 (10.1)	84	26 (8.5)	31	115 (10.4)	170
Cough	7 (2.3)	7	8 (1.6)	8	2 (0.7)	2	17 (1.5)	17
Epistaxis	14 (4.7)	18	23 (4.6)	33	10 (3.3)	12	47 (4.2)	63
Nasal discomfort	7 (2.3)	8	13 (2.6)	13	1 (0.3)	1	21 (1.9)	22
Nasal mucosal disorder	3 (1.0)	3	3 (0.6)	3	2 (0.7)	2	8 (0.7)	8
Nasal septum disorder	2 (0.7)	2	8 (1.6)	8	2 (0.7)	2	12 (1.1)	12
Oropharyngeal pain	6 (2.0)	8	8 (1.6)	8	5 (1.6)	5	19 (1.7)	21
Skin and Subcutaneous Tissue Disorders	4 (1.3)	4	5 (1.0)	5	2 (0.7)	2	11 (1.0)	11
Rash	3 (1.0)	3	0	0	0	0	3 (0.3)	3
Vascular Disorders	1 (0.3)	1	3 (0.6)	4	5 (1.6)	5	9 (0.8)	10
Hypertension	1 (0.3)	1	3 (0.6)	4	5 (1.6)	5	9 (0.8)	10

Source: Trial 060-633 CSR, Table 28, pp135-136

TEAEs (6 months)

After 6 months of double-blind treatment, 691 patients reported 1822 TEAEs. The overall numbers were relatively evenly split between groups. The most commonly reported TEAEs were epistaxis and URI, both of which occurred more frequently in the CIC-HFA groups compared to placebo. Nasal disorders were also more common in the CIC-HFA groups compared to placebo. These will be discussed in the “Nasal TEAEs” section. The most common TEAEs at the 6 month time points are summarized in Table 44.

Table 44. Trial 060-633. Treatment Emergent Adverse Events Occurring in ≥2% of Patients During the 6 Months of Double-Blind Treatment

Preferred Term	CIC-HFA 74 mcg (N=298)		CIC-HFA 148 mcg (N=505)		Placebo (N=307)		Overall (N=1110)	
	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N
Overall	180 (60.4)	505	316 (62.6)	820	195 (63.5)	497	691 (62.3)	1822
Gastrointestinal Disorders	22 (7.4)	33	45 (8.9)	63	30 (9.8)	41	97 (8.7)	137
Abdominal pain upper	4 (1.3)	4	7 (1.4)	8	7 (2.3)	7	18 (1.6)	19
Diarrhoea	3 (1.0)	5	9 (1.8)	11	6 (2.0)	6	18 (1.6)	22
Nausea	9 (3.0)	10	8 (1.6)	8	2 (0.7)	2	19 (1.7)	20
Vomiting	3 (1.0)	3	10 (2.0)	10	5 (1.6)	5	18 (1.6)	18
General Disorders and Administration Site Conditions	19 (6.4)	20	29 (5.7)	35	17 (5.5)	18	65 (5.9)	73
Instillation site discomfort	10 (3.4)	11	9 (1.8)	11	0	0	19 (1.7)	22
Infections and Infestations	115 (38.6)	170	181 (35.8)	257	113 (36.8)	164	409 (36.8)	591
Bronchitis	7 (2.3)	7	11 (2.2)	11	6 (2.0)	6	24 (2.2)	24
Influenza	6 (2.0)	6	9 (1.8)	11	3 (1.0)	4	18 (1.6)	21
Nasopharyngitis	14 (4.7)	17	30 (5.9)	35	19 (6.2)	26	63 (5.7)	78
Pharyngitis streptococcal	7 (2.3)	8	5 (1.0)	5	5 (1.6)	6	17 (1.5)	19
Sinusitis	14 (4.7)	16	27 (5.3)	30	17 (5.5)	18	58 (5.2)	64
Upper respiratory tract infection	43 (14.4)	54	66 (13.1)	74	29 (9.4)	37	138 (12.4)	165
Urinary tract infection	13 (4.4)	13	14 (2.8)	16	9 (2.9)	10	36 (3.2)	39
Viral upper respiratory tract infection	15 (5.0)	16	13 (2.6)	14	7 (2.3)	9	35 (3.2)	39
Injury, Poisoning and Procedural Complications	22 (7.4)	28	28 (5.5)	38	27 (8.8)	34	77 (6.9)	100
Muscle strain	6 (2.0)	7	7 (1.4)	9	2 (0.7)	2	15 (1.4)	18
Musculoskeletal and Connective Tissue Disorders	12 (4.0)	20	45 (8.9)	59	25 (8.1)	37	82 (7.4)	116
Arthralgia	0	0	10 (2.0)	10	4 (1.3)	4	14 (1.3)	14
Back pain	5 (1.7)	12	11 (2.2)	11	10 (3.3)	12	26 (2.3)	35
Musculoskeletal pain	0	0	2 (0.4)	2	6 (2.0)	8	8 (0.7)	10
Nervous System Disorders	30 (10.1)	55	35 (6.9)	52	25 (8.1)	35	90 (8.1)	142
Headache	21 (7.0)	36	17 (3.4)	27	14 (4.6)	18	52 (4.7)	81
Sinus headache	6 (2.0)	10	4 (0.8)	7	7 (2.3)	8	17 (1.5)	25
Respiratory, Thoracic and Mediastinal Disorders	59 (19.8)	119	113 (22.4)	214	52 (16.9)	95	224 (20.2)	428
Cough	9 (3.0)	9	19 (3.8)	19	8 (2.6)	9	36 (3.2)	37
Epistaxis	34 (11.4)	57	57 (11.3)	98	24 (7.8)	42	115 (10.4)	197
Nasal discomfort	8 (2.7)	9	16 (3.2)	16	2 (0.7)	2	26 (2.3)	27
Nasal mucosal disorder	7 (2.3)	7	12 (2.4)	14	2 (0.7)	2	21 (1.9)	23
Nasal septum disorder	5 (1.7)	6	16 (3.2)	21	3 (1.0)	4	24 (2.2)	31
Oropharyngeal pain	12 (4.0)	15	20 (4.0)	22	10 (3.3)	11	42 (3.8)	48
Vascular Disorders	4 (1.3)	4	8 (1.6)	9	9 (2.9)	9	21 (1.9)	22
Hypertension	4 (1.3)	4	7 (1.4)	8	9 (2.9)	9	20 (1.8)	21

Source: Trial 060-633 CSR, Table 29, pp137-138

Over the first 6 weeks of double-blind treatment, relatively few patients discontinued due to TEAEs. Overall, 13 patients withdrew due to TEAEs and these were evenly split between groups. The most common reasons leading to discontinuation fell under the Respiratory, Thoracic, and Mediastinal Disorders and Infections and Infestations SOC. There were no TEAEs leading to discontinuation that had an apparent dose effect, Several TEAEs that lead to discontinuation occurred only in the ciclesonide groups. These included nasal dryness (2 patients), nasal septum disorders (2 patients), increased ALT/AST (1), suicidal ideation (1), instillation site discomfort (1), diverticular perforation (1), and urticaria (1).

After 6 months of double-blind treatment, 30 patients withdrew due to TEAEs. As compared to the 6 week data, a lower percentage of placebo patients withdrew due to TEAEs versus CIC-HFA patients. From the placebo, 74 and 148 mcg groups, 6 (2%), 8 (2.7%), and 16 (3.2%) patients withdrew related to TEAEs. There is some suggestion of a dose response. The overall increase was primarily driven by events in the CIC-HFA groups. From 6 weeks to 6 months the number of patients with TEAEs leading to discontinuation increased by 2 (0.7%), 4 (1.4%), and 11 (2.2%) patients in the placebo, 74 and 148 mcg groups, respectively. The increase in the 74 mcg group was due primarily to events in the Infections and Infestation and Respiratory, Thoracic, and Mediastinal SOCs. For the 148 mcg group the increase was primarily due to Nervous System Disorders and Respiratory, Thoracic, Mediastinal SOC.

Nasal TEAEs:

After the 1st 6 weeks of treatment, 183 patients reported 257 TEAEs. Overall, these were evenly split between all groups. The most common TEAE was epistaxis, followed by URI. Both were more frequent in the CIC-HFA groups. Nasal septum ulcerations were noted, but only in the placebo group. There were also 2 reported nasal ulcers. One (1) in the placebo and 1 in the 148 mcg group.

Table 45. Trial 060-633. Nasal Treatment Emergent Adverse Events After 6 Weeks of Double-Blind Treatment

Preferred Term	CIC-HFA 74 mcg (N=298)		CIC-HFA 148 mcg (N=505)		Placebo (N=307)		Overall (N=1110)	
	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N
Overall	53 (17.8)	78	81 (16.0)	120	49 (16.0)	59	183 (16.5)	257
Acute sinusitis	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Application site erythema	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Application site odour	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Application site pustules	0	0	1 (0.2)	1	1 (0.3)	1	2 (0.2)	2
Epistaxis	14 (4.7)	18	23 (4.6)	33	10 (3.3)	12	47 (4.2)	63
Hyposmia	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Instillation site abnormal sensation	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Instillation site discomfort	8 (2.7)	9	8 (1.6)	10	0	0	16 (1.4)	19
Nasal congestion	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Nasal discomfort	7 (2.3)	8	13 (2.6)	13	1 (0.3)	1	21 (1.9)	22
Nasal disorder	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Nasal dryness	2 (0.7)	3	1 (0.2)	1	0	0	3 (0.3)	4
Nasal mucosal disorder	3 (1.0)	3	3 (0.6)	3	2 (0.7)	2	8 (0.7)	8
Nasal septum disorder	2 (0.7)	2	8 (1.6)	8	2 (0.7)	2	12 (1.1)	12
Nasal septum ulceration	0	0	0	0	2 (0.7)	2	2 (0.2)	2
Nasal ulcer	0	0	1 (0.2)	1	1 (0.3)	1	2 (0.2)	2
Nasopharyngitis	3 (1.0)	3	10 (2.0)	10	10 (3.3)	11	23 (2.1)	24
Postnasal drip	1 (0.3)	1	0	0	1 (0.3)	1	2 (0.2)	2
Respiratory tract infection viral	1 (0.3)	1	0	0	1 (0.3)	1	2 (0.2)	2
Rhinorrhoea	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Sinus headache	3 (1.0)	4	3 (0.6)	5	6 (2.0)	7	12 (1.1)	16
Sinusitis	2 (0.7)	2	6 (1.2)	6	6 (2.0)	6	14 (1.3)	14
Sneezing	2 (0.7)	2	0	0	0	0	2 (0.2)	2
Upper respiratory tract infection	14 (4.7)	14	21 (4.2)	21	5 (1.6)	7	40 (3.6)	42
Viral upper respiratory tract infection	5 (1.7)	6	3 (0.6)	3	3 (1.0)	4	11 (1.0)	13

Source: Trial 060-633 CSR, Table 34, pp148

Nasal TEAEs reported after 6 months of double-blind therapy were more frequent in the CIC-HFA groups compared to placebo. In the placebo, 74 mcg and 148 mcg groups, 102 (33.2%), 117 (39.3%), and 188 (37.2%) patients reported nasal TEAEs. Epistaxis, nasal discomfort, nasal mucosal disorder, and nasal septum disorder, and upper respiratory tract infection were reported more commonly in CIC-HFA groups versus placebo. Only nasal discomfort appeared to have a dose response. Between the 6 week and 6 month time point, the number of nasal septum disorders doubled in the CIC-HFA groups. The increase seen in the placebo group was not as dramatic. No nasal septum perforations were reported. These results are summarized in Table 46.

Table 46. Trial 060-633. Nasal Treatment Emergent Adverse Events After 6 Months of Double-Blind Treatment

Preferred Term	CIC-HFA 74 mcg (N=298)		CIC-HFA 148 mcg (N=505)		Placebo (N=307)		Overall (N=1110)	
	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N
Overall	117 (39.3)	219	188 (37.2)	340	102 (33.2)	171	407 (36.7)	730
Acute sinusitis	3 (1.0)	3	3 (0.6)	3	1 (0.3)	1	7 (0.6)	7
Application site erythema	1 (0.3)	1	1 (0.2)	1	1 (0.3)	1	3 (0.3)	3
Application site odour	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Application site pustules	0	0	1 (0.2)	1	1 (0.3)	1	2 (0.2)	2
Cellulitis	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Epistaxis	34 (11.4)	57	57 (11.3)	98	24 (7.8)	42	115 (10.4)	197
Hyposmia	0	0	1 (0.2)	1	2 (0.7)	2	3 (0.3)	3
Instillation site abnormal sensation	0	0	1 (0.2)	1	0	0	1 (0.1)	1
Instillation site discomfort	10 (3.4)	11	9 (1.8)	11	0	0	19 (1.7)	22
Nasal congestion	1 (0.3)	1	5 (1.0)	5	3 (1.0)	3	9 (0.8)	9
Nasal discomfort	8 (2.7)	9	16 (3.2)	16	2 (0.7)	2	26 (2.3)	27
Nasal disorder	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Nasal dryness	3 (1.0)	4	2 (0.4)	2	0	0	5 (0.5)	6
Nasal mucosal disorder	7 (2.3)	7	12 (2.4)	14	2 (0.7)	2	21 (1.9)	23
Nasal polyps	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Nasal septum disorder	5 (1.7)	6	16 (3.2)	21	3 (1.0)	4	24 (2.2)	31
Nasal septum ulceration	0	0	0	0	2 (0.7)	2	2 (0.2)	2
Nasal ulcer	0	0	1 (0.2)	1	1 (0.3)	1	2 (0.2)	2
Nasopharyngitis	14 (4.7)	17	30 (5.9)	35	19 (6.2)	26	63 (5.7)	78
Paranasal sinus hypersecretion	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Postnasal drip	1 (0.3)	1	0	0	1 (0.3)	1	2 (0.2)	2
Respiratory tract infection viral	1 (0.3)	1	0	0	1 (0.3)	1	2 (0.2)	2
Rhinitis allergic	1 (0.3)	1	2 (0.4)	2	2 (0.7)	2	5 (0.5)	5
Rhinitis seasonal	0	0	0	0	2 (0.7)	2	2 (0.2)	2
Rhinorrhoea	0	0	2 (0.4)	2	2 (0.7)	2	4 (0.4)	4
Seasonal allergy	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Sinus headache	6 (2.0)	10	4 (0.8)	7	7 (2.3)	8	17 (1.5)	25
Sinusitis	14 (4.7)	16	27 (5.3)	30	17 (5.5)	18	58 (5.2)	64
Sneezing	2 (0.7)	2	0	0	0	0	2 (0.2)	2
Swelling face	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Upper respiratory tract infection	43 (14.4)	54	66 (13.1)	74	29 (9.4)	37	138 (12.4)	165
Viral upper respiratory tract infection	15 (5.0)	16	13 (2.6)	14	7 (2.3)	9	35 (3.2)	39

Source: Trial 060-633 CSR, Table 35, pp149-150

Reviewer Comment:

Overall TEAEs at both the 6 week and 6 month time points were similar between groups. However, when examining nasal TEAEs, although similar in overall frequency at 6 weeks, by 6 months there were more in the CIC-HFA groups compared to placebo. This increase was most dramatic for nasal septum disorders. This may imply that as exposure increases, so does local toxicity. The increase in TEAEs leading to

discontinuation from the 6 week to 6 month time point is also supportive of cumulative toxicity. No nasal septum perforations were noted in the 6 week and 6 month data, and the only septum ulcerations were in the placebo group.

Clinical Labs

Laboratory data was collected at visit 1, 3, 6, and 11. Based on mean values, there were no significant differences between groups at any time point, nor was change from baseline significantly different between groups. Shift analysis was also performed and did not reveal any significant differences between CIC-HFA treated patients and placebo treated subjects. With regard to hematology shifts, the results were similar, though 2 patients (1 in the 74 mcg group and 1 in the 148 mcg group) had shifts from low leukocyte counts at baseline to high at a subsequent visit. The patient in the 74 mcg group was noted to have had streptococcal pharyngitis at the time of elevation. The patient in the 148 mcg group was diagnosed with breast cancer during the study, but completed the study. Her leukocyte count was low at baseline and was significantly elevated at visit 11 and an unscheduled visit one month after. Follow-up beyond the last unscheduled visit is unavailable. The elevation was deemed not clinically significant.

There were also patients in all groups with elevations in their liver enzymes between baseline and visit 6 or 11. There was one patient in the placebo group who's ALT and AST increased significantly between the baseline measure and visit 6. This patient completed the study and his liver enzyme returned to normal. There were 2 patients in the 74 mcg group whose ALT and AST became elevated during the double-blind treatment period, but in both cases returned to normal/near normal. One of the patients completed the study and one did not due to leaving the country. One patient in the 148 mcg group also had increases in ALT and AST, but as in the previous cases, they returned to normal. This patient completed the study. There were also 2 patients in the 148 mcg group with isolated increases in ALT. One of the patient's ALT returned to normal, the other was still elevated at the end of the study. Both patients completed the study.

Vital signs and Physical Exam

Overall there were no significant changes from baseline in vital signs between groups. ENT exams were also similar between groups. At baseline, almost all had normal nasal exams (96.7-98%), and few patients had clinically significant worsening. No perforations were seen.

Reviewer Comment:

Clinical laboratory and vital sign/physical exam did not reveal any safety signals. Although some individuals had elevations in liver enzymes, in almost all cases, they returned to normal, and the patient completed the study.

Overall Reviewer Comment Trial 060-633:

Based on the primary and key secondary endpoint, this trial is supportive of the proposed PAR indication. The treatment effect for nasal symptoms is similar to that seen in the Omnaris development program. The results of the other secondary endpoints and exploratory endpoints are in general consistent with the primary and key secondary endpoints. However, no effect at either dose was seen with respect to RQLQ related outcomes. These results are also supportive of a continued treatment effect at the 6 month time point, with regard to nasal symptoms. Not surprisingly, the number of AEs were greater in this trial than the SAR trials. However unlike the shorter SAR trials, there were no nasal septum ulcerations and no septum perforations in the CIC-HFA groups. This is reassuring as the exposure in this study was much longer, but surprising because one may expect that the longer study would be more likely to have such AEs. This may imply that septal ulcerations and perforations reported in the SAR studies were not solely related to CIC-HFA, or may have reflected chance occurrence of rare events.

5.3.5 Trial 060-635

Administrative Information

- **Study title:** A 6-Month Open-Label, Long-Term Safety Extension Study of Once Daily Ciclesonide HFA Nasal Aerosol (148 mcg) in the Treatment PAR in Subjects 12 Years and Older.
- **Study dates:** 3/1/2010-1/3/2011
- **Study sites:** 45 U.S. centers
- **Relevant Allergens:** Perennial Allergens (dust mite, cockroach, molds, animal dander)
- **Study report date:** 2/8/2011

Objectives/Rationale

- To evaluate the long-term safety and tolerability of 148 mcg ciclesonide HFA over 6 months (26 weeks), applied as a nasal aerosol once-daily, in subjects with Perennial Allergic Rhinitis (PAR) who have completed Study 060-633.
- To evaluate the long-term efficacy of ciclesonide 160 mcg applied as a nasal aerosol once-daily, in subjects with PAR who have completed Study 060-633.
- To evaluate the accuracy, functionality, and reliability of the dose indicator

Trial Design and Conduct

This was a 6 month multi-center, open-label, long-term, safety extension studying patients who completed 060-633. Patients in trial 060-633 were screened at that trial's end of study visit. Those that met eligibility criteria were allowed to participate in 060-635. All received ciclesonide 148 mcg daily. Following enrollment, patients returned for study visits at week 4, 6, 8, 12, 16, 20, 24, and 26. Patients were contacted by phone 1 week after the week 26 study visit for the final assessment of AEs. All patients in this

study received ciclesonide 148 mcg once a day (AM dosing). Once a day patients assessed their iTNSS and rTNSS. The iTNSS was indicative of symptoms in the past 10 minutes and the rTNSS was indicative of symptoms in the past 24 hours. The symptom domains and scoring were as in trials 060-622, 060-633, 060-634. The assessment schedule is summarized below in Table 47.

Table 47. Trial 060-635. Assessment Schedule

	Screen	6-month Open-Label Treatment Period								
Visit	1	2	3	4	5	6	7	8	9	FU
Week		4	6	8	12	16	20	24	26	27
Day		28 ±2	42 ±2	56 ±7	84 ±7	112 ±7	140 ±7	168 ±7	182 ±7	189 ±4
Informed consent	X									
Inclusion/Exclusion Review	X									
Physical exam (including ENT)	X								X	
Ear, nose and throat exam (ENT)		X	X	X	X	X	X	X		
Weight	X								X	
Vital Signs	X	X	X	X	X	X	X	X	X	
Serum pregnancy	X	X			X				X	
Clinical lab evaluation	X	X			X				X	
Collect unused study medication		X	X	X	X	X	X	X	X	
Dose indicator satisfaction survey			X		X					
Review ePRO symptom scores and study medication administration		X	X	X	X	X	X	X	X	
Concomitant medication history					X					
AE reporting	X	X	X	X	X	X	X	X	X	

Source: Trial 060-635 CSR, Table 2, pp24

Study Population

A total of 824 patients participated in this study. These patients were taken from the 965 that completed trial 060-633, and conformed to the inclusion and exclusion criteria.

Key Inclusion Criteria

1. Subject has successfully completed all visits of trial 060-633.
2. Subject has given written informed consent and assent, including privacy authorization as well as adherence to concomitant medication withholding periods, prior to participation.
3. Subject is male or female 12 years and older.
4. Subject must be in general good health (defined as the absence of any clinically relevant abnormalities as determined by the Investigator) based on screening physical examination and clinical laboratory tests.
5. Subject, if female 65 years of age or younger, must have a negative urine pregnancy test (performed at Visit 1). Females of childbearing potential must be instructed to and agree to avoid pregnancy during the study and must use an acceptable method of birth control:

- An oral contraceptive, an intrauterine device (IUD), implantable contraceptive, transdermal or injectable contraceptive for at least 1 month prior to entering the study with continued use throughout the study and for thirty days following study participation.
- Barrier method of contraception, eg, condom and/or diaphragm with spermicide while participating in the study.
- Abstinence

Key Exclusion Criteria

1. Female subject who is pregnant or lactating.
2. History of physical findings of nasal pathology, including nasal polyps.
3. Subject has any condition that, in the judgment of the investigator, would preclude the subject from completing the study.

Treatments:

Treatment Groups

All participants in this trial received ciclesonide 148 mcg (74 mcg each nostril) daily.

Concomitant/Restricted Medications

All concomitant medications were recorded in the CRF. No medications were disallowed, however the some medications had the following restrictions:

1. Pimecrolimus cream (1% or greater) and tacrolimus ointment (0.03% or greater) during the study period or planned dose escalation during the study period was not allowed.
2. Short courses (up to 14 days) of antibiotics for intercurrent bacterial infections were allowed.
3. One-time antibiotic and/or systemic steroids were allowed for up to 14 days during the open-label period.
4. Subjects were permitted to receive immunotherapy injections during the study if the therapy was initiated 90 days or more prior to the Screening Visit (Visit 1) and the subject had been on a stable maintenance regimen for at least 30 days prior to the Screening Visit (Visit 1).
5. Hydrocortisone less than or equal to 1% concentration, or equivalent, covering less than or equal to 20% of the total body surface without occlusion, was permitted.
6. Intermittent use (≤ 3 uses per week) of beta-agonists was acceptable for subjects with asthma; however, daily use of these agents was not permitted, except for exercise-induced bronchospasm.
7. Other drugs to treat concurrent diseases were allowed; however, their dosage and frequency were required to be kept as constant as possible throughout the study.

Efficacy Endpoints

The primary objective of this trial was safety; however,, efficacy endpoints were also assessed. The efficacy endpoints were as follows:

- Change from baseline in daily AM rTNSS averaged over the 6-month (Weeks 1-26) treatment period.
- Change from baseline in daily AM iTNSS averaged over the 6-month (Weeks 1-26) treatment period.
- Change from baseline in daily AM rTNSS at each month over the 6-month (Weeks 1-26) treatment period.
- Change from baseline in daily AM iTNSS at each month over the 6-month (Weeks 1-26) treatment period.

Dose Indicator Endpoints

- Ratio (percentage) of correct advances of the dose indicator out of expected advances
- Number/percentage of devices with actuation consistency at Visits 3 and 5, where actuation consistency is defined as a dose indicator count within $\pm 20\%$ of the subject self report of study medication administration
- Number/percentage of devices with major discrepancies, where major discrepancy is defined as a discrepancy of >20 actuations between the dose indicator and subject self report of study medication administration at Visits 3 and 5
- Number and percentage of subjects responding to each question in the subject satisfaction with the dose indicator survey

Safety Assessments

- Spontaneous and elicited adverse events (AEs), serious adverse events (SAEs).
- Nasal AEs, including epistaxis, nasal ulceration, and nasal perforation.
- Physical examinations, including ENT examinations;
- Clinical laboratory evaluations;
- Vital signs (blood pressure and pulse rate).

Compliance Assessments:

Treatment compliance was to be measured using subject report and TNSS scores.

Ethics:

This study was conducted according to Good Clinical Practice, FDA, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this study protocol. No changes were made without the IRB's approval.

Statistical Plan:

Population

No sample size calculations were made as the patients for this trial were recruited from those that completed 060-633. The analysis populations consisted of the enrolled

population, the ITT population, and the PP protocol. These were defined as in trial 060-633.

Patient Groups

Although all patients were to receive CIC-HFA 148 mcg daily (74 mcg each nostril), they were categorized into two groups based on their randomization in trial 060-633. One group consisted of patients who received placebo in trial 060-633, and the other groups consisted of patients who were on ciclesonide. The 3 groups were as follows:

1. PBO-CIC148: Received placebo in 060-633 and CIC-HFA 148 mcg daily in 060-635
2. CIC74-CIC148: Received CIC-HFA 74 mcg daily in 060-633 and CIC-HFA 148 mcg daily in 060-635
3. CIC148-CIC148: Received CIC-HFA 148 mcg daily in 060-633 and CIC-HFA 148 mcg daily in 060-635

Efficacy Analysis

The efficacy endpoints were analyzed in the ITT population. Paired t-tests were used for to assess change from baseline in AM rTNSS averaged over the 6 month period within treatment groups. Between treatment groups, ANCOVA was used. Baseline was defined at average TNSS values for the 4 last 3 weeks of double-blind treatment in trial 060-633.

Reviewer Comment

The trial design, included populations, and restricted medications were reasonable. The efficacy and safety assessment were also typical and appropriate for a long term safety study in PAR. The statistical plan also was reasonable. It should be noted that, the safety and efficacy data are difficult to interpret as there was no placebo group for comparison.

Results

Protocol Amendments

The original protocol was submitted on 8/3/2009 and amended once on 2/8/2010. The amendments included a change in the responsible physician, inclusion of instructions for cleaning the nasal actuator, and cleaning of the nasal actuator by the investigator during study visits. The protocol was also amended such that the medical history was taken from study 060-633.

Protocol Deviations

Of the 824 patients enrolled in this study, there were 156 important protocol deviations (IPDs). Almost all IPDs (153) were related to poor compliance (<80%).

Patient Disposition

A total of 965 patients completed trial 060-633. Patients from site 0029 (22 total) did not participate, as that site did not participate in the extension. Site 0037 was not allowed to

participate in the extension due to site irregularities discussed in section 5.3.4. This site included 20 patients. Of the remaining 923 patients, 825 chose to participate in the extension. One (1) patient was excluded for a positive pregnancy test. No further follow-up was provided on this patient. A total of 824 patients enrolled in trial 060-635. Of the enrolled patients, 683 (82.9%) completed the trial. The reasons for discontinuation included AEs in 14 patients (1.7%), protocol violations in 48 (5.8%), withdrawal by subject in 36 (4.4%), lost to follow-up in 6 (0.7%), physician decision in 6 (0.7%), and other in 31 (3.8%). These results are summarized in Table 48.

Table 48. Trial 060-635. Patient Disposition

Category	Group			Total N(%)
	PBO-CIC148 N(%)	CIC74-CIC148 N(%)	CIC148-CIC148 N(%)	
Screened				825
Enrolled				824
ITT Population	226	216	382	824
PP Population	182 (80.5)	176 (81.5)	310 (81.2)	668 (81.1)
Completed Study	193 (85.4)	179 (82.9)	311 (81.4)	683 (82.9)
Prematurely Discontinued	33 (14.6)	37 (17.1)	71 (18.6)	141 (17.1)
Reason for Discontinuation				
Adverse Event	3 (1.3)	2 (0.9)	9 (2.4)	14 (1.7)
Protocol Violation	18 (8.0)	11 (5.1)	19 (5.0)	48 (5.8)
Withdrawal by Subject	8 (3.5)	7 (3.2)	21 (5.5)	36 (4.4)
Lost to follow-up	0	4 (1.9)	2 (0.5)	6 (0.7)
Physician Decision	1 (0.4)	1 (0.5)	4 (1.0)	6 (0.7)
Other	3 (1.3)	12 (5.6)	16 (4.2)	31 (3.8)

Source: Trial 060-635 CSR, Table 4, pp57

Overall, the reasons for discontinuation were fairly evenly split between groups. No reasons for discontinuation followed a dose response. The most frequent reasons for discontinuation were protocol violations and withdrawal by subject. The most common protocol violations leading to discontinuation were non-compliance and out of window visits. The specific reasons for withdrawal by subject were primarily conflicts due to work/school/travel, relocation, or no longer wanting to participate. Withdrawals due to AEs will be discussed in the safety results.

