CLINICAL REVIEW

Application Type	NDA 21-861
Submission Number	N-000
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Letter Date	September 26, 2007
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Reviewer Name	James Kaiser, M.D.
Review Completion Date	March 6, 2008
Established Name	Olopatadine Hydrochloride
(Proposed) Trade Name	PATANASE® (olopatadine hydrochloride) Nasal Spray
Therapeutic Class	H_1-receptor antagonist, antihistamine
Applicant	Alcon Research, Ltd.
Priority Designation	Standard
Formulation	Nasal spray
Dosing Regimen	Two sprays per nostril twice daily
Indication	[redacted] of symptoms of seasonal allergic rhinitis
Intended Population	Patients with seasonal allergic rhinitis 12 years old and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

There are adequate efficacy and safety data to recommend approval of olopatadine 0.6% nasal spray for the [redacted] of patients with seasonal allergic rhinitis. The chief concern regarding the prior, povidone-containing formulation was the presence of nasal septal perforations occurring in the clinical trials. Alcon's newly-submitted single-dose pharmacodynamic study C-05-64 demonstrated a similar effect on nasal symptoms to that produced with the prior formulation, allowing a presumption that previously-generated efficacy information in seasonal allergic rhinitis would apply to the new product. No nasal septal perforations or other notable safety events occurred in the first 6 months of the 12-month safety trial C-05-69 that would preclude market approval.

A manufacturing site inspection has not been conducted by FDA at the time of this review. I recommend an "Approval" action if the site is found to be acceptable. I recommend an "Approvable" action if the site is found to be unacceptable.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

I do not recommend risk management activities for this application

1.2.2 Required Phase 4 Commitments

I do not recommend Phase 4 commitments for this application

1.2.3 Other Phase 4 Requests

I do not recommend Phase 4 requests for this application.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This is a review of newly submitted data. For review of Alcon's original, December 2004 NDA, see Dr. Charles Lee's Medical Officer review. The key clinical data included in the original NDA were two pivotal 2-week efficacy and safety trials in seasonal allergic rhinitis, a 12-month safety trial in subjects with perennial allergic rhinitis, and two single-dose environmental exposure unit trials. Clinical data also included three additional environmental

exposure unit studies, two 2-week trials and one 8-week clinical trial in subjects with seasonal allergic rhinitis, and 7 clinical pharmacology trials. The NDA was found not approvable. FDA stated in the nonapprovable letter of October 27, 2005, in part:

> Data submitted show that Patanase Nasal Spray has an unfavorable safety profile for use under labeled conditions given its benefits. Patanase Nasal Spray caused nasal irritation and serious damage to the nasal mucosa. In the clinical studies there were unacceptable high frequencies of nasal septal perforation, nasal ulceration, and epistaxis. Preclinical data showed that povidone, an excipient in the formulation, was markedly irritating to the nasal mucosa.

In addition, the NDA was found insufficient to support the proposed indication for [redacted].

The current submission contains two trials whose data provide support for the proposed, povidone-free formulation (Table 1) in the [redacted] of patients with seasonal allergic rhinitis.

[redacted]

C-05-64, a study of the nasal effects of a single dose of olopatadine nasal spray, is a pharmacodynamic link to the older formulation. Its results allow a presumption that the 2-week efficacy in patients with seasonal allergic rhinitis demonstrated for the older, povidone-containing formulation would be the same with use of the current formulation. C-05-69's 6-month safety results show that the new formulation did not result in nasal septal perforations. It was designed to address the safety concerns from the previous formulation. The results of these two studies, in conjunction with the previously submitted clinical and nonclinical information, are sufficient to allow marketing approval of olopatadine 0.6% nasal spray.

Alcon has also conducted other trials of a povidone-containing formulation (Table 2) that are not important to the marketing approval decision about the proposed formulation. However, one of the trials (C-04-70) contains relevant safety information for labeling.

1.3.2 Efficacy

The original marketing submission contained replicate 2-week clinical trials conducted in subjects with seasonal allergic rhinitis. The clinical review of the original marketing submission by Dr. Charles Lee concluded that the data support efficacy of both a 0.4% and 0.6% olopatadine nasal spray formulation, but that there was an efficacy advantage for the 0.6% formulation. The review noted that improvements were noted for runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes and that the data also supported end-of-dosing-interval efficacy. Further efficacy information was not required for the marketing approval decision.

Clinical trial C-05-64, an environmental exposure unit trial, demonstrated that a single dose of the new formulation in symptomatic subjects with seasonal allergic rhinitis results in a similar effect, as measured by the total nasal symptom score at various times over 12 hours, as that produced with the former, povidone-containing formulation. Statistical differences from vehicle control were seen at each time point, including 30 minutes, over a 12-hour period. This finding is a critical link allowing the efficacy data from the prior formulation to support market approval. Olopatadine 0.6% nasal spray produced a statistical difference from placebo at 30 minutes. Because this replicates the finding of the previously-submitted single-dose

environmental unit trial C-03-52, it may now be concluded that symptoms, as recorded on the total nasal symptom score instrument, are improved after 30 minutes.

[redacted]

1.3.3 Safety

The primary evidence of safety of the new formulation comes from the 6-month results from C-05-69, a 12-month vehicle-controlled safety trial in 890 subjects with perennial allergic rhinitis. FDA had agreed, prior to the submission of the NDA, that the 6-month results would in principle be sufficient for a marketing approval decision. The trial collected adverse event information and the results of monthly nasal examinations; it did not collect detailed information on cardiovascular effects or clinical laboratory evaluations. No subject died, and serious adverse events did not form a notable pattern. The chief safety concern regarding the previous povidone-containing formulation of olopatadine nasal spray was the incidence of nasal septal perforations, which occurred in 1 subject on active drug and 2 vehicle control subjects in the clinical program before the drug was reformulated. Alcon reports no nasal septal perforations from either C-05-64 or C-05-69. Nasal ulceration occurred in more olopatadine-treated than vehicle-treated subjects (8.8% compared to 5.8%), but the events were mostly considered of "mild" severity. The adverse event "epistaxis" occurred in 19.3% of olopatadine-treated and 23.4% of vehicle-treated subjects. This is a notably higher than the incidence found in the first 6 months of the previous safety trial in perennial allergic rhinitis (C-01-92; incidence rates of 13.1% and 6.7%, respectively). The reason for the higher incidence is not clear, but this event is not a barrier to marketing approval.

There was no notable increase in somnolence as a reported adverse event in the newly submitted data. However, information previously reviewed regarding olopatadine nasal spray, and information from the use of Allelock (available in Japan as an oral tablet at 2.5 and 5 mg for allergic conditions including allergic rhinitis, urticaria, and itching due to cutaneous diseases and in Korea at 2.5 mg), suggest that a claim for non-sedation is not warranted. As Dr. Lee stated in his review of the original NDA submission:

> Somnolence was reported in the olopatadine clinical development program by 1.1% (13/1163) of patients treated with olopatadine nasal spray 0.6% and by 0.2% (2/1008) of those treated with vehicle placebo nasal spray twice daily. The incidence of somnolence in patients treated with vehicle placebo twice daily was lower than normally seen in SAR trials of antihistamines in adults. The low incidence of somnolence in the vehicle placebo group in the olopatadine program suggests that the study may have been less sensitive in picking up this adverse event. It is possible that

the design of the patient medical problem log may have led people to not record less severe adverse events such as somnolence.

Somnolence was noted in the high dose cardiac safety studies in this application by 13.5% (7/166) of patients treated with olopatadine 5 mg or 20 mg twice daily by mouth. Somnolence was the most common adverse event in the clinical development program for olopatadine 2.5 mg and 5 mg tablets, which are approved in Japan. A cross-study comparison shows that the C_{max} and AUC for olopatadine 0.6% are 16% and 18%, respectively, of those for olopatadine tablets 5 mg orally. There is clearly less systemic exposure to olopatadine 0.6% nasal spray than to the oral product, however, the degree of systemic exposure is sufficient to provide additional support to the conclusion that the incidences of somnolence noted in the clinical development program are not due to chance.

At the dose and concentration proposed for marketing, olopatadine 0.6% nasal spray appears to be associated with somnolence infrequently, but at a rate higher than vehicle placebo. The frequency of somnolence is sufficiently low to be excluded from the table of common adverse events in the ADVERSE REACTIONS section of the olopatadine 0.6% nasal spray label, but is different enough from vehicle placebo that a "non-sedating" claim would be not supported if the product were to be approved.

Safety results from C-05-64 do not add significantly to the understanding of safety. There was no pattern of notable toxicities, as expected from a single-dose trial.

By agreement with FDA, Alcon is to submit a summary of the data from the second 6 months of C-05-69 prior to the deadline for approval of olopatadine 0.6% nasal spray. As of the writing of this review, Alcon has not submitted the 12-month results of trial C-05-69.

The currently-submitted safety data show no nasal septal perforations.

There were no safety concerns specific to males or females, and analyses of adverse events did not reveal other concerning patterns related to age or race. However, there were relatively few subjects who were not "Caucasian" or in the age group 18-64 years, limiting the conclusiveness of these findings.

1.3.4 Dosing Regimen and Administration

The proposed dose and administration is two sprays per nostril twice daily in persons 12 years old and older. As one 100 µl spray contains 665 mcg of olopatadine HCl (600 mcg of olopatadine base) the total daily dose of olopatadine HCl is 5.32 grams; the daily dose of olopatadine base is 4.8 grams.

1.3.5 Drug-Drug Interactions

Alcon presents no analyses of drug-drug interactions. For the 6-month results of clinical trial C-05-69, Alcon states, "No drug interactions involving the test article were reported for patients experiencing adverse events."

1.3.6 Special Populations

The numbers of subjects in the trial C-05-69 or C-04-70 who were outside the 18-64 year age group or who were nonCaucasians were relatively small and minor differences in safety cannot be discerned reliably. There were no notable differences in safety between males and females, nor an unexpected pattern of safety events at the extremes of age.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Olopatadine is an antagonist at the histamine receptor type 1 (H1 receptor), a structural analog of doxepin whose chemical name is (Z)-11-[3-(dimethylamino) propylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid hydrochloride and whose molecular formula is $C_{21}H_{23}NO_3 \cdot HCl$.

The product is a plastic (spray bottle containing 30.5 grams of a nonsterile aqueous solution containing olopatadine hydrochloride, 6.66 mg/ml (equivalent to 600 mcg of olopatadine base), benzalkonium chloride 0.01%, dibasic sodium phosphate, edetate sodium, sodium chloride, hydrochloric acid or sodium hydroxide or both, and purified water. The spray bottle has a manual metered-dose spray pump with a plastic applicator and overcap. The product is intended to be used after priming and is designed to supply 240 sprays of 100 µl, each containing 665 mcg olopatadine HCl.

The product has been modified in a couple of important ways since it was proposed originally in 2004. Alcon has removed povidone from the formulation in order to address nasal toxicities seen in animals and the clinical trials. . In addition, the product pump was redesigned which had led to the formation of degradants suspected of having carcinogenic potential.

2.2 Currently Available Treatment for Indication

Antihistamines are the first-line pharmacologic treatment of the symptoms of allergic rhinitis. Numerous products are available for seasonal allergic rhinitis either over-the-counter or by prescription. Azelastine HCl (Astelin®) is the only antihistamine nasal spray approved in the United States for the treatment of symptoms of seasonal allergic rhinitis.

2.3 Availability of Proposed Active Ingredient in the United States

Olopatadine is available in ophthalmic formulations for the treatment of signs and symptoms of allergic conjunctivitis as olopatadine HCl ophthalmic solution 0.1% (Patanol®) and 0.2% (Patanol® or PatadayTM).

Olopatadine is available in Japan and Korea as Allelock 2.5 mg tablets, and in Japan also as 5 mg tablets. The dosage approved in Japan for treatment of allergic rhinitis, urticaria and itching resulting from cutaneous diseases is 5 mg twice daily.

2.4 Important Issues With Pharmacologically Related Products

Older antihistamines, such as diphenhydramine, hydroxyzine, and chlorpheniramine, have anticholinergic effects that may include dry mouth, tachycardia, and urinary retention. Somnolence also may occur with these antihistamines at greater frequencies than with the newer antihistamines. Epistaxis has been noted with other intranasal spray products with the seasonal allergic rhinitis and perennial allergic rhinitis indications, with incidences of 2% to 11%. Nasal septal perforation is very rare among non-corticosteroid nasal sprays for allergic rhinitis and has only been reported in postmarketing adverse events. Even among corticosteroid nasal sprays with allergic rhinitis indications, nasal septal perforation is uncommon.

2.5 Presubmission Regulatory Activity

Alcon submitted NDA 21,861 on December 24, 2004 for olopatadine HCl for the [redacted] seasonal allergic rhinitis. The NDA had CMC, nonclinical, and clinical deficiencies. The chief clinical issue was the occurrence of nasal septal perforations, ulcerations, and epistaxis. An increase in the incidence of concerning nasal adverse events in vehicle control subjects, and preclinical data, suggested that the presence of povidone was a critical contributor to the increased safety signal. FDA took a nonapprovable action in a letter to Alcon dated October 27, 2005, which made the following clinical points:

- To support approval of olopatadine as a nasal spray product for [redacted] of the symptoms of allergic rhinitis, Alcon must reformulate the product to lessen nasal toxicity and perform studies to confirm that the reformulation has the intended effects.
- To support efficacy in [redacted], at least one trial would have to be conducted using a precise and reliable measure to assess efficacy, limiting the duration of efficacy assessment to a shorter time period than 1 year, such as 4 weeks, and conducting the study in a fashion that would minimize the contribution of seasonal allergens to the symptoms.

Alcon made changes to the product including elimination of povidone, [redacted]. FDA met with Alcon in January and June, 2006, regarding the clinical development plan. FDA stated that Alcon must submit a new long-term safety study. Alcon submitted two Special Protocol Assessments under IND 60116 for a long-term safety study, the latest in November, 2006.

Alcon submitted a Proposed Pediatric Study Request in March 2007, and FDA issued a Written Request on July 19, 2007 for two pediatric studies in patients with allergic rhinitis: 1) a 2-week safety and efficacy study in subjects 6-11 years old and 2) a 2-week safety and pharmacokinetics study in subjects 2-5 years old.

2.6 Other Relevant Background Information

There is no other important background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC and microbiology review have concluded that the characteristics of the product are acceptable. Regarding levels of degradants [redacted] previously seen in the product, the CMC reviewer concludes that no adjustment of the acceptance criteria would be necessary, depending on review of the toxicology reviewer. The toxicology review is summarized in the next section.

Alcon states that the two critical studies in this submission (C-05-64 and C-05-69) were "conducted using the PATANASE PVP-free formulation." Alcon also states that the device to be marketed was used in the critical safety trial C-05-69. The device used in the C-05-64 trial used a prior version of a pump in the device [redacted] as compared to the current [redacted]. According to a CMC review memorandum (March 4, 2008), "no changes have been made to the components of the pump that would be expected to alter the delivery performance." The purpose of the C-05-64 trial was to establish a pharmacodynamic link to the older formulation. The safety findings were not remarkable. I find it reasonable to use the data from this trial in the marketing approval decision.

At the time of this review, FDA inspection of the manufacturing site had not been conducted. I recommend an "Approval" action if the site is found to be acceptable. I recommend an "Approvable" action if the site is found to be unacceptable.

3.2 Animal Pharmacology/Toxicology

Based upon review of the original NDA, FDA requested that Alcon tighten acceptance criteria for the degradants [redacted] or conduct a carcinogenicity study. Alcon currently proposes acceptance criteria for [redacted] of [redacted] of the olopatadine level, respectively, and submits preclinical data related to [redacted] Alcon has not submitted carcinogenicity data for [redacted] but states that [redacted] has not been observed in the current formulation to date.

Alcon's preclinical study for [redacted] was entitled "26-Week Repeated Subcutaneous Dose Carcinogenicity Study In p53+/- Mice with A Toxicokinetic Study in C57BL/6 Mice with [redacted]." The preclinical study for [redacted] is entitled "26-Week Repeated Subcutaneous Dose Carcinogenicity Study In p53+/- Mice with A Toxicokinetic Study in C57BL/6 Mice with [redacted]." The toxicology review concludes that pending Executive Carcinogenicity Assessment Committee concurrence, neither degradant is considered carcinogenic. The ECAC has concluded that the degradants are not carcinogenic. The review concludes that the acceptance criteria for [redacted] are acceptable.

The pharmacology/toxicology review concludes that Alcon should lower the acceptance criterion for [redacted] to no more than [redacted]

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The submission contains reports of two trials using the proposed formulation. C-05-64 was a single-dose trial to establish a pharmacodynamic link to the older formulation to allow previously-established efficacy information to be applied. C-05-69 was a 12-month safety trial in patients with perennial allergic rhinitis whose 6-month results were submitted for a marketing approval decision upon agreement with FDA.

In addition, Alcon submits results from clinical trials of a povidone-containing formulation (Table 2). Of these trials, C-04-70 provides some safety data relevant to labeling. The data from the other trials is not necessary to support efficacy and safety, and these trials are not reviewed in detail.

4.2 Tables of Clinical Studies

Table 1 summarizes C-05-64, used to establish the pharmacodynamic link to the older formulation, and C-05-69, whose 6-month safety results were to address the issue of nasal toxicity.