Patient Demographics

The demographics of this trial were almost identical to trial 060-633. Trial patients were primarily 19 to less than 65 years of age (90.2%), female (64.2%), and white (83.7%). Across the treatment groups, the demographic characteristics were relatively balanced. Demographic information is summarized on Table 49.

Table 49. Trial 060-635. Patient Demographics

Variable	Group			Total N=824(%)
	PBO-CIC148 N=226(%)	CIC74-CIC148 N=216(%)	CIC148-CIC148 N=382(%)	

Mean Age	39.4 (13.1)	38.8 (14.2)	37.9 (12.7)	38.5 (13.2)
Age category				
≥12 to ≤18 years	13 (5.8)	24 (11.1)	27 (7.1)	64 (7.8)
19 to <65 years	205 (90.7)	187 (86.6)	351 (91.9)	743 (90.2)
≥65 years	8 (3.5)	5 (2.3)	4 (1.0)	17 (2.1)
Sex				
Male	74 (32.7)	78 (36.1)	143 (37.4)	295 (35.8)
Female	152 (67.3)	138 (63.9)	239 (62.6)	529 (64.2)
Race				
Caucasian	186 (82.3)	180 (83.3)	324 (84.8)	690 (83.7)
Black	30 (13.3)	30 (13.9)	44 (11.5)	104 (12.6)
Asian	8 (3.5)	3 (1.4)	4 (1.0)	15 (1.8)
American Indian, Alaska Native	0	1 (0.5)	0	1 (0.1)
Pacific Island	0	0	3 (0.8)	3 (0.4)
Other	2 (0.9)	1 (0.5)	4 (1.0)	7 (0.8)
Multiple	0	1 (0.5)	3 (0.8)	4 (0.5)
Ethnicity				
Hispanic	43 (19.0)	42 (19.4)	75 (19.6)	160 (19.4)
Non-Hispanic	183 (81.0)	174 (80.6)	307 (80.4)	664 (80.6)

Source: Trial 060-635 CSR, Table 7, pp65-66

Overall, the demographics information was similar between groups. The baseline AM rTNSS and AM iTNSS were numerically higher in the PBO-CIC148 group compared to the other 2 groups. This is not surprising as that group had been receiving placebo when baseline data was collected.

Compliance

For this 6 month extension trial, compliance was similar between groups. Across groups 81.4% of patients were ≥80% compliant. The compliance in this trial was actually higher than in 060-633.

Reviewer Comment:

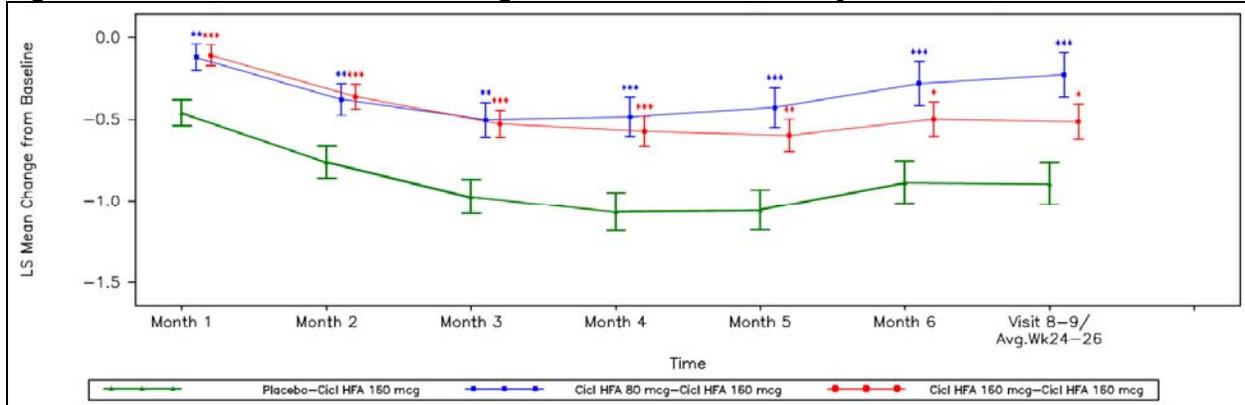
The protocol amendment will not affect interpretation of results. The IPDs, patient discontinuations, and demographics were also well balanced between groups and did not indicate any systemic bias.

Efficacy

In this trial, efficacy was not the primary objective and was used as an assessment of compliance. Change from baseline in the AM rTNSS averaged over each month in the 6 month trial and averaged over the entire 6 month were 2 of the efficacy endpoints. The monthly averages demonstrate that for the PBO-CIC148 group, change from baseline was greater as compared to the other 2 groups. These results are summarized in Figure 15. Baseline values for the PBO-CIC148 group was higher compare to the other 2 groups. Averaged over the entire 6 months, the PBO-CIC148 had greater improvement from baseline as compared to the other 2 treatment groups. The least square mean

change from baseline for PBO-CIC148 was -0.82 with a SE of 0.09. The least square mean change from baseline in the other 2 groups was smaller [CIC74-CIC148= -0.38 (0.09) and CIC148-CIC148= -0.42 (0.07)]. The change from baseline for PBO-CIC148 was statistically greater than the other 2 groups. However, for all groups the change from baseline was statistically significant.

Figure 15. Trial 060-635. LS Mean Change from Baseline in Monthly AM rTNSS



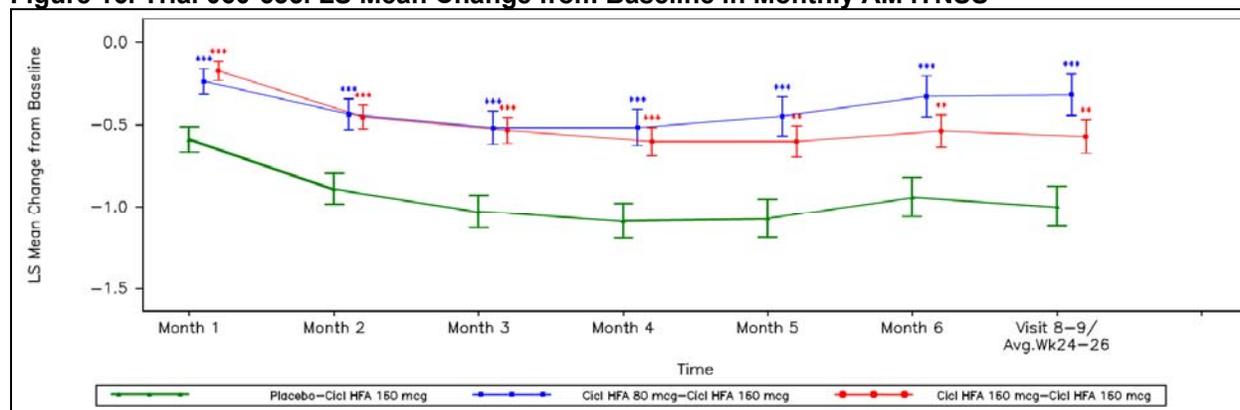
Placebo-Cic HFA 160=PBO-CIC148, Cic HFA 80-Cic HFA 160=CIC74-CIC148, Cic HFA 160-Cic HFA 160=CIC148-CIC148

*p<0.05, **p<0.01, ***p<0.001 compared to PBO-CIC148

Source: Trial 060-635 CSR, Figure 5, pp76

The two other efficacy endpoints were change from baseline in the AM iTNSS averaged over each month in the 6 month trial and averaged over the entire 6 month period. The AM iTNSS data were similar to the rTNSS data. The monthly averages demonstrate that for the PBO-CIC148 group, change from baseline was greater as compared to the other 2 groups (Figure 16). The least square mean change from baseline for PBO-CIC148 was -0.90 with a SE of 0.09. The least square mean change from baseline in the other 2 groups was smaller [CIC74-CIC148= -0.42 (0.09) and CIC148-CIC148= -0.46 (0.07)]. However, as with the rTNSS data, all groups had statistically significant improvement from their own baselines.

Figure 16. Trial 060-635. LS Mean Change from Baseline in Monthly AM iTNSS



Placebo-Cic HFA 160=PBO-CIC148, Cic HFA 80-Cic HFA 160=CIC74-CIC148, Cic HFA 160-Cic HFA 160=CIC148-CIC148

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared to PBO-CIC148

Source: Trial 060-635 CSR, Figure 8, pp85

Dose Indicator Accuracy

For study visits 1-3 and 3-5, 71.5% and 72.5% of the dose indicators were within 20% of patient reported usages. Those that were outside the 20% range were mostly due to overcounting errors (371/423). The sponsor notes that patients were only told to report an actuation when administering the medication, not if they were simply priming the actuator. A subset of the actuators was available for further testing. When using a weight based method to determine accuracy of the counter, the number of over and undercounts decreased.

Reviewer Comment

The efficacy results are suggestive of good compliance in the patient population. The CIC74-CIC148 and CIC148-CIC148 groups did not have worsening of iTNSS/rTNSS, as one may expect if patients stopped taking study medication. It should be noted that both the CIC74-CIC148 and CIC148-CIC148 groups had a statistically significant, though very modest, improvements from baseline. It is unclear why the CIC148-CIC148 group would have seen any change in TNSS, as there was no change in medication. Improvement in the CIC74-CIC148 group makes more sense assuming that there is a dose effect. However, based on previous studies, there is no dose effect. Compliance in the PBO-CIC148 group was also likely good based on the iTNSS/rTNSS data. The PBO-CIC148 group had significant improvement from its baseline, which was nominally greater compared to the other 2 groups. This is not surprising as this patient group had not been exposed to ciclesonide previously. However, it is unclear why the PBO-CIC148 group did not reach the same level of efficacy as the other groups. The higher number of overcounting compared to undercounting errors seen in this study is likely related to underreporting of actuations by patients, as they were not instructed to record test/priming actuation. The weight based method used to estimate dose accuracy is likely more indicative of accuracy.

Safety

Exposure

Of the 824 patients enrolled in this study, 683 completed the entire 6 months of treatment. The mean exposure was 165.9 days. When combining exposure with trial 060-633, a total of 490 patients were exposed to ciclesonide at a dose of at least 74 mcg daily for 12 months (311 patients in the CIC148-CIC148 and 179 patients in CIC74-CIC148).

AEs reported in this trial were unique to this 6 month period. AEs from 060-633 were not carried over.

Deaths/SAEs

There were no deaths in this study, and 15 patients (1.8%) reported SAEs. Rates were similar across groups. One patient did develop immune mediated thrombocytopenia (0009/S016, CIC148-CIC148) on the final visit for trial 060-633. This subject was briefing enrolled, but was withdrawn on day 3. Aside from imprisonment, all SAEs were experienced by one patient only. Overall the total numbers and types of SAEs were similar compared to trial 060-633. The SAEs are summarized in Table 50.

Pregnancy Related

Five (5) pregnancies were reported in this trial. There were two in the CIC148-CIC148 groups and three in the CIC-74-CIC148 group. For the two in the CIC148-CIC148 group, one pregnancy ended with voluntary termination and other ended in an ectopic pregnancy. For the CIC148-CIC148 group, two pregnancies resulted in healthy infants and one resulted in a voluntary termination.

Table 50. Trial 060-635. Serious Adverse Events

System Organ Class/ Preferred Term	PBO-CIC148 (N = 226)		CIC74-CIC148 (N = 216)		CIC148-CIC148 (N = 382)		Total (N = 824)	
	N (%)	Events	N (%)	Events	N(%)	Events	N(%)	Events
Overall	5 (2.2)	13	2 (0.9)	2	8 (2.1)	9	15 (1.8)	24
Cardiac Disorders	1 (0.4)	1	0	0	1 (0.3)	1	2 (0.2)	2
Atrial flutter	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Cardiac failure congestive	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Gastrointestinal Disorders	1 (0.4)	1	0	0	1 (0.3)	1	2 (0.2)	2
Gastroesophageal reflux	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Peritonitis	0	0	0	0	1 (0.3)	1	1 (0.1)	1
General Disorders and Administration Site Conditions	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Chest pain	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Infections and Infestations	1 (0.4)	1	1 (0.5)	1	1 (0.3)	1	3 (0.4)	3
Appendicitis	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Pneumonia	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Pyelonephritis acute	0	0	1 (0.5)	1	0	0	1 (0.1)	1
Injury, Poisoning and Procedural Complications	1 (0.4)	4	0	0	1 (0.3)	1	2 (0.2)	5
Overdose	0	0	0	0	1 (0.3)	1	1 (0.1)	1

Clinical Review
 Robert Lim
 NDA 202129
 Ciclesonide Nasal HFA (CIC-HFA)

Renal injury	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Rib fracture	1 (0.4)	2	0	0	0	0	1 (0.1)	2
Road traffic accident	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Investigations	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Troponin increased	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Neoplasms Benign, malignant and Unspecified	2 (0.9)	2	0	0	0	0	2 (0.2)	2
Breast cancer stage II	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Uterine leiomyoma	1 (0.7)	1	0	0	0	0	1 (0.2)	1
Pregnancy, Puerperium and Perinatal Conditions	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Ectopic pregnancy*	0	0	0	0	1 (0.4)	1	1 (0.2)	1
Psychiatric Disorders	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Mental status changes	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Reproductive System and Breast Disorders	1 (0.4)	1	0	0	1 (0.3)	1	2 (0.2)	2
Endometrial hypertrophy	1 (0.7)	1	0	0	0	0	1 (0.2)	1
Menorrhagia	0	0	0	0	1 (0.4)	1	1 (0.2)	1
Respiratory, Thoracic and Mediastinal Disorders	1 (0.4)	2	0	0	0	0	1 (0.1)	2
Pulmonary edema	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Respiratory failure	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Social Circumstances	0	0	1 (0.5)	1	1 (0.5)	1	2 (0.2)	2
Imprisonment	0	0	1 (0.5)	1	1 (0.5)	1	2 (0.2)	2

Source: Trial 060-635 CSR, Table 21, pp108-109

Adverse Events

A total of 431 patients (52.3%) reported 997 AEs during the 6 month treatment period. The most common AEs were URI, epistaxis, and headache. No AEs demonstrated a dose response with respect to total ciclesonide exposure. The most frequent AE was URI, followed by epistaxis, headache and sinusitis. These results are summarized in Table 51.

Table 51. Trial 060-635. Treatment Emergent Adverse Events Reported by ≥2% of the ITT Population

System Organ Class/ Preferred Term	PBO-CIC148 (N = 226)		CIC74-CIC148 (N = 216)		CIC148-CIC148 (N = 382)		Total (N = 824)	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Overall	119 (52.7)	285	114 (52.8)	251	198(51.8)	461	431(52.3)	997
Infections and Infestations	65 (28.8)	90	63 (29.2)	90	111(29.1)	155	239(29.0)	335
Bronchitis	6 (2.7)	7	5 (2.3)	7	10 (2.6)	10	21 (2.5)	24
Nasopharyngitis	7 (3.1)	7	9 (4.2)	10	15 (3.9)	18	31 (3.8)	35
Sinusitis	8 (3.5)	9	9 (4.2)	10	22 (5.8)	23	38 (4.7)	42
URI	15 (6.6)	17	14 (6.5)	17	32 (8.4)	38	61 (7.4)	72
Viral URI	2 (0.9)	2	10 (4.6)	11	5 (1.3)	7	17 (2.1)	20
UTI	7 (3.1)	8	4 (1.9)	4	11 (2.9)	11	22 (2.7)	23
Musculoskeletal and Connective Tissue Disorders	17 (7.5)	19	14 (6.5)	16	29 (7.6)	33	60 (7.3)	68
Back pain	7 (3.1)	7	4 (1.9)	4	10 (2.6)	12	21 (2.5)	23
Nervous System Disorders	16 (7.1)	18	14 (6.5)	26	32 (8.4)	46	62 (7.5)	90
Headache	10 (4.4)	12	11 (5.1)	21	18 (4.7)	23	39 (4.7)	56
Respiratory, Thoracic and Mediastinal Disorders	32 (14.2)	51	29 (13.4)	40	39 (10.2)	61	100 (12.1)	152
Cough	2 (0.9)	3	5 (2.3)	5	4 (1.0)	4	11 (1.3)	12
Epistaxis	16 (7.1)	23	11 (5.1)	15	19 (5.0)	26	46 (5.6)	64
Nasal septum disorder	5 (2.2)	5	5 (2.3)	5	3 (0.8)	4	13 (1.6)	14
Oropharyngeal pain	4 (1.8)	5	4 (1.9)	4	12 (3.1)	12	20 (2.4)	21

URI= Upper Respiratory Tract Infection, UTI=Urinary Tract Infection

Source: Trial 060-635 CSR, Table 19, pp103

The most frequent AE was URI (viral or otherwise). Compared to 060-633 (6 month data), the frequency of AEs were lower and the AEs were less diverse. This is somewhat surprising as one would may expect that the AEs would increase with increased exposure.

Of the 824 patients enrolled in this trial, 14 patients discontinued due to AEs. Adverse events leading to discontinuation were unique to each patient base on preferred term. The CIC148-CIC148 group had the most patients with adverse events leading to discontinuation (6 patients (1.6%), compared to 2 patients (0.9%) in both the PBO-CIC148 and CIC74-CIC148 groups). Only 3 patients discontinued due to local TEAEs. Patient 0050/S011 (PBO-CIC148) withdrew on open-label treatment day 8 due to an upper respiratory tract infection. Patient 0044/S030 from the CIC74-CIC148 group withdrew after 84 days of open-label treatment due to intermittent epistaxis. Patient 0010/S027 (CIC148-CIC148) withdrew on open-label treatment day 127 due to application site pustules. Only the local TEAE was deemed as having a relationship to study medication.

One cataract was also reported in this trial. It occurred in 71 year old male patient (0048/S031, PBO-CIC148) on open-label treatment day 14. The investigator felt that an relationship to study drug was unlikely.

Local TEAEs

As local toxicity was a concern, the sponsor specifically reported local AEs, defined as those occurring in the middle ear, nose, throat, and upper respiratory tract down to the larynx. Over all, there was no apparent relationship between total ciclesonide exposure and local AEs. However for sinusitis, there did seem to be a dose relationship. There were no nasal septum perforations, but there were septum ulcerations. These results are summarized in Table 52.

Table 52. Trial 060-635. Local Treatment Emergent Adverse Events

System Organ Class/ Preferred Term	PBO-CIC148 (N = 226)		CIC74-CIC148 (N = 216)		CIC148-CIC148 (N = 382)		Total (N = 824)	
	N (%)	Events	N (%)	Events	N(%)	Events	N(%)	Events
Overall	64 (28.3)	109	67 (31)	102	111 (29.1)	170	242 (29.4)	381
Acute Sinusitis	3 (1.3)	4	2 (0.9)	2	4 (1)	4	9 (1.1)	10
Application Site Pustules	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Cough	2 (0.9)	3	5 (2.3)	5	4 (1)	4	11(1.3)	12
Dysphonia	1 (0.4)	1	1 (0.5)	1	0	0	2 (0.2)	2
Ear Congestion	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Ear Discomfort	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Ear Infection	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Ear Pain	2 (0.9)	2	1 (0.5)	1	2 (0.5)	2	5 (0.6)	5
Epistaxis	16 (7.1)	23	11 (5.1)	15	19 (5.0)	26	46 (5.6)	64
Eustachian Tube Dysfunction	0	0	1 (0.5)	1	1 (0.3)	1	2 (0.2)	2
Instillation Site Discomfort	4 (1.8)	4	1 (0.5)	1	2 (0.5)	2	7 (0.8)	7
Instillation Site Dryness	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Nasal Congestion	1 (0.4)	1	1 (0.5)	1	3 (0.8)	3	5 (0.6)	5
Nasal Discomfort	1 (0.4)	1	1 (0.5)	2	0	0	2 (0.2)	3
Nasal Dryness	2 (0.9)	2	0	0	0	0	2 (0.2)	2
Nasal Mucosal Disorder	1 (0.4)	1	2 (0.9)	2	0	0	3 (0.4)	4
Nasal Edema	0	0	0	0	2 (0.5)	2	2 (0.2)	2
Nasal Polyps	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Nasal Septum Disorder	5 (2.2)	5	5 (2.3)	5	3 (0.8)	4	13 (1.6)	14
Nasal Septum Ulceration	1 (0.4)	1	1 (0.5)	1	2 (0.5)	2	4 (0.5)	4
Nasopharyngitis	7 (3.1)	7	9 (4.2)	10	15 (3.9)	18	31 (3.8)	35
Oropharyngeal Pain	4 (1.8)	5	4 (1.9)	4	12 (3.1)	12	20 (2.4)	21
Otitis Media	3 (1.3)	4	2 (0.9)	2	2 (0.5)	2	7 (0.8)	8
Otitis Media Acute	0	0	1 (0.5)	1	0	0	1 (0.1)	1
Parasthesia Mucosal	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Pharyngitis	1 (0.4)	1	3 (1.4)	3	1 (0.3)	1	5 (0.6)	5
Pharyngitis Strept	2 (0.9)	2	3 (1.4)	3	6 (0.6)	6	11 (1.3)	11
Rhinitis Allergic	1 (0.4)	1	0	0	0	0	1 (0.1)	1
Rhinitis Seasonal	0	0	0	0	2 (0.5)	2	2 (0.2)	2
Rhinorrhea	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Sinus Congestion	0	0	0	0	1 (0.3)	1	1 (0.1)	1
Sinus Headache	1 (0.4)	1	2 (0.9)	3	7 (1.8)	7	10 (1.2)	11
Sinusitis	8 (3.5)	9	9 (4.2)	10	22 (5.8)	23	39 (4.7)	42
Sneezing	0	0	1 (0.5)	1	0	0	1 (0.1)	1
Tympanic Membrane Disorder	1 (0.4)	2	0	0	0	0	1 (0.1)	2
Tympanic Membrane Hyperemia	1 (0.4)	2	0	0	0	0	1 (0.1)	2
Tympanic Membrane Perforation	1 (0.4)	1	0	0	0	0	1 (0.1)	1
URI	15 (6.6)	17	14 (6.5)	17	32 (8.4)	38	61 (7.4)	72
Viral URI	2 (0.9)	2	10 (4.6)	11	5 (1.3)	7	17 (2.1)	20
Viral Pharyngitis	1 (0.4)	1	0	0	0	0	1 (0.1)	1

Source: Trial 060-635 CSR, Table 14.3.1.7

Clinical Labs

Mean changes in lab values were small and similar across groups. Shift analysis was also performed demonstrating that incidence of shifts were small and similar between groups. Although as a whole, changes in lab values were minimal, on an individual level, some patients did have clinically significant lab abnormalities. However, clinically significant lab abnormalities were rare. A total of 14 patients had clinically significant abnormalities in hematology, chemistries, or urinalysis.

Vital Signs

Based on mean values, there were no significant changes in vital sign parameters. Hypertension was reported as a TEAE in 1.1% of patients [1 (0.4%), 2 (0.9%), and 6 (1.6%) patients in the PBO-CIC148, CIC74-CIC148, and CIC148-CIC148 groups respectively]. There was also one patient with an episode of sinus bradycardia.

ENT exam

Four (4) patients (0.5%) were diagnosed with nasal septum ulceration and 3 of the 4 had epistaxis.

Reviewer Comment:

Compared to the 6 month data from trial 060-633, the frequency and distribution of SAEs were similar. Note that the SAEs/AEs reported in this trial were unique to this 6 month period. The TEAEs though were fewer and less diverse. This decrease may be related to the fact that patients who had TEAEs in the 060-633 may have been less likely to continue in this trial. The local AEs in this trial were also similar to the 6 month data for 060-633. However, 4 patients on ciclesonide developed nasal septal ulcerations, as compared to zero in 060-633. There was no apparent effect with increased exposure. Although no nasal septum ulcerations were noted in the ciclesonide groups in trial 060-633, in the 2 week trial 060-622, septum ulcerations were noted in both ciclesonide groups (5 patients total) and placebo groups (1 patient). Nasal septal ulcerations have also been noted in other nasal steroid development programs. In this trial, ciclesonide was well tolerated and the adverse events seen were typical for a nasal steroid.

Overall Reviewer Comment Trial 060-635

Based on the compliance and efficacy endpoints, patients were relatively compliant with therapy given the length of study. With regarding to safety endpoints, ciclesonide was well tolerated, and seems to have demonstrated a safety profile similar to other nasal steroids. After an additional 6 months of exposure (CIC74-CIC148 and CIC148-CIC148), the safety profile of ciclesonide remained essentially the same.

6 Review of Efficacy

Efficacy Summary

The proposed indication for this product (CIC-HFA) is the treatment of symptoms associated with seasonal and perennial allergic rhinitis in patients ≥ 12 years of age. The proposed dose is 74 mcg per day (37 mcg per nostril). The sponsor explored higher doses, however, no benefit to increased dosing was seen. The proposed indication is broader than many other inhaled nasal corticosteroids, in that it is not specific to nasal symptoms. In addition, label claims include improvement in rTOSS and RQLQ(S). Omnaris, a nasal corticosteroid with the same active ingredient manufactured by the same company, does not carry the broader indication nor the RQLQ(S) label claim. However, neither the indication nor the label claim are unique. Veramyst, also an inhaled nasal corticosteroid, is indicated to treat both ocular and nasal symptoms associated with AR, and has a label claim to improve RQLQ.

Support for the efficacy of the 74 mcg daily dose for the treatment of nasal symptoms associated with SAR is derived from trials 060-622 and 060-634. Both trials individually demonstrated a significant improvement in nasal symptoms based on the primary endpoint and supported by iTNSS related key secondary endpoint. The data from these trials were also combined with a similar conclusion. CIC-HFA at 74 mcg daily demonstrated a statistically significant improvement in the AM and PM rTNSS averaged over the 2 week treatment period compared to placebo (the primary endpoint). The treatment difference from placebo based on the sponsor pooled data was 0.98 with a 95% confidence interval of (0.7, 1.27). Individually, the difference from placebo was 0.94 and 1.04 for trials 060-622 and 060-633, respectively.

Efficacy was further supported by the nasal symptom related key secondary endpoints. CIC-HFA (74 mcg) demonstrated a significant change from baseline for AM and PM iTNSS averaged over the 2 week treatment period compared to placebo. The treatment difference was similar to the primary endpoint [0.89 (0.61, 1.17), sponsor pooled data]. Similar findings were also seen in dose ranging trial M1-602. Based on this data, CIC-HFA (74 mcg) is effective in treating the nasal symptoms associated with SAR. The 148 mcg daily dose had similar results for the primary endpoint and nasal symptom related key secondary endpoints, however, usage of the higher dose did not increase efficacy.

Based on their analysis of both trials 060-622 and 060-633 individually and when pooled, the sponsor concluded that CIC-HFA at 74 mcg was efficacious at treating the ocular symptoms associated with SAR (rTOSS related key secondary endpoint). For sponsor's analysis of the 148 mcg dose, the data was not as robust. The 148 mcg dose did not show efficacy with respect to rTOSS in trial 060-634, but did in 060-622. Sponsor analysis of the pooled data demonstrated that the 148 mcg group had numerical improvement in the rTOSS compared to placebo and the 95% confidence intervals did not cross zero (see Table 56 and Table 58). Based on this, sponsor concluded that like the 74 mcg dose, the 148 mcg dose is efficacious with regard to

ocular symptoms. It is important to note that the sponsor analysis only included the population subset with baseline ocular symptoms (baseline rTOSS \geq 5.0), *not* the entire study population.

As the sponsor's analysis of the ocular symptoms did not include the entire patient population, it was not likely representative of the whole SAR population. FDA biostatisticians reanalyzed the rTOSS related key secondary endpoint for the total population in both SAR trials. In this analysis, a modest statistically significant effect was seen in trial 060-622 at both the 74 mcg (0.5, $p < 0.001$) and 148 mcg ciclesonide (0.5, $p < 0.001$) doses. However, in trial 060-634, a statistically significant treatment effect based on rTOSS was only seen for the 74 mcg dose, but not the 148 mcg dose (0.4, $p = 0.024$ and 0.3, $p = 0.055$ for the 74 and 148 mcg dose, respectively). Although the rTOSS results from trial 060-634 were weaker in comparison to 060-622, the 74 mcg daily dose in both SAR trials resulted in statistically significant improvements. As such, this weight of evidence is sufficient to support the label claim that CIC-HFA at 74 mcg daily improves ocular symptoms related to SAR.

Based on their analysis of both SAR trials 060-622 and 060-633 individually and when pooled, the sponsor concluded that CIC-HFA at 74 and 148 mcg dose was efficacious at improving disease related quality of life. However, as in their analysis of ocular symptoms, the sponsor based their conclusion on the analysis of only a subset of study patients with baseline impairment (baseline RQLQ \geq 3.0). As such, FDA biostatisticians reanalyzed the RQLQ related key secondary endpoint for the total population in both SAR trials. The results of the FDA analysis demonstrated that both doses of CIC-HFA improved RQLQ scores over the 2 weeks of treatment in both trials. For both trials, the treatment difference from placebo was marginal (0.6 and 0.5 for the 74 mcg dose for trials 060-622 and 060-634, respectively. MCID \geq 0.5), but clinically and statistically significant (based on MCID and unadjusted p-values). These results support the label claim that CIC-HFA at 74 mcg daily improves RQLQ scores.

Overall, with regard to SAR, CIC-HFA at 74 mg daily is effective at treating symptoms associated with SAR, and does modestly improve ocular symptoms and disease related quality of life.

Support for the PAR indication comes from a single trial (060-633) in PAR as well as the totality of the SAR data. In this trial, the 74 mcg dose demonstrated efficacy with respect to its primary and key secondary endpoints. CIC-HFA at 74 mcg daily compared to placebo demonstrated a statistically significant improvement in the AM and PM rTNSS averaged over the 1st 6 weeks of the treatment period (the primary endpoint). The treatment difference from placebo was 0.69 with a 95% confidence interval of (0.35, 1.08). Efficacy was further supported by the key secondary endpoint. CIC-HFA (74 mcg) demonstrated a significant change from baseline for AM and PM iTNSS averaged over the same period compared to placebo. The treatment difference was 0.58 (0.25, 0.92). Similar results for the 148 mcg dose were seen. Although, based on sponsor analysis, there was also some demonstration of improvement in RQLQ(S) compared to placebo

in the sponsor's analysis, the p-values were not adjusted for multiple comparisons, the magnitude of improvement was marginal (0.55 and 0.37 for the 74 and 148 mcg dose, respectively), and the analysis was only performed on a subset of the total population (baseline RQLQ \geq 3.0). The data was reanalyzed for the total patient population by the FDA. Based FDA analysis, the treatment effect was not clinically significant with an improvement of just 0.3 for both doses (MCID \geq 0.5). Due to this, (b) (4) the proposed PAR indication is appropriate.

In summary, based on the information provided in this application, CIC-HFA is efficacious in the treatment of symptoms associated with SAR and PAR, including nasal and ocular symptoms, at the 74 mcg/day dose. In addition, CIC-HFA at this dose also modestly improves disease related quality of life in SAR patients, but not PAR patients.

6.1 Seasonal Allergic Rhinitis

CIC-HFA is proposed for the treatment of the symptoms associated with SAR and PAR in adults and children 12 years and older at a dose of 74 mcg per day. The indication for SAR will be discussed here in section 6.1, and PAR in section 6.2. This indication is broader than the aqueous version of ciclesonide (Omnaris), which is only indicated to treat the nasal symptoms associated with AR, but not ocular symptoms. For (b) (4) SAR (b) (4), the sponsor has included label claims for improvement in disease related quality of life (RQLQ).

6.1.1 Methods

To support efficacy, for SAR, 2 phase 3 trials (060-622 and 060-634) were submitted by the sponsor. These were randomized, placebo controlled, multi-center trials. Both trials were performed in Texas and all subjects were allergic to Mountain Cedar pollen. Ambient pollen counts were made throughout both studies. Both were reviewed in section 5.3. These trials were adequately designed to assess the efficacy of the CIC-HFA with regard to nasal symptoms. However, the efficacy endpoints related to ocular symptoms (TOSS) and quality of life (RQLQ) were insufficient as for both, the sponsor based efficacy conclusions on only the subset of patient who had baseline ocular symptoms (TOSS \geq 3.0) or impairment in quality of life (RQLQ \geq 3.0). For this reason, key secondary endpoints related to TOSS and RQLQ were reanalyzed in the total population by FDA biostatisticians.

6.1.2 Demographics

Demographics for both studies can be found in section 5.3 (Table 15 and Table 23).

6.1.3 Subject Disposition

For studies 060-622 and 060-634 a total of 3192 patients were screened, 444 patients failed screening, and 370 failed at randomization. This left 1378 patients in the intent to treat population. Patient disposition is summarized in Table 53.

Table 53. Trials 060-622 and 060-633. Combined Patient Disposition

Category	Ciclesonide HFA Dose			Total
	CIC-HFA 74 mcg	CIC-HFA 148 mcg	Placebo	
Screened				3192
Enrolled				1748
Randomized				1378
ITT Analysis Set	463	460	455	1378
PP Analysis Set	437	439	422	1298
Completed Study	444 (95.9)	447 (97.2)	421 (92.5)	1312 (95.2)
Prematurely Discontinued	19 (4.1)	13 (4.1)	34 (7.5)	66 (4.8)
Reason for Discontinuation				
Adverse Event	6 (1.3)	3 (0.7)	7 (1.5)	16 (1.2)
Protocol Violation	2 (0.4)	4 (0.9)	2 (0.4)	8 (0.6)
Withdrawal by Subject	4 (0.9)	0	11 (2.4)	15 (1.1)
Lost to follow up	2 (0.4)	0	4 (0.9)	6 (0.4)
Other	5 (1.1)	6 (1.3)	10 (2.2)	21 (1.5)

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily

The primary reason in both trials for randomization failure was lack of sufficient SAR symptoms. Discontinuations were higher in the placebo group compared to CIC-HFA groups. The most common reasons were “other,” AEs, and withdrawal by subject. AEs leading to withdrawal will be discussed in section 7. Within the “other” and “withdrawal by subject” categories, the most common specific reason was lack of efficacy. Lack of efficacy was reported most frequently in the placebo group (10 patients, 2.2%) vs the 74 mcg (4 patients, 0.9%) and 148 mcg (1 patient, 0.2%). The discontinuations due to lack of efficacy seemed to follow an inverse dose response, implying that CIC-HFA had a SAR treatment effect. Discontinuations due to AEs will be discussed in section 7.3.3.

6.1.4 Analysis of Primary Endpoint

Trials 060-622 and 060-634 had an identical primary endpoint, which was change from baseline in the AM and PM rTNSS averaged over the 2 week treatment period. Baseline was defined as the average of the responses obtained during the run-in period up to 6 days prior to randomization. The rTNSS was the sum of four individual symptoms scores (runny nose, itchy nose, sneezing, and nasal congestion) which are graded 0-3 (absent, mild, moderate, severe; see section 5.3.1). The rTNSS score was indicative of

symptoms in the past 12 hours. Reflective TNSS as a primary endpoint in SAR trials is appropriate and commonly used in inhaled nasal corticosteroid development programs.

In these trials, both doses of CIC-HFA demonstrated a significant improvement in rTNSS as compared to control. This improvement was modest, but on par with dose ranging trial M1-602 and with previous Omnaris trial data. There was also no added benefit for the 148 mcg dose of CIC-HFA. The results are summarized in Table 54.

Table 54. Pooled Data. SAR Primary Endpoint (Change from Baseline for Average AM/PM rTNSS During the 2 Week Treatment Period)

Average AM and PM rTNSS	N	Baseline (SD)	Change from baseline-LS Mean (SE)	Difference from placebo		
				LS Mean	95% CI	p-value
060-622						
74 mcg	237	9.32 (1.77)	-1.45 (0.14)	0.94	(0.57, 1.32)	<0.0001
148 mcg	234	9.46 (1.67)	-1.59 (0.14)	1.08	(0.70, 1.45)	<0.0001
Placebo	235	9.10 (1.80)	-0.51 (0.14)			
060-634						
74 mcg	226	9.34 (1.88)	-1.75 (0.15)	1.04	(0.61, 1.46)	<0.0001
148 mcg	225	9.26 (1.8)	-1.74 (0.15)	1.02	(0.59, 1.45)	<0.0001
Placebo	218	9.28 (1.77)	-0.72 (0.16)			
060-622 and 060-634						
74 mcg	463	9.33 (1.83)	-1.60 (0.10)	0.98	(0.70, 1.27)	
148 mcg	459	9.36 (1.74)	-1.66 (0.10)	1.04	(0.75, 1.32)	
Placebo	452	9.19 (1.79)				

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily
 Source: ISE, Table 13, pp54

The individual trials demonstrated a significant treatment effect, as did the pooled data, Although a combined p-value was not provided by the sponsor, given that the p-values were so small in the individual trials and that the 95% confidence interval for the combined analysis did not cross zero, one can conclude that both doses are efficacious with regard to the primary endpoint.

6.1.5 Analysis of Secondary Endpoints(s)

Key Secondary Endpoints

In order to support the proposed indication, the trials 060-622 and 060-634 had multiple secondary endpoints. These were divided into “key secondary endpoints” and “other secondary endpoints.” Trial 060-622 and 060-634 had two key secondary endpoints in common. These were change from baseline in the following parameters:

- The average of AM and PM instantaneous TNSS over the 2 week treatment period
- The average of AM and PM rTOSS over the 2 week treatment period in patients with a baseline rTOSS ≥ 5.0

Trial 060-634, also included change in RQLQ(S) at visit 5 compared to baseline in impaired patients (baseline RQLQ(S) score ≥ 3.0) as a key secondary endpoint. This endpoint was categorized as an “other secondary endpoint” in trial 060-622, but for the purposes of this review, it will be considered as a “key secondary endpoint.”

Key secondary endpoints for each dose were not to be analyzed unless 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: iTNSS, rTOSS, and RQLQ(S).

AM/PM iTNSS

Instantaneous TNSS is indicative of the symptoms experienced in the 10 minutes prior. It is scored in a manner similar to rTNSS. This endpoint is typical for a SAR study and is supportive of the proposed indication. For both CIC-HFA doses, there was significant improvement in the AM/PM iTNSS averaged over the two week treatment period compared to placebo. Although CIC-HFA improved these scores, as with the primary endpoint, there was no benefit from the higher (148 mcg) dose. The individual and combined results of the two SAR studies are summarized in Table 55.

Table 55. Pooled Data. SAR Key Secondary Endpoint 1 (Change from Baseline for Average AM/PM iTNSS During the 2 Week Treatment Period)

Average AM/PM iTNSS	N	Baseline (SD)	Change from baseline-LS Mean (SE)	Difference from placebo		
				LS Mean	95% CI	p-value
060-622						
74 mcg	237	8.68 (2.05)	-1.34 (0.13)	0.87	(0.50, 1.25)	<0.0001
148 mcg	234	8.94 (2.00)	-1.47 (0.13)	1.00	(0.63, 1.37)	<0.0001
Placebo	234	8.61 (2.06)	-0.47 (0.13)			
060-634						
74 mcg	226	8.60 (2.15)	-1.58 (0.15)	0.90	(0.49, 1.32)	<0.0001
148 mcg	225	8.64 (2.14)	-1.51 (0.15)	0.83	(0.42, 1.25)	0.0002
Placebo	218	8.53 (2.21)	-0.68 (0.15)			
060-622 and 060-634						
74 mcg	463	8.64 (2.10)	-1.46 (0.10)	0.89	(0.61, 1.17)	
148 mcg	459	8.79 (2.07)	-1.49 (0.10)	0.91	(0.64, 1.19)	
Placebo	452	8.57 (2.13)	-0.57 (0.10)			

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily

Source: ISE, Table 14, pp57

From these results, it can be concluded that CIC-HFA at both dose is effective in the treatment of SAR with respect to iTNSS endpoint. This endpoint supports a 24 hour duration of action and once daily dosing.

AM/PM rTOSS

The TOSS is comprised of 3 symptom domains (ocular tearing, itching, and redness) scored from 0-3. The reflective score is indicative of the previous 12 hours of symptoms.

This endpoint has been used in previous inhaled nasal corticosteroid development programs, however was not used in the previous Omnaris trials. For trial 060-622, at both CIC-HFA doses there was significant improvement from baseline in the AM/PM rTOSS averaged over the 2 week treatment period compared to placebo for those whose baseline rTOSS was ≥ 5 . However, for trial 060-634, statistical significance was only seen the 74 mcg dose, though the p-value was not as impressive as in trial 060-622. These results are summarized in Table 56.

Table 56. Pooled Data. SAR Key Secondary Endpoint 2 (Change from Baseline for Average AM/PM rTOSS During the 2 Week Treatment Period for patients with baseline score ≥ 5)

Average AM/PM rTOSS	N	Baseline (SD)	Change from baseline-LS Mean (SE)	Difference from placebo		
				LS Mean	95% CI	p-value
060-622 (baseline score ≥ 5)						
74 mcg	164	6.89 (1.19)	-1.06 (0.12)	0.61	(0.28, 0.95)	0.0007
148 mcg	160	7.01 (1.11)	-1.05 (0.12)	0.60	(0.27, 0.94)	0.0009
Placebo	147	6.95 (1.23)	-0.44 (0.12)			
060-634 (baseline score ≥ 5)						
74 mcg	159	7.13 (1.19)	-1.40 (0.13)	0.52	(0.15, 0.89)	0.0124
148 mcg	161	7.04 (1.22)	-1.21 (0.13)	0.34	(-0.03, 0.71)	0.1444
Placebo	164	6.97 (1.19)	-0.88 (0.13)			
060-622 and 060-634 (baseline score ≥ 5)						
74 mcg	323	7.01 (1.20)	-1.23 (0.09)	0.57	(0.32, 0.82)	
148 mcg	321	7.03 (1.17)	-1.13 (0.09)	0.47	(0.22, 0.72)	
Placebo	311	6.96 (1.21)	-0.66 (0.09)			

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily
 Source: ISE, Table 16, pp59

As this analysis was based on only a subset of patients, no efficacy conclusions regarding the total SAR patient population can be made. This data was reanalyzed by FDA biostatistics to include the entire patient population. Based on this reanalysis, the treatment effect was marginal, but statistically significant for both doses in trial 060-622. However, in trial 060-634, the treatment effect was marginal at both doses (74mcg and 148 mcg daily), but was only statistically significant for the 74 mcg daily dose. This is summarized in Table 57.

Table 57. FDA Analysis of Change from Baseline in AM/PM rTOSS over 2 Week Treatment Period in the Total Patient Population

Average AM/PM rTOSS	Difference from placebo			
	N	LS Mean	95% CI	p-value
060-622 (total patient population)				
74 mcg	237	0.5	(0.3, 0.8)	<0.001
148 mcg	234	0.5	(0.2, 0.8)	<0.001
Placebo	234			
060-634 (total patient population)				
74 mcg	226	0.4	(0.1, 0.7)	0.024
148 mcg	225	0.3	(0.0, 0.6)	0.055
Placebo	218			

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily
 p-values are significant at the 0.025 level based on Bonferroni correction

Although the rTOSS data from trial 060-634 were not as impressive as 060-622, the 74 mcg daily dose resulted in statistically significant improvement in reflective ocular symptoms in both trials. As such, the presented data are sufficient to support the label claim regarding improvement in nasal symptoms.

RQLQ(S)

This outcome measure has been used in previous inhaled nasal corticosteroid development programs; however, it was not used in the Omnaris trials. This score incorporates 7 quality of life domains, which are each scored 0-6. The minimally clinically important difference (MCID) is a change of ≥ 0.5 . This MCID has been used in previous nasal steroid development programs and the scientific literature. For both trials 060-622 and 060-634, the 74 mcg dose demonstrated statistically significant improvement compared to placebo. For the 148 mcg dose, in trial 060-622, there was also improvement compared to placebo, but in trial 060-634, no p-value was calculated due to the pre-specified analysis plan. However, the point estimate and 95% confidence interval for the treatment effect for the 148 mcg dose is similar to the 74 mcg dose (trial 060-634). The results are summarized in Table 58.

Table 58. Pooled Data. SAR Key Secondary Endpoint 3 [Change from Baseline for RQLQ(S) in Patients with a Baseline Score ≥ 3.0]

RQLQ(S)	N	Baseline (SD)	Change from baseline-LS Mean (SE)	Difference from placebo		
				LS Mean	95% CI	p-value
060-622 (baseline score ≥ 3)						
74 mcg	186	4.52 (0.77)	-1.05 (0.10)	0.62	(0.36, 0.89)	<0.0001
148 mcg	181	4.49 (0.78)	-1.07 (0.10)	0.64	(0.37, 0.91)	<0.0001
placebo	180	4.43 (0.83)	-0.42 (0.10)			Unadjusted
060-634 (baseline score ≥ 3)						
74 mcg	162	4.42 (0.87)	-1.44 (0.11)	0.64	(0.33, 0.95)	0.0124
148 mcg	148	4.3 (0.8)	-1.41 (0.12)	0.62	(0.30, 0.94)	ND
placebo	145	4.36 (0.78)	-0.79 (0.12)			
060-622 and 060-634 (baseline score ≥ 3)						
74 mcg	348	4.47 (0.82)	-1.24 (0.07)	0.63	(0.43, 0.84)	
148 mcg	329	4.41 (0.79)	-1.24 (0.07)	0.63	(0.43, 0.84)	
placebo	325	4.40 (0.80)	-0.61 (0.07)			

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily
 Source: ISE, Table 18, pp64

As with the rTOSS key secondary endpoint, this analysis was based on only a subset of patients, and was reanalyzed by FDA biostatistics to include the entire patient populations. Based on this reanalysis, the treatment effect was modest with a treatment difference from placebo for both doses at 0.6 and 0.5 for trials 060-622 and 060-634, respectively. This is summarized in Table 59.

Table 59. FDA Analysis of Change from Baseline in RQLQ over 2 Week Treatment Period in the Total Patient Population

Average AM/PM rTOSS	N	Difference from placebo		
		LS Mean	95% CI	p-value
060-622 (total patient population)				
74 mcg	237	0.6	(0.4, 0.8)	<0.001
148 mcg	232	0.6	(0.4, 0.8)	<0.001
Placebo	234			
060-634 (total patient population)				
74 mcg	226	0.5	(0.3, 0.8)	<0.001
148 mcg	225	0.5	(0.3, 0.8)	<0.001
Placebo	220			

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily
 p-values are significant at the 0.025 level based on Bonferroni correction

Based on the FDA analysis, the 74 mcg dose significantly improved RQLQ(S) scores after 2 weeks of treatment in both trials individually. However, the higher dose confers no added benefit.

Based on the primary and key secondary endpoints, the 74 and 148 mcg doses are efficacious in the treatment of symptoms associated with SAR. There is also modest improvement in disease related quality of life. These endpoints also demonstrate that there is no added benefit from the 148 mcg dose.

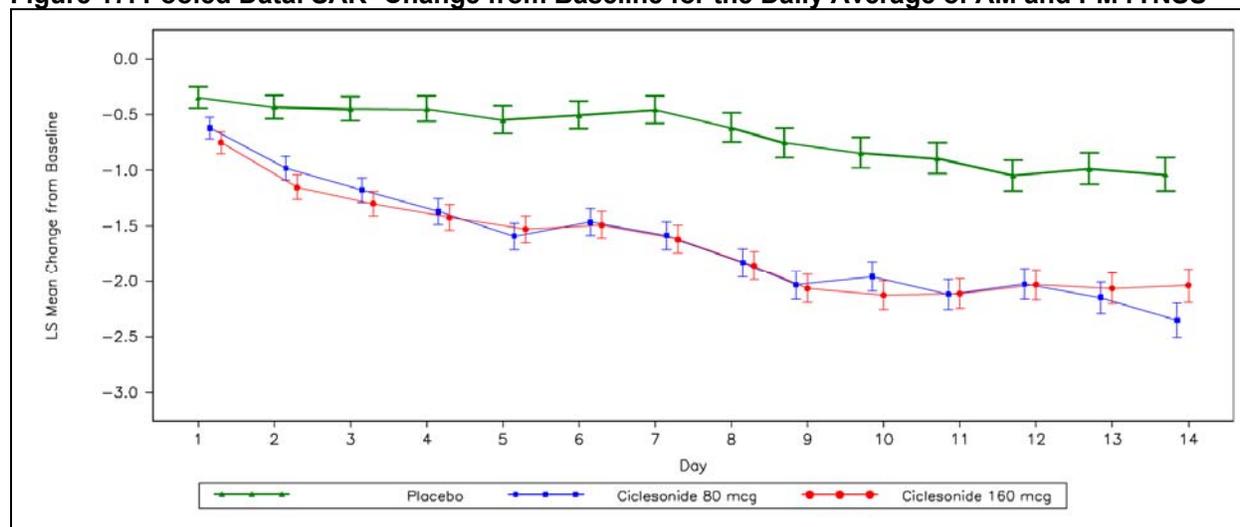
Other Secondary Endpoints

These endpoints examined change from baseline in AM, PM, and average AM/PM symptoms scores (rTNSS, iTNSS, rTOSS, iTOSS) at each day, averaged over each week, and averaged over the 2 week treatment period (except when it was a primary or key secondary endpoint). Similar analysis was also done breaking each composite score into individual domains. When a value for difference from placebo is reported in the subsequent sections, it will be followed by the 95% confidence interval in parentheses. All endpoints associated with ocular symptoms and quality of life were only evaluated in the symptomatic/impaired patient subset. As these were not 'key' endpoints, these were not reanalyzed by the FDA. Endpoints associated with nasal symptoms were evaluated in all patients in the trials.

rTNSS

Much like in the individual trials, in pooled data for the average AM and average PM rTNSS over the 2 week treatment period demonstrated significant improvement compared to placebo. For the AM rTNSS, the difference from placebo was 0.99 (0.7, 1.27) and 1 (0.72, 1.29) for the 74 and 148 mcg group respectively. For the PM rTNSS, the difference from placebo was 0.98 (0.69, 1.27) and 1.06 (0.77, 1.35) for the 74 and 148 mcg group respectively. The individual symptom scores had similar results. The pooled data also demonstrated that there was a decrease in the average AM/PM rTNSS each day that was consistent with the primary endpoint (See Figure 17). As with all the other results, there was no dose effect.

Figure 17. Pooled Data. SAR- Change from Baseline for the Daily Average of AM and PM rTNSS

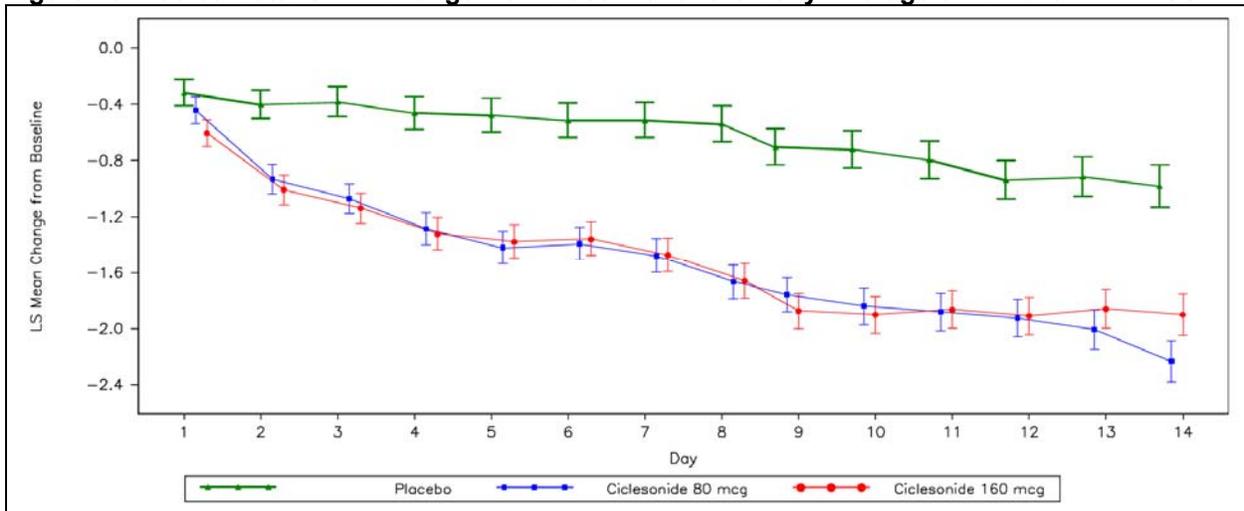


Ciclesonide 80 mcg= CIC-HFA 74mcg daily, Ciclesonide 160 mcg=CIC-HFA 148 mcg daily
Source: ISE, Figure 17.1

*i*TNSS

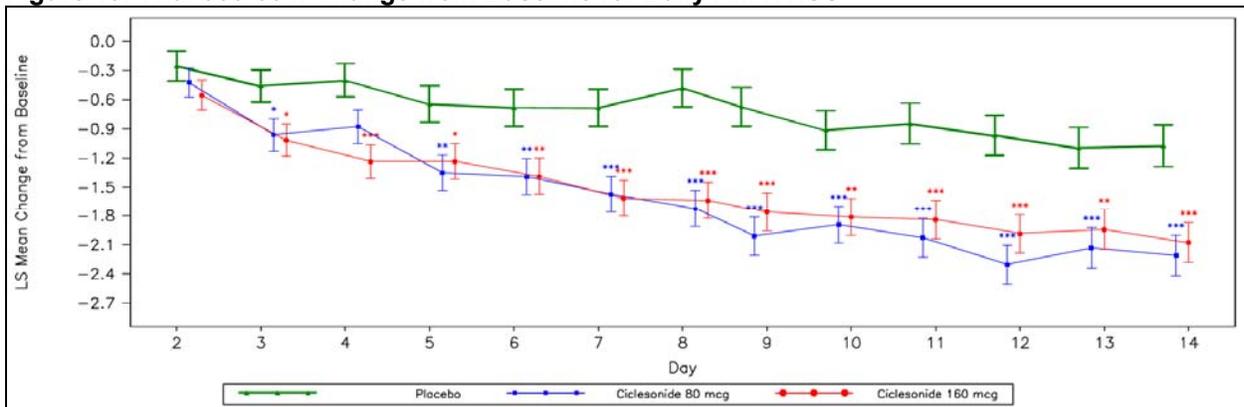
The pooled data for the average AM and average PM *i*TNSS over the 2 week treatment period demonstrated significant improvement in the CIC-HFA groups compared to placebo. For the AM *i*TNSS, the difference from placebo was 0.88 (0.6, 1.15) and 0.88 (0.6, 1.15) for the 74 and 148 mcg group respectively. For the PM *i*TNSS the difference from placebo was 0.9 (0.61, 1.19) and 0.94 (0.65, 1.23) for the 74 and 148 mcg group respectively. The individual symptom scores had similar results. The pooled data also demonstrated that there was a decrease in the average AM/PM *i*TNSS each day that mirrored the primary endpoint (see Figure 18). The sponsor did not pool data for the change from baseline in AM *i*TNSS for each day. However in the individual studies (060-622 and 060-634), starting at day 3 there was improvement in AM *i*TNSS in the ciclesonide HFA treated groups compared to placebo. These results are summarized in Figure 19 and Figure 20. These AM *i*TNSS results are supportive of the once daily dosing regimen.

Figure 18. Pooled Data. SAR- Change from Baseline for the Daily Average of AM and PM iTNSS



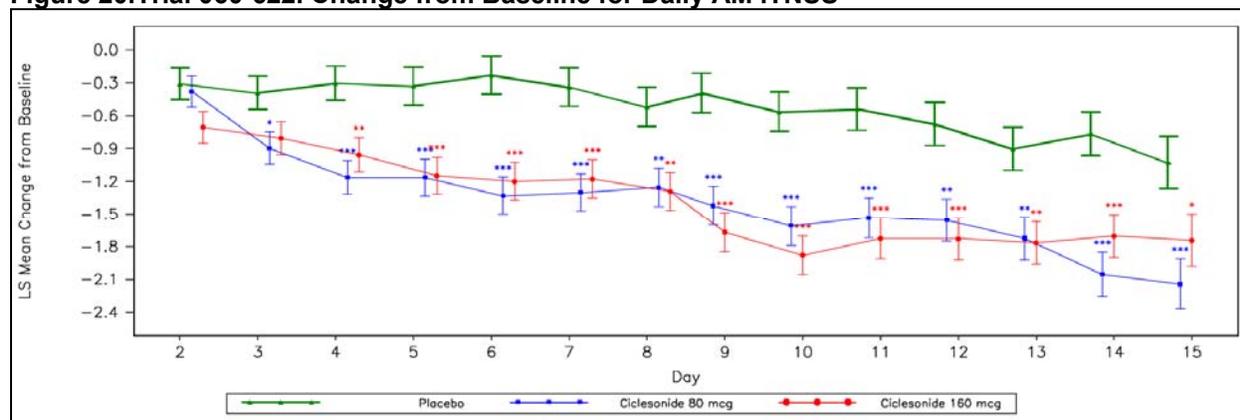
Ciclesonide 80 mcg= CIC-HFA 74mcg daily, Ciclesonide 160 mcg=CIC-HFA 148 mcg daily
 Source: ISE, Figure 18.1

Figure 19. Trial 060-634. Change from Baseline for Daily AM iTNSS



Ciclesonide 80 mcg= CIC-HFA 74mcg daily, Ciclesonide 160 mcg=CIC-HFA 148 mcg daily
 *p<0.05, **p<0.01, ***p<0.001, p-values unadjusted for multiplicity
 Source: Trial 060-634 CSR, Table 14.4.5

Figure 20. Trial 060-622. Change from Baseline for Daily AM iTNSS



Ciclesonide 80 mcg= CIC-HFA 74mcg daily, Ciclesonide 160 mcg=CIC-HFA 148 mcg daily

*p<0.05, **p<0.01, ***p<0.001, p-values unadjusted for multiplicity

Source: Trial 060-634 CSR, Table 14.4.5

rTOSS

The pooled data for the change from baseline in the AM, PM, and average AM/PM rTOSS for each day and averaged over each week of treatment for patients with baseline rTOSS ≥ 5 mirrored the key secondary endpoint. For all of these endpoints, both doses demonstrated improvement compared to placebo. However, the 148 mcg dose consistently had a lesser nominal treatment effect compared to the 74 mcg dose.

iTOSS

The pooled data for the change from baseline in the AM and PM iTOSS averaged over the 2 week treatment period was similar to individual trial data. Both doses of ciclesonide HFA demonstrated improvement in the AM and PM iTOSS averaged over the treatment period compared to placebo [74 mcg= 0.56 (0.29, 0.82) and 148 mcg= 0.55 (0.29, 0.81)]. With respect to daily averages of AM/PM iTOSS over the treatment period, the 74 mcg dose demonstrated improvement from baseline compared to placebo throughout the 2 week treatment period. However, while the 148 mcg initially demonstrated improvement from placebo during the 1st week of treatment in daily AM/PM iTOSS, near the end of week 2, the improvement was lost.

Based the pooled results from trials 060-622 and 060-634 for the 'other' secondary endpoints are supportive for the efficacy of CIC-HFA in treating nasal symptoms associated with SAR when given at 74 mcg/day. No conclusions can be made from the results of sponsor analysis of TOSS related 'other' secondary endpoints, as that data was only analyzed in a subset of the SAR population.