Table 1. Clinical trials providing support for the current formulation in the current NDA resubmission

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects
C-05-64	Efficacy of single dose in Environmental Exposure Unit	PVP-free olopatadine 0.6% single dose PVP-free vehicle single dose	single dose	Randomized, double-blind, vehicle controlled, parallel group	406 olopatadine: 204 vehicle: 202	SAR, at least 18 years
C-05-69	Safety	PVP-free olopatadine 0.6% twice daily PVP-free vehicle twice daily	up to 12 months; interim report submitted with data up to 6 months	Randomized, double-blind, vehicle controlled, parallel group	890, randomized equally to active and vehicle	PAR, at least 12 years

Table 2 summarizes submitted trials of a povidone-containing formulation. Trial C-04-70 contains safety information of importance to labeling.

Table 2. Clinical trials of PVP-containing formulations since NDA filing

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects
C-04-70	Safety and efficacy	olopatadine 0.6%, PVP [redacted] vehicle azelastine 0.1% twice daily dosing	16 days	Randomized, double-blind, parallel-group vehicle and active controlled	544: olopatadine 180 vehicle 176 azelastine 188	SAR, 12 to 77 years

4.3 Review Strategy

This review focuses on the two clinical trials using the proposed povidone-free formulation summarized above: C-05-64, a single-dose trial used to establish the pharmacodynamic link to the older formulation, and C-05-69, a 12-month safety trial. By agreement with FDA, Alcon submitted the first 6 months of data from C-05-69 for the marketing approval decision, with the 12-month results to be seen as supportive.

Alcon submitted reports of trials testing a povidone-containing formulation (Table 2). Trial C-04-70, since it was of a design similar to that of the critical efficacy trials submitted in the original NDA, contains additional safety information of relevance to labeling. The other trials are of limited usefulness [redacted]

This review does not integrate the submitted studies for an evaluation of efficacy. Trial C-04-70's results are not considered important to the marketing approval decision. Trial C-05-64 had a primary endpoint that used the total nasal symptom score; however, this was a single-dose study whose purpose was to establish a pharmacodynamic link to the prior single-dose information.

The integrated summary of safety is primarily a comparison of the safety of the new formulation and the older formulation. It also contains a summary of the safety of olopatadine in the prior formulation, combining the results of C-02-10, C-02-37, and C-04-70.

4.4 Data Quality and Integrity

FDA conducted no audits for this resubmission. Alcon reported financial conflicts of interest for two investigators in [redacted], the primary trial submitted to establish the safety of the

newly formulated product. The numbers of subjects involved (see the review of the trial appended) was not sufficient to merit an investigation.

4.5 Compliance with Good Clinical Practices

Alcon states that the clinical trials submitted were conducted in compliance with Good Clinical Practice. In addition, Alcon states that it did not and will not use in any capacity the services of any person debarred under section 306 of the federal FD&C Act in connection with this NDA application.

4.6 Financial Disclosures

Two investigators for trial [redacted] reported financial conflicts of interest: [redacted] reported expense, honorarium, and consulting fees totaling $31,223.46 and $31,742.50, respectively. The numbers of subjects studied by these investigators was too small to influence the judgment of safety substantially.

These investigators also reported financial conflicts of interest for [redacted] which is not a critical or supportive trial for the approval of olopatadine nasal spray.

5 CLINICAL PHARMACOLOGY

The submission contains no new pharmacokinetic analyses. Alcon determined olopatadine concentrations in a subset of subjects from the safety trial C-05-69 to assist in determining that subjects were exposed to olopatadine.

Trial C-05-69 enrolled 890 subjects, of whom blood samples were collected from 159 in the olopatadine treatment group and 160 from the vehicle control group. Blood samples were collected at months 1 and 5 during treatment. Approximately 90% of the olopatadine subset had quantifiable olopatadine plasma concentrations.

The conclusion of the pharmacology review is that the olopatadine drug concentration data suggested a high degree of patient compliance among the tested subjects, and because of the randomized nature of treatment in the entire trial, among the entire trial population as well.

5.1 Pharmacokinetics

Alcon did not submit new information on the pharmacokinetics of olopatadine resulting from exposure to the proposed formulation.

5.2 Pharmacodynamics

Alcon submitted two high-dose cardiac safety studies in the original NDA submission. As Dr. Lee states in his review of these trials, study C-00-23 suggested that there is no QTc prolongation with olopatadine 5 mg solution twice daily by mouth. Study C-02-54 suggested that there is no QTc prolongation with olopatadine 20 mg twice daily by mouth for 14 days. A dose of 5 mg twice daily is approximately twice the proposed daily dose of olopatadine 0.6% nasal spray.

Alcon previously submitted C-02-54, a cardiovascular safety and pharmacokinetics study of twice-daily dosing of 20 mg olopatadine solution or placebo for 14 days in healthy adults. Dr. Sandra Suarez, the Office of Clinical Pharmacology reviewer, noted that some placebo corrected ΔQTc values (ΔΔQTc) were higher than 10 msec at some time points due to large negative ΔQTc values for placebo. Dr. Suarez concludes in her review of this trial that the lack of a positive control in the study makes differences from placebo in corrected QTc values uninterpretable. However, she concludes that "the lack of cardiovascular safety concerns from the phase 3 clinical trials, lack of postmarketing cardiovascular signal for the approved olopatadine tablet, no influence on the QT interval in hypokalemia-anesthetized dogs, and lack of potential for drug-drug interactions also suggest that olopatadine is unlikely to prolong QTc interval at the proposed therapeutic dose."

Alcon did not submit new information on the pharmacodynamics of olopatadine resulting from exposure to the proposed formulation.

5.3 Exposure-Response Relationships

Alcon did not submit new information on exposure-response relationships with olopatadine.

6 INTEGRATED REVIEW OF EFFICACY

The intent of the resubmission was to establish a pharmacodynamic link from the older, povidone-containing formulation to the proposed povidone-free formulation and to address safety findings from the original NDA. The pharmacodynamic link was established in trial C-05-64, which showed an effect on the total nasal symptom score over the 12 hours after a single dose given to symptomatic subjects with seasonal allergic rhinitis in an environmental exposure unit that was similar to that demonstrated in the single-dose trial C-01-83. This effect is discussed in the review of trial C-05-64. C-05-64 was not designed to establish clinical efficacy. Clinical trial C-05-69, the safety trial, was also not designed to evaluate efficacy in seasonal allergic rhinitis as its population was subjects with perennial allergic rhinitis, and it included as an effect measure a symptom score that is not adequate to measure efficacy.

6.1 Indication

Alcon proposes the following indication statement:

> Patanase® Nasal Spray is indicated for the [redacted] of the symptoms of seasonal allergic rhinitis [redacted] in patients 12 years of age and older.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This section will focus on a comparison of the safety of the previously proposed formulation as determined in the long-term trial C-01-92 using the prior formulation and in C-05-69, using the current formulation, to discern the possible emergence of new safety issues as a result of administration of the new formulation. The comparison is appropriate because C-01-92 had a similar design and subject population to C-05-69. This comparison is conducted using findings up to 6 months (day 185 +5 days for the visit window). The final 12-month results of C-05-69 were not available for this comparison. In both C-01-92 and C-05-69 trials, subjects of either sex, aged 12 years and older, with perennial allergic rhinitis, were randomized equally to vehicle or olopatadine 0.6% nasal spray, two sprays twice a day in each nostril. Subjects, whose demographic characteristics were similar between the two trials, were seen monthly. Nasal examinations were conducted at clinic visits in C-01-92, but C-05-69 incorporated a detailed examination if necessary that was not a feature of C-01-92. Monitoring was otherwise similar enough to permit a comparison of safety between the two trials.

Rates of most adverse events were similar between the two trials. Two subjects in trial C-05-69 experienced serious depression, which is a concern. Postmarketing reports should be monitored for this adverse event. Other serious adverse events did not exhibit a concerning pattern in either trial.

The concerning event of nasal septal perforation did not occur in C-05-69. Epistaxis was reported more frequently in C-05-69 than in C-01-92 (Table 7). In trial C-05-69, epistaxis occurred in 19.3% of subjects as compared to 23.4% of vehicle control subjects; in trial C-01-92, the corresponding rates were 13.1% and 6.7%. The reason for this difference is unclear. It may be a result of differences in reporting during the trial, or the lowering of the pH of the formulation from 4.0 to 3.7, or another factor. The frequency of epistaxis is not a barrier to approval; most of the events were judged of mild severity (122/129 in the olopatadine group and 147/152 in the vehicle control group); the rest were of moderate severity. The incidence of adverse events commonly associated with antihistamines was not notably different in C-05-69 (Table 11).

In addition, Alcon has submitted an analysis of adverse event rates combining data from trials C-02-10, C-02-37, and C-04-70. As described in the review of trial C-04-70 (see the appendix), these were all randomized, vehicle-controlled, 2-week double-blind trials in subjects 12 years old or older with seasonal allergic rhinitis. These three trials all studied the same povidone-containing formulation of olopatadine nasal spray. Demographics and exposure to trial medication in the trials were similar. In the pooled data (Table 10), taste perversion or dysgeusia was the most common adverse event that occurred more frequently than in vehicle control (12.8% as compared to 0.8%).

In the pooled data from trials C-02-10, C-02-37, and C-04-70, somnolence occurred in 5 (0.9%) of olopatadine-treated subjects and 2 (0.3%) of vehicle-treated subjects. As Dr. Charles Lee stated in his original NDA review:

> Somnolence was reported in the olopatadine clinical development program by 1.1% (13/1163) of patients treated with olopatadine nasal spray 0.6% and by 0.2% (2/1008)

of those treated with vehicle placebo nasal spray twice daily. The incidence of somnolence in patients treated with vehicle placebo twice daily was lower than normally seen in SAR trials of antihistamines in adults. The low incidence of somnolence in the vehicle placebo group in the olopatadine program suggests that the study may have been less sensitive in picking up this adverse event. It is possible that the design of the patient medical problem log may have led people to not record less severe adverse events such as somnolence.

Somnolence was noted in the high dose cardiac safety studies in this application by 13.5% (7/166) of patients treated with olopatadine 5 mg or 20 mg twice daily by mouth. Somnolence was the most common adverse event in the clinical development program for olopatadine 2.5 mg and 5 mg tablets, which are approved in Japan. A cross-study comparison shows that the Cmax and AUC for olopatadine 0.6% are 16% and 18%, respectively, of those for olopatadine tablets 5 mg orally. There is clearly less systemic exposure to olopatadine 0.6% nasal spray than to the oral product, however, the degree of systemic exposure is sufficient to provide additional support to the conclusion that the incidences of somnolence noted in the clinical development program are not due to chance.

At the dose and concentration proposed for marketing, olopatadine 0.6% nasal spray appears to be associated with somnolence infrequently, but at a rate higher than vehicle placebo. The frequency of somnolence is sufficiently low to be excluded from the table of common adverse events in the ADVERSE REACTIONS section of the olopatadine 0.6% nasal spray label, but is different enough from vehicle placebo that a "non-sedating" claim would be not supported if the product were to be approved.

The review of postmarketing and spontaneous adverse event reports for olopatadine ophthalmic solution 0.1% (Patanol®) for the original NDA did not identify a safety signal relevant to olopatadine nasal spray. The current update does not identify a new safety signal. The original NDA review noted that Japanese postmarketing adverse event reports for olopatadine 2.5 and 5 mg tablets suggested that olopatadine tablets may be associated with hepatic function abnormalities and noted that the Japanese regulatory agency had added hepatic function abnormal, liver disorder, acute hepatitis, and jaundice to the product label for olopatadine 2.5 mg and 5 mg tablets based these postmarketing reports. Updated information shows that liver-related adverse events continue to be reported. There was no signal for hepatic function abnormality in the olopatadine nasal spray program at the time of submission of the original NDA, and laboratory monitoring (including liver function testing) was not required in the submitted studies for the current proposed formulation. If approved, postmarketing adverse event reports for olopatadine nasal spray should be monitored for cases of hepatic function abnormalities.

The clinical trial adverse event data were presented as coded in COSTART terminology. Since this contained appropriate codes, it was adequate for an assessment of safety. Many of the tables in this integrated summary of safety are presented in COSTART. However, Alcon will

present its adverse event information for labeling in MedDRA terminology, which also contains appropriate terms.

7.1.1 Deaths

There have been no deaths in the clinical program for the new formulation of olopatadine nasal spray. There was one death in Alcon clinical trials of olopatadine nasal spray. A 41-year-old woman taking olopatadine 0.6% nasal spray in C-01-92 developed abdominal pain, perforated gastric ulcer, bacterial peritonitis, and sepsis and died of sepsis on study day [redacted] This case is described in the original NDA review.

7.1.2 Other Serious Adverse Events

There were 15 subjects with 22 serious adverse events in the 12 months of C-01-92; the only event type that occurred more than once in the treatment group was medical/surgical procedure (hysterectomy and reconstruction of the bladder in one subject and gastric bypass surgery in another). In C-05-69, depression requiring hospitalization occurred in two subjects in the olopatadine treatment group. It is possible that these were chance events; however, depression should be monitored postmarketing if the product is approved. Surgical/medical procedure occurred in two subjects in the olopatadine treatment group (knee replacement and cholecystectomy) but not in the vehicle group. A serious abdominal adverse event (appendicitis and intestinal obstruction) occurred in one subject each in the olopatadine treatment group and one subject in the vehicle control group. Other events were various in nature (Table 41).

There was one serious adverse event in trial C-02-10 (syncope), which occurred in a subject on olopatadine and no serious adverse events in trial C-02-37 or in vehicle or olopatadine-treated subjects in C-04-70.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

See the next section.

7.1.3.2 Adverse events associated with dropouts

Safety trials C-01-92 and C-05-69

For the first 6 months of C-01-92 and C-05-69, similar numbers of subjects dropped out due to adverse events. In C-01-92, 3.5% of olopatadine and 4.1% of vehicle control subjects discontinued due to adverse events; in C-05-69, 4.9% of olopatadine and 3.4% of vehicle control subjects discontinued due to adverse events.

The numbers of subjects discontinuing due to adverse events was similar in the first 6 months of trials C-01-92 and C-05-69 (Table 3).

Table 3. Comparison of dropout rates due to adverse events in the first 6 months of C-01-92 and C-05-69

	N	n (%)
Olopatadine		
C-01-92*	459	16 (3.5)
C-05-69	445	22 (4.9)
Vehicle		
C-01-92*	465	19 (4.1)
C-05-69	445	15 (3.4)

*PVP[redacted]-containing formulation
[Source: Alcon Table 4.3.-1]

Alcon did not provide a summary of numbers of subjects in C-01-92 who discontinued for adverse events (regardless of attribution of treatment causality) by adverse event type. Table 4, constructed by this reviewer, compares adverse events associated with withdrawal, using the events that occurred in 2 or more subjects in C-01-92 as the basis for comparison. The full table of events leading to discontinuation in C-05-69 is in Table 42. Adverse events not shown in Table 4 for C-05-69 did not occur at greater than 1 subject per treatment arm, except for rhinitis (3 events in the olopatadine treatment group and 1 in the vehicle treatment group). The proportions of subjects who have discontinued in the first 6 months of C-05-69 is similar to that in the 12 months of C-01-92. Sinusitis as a cause for discontinuation occurred more frequently in both treatment arms in C-05-69, and rhinitis (olopatadine 3 events, vehicle control, 1 event) occurred slightly more frequently. The numbers and nature of discontinuations is not a cause for concern for the new proposed formulation.

Table 4. Comparison of adverse events leading to discontinuation in the 12 months of C-01-92*; similar events used for comparison from the 6 months of C-05-69**

	C-01-92		C-05-69	
Adverse event (COSTART)	**Olopatadine 0.6% PVP N = 459**	**Vehicle PVP N = 465**	**Olopatadine 0.6% N =445**	**Vehicle N = 445**
Patients withdrawing because of adverse events	23 (5.0)	25 (5.4)	22 (4.9%)	16 (3.6%)
All adverse events resulting in withdrawal	29	28	30	20
Taste perversion	4	0	2	0
Nasal discomfort	3	1	0	2
Headache	2	4	1	2
Nasal ulcer	2	2	2	0
Epistaxis	2	1	3	1
Allergic reaction	1	1	**	**
Asthma	1	1	0	2
Sinusitis	1	1	4	4
Dizziness	0	3	0	2
Infection	0	2	-	-
Migraine	0	2	-	-
Nasal septum disorder	0	2***	0	1***

*Events listed for C-01-92 are those that occurred in 2 or more subject overall in the trial
** Adverse events not shown for C-05-69 did not occur at greater than 1 subject per treatment arm except rhinitis (3 olopatadine, 1 vehicle) (see Table 42 for the full table of events leading to discontinuation in C-05-69).
**1 event with Costart term "allergy" occurred in each treatment arm of C-05-69
***Events in C-01-92 were nasal septal perforations; in C-05-69, "Deviated septum at left naris"
[Sources: NDA original submission Medical Officer review and C-05-69 data set AE01.jmp]

Pooled 2-week trials in seasonal allergic rhinitis

Table 5 shows a pooled analysis of the rates of adverse events in the pooled seasonal allergic rhinitis trials (C-02-10, C-02-37, and C-04-70) leading to discontinuation.

Table 5. Summary of adverse events leading to discontinuation in combined trials C-02-10, C-02-37, and C-04-70 (povidone-containing formulation)

Adverse Event (COSTART)	Olopatadine 0.6% N = 587	Vehicle N = 593
	N (%)	N (%)
Headache	4 (0.7%)	1 (0.2%)
Flu syndrome	2 (0.3%)	
Pharyngitis	2 (0.3%)	
Taste perversion	2 (0.3%)	
Cough increased	1 (0.2%)	
Dizziness	1 (0.2%)	
Dyspepsia	1 (0.2%)	
Epistaxis	1 (0.2%)	1 (0.2%)
Gastroenteritis	1 (0.2%)	
Migraine	1 (0.2%)	
Nausea	1 (0.2%)	1 (0.2%)
Pain	1 (0.2%)	
Pneumonia	1 (0.2%)	
Pruritus	1 (0.2%)	
Rhinitis	1 (0.2%)	
Sinusitis	1 (0.2%)	3 (0.5%)
Sneezing	1 (0.2%)	
Syncope	1 (0.2%)	
Arthropod bite		1 (0.2%)
Bronchitis		
Contact dermatitis		1 (0.2%)
Vomiting		1 (0.2%)

[Source: Alcon response to FDA February 25, 2008 request, Table D-3]

In the pooled subject population, 2.4% of olopatadine-treated and 1.3% of vehicle-treated subjects discontinued (Table 6).

Table 6. Summary of subjects discontinuing due to adverse events in combined trials C-02-10, C-02-37, and C-04-70

Trial	Treatment group	Subjects discontinuing
C-02-10	Olopatadine 0.6% n=223	6 (2.7%)
	Vehicle n=225	1 (0.4%)
C-02-37	Olopatadine 0.6% n=184	3 (1.6%)
	Vehicle n=192	2 (1%)
C-04-70	Olopatadine 0.6% n=180	5 (2.8%)
	Vehicle n=176	5 (2.8%)
Total	Olopatadine 0.6% n=587	14 (2.4%)
	Vehicle n=593	8 (1.3%)

[Data from Alcon response to FDA February 25, 2008 request, Tables A-1, B-1, C-1, and D-1]

7.1.3.3 Other significant adverse events: nasal adverse events

Comparison of safety trials in perennial allergic rhinitis

Adverse events related to the nose are the most important aspect of the safety analysis of olopatadine identified in the review of the original NDA. Table 7 shows a comparison of the most frequent nasal adverse events occurring in the first 6 months of C-01-92 and C-05-69 (events that occurred at an incidence of at least 1% in either trial olopatadine group). These adverse events were reported generally more frequently in both treatment groups in C-05-69, the adverse events "nasal ulceration," "epistaxis," and, in particular, "rhinitis." The presence of olopatadine in the formulation was not associated with a remarkable increase over vehicle in events, except possibly in the case of nasal ulceration events (a 3% increase over vehicle control). The reason for this overall increase in nasal events is not clear. Two possible explanations are that the decrease in pH of the formulation (from 4.0 to 3.7) results in a formulation that is more irritating to the nose, or that reporting was better in the later trial, C-05-69.

Table 7. Comparison of the most frequent* nasal adverse events in the first 6 months of C-01-92 and C-05-69

	C-01-92		C-05-69	
Coded AE (COSTART)	**Olopatadine 0.6% PVP**	**Vehicle PVP**	**Olopatadine 0.6%**	**Vehicle**
Epistaxis	60 (13.1)	31 (6.7)	86 (19.3)	104 (23.4)
Rhinitis	32 (7.0)	43 (9.2)	104 (23.4)	103 (23.1)
Sinusitis	37 (8.1)	39 (8.4)	47 (10.6)	47 (10.6)
Pharyngitis	23 (5.0)	31 (6.7)	35 (7.9)	30 (6.7)
Ulcer nasal	13 (2.8)	16 (3.4)	39 (8.8)	26 (5.8)
Discomfort nasal	6 (1.3)	7 (1.5)	12 (2.7)	13 (2.9)
Dry nose	8 (1.7)	1 (0.2)	7 (1.6)	2 (0.4)

*Occurring in either of the olopatadine groups at an incidence of ≥1%
[Source: Alcon Table 4.2.-3]

A crucial component of the evaluation of safety in these trials was the nasal examination. This aspect is discussed in section 7.1.7.5 (Special assessments: Nasal examination).

Pooled 2-week trials in seasonal allergic rhinitis

Nasal adverse events for the two-week seasonal allergic rhinitis trials C-02-10, C-02-37, and C-04-70 are shown in a combined table of all adverse events from these trials (Table 9, below). Epistaxis, pharyngitis, and rhinitis were nasal events whose incidence was greater than 1% and that occurred more frequently than in vehicle control.

7.1.4 Other Search Strategies

I used no alternative search strategies in the evaluation of this submission.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Clinical trials C-01-92 and C-05-69 called for subjects to attend clinic visits monthly during treatment. At this visit clinic personnel assessed the health history of the subjects, including the solicitation of adverse events, and reviewed a medical problem log on which subjects recorded changes in health between clinic visits. Adverse events were to be recorded as the result of a clinically significant change in vital signs, physical examination, and (in C-01-92) ECG. Importantly, clinically significant changes from baseline in the nasal examination, conducted monthly, were recorded as adverse events. In trial C-05-69 this was a two-step process, in which an initial examination (like the one in C-01-92) may have suggested the need for a more detailed assessment of the nature of the adverse event. This is one reason that the incidence and severity of nasal adverse events cannot be compared directly between the two trials.

The schedule of ascertainment of adverse events in the two-week seasonal allergic rhinitis trials was similar. Among the trials, C-02-37 did not provide for a medical problem log; the other trials did. Subjects were scheduled for a telephone call at a week after treatment and were seen in clinic at 2 weeks.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were categorized using conventional dictionaries. The categorization was adequate, based on a comparison of a selection of adverse event descriptions with COSTART terms.

7.1.5.3 Incidence of common adverse events

See the next section.

7.1.5.4 Common adverse event tables

Comparison of safety trials in perennial allergic rhinitis

Table 8 shows a comparison of the most frequent systemic (that is, non-nasal) adverse events occurring in the first 6 months of trials C-01-92 and C-05-69. The most notable difference between the two trials was the incidence of "infection" and headache, which were reported somewhat more frequently in C-05-69, but at a similar frequency in the two treatment groups in the trial. These data do not show a change in the systemic risk profile with the new formulation.

Table 8. Comparison of most frequent* nonnasal adverse events in the first 6 months of C-01-92 and C-05-69

	C-01-92		C-05-69	
Adverse event (COSTART)	Olopatadine 0.6 PVP n=459	Veh PVP n=465	Olopatadine 0.6% n=445	Vehicle n=445
Body as a Whole				
Infection	44 (9.6)	55 (11.8)	67 (15.1)	65 (14.6)
Headache	36 (7.8)	42 (9)	55 (12.4)	59 (13.3)
Cold Syndrome	55 (12)	46 (9.9)	52 (11.7)	52 (11.7)
Allergy	18 (3.9)	15 (3.2)	19 (4.3)	20 (4.5)
Injury Accidental	7 (1.5)	3 (0.6)	19 (4.3)	32 (7.2)
Flu Syndrome	16 (3.5)	14 (3)	13 (2.9)	19 (4.3)
Pain Back	16 (3.5)	23 (4.9)	12 (2.7)	12 (2.7)
Surg/Med Proc	8 (1.7)	9 (1.9)	11 (2.5)	14 (3.1)
Pain	12 (2.6)	14 (3.0)	6 (1.3)	6 (1.3)
Cardiovascular System				
Hypertension	3 (0.7)	5 (1.1)	13 (2.9)	15 (3.4)
Digestive System				
Diarrhea	10 (2.2)	5 (1.1)	11 (2.5)	6 (1.3)
Gastroenteritis	11 (2.4)	19 (4.1)	11 (2.5)	12 (2.7)
Musculoskeletal System				
Arthralgia	14 (3.1)	11 (2.4)	10 (2.2)	17 (3.8)
Respiratory System				
Asthma	12 (2.6)	14 (3.0)	19 (4.3)	17 (3.8)
Cough Increased	10 (2.2)	8 (1.7)	16 (3.6)	14 (3.1)
Bronchitis	19 (4.1)	18 (3.9)	15 (3.4)	10 (2.2)
Special Senses				
Taste Perversion	44 (9.6)	4 (0.9)	29 (6.5)	3 (0.7)

*Events occurring at an incidence of over 2.5%
[Source: Alcon Table 4.2.-7]

Pooled 2-week trials in seasonal allergic rhinitis

Table 9 is a summary of adverse events that occurred in 1% or greater in the olopatadine treatment group and at an incidence greater than in vehicle control.

Table 9. Summary of subjects with adverse events occurring at 1% or over in the olopatadine group and at a frequency greater than vehicle in combined C-02-10, C-02-37, and C-04-70

Adverse Event (COSTART)	Olopatadine Nasal 0.6% N = 587	Vehicle N = 593
	N (%)	N (%)
Nasal events		
Epistaxis	18 (3.1)	10 (1.7)
Pharyngitis	15 (2.6)	11 (1.9)
Rhinitis	16 (2.7)	7 (1.2)
Body as a Whole		
Headache	34 (5.8)	31 (5.2)
Respiratory System		
Cough Increased	7 (1.2)	3 (0.5)
Special Senses		
Taste Perversion	75 (12.8)	5 (0.8)
Hyperemia Eye	10 (1.7)	6 (1.0)
Urogenital System		
Urinary tract infection	7 (1.2)	3 (0.5)

[Data from Alcon response to FDA February 21, 2008 request, Table D-1]

Alcon also provided the analysis coded in MedDRA (Table 10). Alcon stated that the MedDRA terminology was applied to the adverse event descriptions, that is, it was not a translation from COSTART. This table is useful as MedDRA terms will be used for labeling. The difference in terminology does not change the reported incidence of events appreciably.

Table 10. Summary of subjects with adverse events occurring at 1% or over in the olopatadine group and at a frequency greater than vehicle in combined C-02-10, C-02-37, and C-04-70 (MedDRA terminology)

Adverse Event (MedDRA)	Olopatadine Nasal 0.6% N = 587	Vehicle N = 593
	N (%)	N (%)
Infections and Infestations		
Urinary Tract Infection	7 (1.2)	3 (0.5)
Nervous System Disorders		
Dysgeusia	75 (12.8)	5 (0.8)
Headache	26 (4.4)	24 (4.0)
Respiratory, thoracic, and mediastinal disorders		
Epistaxis	19 (3.2)	10 (1.7)
Pharyngolaryngeal pain	13 (2.2)	8 (1.3)
Postnasal drip	9 (1.5)	5 (0.8)
Cough	8 (1.4)	3 (0.5)

[Data fromAlcon response to FDA February 21, 2008 request, Table D-2]

Examination of adverse events with respect to age (12-17, 18-64, and ≥65), sex, and race, did not show any remarkable patterns. However, the numbers of nonCaucasians and subjects outside the 18-64-year age category were small, making comparative estimates of event rates problematic.

7.1.5.5 Identifying common and drug-related adverse events

Comparison of safety trials in perennial allergic rhinitis

Table 11 shows a comparison of the 12-month results from trial C-01-92 and the 6-month data from trial C-05-69 regarding adverse events associated with antihistamines and anticholinergic drugs. The data does not suggest that the change in formulation has changed the risk of any of these events notably.

Table 11. Comparison of C-01-92 12-month and C-05-69 6-month incidence of adverse events commonly associated with antihistamines and anticholinergic drugs

COSTART term	C-01-92 (12 months)		C-05-69 (6 months)	
	Olopatadine 0.6% PVP [redacted] n=459	Vehicle PVP [redacted] n=465	Olopatadine 0.6% n=445	Vehicle n=445
Dyspepsia	14 (3.1)	9 (1.9)	9 (2)	6 (1.3)
Nausea	6 (1.3)	4 (0.9)	5 (1.1)	9 (2)
Fatigue	5 (1.1)	1 (0.2)	4 (0.9)	4 (0.9)
Somnolence	3 (0.7)	1 (0.2)	1 (0.2)	0
Constipation	3 (0.7)	0	2 (0.4)	4 (0.9)
Dry mouth	2 (0.4)	2 (0.4)	4 (0.9)	3 (0.7)
Weight increase	1 (0.2)	0	5 (1.1)	0
Urinary retention	0	1 (0.2)	0	0

[Sources: Medical Officer original NDA review; Alcon Table 14.3.1.3.1.-1]

Pooled 2-week trials in seasonal allergic rhinitis

Table 12 shows the combined incidence of adverse events commonly associated with antihistamines and anticholinergic drugs in the 2-week controlled trials.

Table 12. Incidence of adverse events commonly associated with antihistamines and anticholinergic drugs in combined trials C-02-10, C-02-37, and C-04-70

COSTART term	Olopatadine 0.6% n= 587	Vehicle n= 593
Dyspepsia	5 (0.9)	1 (0.2)
Nausea	3 (0.5)	7 (1.2)
Fatigue	3 (0.5)	2 (0.3)
Somnolence	5 (0.9)	2 (0.3)
Constipation	2 (0.3)	1 (0.2)
Dry mouth	5 (0.9)	1 (0.2)
Weight increase	1 (0.2)	0
Urinary retention	0	1 (0.2)

[Data from Alcon response to FDA Request of February 21, 2008, Table D-1]

7.1.5.6 Additional analyses and explorations

I did not perform additional analyses and explorations.

7.1.6 Less Common Adverse Events

See section 7.1.5.5, adverse events associated with antihistamines and anticholinergic drugs. See section 7.1.3.3 for a review of the incidence of nasal ulcer and epistaxis, which are of concern in the use of a nasal spray.

7.1.7 Laboratory Findings

Laboratory evaluation was not included in the safety plan for the newly submitted trials of the proposed formulation. See the review of the original NDA for a discussion of all laboratory analyses.

7.1.7.1 Overview of laboratory testing in the development program

See Dr. Lee's review of the original NDA submission for an overview of laboratory evaluations in the development program.

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

See section 7.1.7.

7.1.7.3 Standard analyses and explorations of laboratory data

See section 7.1.7.

7.1.7.4 Additional analyses and explorations

I did not perform additional analyses and explorations.

7.1.7.5 Special assessments: Nasal examination

The incorporation in C-05-69 of a second, more detailed examination in certain subjects provided additional information on the effects of olopatadine on the nose.

While three nasal septal perforations occurred in C-01-92 (two in the vehicle control group and one in the olopatadine treatment group), no nasal septal perforations occurred in C-05-69.

Table 13 shows a comparison of the nasal examination in C-01-92 with its counterpart, the initial examination in C-05-69. The data are expressed as the numbers of subjects with a change in the nasal examination from baseline to any visit. In C-05-69 there was a notable increase compared to C-01-92 in the incidence of "blood in the nose" and "possible ulcerations" that was present for both treatment groups. Epistaxis and nasal ulceration in trial C-05-69 were primarily graded as "mild," however. The second part of the nasal exam in C-05-69 showed that verified ulceration occurred in fewer subjects than had "possible ulceration" (41 olopatadine-treated subjects and 28 vehicle-treated subjects who had a second examination). One potential cause of the increase in these events is the lowering of the pH of the formulation from 4.0 to 3.7. Another potential cause could be differences in monitoring.

Table 13. Subjects with change in nasal parameters from baseline - Baseline to Month 6 Data Set (Section A in C-05-69)

			Anatomic abnormality			Blood in the nose		
Olopatadine 0.6%		Total	N	n	%	N	n	%
	C-01-92*	459	451	2	0.4	451	43	9.5
	C-05-69	445	438	5	1.1	438	67	15.3
Vehicle								
	C-01-92*	465	451	4	0.9	451	23	5.1
	C-05-69	445	438	0	0	438	87	19.9
			Infection			Possible ulcerations		
Olopatadine 0.6%		Total	N	n	%	N	n	%
	C-01-92*	459	451	19	4.2	451	11	2.4
	C-05-69	445	438	18	4.1	438	67	15.3
Vehicle								
	C-01-92*	465	451	21	4.7	451	14	3.1
	C-05-69	445	438	12	2.7	438	61	13.9

**Povidone [redacted]-containing formulation
[Source: ISS Table 4.4.4.-1]
Note: no nasal perforations occurred in C-05-69; one olopatadine- and two vehicle control-treated subjects experienced nasal perforations in C-01-92

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

See Dr. Lee's review of the original NDA submission for an overview of vital signs testing in the development program. Vital signs were tested in C-01-92 at baseline and at days 30, 90, 180, 270, and at end of trial participation; they were tested at baseline and monthly in C-05-69.

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

This review discusses vital signs testing in the long-term trials C-05-69 and C-01-92.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Table 14 shows Alcon's analysis of mean changes in pulse and systolic and diastolic blood pressure changes from baseline to the 6 months in trials C-01-92 and C-05-69. The results show minor changes from baseline to exit in both groups.

Table 14. Comparison of cardiovascular determinations in C-01-92 and C-05-69: Mean changes from baseline to exit visit (6 months) in olopatadine treatment groups

			Overall population		12-17 yrs		18-64 yrs		≥65 yrs	
Parameter	Trial	Statistic	Olo 0.6%	Vehicle	Olo 0.6%	Vehicle	Olo 0.6%	Vehicle	Olo 0.6%	Vehicle
Pulse (bpm)	C-01-92*	*N*	*442*	*434*	*56*	*51*	*379*	*372*	*7*	*11*
		Mean	1.7	1.0	3.0	2.8	1.5	0.6	-1.7	7.0
	C-05-69	*N*	*439*	*438*	*46*	*53*	*382*	*376*	*11*	*9*
		Mean	-0.1	-0.7	-1.2	-2.4	-0.1	0.6	4.4	2.4
Systolic blood pressure (mmHg)	C-01-92*	*N*	*442*	*434*	*56*	*51*	*379*	*372*	*7*	*11*
		Mean	0.6	-0.7	0.3	1.1	0.8	-0.9	-8.2	-2.2
	C-05-69	*N*	*439*	*438*	*46*	*53*	*382*	*376*	*11*	*9*
		Mean	-2.2	-1.8	0.1	0.4	-2.3	-2.0	-8.3	-5.2
Diastolic blood pressure (mmHg)	C-01-92*	*N*	*442*	*434*	*56*	*51*	*379*	*372*	*7*	*11*
		Mean	-0.5	-0.8	-0.6	1.3	-0.4	-1.2	-6.0	-0.5
	C-05-69	*N*	*439*	*438*	*46*	*53*	*382*	*376*	*11*	*9*
		Mean	-1.3	-2.1	-0.3	-2.9	-1.4	-2.0	-2.3	-2.3

*Povidone [redacted]-containing formulation
[Source: Alcon Tables 4.4.3.-1 and 4.4.3.-2]

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Alcon's integrated summary of safety does not include a comparison of outliers or shifts from normal. However, neither the original review of C-01-92 nor the current review of C-05-69 identified concerning patterns of toxicity based on shift analysis.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Alcon's integrated summary of safety does not include a comparison of outliers or dropouts or vital sign abnormalities. However, neither the original review of C-01-92 nor the current review of C-05-69 identified concerning patterns of toxicity based on vital sign abnormalities considered as adverse events.