6.1.6 Other Endpoints

Onset of action

In trial 060-622, onset of action for nasal and ocular symptoms was formally evaluated by assessing iTNSS and iTOSS more frequently during days 1 and 2 of the double-blind

treatment period. Onset of action was defined as the first time point when there was statistically significant (one-sided $p \leq 0.025$) improvement in iTNSS. This occurred 36 hours after the first dose. Using the same criteria, the sponsor also conducted a similar analysis of the data from trial 060-634. This demonstrated that the onset of action occurred 12 hours post-dose on day 2 (36 hours). Prior to this time point, there was no significant improvement in iTNSS. These results are summarized in Table 60. ^{(b) (4)}

Table 60. Change from Baseline for iTNSS 36 Hours after 1st Dose

iTNSS 36 hours after 1 st dose	N	Change from baseline- LS Mean (SE)	Difference from placebo		
			LS Mean	95% CI	p-value
060-622					
74 mcg	235	-1.35 (0.16)	0.58	(0.12, 1.03)	0.0067
148 mcg	233	-1.59 (0.17)	0.82	(0.36, 1.28)	0.0002
Placebo	232	-0.77 (0.17)			
060-634					
74 mcg	224	-1.39 (0.18)	0.60	(0.1, 1.1)	0.0094
148 mcg	224	-1.35 (0.18)	0.56	(0.06, 1.06)	0.0141
Placebo	216	-0.79 (0.18)			

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily

Source: ISE EOT, Tables 16.2.1, 16.4.1

6.1.7 Subpopulations

For both studies, a subgroup analysis was performed based on age, race, gender, and baseline severity. Patients were divided into 3 subgroups by age: 12 to ≤ 18 , 19 to < 65 , and ≥ 65 years of age; and 3 subgroups by race: White, Black, Other. Across all treatment groups, 89-90% of patients were between 19 to < 65 years old, 88-93% were white, and 62-65% were female. A summary of the pooled subpopulation analysis can be found in Table 61. The subgroup analysis for the key secondary endpoints demonstrated similar trends.

Table 61. Pooled Data. SAR Subgroup Analysis of Primary Endpoint

Subgroup	Change from Baseline LS Mean (SE)			Treatment Difference from Placebo LS Mean Difference (95% CI)		
	12 to ≤18	19 to <65	≥65	12 to ≤18	19 to <65	≥65
74 mcg	N=32 -1.17 (0.35)	N=414 -1.61 (0.11)	N=17 -1.34 (0.63)	1.39 (0.37, 2.42)	0.99 (0.68, 1.29)	0.46 (-1.19, 2.12)
148 mcg	N=28 -0.37 (0.40)	N=414 -1.73 (0.11)	N=17 -0.90 (0.60)	0.59 (-0.55, 1.72)	1.10 (0.80, 1.41)	0.03 (-1.43, 1.48)
Placebo	N=22 0.22 (0.41)	N=402 -0.63 (0.11)	N=28 -0.88 (0.51)			
Subgroup	White	Black	Other	White	Black	Other
74 mcg	N=409 -1.68 (0.11)	N=39 -1.03 (0.50)	N=15 -1.85 (0.57)	1.09 (0.80, 1.39)	0.22 (-1.00, 1.44)	0.80 (-1.20, 2.80)
148 mcg	N=427 -1.72 (0.11)	N=20 -0.50 (0.61)	N=12 -1.89 (0.61)	1.13 (0.83, 1.42)	-0.32 (-1.76, 1.12)	0.85 (-1.25, 2.95)
Placebo	N=409 -0.59 (0.11)	N=36 -0.81 (0.48)	N=7 -1.04 (0.86)			
Subgroup	Male	Female		Male	Female	
74 mcg	164 -1.41 (0.17)	299 -1.72 (0.13)		0.97 (0.51, 1.43)	0.99 (0.63, 1.36)	
148 mcg	175 -1.57 (0.16)	284 -1.70 (0.13)		1.14 (0.68, 1.60)	0.97 (0.61, 1.34)	
Placebo	169 -0.43 (0.17)	283 -0.73 (0.14)				

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily
 Source: ISE, Tables 19, 20, 21, pp67-70

The pooled data demonstrated that gender had no effect of efficacy. However, CIC-HFA at either dose tended to have a lesser treatment effect in Blacks compared to Whites and Others. CIC-HFA also tended to be more effective in the 19 to <65 year old population compared to the 12 to ≤18 and ≥65 year old population. However, even when pooling the data, the numbers remained small.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This NDA proposes a single dose strength for CIC-HFA nasal aerosol which is 74 mcg once daily (37 mcg each nostril once daily). A single phase 2b dose ranging trial (M1-602, reviewed in section 5.3.1) was performed using 3 doses; 74 mcg (37 mcg each nostril once daily), 148 mcg (74 mcg each nostril once daily), and 282 mcg (141 mcg each nostril once daily). Results from this trial demonstrated that all three doses improved rTNSS and iTNSS over the 2 week treatment period compared to placebo. Although all doses were effective, no dose response was demonstrated, implying that either this drug had a flat dose response, or all doses chosen were on the flat portion of the dose response curve. Based on the results of M1-602, the sponsor carried forward the 74 mcg and 148 mcg for their 2 phase 2 SAR trials. These results again demonstrated that essentially, the 74 mcg dose was equivalent to the 148 mcg in terms of efficacy.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No tolerance effects were observed in the pivotal SAR trials. CIC-HFA remained effective for the 2 weeks of exposure.

6.1.10 Additional Efficacy Issues/Analyses

None

6.2 Perennial Allergic Rhinitis (PAR)

CIC-HFA is proposed for the treatment of the symptoms associated with SAR and PAR in adults and children 12 years and older at a dose of 74 mcg per day.

This section will discuss the PAR indication.

6.2.1 Methods

To support efficacy for PAR, 1 phase 3 trial (060-633) was submitted by the sponsor. This was a randomized, placebo controlled, multi-center trial. This single study was reviewed in depth in section 5.3.4. Since the product demonstrated efficacy in SAR and the two diseases are closely related, replicative studies in PAR are not required for approval.

6.2.2 Demographics

See section 5.3.4.

6.2.3 Subject Disposition

See section 5.3.4.

6.2.4 Analysis of Primary Endpoint(s)

The primary endpoint for trial 060-633 was change from baseline for AM and PM rTNSS averaged over the first 6 weeks of treatment. This endpoint is typical of PAR trials and was similar to the endpoint used in the Omnaris development program (PAR). Both the 74 and 148 mcg doses demonstrated statistically significant improvement from baseline compared to placebo. There was no additional benefit from use of the higher dose. In fact, the higher dose had a numerically lower treatment effect (see Table 62).

Table 62. Results for PAR Primary Endpoint (Change from Baseline for Average AM/PM rTNSS for the 1st 6 Weeks of Treatment)

Treatment	N	Baseline (SD)	Change from baseline-LS Mean (SE)	Difference from placebo		
				LS Mean	95% CI	p-value
Average AM and PM rTNSS over the 1st 6 weeks of Treatment						
74 mcg	298	8.53 (1.82)	-1.97 (0.13)	0.69	(0.35, 1.04)	0.0001
148 mcg	504	8.50 (1.81)	-1.82 (0.10)	0.54	(0.24, 0.84)	0.0010
Placebo	305	8.62 (1.88)	-1.28 (0.13)			

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily
 Source: Trial 0060-633 CSR, Table 14, pp88

6.2.5 Analysis of Secondary Endpoints(s)

The key secondary endpoint for trial 060-633 was change from baseline for AM and PM iTNSS averaged over the first 6 weeks of treatment. This endpoint is typical of PAR trials was similar to endpoint used in the Omnaris development program. Both the 74 and 148 mcg doses demonstrated statistically significant improvement from baseline compared to placebo. This result mirrored the primary endpoint in that not only was there no additional benefit with the higher dose, but the higher dose also had a lesser numerical treatment effect compared to the lower dose (Table 63).

Table 63. Results for PAR Key Secondary Endpoint

Treatment	N	Baseline (SD)	Change from baseline-LS Mean (SE)	Difference from placebo		
				LS Mean	95% CI	p-value
Average AM and PM iTNSS over the 1st 6 weeks of Treatment						
74 mcg	298	7.66 (2.28)	-1.77 (0.12)	0.58	(0.25, 0.92)	0.0014
148 mcg	504	7.64 (2.27)	-1.60 (0.10)	0.42	(0.12, 0.72)	0.0122
Placebo	305	7.70 (2.38)	-1.18 (0.12)			

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily
 Source: Trial 0060-633 CSR, Table 15, pp92

Another important secondary endpoint for this trial was change from baseline in RQLQ(S) for impaired patients (baseline RQLQ(S) ≥ 3) at week 6 and month 6. For both CIC-HFA doses there was statistically significant improvement compared to placebo at week 6. However, for the 148 mcg dose, the difference from placebo was <0.5 , the minimal clinically important difference (MCID). The differences compared to placebo for the 74 and 148 mcg groups were 0.55 and 0.37, respectively. This same endpoint was assessed at the 6 months. Again, both demonstrated statistically significant improvement (unadjusted p-values) compared to baseline. However, neither dose had improvement greater than the MCID. The difference compared to placebo for the 74 and 148 mcg groups were 0.40 and 0.37, respectively (Table 64).

Table 64. Results for PAR Secondary Endpoint (Change from Baseline for RQLQ(S) for Impaired Patients at week 6 and month 6)

Treatment	N	Baseline (SD)	Change from baseline-LS Mean (SE)	Difference from placebo		
				LS Mean	95% CI	p-value
RQLQ(S) 6 weeks (baseline ≥ 3.0)						
74 mcg	142	4.16 (0.77)	-1.57 (0.11)	0.55	(0.26, 0.84)	0.0002
148 mcg	261	4.05 (0.76)	-1.39 (0.09)	0.37	(0.12, 0.63)	0.0039
placebo	149	4.12 (0.78)	-1.02 (0.11)			
RQLQ(S) 6 months (baseline ≥ 3.0)						
74 mcg	146	4.16 (0.77)	-1.67 (0.11)	0.40	(0.11, 0.69)	0.0069
148 mcg	256	4.05 (0.76)	-1.64 (0.09)	0.37	(0.11, 0.62)	0.0052
placebo	156	4.12 (0.78)	-1.27 (0.11)			

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily

p-values unadjusted for multiplicity

Source: Trial 060-633 CSR, Table 19 and 20, pp107 &109

As in the SAR studies, the sponsor analyzed the RQLQ endpoint for the patient subset that was impaired at baseline. This data was reanalyzed for the entire population by the FDA, and demonstrated that at 6 weeks, while CIC-HFA at either dose demonstrated statistically significant impact on RQLQ scores, the treatment difference from placebo while statistically significant, was not clinically significant (MCID ≥ 0.5). This is summarized in Table 65.

Table 65. FDA Analysis of Change from Baseline in RQLQ over the 1st 6 Weeks of Treatment in the Total Patient Population

	Ciclesonide Dose		
	74 mcg	148 mcg	Placebo
Overall RQLQ at the end the 6 weeks of treatment (all patients)			
N	298	505	305
Treatment difference vs. Pbo (95% CI)	0.3 (0.1, 0.5)	0.3 (0.1, 0.4)	
p-value vs. Pbo	0.002	0.002	

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily

p-values are significant at the 0.025 level based on Bonferroni correction

Another important secondary endpoint was change from baseline AM iTNSS averaged over the 6 week treatment period. This endpoint was meant to justify the once daily dosing in the setting of PAR. Trial results demonstrated that after the 1st 6 weeks of therapy, both doses of CIC-HFA improved AM iTNSS from baseline as compared to placebo. The improvement was modest, though similar to the SAR data. These data are summarized in Table 66.

Table 66. PAR Results. Change from Baseline in AM iTNSS Averaged Over the 6 Week Treatment Period

Treatment	N	Baseline (SD)	Change from baseline-LS Mean (SE)	Difference from placebo		
				LS Mean	95% CI	p-value
Average AM iTNSS after 6 weeks						
74 mcg	297	6.24 (2.57)	-1.78 (0.12)	0.54	(0.21, 0.88)	0.0016
148 mcg	503	6.33 (2.69)	-1.67 (0.1)	0.44	(0.14, 0.74)	0.004
placebo	304	6.83 (2.57)	-1.23 (0.12)			

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily

p-values unadjusted for multiplicity

Source: Trial 060-633 CSR, Table 14.2.4.1.1

Based on the primary and key secondary endpoint, this trial is supportive of the proposed PAR indication. The results of the other secondary endpoints are in general consistent with the primary and key secondary endpoints. (b) (4)

6.2.6 Other Endpoints

See section 5.3.4 for exploratory endpoint results.

6.2.7 Subpopulations

Subgroup analysis by age and ethnicity did not reveal any differences between groups. However, the point estimate for the treatment effect of the CIC-HFA 74 mcg in terms of rTNSS was greater in females [0.9, (0.5, 1.4)] compared to males [0.2, (-0.4, 0.8)]. This observed gender difference is not likely clinically significant for several reasons. First, while the point estimates are different between sexes, the confidence intervals are widely overlapping. Second, SAR and PAR are also closely related disease entities, and no gender difference was observed in the SAR studies. (See section 5.3.4)

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No formal dose ranging studies were performed for the PAR indication, however given the similarity in pathophysiology of PAR to SAR, the SAR dose ranging data can be applied to PAR.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No tolerance effects were observed in the pivotal PAR trial. CIC-HFA remained effective for the first 6 weeks of exposure. After 6 months, efficacy was still seen in terms of AM/PM rTNSS and iTNSS (see Figure 13 and Figure 14, section 5.3.4).

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

This NDA submission contains adequate data to support the safety of CIC-HFA in patients 12 years and older when given 74 mcg once daily (37 mcg each nostril once daily) for the treatment of symptoms associated with seasonal and perennial allergic rhinitis. The evidence for safety is based primarily on the assessments performed in the completed phase 3 efficacy trials (060-622, 060-633, 060-634) and the open-label safety trial 060-635 (a 6 month extension of 060-633). This safety data is supplemented by the phase 2b dose ranging trial M1-602 and HPA-axis trial 060-610.

The most common AEs reported for CIC-HFA after 2-6 weeks of exposure were epistaxis, nasal discomfort/instillation site discomfort, headache, and URI. Of these, only epistaxis exhibited a dose response. Following 6 months of exposure, the most common AEs were URI, nasal discomfort/instillation site discomfort, epistaxis, nasopharyngitis, and headache. Most of the common AEs in the Respiratory, Thoracic, and Mediastinal disorders SOC demonstrated a dose response. Additionally, local AEs for both exposure periods also demonstrated a dose response. In both exposure groups, there were no apparent differences in AEs when subgrouped by age, gender, or race. Comparing the AEs between trials, overall the results were consistent.

No deaths were reported and SAEs were rare. No SAEs were likely related to CIC-HFA. However, there were 2 nasal septal perforations noted in this clinical development program. Both occurred during 2 week exposures to the 74 mcg dose (M1-602 and 060-622). No nasal septum perforations were reported in the 6 and 12 month studies. In one case, the lesion was examined by an independent ENT who noted that perforation was well healed and may have been present for months to years. This independent assessment was performed approximately 2 months after the lesion was noted by the site investigator during nasal exam. Per report, the site investigator examined a picture of the lesion taken by the independent ENT and thought it looked the same as it had 2 months previously. The 2nd case of septum perforation occurred in a patient during the dose ranging trial following 2 weeks of double blind treatment. Of note, after 1 week of single blind placebo, bilateral nasal septum erosions were noted. This patient had a history of nasal polyps status post resection (1993), nasal septum perforation (1998, location not recorded), and recurrence of nasal polyps (1999). No perforation was noted in the clinic note from 1999. Neither patient was noted to have abnormalities on nasal exam during screening. The local toxicity noted above is concerning. However, it is reassuring that in the 6 and 12 month safety studies, no additional nasal septum perforations were seen, and in preclinical studies with Alvesco (b) (4)

(b) (4), no nasal toxicity was reported. Nasal erosions/ulcerations were also noted in this development program (based on this medical officer’s review of AE verbatim terms). This AE seemed to have a dose response. Of note, ulcerations were not seen in the Omnaris development program until after marketing.

In summary, the safety database is sufficient to support the approval of ciclesonide HFA in patients 12 years and older. However, a post-marketing trial comparing the risk profile of CIC-HFA to Omnaris is warranted given the occurrence of nasal septum perforations, imbalance in local AEs, and insufficient ocular safety data in this development program.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical review of safety is based on data from phase 2b/3 PAR/SAR trials. These trials are summarized in Table 67.

Table 67. Total Patients in Safety Database (SAR and PAR)

	Placebo	Ciclesonide	Total
Total Unique Patients	967	2220	3187
Phase 2b/3 SAR/PAR short-term treatment (2-6 weeks) pooled safety data			
M1-602: Phase 2 SAR 2-week treatment study	130	383	513
060-610: Phase 3 PAR 6-week treatment study	75	111	186
060-622: Phase 3 SAR 2-week treatment study	235	472	707
060-633 [first 6 weeks]: Phase 3 PAR 6-month treatment study	307	803	1110
060-634: Phase 3 SAR 2-week treatment study	220	451	671
Phase 3 PAR chronic-treatment (6 months) study			
060-633: Phase 3 PAR 6-month treatment study	307	803	1110

Source: ISS, Table 9, pp54

Trial 060-610 was an HPA axis study and was not discussed in detail in this review, but is summarized in Section 7.3.5 and 4.4.2. The other trials in Table 67 were reviewed in depth in section 5.3. A total of 2220 patients were exposed to ciclesonide HFA at 74mcg/day or greater for ≥2 weeks. Of these, 803 patients were exposed for 6 months. The sponsor’s integrated safety summary (ISS) also presented supportive safety data from small phase 1 and 2 trials; however, for this NDA review, these data will not be discussed.

7.1.2 Categorization of Adverse Events

Adverse events were defined as any reaction, side effect or other undesirable event that occurred in conjunction with the use of study drug. Serious AEs were defined as any untoward medical occurrence that results in death, was life-threatening, required hospitalization/prolongation of hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital birth defect. All AEs were to be collected using medical terminology and mapped to system organ classes and preferred terms using MedDRA version 12.1 for the Integrated Summary of Safety (ISS). Treatment emergent AEs (TEAEs) are the focus of the analysis in the ISS. These are defined as AEs that occurred after the patient had received at least one dose of study drug.

Adverse event data was collected from the time informed consent was obtained until the end of the studies. Serious adverse event data was collected until 30 days post last dose and followed until resolution or until the patient was lost to follow-up. Non-leading questions were used to elicit adverse events. All AEs were evaluated for duration, intensity, seriousness, and causal relationship to study medication.

For TEAEs involving the nose, ulcers involving the nasal septum were coded (MedDRA PT) as nasal septum ulcers. Ulcers not including the septum were coded as nasal ulcers. Non-ulcerative nasal lesions were coded as either nasal septum disorder or nasal mucosal disorder depending on the location of the lesion. Perforations on the nasal septum were coded to the preferred term 'nasal septum perforation'. Any term related to the nose and containing 'blood', 'bloody', or 'bleed' was coded as 'epistaxis'.

For clinical laboratory tests following outside the laboratory's stated range of normal, investigators made a determination if the changes were clinically meaningful.

The sponsor was also asked to re-classify/re-analyzed specific local TEAEs that occurred in the 2-6 week exposure group. This was because some of the sponsors preferred terms (PT) seemed to unnecessarily split similar AEs into separate groups. 'Nasal septum disorder,' 'nasal mucosal disorders,' 'nasal ulcer,' and 'nasal septum ulceration' were combined into a single group (nasal mucosal/septum disorders), as the lesions described in each individual group only differed by location. The division of septum versus non-septum is somewhat arbitrary. The nasal mucosal/septum disorders group was further subdivided in the following manner:

- 1) Non-ulcerative lesions (e.g. abrasions, excoriations, scabs, irritation)
 - a) Irritation
 - b) Abrasions/excoriations/scabs
- 2) Erosions and ulcerations
 - a) Erosions
 - b) Ulcerations
- 3) Other

Nasal erosions and ulcerations were grouped together as the sponsor did not define how these lesions were differentiated. Additionally, in the individual CSR's, AEs containing the verbatim term 'erosion' were coded to 'ulceration,' but in the ISS, the verbatim term 'erosion' was coded to 'nasal mucosal disorder' or 'nasal septum disorder.' 'Instillation site discomfort' was also grouped with 'nasal discomfort' as AEs in both these groups were essentially identical.

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

In the ISS, the sponsor provided a pooled analysis of the trials summarized in Table 67. These results were divided into short term safety (2-6 week exposure) and long term safety (6 month exposure). The 2-6 week data came from Trials M1-602, 060-610, 060-622, 060-634 and 060-633 (1st 6 weeks of exposure). The 6 month data came from 060-633 and included the AEs reported at the 6 week time point also. The 1 year data came from the open label safety extension trial 060-635.

7.2 Adequacy of Safety Assessments

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

Overall the size of the safety database was adequate for this application. The extent of exposure in the short-term (2-6 weeks) trials was similar across groups. A total of 2220 patients were received at least one dose of ciclesonide, and 1935 patients received ciclesonide for >2 to ≤8 weeks. Average duration of treatment was similar between patient groups. The short-term exposure data are summarized in Table 68.

Table 68. Short Term Safety Exposure [2-6 weeks, Trials M1-602, 060-610, 060-622, 060-633 (1st 6 weeks), and 060-634]

Parameter	Category/Statistic	Placebo	Ciclesonide Dose			
			74 mcg	148 mcg	282 mcg	Total
Exposure (Days)	Mean (SD)	25.3 (14.02)	23.9 (13.41)	28.1 (14.19)	21.9(12.07)	25.9 (13.91)
Exposure Category N (%)	Single dose	8 (0.8)	1 (0.1)	4 (0.3)	1 (0.5)	6 (0.3)
	>0 to ≤1 week	14 (1.4)	11 (1.2)	7 (0.6)	2 (1.1)	20 (0.9)
	>1 to ≤2 week	120 (12.4)	119 (13.5)	120 (10.4)	20 (10.8)	259 (11.7)
	>2 to ≤4 week	454 (46.9)	464 (52.5)	471 (41)	114 (61.3)	1049 (47.3)
	>4 to ≤6 week	173 (17.9)	88 (10)	236 (20.5)	48 (25.8)	372 (16.8)
	>6 to ≤8 week	198 (20.5)	201 (22.7)	312 (27.1)	1 (0.5)	514 (23.2)
	Total	967	884	1150	186	2220

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily, 282mcg=141mcg each nostril daily

Source: ISS, Table 15, pp63

For the long- term data, (6-26 weeks), 803 patients received at least one dose of ciclesonide, 767 patients received ciclesonide for >6 to ≤29 weeks, and 432 patients received ciclesonide for >26 weeks. The total exposure for this drug meets ICH guidelines for 6 month (>300 patients). The extent of exposure was similar between patient groups. The long-term data are summarized in Table 69.

Table 69. Long Term Safety Exposure (6-26 weeks, Trial 060-633)

Parameter	Category/Statistic	Placebo	Ciclesonide Dose		
			74	148	Total
Exposure (Days)	Mean (SD)	168 (40.71)	168.9 (41.53)	170.2 (38.31)	169.7 (39.52)
Exposure Category N (%)	Single dose	4 (1.3)	1 (0.3)	2 (0.4)	3 (0.4)
	>0 to ≤1 week	1 (0.3)	1 (0.3)	0	1 (0.1)
	>1 to ≤2 week	1 (0.3)	5 (1.7)	2 (0.4)	7 (0.9)
	>2 to ≤4 week	5 (1.6)	2 (0.7)	11 (2.2)	13 (1.6)
	>4 to ≤6 week	3 (1)	5 (1.7)	7 (1.4)	12 (1.5)
	>6 to ≤13 week	8 (2.6)	11 (3.7)	11 (2.2)	22 (2.7)
	>13 to ≤26 week	131 (42.7)	105 (35.2)	208 (41.2)	313 (39)
	>26 to ≤29 week	154 (50.2)	168 (56.4)	264 (52.3)	432 (53.8)

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily

Source: ISS, Table 16, pp64

The demographic data for each study (except for 060-610) can be found in section 5.3.

7.2.2 Explorations for Dose Response

Adverse event dose response relationships were analyzed for the both the short tem (2-6 weeks) and long term (6 month) exposures. No SAEs for either exposure period showed a dose response. With regard to TEAEs, for both exposure periods a dose response was demonstrated for multiple TEAEs.

For the 2-6 week data, epistaxis and nasal septum disorders demonstrated a dose response. In the placebo, 74mcg, 148mcg, and 282mcg groups 2.8%, 2.9%, 3.5%, and 7.5% of patients, respectively, experienced epistaxis. For nasal septum disorders, 0.7%, 1%, 1.2%, and 1.6% of patients in the placebo, 74mcg, 148mcg, and 282mcg groups, respectively, reported this adverse event.

Based on the local AE re-classification/re-analysis (see 7.1.2) requested by the Division, there was some evidence of a dose response for 'nasal mucosal/septum disorders.' In the placebo, 74mcg, 148mcg, and 282mcg groups 1.8%, 1.8%, 2.0%, and 2.2% of patients, respectively, experienced a nasal mucosal/septum disorder. A dose response was also evident for nasal lesions described as abrasions/excoriations/scabs (in the placebo, 74mcg, 148mcg, and 282mcg groups 0.1%, 0.2%, 0.6%, and 1.1% of patient, respectively).

Based on the sponsor's original AE classifications, for the 6 month data, the 3 following TEAEs demonstrated a dose response:

1. Nasal discomfort (0.7%, 2.7%, and 3% of patients from the placebo, 74 mcg and 148 mcg groups, respectively)
2. Nasal septum disorder (1%, 1.7%, and 2.8% of patients, respectively)
3. Nasal mucosal disorder (0.3%, 2%, and 2.6% of patients, respectively)

The 6 month local TEAEs were also re-classified/re-analyzed (as described in section 7.1.2). Based on this, the following local TEAEs also demonstrated a dose response:

1. Nasal mucosal/septum disorders (2.9%, 3.7%, and 5.9% of patients from the placebo, 74 mcg and 148 mcg groups, respectively)
2. Nasal irritation (1.3%, 2%, and 2.0% of patients from the placebo, 74 mcg and 148 mcg groups, respectively)
3. Nasal abrasion/excoriation/scab (0.3%, 1.7%, and 2.4% of patients from the placebo, 74 mcg and 148 mcg groups, respectively)
4. Nasal erosion (0.3%, 0.7%, and 1.4% of patients from the placebo, 74 mcg and 148 mcg groups, respectively)

In addition, URI and epistaxis were also more frequent in ciclesonide groups compared to placebo, though they did not follow a dose response. For URI, 9.4%, 14.4%, and 12.9% of patients in the placebo, 74 mcg and 148 mcg groups, respectively reported this AE. Epistaxis was reported by 7.8%, 11.4%, and 11.3% of patients in the placebo, 74 mcg and 148 mcg groups, respectively. Also the re-classified/re-analyzed AE of 'nasal discomfort' for the 6 month exposure data was also far more frequent in the CIC-HFA groups compared to placebo (0.7% and 5.2% for placebo versus all CIC-HFA groups). The reported dose response for the above stated AEs is not surprising and is similar to other nasal corticosteroids.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

Clinical laboratory testing was performed in each trial as per Table 4, Table 12, and Table 31. The assayed labs and their normal ranges are summarized in Table 70.

Table 70. Routine Labs and Ranges

Parameter (Normal Range)	Potentially Clinically Significant Low	Potentially Clinically Significant High
Hematology		
WBC (4.5-13.5 x 10 ⁹ /L)	≤ 2.8 x 10 ⁹ /L	≥ 16 x 10 ⁹ /L
Neutrophils (40.0-72.0%)	≤ 15%	≥ 85%
Lymphocytes (22.2-45.0%)	NA	≥ 75%
Monocytes (0.0-12.0%)	NA	≥ 15%
Eosinophils (0.0-4.5%)	NA	≥ 10%
Basophils (0.0-1.8%)	NA	≥ 10%
Hemoglobin (Female: 11.2-16.0 g/dL; Male: 11.8-17.5 g/dL)		
6 months-13 years	≤ 9.5 g/dL	≥ 17.5 g/dL
14-18 years		
Female	≤ 9.5 g/dL	≥ 17.5 g/dL
Male	≤ 11.5 g/dL	≥ 19.0 g/dL
> 18 years		
Female	≤ 9.5 g/dL	≥ 17.5 g/dL
Male	≤ 11.5 g/dL	≥ 19.0 g/dL
Hematocrit (Female: 34.3-48.9%; Male: 35.4-54.1%)		
6 months-13 years	< 30%	> 50%
14-18 years		
Female	< 32%	> 54%
Male	< 37%	> 60%
> 18 years		
Female	≤ 32%	≥ 54%
Male	≤ 37%	≥ 60%
RBC (3.8-5.9 x 10 ¹² /L)	≤ 3.5 x 10 ¹² /L	≥ 6.4 x 10 ¹² /L
Platelet count (130-442 x 10 ⁹ /L)	≤ 75 x 10 ⁹ /L	≥ 700 x 10 ⁹ /L
Chemistry		
Sodium (135-148 mmol/L)	≤ 126 mmol/L	≥ 156 mmol/L
Potassium (3.5-5.3 mmol/L)	≤ 3 mmol/L	≥ 6 mmol/L
Chloride (98-109 mmol/L)	≤ 90 mmol/L	≥ 118 mmol/L
Bicarbonate (23-30 mmol/L)	≤ 16 mmol/L	≥ 35 mmol/L
Calcium (8.4-10.7 mg/dL)	< 8.2 mg/dL	≥ 12 mg/dL
Magnesium (1.2-2.1 mEq/L)	< 1.2 mEq/L	> 2.3 mEq/L
Phosphate (2.4-5.4 mg/dL)	≤ 1.7 mg/dL	≥ 5.3 mg/dL
AST (0-45 U/L)	NA	3 x ULN
ALT (0-55 U/L)	NA	3 x ULN
Alkaline phosphatase (37-483 U/L)	NA	3 x ULN
Creatinine Female (0.5-1.1 mg/dL) Male (0.5-1.3 mg/dL)	NA	≥ 2 mg/dL
BUN (6-23 mg/dL)	NA	≥ 30 mg/dL
Total bilirubin (0.3-1.5 mg/dL)	NA	≥ 2 mg/dL
Total protein (5.9-8.1 g/dL)	≤ 4.5 g/dL	≥ 10 g/dL
Albumin (3.2-5.4 g/dL)	≤ 2.5 g/dL	NA
Uric Acid Female (2.4-7.6 mg/dL) Male (2.4-8.7 mg/dL)	NA	≥ 8.5 mg/dL ≥ 10.5 mg/dL
Glucose, random (56-115 mg/dL)	≤ 40 mg/dL	≥ 175 mg/dL
Urinalysis		
Protein (Negative)	NA	> 2+
Ketones (Negative)	NA	4+
Glucose (Negative)	NA	4+

Source: ISS, Table 7, pp49

7.2.5 Metabolic, Clearance, and Interaction Workup

Specific metabolic, clearance and interaction safety studies were not conducted for this development program. However reference was made to the Omnaris program (NDA 22,004). This is acceptable because Omnaris contains the same active ingredient as CIC-HFA.