7.1.8.4 Additional analyses and explorations

I performed no additional analyses and explorations of the vital sign data.

7.1.9 Electrocardiograms (ECGs)

Alcon did not perform electrocardiographic monitoring in C-05-69. FDA had told Alcon in a meeting of June 30, 2006 that further electrocardiographic data would not be needed provided that the new formulation stayed as a solution and that systemic exposure would not be expected to change. No comparison of the new formulation to the older formulation on potential electrocardiographic effects is possible.

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

Dr. Charles Lee's clinical review of the original NDA included a summary of the electrocardiographic testing in the development program:

> ECGs were performed as safety endpoints in 10 studies in this application: in three PK and safety studies with oral olopatadine (C-00-23, C-02-54, and C-03-10), two PK and safety studies with single dose exposure to olopatadine 0.6% nasal spray (C-02-46 and C-03-11), three non-pivotal SAR studies (C-00-10, C-00-33, and C-01-05), one PK study (C-00-58) with 0.1% and 0.2% concentrations of olopatadine, and one long-term pivotal PAR study (C-01-92). For each study, the effects of olopatadine on ECG parameters were analyzed, including an evaluation of mean changes in ECG intervals, categorical analysis of QT/QTc data, and evaluation of ECG abnormalities [Module 2, Volume 7, Section 2.7.4.4, page 76].

ECG evaluation was not performed as a safety parameter in the trials submitted in support of the new proposed formulation.

Dr. Lee summarized the preclinical cardiovascular and electrocardiographic preclinical results in his original NDA review:

> In non-clinical studies, olopatadine showed an antihypertensive effect in dogs in a dose dependent manner at 20, 50, & 100 mg/kg (59% decrease at high dose) with decreased total peripheral resistance. At <5mg/kg iv, no effects on heart rate, ECG & respiratory rate were observed. At <30mg/kg iv there were no effects on QTc. The IC50 for hERG channel is 1000X greater than for terfenadine. In studying the effect of the combination of olopatadine and itraconazole (to block CYP 3A4) on the ECG in conscious dogs, olopatadine alone causes a greater increase in heart rate and mean blood pressure (in contrast to an earlier experiment where olopatadine caused hypotension) than when administered along with itraconazole, while QT tended to be less affected. These data suggest that olopatadine may not elicit QT prolongation even when co-administered with the CYP 3A4-inhibitor itraconazole. In another study on the effects of olopatadine HCl on cloned hERG channels, olopatadine blocked hERG channels with an IC50 of 1.1 mM. This block showed no use or time dependence [Gary Bond, Ph.D., Pharmacology Review, NDA 21-861, N-000, 12/24/04].

Alcon previously submitted C-02-54, a cardiovascular safety and pharmacokinetics study of twice-daily dosing of 20 mg olopatadine solution or placebo for 14 days in healthy adults. Dr. Sandra Suarez, the Office of Clinical Pharmacology reviewer, found that some placebo corrected ΔQTc values (ΔΔQTc) were higher than 10 msec at some time points due to large negative ΔQTc values for placebo. Dr. Suarez concludes in her review of this trial that the lack of a positive control in the study makes differences from placebo in corrected QTc values uninterpretable. However, she concludes that "the lack of cardiovascular safety concerns from the phase 3 clinical trials, lack of postmarketing cardiovascular signal for the approved olopatadine tablet, no influence on the QT interval in hypokalemia-anesthetized dogs, and lack of potential for drug-drug interactions also suggest that olopatadine is unlikely to prolong QTc interval at the proposed therapeutic dose."

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

See section 7.1.9.

7.1.9.3 Standard analyses and explorations of ECG data

See section 7.1.9.1

7.1.9.4 Additional analyses and explorations

Alcon did not perform any special clinical studies for this submission. The original NDA review discusses two high-dose cardiac safety studies performed by Alcon.

7.1.10 Immunogenicity

Alcon did not test for the presence of olopatadine antibodies in the clinical program. Olopatadine, as a small molecule, is not expected to be immunogenic.

7.1.11 Human Carcinogenicity

Alcon did not perform human carcinogenicity studies in the clinical program.

7.1.12 Special Safety Studies

Alcon conducted two high-dose cardiac safety trials and submitted the results with the original NDA. These trials are discussed in the original clinical and pharmacology/biopharmaceutics reviews.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

In this submission Alcon has reported no withdrawal phenomena or abuse. There were no reports of withdrawal or rebound phenomena in the clinical development program described in the original NDA.

7.1.14 Human Reproduction and Pregnancy Data

The clinical trials in this submission, as well as the original submission, excluded pregnant females. Three subjects in trial C-05-69, one in the olopatadine treatment group and two in the vehicle group, discontinued participation as a result of becoming pregnant, but the outcome of pregnancy is not reported.

The original NDA review summarized product labeling for olopatadine 0.1% ophthalmic solution (Patanol). This information has not been revised, but is included here for ease of review:

> Olopatadine administered to male and female rats at oral doses of 62,500 times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of 7,800 times the maximum recommended ocular human use level.

> Pregnancy: Pregnancy Category C. Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 93,750 times the MROHD and rabbits treated at 400 mg/kg/day, or 62,500 times the MROHD, during organogenesis showed a decrease in live fetuses. There are, however, no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.
>
> Nursing Mothers: Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PATANOL® (olopatadine hydrochloride ophthalmic solution) 0.1% is administered to a nursing mother.

Olopatadine is available in Japan and Korea as 2.5 mg tablets, and in Japan also as 5 mg tablets. In Japan it is approved for treatment of allergic rhinitis, urticaria and itching resulting from cutaneous diseases. Product labeling for Allelock, states,

> Allelock should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. Safety of the administration during pregnancy has not been established.
>
> Lactating women should not be given Allelock. If treatment with this drug is judged to be essential, breast feeding must be discontinued during treatment. Animal studies (rats) reported excretion of this drug in breast milk and weight increase inhibition of the neonates.

7.1.15 Assessment of Effect on Growth

Alcon has not conducted studies of the effect of olopatadine nasal spray on growth in the overall clinical development program. Labeling for Pataday and Patanol do not contain information on growth; nor does product labeling for Allelock. There were no reports of the effect on growth in Alcon's literature submission. A PubMed search using the terms "olopatadine" and "growth" as text words did not produce any published work on olopatadine and growth.

7.1.16 Overdose Experience

Alcon's postmarketing reports for the ophthalmic solution since the time of the original submission state that no one has reported an overdose as a postmarketing event. The December 18, 2006 to December 17, 2007 periodic update report for Allelock lists 5 cases of overdose:

- 61 year-old man took 35 mg and experienced somnolence, and "spontaneously recovered" after two days
- 16 year-old boy took 130 mg, had somnolence, and slept through the following day
- 3 year old who may have taken 22.5 mg, whose symptoms are not described, but who "spontaneously recovered" the following day

- 13 year-old boy took 40 mg and had no adverse reaction
- 89 year-old who took 40 mg along with other medications (epinastine, fluvoxamine maleate, and famotidine, who was found after 12 hours, and had "no abnormality such as sleepiness."

These reports do not point to a new safety concern with overdose.

7.1.17 Postmarketing Experience

Ophthalmic formulation

Olopatadine has been marketed by Alcon as an ophthalmic solution at 1 mg/ml and 2 mg/ml. Alcon provided postmarketing information regarding olopatadine ophthalmic formulations from December 1, 2004 through January 31, 2008. The great majority of the product was sold as the [redacted]. During this time period, about [redacted] were sold (this includes sales of [redacted] each); somewhat less than [redacted] were sold. Sales of the 2 mg/ml solution are orted during the time period starting July 1, 2007; sales of the [redacted] solution were about [redacted]. Sales figures cannot be used to determine the numbers of patients because of the intended episodic nature of the intended use (for symptoms). During the time period of the reports Alcon reports no regulatory actions taken for the product for safety reasons, no reports of drug interactions, overdose, or spontaneous reports of abuse or misuse. A total of 302 MedDRA terms were reported during the time period associated with use of the 1 mg/ml solution, of which about 62% were eye disorders. The rest were in various organ classes; somnolence was reported 3 times and abnormal hepatic function once. Of the 16 MedDRA terms reported with the 2 mg/ml solution, 4 were eye disorders, and the rest various, with no reports of somnolence or abnormal hepatic function). One case of use during pregnancy was reported, without outcome data. Four serious medically-confirmed cases were reported in different organ systems associated with the use of olopatadine ophthalmic preparations. The small number of cases and their varied nature do not suggest a pattern of toxicity.

Oral formulation

Olopatadine is available in Japan and Korea as Allelock 2.5 mg tablets, and in Japan also as 5 mg tablets. In Japan it is approved for treatment of allergic rhinitis, urticaria and itching resulting from cutaneous diseases. Alcon provided postmarketing summaries for Allelock for the time period December 18, 2004 to December 17, 2005 and December 18, 2006 to December 17, 2007. In the former time period [redacted] 2.5-mg tablets and [redacted] 5-mg tablets were sold; in the latter period, [redacted] 2.5-mg tablets and [redacted] 5-mg tablets were sold. Patient numbers are not reported.

The December 2004-December 2005 report contains an updated summary of a postmarketing clinical experience investigation involving cases actively collected. Among 7880 patients reviewed for safety, the incidences of events were not different from those reported from the review of this surveillance in the original NDA. The most common adverse events were somnolence (5.9%), malaise (0.33%), thirst (0.28%), aspartate aminotransferase increased (0.18%), alanine aminotransferase, blood LDH, and gamma glutamyltransferase increased (each 0.15%), eosinophil count increased and hemoglobin decreased (0.14% each) and dizziness and headache (each 0.13%). The outcomes of 3 pregnancies were reported: there was one miscarriage, and no problems were reported for the other two for either mother or child.

Between December 18, 2004 to December 17, 2005, 18 serious adverse reactions from 14 patients were reported. Liver disorder was reported in two patients and hepatic function abnormal and hepatitis in one patient each; other reactions were various. Between December 18, 2006 to December 17, 2007, 16 serious drug reactions occurred, of which three were liver-related: hepatic function abnormal, jaundice, and liver disorder.

In summary, the review of postmarketing and spontaneous adverse event reports for olopatadine ophthalmic solution 0.1% (Patanol®) in the original NDA did not identify a safety signal relevant to olopatadine nasal spray. The current update does not identify a new safety signal. The original NDA review noted that Japanese postmarketing adverse event reports for olopatadine 2.5 and 5 mg tablets suggested that olopatadine tablets may be associated with hepatic function abnormalities and noted that the Japanese regulatory agency had added hepatic function abnormal, liver disorder, acute hepatitis, and jaundice to the product label for olopatadine 2.5 mg and 5 mg tablets based these postmarketing reports. Updated information shows that liver-related adverse events continue to be reported. There has no signal for hepatic function abnormality in the olopatadine nasal spray program. However, if olopatadine 0.6% nasal spray is approved, postmarketing adverse event reports for olopatadine nasal spray should be monitored for cases of hepatic function abnormalities.

Reviewer comment

Postmarketing information reviewed here does not include Allelock information for the period December 18, 2005 to December 17, 2006. This information was requested from Alcon in February, 2008, but did not arrive in time for review. The current submission contains two of three years of data requested. In addition, information for the period December 200-2004 regarding Allelock, related to the use of over [redacted] tablets, was reviewed in the original NDA submission. The missing information is very unlikely to change the understanding of the safety of olopatadine notably, and the decision on market approvability for olopatadine nasal spray can be made without it.

Review of the submitted postmarketing data does not suggest a safety concern that would preclude market approval.

7.2 Adequacy of Patient Exposure and Safety Assessments

The chief source of safety data in the current submission, C-05-69, exposed over 300 subjects to olopatadine 0.6% nasal spray at the proposed dose and frequency for over 6 months. FDA discussed the design of trial C-05-69 with Alcon prior to the NDA submission and stated that 6 months of data would be sufficient for a marketing approval decision.

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

7.2.1.1 Study type and design/patient enumeration

The submission contains two trials studying the proposed formulation (Table 1). Trial C-05-69, the primary source of safety information, enrolled 890 subjects, of whom 445 received olopatadine 0.6% nasal spray. C-05-64 was a single-dose pharmacodynamic trial in an environmental exposure unit in symptomatic subjects with seasonal allergic rhinitis (C-05-64) that enrolled 406 subjects, of whom 204 received olopatadine 0.6% nasal spray. This single-dose trial provides very little safety information. It is reviewed in the appendix.

The results of trial C-04-70, a trial that studied the prior formulation of olopatadine, may be pooled with those of trials C-02-10 and C-02-37 to gain a better understanding of the rates of safety events with two weeks of exposure in subjects with seasonal allergic rhinitis. Trial C-04-70 enrolled 180 subjects in the olopatadine and 176 subjects in the vehicle control groups.

7.2.1.2 Demographics

Dr. Charles Lee's review of the original NDA describes the demographics of the overall clinical program for the povidone-containing formulation as fairly comparable to that of the general population. The demographics of currently submitted trials are similar to the ones previously submitted, as shown below.

Table 15 shows that the demographics of C-01-92 were similar to those of the currently-submitted safety trial, C-05-69 (see Table 31).

Table 15. Demographics of subjects in previously submitted safety trial C-01-92 (povidone-containing formulation)

Characteristic	Vehicle placebo N = 465		Olopatadine NS, 0.6% N = 459		Total N = 924	
Gender	n	(%)	n	(%)	n	(%)
Male	165	(35.5)	156	(34.0)	321	(34.7)
Female	300	(64.5)	303	(66.0)	603	(65.3)
Race	n	(%)	n	(%)	n	(%)
Caucasian	368	(79.1)	360	(78.4)	728	(78.8)
Black	33	(7.1)	29	(6.3)	62	(6.7)
Asian	19	(4.1)	16	(3.5)	35	(3.8)
Hispanic	42	(9.0)	49	(10.7)	91	(9.8)
Other	3	(0.6)	5	(1.1)	8	(0.9)
Age, years						
Mean age	35.2		36.9		36.1	
SD	13.9		13.9		13.9	
Range	12-79		12-78		12-79	
Age subgroups, years	n	(%)	n	(%)	n	(%)
0-12	7	(1.5)	7	(1.5)	14	(1.5)
13-64	447	(96.1)	445	(96.9)	892	(96.5)
>64	11	(2.4)	7	(1.5)	18	(1.9)

[Source: Medical Officer's review of original NDA, Table 91, based on original Alcon NDA, Module 5, volume 65, pp99-100]

Table 16 shows that the demographics of C-04-70 were similar to the demographics of the previously submitted efficacy and safety trials in seasonal allergic rhinitis, C-02-10 and C-02-37.

Table 16. Demographics of short-term trials of povidone-containing formulation in seasonal allergic rhinitis

	C-02-10		C-02-37		C-04-70	
	Olopatadine 0.6% n=223	Vehicle n=225	Olopatadine 0.6% n=184	Vehicle n=192	Olopatadine 0.6% n=180	Vehicle n=176
Age						
Mean (yrs)	37.2	40.3	35.6	35.5	35.7	36.6
Std dev. (yrs)	14.9	14.9	12.6	13.9	12.8	13.1
Min, max (yrs)	12, 75	12, 80	12, 71	12, 80	12, 70	12, 77
Ranges (yr) (n, %)						
12 - 64 years	211 (94.6)	209 (92.9)	181 (98.4)	187 (97.4)	177 (98.3)	174 (98.9)
≥65	11 (4.9)	15 (6.7)	3 (1.6)	5 (2.6)	3 (1.7)	2 (1.1)
Sex (n,%)						
Male	79 (35.6)	86 (38.4)	63 (34.2)	80 (41.7)	52 (28.9)	61 34.7)
Female	143 (64.4)	138 (61.6)	121 (65.8)	112 (58.3)	128 (71.1)	115 (65.3)
Race (n,%)						
Caucasian	140 (63.1)	149 (66.5)	138 (75.0)	142 (74.0)	136 (75.6)	133 (75.6)
Black	16 (7.2)	6 (2.7)	16 (8.7)	23 (12.0)	19 (10.6)	18 (10.2)
Asian	7 (3.2)	1 (0.4)	2 (1.1)	2 (1.0)	2 (1.1)	2 (1.1)
Hispanic	58 (26.1)	67 (29.9)	24 (13.0)	23 (12.0)	22 (12.2)	23 (13.1)
Other	1 (0.5)	1 (0.4)	4 (2.2)	2 (1.0)	1 (0.6)	0

[Sources: Alcon C-04-70 trial report Tables 11.2.1.-1 and 11.2.1.-2; Medical Officer's review of original NDA, Tables 34 and 60]

Table 17 shows a summary of the demographics from C-02-10, C-02-37, and C-04-70.

Table 17. Summary of demographics from combined C-02-10, C-02-37, and C-04-70

	Olopatadine 0.6% n=587	Vehicle n=593	Combined n=1180
Age			
Ranges (yr) (n, %)			
12-17	53 (9.0)	53 (8.9)	106 (9.0)
18 - 64 years	517 (88.1)	518 (87.3)	1035 (87.7)
≥65	17(2.9)	22 (3.7)	39 (3.3)
Sex (n,%)			
Male	194 (33.0)	227 (38.3)	421(35.7)
Female	393 (67.0)	366(61.7)	759 (64.3)
Race (n,%)			
Caucasian	414 (70.5)	424 (71.5)	838 (71.0)
Black	51 (8.7)	47 (7.9)	98 (8.3)
Asian	11 (1.9)	5 (0.8)	16 (1.4)
Hispanic	105(17.9)	114 (19.2)	219 (18.6)
Other	6 (1.0)	3 (0.5)	9 (0.8)

[Source: data from Alcon response to FDA February 27, 2008]

7.2.1.3 Extent of exposure (dose/duration)

Table 18 shows exposure to study drug up to the 6-month time point in trials C-01-92 and C-05-69. In C-01-92, exposure was slightly greater in the olopatadine group, a pattern that was

reversed in C-05-69, but the differences are slight. Between 77-81% of subjects stayed on treatment for at least 180 days in the two trials.

Table 18. Exposure up to 6 months in trials C-01-92 and C-05-69 (n, % of group or total)

Trial	Treatment	N	1-30 days	31-60 days	61-120 days	121-179 days	≥180 days
C-01-92	Olopatadine 0.6% PVP [redacted]	459	14 (3.1)	14 (3.1)	21 (4.6)	37 (8.1)	373 (81.3)
	Vehicle PVP [redacted]	465	26 (5.6)	24 (5.2)	25 (5.4)	33 (7.1)	357 (76.8)
	Total	*924*	*40 (4.3)*	*38 (4.1)*	*46 (5.0)*	*70 (7.6)*	*730 (79.0)*
C-05-69	Olopatadine 0.6%	445	26 (5.8)	8 (1.8)	34 (7.6)	41 (9.2)	336 (75.5)
	Vehicle	445	25 (5.6)	12 (2.7)	26 (5.8)	30 (6.7)	352 (79.1)
	Total	*890*	*51 (5.7)*	*20 (2.2)*	*60 (6.7)*	*71 (8.0)*	*688 (77.3)*

[Source: Alcon Table 4.1.-1]

Table 19 shows exposure data from the 2-week seasonal allergic rhinitis trials. Exposure was sufficiently similar among the trial to allow pooling the safety information from these trials.

Table 19. Exposure in 2-week seasonal allergic rhinitis trials

		1-6 days	7-16 days	>16 days	Mean (days)	Median (days)
C-02-10	Olopatadine 0.6% n=223	5 (2.2)	206 (92.4)	12 (5.4)	14.9	15
	Vehicle n=225	2 (0.9)	206 (91.6)	17 (7.6)	15.1	15
C-02-37	Olopatadine 0.6% n=184	5 (2.7)	113 (61.4)	66 (35.9)	15.7	16
	Vehicle n=192	2 (1.0)	119 (62.0)	71 (37.0)	16	16
C-04-70	Olopatadine 0.6% n=180	1 (0.6%)	86 (47.8%)	93 (51.7)	16.8	17
	Vehicle n=176	3 (1.7%)	84 (47.7%)	89 (50.6)	16.5	17

[Sources: Alcon C-04-70 trial report Tables 12.1.-4 and text; Medical Officer's review of original NDA, Tables 52 and 78]

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No clinical studies other than C-05-69 and C-05-64 provided data for safety of the proposed formulation.

7.2.2.2 Postmarketing experience

I review Alcon's submission of postmarketing data in section 7.1.17.

7.2.2.3 Literature

Alcon provided abstracts of laboratory studies, case reports, clinical trials, and reviews, of various formulations of olopatadine in response to a request for a summary of literature regarding olopatadine published since submission of the original NDA. This submission did not contain information affecting the judgment of safety and efficacy of the proposed product in the current NDA.

7.2.3 Adequacy of Overall Clinical Experience

The clinical data in the current submission, in conjunction with previously provided information related to safety, are adequate for an assessment of the safety of the proposed formulation.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Alcon submitted new animal studies to address the toxicology of potential degradants. These studies were deemed adequate by the toxicology reviewer.

7.2.5 Adequacy of Routine Clinical Testing

In trial C-05-69 subjects attended monthly visits at which adverse events are assessed and nasal exams conducted. This trial did not include evaluation of ECG or clinical laboratory determinations. However, the trial was intended primarily to address the issue of nasal toxicity, and included a more intensive evaluation of the nose in case initial examination indicated a clinically significant change from the baseline examination. In this sense C-05-69 provided a more intensive and potentially more accurate assessment of nasal toxicities than C-01-92.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The submission contains no new information about metabolism and clearance, nor a systematic exploration of drug interactions. However, the original NDA contained adequate information, and new information is not required.

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

Nasal septal perforations, which were noted with the previous formulation of olopatadine, are not expected for a nasal antihistamine, but have been seen with nasal corticosteroids. The toxicity that was addressed in the current submission was not thought to be a drug effect, but a byproduct of the formulation. C-05-69 was designed to look intensively at the effects of the product on the nose by incorporating a potentially two-part nasal examination. This examination was adequate to address the issue of nasal effects noted with the povidone-containing formulation. No special measures were taken to look for antihistamine class effects.

As pointed out in the review of the original NDA, the incidence of somnolence in subjects treated with placebo twice daily in the clinical development program for olopatadine nasal spray up to the time of the original NDA submission (2/1008) was lower than normally seen in seasonal allergic rhinitis trials of antihistamines in adults. This suggests that the sensitivity of the clinical trials to the detection of somnolence was lower than optimal.

I do not recommend special postmarketing studies of the expected incidence of somnolence in postmarketing studies. However, based on the overall data in the clinical program, I recommend [redacted]

7.2.8 Assessment of Quality and Completeness of Data

The data were collected adequately to permit an assessment of safety.

7.2.9 Additional Submissions, Including Safety Update

By agreement with FDA, Alcon is to submit a summary of 12-month safety in trial C-05-69 for review prior to the marketing approval decision.

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

The important treatment-related adverse events seen in the review of the original NDA, as summarized by Dr. Charles Lee, were epistaxis, taste perversion, dry nose, somnolence, nasal ulcer, nasal septum disorder, and nasal septum perforation.

Table 43 shows events that occurred more frequently in olopatadine-treated subjects than in vehicle-treated subjects in trial C-05-69. Nasal ulcers (occurring in 8.8% of olopatadine-treated and 5.8% of vehicle treated subjects) and taste perversion (occurring in 6.5% of olopatadine-treated and 0.7% of vehicle treated subjects) were the most notable events. No nasal septal perforations occurred in trial C-05-69. Epistaxis occurred commonly in the trial as a whole (19.3% of olopatadine-treated and 23.4% of vehicle-treated subjects).

Trial C-05-69 was adequately designed to address the issue of nasal septal perforations. Safety findings in the current submission are not a bar to marketing approval of the proposed formulation.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

For the important events of local nasal toxicity, it is not appropriate to pool results from the long-term safety trials C-01-92 and C-05-69, as they studied different formulations. However, it is appropriate to pool safety results from trial C-04-70 with the safety data from the previously-submitted seasonal allergic rhinitis 20-week trials. The general features of these trials have been discussed in previous sections.

7.4.2 Explorations for Predictive Factors

Review of the adverse event data from C-05-69 did not reveal patterns according to the sex or race of the subject, although there were relatively few non-Caucasian subjects. There were too few subjects outside the age group 18-64 to associate greater risk with extremes of age. Alcon did not perform a study of a new dose level or frequency, for time dependency, or drug-disease interactions for this submission. For information on drug-demographic interactions, see section 7.4.2.

7.4.3 Causality Determination

The information in this submission is from trials that were vehicle-controlled. The comparison to an inactive treatment provides compelling evidence of treatment relationship.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The support for the dosing regimen for olopatadine 0.6% nasal spray is summarized in the review of the original NDA. Alcon proposes that the recommended dose of olopatadine 0.6% nasal spray is two sprays per nostril twice daily.

8.2 Drug-Drug Interactions

The current submission contains no new formal analysis of drug-drug interactions. This information was not required.

8.3 Special Populations

8.4 Pediatrics

Alcon's efficacy trials studied a population as young as 12 years old. As summarized in section 2.5 of this review, at Alcon's request, on July 19, 2007, FDA issued a Written Request for pediatric studies. Alcon has submitted two pediatric study protocols to IND 60116. In the current NDA submission, Alcon is requesting a deferral of submission of information regarding use of olopatadine 0.6% nasal spray in patients from the age of 2 to 12 years old. In the October 15, 2007 FDA letter of acknowledgement of receipt of NDA 21861, FDA deferred submission of pediatric studies until July 1, 2009. Alcon states that enrollment into the first of the pediatric trials has begun, and that all trials and data conducted in pediatric patients will be submitted to FDA on or before July 1, 2009.

Alcon also requests a waiver of any requirement to submit information on the use of olopatadine 0.6% nasal spray in patients below the age of 2 years. Alcon's reasons are 1) It is unlikely that the product would be used in a substantial number of patients because

nonpharmacologic treatments, such as avoidance of allergens, may be used first, and 2) it is "highly impractical" to treat children under 2 years of age with nasal sprays and studies would "pose a significant problem." FDA may grant a waiver of the requirement to perform studies below the age of 2 years because seasonal allergic rhinitis does not occur below the age of 2 years.

8.5 Advisory Committee Meeting

The submission does not require input from an advisory committee.

8.6 Literature Review

FDA asked Alcon to submit a summary of the literature regarding olopatadine published since the time of the original NDA submission until the cutoff date for the resubmission. Alcon provided abstracts of laboratory studies, case reports, clinical trials, and reviews, of various formulations of olopatadine. This information does not change the judgment of safety and efficacy of the proposed product in the current NDA.

8.7 Postmarketing Risk Management Plan

Because Alcon's olopatadine 0.6% nasal spray cannot be approved at this time, recommendations on risk management activity would be premature.

8.8 Other Relevant Materials

Alcon submitted labeling for Allelock. Allelock is available as 2.5 and 5 mg tablets. The Core Data sheet contains a summary of "Adverse Reactions" using data "from clinical trials before approval, drug use-results survey and special survey for long-term use include a total of 1,402 adverse reactions reported from 1,056 patients (11.0%) among 9,620 patients treated."

The report states that the most frequently observed adverse reactions included sleepiness in 674 patients (7.0%), ALT (GPT) increased in 68 (0.7%), malaise in 53 (0.6%), AST (GOT) increased in 46 (0.5%), and thirst in 36 (0.4%).

Labeling for Allelock states the following as "clinically significant adverse reactions:" "Hepatic function disorder with increases of AST (GOT), ALT (GTP), γ-GTP, LDH and Al-P, etc. and jaundice may occur."

Reactions occurring in ≥0.1% to <5% were:

- Rash, including erythema, etc., edema (face, extremities, etc.)
- Malaise, thirst, dizziness, headache,/dull headache
- Abdominal discomfort, abdominal pain, diarrhea, nausea
- Hepatic function abnormal [GOT, GPT, γ-GT, LDH, Al-P and T-Bil increased]
- Leukocytosis, leucopenia, eosinophilia, lymphopenia
- Occult blood in urine
- Serum cholesterol increased

Reactions occurring in <0.1% were:

- Itching, dyspnea
- Numbness, mental concentration decreased
- Constipation, stomatitis/angular stomatitis, tongue pain, heartburn, increased appetite
- BUN increased, blood creatinine increased, urinary protein positive, dysuria, pollakiuia
- Palpitation, blood pressure increased
- Urine sugar positive, chest discomfort, taste abnormality, weight increased, hot flushes

Other disorders whose incidence is unknown were "involuntary movement (face, extremities, etc.)," menstrual disorder, myalgia, and arthralgia.

The methods used to produce the summaries were not included in the labeling. In addition, potential population differences may complicate the understanding of these data, which do not come from the U.S. population. There was no signal for hepatic function abnormality in the olopatadine nasal spray clinical program. Nor did serious adverse events occur with any pattern to suggest toxicity. However, I concur with Dr. Charles Lee's recommendation from the review of the original NDA that postmarketing adverse event reports for olopatadine nasal spray should be monitored for cases of hepatic function abnormalities.

This review includes the adverse reactions summary as an indicator of potential safety issues that may occur with the use of olopatadine nasal spray.

9 OVERALL ASSESSMENT

9.1 Conclusions

The current resubmission provides data sufficient to judge that the efficacy measured in the pivotal 2-week trials in seasonal allergic rhinitis submitted with the original NDA would be applicable to the current formulation. Similarly, the 6-month results of the 12-month safety trial in subjects with perennial allergic rhinitis showed no findings that would preclude marketing approval of olopatadine 0.6% nasal spray. Specifically, there were no nasal septal perforations and other nasal findings were acceptable. No new systemic findings were apparent.

9.2 Recommendation on Regulatory Action

The submission contains information adequate to approve Alcon's olopatadine 0.6% nasal spray for its intended use. I recommend an "Approvable" action if the manufacturing site inspection cannot be completed during this review cycle.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

I do not recommend risk management activities for this application.

9.3.2 Required Phase 4 Commitments

I do not recommend Phase 4 commitments for this application

9.3.3 Other Phase 4 Requests

I do not recommend Phase 4 requests for this application.

9.4 Labeling Review

9.5 Comments to Applicant

I recommend that the Division of Pulmonary and Allergy Products send comments based on the comments in the preceding section to Alcon.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 C-05-64: Olopatadine Nasal Spray 0.6% vs Vehicle in Treating Seasonal Allergic Rhinitis Patients in an Environmental Exposure Chamber

10.1.1.1 Protocol

10.1.1.1.1 Objective and overall design

Trial C-05-64 was a single-center, single-dose, vehicle-controlled, randomized, double-blind trial whose principal objective was the determination of efficacy of the newly-proposed, povidone-free olopatadine nasal spray formulation. The trial was designed to assess subjective responses in a population of allergen responders on a self-reported nasal symptom score questionnaire after exposure to allergen in an environmental exposure unit, and was intended to

provide crucial evidence supporting the clinical efficacy of the new formulation of olopatadine nasal spray. The trial in large part replicated the design of trial C-01-83, a single-dose, environmental unit trial submitted with the original NDA, except that in C-05-64 only one dose level was tested.

10.1.1.1.2 Procedures

This review will discuss protocol procedures first (Table 20 and Table 21), as this will give context to eligibility criteria, to be described subsequently.

During a qualifying phase candidates for randomization were to attend 4 visits: a Screening Visit (Visit 1), two Priming Visits (Visit 2a and 2b) and a Treatment Day Visit (Visit 3 pre-dose). Candidates were to be screened by medical history and nasal and skin prick tests at Visit 1. Qualifying candidates were to attend Visit 2a, at which medical histories and medications were reviewed for changes that could affect eligibility. At this visit they were to be exposed to short ragweed allergen for 3 hours in an environmental exposure unit (EEU), a room approximately 40 feet wide, 60 feet long, and 10feet high in which pollen is dispersed in HEPA-filtered air to an average pollen count of 3500±500 grains/m^3. Candidates recorded their nasal symptoms as a Total Nasal Symptom Score (TNSS): For each of the symptoms "runny nose," "itchy nose," "stuffy nose," and sneezing, the subject was to record a response on a scale from 0-3 (none, mild, moderate, and severe). Those who recorded a score of at least 6 out of a possible 12, with at least 2 for runny nose, on 2 consecutive diary cards were to proceed to a second priming visit (2b), at which the procedures were to be repeated. Candidates who recorded the same minimal score were to proceed to Visit 3 at least 24 hours but not more than 2 weeks after visit 2b. At Visit 3 candidates had to qualify again for receipt of the test article by recording 6 out of a possible 12 points on any of the 4 qualifying diary cards in the absence of unilateral or bilateral complete nasal blockage. Candidates who failed qualification at any visit prior to the final allergen exposure session (Visits 1, 2a, 2b, or 3a) were to be considered screening or priming failures. While continuing exposure to allergen at Visit 3, qualified subjects were randomized to self treatment (under observation) with either olopatadine nasal spray or vehicle, 2 sprays per nostril. Exposure to allergen continued for another 12 hours. Subjects recorded instantaneous symptom scores on the TNSS, which were the primary outcome determinations.

The trial did not require assessment of the effect of the trial drug on hematology, serum chemistry or electrocardiography.