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

Given the known potential for HPA axis suppression with inhaled corticosteroids, the sponsor conducted several HPA axis studies (trials FHP-017, M1-601, and 060-010). In trials FHP-017 and M1-601, serum cortisol AUC_{0-24hr} was measured after 7 daily doses of CIC-HFA at 282 mcg and 14 daily doses at 148 or 282 mcg, respectively. Trial 060-010 assessed HPA axis effects of CIC-HFA (serum cortisol AUC_{0-24hr}) after 6 weeks of exposure.

Nasal exams were also conducted at each study visit in all pivotal trials to assess for local corticosteroid related AEs. No ophthalmic examinations were performed as data were available from the Omnaris (ciclesonide aqueous nasal spray) development program. Trials from that program demonstrated that there were some minor differences in intraocular pressure and cataract formation in patients who received Omnaris versus placebo. However, after review by the primary reviewer and an FDA ophthalmologist, it was concluded that the findings did not represent a risk above and beyond that seen with other nasal steroids, and that overall, there was no evidence of an adverse effect of ciclesonide treatment on the ophthalmologic tract. While there was agreement at the pre-IND meeting that the Omnaris ocular safety would be sufficient, new information submitted in this NDA brought that agreement into question. Specifically, CIC-HFA has significantly higher retention in the nasal cavity and also has increased systemic exposure compared to Omnaris. Due to these differences, Nycomed will be required to submit further ocular safety data.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in this development program.

7.3.2 Nonfatal Serious Adverse Events

In the 2-6 week exposure group (trials M1-602, 060-610, 060-622, 060-634, and 1st 6 weeks of 060-633), 6 patients reported 8 treatment emergent SAEs. These were evenly distributed across patient groups (placebo=0.1%, 74 mcg= 0.2%, 148 mcg=0.3%, and 282 mcg=0%). The SAEs were as follows:

Placebo group:

1. Patient 060-633-0038/S001: SAE- hypertension and atrioventricular heart block. Patient was discontinued.

CIC-HFA 74mcg (37 mcg each nostril daily):

1. Patient 060-633-0017/S057: SAE- suicidal ideation. The patient was 28 year old female with a history of depression. This resolved after a 3 day hospitalization. Patient was discontinued. This SAE was included in both the 2-6 week exposure group and the 6 month exposure group.
2. Patient 060-633-0010/S034: SAE- ovarian cyst and pelvic adhesions. The patient was 31 year old female with a history of endometriosis, bilateral, ovarian cysts, pelvic adhesions, prior laparoscopy, and ovarian cyst. Completed trial.

CIC-HFA 148 mcg (74 mcg each nostril daily):

1. Patient 060-633-0007/S018: SAE-GERD. The patient was a 48 year old woman with a history of hypertension and constipation. Completed trial.
2. Patient 060-633-0029/S018: SAE- diverticular perforation. The patient was a 57 year old woman with a history of diverticulosis (colonoscopy prior to enrollment), hypertension, hypothyroidism. Patient was discontinued.
3. Patient 060-633-0029/S024: SAE- breast cancer. The patient was a 40 year old woman without significant medical history except for SAR/PAR. Patient completed study. SAE was considered ongoing at end of trial. This SAE was included in both the 2-6 week exposure group and the 6 month exposure group.

The SAEs reported for the 2-6 week exposure groups were not likely related to ciclesonide exposure. Aside from the breast cancer SAE, all patients had factors that would have predisposed them to developing the reported SAE.

In the 6 month exposure group (trial 060-633), treatment emergent SAEs were similar between groups and ranged between 1.6-2%. A total of 20 patients reported 28 treatment emergent SAEs. Of these, 9 patients discontinued as a result. The 6 month exposure data included the same SAEs from the 1st 6 weeks of trial 060-633 that were reported in the 2-6 week exposure group. The SAEs are summarized Table 71.

Table 71. Serious Adverse Events After 6 months of Exposure

Ciclesonide Dose	Placebo (n=307)		CIC-HFA 74 mcg (n=298)		CIC-HFA 148 mcg (n=505)		Overall (n=1110)	
	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N	Subject N (%)	Event N
Overall	6 (2.0)	8	6 (2.0)	7	8 (1.6)	13	20 (1.8)	28
Blood and Lymphatic System Disorders	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Thrombocytopenia	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Cardiac Disorders	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Atrioventricular block	1 (0.3)	1	0	0	0	0	1 (0.1)	1

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second degree								
Gastrointestinal Disorders	2 (0.7)	2	0	0	2 (0.4)	4	4 (0.4)	6
Colonic atony	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Diverticular perforation	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Megacolon	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Pancreatitis	2 (0.7)	2	0	0	0	0	2 (0.2)	2
Vomiting	0	0	0	0	1 (0.2)	1	1 (0.1)	1
General Disorders and Administration Site Conditions	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Hernia obstructive	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Infections and Infestations	0	0	2 (0.7)	2	0	0	2 (0.2)	2
Appendicitis	0	0	1 (0.3)	1	0	0	1 (0.1)	1
Pneumonia	0	0	1 (0.3)	1	0	0	1 (0.1)	1
Musculoskeletal and Connective Tissue Disorders	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Scleroderma	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Neoplasms Benign, Malignant and Unspecified	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Breast Cancer	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Nervous System Disorders	0	0	0	0	2 (0.4)	2	2 (0.2)	2
Embolic cerebral infarction	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Mononeuropathy multiplex	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Pregnancy, Puerperium and Perinatal Conditions	1 (0.3)	1	1 (0.3)	1	1 (0.2)	1	3 (0.3)	3
Abortion	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Abortion spontaneous	1 (0.3)	1	1 (0.3)	1	0	0	2 (0.2)	2
Psychiatric Disorders	0	0	1 (0.3)	1	0	0	1 (0.1)	1
Suicidal ideation	0	0	1 (0.3)	1	0	0	1 (0.1)	1
Reproductive System and Breast Disorders	1 (0.3)	1	2 (0.7)	3	1 (0.2)	2	4 (0.4)	6
Cystocele	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Menorrhagia	0	0	1 (0.3)	1	0	0	1 (0.1)	1
Ovarian cyst	1 (0.3)	1	1 (0.3)	1	0	0	2 (0.2)	2
Pelvic adhesions	0	0	1 (0.3)	1	0	0	1 (0.1)	1
Rectocele	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Respiratory, Thoracic, and Mediastinal Disorders	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Respiratory failure	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Social Circumstances	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Imprisonment	0	0	0	0	1 (0.2)	1	1 (0.1)	1
Vascular Disorders	1 (0.3)	1	0	0	0	0	1 (0.1)	1
Hypertension	1 (0.3)	1	0	0	0	0	1 (0.1)	1

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily

Source: ISS, Table 24, pp79-80

The reported SAEs were primarily isolated occurrences (based on preferred term), except for abortion/spontaneous abortion which was reported in one patient in each of the three groups. Of the 28 reported SAEs, only 3 at the 74 mcg dose and 2 at the 148 mcg were thought to be potentially reflective of potential systemic corticosteroid effects by the sponsor. For the 74 mcg group, these included suicidal ideation, pneumonia, and appendicitis. The suicidal ideation was described in the preceding paragraph (060-633-

0017/S057). The pneumonia (patient 060-633-0027/S005, 74mcg) occurred in a 15 year old patient with asthma and a history a complicated pneumonia (18 months prior). The pneumonia was diagnosed on day 41 of treatment. The appendicitis (patient 060-633-0048/S014, 74 mcg) occurred in 17 year old female with SAR/PAR on day 94 of treatment. The pneumonia could have potentially been related to the systemic effects of corticosteroids, but due to the isolated nature of this event, causality cannot be assigned.

In the 148 mcg group, potentially related SAEs, as determined by the sponsor, included thrombocytopenia and mononeuropathy multiplex and scleroderma. In the patient with thrombocytopenia (060-633-0009/S016), the patient had a personal history of easy bruising and frequent nose bleeds, and a family history of bleeding. For the patient with the AE of scleroderma and mononeuropathy multiplex, the patient had a history of scleroderma. This patient also reported the SAEs of colonic atony and megacolon. For both these patients, the SAE was more likely related to an underlying medical history versus ciclesonide exposure.

Overall, almost all SAEs reported for both the short term and long term exposures were isolated events. As such causality cannot be assigned. For the SAEs that could potentially have been related to corticosteroid exposure, after examination of the narratives, there did not appear to be a likely relationship.

7.3.3 Dropouts and/or Discontinuations

Patient Disposition

In the 2-6 week exposure group (trials M1-602, 060-610, 060-622, 060-634, and 1st 6 weeks of 060-633), approximately 94% of patients completed their studies.

Discontinuation was highest in the placebo group. The most common reasons for discontinuation in order of frequency were AEs, withdrawal of consent, other, protocol violation, lost to follow-up, and physician decision. These results are summarized in Table 72.

Table 72. Patient Discontinuation during 2-6 Week Exposure

Ciclesonide Dose	Placebo (n=967)		74 mcg (n=884)		148 mcg (n=1150)		282 mcg (n=186)		Total Ciclesonide (n=2220)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Completed the study	911	(94.2)	847	(95.8)	1110	(96.5)	179	(96.2)	2136	(96.2)
Discontinued early	56	(5.8)	37	(4.2)	40	(3.5)	7	(3.8)	84	(3.8)
Adverse event	13	(1.3)	10	(1.1)	10	(0.9)	1	(0.5)	21	(0.9)
Withdrawal of consent	19	(2.0)	10	(1.1)	8	(0.7)	3	(1.6)	21	(0.9)
Other	15	(1.6)	6	(0.7)	12	(1.0)	2	(1.1)	20	(0.9)
Protocol violation	2	(0.2)	3	(0.3)	5	(0.4)	1	(0.5)	9	(0.4)
Lost to follow-up	5	(0.5)	7	(0.8)	2	(0.2)	0		9	(0.4)
Physician decision	2	(0.2)	1	(0.1)	3	(0.3)	0		4	(0.2)

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily, 282mcg=141mcg each nostril daily
 Source: ISS, Table 10, pp56

AEs, withdrawal of consent and other were more frequent in the placebo group compared to ciclesonide groups. The most common reason cited for other and withdrawal of consent was lack of efficacy.

In the 6 month exposure group, at least 86% of patients across all groups completed the study. The 3 most common reasons for discontinuation were withdrawal of consent, AE, or lost to follow-up. More patients in the CIC-HFA groups discontinued due to lost to follow-up and AEs compared to the placebo group. The most common reasons for withdrawal of consent were relate to patient inconvenience or relocation. These results are summarized in Table 73.

Table 73. Patient Discontinuation During 6 Month Exposure

Ciclesonide Dose	Placebo (n=307)		74 mcg (n=298)		148 mcg (n=505)		Total Ciclesonide (n=803)	
	N	(%)	N	(%)	N	(%)	N	(%)
Completed the study	265	(86.3)	261	(87.6)	439	(86.9)	700	(87.2)
Discontinued early	42	(13.7)	37	(12.4)	66	(13.1)	103	(12.8)
Withdrawal of consent	12	(3.9)	13	(4.4)	15	(3.0)	28	(3.5)
Adverse event	6	(2.0)	8	(2.7)	16	(3.2)	24	(3.0)
Lost to follow-up	4	(1.3)	8	(2.7)	9	(1.8)	17	(2.1)
Other	13	(4.2)	4	(1.3)	11	(2.2)	15	(1.9)
Protocol violation	4	(1.3)	2	(0.7)	8	(1.6)	10	(1.2)
Physician decision	3	(1.0)	2	(0.7)	7	(1.4)	9	(1.1)

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily
 Source: ISS, Table 11, pp57

Discontinuation related to TEAEs-- 2-6 weeks exposure.

In the 2-6 week exposure group (trials M1-602, 060-610, 060-622, 060-634, and 1st 6 weeks of 060-633), 35 patients discontinued study medication due to TEAEs. These were fairly evenly distributed across patient groups (placebo=1.3%, 74 mcg= 1.2%, 148 mcg=0.9%, 282 mcg=0.5%). The fewest TEAEs leading to discontinuation were

reported in the highest dose group. The TEAEs leading to discontinuation are summarized in Table 74.

Table 74. Treatment Emergent Adverse Events Leading to Discontinuation During the 2-6 Week Exposure Period.

Ciclesonide Dose	Placebo (n=967)	CIC-HFA 74 mcg (n=884)	CIC-HFA 148 mcg (n=1150)	CIC-HFA 282 mcg (n=186)	CIC-HFA Total (n=2220)
System Organ Class/ Preferred Term	Subject N(%)	Subject N(%)	Subject N(%)	Subject N(%)	Subject N(%)
Overall	13 (1.3)	11 (1.2)	10 (0.9)	1 (0.5)	22 (1)
Infections Infestations	7 (0.7)	7 (0.8)	3 (0.3)	0	10 (0.5)
Sinusitis	2 (0.2)	2 (0.2)	1 (0.1)	0	3 (0.1)
Bronchitis	1 (0.1)	2 (0.2)	0	0	2 (0.1)
Ear Infection	0	1 (0.1)	0	0	1 (0.05)
Tonsillitis	0	1 (0.1)	0	0	1 (0.05)
Pharyngitis Strep	0	1 (0.1)	0	0	1 (0.05)
URI	1 (0.1)	1 (0.1)	0	0	1 (0.05)
Pharyngitis	0	0	1 (0.1)	0	1 (0.05)
Influenza	1 (0.1)	0	1 (0.1)	0	1 (0.05)
Fungal Infection	1 (0.1)	0	0	0	0
Nasopharyngitis	1 (0.1)	0	0	0	0
Otitis Media	1 (0.1)	0	0	0	0
Viral URI	1 (0.1)	0	0	0	0
Respiratory, Thoracic, & Mediastinal Disorders	3 (0.3)	1 (0.1)	2 (0.2)	1 (0.5)	4 (0.2)
Nasal Septum Disorder	0	0	2 (0.2)	0	2 (0.1)
Nasal Dryness	0	0	1 (0.1)	0	1 (0.05)
Epistaxis	1 (0.1)	0	1 (0.1)	0	1 (0.05)
Nasal Discomfort	0	0	0	1 (0.5)	1 (0.05)
Asthma	1 (0.1)	0	0	0	0
Rhinitis Seasonal	1 (0.1)	0	0	0	0
Skin & Subcutaneous Tissue Disorders	0	1 (0.1)	2 (0.2)	0	3 (0.1)
Rash Papular	0	1 (0.1)	0	0	1 (0.05)
Rash	0	0	1 (0.1)	0	1 (0.05)
Urticaria	0	0	1 (0.1)	0	1 (0.05)
Psychiatric Disorder	1 (0.1)	1 (0.1)	1 (0.1)	0	2 (0.1)
Suicidal Ideation	0	1 (0.1)	0	0	1 (0.05)
Insomnia	1 (0.1)	0	1 (0.1)	0	1 (0.05)
General Disorders and Administrative Site Conditions	0	1 (0.1)	0	0	1 (0.05)
Instillation site discomfort	0	1 (0.1)	0	0	1 (0.05)
Immune System Disorder	0	1 (0.1)	0	0	1 (0.05)
Drug Hypersensitivity	0	1 (0.1)	0	0	1 (0.05)
Nervous System Disorder	1 (0.1)	1 (0.1)	0	0	1 (0.05)

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Headache	0	1 (0.1)	0	0	1 (0.05)
Sinus Headache	0	1 (0.1)	0	0	1 (0.05)
Migraine	1 (0.1)	0	0	0	0
GI disorders	1 (0.1)	0	1 (0.1)	0	1 (0.05)
Diverticular Perforation	0	0	1 (0.1)	0	1 (0.05)
Nausea	1 (0.1)	0	0	0	0
Vomiting	1 (0.1)	0	0	0	0
Investigations	0	0	1 (0.1)	0	1 (0.05)
AST increase	0	0	1 (0.1)	0	1 (0.05)
ALT increase	0	0	1 (0.1)	0	1 (0.05)
Cardiac Disorders	1 (0.1)	0	0	0	0
AV block, 2 nd degree	1 (0.1)	0	0	0	0
Eye Disorder	1 (0.1)	0	0	0	0
Conjunctivitis	1 (0.1)	0	0	0	0
Vascular Disorders	1 (0.1)	0	0	0	0
Hypertension	1 (0.1)	0	0	0	0

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily, 282mcg=141mcg each nostril daily
 Source: ISS, Table 25, pp83-84

The SOC with the most TEAEs leading to discontinuation was Infections and Infestations. The TEAEs were most common on the placebo group. There was no correlation with ciclesonide dose. Except for bronchitis and sinusitis, all TEAEs leading to discontinuation were isolated events. Time to onset of AEs (approximately 7 days) was also similar between dose groups, and did not suggest a dose response.

Discontinuations related to local TEAEs at 2-6 weeks of exposure:

After 2-6 weeks of exposure 19 patients withdrew from treatment due to local treatment adverse events. Overall, local TEAEs leading to discontinuation were similar. From the placebo, 74 mcg, 148 mcg, and 282 mcg groups; 7 (0.7%), 7 (0.8%), 4 (0.3), and 1(0.5) patients, respectively withdrew due to local TEAEs. These are summarized in Table 75.

Table 75. Local TEAEs Leading to Discontinuation During 2-6 Weeks of Exposure

Ciclesonide Dose	Placebo (n=967)	CIC-HFA 74 mcg (n=884)	CIC-HFA 148 mcg (n=1150)	CIC-HFA 282 mcg (n=186)	CIC-HFA Total (n=2220)
Preferred Term	Subject n(%)	Subject n(%)	Subject n(%)	Subject n(%)	Subject n(%)
Overall	7 (0.7)	7 (0.8)	4 (0.3)	1 (0.5)	12 (0.5)
Epistaxis	1 (0.1)	0	1 (0.1)	0	1(0.05)
Nasopharyngitis	1 (0.1)	0	0	0	0
Otitis Media	1 (0.1)	0	0	0	0
Rhinitis Seasonal	1 (0.1)	0	0	0	0
Sinusitis	2 (0.2)	2 (0.2)	1 (0.1)	0	3 (0.1)
URI	1 (0.1)	1 (0.1)	0	0	1(0.05)
Viral URI	1 (0.1)	0	0	0	
Ear infection	0	1 (0.1)	0	0	1(0.05)
Instillation site/nasal discomfort	0	1 (0.1)	0	1 (0.5)	2(0.1)
Nasal Dryness	0	1 (0.1)	1 (0.1)	0	2(0.1)
Pharyngitis Strept	0	1 (0.1)	0	0	1 (0.05)
Pharyngitis	0	0	1 (0.1)	0	1 (0.05)
Sinus headache	0	1 (0.1)	0	0	1 (0.05)
Nasal Septum Disorder	0	0	2 (0.2)	0	2 (0.1)
Tonsillitis	0	1 (0.1)	0	0	1 (0.05)

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily, 282mcg=141mcg each nostril daily

Although overall numbers were similar, when examining particular local TEAEs of interest, some imbalances were present. Discontinuations due to nasal septum disorders were present only in the CIC-HFA 148 mcg dose group. In one patient (060-633-0015/S002), bilateral nasal crusting of the anterior septum was noted on day 43 of treatment. Previously, the patient had reported epistaxis on 2 separate occasions, originating from the left anterior septum. Based on these events, the patient was discontinued. When seen for follow up, after cessation of CIC-HFA, the AEs had resolved. The investigator felt these were related to CIC-HFA. In the other patient (060-633-0029/S034), a nasal septum abrasion was identified during ENT exam on day 43 of treatment. This was treated with Nasacort and saline gel and assessed as possibly related to treatment. This was not resolved at the end of study visit. Additionally, nasal discomfort as a reason for withdrawal was only cited in CIC-HFA patients (2). Patient 060-633-0015/S008, had repeated reports of nasal discomfort (instillation site discomfort) occurring intermittently while on CIC-HFA 74 mcg. She also reported nasal dryness and was noted to have mild epistaxis originating from the anterior turbinate. Due to these events, she was discontinued. The investigator felt that the AEs were definitely related to CIC-HFA. This patient recovered. Patient M1-602-5223/S766 also discontinued due to nasal discomfort. This patient was treated with CIC-HFA 282mcg. For both patients the discomfort was described as burning. As there were relative few local TEAEs leading to discontinuation, these were not re-classified/re-analyzed as in sections 7.1.2

Discontinuations related to TEAEs--6 month exposure.

After 6 months of double-blind treatment, 30 patients withdrew due to TEAEs. From the placebo, 74 and 148 mcg groups, 6 (2%), 8 (2.7%), and 16 (3.2%) patients withdrew related to TEAEs. As compared to the short term data, at 6 months, there is some suggestion of a dose response. TEAEs leading to discontinuation are summarized in Table 76.

Table 76. Treatment Emergent Adverse Events Leading to Discontinuation During the 6 Month Exposure Period.

Ciclesonide Dose	Placebo (N=307)	CIC-HFA 74 mcg (N=298)	CIC-HFA 148 mcg (N=505)	CIC-HFA Total (N=803)
System Organ Class/ Preferred Term	Subject N(%)	Subject N(%)	Subject N(%)	Subject N(%)
Overall	6 (2)	8 (2.7)	16 (3.2)	24 (3.0)
Respiratory, Thoracic, & Mediastinal Disorders	1 (0.3)	3 (1)	7 (1.4)	10(1.2)
Epistaxis	1 (0.3)	2 (0.7)	2 (0.4)	4 (0.5)
Nasal Mucosal Disorder	0	0	3 (0.6)	3 (0.4)
Asthma	0	0	2 (0.4)	2 (0.2)
Nasal Septum Disorder	0	0	2 (0.4)	2 (0.2)
Nasal Dryness	0	1 (0.3)	1 (0.2)	2 (0.2)
Nervous System Disorder	0	1 (0.3)	4 (0.8)	5 (0.6)
Headache	0	1 (0.3)	1 (0.2)	2 (0.2)
Sinus Headache	0	1 (0.3)	0	1 (0.1)
Dizziness	0	0	1 (0.2)	1 (0.1)
Embolic cerebral infarct	0	0	1 (0.2)	1 (0.1)
Mononeuropathy multiplex	0	0	1 (0.2)	1 (0.1)
Infections and Infestations	2 (0.7)	4 (1.3)	0	4 (0.5)
Lobar pneumonia	0	1 (0.3)	0	1 (0.1)
Pneumonia	0	1 (0.3)	0	1 (0.1)
URI	0	1 (0.3)	0	1 (0.1)
Sinusitis	1 (0.3)	1 (0.3)	0	2 (0.2)
Bronchitis	1 (0.3)	0	0	0
Fungal infection	1 (0.3)	0	0	0
GI disorders	1 (0.3)	0	2 (0.4)	2 (0.2)
Colonic Atony	0	0	1 (0.2)	1 (0.1)
Diverticular Perforation	0	0	1 (0.2)	1 (0.1)
Megacolon	0	0	1 (0.2)	1 (0.1)
Pancreatitis	1 (0.3)	0	0	0
Pregnancy, Puerperium, & Perinatal Conditions	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)
Abortion spontaneous	0	1 (0.3)	1 (0.2)	2 (0.2)
Abortion	0	0	1 (0.2)	1 (0.1)
High-risk pregnancy	1 (0.3)	0	0	0
General Disorders & Administrative Site Conditions	0	1 (0.3)	0	1 (0.1)
Instillation site discomfort	0	1 (0.3)	0	1 (0.1)
Psychiatric Disorders	0	1 (0.3)	0	1 (0.1)
Suicidal ideation	0	1 (0.3)	0	1 (0.1)

Investigations	0	0	1 (0.2)	1 (0.1)
ALT	0	0	1 (0.2)	1 (0.1)
AST	0	0	1 (0.2)	1 (0.1)
Musculoskeletal & Connective Tissue Disorders	0	0	1 (0.2)	1 (0.1)
Scleroderma	0	0	1 (0.2)	1 (0.1)
Skin & Subcutaneous Tissue Disorders	0	0	1 (0.2)	1 (0.1)
Urticaria	0	0	1 (0.2)	1 (0.1)
Social Circumstances	0	0	1 (0.2)	1 (0.1)
Imprisonment	0	0	1 (0.2)	1 (0.1)
Cardiac Disorders	1 (0.3)	0	0	0
Atrioventricular block 2nd degree	1 (0.3)	0	0	0
Vascular Disorders	1 (0.3)	0	0	0
Hypertension	1 (0.3)	0	0	0

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily
 Source: ISS, Table 26, pp86

The SOC with the most TEAEs leading to discontinuation was Respiratory, Thoracic, and Mediastinal Disorders. The TEAEs reported were primarily local nasal TEAEs. The Respiratory, Thoracic, and Mediastinal Disorders SOC also demonstrated a dose response, and was the primary driver in the overall dose response seen in TEAEs leading to discontinuation. Aside from TEAEs in the Respiratory, Thoracic, and Mediastinal Disorder, TEAEs leading to discontinuation were isolated events.

Discontinuations related to local TEAEs--6 month exposure.

In the 6 months exposure group, 19 patients withdrew due to local TEAEs. Overall, discontinuations due to local TEAEs were more frequent in CIC-HFA treatment groups compared to placebo. These results are summarized in Table 77.

Table 77. Local TEAEs leading to discontinuation after 6 months of exposure

Ciclesonide Dose	Placebo (n=307)	CIC-HFA 74 mcg (n=298)	CIC-HFA 148 mcg (n=505)	CIC-HFA Total (n=803)
System Organ Class/ Preferred Term	Subject N(%)	Subject N(%)	Subject N(%)	Subject N(%)
Overall	2 (0.7)	5 (1.7)	5 (1)	10 (1.2)
Epistaxis	1 (0.3)	2 (0.7)	2 (0.4)	4 (0.5)
Nasal Dryness	0	1 (0.3)	1 (0.2)	2 (0.2)
Nasal Septum Disorder	0	0	1 (0.2)	1 (0.1)
Nasal Mucosal Disorder	0	0	3 (0.6)	3 (0.4)
Instillation Site discomfort	0	1 (0.3)	0	1 (0.1)
Sinus Headache	0	1 (0.3)	0	1 (0.1)
Sinusitis	1 (0.3)	1 (0.3)	0	1 (0.1)
URI	0	1 (0.3)	0	1 (0.1)

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily

For the 6 month exposure data, the imbalance in local TEAEs leading to discontinuation was more pronounced compared to the 2-6 week data. Discontinuation due to nasal dryness, nasal mucosal disorders, nasal septum disorders, and instillation site discomfort only occurred in CIC-HFA patients.

In the 74 mcg treatment group, 5 patients withdrew due to local TEAEs. Patient 060-633-001/S016 withdrew consent at day 43 of treatment following several episodes of moderate to severe epistaxis originating from the left nostril. On ENT exam, she was noted to have dry and irritated nasal septum mucosa. Patient 060-633-0015/S008 discontinued due to instillation site discomfort, and was discussed previously. Patient 060-633-0018/S028 was discontinued due to 3 episodes of epistaxis that were mild to moderate in severity. Patient 060-633-0031/S013 was discontinued due to sinusitis and was treated with antibiotics. Patient 060-633-0047/S011 was discontinued due to an URI. She was treated with Claritin, prednisone, and pseudoephedrine. All TEAEs were resolved at the end of study. All TEAEs except for sinusitis and URI were deemed possibly related to study medication.

In the 148 mcg dose group, 5 patients withdrew due to local TEAEs. Patient 060-633-0015/S002 withdrew due to epistaxis, nasal septum disorder, and nasal dryness. This patient has been previously discussed. Patient 060-633-0018/S014 discontinued due to epistaxis and nasal mucosal disorder (nasal erosion) noted at treatment day 146. Her symptoms improved following cessation of CIC-HFA. The TEAEs were deemed as definitely related. Patient 060-633-0029/S017 and 060-633-0029/S020 both withdrew due to nasal mucosal disorder (abrasion). In both patients, the lesions were noted on multiple occasions during treatment. Both patients were treated symptomatically with saline gel and ocean spray. On follow up visits, the lesions were still evident, though improved in one patient. Both were deemed as possibly related to treatment. Patient 060-633-0029/S034 was discontinued due to nasal septum disorder (abrasion), and discussed previously.