Table 20. C-05-64: Procedures

Procedures	Visit 1 Screening	Visits 2a - 2b Priming-Baseline*	Visit 3 Treatment*
Informed Consent	X		
Inclusion/Exclusion Criteria	X	X	
Medical and medication history	X	X	X
Nasal Exam	X	X[1]	X
Vital Signs (pulse and blood pressure)	X	X[1]	X
Urine Pregnancy Test if applicable	X		X
Allergic diagnostic test (skin prick) if not in last 12 mo	X		
Review changes in med history and concomitant medications		X	X
Assess allergy symptoms to determine eligibility		X	X
Test article administration			X
Symptom diaries issued and collected		X	X
Medical Problems from first EEC exposure until randomization		X	X
Adverse Events reporting			X
Global Assessment Question (4-12 hrs after test article given)			X
Complete exit form			X

* Visits should not have been less than 24 hours or more than 2 weeks after prior visits.
[1] at Visit 2b
[Source: Alcon Table 9.1.-1]

Table 21. C-05-64: Procedures at Visit 3 (Qualifying and treatment visit)

Event	Time relative to treatment (hr:min)
Patients report to clinic	-3:00
Medical Problem Assessment	Prior to pollen exposure
Pollen exposure begins	-2:00
Qualifying diary cards	-1:30, -1:00, -0:45, -0:30
Medical Problem Assessment & Nasal Congestion Check	Prior to test article administration
Patient blows nose and then receives test article	0:00
Nasal symptom evaluations on diary card	Every 30 mins starting at 0:30-4:00, then every hour from 5:00-12:00
Obtain Vital Signs	1:00 - 3:00 (60-180 minutes)
Global Assessment Question	4:00 and 12:00
Nasal Exam	From 4-12 hrs post dose
Final adverse event assessment	12:00

[Source: Alcon Table 9.1.3.-1]

10.1.1.1.3 Subject eligibility

Subjects were to have seasonal allergic rhinitis and have skin test reactivity to short ragweed allergen. They were to fulfill eligibility criteria assessed during participation in the protocol. Specific medical eligibility criteria were:

Inclusion

- Age at least 18 years
- At least a two-year history of non-recalcitrant seasonal allergic rhinitis during the fall allergy season
- Positive case history and positive skin prick and/or intradermal test for short ragweed allergen (≥3-mm wheal greater than the diluent after skin prick testing, or ≥7-mm wheal greater than the diluent after intradermal testing) within the 12 months prior to Visit 1. If getting a skin test at Visit 1, specified washout times for antihistamines were to be followed
- "Priming" requirement: Fulfillment of the following criteria on each of two consecutive diary cards at a priming visit:

- a minimum TNSS of 6 out of 12, including a score of at least 2 for runny nose

--Patients must meet these same criteria at both priming visits of 3 hours chamber duration in order to proceed to the treatment visit (Visit 3).

- At the treatment visit (Visit 3), a minimum TNSS of 6 out of 12 (including a score of at least 2 for runny nose) on any one of four qualifying diary cards

- Observance of drug washout times, prior to Visit 2a and subsequent visits
- Absence of significant anatomic abnormalities, infection, bleeding, and mucosal ulcerations on nasal exam performed at screening, qualifying priming visit and prior to administration of test article

Exclusion

- Concurrent disease that might complicate or interfere with investigation or evaluation of the study medications such as:
    - Rhinitis medicamentosa
    - Large obstructive nasal polyps
    - Other anatomic nasal deformity that may interfere with the patient's participation in the study, as identified by nasal examination prior to administration of test article
    - Documented evidence of acute or significant chronic sinusitis, or upper respiratory tract infection as determined by the individual investigator
    - Asthma, with the exception of mild intermittent asthma as outlined in the National Asthma Education and Prevention Program Guidelines II, Step I
    - Congestion that would, in the opinion of the investigator, interfere with successful nasal drug administration/absorption (in either nostril)
- Use of prohibited medication
- Known non-responder to antihistamines for symptoms of SAR
- Chronic or intermittent use of inhaled, oral, intramuscular, intravenous, or potent or superpotent topical corticosteroids
- Chronic use of long acting antihistamines and other concomitant medications (e.g., tricyclic antidepressants) that would affect assessment of the effectiveness of study drug(s)
- Any systemic disorder that could interfere with the evaluation of the study medication(s)
- Upper or lower respiratory infection requiring antibiotics within 14 days of the first priming visit
- Diagnosis of sinusitis within 30 days of the initial priming visit
- Any ocular disorder (other than allergic conjunctivitis) including presumed infectious ocular disease (bacterial, fungal, viral, etc.), which could interfere with the evaluation of the study medication
- Hypersensitivity to the study drug(s) or any component of the test articles including benzalkonium chloride

- History of severe or uncontrolled cardiovascular, hepatic, renal and/or other disease/illness that could be expected to interfere with the study.
- History, or evidence, of nasolacrimal drainage system malfunction.
- The need for chronic or intermittent use of any nasal spray (prescription or over the counter) during the study period.

In addition, the protocol included criteria applied to women to avoid pregnancy, to avoid potential interference with participation due to drug use or knowledge of the study protocol, to exclude subjects who had participated in another investigational study within 30 days. The protocol allowed discretion for the investigator to enroll subjects with vital sign measurements outside specified ranges (systolic blood pressure 95 to 160 mmHg, diastolic blood pressure 55 to 90 mmHg, and pulse rate 50 to 100 beats/min) if these were not considered clinically relevant.

10.1.1.1.4 Trial treatment and its blinding

Subjects were to treat themselves with olopatadine or vehicle, 2 sprays per nostril.

The site was to provide trial treatment in white plastic bottles containing a minimal fill volume of 30 ml and delivering 100 µl per actuation once primed. Although olopatadine is known to have a bitter taste, Alcon took physical measures to blind the treatments. Bottles were to be masked with a label with the protocol number, subject number, and a statement that the treatment was to limited to nasal investigational use only.

10.1.1.1.5 Concomitant medications

Prospective patients were not to take specified medications for specified times prior to and after visit 2a. These medications were substantially the same as those for trial C-05-69 (see Concomitant medication section of the review for that trial), with the following additional prohibitions:

- Initiation of or change in immunotherapy
- Systemic, inhaled or ocular corticosteroids within 30 days
- Leukotriene pathway modifiers, systemic and topical anticholinergics, and systemic antifungal agents within 14 days
- Ocular anti-allergy medications within 7 days
- Oral decongestants, all over-the-counter cold and cough and sleep aids without components listed in other criteria (except saline), as-needed nonsteroidal anti-inflammatory agents, and aspirin (except low-dose for cardiac prophylaxis) within 3 days
- Nasal or ocular saline, or both, within 24 hours

Other drugs were permitted if they would not be expected to interfere with the ability of the subject to participate in the study, after review with the sponsor.

10.1.1.1.6 Analysis

The primary objective of the trial was to measure the superiority of olopatadine nasal spray compared to vehicle over 12 hours after administration as a single dose. The protocol states that differences between treatments at each time point would be used to evaluate the onset of action of each treatment arm.

<u>Populations</u>

The protocol defined the intent-to-treat and safety populations both as all subjects who received trial drug.

Primary effect measurement

The primary efficacy variable was the change from baseline in the TNSS, compared between treatment groups using 2-sample t-tests, with a 2-sided alpha of 0.05.

Secondary effect measurements

Secondary effect variables were 1) changes from baseline to each time point in each of the component scores of the TNSS measured using 2-sample t-tests and 2) the difference between treatment groups in the Patient's Global Rating Scale at each time point using a Cochran-Mantel Haenszel rank scores test. Tests used a 2-sided alpha of 0.05.

Sample size

The sample size of the trial was justified using an assumed treatment difference of 0.65 units in the TNSS change from baseline, with an approximate standard deviation of 2.0 units, and a 2-sided alpha of 0.05. Alcon calculated that this would give approximately 90% power to detect a significant treatment difference.

10.1.1.1.7 Protocol revisions

Alcon made no changes to the protocol or its analysis.

10.1.1.2 RESULTS

10.1.1.2.1 Trial initiation and completion

The trial was started on January 16, 2006 and was completed on March 11, 2006.

10.1.1.2.2 Identification of treatments used

The lot and formula identification numbers of the treatments are shown in Table 22.

Table 22. C-05-64: Identification of treatments

Treatment	Lot number	Formulation identification number
Olopatadine 0.6%	05-600187-1	109941 v.4
Vehicle	05-600188-1	109970 v.2

Alcon used the to-be-marketed olopatadine nasal spray formulation but not the to-be-marketed device for this trial. The device tested in this trial used a prior version of a pump [redacted] as compared to the current [redacted]. According to a CMC review memorandum (March 4, 2008) regarding the current pump, "no changes have been made to the components of the pump that would be expected to alter the delivery performance." The device used in this trial would be expected to perform as the to-be-marketed device would.

10.1.1.2.3 Subjects

Enrollment and disposition

Four hundred six subjects were enrolled, randomized to treatment, and received trial treatment. No one discontinued.

Demographics and baseline total nasal symptom score

Demographics (Table 23) were balanced between the treatment groups and reflected a population that included very few in the geriatric age group, were balanced by sex, and were predominantly Caucasian.

Table 23. C-05-64: Demographics (ITT and safety population)

	Olopatadine 0.6% n=204	Vehicle n=202
Age		
Mean (yrs)	37.0	36.5
Std dev. (yrs)	12.0	11.5
Min, max (yrs)	18,79	18,76
Ranges (yr) (n, %)		
18 - 64 years	197 (96.6)	198 (98.0)
≥64	7 (3.4)	4 (2.0)
Sex (n,%)		
Male	107 (52.5)	100 (49.5)
Female	97 (47.5)	102 (50.5)
Race (n,%)		
Caucasian	96 (47.1)	106 (52.5)
Black	49 (24.0)	50 (24.8)
Asian	30 (14.7)	19 (9.4)
Hispanic	11 (5.4)	9 (4.5)
Other	18 (8.8)	18 (8.9)

[Source: Alcon Table 11.2.1.-2]

The baseline TNSS was the average of the last two diary cards collected during the allergen exposure prior to treatment (at Visit 3). The scores on each symptom could range from 0-3, so the total could be from 0-12. Scores indicated the presence of symptoms in the trial population, and were balanced between the treatment groups.

Table 24. C-05-64: Baseline instantaneous symptom scores*

		Olopatadine 0.6% n=204	Vehicle n=202
Total Nasal Symptom Score (TNSS)	Mean±std	9.8 ± 1.8	9.5 ± 1.8
	Min, max	4.5, 12.0	3.5, 12.0
Runny Nose	Mean±std	2.6 ± 0.5	2.5± 0.5
	Min, max	1.0, 3.0	1.0, 3.0
Itchy Nose	Mean±std	2.5 ± 0.6	2.5 ± 0.6
	Min, max	1.0, 3.0	0.5, 3.0
Stuffy Nose	Mean±std	2.5 ± 0.5	2.5± 0.6
	Min, max	1.0, 3.0	0.0, 3.0
Sneezing	Mean±std	2.1 ± 0.8	2.1 ± 0.8
	Min, max	0.0, 3.0	0.0, 3.0

*In the presence of allergen in an environmental exposure chamber; average of last 2 diary cards
[Source: Alcon Table 11.2.2.-1]

10.1.1.2.4 Protocol deviations

Protocol deviations occurred in a small number of subjects (22 vehicle, 28 olopatadine). Alcon identified three subjects (all in the olopatadine treatment group) who had what were considered deviations that might affect the efficacy assessment: Two subjects left the environmental chamber temporarily after dosing, and one inadequately washed out an excluded

medication. The most common deviation concerned the nasal examination; this deviation occurred equally in the treatment groups (14 olopatadine subjects, 12 vehicle subjects). The number and nature of the deviations would not be expected to have a notable impact on the effect conclusions of the trial.

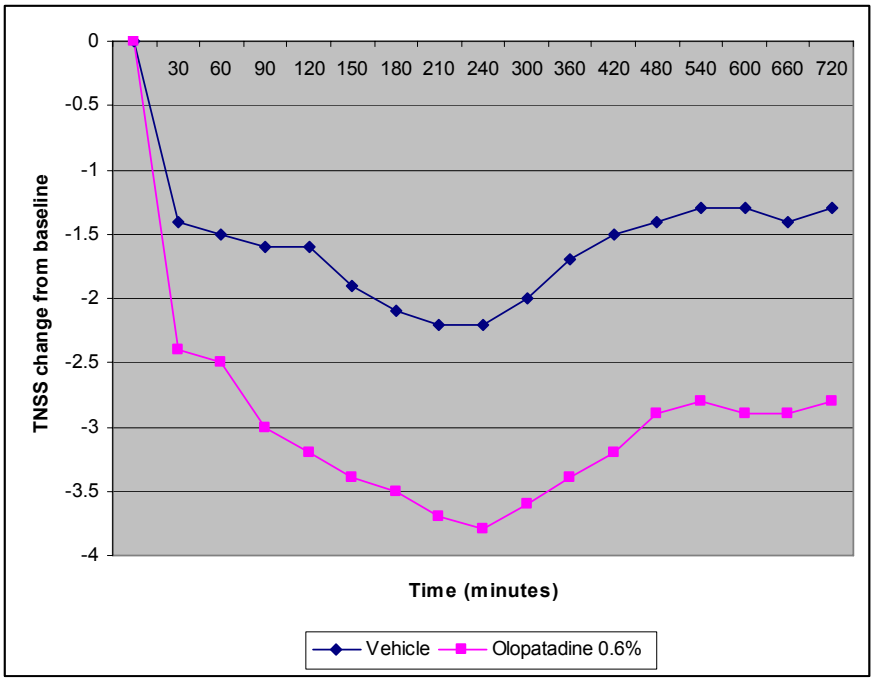
10.1.1.2.5 Compliance to trial treatment

Site personnel were to supervise the administration of the single dose of trial medication. All subjects received a single dose of trial medication.

10.1.1.2.6 Effect (12-hour symptoms)

Figure 1 illustrates the primary outcome, the total nasal symptom score analysis by treatment group expressed as mean change from baseline over the 12 hours after treatment. The analysis uses the last observation carried forward. The statistical test yielded a p-value less than 0.05 at each time point, a result that is corroborated by the analysis of the FDA statistical reviewer.

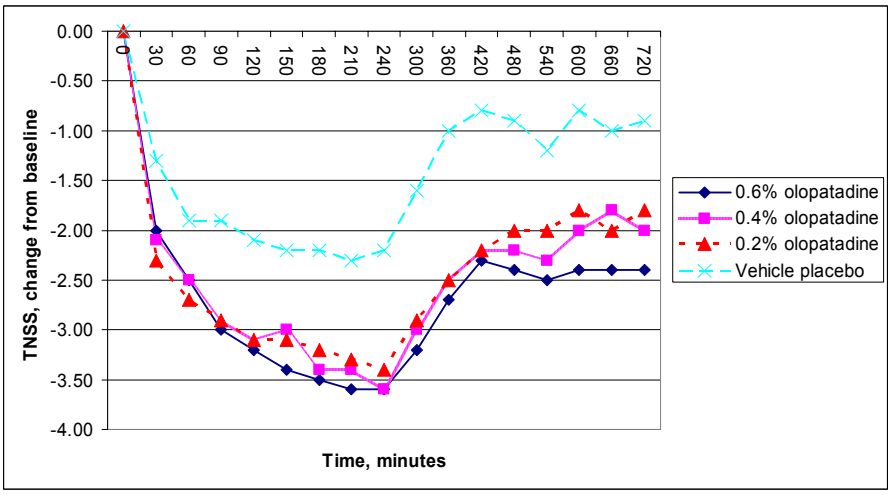
Figure 1. C-05-64: Mean change in Total Nasal Symptom Score at baseline and 12 hrs after treatment (Primary analysis, LOCF)



[Source: Data in Alcon Table 14.2.1.-1]

The treatment effect, including the effects at 30 minutes and 12 hours, is similar to that produced in the single-dose EEU trials C-01-83 and C-03-52, presented in the original NDA. For comparison, I reproduce here Dr. Charles Lee's figure representing the results of C-01-83 (Figure 2):

Figure 2. Data from previous formulation of olopatadine: Trial C-01-83 (Change from baseline TNSS after single dose of vehicle, olopatadine 0.2%, 0.4%, or 0.6%)



[Source: Medical Officer NDA21-861 review, Figure 1]

In C-01-83 and C-03-52, the comparison to placebo achieved a p-value of <0.05 at 90 and 30 minutes, respectively. Because Alcon has demonstrated a statistical difference between olopatadine 0.6% nasal spray in replicate trials at 30 minutes, the onset of action for a single dose may be assessed at 30 minutes.

Secondary outcomes

Individual component scores for the TNSS

The patterns of response from each of the component scores of the TNSS are similar to that of the TNSS, supporting the primary endpoint. For each component there is an early decline followed by persistent improvement compared to vehicle out to the last measurement. For runny nose, itchy nose, and sneezing, Alcon's statistical test yielded a p-value less than 0.05 at each time point throughout the measurement period. For stuffy nose, p-values were less than 0.05 for all time points except 60, 540, and 660 minutes. The FDA statistical review confirms that the components of the TNSS behaved similarly to the total.

Subject global rating scale

The results of the global 7-point rating scale were consistent with the TNSS. Scores overall were worse at 12 hours than at 4 hours in both treatment groups, but remained better than vehicle control overall in the olopatadine treatment group.

10.1.1.2.7 Safety

Adverse events were collected as solicited comments and as observations by the trial investigator and were coded using the COSTART system. Adverse events were coded when there were changes in health after initiation of trial treatment, including changes in concomitant medications due to a new medical diagnosis or a worsening illness. An adverse event was to be recorded for the emergence of a finding on the nasal examination. Changes in rhinitis symptoms recorded on diary cards for efficacy were not recorded as adverse events.

Exposure

All subjects received one dose of trial treatment.

Adverse events

There were no deaths or serious adverse events. No one discontinued due to an adverse event.

Table 25 shows that adverse events were rare, which is expected after a single dose of a nasal antihistamine. Headache was the most common adverse event, occurring more frequently in the vehicle control group.