Overall, in the short term exposure data (2-6 weeks), discontinuations due to TEAEs were similar between placebo and CIC-HFA groups. However, when examining local TEAEs that lead to discontinuation, nasal septum disorder, nasal dryness, and instillation site discomfort occurred only in the CIC-HFA groups. The occurrence of these TEAEs in only the CIC-HFA groups imply that were likely related to local toxicity of CIC-HFA.

When examining the 6 month safety data, an imbalance in TEAEs leading to discontinuation is obvious. This imbalance can be seen when examining all TEAEs, and is further accentuated when analyzing the local TEAEs. This is not necessarily surprising given the known local effects of nasal corticosteroids and the relatively high nasal deposition of this product.

7.3.4 Significant Adverse Events

In this section, severe AEs will be discussed. Local AEs were considered significant, but will be discussed in section 7.3.5. AEs leading to drop out /discontinuation were also considered significant, but were discussed in 7.3.3.

In the 2-6 week exposure group, the majority of AEs across group were mild to moderate. The SOC with most frequent severe AEs was nervous system disorders, with an incidence of 0.5%, 0.7%, 0.9% and 0.5% in the placebo, 74, 148, and 282 mcg groups, respectively. The next most common SOC was infections and infestations with an incidence 1%, 0.5%, 0.4% and 0.4% in the placebo, 74, 148, and 282 mcg groups, respectively. The most common severe AEs were headache, sinus headache and instillation site discomfort. Headache and instillation site discomfort were only reported in the ciclesonide groups. These events are summarized in Table 78.

Table 78. Severe TEAEs Experienced by ≥2 Patients During the 2-6 Week Exposure

Ciclesonide Dose	Placebo (n=967)		CIC-HFA 74 mcg (n=884)		CIC-HFA 148 mcg (n=1150)		CIC-HFA 282 mcg (n=186)		Total Ciclesonide (n=2220)	
	Subject	(%)	Subject	(%)	Subject	(%)	Subject	(%)	Subject	(%)
System Organ Class/ Preferred Term										
Overall	29	(3.0)	16	(1.8)	34	(3.0)	8	(4.3)	58	(2.6)
Nervous System Disorders	4	(0.4)	6	(0.7)	10	(0.9)	1	(0.5)	17	(0.8)
Headache	0		4	(0.5)	5	(0.4)	0		9	(0.4)
Sinus headache	2	(0.2)	2	(0.2)	3	(0.3)	1	(0.5)	6	(0.3)
Migraine	2	(0.2)	0		2	(0.2)	0		2	(0.1)
Infections & Infestations	0		2	(0.2)	1	(0.1)	0		3	(0.1)
Gastroenteritis	0		2	(0.2)	1	(0.1)	0		3	(0.1)
General Disorders & Administrative Site Conditions	0		2	(0.2)	1	(0.1)	1	(0.5)	4	(0.2)
Instillation site discomfort	0		2	(0.2)	1	(0.1)	1	(0.5)	4	(0.2)
Musculoskeletal & Connective Tissue Disorders	0		0		2	(0.2)	0		2	(0.1)
Pain in extremity	0		0		2	(0.2)	0		2	(0.1)

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily, 282mcg=141mcg each nostril daily
 Source: ISS, Table 37, pp106

For the 6 month exposure data, most the AEs were mild to moderate. The overall incidence of severe SAE was the lowest in the 74 mcg dose group. The most common SOC with severe AEs was infections and infestations, with an incidence of 2.3%, 2%, and 3.6% in the placebo, 74, and 148 mcg groups, respectively. The next most common

SOC was nervous system disorders with an incidence 1.6%, 1.3%, and 1.8% in the placebo, 74, and 148 mcg groups, respectively. In the ciclesonide treated groups, the most common severe AEs were URI, headache, nasopharyngitis, and sinus headache. These events are summarized in Table 79.

Table 79. Severe TEAEs Experienced by ≥2 Patients During the 6 Month Exposure

Ciclesonide Dose	Placebo (n=307)		74 mcg (n=298)		148 mcg (n=505)		Total Ciclesonide (n=803)	
	Subject	(%)	Subject	(%)	Subject	(%)	Subject	(%)
Overall	30	(9.8)	15	(5.0)	48	(9.5)	63	(7.8)
Infections & Infestations	6	(1.9)	1	(0.3)	18	(3.6)	19	(2.4)
URI	3	(1.0)	1	(0.3)	6	(1.2)	7	(0.9)
Nasopharyngitis	1	(0.3)	0		4	(0.8)	4	(0.5)
Acute sinusitis	0		0		2	(0.4)	2	(0.2)
Vaginitis bacterial	0		0		2	(0.4)	2	(0.2)
Sinusitis	1	(0.3)	0		2	(0.4)	2	(0.2)
Bronchitis	1	(0.3)	0		2	(0.4)	2	(0.2)
Nervous System Disorders	4	(1.4)	4	(1.4)	5	(1)	9	(1.1)
Headache	2	(0.7)	2	(0.7)	3	(0.6)	5	(0.6)
Sinus headache	2	(0.7)	2	(0.7)	2	(0.4)	4	(0.5)
Gastrointestinal Disorders	1	(0.3)	0		5	(1)	5	(0.6)
Vomiting	0		0		3	(0.6)	3	(0.4)
Diarrhea	1	(0.3)	0		2	(0.4)	2	(0.2)
Injury, Poisoning, & Procedural Complications	0		1	(0.3)	5	(1)	6	(0.7)
Muscle strain	0		0		3	(0.6)	3	(0.4)
Procedural pain	0		1	(0.3)	2	(0.4)	3	(0.4)
Respiratory, Thoracic, & Mediastinal Disorders	0		0		2	(0.4)	2	(0.2)
Epistaxis	0		0		2	(0.4)	2	(0.2)
Musculoskeletal & Connective Tissue Disorders	0		0		2	(0.4)	2	(0.2)
Pain in extremity	0		0		2	(0.4)	2	(0.2)

Source: ISS, Table 38, pp107

The sponsor did not provide information on severe AE experienced by only 1 patient. On review of the raw data for the entire exposure period, there were 58 (6%), 28 (3.2%), 74 (6.4%), and 10 (5.4%) severe AEs in the placebo, 74, 148, and 282 mcg groups, respectively.

7.3.5 Submission Specific Primary Safety Concerns

Due to the local action of the CIC-HFA, local AEs were of particular concern. The local AEs of concern included nasal septum perforations, ulcerations, and epistaxis. These were detected based on medical history and ENT exam by the site investigator. The inclusion/exclusion criteria also excluded those with a history of physical findings of nasal pathology, including nasal polyps or other significant respiratory tract malformations; recent nasal biopsy; nasal trauma; nasal ulcers or perforations; or surgery (all within the last 60 days prior to screening visit). In the 2-6 week exposure group (M1-602, 060-610, 060-622, 060-634, and the first 6 weeks of 060-633), 12.7% of patients in the placebo group had at least 1 local AE. Of those in the 74, 148, and 282 mcg groups, 13.9%, 14.3%, and 19.4% had local AEs, respectively. There was a clear dose response to overall local AEs; however, on an individual level, dose responses were only noted for epistaxis, URI, and nasal septum disorder. The most common local AE was epistaxis. The local AEs are summarized in Table 80.

Table 80. Local AEs During 2-6 Week Exposure

Ciclesonide Dose	Placebo (N=967)		74 mcg (N=884)		148 mcg (N=1150)		282 mcg (N=186)		Total Ciclesonide (N=2220)	
	Subject	(%)	Subject	(%)	Subject	(%)	Subject	(%)	Subject	(%)
Overall	123	(12.7)	123	(13.9)	165	(14.3)	36	(19.4)	324	(14.6)
Epistaxis	27	(2.8)	26	(2.9)	40	(3.5)	14	(7.5)	80	(3.6)
URI	8	(0.8)	15	(1.7)	21	(1.8)	2	(1.1)	38	(1.7)
Instillation site discomfort	5	(0.5)	16	(1.8)	16	(1.4)	2	(1.1)	34	(1.5)
Nasal discomfort	12	(1.2)	13	(1.5)	18	(1.6)	2	(1.1)	33	(1.5)
Oropharyngeal pain	9	(0.9)	11	(1.2)	12	(1.0)	3	(1.6)	26	(1.2)
Nasal septum disorder	7	(0.7)	9	(1.0)	14	(1.2)	3	(1.6)	26	(1.2)
Nasopharyngitis	15	(1.6)	4	(0.5)	12	(1.0)	5	(2.7)	21	(0.9)
Sinusitis	12	(1.2)	7	(0.8)	12	(1.0)	0		19	(0.9)
Nasal mucosal disorder	7	(0.7)	8	(0.9)	9	(0.8)	1	(0.5)	18	(0.8)
Cough	7	(0.7)	7	(0.8)	9	(0.8)	1	(0.5)	17	(0.8)
Sinus headache	7	(0.7)	4	(0.5)	6	(0.5)	1	(0.5)	11	(0.5)
Ear pain	4	(0.4)	3	(0.3)	6	(0.5)	1	(0.5)	10	(0.5)
Viral URI	3	(0.3)	5	(0.6)	3	(0.3)	0		8	(0.4)
Nasal congestion	1	(0.1)	1	(0.1)	5	(0.4)	1	(0.5)	7	(0.3)
Nasal dryness	0		5	(0.6)	1	(0.1)	0		6	(0.3)
Pharyngitis streptococcal	4	(0.4)	4	(0.5)	2	(0.2)	0		6	(0.3)
Otitis media	3	(0.3)	2	(0.2)	4	(0.3)	0		6	(0.3)
Sneezing	1	(0.1)	3	(0.3)	2	(0.2)	0		5	(0.2)
Nasal mucosal hypertrophy	2	(0.2)	3	(0.3)	0		2	(1.1)	5	(0.2)
Nasal edema	2	(0.2)	2	(0.2)	3	(0.3)	0		5	(0.2)
Acute sinusitis	0		3	(0.3)	0		0		3	(0.1)

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Throat irritation	0		0		3	(0.3)	0		3	(0.1)
Nasal septum perforation	0		2	(0.2)	0		0		2	(0.1)
Tonsillar disorder	0		0		2	(0.2)	0		2	(0.1)
Application site pustules	1	(0.1)	0		2	(0.2)	0		2	(0.1)
Rhinorrhea	1	(0.1)	0		2	(0.2)	0		2	(0.1)
Dysphonia	0		1	(0.1)	1	(0.1)	0		2	(0.1)
Ear discomfort	0		1	(0.1)	1	(0.1)	0		2	(0.1)
Pharyngitis	0		1	(0.1)	1	(0.1)	0		2	(0.1)
Pharyngeal disorder	0		0		1	(0.1)	1	(0.5)	2	(0.1)
Anosmia	0		1	(0.1)	0		0		1	(0.0)
Application site odor	0		1	(0.1)	0		0		1	(0.0)
Ear infection	0		1	(0.1)	0		0		1	(0.0)
Pharyngeal ulceration	0		1	(0.1)	0		0		1	(0.0)
Sinus polyp degeneration	0		1	(0.1)	0		0		1	(0.0)
Tonsillitis	0		1	(0.1)	0		0		1	(0.0)
Tympanic membrane perforation	0		1	(0.1)	0		0		1	(0.0)
Postnasal drip	1	(0.1)	1	(0.1)	0		0		1	(0.0)
Ear congestion	0		0		1	(0.1)	0		1	(0.0)
Hyposmia	0		0		1	(0.1)	0		1	(0.0)
Instillation site abnormal sensation	0		0		1	(0.1)	0		1	(0.0)
Instillation site dryness	0		0		1	(0.1)	0		1	(0.0)
Parosmia	0		0		1	(0.1)	0		1	(0.0)
Pharyngeal erythema	0		0		1	(0.1)	0		1	(0.0)
Rhinitis allergic	0		0		1	(0.1)	0		1	(0.0)
Tonsillar hypertrophy	0		0		1	(0.1)	0		1	(0.0)
Dry throat	1	(0.1)	0		1	(0.1)	0		1	(0.0)
Nasal ulcer	1	(0.1)	0		1	(0.1)	0		1	(0.0)
Nasal mucosal discoloration	0		0		0		1	(0.5)	1	(0.0)
Upper respiratory tract congestion	0		0		0		1	(0.5)	1	(0.0)
Laryngitis	2	(0.2)	0		0		0		2	(0.1)
Nasal septum ulceration	2	(0.2)	0		0		0		0	
Otorrhea	1	(0.1)	0		0		0		0	
Rhinitis	1	(0.1)	0		0		0		0	
Rhinitis seasonal	1	(0.1)	0		0		0		0	
Viral pharyngitis	1	(0.1)	0		0		0		0	

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily, 282mcg=141mcg each nostril daily
 Source: ISS, Table 41, pp113-114

Two (2) nasal septum perforations were noted in the 74 mcg groups and occurred during the 2 week treatment period. One septum perforation was noted on physical exam at the end of the trial 060-634 (0003/S150). The investigator noted that

perforation appeared well healed. The patient had no other symptoms. No perforation was noted on the initial exam. An independent ENT also examined this patient (2 months later) and felt that the lesion could have been there for months to years. The investigator examined the photos taken by the ENT and did not think that the appearance of the lesion had changed since it was first noted during the study. In the nasal septum perforation noted in trial M1-602, the patient (5357/80294) was noted to have inflammation of the turbinates at screening (no perforation or nasal polyp was noted), following 1 week of single blind placebo, she was noted to have bilateral nasal septum erosions, and after the 2 week treatment period, she had nasal septum perforation. She did not report epistaxis, but did have moderate nasal symptoms. This patient did have a history of nasal polyps status post resection (1993), nasal septum perforation (1998), and recurrence of nasal polyps (1999). The clinic note from 1999, while commenting on the polyps, makes no mention of the nasal septum perforation. The perforations are of great concern as these are very rare events. In the preclinical development program for Alvesco (IND 53,391), chronic inhalational studies performed in rats and dogs did not reveal any nasal pathology in the vehicle (w/w alcohol ^{(b) (4)} and HFA 134a ^{(b) (4)}) or test product.

The sponsor was also asked to re-classify/re-analyzed specific local TEAEs for the reasons and in the manner stated in section 7.1.2. These results are summarized in Table 81.

Table 81. Re-classified/re- analyzed local TEAEs for the 2-6 week exposure

Ciclesonide Dose	Placebo (N=967)		74 mcg (N=884)		148 mcg (N=1150)		282 mcg (N=186)		Total Ciclesonide (N=2220)	
	Subject	(%)	Subject	(%)	Subject	(%)	Subject	(%)	Subject	(%)
Nasal discomfort	17	(1.8)	28	(3.2)	33	(2.9)	4	(2.2)	65	(2.9)
Nasal Mucosal/Septum disorders	17	(1.8)	16	(1.8)	23	(2.0)	4	(2.2)	43	(1.9)
Non-ulcerative lesions	11	(1.1)	12	(1.4)	15	(1.3)	4	(2.2)	31	(1.4)
Irritation	10	(1.0)	11	(1.2)	8	(0.7)	2	(1.1)	21	(0.9)
Abrasion/excoriation/scabs	1	(0.1)	2	(0.2)	7	(0.6)	2	(1.1)	31	(1.4)
Erosions/ulcerations	5	(0.5)	4	(0.5)	6	(0.5)	0	0	10	(0.5)
Erosions	2	(0.2)	4	(0.5)	5	(0.4)	0	0	9	(0.4)
Ulcerations	3	(0.3)	0	0	1	(0.1)	0	0	1	(0.04)
Other	1	(0.1)	0	0	2	(0.2)	0	0	2	(0.1)

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily, 282mcg=141mcg each nostril daily

Overall, this re-classification does not change the conclusion that there is an imbalance in local TEAEs between placebo and CIC-HFA treated patients. However, it does make dose response relationships more obvious and that TEAEs located in the nasal cavity were more frequent in CIC-HFA groups compared to placebo.

Local AEs after 6 months of exposure were also analyzed. This data came from trial 060-633 only. The events also include those that were reported in the 2-6 week exposure from trial 060-633, but not from the 2 week data from the SAR trials. As such, the nasal septum perforations were not reported in this data set. The two most common

local AEs were URI and epistaxis, both of which were more common in the ciclesonide group compared to placebo. However, there was no clear dose response within the ciclesonide groups. Dose responses were demonstrated for cough, nasal discomfort, nasal mucosal disorder and nasal septum disorders. As compared to the 2-6 week data, there were more local AEs that were more frequent in the ciclesonide groups compared to placebo, and more that exhibited a dose response. This is likely due to the increased exposure. Local AEs are summarized in Table 82.

Table 82. Local TEAEs Following 6 Month Exposure

Ciclesonide Dose	Placebo (N=307)		74 mcg (N=298)		148 mcg (N=505)		Total Ciclesonide (N=803)	
	Subject	(%)	Subject	(%)	Subject	(%)	Subject	(%)
System Organ Class/ Preferred Term								
Overall	117	(38.1)	126	(42.3)	216	(42.8)	342	(42.6)
URI	29	(9.4)	43	(14.4)	65	(12.9)	108	(13.4)
Epistaxis	24	(7.8)	34	(11.4)	57	(11.3)	91	(11.3)
Nasopharyngitis	21	(6.8)	18	(6.0)	33	(6.5)	51	(6.4)
Sinusitis	17	(5.5)	14	(4.7)	27	(5.3)	41	(5.1)
Oropharyngeal pain	10	(3.3)	12	(4.0)	20	(4.0)	32	(4.0)
Cough	8	(2.6)	9	(3.0)	19	(3.8)	28	(3.5)
Nasal discomfort	2	(0.7)	8	(2.7)	15	(3.0)	23	(2.9)
Viral URI	5	(1.6)	11	(3.7)	11	(2.2)	22	(2.7)
Nasal mucosal disorder	3	(1.0)	8	(2.7)	14	(2.8)	22	(2.7)
Nasal septum disorder	3	(1.0)	5	(1.7)	16	(3.2)	21	(2.6)
Instillation site discomfort	0		10	(3.4)	9	(1.8)	19	(2.4)
Pharyngitis streptococcal	5	(1.6)	7	(2.3)	5	(1.0)	12	(1.5)
Sinus headache	7	(2.3)	6	(2.0)	4	(0.8)	10	(1.2)
Otitis media	1	(0.3)	2	(0.7)	5	(1.0)	7	(0.9)
Acute sinusitis	1	(0.3)	3	(1.0)	3	(0.6)	6	(0.7)
Ear pain	2	(0.7)	1	(0.3)	5	(1.0)	6	(0.7)
Nasal dryness	0		3	(1.0)	2	(0.4)	5	(0.6)
Nasal congestion	2	(0.7)	1	(0.3)	4	(0.8)	5	(0.6)
Throat irritation	0		0		3	(0.6)	3	(0.4)
Rhinitis allergic	2	(0.7)	1	(0.3)	2	(0.4)	3	(0.4)
Sneezing	0		2	(0.7)	0		2	(0.2)
Rhinorrhea	2	(0.7)	0		2	(0.4)	2	(0.2)
Dry throat	0		1	(0.3)	1	(0.2)	2	(0.2)
Ear discomfort	0		1	(0.3)	1	(0.2)	2	(0.2)
Dysphonia	1	(0.3)	1	(0.3)	1	(0.2)	2	(0.2)
Pharyngitis	3	(1.0)	1	(0.3)	1	(0.2)	2	(0.2)
Anosmia	0		1	(0.3)	0		1	(0.1)
Application site odor	0		1	(0.3)	0		1	(0.1)
Otitis media acute	0		1	(0.3)	0		1	(0.1)
Sinus polyp degeneration	0		1	(0.3)	0		1	(0.1)
Swelling face	0		1	(0.3)	0		1	(0.1)

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Postnasal drip	1	(0.3)	1	(0.3)	0		1	(0.1)
Aphonia	0		0		1	(0.2)	1	(0.1)
Application site cellulitis	0		0		1	(0.2)	1	(0.1)
Ear congestion	0		0		1	(0.2)	1	(0.1)
Eustachian tube dysfunction	0		0		1	(0.2)	1	(0.1)
Herpes pharyngitis	0		0		1	(0.2)	1	(0.1)
Instillation site abnormal sensation	0		0		1	(0.2)	1	(0.1)
Pharyngeal disorder	0		0		1	(0.2)	1	(0.1)
Pharyngeal erythema	0		0		1	(0.2)	1	(0.1)
Tonsillar disorder	0		0		1	(0.2)	1	(0.1)
Tympanic membrane perforation	0		0		1	(0.2)	1	(0.1)
Application site pustules	1	(0.3)	0		1	(0.2)	1	(0.1)
Laryngitis	1	(0.3)	0		1	(0.2)	1	(0.1)
Nasal ulcer	1	(0.3)	0		1	(0.2)	1	(0.1)
Viral pharyngitis	1	(0.3)	0		1	(0.2)	1	(0.1)
Ear infection	2	(0.7)	0		1	(0.2)	1	(0.1)
Hyposmia	2	(0.7)	0		1	(0.2)	1	(0.1)
Nasal polyps	1	(0.3)	0		0		0	
Otorrhea	1	(0.3)	0		0		0	
Paranasal sinus hypersecretion	1	(0.3)	0		0		0	
Seasonal allergy	1	(0.3)	0		0		0	
Tonsillar cyst	1	(0.3)	0		0		0	
Tympanic membrane disorder	1	(0.3)	0		0		0	
Nasal septum ulceration	2	(0.7)	0		0		0	
Rhinitis seasonal	2	(0.7)	0		0		0	
Tympanic membrane hyperemia	2	(0.7)	0		0		0	

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily
 Source: ISS, Table 42, pp116-117

The local TEAE data for the 6 month exposure was also re-classified and re-analyzed in a manner similar to the 2-6 week exposure data. These results are summarized in Table 83

Table 83. Re-classified/re-analyzed local TEAEs during 6 month exposure

Ciclesonide Dose	Placebo (N=307)		CIC-HFA 74 mcg (N=298)		CIC-HFA 148 mcg (N=505)		CIC-HFA Total (N=803)	
	Subject	(%)	Subject	(%)	Subject	(%)	Subject	(%)
Nasal discomfort	2	(0.7)	17	(5.7)	25	(5.0)	42	(5.2)
Nasal Mucosal/Septum disorders	9	(2.9)	11	(3.7)	30	(5.9)	41	(5.1)
Non-ulcerative lesions	5	(1.6)	10	(3.4)	21	(4.2)	31	(3.9)
Irritation	4	(1.3)	6	(2.0)	10	(2.0)	16	(2.0)
Abrasion/excoriation/scabs	1	(0.3)	5	(1.7)	12	(2.4)	17	(2.1)
Erosions/ulcerations	4	(1.3)	2	(0.7)	8	(1.6)	10	(1.2)
Erosions	1	(0.3)	2	(0.7)	7	(1.4)	9	(1.1)
Ulcerations	3	(1.0)	0	0	1	(0.2)	1	(0.1)
Other	1	(0.3)	0	0	1	(0.2)	1	(0.1)

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily

Based on this re-analysis, the occurrence of nasal discomfort and nasal mucosal/septum disorders is relatively high and follows a dose response. Within nasal mucosal/septum disorders, 'abrasion/excoriation/scabs,' 'irritation,' and 'erosions' also followed a clear dose response. In addition, almost all of the re-classified/re-analyzed local TEAEs are much more frequent in patients treated with CIC-HFA compared to placebo.

The frequency of epistaxis (3.6%) for this product was lower than for Omnaris (4.9%) and Veramyst (6%) when comparing 2-6 week exposure times across studies. As this was unexpected, data for epistaxis was reviewed in depth. Coding for epistaxis was reviewed, and the coding from verbatim term to preferred term was consistent and accurate. In the sponsor's analysis, a total of 191 patients who received ciclesonide (2-6 week exposure + 6month exposure) had epistaxis compared to 194 when reviewed by this medical officer. The ITT population was also not significantly different than the safety population. The reason for the discrepancy in epistaxis is not clear, as one would expect all nasal steroids to have similar rates, although since differences were small and based on cross study comparisons, no conclusions can be drawn. No fungal infections of the oropharynx were reported.

Based on both the sponsor's original local TEAE classification and re-classification, it is clear that there is an imbalance between the placebo and CIC-HFA groups with respect to local TEAEs. This finding is not surprising given the known local toxicity of nasal steroids.

HPA Axis Suppression

The HPA axis was evaluated in subjects 12 years and older in trials FHP-017, M1-601, and 060-010. In trials FHP-017 and M1-601, serum cortisol levels were measured after 7 daily doses of CIC-HFA at 282 mcg and 14 daily doses at 148 or 282 mcg, respectively. In both trials, no significant differences were seen in the serum cortisol AUC_{0-24hr} for those exposed to ciclesonide versus placebo. However, these were relatively short exposures to ciclesonide, therefore trial 060-010 was performed. This

trial assessed HPA axis effects of ciclesonide (serum cortisol AUC_{0-24hr}) after 6 weeks of exposure. Patients (12 years and older) were divided into 4 treatment groups which were as follows:

- 1) Placebo HFA daily + Dexamethasone (DEX) 6mg
- 2) Placebo HFA daily +Placebo DEX
- 3) Ciclesonide HFA 148 mcg daily
- 4) Ciclesonide HFA 282 mcg daily

For groups 1 and 2, the DEX (or DEX placebo) was started 4 days prior to the 2nd collection of 24 hour serum cortisol levels (end of treatment). Results are summarized in Table 84.

Table 84. Trial 060-610. Change from Baseline in Serum Cortisol AUC (0-24hr) (mcg*hr/dL) in Per Protocol Population

	Placebo HFA+DEX	Placebo HFA +Placebo DEX	CIC-HFA dose	
			148 mcg	282 mcg
Cortisol AUC _{0-24hr}				
N	18	57	60	50
Baseline (SD)	167.7 (36.3)	173.1 (53.5)	171.7 (40.1)	183.2 (61.9)
End of Treatment (SD)	13 (14.3)	169.9 (48.3)	170.6 (47.4)	178 (55.5)
Change from baseline (SD)	-154.4 (40)	-2.7 (41.1)	-1.5 (34.1)	-7.7 (33.7)
LS Mean Change from baseline (SE)		-5 (4.6)	-2.6 (4.6)	-4.6 (5)
Treatment difference vs. Pbo (95% CI)			-2.4 (-15.1, 10.2)	-0.5 (-13.9, 13)

148mcg=74mcg each nostril daily, 282mcg=141mcg each nostril daily

Source: Trial 060-610 CSR, Table 13, pp102

Numerically, the LS mean changes from baseline for the ciclesonide groups are similar to the placebo HFA+placebo DEX group. Statistically, the ciclesonide groups demonstrated non-inferiority compared to the placebo HFA+placebo DEX groups based on a pre-specified non-inferiority margin (upper limit of the 95% confidence interval for the LS mean difference from Placebo HFA+Placebo DEX <38 mcg*hr/dL). This non-inferiority margin was chosen as in the prior HPA axis studies using Omnaris, the baseline serum cortisol AUC_{0-24hr} was on average 190 mcg*hr/dL and the sponsor chose a 20% non-inferiority margin. Thus, 6 weeks of treatment at 2-4 times the proposed CIC-HFA dose did not suppress the HPA axis. However, it should be noted that based on the point estimate for change from baseline in serum cortisol levels, the 282 mcg treatment had greater suppression compared to the 148 mcg and placebo groups. This implies that at higher doses, CIC-HFA may cause subtle HPA axis suppression. The positive control (Placebo HFA+DEX) also demonstrated that the assay would have been able to detect HPA axis suppression. The sponsor also collected nasal symptom data as a measure of efficacy and to assess for compliance.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In all studies adverse events included those spontaneously reported by the patient and those elicited by non-leading questions. The most common adverse events reported in the 2-6 week exposure period were epistaxis, headache, and URI. It also should be noted that when re-classifying AEs as in section 7.1.2, nasal discomfort (instillation site discomfort+nasal discomfort) (3.2%) became one of the most common AEs. Of these, only epistaxis demonstrated a dose response. However, the following AEs were more common in CIC-HFA groups versus placebo, and can possibly be linked to nasal steroid administration: nasal discomfort, nasal septum disorder, oropharyngeal pain, URI, headache, and instillation site discomfort. These results are summarized in Table 85.

Table 85. TEAE Reported in ≥1% of Patients During 2-6 Week Exposure

Ciclesonide Dose	Placebo (N=967)		CIC-HFA 74 mcg (N=884)		CIC-HFA 148 mcg (N=1150)		CIC-HFA 282 mcg (N=186)		CIC-HFA Total (N=2220)	
	Subject	(%)	Subject	(%)	Subject	(%)	Subject	(%)	Subject	(%)
Overall	242	(25.0)	222	(25.1)	315	(27.4)	50	(26.9)	587	(26.4)
Respiratory, Thoracic, & Mediastinal Disorders	57	(5.8)	62	(6.9)	84	(7.3)	24	(12.9)	170	(7.7)
Epistaxis	27	(2.8)	26	(2.9)	40	(3.5)	14	(7.5)	80	(3.6)
Nasal discomfort	12	(1.2)	13	(1.5)	18	(1.6)	2	(1.1)	33	(1.5)
Nasal septum disorder	7	(0.7)	9	(1.0)	14	(1.2)	3	(1.6)	26	(1.2)
Oropharyngeal pain	9	(0.9)	11	(1.2)	12	(1.0)	3	(1.6)	26	(1.2)
Nasal mucosal hypertrophy	2	(0.2)	3	(0.3)	0		2	(1.1)	5	(0.2)
Infections & Infestations	47	(4.8)	47	(5.4)	62	(5.2)	9	(4.9)	118	(5.3)
URI	8	(0.8)	15	(1.7)	21	(1.8)	2	(1.1)	38	(1.7)
Urinary tract infection	9	(0.9)	12	(1.4)	12	(1.0)	0		24	(1.1)
Nasopharyngitis	15	(1.6)	4	(0.5)	12	(1.0)	5	(2.7)	21	(0.94)
Sinusitis	12	(1.2)	7	(0.8)	12	(1.0)	0		19	(0.85)
Bronchitis	3	(0.3)	9	(1.0)	5	(0.4)	2	(1.1)	16	(0.72)
Nervous System Disorders										
Headache	15	(1.6)	27	(3.1)	16	(1.4)	5	(2.7)	48	(2.2)
General Disorders & Administrative Site Conditions	7	(0.7)	16	(1.8)	20	(1.7)	4	(2.2)	40	(1.8)
Instillation Site Discomfort	5	(0.5)	16	(1.8)	16	(1.4)	2	(1.1)	34	(1.5)
Fatigue	2	(0.2)	0		4	(0.3)	2	(1.1)	6	(0.27)
Gastrointestinal Disorders	10	(1)	12	(1.4)	14	(1.2)	5	(2.7)	31	(1.8)
Nausea	5	(0.5)	8	(0.9)	7	(0.6)	2	(1.1)	17	(0.76)
Diarrhea	5	(0.5)	4	(0.5)	7	(0.6)	3	(1.6)	14	(0.63)

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily
 Source: ISS, Table 27, pp90

The most common AEs reported during the 6 month exposure period were URI, epistaxis, nasopharyngitis, sinusitis, and headache. It also should be noted that when re-classifying AEs as in section 7.1.2, nasal discomfort (instillation site discomfort+nasal discomfort) (5.7%) and nasal mucosal/septum disorders (4%) are also common. Overall the types of AEs reported were similar to the 2-6 week data, and AEs previously reported for nasal steroids. All the AEs in the Respiratory, Thoracic and Mediastinal Disorders SOC demonstrated a dose effect. Aside from that, no other AEs demonstrated a clear dose effect, though many were more frequent in CIC-HFA treated patients versus placebo. These results are summarized in Table 86.

Table 86. TEAE Reported in ≥1% of Patients During 6 Month Exposure

Ciclesonide Dose	Placebo (N=307)		74 mcg (N=298)		148 mcg (N=505)		Total Ciclesonide (N=803)	
	Subject	(%)	Subject	(%)	Subject	(%)	Subject	(%)
System Organ Class/ Preferred Term								
Overall	195	(63.5)	180	(60.4)	316	(62.6)	496	(62)
Infections & Infestations	110	(35.7)	138	(46.7)	203	(40.9)	341	(42.5)
URI	29	(9.4)	43	(14.4)	65	(12.9)	108	(13.4)
Nasopharyngitis	21	(6.8)	18	(6.0)	33	(6.5)	51	(6.4)
Sinusitis	17	(5.5)	14	(4.7)	27	(5.3)	41	(5.1)
Urinary tract infection	9	(2.9)	13	(4.4)	14	(2.8)	27	(3.4)
Viral URI	5	(1.6)	11	(3.7)	11	(2.2)	22	(2.7)
Bronchitis	6	(2.0)	7	(2.3)	11	(2.2)	18	(2.2)
Influenza	3	(1.0)	6	(2.0)	9	(1.8)	15	(1.9)
Pharyngitis streptococcal	5	(1.6)	7	(2.3)	5	(1.0)	12	(1.5)
Gastroenteritis viral	4	(1.3)	3	(1.0)	5	(1.0)	8	(1)
Viral infection	3	(1.0)	2	(0.7)	6	(1.2)	8	(1)
Otitis media	1	(0.3)	2	(0.7)	5	(1.0)	7	(0.9)
Acute sinusitis	1	(0.3)	3	(1.0)	3	(0.6)	6	(0.8)
Gastroenteritis	4	(1.3)	3	(1.0)	3	(0.6)	6	(0.8)
Vulvovaginal mycotic infection	0		3	(1.5)	2	(0.6)	5	(0.6)
Pneumonia	2	(0.7)	3	(1.0)	1	(0.2)	4	(0.5)
Vaginitis bacterial	0		0		3	(1.0)	3	(0.4)
Respiratory, Thoracic, & Mediastinal Disorders	50	(16.4)	79	(26.5)	143	(28.5)	222	(27.6)
Epistaxis	24	(7.8)	34	(11.4)	57	(11.3)	91	(11.3)
Oropharyngeal pain	10	(3.3)	12	(4.0)	20	(4.0)	32	(4)
Cough	8	(2.6)	9	(3.0)	19	(3.8)	28	(3.5)
Nasal discomfort	2	(0.7)	8	(2.7)	15	(3.0)	23	(2.9)
Nasal mucosal disorder	3	(1.0)	8	(2.7)	14	(2.8)	22	(2.7)
Nasal septum disorder	3	(1.0)	5	(1.7)	16	(3.2)	21	(2.6)
Nasal dryness	0		3	(1.0)	2	(0.4)	5	(0.6)
Gastrointestinal Disorders	25	(8.2)	24	(8)	41	(8.2)	65	(8.1)
Nausea	2	(0.7)	9	(3.0)	8	(1.6)	17	(2.1)
Vomiting	5	(1.6)	3	(1.0)	10	(2.0)	13	(1.6)
Toothache	5	(1.6)	5	(1.7)	7	(1.4)	12	(1.5)
Diarrhea	6	(2.0)	3	(1.0)	9	(1.8)	12	(1.5)
Abdominal pain upper	7	(2.3)	4	(1.3)	7	(1.4)	11	(1.4)
Nervous System Disorders	22	(7.2)	30	(10)	23	(4.6)	53	(6.5)
Headache	14	(4.6)	21	(7.0)	17	(3.4)	38	(4.7)
Sinus headache	7	(2.3)	6	(2.0)	4	(0.8)	10	(1.2)
Tension headache	1	(0.3)	3	(1.0)	2	(0.4)	5	(0.6)
Musculoskeletal & Connective Tissue Disorders	21	(7)	11	(3.7)	47	(9.4)	58	(7.1)
Back pain	10	(3.3)	5	(1.7)	11	(2.2)	16	(2)
Pain in extremity	2	(0.7)	1	(0.3)	9	(1.8)	10	(1.2)
Arthralgia	4	(1.3)	0		10	(2.0)	10	(1.2)
Myalgia	3	(1.0)	2	(0.7)	7	(1.4)	9	(1.1)
Neck pain	2	(0.7)	0		8	(1.6)	8	(1)
Muscle spasms	0		3	(1.0)	2	(0.4)	5	(0.6)

Injury, Poisoning, & Procedural Complications	5	(1.7)	11	(3.7)	12	(2.4)	23	(2.84)
Muscle strain	2	(0.7)	6	(2.0)	7	(1.4)	13	(1.6)
Procedural pain	3	(1.0)	5	(1.7)	5	(1.0)	10	(1.24)
General Disorders & Administrative Site Conditions	3	(1)	14	(4.7)	14	(2.8)	28	(3.5)
Instillation site discomfort	0		10	(3.4)	9	(1.8)	19	(2.4)
Pyrexia	3	(1.0)	4	(1.3)	5	(1.0)	9	(1.1)
Skin & Subcutaneous Tissue Disorders								
Rash	0		3	(1.0)	2	(0.4)	5	(0.6)
Investigations								
Blood pressure increased	3	(1.0)	1	(0.3)	6	(1.2)	7	(0.9)
Reproductive System & Breast Disorders	1	(0.5)	3	(2)	0		3	(0.37)
Ovarian cyst	1	(0.5)	2	(1.0)	0		2	(0.25)
Benign prostatic hyperplasia	0		1	(1.0)	0		1	(0.12)
Ear & Labyrinth Disorders								
Ear pain	2	(0.7)	1	(0.3)	5	(1.0)	6	(0.75)
Vascular Disorders								
Hypertension	6	(2.0)	3	(1.0)	2	(0.4)	5	(0.6)

74mcg=37mcg each nostril daily, 148mcg=74mcg each nostril daily
 Source: ISS, Table 28, pp93

Overall the common AEs reported in this development program were typical and expected for a nasal corticosteroid.

7.4.2 Laboratory Findings

Clinical laboratories were measured at baseline (screening visit for trial 060-622/634, visit 3 for 060-633, and visit 3b for 060-610). The end of study/early termination time point was defined as the last scheduled post-baseline visit. For the 2-6 week exposure data in trial 060-633, visit 6 (6 weeks) was defined as the post-baseline value. For the 6 month data in trial 060-633, baseline data was designed as in the 2-6 week data, and EOS/EOT was defined as the last scheduled post-baseline value. No laboratories were taken in study M1-602. Potentially clinically significant lab changes were pre-specified by the sponsor (see Table 70). Clinical significance was determined by the individual investigator.

Chemistries and Hematology

In general, review of clinical laboratory findings did not identify any specific safety concerns. The lab results were pooled in the same fashion as the adverse event data, though trial M1-602 was not included. For the 2-6 week exposure, mean changes from baseline were small and similar between groups. Shift analysis also demonstrated minimal differences between placebo and ciclesonide groups.

Potentially clinically significant (PCS) lab changes were relatively infrequent and evenly distributed. However, more individuals treated with ciclesonide had PCS increases in serum glucose [11 (1.3%) and 32 (1.7%) patients in the placebo and ciclesonide groups, respectively] and phosphate [5 (0.6%) versus 33 (1.8%) patients]. These were also the most common lab abnormalities. Effects on serum glucose are of some concern as this could be related to systemic corticosteroids exposure. However, the total numbers were small and likely represent noise. Clinically significant lab changes were even more infrequent and were evenly distributed across all groups.

When analyzing the clinical lab data from the 6 month exposure group, the results were similar to the 2-6 week exposure group. Mean change for both chemistry and hematology labs were similar between all groups. Shift analysis also demonstrated minimal differences. When examining PCS changes, as with the 2-6 week data, more patients receiving ciclesonide had PCS increases in serum glucose and phosphate compared to the placebo group. The overall numbers/percentage of patients with glucose or phosphate abnormalities was lower at 6 months compared to the 2-6 week time point. Clinically significant lab changes were more infrequent and were evenly distributed across all groups.

Overall, the post-baseline differences in clinical labs were minimal and similar between groups at both the 2-6 week time point and 6 month time point.

7.4.3 Vital Signs

For both the 2-6 week data and the 6 month data, mean changes in vital sign parameters were similar between groups. PCS vital sign changes were evenly distributed and were most commonly changes from baseline in temperature (low). The changes in temperature were likely related to noise and not clinically significant.

7.4.4 Electrocardiograms (ECGs)

No designated ECG study was performed, nor was ECG data collected for the pivotal trials.

7.4.5 Special Safety Studies/Clinical Trials

Nasal Exams

Due to the concern for local toxicity, ENT exams were performed by the investigator with all study visits. In general, abnormal findings were similar between groups. The percent of patients with exams that worsened was low and similar between groups. Reports of nasal septum perforation, nasal ulcer, and epistaxis have already been discussed.

7.4.6 Immunogenicity

Immunogenicity was not specifically assessed in the development program. Ciclesonide is a small molecular entity that is not known to be immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

From the 2-6 week exposure data, epistaxis and nasal septum disorders demonstrated a clear dose response. The 6 month exposure data had more AEs demonstrating a dose response. These included nasal discomfort, nasal septum disorder, cough, and nasal mucosal disorder. While epistaxis did not have a clear dose response in the 6 month exposure data, it was more frequent in the CIC-HFA groups versus placebo. In addition, severe epistaxis was only observed in the 148 mcg group (1 patient). There was also a dose response with respect to onset of epistaxis (82.5 days, 72.5 days and 54 days for the placebo, 74 mcg and 148 mcg groups, respectively). Kaplan-Meier plots of the onset of first TEAEs and first local TEAEs did not demonstrate obvious differences in cumulative incidence at any time points for the placebo, 74 and 148 mcg groups (based on visualization) in the 2-6 week exposure group. However, for both TEAEs and local TEAEs, at time points beyond 15-20 days, the cumulative incidence appeared higher for the 282 mcg group compared to all other groups.

For reasons discussed in section 7.1.2, some local adverse events were re-classified and re-analyzed. Based on this new grouping, there was dose response for 'nasal mucosal/septum disorders' and nasal abrasion/excoriation/scabs in the 2-6 week exposure group.

The 6 month local TEAEs were also re-classified/re-analyzed as above (and as described in section 7.1.2). Based on this the following local TEAEs also demonstrated a dose response:

1. Nasal mucosal/septum disorders
2. Nasal irritation
3. Nasal abrasion/excoriation/scabs
4. Nasal erosions

7.5.2 Time Dependency for Adverse Events

The only time dependency observed for adverse events was the onset of epistaxis. As stated in section 7.5.1, with increasing doses, onset of epistaxis was sooner. Otherwise, there was no apparent time dependency for most the commonly observed TEAEs or local TEAEs in the 2-6 week or 6 month exposure data.

7.5.3 Drug-Demographic Interactions

Subgroup analysis of the AE data did not reveal any apparent drug-demographic interactions.

7.5.4 Drug-Disease Interactions

This was not assessed in this development program.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies were performed. The sponsor made reference to two drug-drug interaction studies performed in the Alvesco development program. In study FHP-019 (Alvesco), erythromycin was administered with orally inhaled ciclesonide and no changes in the PK parameters were noted. In study CP-036, (Alvesco), ketoconazole administered with orally inhaled ciclesonide caused elevations in des-ciclesonide AUCs, whereas ciclesonide AUCs remained unchanged.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Specific evaluations for carcinogenicity were conducted for this application. Ciclesonide is a well known chemical entity and is not known to be carcinogenic.

7.6.2 Human Reproduction and Pregnancy Data

This development program did not include adequate and well-controlled studies in pregnant women, nor were such trials included in the Omnaris (ciclesonide aqueous nasal spray) or Alvesco (ciclesonide oral HFA) development programs. During the ciclesonide nasal HFA development program 9 patients receiving study drug became pregnant (1 in M1-601 and 8 in 060-633). Three (3) pregnancies ended in voluntary termination, 1 ended with abortion (unknown if voluntary), 1 ended with a spontaneous abortion, 2 ended with normal infants, 1 ended with a preterm infant with congenital anomalies, and the remaining 1 had an unknown outcome (lost to follow-up).

7.6.3 Pediatrics and Assessment of Effects on Growth

This development program did not assess the effects on growth in pediatrics. However, these effects were studied in the Alvesco development program, which this NDA has referenced. In the Alvesco program, study M1-203 demonstrated no differences in growth velocity in prepubertal children given Alvesco versus placebo. Other studies

have demonstrated that the effect of Alvesco on growth is similar or less than other orally inhaled corticosteroids (fluticasone and budesonide). Since the systemic exposure to ciclesonide is greater with Alvesco than with CIC-HFA, further growth studies with CIC-HFA are not needed.

Nycomed plans to perform pediatric studies to support efficacy and safety. They propose to evaluate the 2-11 year old population in a sequential manner. First, they plan on performing trials in the 6-11 year old population to determine dose, efficacy, and safety in the setting of SAR and PAR. The sponsor also plans an HPA axis study. Once dosing is determined in the 6-11 year old population, they plan on studying the 2-5 year old age group. This age group will have a separate HPA axis study. It should be noted that at present, Nycomed only plans to use [REDACTED] (b) (4) in their pediatric dose ranging trial. Given the flat dose response, the presence of nasal septum perforations in the adult program, and the increased systemic and local exposure in the proposed product versus Omnaris, lower doses should be included in the dose ranging trials. This was discussed with Nycomed during a teleconference on 9/28/11. In response, Nycomed stated [REDACTED] (b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose were reported. Based on the low systemic bioavailability, and the nature of ciclesonide, drug abuse potential, withdrawal, and rebound are not anticipated. If used at excessive doses for prolonged periods, hypercorticism may occur and abrupt cessation may theoretically precipitate adrenal crisis. In the post-marketing data for Omnaris and Alvesco, there have been 6 reports of overdosage. Only one of the 6 cases reported an AE, which was sneezing.

7.7 Additional Submissions / Safety Issues

The sponsor submitted a 120 day safety update with exposure data for up to one year. This data was from trial 060-635, an open label extension of 060-633. The nature and distribution of the SAEs and AEs were consistent with the 6 month data. No new safety signals were identified (see section 5.3 for trial review).

8 Postmarket Experience

Ciclesonide is approved for use in the U.S. and multiple other countries as an aqueous nasal spray (Omnaris) and as an oral HFA (Alvesco). Post-marketing information is available for both. Between January 2005 to July 2010, 2106 AEs pertaining to ciclesonide oral HFA (Alvesco) have been reported world wide. Of these 1815 were

non-serious and 291 were serious. With regard to Omnaris, between April 2008 and July 2010, 977 AEs were reported, 916 were non-serious and 61 were serious. No nasal septum perforations were reported; however, there was one nasal ulceration (which had not been observed in their development program.)

9 Appendices

9.1 Literature Review/References

The sponsor references 19 articles from the scientific literature in the integrated summary of efficacy. To supplement this list, this reviewer also searched PubMed with the search terms “ciclesonide” and “safety,” limited to human studies written in English. A total of 61 articles were retrieved. No new safety signals were identified from this literature search.

9.2 Labeling Recommendations

Labeling negotiations are ongoing at the time of this review. Based on the efficacy data, CIC-HFA improves the symptoms associated with SAR and has a modest effect on ocular symptoms and RQLQ scores as claimed in the label. However, in the setting of PAR, CIC-HFA does not have a clinically significant effect on RQLQ and this language will be taken out of the label. Additionally, their claim for onset of action [REDACTED] (b) (4), while factually correct, is misleading in that onset action based on 060-622/633 and 060-634 is 36 hours. This will be changed.

Based on the safety data, additional warnings will be included regarding nasal septal perforations and AE tables will be modified to include the re-classified/re-analyzed TEAEs (see 7.1.2) where appropriate. As we are requiring additional ocular safety data, [REDACTED] (b) (4) the general statement regard glaucoma and cataracts will remain.

9.3 Advisory Committee Meeting

Ciclesonide is not a new molecular entity and no new indications were proposed. An Advisory Committee Meeting was not warranted.

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/s/

ROBERT H LIM
12/16/2011

THERESA M MICHELE
12/16/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 28, 2011

TO: Collete Jackson, Regulatory Project Manager
Robert Lim, M.D., Medical Officer
Theresa M. Michele, M.D., Team Leader
Division of Pulmonary, Allergy and Rheumatology Products (DPAAP)

THROUGH: Lauren Iacono-Connors, Ph.D.
Acting Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Jean Mulinde, M.D.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations (*formerly* Division of Scientific Investigations)

SUBJECT: Evaluation of Clinical Inspections

NDA: 202129

APPLICANT: Sunovion Pharmaceuticals, Inc.

DRUG: ciclesonide HFA nasal aerosol
NME: No

THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review
INDICATION: Treatment of symptoms associated with seasonal and perennial
allergic rhinitis in adults and adolescents 12 years of age and older

CONSULTATION REQUEST DATE: May 26, 2011 (signed)
DIVISION ACTION GOAL DATE: January 20, 2012
PDUFA DATE: January 21, 2011

I. BACKGROUND:

Allergic rhinitis is a heterogeneous disorder characterized by nasal itch, sneezing, rhinorrhea, and nasal obstruction, as well as allergic conjunctivitis. The incidence increases from infancy, peaks in childhood and adolescence, and decreases in the elderly. Intranasal corticosteroids agents treat the allergen-induced inflammatory response reducing nasal congestion, itching, and sneezing due to allergic rhinitis.

In the U.S., ciclesonide has been approved for the treatment of asthma. Ciclesonide is a non-halogenated glucocorticoid that is cleaved by intracellular esterases at carbon position 21 to form a biologically active metabolite, RM1, with 120-fold greater affinity for the glucocorticoid receptor. The R-epimer of racemic ciclesonide was selected for development (b) (4)

Results from four adequate and well-controlled studies were submitted in support of the Applicant's requested labeling for treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years and older.

Protocol M1-602

Study M1-602 was a Phase II, double-blind, randomized (1:1:1:1 ratio), placebo-controlled, parallel group, multicenter, dose-ranging study to assess the efficacy and safety of ciclesonide HFA nasal aerosol in adult and adolescent patients 12 years and older with Seasonal Allergic Rhinitis (SAR). The primary objective of this study was to determine the optimal dose of ciclesonide HFA, applied as a nasal aerosol, in patients with SAR, with the following doses investigated: placebo, 80, 160 and 320 mcg daily of the study drug for a two-week duration. The primary efficacy endpoint was average of AM and PM patient-reported reflective Total Nasal Symptom Score (TNSS) over the two-week treatment period.

Protocol 060-622

Study 60-622 was a randomized, multicenter, double-blind, placebo-controlled, parallel group, Phase III study to assess the efficacy and safety of ciclesonide HFA nasal aerosol (80 and 160 mcg once daily) for the treatment of Seasonal Allergic Rhinitis to Mountain Cedar in subjects 12 years and older. The primary objective was to demonstrate the efficacy of ciclesonide HFA applied as a nasal aerosol (80 mcg and 160 mcg) once daily compared to placebo in subjects with SAR. The primary efficacy endpoint was the change from baseline in subject-reported AM and PM reflective TNSS averaged over the two-week treatment period where baseline was defined as the average of the responses obtained during the run-in period up to 6 days prior to randomization and includes the AM score prior to randomization.

Protocols 060-634

This study was almost similar in design to study 060-622. Study 60-634 was a six month randomized, double-blind, placebo-controlled, parallel group, efficacy and safety study of ciclesonide HFA Nasal Aerosol (80 and 160 mcg applied once daily) for the treatment of perennial allergic rhinitis in Subjects 12 years and older. The primary objective was to demonstrate the efficacy of ciclesonide HFA applied as a nasal aerosol (80 and 160 mcg once daily) compared to placebo in subjects with SAR. The primary study endpoint was the change from baseline in daily subject-reported AM and PM reflective TNSS averaged over the 2-week treatment period. Baseline was defined as the average of the responses obtained during the run-in Period up to 6 days prior to randomization and includes the AM score prior to randomization.

Protocol 060-633

Study 060-633 was a six month, randomized, double-blind, placebo-controlled, parallel group, efficacy and safety Study of ciclesonide HFA Nasal Aerosol (80 and 160 mcg once daily) for the treatment of perennial allergic rhinitis. The primary objective was to compare and to evaluate the efficacy of ciclesonide HFA nasal aerosol (80 and 160 mcg applied once daily) versus placebo over 6 weeks, applied as a nasal aerosol, in subjects with Perennial Allergic Rhinitis. The primary efficacy endpoint was the change from baseline in daily subject-reported AM and PM reflective TNSS averaged over the first 6 weeks of double-blind treatment, where baseline was defined as the average of the responses obtained during the placebo run-in period up to 6 days prior to randomization and includes the AM score prior to randomization. Patients were allowed to continue in a 6 month open-label safety extension study.

While this product is not a new molecular entity, verification of data submitted in support of the requested new indication (treatment of adolescent and adult seasonal and perennial allergic rhinitis) was considered essential by the review division. In addition to being high enrollment sites, a concern was the occurrence of nasal septal perforation observed in submitted studies. DPARP deemed it rare for nasal septal perforations to occur in a nasal steroid development program for allergic rhinitis. Dr. Jacob's (study protocol 060-634) and Goldberg's (study protocol M1-602) site, respectively, each contributed one of the two nasal septal perforations reported in the NDA.

II. RESULTS (by protocol/site):

Name of CI	City, State	Protocol/Study Site	Insp. Date	EIR Received Date	Final Classification
Pinkus Goldberg, M.D.	Indianapolis, IN	Study Protocol M1-602 Site #5357 Study Protocol 060-033 Site #10	7/6-7/14, 2011	VAI	VAI
Robert Lee Jacobs, M.D.	San Antonio, TX	Study Protocol 060-622 Site #003 Study Protocol 060-634 Site #003 Study Protocol 060-633 Site #014	7/25- 8/12, 2011	Pending	Pending (Preliminary: NAI)

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Preliminary= The Establishment Inspection Report (EIR) has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATOR

1. Pinkus Goldberg, M.D./Study Protocols M1-602 Site 5357 and 060-033 Site #010

Clinical Research Center of Indiana
3266 N. Meridian St. Suite 900
Indianapolis, IN 46208

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from July 6 – July 14, 2010.

For Study Protocol M1-602, a total of 29 subjects were screened, 17 were randomized and completed the study. There was no under-reporting of serious adverse events. An audit of 17 randomized study subjects was conducted.

For Study Protocol Study 060-633, a total of 36 subjects were screened, 29 were randomized and 27 subjects completed the study. There was no under-reporting of serious adverse events. An audit of 17 randomized study subjects' entire records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for randomized subjects whose records were audited, were verified against the case report forms and NDA subject line listings.

No discrepancies were noted. In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a four-item Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for mainly isolated minor protocol deviations or regulatory deficiencies in recordkeeping.

(A) Salient findings of the inspection included the following examples:

- (1) Subject #0005PKN in Study M1-602 was not excluded from the study, despite bilateral nasal septal erosions noted at randomization visit, and
- (2) Subject #0024JWM in Study M1-602 was enrolled without obtaining prior participant assent, and

(3) Eligibility statements after subjects' screening was not signed by the principal investigator for subjects enrolled in Study 060-633.

OSI Medical Officer's Comments: (See item #1 above)

The clinical site was inspected due to potential concerns with nasal septal perforation. For this specific case (Subject #0005PKN in Study M1-602), the patient's pre-existing condition may have contributed to the adverse event report.

OSI Medical Officer's Comments: (See item #3 above)

For enrolled subjects in Study 060-633, whose eligibility statements were not signed initially by the principal investigator in item #3 above, this finding was not considered critical. The eligibility forms were signed after randomization. There was no evidence that the major eligibility criteria were violated in this study.

The field investigator also listed as an observation that eight subjects enrolled in Study M1-602 were also enrolled subsequently, after a gap between studies, in Study 060-633, in apparent violation of study eligibility criteria.

OSI Medical Officer's Comments: Based on further review of the protocols for Study M1-602 and Study 060-633, it appears that somewhat conflicting information is related to subject eligibility for subsequent investigational study enrollment. Specifically, Protocol M1-602 exclusion items #3 and #14 and Protocol 060-633 exclusion items #4 and #12 contain statements that may be interpreted as conflicting statements. Exclusion criteria #3 or #4, respectively, state: participation in any investigational drug trial within the 30 days preceding the screening visit or planned participation in another investigational drug trial at any time during this trial. Exclusion criteria #12 or #14, respectively, state: previous participation in an intranasal ciclesonide HFA nasal aerosol study. Of note, all eight subjects listed in the Form FDA 483 observations completed Study M1-602 in 2007 and were not enrolled in Study 060-633 until 2009. This observation was discussed with reviewers in DPARP, who concurred with OSI that this was not a critical finding, nor would re-enrollment of eight subjects at this site be expected to have a significant impact on analyses.

d. Data acceptability/reliability for consideration in the NDA review decision.

The regulatory violations noted above, related to lack of adherence to the study protocol and incomplete record keeping are considered sporadic or minor in nature and to not significantly impact overall study data reliability. Data submitted by this clinical site appear acceptable for this specific indication.

2. Robert Lee Jacobs, M.D./Study Protocols 060-022 Site #003, 060-634 Site #003, and 060-033 Site #014

Biogenics Research Institute
8233 Fredericksburg Road
San Antonio, TX 78229

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from July 25-August 12, 2011.

For Study Protocol 060-622, a total of 146 subjects were screened, 124 subjects were randomized, and 121 subjects completed the study. There was no under-reporting of serious adverse events noted. An audit of 28 of enrolled study subjects was conducted.

For Study Protocol 060-634, a total of 162 subjects were screened, 100 subjects were randomized, and 100 subjects completed the study. There was no under-reporting of serious adverse events noted. An audit of 37 of enrolled study subjects was conducted.

For Study Protocol 060-633, a total of 48 subjects were screened, 39 subjects were randomized and 37 subjects completed the study. There was no under-reporting of serious adverse events noted. An audit of 23 of enrolled study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Based on OSI review of preliminary inspection results, it appears that the study was conducted adequately. Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and NDA subject line listings. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data, in support of clinical efficacy and safety from this clinical site, appear acceptable for this specific indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two U.S. clinical investigator sites were inspected in support of this application; Dr. Goldberg's site for Protocols M1-602 and 060-033 and Dr. Jacob's site for Protocols 060-622, 060-634, and 060-633. Based on review of inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication.

While a Form FDA 483 was issued to Dr. Goldberg for observations that are consistent with regulatory violations, the violations (related to lack of adherence to the study protocol and incomplete record keeping) are considered sporadic or minor in nature and to not significantly impact overall study data reliability from this site. The final classification for the inspection of Dr. Goldberg is Voluntary Action Indicated (VAI).

Based on preliminary inspectional findings received for the inspection of Dr. Jacob's site, no regulatory violations were observed and the data from this site are considered reliable.