Table 25. C-05-69: Adverse events occurring in at least 2 subjects in the trial (n,%)

Adverse event	Olopatadine 0.6% N =204	Vehicle N =202
Epistaxis	7 (3.4)	7 (3.5)
Rhinitis	0 (0)	2 (1)
Headache	8 (3.9)	19 (9.4)
Abdominal pain	1 (0.5)	1 (0.5)
Face edema	0	2 (1)
Vomit	1 (0.5)	2 (1)
Dyspepsia	1 (0.5)	1 (0.5)
Pruritus	1 (0.5)	1 (0.5)
Eye edema	0	2 (1)

[Source: Alcon Table 14.3.1.3.1.-1]

The frequency of epistaxis in this study was higher than the frequencies noted in Alcon's previously submitted single-dose environmental chamber studies C-03-52 (0% olopatadine 0.6%, 0.7% vehicle placebo) and C-01-83 (1.3% olopatadine 0.6%, 2.5% vehicle placebo). All the trials were conducted in Ontario, Canada. One possible reason for the discrepancy in epistaxis rates is that C-05-64 was conducted during the winter months, while C-03-52 was conducted during April through June and Study C01-83 was conducted during June and July. Winter weather conditions may have contributed to the increase in epistaxis rates.

Nasal examination

The nasal examination in 6 subjects in the olopatadine treatment group (3.0%) and 5 in the vehicle control group (2.5%) demonstrated bleeding. The nasal examination in 1 subject, in the vehicle control group, demonstrated infection. This review discusses bleeding immediately above. The nasal examination data do not suggest a concern for the safety of the product.

Concomitant medications

Information collected on concomitant medication use from a single-dose trial is of limited usefulness. Alcon recorded medications taken for adverse events. One subject in the olopatadine group took a medication for the adverse event "migraine and vomiting." Three subjects in the vehicle control group took medications for adverse events (headache; headache and vomiting; dizziness and headache). These data do not reveal any new safety concerns.

Cardiovascular findings

Vital signs were obtained at screening, baseline (visit 2b), and at 1-3 hours after the single dose at visit 3. Mean systolic and diastolic blood pressures (Table 26) were lower in the olopatadine treatment group at the exit vital sign determination, but by a clinically insignificant amount. Shift table analysis (Table 27) shows that this was accounted for by a small number of

subjects who had high baseline blood pressure that was normal at exit. Changes in pulse were not notably different between the treatment groups.

Table 26. C-05-64: Pulse and blood pressures at baseline and exit

			Baseline	Exit	Change from baseline
Pulse	Olopatadine 0.6%	N	204	204	204
		Mean±sdev (min, max)	73.1±12.4 (47, 126)	71.4±11.8 (45, 126)	-1.7±10.0 (-44, 28)
	Vehicle	N	202	202	202
		Mean±sdev (min, max)	73.1±10.8 (52,111)	71.7±10.9 (46, 105)	- 1.4±8.1 (-30, 22)
SBP	Olopatadine 0.6%	N Mean	204	204	204
		Mean±sdev (min, max)	126.8±18.0 (76,191)	123.0±16.7 (89, 179)	-3.9±12.2 (-37,37)
	Vehicle	N	202	202	202
		Mean±sdev (min, max)	124.8±16.4 (85,178)	123.7± 15.6 (85, 172)	- 1.1±15.1 (-76, 77)
DBP	Olopatadine 0.6%	N	204	204	204
		Mean±sdev (min, max)	76.6±10.5 (50, 113)	74.6±9.3 (51, 109)	-2.0±7.1 (-23, 17)
	Vehicle	N	202	202	202
		Mean±sdev (min, max)	74.7± 9.6 (50, 107)	73.8±8.9 (52, 100)	-0.9±8.1 (-25, 37)

[Source: Alcon Tables 12.5.2.2.-1, 12.5.2.2.-2, and 12.5.2.2.-3]

Table 27. C-05-64: Pulse and systolic and diastolic blood pressure: Comparison, baseline to exit

		Low Baseline			Normal Baseline			High Baseline		
Pulse	**N**	**Low**	**Normal**	**High**	**Low**	**Normal**	**High**	**Low**	**Normal**	**High**
Olopatadine 0.6%	204	12	11	0	16	152	2	0	9	2
Vehicle	202	10	11	0	15	162	1	0	1	2
SBP										
Olopatadine 0.6%	204	2	5	0	9	139	12	0	18	19
Vehicle	202	2	4	1	6	142	12	0	1	14
DBP										
Olopatadine 0.6%	204	1	3	0	4	171	3	0	13	9
Vehicle	202	2	2	0	5	177	5	0	6	5

* If an increase and decrease of the same magnitude occurred, the increase is reported.
[Source: Alcon Tables 12.5.2.2.-4, 12.5.2.3.-4, and 12.5.2.4.-4]

10.1.1.3 Summary of trial C-05-64

Trial C-05-64 was adequately conducted and demonstrated a similar treatment effect to the previously submitted single-dose environmental exposure unit study C01-83. No safety issues emerged from this single-dose study.

This trial provides an adequate pharmacodynamic link between the previous povidone-containing formulation and the current povidone-free formulation of olopatadine 0.6% nasal spray. It is reasonable to infer that the proposed povidone-free formulation would confer similar clinical efficacy to the povidone-containing previous formulation in SAR.

10.1.2 C-05-69: Safety Study of Olopatadine Nasal Spray

10.1.2.1 Protocol

10.1.2.1.1 Objective and overall design

Trial C-05-69 was a one-dose-level, randomized, double-blind, vehicle-controlled 12-month trial whose principal objective was the determination of safety of the newly-proposed, povidone-free olopatadine nasal spray formulation. As part of a prespecified plan, and with agreement of FDA, 6-month results have been submitted to FDA. The trial was intended to enroll at least 800 subjects with perennial allergic rhinitis with the aim of obtaining at least 300 subjects on active treatment evaluated for safety at 6 months. Visits, which include nasal examinations, occurred monthly. In order to support compliance with treatment, a subset of subjects were tested for blood olopatadine levels and the entire trial population answered a self-administered effectiveness question at one month.

The protocol used was version 3.0, effective November 28, 2006.

10.1.2.1.2 Procedures

This review will discuss protocol procedures (Table 28) first, as this will give context to eligibility criteria, to be described subsequently.

Informed consent was to be obtained at visit 1. Alcon selected a subset of sites at which to obtain consent for an addition set of blood draws for olopatadine concentrations (investigators were not to inform subjects at which visits the blood draws were to be performed). Olopatadine blood levels were to provide an additional measure of compliance. The subjects who agreed to have blood levels of olopatadine drawn also agreed to have some serologic testing. Subjects with antibody to hepatitis B surface antigen, hepatitis C, or with a positive test on an HIV ELISA screen were not to have their blood drawn for olopatadine blood levels. Investigators were to perform the first nasal examination (see below for more details), and determine other parameters as described in Table 28.

At recurring clinic visits the site was to give subjects two bottles of medication, which included a "back-up" bottle. The primary bottle was to be weighed, then primed (pumped 5 times or until a fine mist appeared) for the subject. The backup bottle was to be neither weighed nor primed. The subject was to receive a dosing diary upon which to record medication use. Subjects are to use the medication every 12 hours to the extent possible, and to store the medication upright at room temperature.

At subsequent visits, the sites weigh the bottles, dispense new primary bottles, and make other assessments according to Table 28. Blood was to be drawn for olopatadine concentrations in the subset of subjects who had agreed to have this test at day 30 and day 150.

Subjects are to be withdrawn for a nasal septal perforation and may be withdrawn at the discretion of the investigator for use of numerous medications or rescue medication (pseudoephedrine) for 7 days or more or a concerning nasal ulceration. The protocol specified that withdrawals would be classified under the categories adverse event, treatment failure, loss to follow-up, patient decision unrelated to an adverse event, protocol violation, or other.

The protocol included a crude measure of effect to assist in the determination that subjects were taking trial medication. At trial visits subjects placed the answer to a symptom question in the case report form (see "Analysis" below). This question is not a component of the TNSS, so the results cannot be compared directly.

The protocol did not require the assessment of hematology, chemistry or electrocardiographic data.

Table 28. C-05-69 Procedures

	Visit 1 Day 1	Visit 2 Day 30 ±5	Visit 3-5 Days 60, 90, 120 ±5	Visit 6 Day 150 ±5	Visit 7 Day 180 ±5	Visit 8-12 Days2 210,240, 270,300, 330 ±5	Visit 13 Day 365 (or Early Exit) ±10
Sign consent, verify inclusion/exclusion criteria	X						
Pregnancy test (if applicable)	X				X		X
Record medical and medication history	X						
Allergic diagnostic skin test if not performed in last year	X						
Subset of subjects (pk) - serology testing	X						
Dispense daily dosing diary	X	X	X	X	X	X	
Dispense medical problems log	X	X	X	X	X	X	
Nasal exam	X	X	X	X	X	X	X
Physical examination	X				X		X
Vital signs (blood pressure and pulse)	X	X	X	X	X	X	X
Patient effect questionnaire	X	X	X	X	X	X	X
Record changes in medical history and concomitant medications		X	X	X	X	X	X
Collect daily dosing diary		X	X	X	X	X	X
Review/emphasize dosing compliance		X	X	X	X	X	
Collect/review/issue medical problems page		X	X	X	X	X	X
Assess for adverse events (starts after first dose)	X	X	X	X	X	X	X
Weigh and dispense study medication	X	X	X	X	X	X	
Collect and weigh study medication		X	X	X	X	X	X
Subset of subjects - blood draw for plasma level analysis		X		X			
Complete exit form							X

[Source: Alcon C-05-69 protocol Table 17.-1]

10.1.2.1.3 Nasal examination

The long-term safety trial in PAR subjects submitted with the original NDA included a nasal examination at each visit. Because of the concerns over nasal septal perforation from the previous formulation, the current trial includes a nasal examination that can be made more detailed upon certain initial findings.

Alcon prepared investigators to perform the nasal examination with instructions delivered by Dr. Bradley Marple of Alcon and Dr. Robert Lanier, one of the trial investigators. The nasal examination was to be performed at each trial visit and was a component of eligibility (subjects with abnormalities on nasal examination were not to be permitted into the trial).

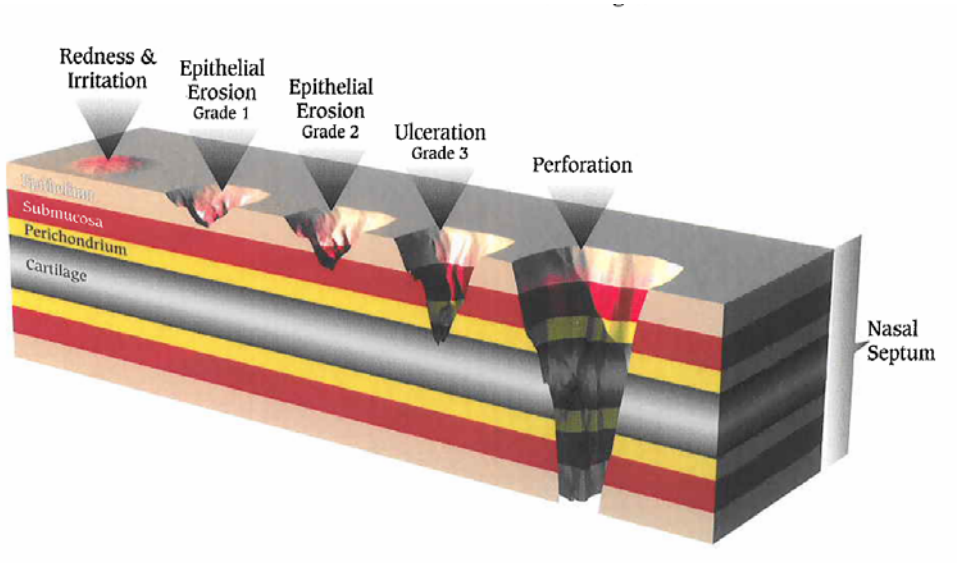
Baseline examination

The baseline examination was performed as one of the prerequisites of enrollment. It involves decongestion with oxymetazoline followed by flushing of the nasal cavities with saline, then inspection of the nose from 3 positions (head up 30 degrees, head neutral, and head down 30 degrees) using a nasal speculum with transilluminator. The finding of any "evidence of infection," "significant anatomic abnormality," ulceration of the mucosa, or blood in the nose found, would disqualify the person from enrollment.

Postrandomization examination

The postrandomization examination was a potentially two-step procedure (Sections A and B). Initially the investigator was to use a transilluminator and a nasal speculum for the examination, but not to decongest the nose. Findings in Section A are recorded as "evidence of infection," "significant anatomic abnormalities," possible ulceration of the mucosa," and "blood in the nose." Section A only was required if "evidence of infection" were found without other findings; an adverse event form must be filled out. Other findings require a Section B examination and an adverse event form that records the findings of that examination. Section B of the examination requires use of decongestant. Alcon referred examiners to an illustration of the various potential grades of damage to the nasal septum (from minimal damage through complete perforation of the septum, Figure 3). The finding of a nasal septal perforation requires confirmation with an otolaryngologist (or another otolaryngologist if the first examiner were one).

Figure 3. C-05-69: Illustration provided to guide detailed nasal examination Section B



[Source: Alcon Figure 12.5.1.-1]

Section B findings were to be recorded in relation to those in Section A as shown in Table 29.

Table 29. C-05-69: Reporting of nasal examination findings

Section A finding	Section B finding
Evidence of infection	(no examination required)
Significant anatomic abnormalities	Nasal perforation
	Intranasal mass
Possible ulceration of the mucosa	Redness, irritation
	Epithelial erosion Grade I
	Epithelial erosion Grade II
	Ulceration of the mucosa Grade III
Blood in the nose	Nasal Bleeding

[derived from C-05-69 case report form]

10.1.2.1.4 Subject eligibility

Subjects were to fulfill the following medical eligibility criteria:

Inclusion

1. One year history of non-recalcitrant perennial allergic rhinitis
2. Allergy to a perennial allergen, defined by positive case history and positive skin prick and/or intradermal test (≥3-mm wheal greater than the diluent after skin prick testing, or ≥7-mm wheal greater than the diluent after intradermal testing) within the 1 year prior to Visit 1.
3. Patient must be 12 years of age or older.
4. Nasal exam must confirm absence of significant anatomic abnormalities or evidence of infection, ulceration of the mucosa, and blood in the nose at Visit 1.

In addition, the protocol required washout times for specified medications (see section on concomitant medications) prior to Visit 1 and criteria applied to women to avoid pregnancy.

Exclusion

1. Concurrent disease or nasal exam finding that might complicate or interfere with investigation or evaluation of the study medications such as rhinitis medicamentosa, large obstructive nasal polyps, or other anatomic nasal deformity
2. A confirmed diagnosis of chronic rhinosinusitis within the last year
3. Congestion that would, in the opinion of the investigator, interfere with successful nasal drug administration/absorption (in either nostril)
4. Any systemic disorder that could interfere with the evaluation of the study medication(s)
5. Hypersensitivity to the study drug(s) or any component of the test articles, including benzalkonium chloride
6. History of severe, unstable or uncontrolled cardiovascular, hepatic, renal and/or other disease/illness that could be expected to interfere with the study.

In addition, the protocol excluded persons who had participated in any other Alcon olopatadine nasal spray trial and allowed the medical monitor discretion to declare any person ineligible for a sound medical reason.

10.1.2.1.5 Trial treatment and its blinding

Trial treatments are provided in masked white bottles as in trial C-05-64 (see above). Subjects are encouraged to follow an every-12 hour schedule and are given a medication diary in which to record medication use.

The protocol contains detailed instructions to investigators to convey to subjects regarding use of the trial medication. These instructions include washing hands with soap and

water, tilting the head forward, not spraying toward the nasal septum, breathing in gently while depressing the applicator and breathing out after each spray, and not blowing the nose for several minutes after using the spray.

Comment

As in trial C-05-64, the adequacy of the physical measures to blind the treatments was uncertain. Alcon did not administer a blinding questionnaire.

10.1.2.1.6 Concomitant medications

Prohibited

Prospective patients were not to take specified medications for specified times prior to visit 1:

- 14 days: nasal corticosteroids; nasal ipratropium bromide (or atropine), nedocromil or sodium cromolyn, loratadine (Claritin®), desloratadine (Clarinex®), or levocabastine; antiarrhythmic agents (disopyramide, procainamide HCl, quinidine sulfate, flecainide, propafenone, amiodarone, bretylium, dofetilide, ibutilide fumarate (Corvert), N-acetylprocainamide, Sotalol HCl (Betapace)
- 7 days: nasal sprays not specified above, topical nasal decongestants, herbal products used to relieve allergy symptoms, chlorpheniramine, clemastine fumarate, brompheniramine maleate, hydroxyzine, hydroxyzine pamoate, azatadine maleate, azelastine 0.1 % nasal spray (Astelin®), cetirizine HCl (Zyrtec®), fexofenadine HCl (Allegra®)
- 3 days: Diphenhydramine, promethazine HCl, cyproheptadine HCl (Periactin®), triprolidine HCl, and acrivastine
- Sleep aids containing any of the antihistamines were prohibited for the relevant time period

The protocol states that "limited intermittent use" of these treatments other than nasally administered medications and antiarrhythmic agents (for less than 7 consecutive days) was allowed at the discretion of the investigator.

Dispensed rescue medication

Investigators are to dispense small quantities of pseudoephedrine for subjects to use as rescue medication upon agreement of the investigator.