Note: Observations noted above, for Dr. Jacobs' site are based on the preliminary communications from the field investigator; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

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

/s/

ANTHONY J ORENCIA
09/28/2011

LAUREN C IACONO-CONNORS
09/28/2011

JEAN M MULINDE
09/29/2011

1. General Information

Nycomed GmbH has submitted a 505(b)(2) application for Ciclesonide HFA nasal inhaler “for treatment of symptoms associated with seasonal and perennial allergic rhinitis (PAR and SAR) in adults and adolescents 12 years of age and older” (proposed label). It will be nasally administered using a metered dose inhaler (MDI) with a nasal adaptor. The proposed dose is 80mcg daily (40mcg each nostril). This drug/device was developed in the U.S. by Sunovion (formerly Sepracor) under IND 76,674. The proposed dosing is 40mcg each nostril daily. Ciclesonide is a non-halogenated glucocorticoid that is rapidly metabolized to des-ciclesonide. This metabolite has a very high affinity for the glucocorticoid receptor, and is primarily responsible for this drug’s pharmacologic activity. The sponsor developed this product to meet the needs of patients who prefer an HFA delivery system over a nasal spray.

An aqueous suspension of ciclesonide is currently approved for use in patients with SAR/PAR as a nasal spray in patients 6 years old and older (Omnaris, NDA 22,004). In addition, ciclesonide is also approved to be delivered via an MDI for chronic therapy in asthma in patients 12 years and older (Alvesco, NDA 21,658). Nycomed plans to use these approved products as the basis for the 505(b)(2) submission route.

2. Regulatory History

Prior to submission of this NDA, this product have been the subject of multiple regulatory proceedings (as IND 74,674), summarized below:

10/16/06: Pre-IND meeting

11/10/06: IND submission

12/15/08: EOP2 meeting. The major points of discussion were as follows:

- Agreement to carry forward the 80 mcg and 160 mcg doses for evaluation in phase 3, with the caveat that depending on the results of the phase 3 trials, lower doses may be required for evaluation in the pediatric population.
- 12 months of long-term safety data would be needed. A reasonable approach would be for the Sponsor to plan for a one-year study, but to examine the 6-month data, and if found acceptable, submit the NDA with plans to submit the one-year data at the time of the 4- month safety update. The Division also commented that a controlled safety study was preferred, and that in the absence of a control arm, all adverse events would be attributable to the proposed product.
- Agreement that the overall design of the proposed HPA axis study appeared adequate, but that patients 12 years and older should be included.
- Statement that the proposed HPA-axis study should include an assessment of efficacy, and, if feasible, PK measurements to assure compliance.
- Statement that the results of the HPA-axis study would ultimately be described (compared to placebo) in the clinical pharmacology section of a label, without statements regarding non-inferiority.
- Agreement that two SAR trials and one PAR trial would be sufficient to support efficacy provided that they all showed the desired result.

11/3/10: Pre-NDA meeting. The major points of discussion were as follows:

- Agreement that the likely effective dose is 80mcg/day, pending review of data.
- Agreement that the clinical development program (two phase 3 SAR studies, and one phase 3 PAR study) would be adequate to support review.
- Agreement that data from the two replicate SAR trials (060-622 and 060-634) could be pooled.
- Statement that the scintigraphy study appeared reasonable, but it is unlikely that the results would be included in the product label.
- Agreement that Alvesco growth study 343 provided sufficient data for the proposed product such that no further growth studies are needed.

10/20/06: NDA 22,004 was approved for ciclesonide nasal spray (Omnaris)

01/10/08: NDA 21,658 was approved for ciclesonide HFA inhalational solution (Alvesco)

3. Marketing History

This product has not been approved or marketed in the US or in any foreign countries. However ciclesonide as an aqueous suspension have been approved (10/20/06) and marketed in the U.S. as Omnaris for the treatment of SAR/PAR. Marketing authorizations have also been granted in 8 additional countries. Additionally, ciclesonide has also been approved (1/10/08) marketed in the U.S. as an inhalational aerosol containing HFA-134a and ethanol delivered via an MDI for the treatment of asthma (Alvesco). Marketing approval has been granted in 58 countries. The canister used for Alvesco is identical to the one for the proposed product.

4. Items Required for Filing

The following items pertinent to a clinical review are included in the submission.

- Application form (FDA 356h): 1.1.2
- Index : eCTD
- Summary 2.7 (clinical summary)
- Clinical technical section
 - Clinical study reports
 - Study report 5.3.5.1
 - Reports of analyses of data from more than one study: 5.3.5.3
 - Integrated summary of efficacy 2.7.3
 - Integrated summary of safety 5.3.5.3
 - Good Clinical Practice: within the body of each study report
 - Debarment certification: 1.3.3
 - Pediatric use: 1.9.1- Waiver, 1.9.2- deferral
- Labeling: 1.14

- Case report forms: 5.3.5.1
- Financial disclosure 1.3.4

5. Development Program

This clinical development program includes 10 clinical trials. Six were phase 1 or 2 trials assessing PK, PD, safety, lung deposition, HPA axis effects, and dose ranging. The phase 3 trials consisted of two replicated safety and efficacy trials in patients with SAR (060-622 and 060-634) and one safety and efficacy trial in PAR patients (060-633). Doses used in these studies were 80 and 160 mcg daily, based on results from the dose ranging study (M1-602). Study 060-633 is being extended as an open label safety study (060-635) for an additional 6 months. These results will be reported in the 120 day safety update. The studies are summarized in the table below:

Table 1. Studies in Clinical Development Program

Study	Objective	Design	Population	Ciclesonide Dose	Status
Phase 1 and 2					
M1-422	PK	R, OL, CO	Healthy Subjects 18-30 years old N=30	HFA nasal 320 mcg x1 AQ nasal 300 mcg x1 HFA oral 320 mcg x1	Completed
060-101	Lung deposition	OL	Healthy Subjects N=10	99mTc Ciclesonide HFA nasal 160 mcg x1 AQ nasal 200 mcg x1	Completed
M1-601	PK, safety, HPA axis	R, DB, PC, 3 way CO	PAR patients 18-60 years old N=18 Healthy Subjects 18-60 years old N=18	HFA nasal: 320 mcg qDay x 14 days 160 mcg qDay x 14 days	Completed
060-610	Safety, HPA axis	MC, R, DB, PC	PAR patients >=12 years N=310	HFA nasal: 160 mcg qDay x 6 weeks (N=60) 320 mcg qDay x 6 weeks (N=51) AQ nasal: 200 mcg q Day x 6weeks (N=48) Dexamethasone Oral: 6 mg qDay x 4 days (placebo groups only (N=94)	Completed
FHP-017	Pilot study for efficacy	R, DB, PC, 2 way CO	SAR patients 18-45 years old N=24	HFA nasal (pilot actuator) 400 mcg qDay x 7 days	Completed
M1-602	Dose range, safety, efficacy	MC, R, DB, PC	SAR patients >= 12 years old N=513	HFA nasal: 80 mcg qDay x 2 weeks (N=22) 160 mcg qDay x 2 weeks (N=125) 320 mcg qDay x 2 weeks (N=136)	Completed
Phase 3					
060-622	Safety/efficacy in SAR	MC, R, DB, PC	SAR patients >=12 years old N=707	HFA nasal: 80 mcg qDay x 2 weeks (N=237) 160 mcg qDay x 2 weeks (N=235)	Completed
060-634	Safety/efficacy in SAR	MC, R, DB, PC	SAR patients >=12 years old N=671	HFA nasal: 80 mcg qDay x 2 weeks (N=226) 160 mcg qDay x 2 weeks (N=225)	Completed

060-633	Safety/efficacy in PAR	MC, R, DB, PC	PAR patients ≥ 12 years old N=1111	HFA nasal: 80 mcg qDay x 6 weeks (N=298) 160 mcg qDay x 6 weeks (N=506)	Completed
060-635	Long-term safety (extension of 060-633)	OL	PAR patients ≥ 12 years old	HFA nasal 160 mcg qDay x 26 weeks	Ongoing. Full results to be reported at 120 day update

R=randomized, DB=double-blind, PC=placebo controlled, MC=multi-center, OL=open label, CO=cross-over, HFA nasal= test product, AQ nasal=Omnaris, HFA oral=Alvesco.

6. Clinical Studies

Only studies pertinent to the proposed indication will be reviewed below. This will include studies M1-602, 060-622, 060-634, and 060-633. Study report for 060-635 will be provided at the 120 day update.

6.1. Study M1-602

This was double-blind, randomized, placebo controlled, dose ranging study where SAR patients were given either 80 mcg, 160 mcg, or 320 mcg daily of the test product for 2 weeks. The study consisted of a run in period and a treatment period. During the run-in period, all patients received placebo and assessed/recorded their instantaneous and reflective nasal (iTNSS/rTNSS) and non-nasal symptoms (iTOSS/rTOSS). Following the run-in period, patients were randomized to one of the three doses and followed for 14 days. Patients were required to have positive skin prick tests to the relevant allergens and no nasal pathology by history or exam. In order to randomized, they also had to be sufficiently symptomatic based on rTNSS.

A total of 513 patients were randomized and 498 completed the study. The number of discontinuations were low and similar between treatment groups. Reasons for discontinuation were also similar. The most common reasons were adverse events.

The primary endpoint was change from baseline in of the average AM/PM rTNSS over the 2 week period. Key secondary endpoints were change from baseline in the average AM/PM iTNSS, average AM iTNSS, Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), and AM rTOSS. The study results for the primary and key secondary efficacy endpoints are summarized in the table below:

Table 2. Efficacy Results for M1-602

	Ciclesonide Dose			
	80 mcg	160 mcg	320 mcg	Placebo
Avg AM/PM rTNSS				
N	122	125	136	129
Change from baseline over the 2 week treatment period				
LS Mean (SE)	-1.98 (0.18)	-2.21 (0.18)	-2.12 (0.17)	-1.32 (0.18)
Treatment difference vs. Pbo (95% CI)	0.66 (0.16, 1.16)	0.90 (0.4, 1.39)	0.81 (0.32, 1.29)	
p-value vs. Pbo	0.01	<.0001	0.001	
Avg AM/PM iTNSS				
N	122	125	136	129
Change from baseline over				

the 2 week treatment period				
LS Mean (SE)	-1.89 (0.18)	-2.00(0.18)	-1.89(0.17)	-1.14 (0.18)
Treatment difference vs. Pbo (95% CI)	0.75 (0.25, 1.25)	0.86 (0.36, 1.35)	0.75 (0.26, 1.23)	
p-value vs. Pbo	0.003	<0.001	0.002	
AM iTNSS				
N	122	125	136	129
Change from baseline over the 2 week treatment period				
LS Mean (SE)	-1.92 (0.19)	-2.06 (0.18)	-1.89 (0.18)	-1.03 (0.18)
Treatment difference vs. Pbo (95% CI)	0.88 (0.37, 1.39)	1.03 (0.52, 1.53)	0.86 (0.36, 1.35)	
p-value vs. Pbo	<0.001	<0.001	<0.001	
RQLQ				
N	79	86	87	90
Change from baseline over the 2 week treatment period				
LS Mean (SE)	-1.56 (0.15)	-1.32 (0.15)	-1.50 (0.14)	-1.24 (0.14)
Treatment difference vs. Pbo (95% CI)	0.32 (-0.09, 0.72)	0.08 (-0.31, 0.48)	0.26 (-0.14, 0.65)	
p-value vs. Pbo	>0.05	>0.05	>0.05	
AM reflective non-nasal symptoms				
N	121	125	136	129
Change from baseline over the 2 week treatment period				
LS Mean (SE)	-1.54 (0.18)	-1.45 (0.18)	-1.51 (0.17)	-1.06 (0.17)
Treatment difference vs. Pbo (95% CI)	0.48 (-0.01, 0.97)	0.38 (-0.11, 0.87)	0.45 (-0.03, 0.92)	
p-value vs. Pbo	>0.05	>0.05	>0.05	

Aside from the RQLQ and change in AM reflective non-nasal symptoms scores, the other endpoints all demonstrated a statistically significant improvement in those who receive ciclesonide versus placebo. However there is no difference in improvement between doses. Those who received the highest dose of the test article had similar improvement in scores as compared to those who received the lowest dose.

No deaths occurred during this study. With regard to adverse events, there were similar numbers of treatment emergent AEs across all treatment groups and were similar to placebo. Discontinuations due to TEAEs were also similar across all groups. The most common TEAE's were headache and nasal discomfort. There was no apparent relationship between dose and TEAEs.

Notably, one patient in this study had inflammation of the turbinates during the screening exam, septal erosions at the end of the run-in period, and a septal perforation at the end of the 2 week period. This patient had been receiving the 80 mcg dose.

Reviewer comment:

From this study, the test article appears to improve nasal symptoms related to SAR, but not non-nasal symptoms. Based on this study, dosing at 80 mcg or greater will likely be effective. However a "no effect" dose was not identified. It is unclear if 80 mcg is the minimally effective dose. Further improvement in symptoms does not appear to be dose related. The AE profile is similar to other nasal corticosteroids. With regard to the septal perforation, it is unclear why the

patient was allowed to proceed at the end of the run-in period, as an inclusion criteria was lack of nasal pathology.

6.2. Study 060-622

This was double-blind, randomized, placebo controlled, parallel group, multi-center study in SAR patients given either 80 mcg or 160 mcg of the test product for 2 weeks. The study consisted of a screening period from days 3-30 (visit 1), followed by a 7 day single blind placebo run in period (visit 2), a 14 day treatment period (started visit 3), and a wash-out period (7 days). Visit 4 occurs after 1 week of treatment. Visit 5 occurs after 14 days of treatment. After the wash-out period, a final telephone assessment was performed. Patients were required to have a positive skin prick test to Mountain Cedar and have a 2 year history of SAR. Patients were excluded if they planned to leave the study area for more than 2 days. To be randomized the patients had to be sufficiently symptomatic based on rTNSS.

Each site recorded pollen counts and rainfall throughout the study. The single blind run-in visit was scheduled when Mountain Cedar pollen counts were elevated for at least 3 consecutive days (≥ 50 grains per cubic meter). Randomization of all subjects occurred within 14 consecutive days.

A total of 1096 patients were screened for this study, a total of 912 patients enrolled, and 707 patients were eventually randomized. The primary reason for randomization failure was lack of sufficient symptoms. Approximately twice as many patients dropped out of the placebo group as compared to the treatment groups.

The primary endpoint was change from baseline in of the average AM/PM rTNSS over the 2 week period. Key secondary endpoints were change from baseline in the average AM/PM iTNSS, and AM/PM rTOSS. The results for the primary and key secondary endpoints are summarized in the table below

Table 3. Efficacy Results Study 060-622

	Ciclesonide Dose		
	80 mcg	160 mcg	Placebo
Avg AM/PM rTNSS over the two week double blind period			
N	237	235	235
Change from baseline			
LS Mean (SE)	-1.45 (0.14)	-1.59 (0.14)	-0.51 (0.14)
Treatment difference vs. Pbo (95% CI)	0.94 (0.57, 1.32)	1.08 (0.7, 1.45)	
p-value vs. Pbo	<0.0001	<0.0001	
Avg AM/PM iTNSS over the two week double blind period			
N	237	235	235
Change from baseline			
LS Mean (SE)	-1.34 (0.13)	-1.47 (0.13)	-0.47 (0.13)
Treatment difference vs. Pbo (95% CI)	0.87 (0.5, 1.25)	1.00 (0.63, 1.37)	
p-value vs. Pbo	<0.0001	<0.0001	
Avg AM/PM rTOSS over the two week double blind period			
N	164	160	147
Change from baseline over the 2 week treatment period			
LS Mean (SE)	-1.06 (0.12)	-1.05 (0.12)	-0.44 (0.12)

Treatment difference vs. Pbo (95% CI)	0.61 (0.28, 0.95)	0.60 (0.27, 0.94)	
p-value vs. Pbo	0.0007	0.0009	

Treatment with ciclesonide is associated with statistically significant improvement in the primary and key secondary endpoints. The improvement is modest, but on par with data from the Omnaris trials. There is again no difference between doses.

Safety evaluation was performed on the ITT population. The mean duration of exposure was between 14.2 and 14.5 days across treatment groups. There were no deaths in this study. Three (3) patients reported 4 SAEs. For 2 of the 3 patients (3/4 of the SAEs), the SAEs occurred either during the screening phase or single blind placebo run-in phase. The remaining SAE was gastroesophageal reflux and occur six days after starting study medication (160 mcg). The subject presented to the ER with abdominal and chest pain. Subsequent work up lead to the diagnosis of GERD. Treatment emergent AEs occurred most frequently in the placebo group (24.7%). In the 80 mcg and 160 mcg treatment groups 21.5% and 18.7% of subjects reported TEAEs, respectively. The most common was epistaxis (placebo, 80 mcg, and 160 mcg were 4.3%, 3.4%, and 2.1% of subjects, respectively). Only 7/707 patients withdrew due to AE's. With regard to nasal specific TEAEs, they were evenly distributed across all groups. No septal perforations were reported, though there were several episodes of nasal ulceration (0.4%, 1.3%, and 0.9% of subjects in the placebo, 80 mcg, and 160 mcg groups, respectively). These resolved without intervention. Mean clinical lab values did not change significantly between baseline and end of study. However one patient did develop elevations in ALT and AST.

6.3. Study 060-634

This study was almost identical in design to study 060-622.

A total of 1096 patients were screened for this study, a total of 860 patients enrolled, and 671 patients were eventually randomized. The primary reason for randomization failure was lack of sufficient symptom severity. More patients dropped out of the placebo group as compared to the treatment groups. The most common reasons for discontinuation were adverse events or withdrawal by the subject. Both were more frequent in the placebo group compared to ciclesonide groups.

The primary endpoint was change from baseline in of the average AM/PM rTNSS over the 2 week period. Key secondary endpoints were change from baseline in the average AM/PM iTNSS, AM/PM rTOSS, RQLQ(S). The results for the primary and key secondary endpoints are summarized in the table below

Table 4. Efficacy Results 060-634

	Ciclesonide Dose		
	80 mcg	160 mcg	Placebo
Avg AM/PM rTNSS over the two week double blind period			
N	226	225	220
Change from baseline			
LS Mean (SE)	-1.75 (0.15)	-1.74 (0.15)	-0.72 (0.16)
Treatment difference vs. Pbo (95% CI)	1.04 (0.61,1.46)	1.02 (0.59, 1.45)	
p-value vs. Pbo	<0.0001	<.0001	
Avg AM/PM iTNSS over the two week double blind period			
N	226	225	220
Change from baseline			
LS Mean (SE)	-1.58 (0.15)	-1.51 (0.15)	-0.68 (0.15)

Treatment difference vs. Pbo (95% CI)	0.90 (0.49, 1.32)	0.83 (0.42, 1.25)	
p-value vs. Pbo	<0.0001	0.0002	
Avg AM/PM rTOSS over the two week double blind period			
N	159	161	165
Change from baseline over the 2 week treatment period			
LS Mean (SE)	-1.40 (0.13)	-1.21 (0.13)	-0.88 (0.13)
Treatment difference vs. Pbo (95% CI)	0.52 (0.15, 0.89)	0.34 (-0.03, 0.71)	
p-value vs. Pbo	0.0124	0.1444	
Overall RQLQ(S) at end of 2 week period			
N	162	148	147
Change from baseline over the 2 week treatment period			
LS Mean (SE)	-1.44 (0.11)	-1.41 (0.12)	-0.88 (0.13)
Treatment difference vs. Pbo (95% CI)	0.64 (0.33, 0.95)	0.62 (0.3, 0.94)	
p-value vs. Pbo	0.0124	N/A	

Treatment with ciclesonide is associated with statistically significant improvement in the primary and key secondary endpoints for the 80 mcg dose, though not at the 160 mcg dose for the key secondary endpoints. Comparison of the 160 mcg dose to placebo for the RQLQ end point was not performed due to the stopping rule implemented from the pre-specified multiple comparison procedure [the 160 mcg dose compared to placebo was not statistically significantly different ($p < 0.025$) for the rTOSS endpoint, so further analysis for subsequent key secondary endpoints were not done].

Safety evaluation was performed on the ITT population. The mean duration of exposure was between 14.6 and 14.8 days across all treatment groups. There were no deaths in this study. Two (2) patients reported 2 SAEs. One SAE was for lung neoplasm and was detected during the screening phase, and the other occurred during the single blind run-in phase. Treatment emergent AEs were evenly distributed across all groups. The most common was epistaxis (placebo, 80 mcg, and 160 mcg were 1.8%, 1.3%, and 2.7% of subjects, respectively). Only 9/671 patients withdrew due to AE's. With regard to nasal specific TEAEs, they were relatively evenly distributed across all groups. One (1) septal perforation was reported in the 80 mcg group. There was also an increased number of nasal mucosal disorders and nasal septal disorders in the ciclesonide groups in the treatment groups. They were more frequent in the 160 mcg groups compared to the 80 mcg group.

Reviewer comment for trials 060-622 and 060-634:

Both of these trials demonstrated statistically significant improvement in both reflective and instantaneous TNSS, though those increases were modest. Of note, both pivotal trials in SAR were conducted in the Mountain Cedar population, which is known to be a stronger allergen than other grass and tree pollens. This suggests that the efficacy may be less demonstrable in other SAR populations and will be noted in the label.

Only one study demonstrated improvement in ocular symptoms at the end of the 2 week treatment period. The higher dose did not demonstrate any additional benefit compared to the lower dose (statistically or nominally). Based on these studies, it is clear that the 80 mcg dose can improve nasal symptoms in SAR, however, it is unclear if that dose is the minimally effective dose. When studies are performed on children, lower dosing may be indicated.

It is concerning that there are two nasal septal perforations noted (one in this trial and one in Study 060-602. While septal perforations are observed with other nasal corticosteroids, this adverse event has generally been seen post-marketing rather than in clinical trials. Specific attention will be given to this issue during the review.

6.4. Study 060-633

This was a 6 month multi-center, randomized, double-blind placebo controlled, parallel group efficacy and safety study of ciclesonide in patients with 12 years and older with PAR. Patients were given either placebo, 80 mcg or 160 mcg daily following randomization. This study consisted of a screening period (7-21 days) from visit 1 to 2, followed by a single blind run in period (7-10 days) from visit 2 to 3. The double blind treatment period lasted 26 weeks beginning at visit 3 (randomization), and consisted of clinic visits at week 2, 4, 6, 10, 14, 18, 22, and 26. Patients were required to have positive skin prick test to house dust mite, cockroach, molds, and animal dander, and have had a diagnosis of PAR for 2 years. Patients had to be sufficiently symptomatic to be randomized. At the end of this study, patients were allowed to continue in a 6 month open label extension (060-635).

A total of 1866 patients were screened for this study, a total of 1551 patients enrolled, and 1111 patients were eventually randomized. The primary reason for randomization failure was lack of sufficient symptom severity. Similar numbers of patients dropped out across all groups. The most common reasons for discontinuation were adverse events or withdrawal by the subject. More patients in the ciclesonide groups dropped out due to AEs compared to the placebo group. This occurred in a dose dependent fashion (2%, 2.7%, 3.2%).

The primary endpoint was change from baseline in of the average AM/PM rTNSS over the first 6 weeks of treatment. Key secondary endpoints were change from baseline in the average AM/PM iTNSS over the first 6 weeks of treatment. The results for the primary and key secondary endpoints are summarized in the table below:

Table 5. Efficacy Results Study 060-633

	Ciclesonide Dose		
	80 mcg	160 mcg	Placebo
Avg AM/PM rTNSS over the first 6 weeks of treatment			
N	298	504	305
Change from baseline			
LS Mean (SE)	-1.98 (0.13)	-1.82 (0.10)	-1.28 (0.13)
Treatment difference vs. Pbo (95% CI)	0.69 (0.35, 1.04)	0.54 (0.24, .84)	
p-value vs. Pbo	<0.0001	0.0006	
Avg AM/PM iTNSS over the first 6 weeks of treatment			
N	298	504	305
Change from baseline			
LS Mean (SE)	-1.76 (0.12)	-1.60 (0.10)	-1.18 (0.12)
Treatment difference vs. Pbo (95% CI)	0.58 (0.25, 0.92)	0.42 (0.12, 0.72)	
p-value vs. Pbo	0.0007	0.0061	

Ciclesonide appeared to have a statistically significant effect in terms of the primary and key secondary endpoints.

Safety evaluation was performed on the ITT population at the 6 week and 6 month timepoint. The mean duration of exposure was between 168.8 to 170.2 days across treatment groups. There were no deaths in this study. Twenty (20) patients reported 28 SAEs after 6 months of therapy. The SAEs were evenly distributed across all groups. At 6 weeks and 6 month timepoint, overall treatment emergent AEs were relatively evenly distributed across all groups. The most common 6 week TEAE was epistaxis (placebo, 80 mcg, and 160 mcg were 3.3%, 4.7%, and 4.6% of subjects, respectively). At 6 months, epistaxis occurred more frequently in the 80 mcg and 160 mcg groups compared to placebo. During the first 6 weeks, 13/1110 patients withdrew due to TEAE's. With regard to nasal specific TEAEs at 6 weeks, higher total numbers were reported in the 160mcg group, however percentages were similar across all groups.

Two (2) septal perforations were reported at the 6 month timepoint, and both were in the placebo group. There were also an increased number of nasal mucosal disorders and nasal septal disorders (6 month data) in the ciclesonide groups than in the treatment groups. Both seemed to be dose related.

Reviewer comment:

Similar to the SAR data, the effect of the test article on nasal symptoms is statistically significant, but modest. Symptoms did not improve in a dose responsive manner. Known AEs related to nasal corticosteroids were also present (epistaxis, nasal septum disorders, nasal mucosal disorders). Not surprisingly, these were higher in frequency at the 6 month time point compared to the 6 week timepoint.

7. Brief Review of Proposed Labeling

Proposed labeling has been included in this submission. A brief review was performed. The content and format is presented in the Physician Labeling Review (PLR) format. Much of the language is taken from the Omnaris and Alvesco label. However, Nycomed's stated indication is for "treatment of symptoms associated with seasonal and perennial allergic rhinitis," and is not limited to nasal symptoms as was the case with Omnaris. In the "Clinical Studies" section, Nycomed also adds language regarding TOSS and RQLQ. Based on preliminary review, it is unclear if the claims of improvement of TOSS and RQLQ are warranted. Although there was statistically significant improvement at the 80 mcg dose, that was not the case for the 160 mcg dose. The lack of response to the higher dose and relatively small treatment effect at the lower dose may imply that the findings are a false positive. Of note, both pivotal trials in SAR were conducted in the Mountain Cedar population. This will be noted in the label.

With regards to safety, [REDACTED] (b) (4)
[REDACTED] in both studies 060-634 and M1-602, there was one septal perforation in the ciclesonide groups.

8. DSI/Audit

For studies 060-622 and 060-634, 6 of the 8 total study sites received a QA-GCP audit. For study 060-633 a total of 14 sites were audited. This included the top 9 sites in terms of randomized patients. However, a request for DSI consultation will be submitted. The consultation request will include the following sites for inspection:

Frank Hempel Jr., MD (Site 2 in studies 060-622/060-634 and site 12 in study 060-633)
Central Texas Health Research
4410 Medical Drive, Ste 360
San Antonio, TX

This site randomized the 3rd most patients overall in studies 060-622 and 060-634, and had the highest number of AEs. This site also randomized an average number of patients in study 060-633. This site was also not previously audited.

A second site is as follows:

Stephen A. Tilles, MD
ASTHMA, Inc.
4540 Sand Point Way NE, Suite 100
Seattle, WA 98105

This site had the highest number of AEs (total and nasal), was not previously audited, and recruited an average number of patients for study 060-633.

9. Pediatric Development

The sponsor requests a waiver for the 0-2 year old population, and a deferral for the studies in the 2-11 year old age group. The sponsor plans the following pediatric trials once adolescent and adults studies have been completed and incorporated into the marketing application:

- 1) PK study comparing ciclesonide nasal aerosol compared to ciclesonide nasal spray to inform dosing in the pediatric population.
- 2) One 2 week SAR study in pediatric patients aged 2-11 years
- 3) One 12 week PAR study in pediatric patients aged 2-11 years. The primary endpoint would be assessed at 6 weeks, and an additional 6 weeks of safety data would be collected. Urinary cortisol data will be collected on a subset of patients 6-11 years old.

Reviewer comment:

The sponsor does not plan formal dose ranging studies in the pediatric population. They cite previous Omnaris studies demonstrating that doses lower than the adult/adolescent doses were not effective in the pediatric population. However, given that this is a new delivery system and a "no effect" dose was not demonstrated in the current studies, dose ranging studies may be required in their pediatric studies.

10. Summary

This is a 505(b)(2) application for the ciclesonide HFA nasal aerosol submitted by Nycomed. The reference products are Omnaris (NDA 22,004) and Alvesco (NDA 21,658). The proposed indication is for the treatment of symptoms associated with allergic and perennial rhinitis in the ≥ 12 year old population. In this application, they have submitted 3 pivotal studies, one dose ranging studies, and several supporting studies.

This submission is adequate to allow for filing.

11. Review Timeline

Milestone	Target date for completion
Filing meeting	5/2/11
Filing review	5/4/11
Trial M1-602	5/13/11
Trial 060-622/634	6/3/11
Trial 060-633	6/21/11
Trial 060-635 (120 day safety update)	7/27/11
Analysis of key trials complete	8/1/11
Mid-cycle review	8/12/11
Integrated Summary of Efficacy	8/19/11
Integrated Summary of Safety	9/2/11
Initial Draft Primary Review to TL	10/2/11
Draft Label Review to TL	11/16/11
Wrap up meeting	12/6/11
Label due	12/13/11
Final Primary Review	12/16/11
PDUFA Action date (10 months)	1/20/12

12. Comments for the 72 day letter

We note that the improvements in ocular symptom score and RQLQ were not consistent in trials 060-622 and 060-634 at the higher ciclesonide dose. Whether or not this discrepancy will affect your proposed labeling claims regarding these outcomes will be a review issue.

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

/s/

ROBERT H LIM
05/05/2011

THERESA M MICHELE
05/05/2011