10.1.2.1.7 Analysis

Populations

The protocol defines four populations:

- Safety: those who receive drug
- Efficacy: intent-to-treat (ITT): those who receive drug and have at least one clinic visit while on trial treatment.
- Per protocol: ITT population, meeting eligibility criteria
- Pharmacokinetic ITT: safety population who have a "reported" bioanalytical result (concentration value or below the limit of quantification (BLQ)) for at least one post-dose pharmacokinetic blood draw

Primary effect measurement

The subject-assessed measure of treatment effect was a question on a 4-point scale:

I would rate the study medication's effectiveness for relieving my allergy symptoms since my last visit as:

1. Complete Relief
2. Moderate Relief
3. Mild Relief
4. No Relief

This question was used to assess effect on symptoms in Alcon's previous long-term safety trial, previously submitted to the NDA. A clinically important minimal difference has not been established for this question. However, the intent of this assessment was to ascertain if there was any treatment effect, as a measure of confirmation that subjects had been taking trial treatment, and not to demonstrate efficacy.

The primary effect analysis was to be a two-sample t-test on the comparison between treatment groups of the mean value of the patient questionnaire at day 30. Secondary efficacy analysis was to be performed on the average number of days of rescue medication use and the mean response to the patient questionnaire over the duration of the trial (average of visits 2-13 or last visit).

Safety

Safety was to be assessed through comparison of adverse events and results of the nasal examinations. Serious adverse events are defined as death or events that are life-threatening, result in an inpatient hospitalization or prolongation of an existing hospitalization, result in a persistent or significant disability or incapacity, or are a congenital anomaly or birth defect. They also include events that may jeopardize the subject and may require medical or surgical intervention to prevent one of these outcomes.

Compliance was to be assessed through examination of diary dosing records, the recording of bottle weights, and by olopatadine blood levels in a subset of patients.

The protocol specifies that an interim data base lock would occur after all subjects had completed the day 180 evaluation. Regarding maintenance of the blind, the protocol states, "only selected Alcon Biostatistics, Investigational Product Safety, and Pharmacokinetics/Drug Metabolism staff will be aware of treatment assignments at the patient level. Alcon Clinical Science personnel will have access only to the study results summarized by treatment group. All patients, investigators and Alcon staff who have contact with patients and investigators will remain masked with regard to patient-level treatment assignments during and after interim analysis."

10.1.2.1.8 Protocol revisions

All protocol revisions were made prior to the initiation of the trial. Notable revisions included:

- Change to a two-arm design testing povidone-free active and vehicle arms from a three-arm design comparing olopatadine nasal spray containing povidone 0.5% to povidone-free vehicle and povidone-free placebo.
- Addition of determination of blood levels of olopatadine in a subset of subjects as a measure of subject adherence to treatment
- Removal of the requirement for trained physicians to conduct the nasal examination
- Addition of a statistical test for superiority and a change in the primary endpoint measure to be at day 30 rather than an average of all on-treatment visits
- Addition of clinical sites so that less than 1/3 of the principal investigators would have been used in prior Alcon olopatadine nasal spray clinical trials

Since Alcon made these revisions to the trial prior to its initiation, they could not affect the integrity or interpretation of the trial.

10.1.2.2 RESULTS

10.1.2.2.1 Trial initiation and interim last visit dates

The trial was started on December 6, 2006. The last 6-month visit date for analysis was July 31, 2007.

10.1.2.2.2 Financial conflict of interest

Two investigators, [redacted] reported financial conflicts of interest: [redacted]. The numbers of subjects enrolled by these two investigators was insufficient to alter the results of the trial substantially.

10.1.2.2.3 Identification of trial drug lots

The lot and formula identification numbers of the treatments are shown in Table 30. Alcon tested the to-be-marketed device and olopatadine nasal spray formulation.

Table 30. C-05-69: Identification of treatments

Treatment	Lot number	Formulation identification number
Olopatadine 0.6%	06-500834-1	FID 109941
	06-600215-1	
Vehicle	06-500816-1	FID 109970
	06-500835-1	
	07-500853-1	

10.1.2.2.4 Subjects

Enrollment

In pre-study discussions, FDA had told Alcon that not more than one third of the sites in the trial should have previously participated in studies in the NDA. In response, Alcon increased the number of sites and complied with that requirement.

Eighty sites, all in the U.S., enrolled 890 subjects. No site accounted for a notable preponderance of subjects, with enrollment ranging from 2-18 per site, and most sites enrolling around 12 subjects.

Demographics

Age, sex, and "race" were balanced between the treatment groups (Table 31). There were about twice as many women as men in the trial, and the great majority of subjects were Caucasian. The trial enrolled very few subjects in the geriatric age group.

Table 31. C-05-69: Demographics (ITT and safety population)

	Olopatadine 0.6% n=445	Vehicle n=445
Age		
mean (yrs)	36.5	37.0
median (yrs)	37.0	37.0
min, max (yrs)	12,73	12,76
Ranges (yr) (n, %)		
12 - 17	46 (10.3)	53 (11.9)
18 - 64 years	388 (87.2)	383 (86.1)
≥65 - <75 years	11 (2.5)	8 (1.8)
≥75 - <85 years	0	1 (0.2)
Sex (n,%)		
Male	163 (36.6)	149 (33.5)
Female	282 (63.4)	296 (66.5)
Race (n,%)		
Caucasian	359 (80.7)	361 (81.1)
Black	43 (9.7)	39 (8.8)
Asian	4 (0.9)	6 (1.3)
Hispanic	32 (7.2)	37 (8.3)
Other	7 (1.6)	2 (0.4)

[Sources: Alcon Tables 11.2.1.-1 and 11.2..-2]

Disposition

A slightly greater fraction of subjects discontinued in the olopatadine group for adverse events or for treatment failure (Table 32). See the safety review for a discussion of discontinuations for adverse events.

Table 32. C-05-69: Summary of reasons for discontinuation (ITT and safety population)

Reason	Olopatadine 0.6% n=445	Vehicle n=445
Adverse event	22 (4.9)	16 (3.6)
Lost to monitoring	16 (3.6)	15 (3.4)
Decision unrelated to adverse event	19 (4.3)	21 (4.7)
Treatment failure	20 (4.5)	16 (3.6)
Protocol violation	7 (1.6)	6 (1.3)
Other	8 (1.8)	9 (2)
TOTAL	92 (20.6)	83 (18.7)

[Source: Alcon Table 10.1.-7]

The numbers of subjects in each treatment group who had discontinued at each monthly visit was approximately equal (Table 33).

Table 33. C-05-69: Cumulative discontinuations by trial day (ITT and safety population)

	D1	D30	D60	D90	D120	D150	D180
Olopatadine 0.6% n=445	0	19	29	43	59	71	83
Vehicle n=445	0	14	28	41	54	64	72

[Source: Alcon Table 10.1.-1]

10.1.2.2.5 Protocol deviations

Visit time window violation was fairly common in both treatment groups but would not be expected to have a notable effect on the interpretation of the trial. Cardiovascular protocol

deviations were generally related to the taking of blood pressure. Table 34 shows that in general other protocol deviations were not common and were fairly balanced between treatment groups. Because of their importance to the trial, deviations in the nasal examination were examined. The great majority of violations of the nasal examination pertained to decongestant either being used or not being used. Protocol deviations overall in trial C-05-69 would not be expected to change the interpretation of the trial or cast doubt on the trial's integrity.

Table 34. C-05-69: Summary of subjects with protocol deviations

Protocol deviation	Olopatadine 0.6% n=445	Vehicle n=445
General		
Incorrect randomization	2 (0.4)	1 (0.2)
Visit window violation	122 (27.4)	120 (27.0)
Prohibited medication	17 (3.8)	22 (4.9)
Non-compliance with med	13 (2.9)	8 (1.8)
Visit		
Physical examination	4 (0.9)	9 (2)
Nasal examination	25 (5.6)	28 (6.3)
Cardiovascular	51 (11.5)	47 (10.6)
Study medication	39 (8.8)	42 (9.4)
Effect questionnaire	19 (4.3)	15 (3.4)
Dosing diary	10 (2.2)	13 (2.9)
Medical problem	5 (1.1)	12 (2.7)
Pregnancy	7 (1.6)	1 (0.2)
Other	11 (2.5)	15 (3.4)

[Source: Alcon data set DEVI01.jmp]

10.1.2.2.6 Compliance to trial treatment

Subjects filled out a dosing diary for each day on the trial, and Alcon analyzed these data as a proportion of the doses expected (Table 35). Subjects in each group took an average of approximately 81% of potential doses, with a median of 85%, according to the dosing diary.

Table 35. C-05-69: Dosing diary percent of doses taken compared to expected (ITT population)

	Olopatadine 0.6% n=440*	Vehicle n=439*
Mean ± std. deviation	81.2 ± 13.1	81.3 ± 13.1
Median	85.3	85.1
25^{th}, 75^{th} percentile	82.4, 86.3	83.1, 86.1
min, max	3,99	3,99

*Use data for 11 subjects were missing.
[Source: Alcon Table 11.4.1.3-1]

Bottles were to be weighed at each visit as a measure of compliance. The difference between dispensed weight and returned weight was to be calculated as bottle weight used. Alcon's analysis of bottle weight data, using observed data only, is shown in Table 36. This shows that there was notable variability in the determination of bottle weights (including some notable outlier values). However, the overall data suggest that treatments were approximately evenly taken by the two treatment groups.

Table 36. C-05-69: Analysis of bottle weight used (grams at each visit)

Visit	Treatment	N	Mean ± std. deviation	Median	25th, 75th percentile	min, max
Day 30	olo 0.6%	415	18.0 ± 5.9	19.10	14.0, 22.5	1.3, 36.0
	vehicle	422	19.0 ± 5.9	19.9	15.2, 22.6	2.1, 47.4
Day 60	olo 0.6%	409	18.0 ± 6.2	19.0	13.6, 22.2	0.5, 41.5
	vehicle	406	18.7 ± 5.8	19.3	14.7, 22.8	0.9, 37.5
Day 90	olo 0.6%	395	17.9 ± 6.0	18.3	13.7, 22.4	-6.0, 30.0
	vehicle	390	19.1 ± 6.6	20.1	15.5, 22.7	-0.3, 86.8
Day 120	olo 0.6%	378	18.2 ± 5.9	18.9	14.1, 22.8	0, 36.5
	vehicle	386	18.9 ± 5.8	20.1	15.1, 23.2	2.1, 33.1
Day 150	olo 0.6%	369	17.9 ± 5.7	18.4	14.3, 22.4	-0.2, 30.3
	vehicle	371	18.3 ± 5.8	19.1	14.9, 22.1	-13.7, 47.9
Day 180	olo 0.6%	354	20.1 ± 6.3	21.5	16.5, 24.9	-0.3, 32.9
	vehicle	363	19.9 ± 6.0	21.1	16.5, 24.5	-0.03, 30.3

[Source: Data from Alcon table 14.2.3.-2]

The pharmacology substudy was reviewed by FDA pharmacology reviewers (see separate review). This section is a summary of their review, which appears in a separate document.

Of the 890 subjects enrolled, blood samples were collected from 159 in the olopatadine treatment group and 160 from the vehicle control group. Blood samples were collected at months 1 and 5 during treatment and assessed for olopatadine concentrations using a validated method with a limit of quantitation of 0.05 ng/ml. Approximately 90% of the olopatadine subset had quantifiable olopatadine plasma concentrations.

The conclusion of the pharmacology review is that the olopatadine drug concentration data suggested a high degree of patient compliance among the tested subjects, and because of the randomized nature of treatment in the entire trial, among the entire trial population as well.

10.1.2.2.7 Effect on symptoms as assessed by questionnaire

This review will focus on the analysis of the ITT population to minimize potential biases introduced by the selection of other populations. All subjects who were randomized had an on-treatment visit, and are in the ITT population.

Scores on the subject-assessed questionnaire could range from 1-4, so potentially a difference in the groups of 3 points could occur. Treatment with olopatadine resulted in a difference from vehicle control of 0.2 points (Table 37). Questionnaire data for 29 subjects were missing. This small amount of data would not be expected to change the overall result notably.

Table 37. C-05-69: Primary analysis: Symptom questionnaire at 30 days*; ITT population, LOCF)

Statistic	**Olopatadine 0.6% n=431***	**Vehicle n=430****
Mean ± std. deviation	2.5 ± 0.9	2.7 ± 0.9
Median	2.0	3.0
25th, 75th percentile	2.0, 3.0	2.0, 3.0
min, max	1,4	1,4
p-value on means	0.001	

*Scores ranged from 1 (complete relief) to 4 (no relief)
**Questionnaire data for 29 subjects were missing.
[Source: Alcon Table 11.4.1.1-1]

The FDA statistician verified the results of Alcon's analysis. This difference, measured at 30 days, is the same treatment effect seen in Alcon's previously-submitted safety trial, in which the result was measured at 12 months.

Exploratory analyses of the primary outcome variable

Alcon's submitted an analysis of the per-protocol population (not shown in this review) which was consistent with the analysis of the ITT population.

Alcon explored the distribution of scores in the ITT population (Table 38). While the percents of subjects with complete relief were smaller than those with moderate and mild relief, the intertreatment group difference was greater in favor of olopatadine in the complete relief category, supporting the primary endpoint.

Table 38. C-05-69: Primary outcome analysis (LOCF)

Score on symptom questionnaire	Olopatadine 0.6% n=431*	Vehicle n=430*
Complete (=1)	67 (16%)	45 (11%)
Moderate (=2)	164 (38%)	153 (36%)
Mild (=3)	137 (32%)	134 (31%)
No relief (=4)	63 (15%)	98 (23%)
p-value (CMH rank scores test)	0.002	

*Questionnaire data for 29 subjects were missing.
[Source: Alcon Table 11.4.1.1.1.-2]

Alcon analyzed the percent of patients with complete relief, complete or moderate relief, and some relief. These do not contribute additional information to the analysis of the distribution of scores, and are not reported here.

Subset analyses of the primary outcome variable

The trend of primary outcome results was maintained for each sex. For males (n=304), mean scores for treatment with olopatadine and vehicle were 2.5 and 2.8, respectively, and for females (n=557), 2.4 and 2.6, respectively. Median scores for males and females were 2.0 and 3.0 for treatment with olopatadine and vehicle, respectively.

Mean and median scores in the 18-64 year age subgroup (n=743) were the same as the overall trial population. In the geriatric subgroup (n=20) mean and median scores on the symptom questionnaire were consistent with the pattern in the 18-64 year-old subgroup (olopatadine mean 2.3, vehicle mean 3.0; medians 2.0 and 3.0, respectively); however, mean scores on the questionnaire in the adolescent subjects (n=98) trended in the opposite direction (olopatadine 2.5, vehicle, 2.4) while the median scores were equal in the adolescent subjects (2.0). These results must be interpreted with caution, as the numbers of subjects in the adolescent and geriatric age groups is small.

Mean and median scores among Caucasians (n= 701) were the same as the overall trial population. Scores among "blacks" (n= 80) trended in the opposite direction to those of the Caucasians (olopatadine mean 2.5, vehicle mean 2.3; medians 3.0 and 2.0, respectively) while those among Hispanics (overall n= 62) were more consistent with Caucasians (olopatadine mean 2.4, vehicle mean 2.7; median 3.0 for both treatment groups). These results, as well as the results (not summarized in this review) among Asians (n=10) and "others" (n=8) must be interpreted with caution, as the numbers of subjects in the nonCaucasians groups is small.

Secondary outcomes

- *Response to patient questionnaire over 6 months of the trial.* These scores were nearly the same as those in the primary analysis.

- Rescue medication use (Table 39). For the purposes of the interim analysis, the analysis of rescue medication use was to be the average use from visits 2 through 7. The discrepancy between the mean use and median use indicates that a minority of subjects with greater use "drove" the mean use data. These results do not substantially alter the assessment of efficacy as established for patients with seasonal allergic rhinitis.

Table 39. C-05-69: Days of rescue medication use to day 30 (LOCF)

	Olopatadine 0.6% n=440*	Vehicle n=439*
Mean ± std. deviation	6.5 ± 14.6	5.7 ± 12.1
Median	0	1.0
25th, 75th percentile	0.0, 6.0	0.0, 6.0
min, max	0, 138	0, 155
p-value (2-sample t-test on means)	0.33	

*Use data for 11 subjects were missing.
[Source: Alcon Table 11.4.1.2-2]

10.1.2.2.8 Safety

Adverse events were coded using the COSTART system. Adverse events were recorded when there were changes in health, changes in concomitant medications due to a new medical diagnosis or worsening illness, for nasal or physical examination findings, or a cardiovascular parameter. Adverse events were collected as solicited comments and as observations by the trial investigator.

Exposure

Exposure was similar between the treatment groups, and adequate to allow for an assessment of safety (Table 40).

Table 40. C-05-69: Exposure (Safety population)

	1-30 days	31-60 days	61-120 days	121-179 days	≥180 days	Mean ±sdev	Median (min, max)
Olopatadine 0.6% n=445	26 (5.8%)	8 (1.8%)	34 (7.6%)	41 (9.2%)	336 (75.5%)	161 ± 48	182 (1,200)
Vehicle n=445	25 (5.6%)	12 (2.7%)	26 (5.8%)	30 (6.7%)	352 (79.1%)	162 ± 48	182 (1,191)

[Source: Alcon Tables 12.1.-2 and 12.1.-3]

Adverse events

Deaths

There were no deaths.

Serious adverse events

Twelve subjects in the olopatadine treatment arm and 7 subjects in the vehicle arm had serious adverse events (Table 41). Two subjects in the olopatadine treatment group were hospitalized for depression:

1) A 40 year-old woman with a history of depression, seasonal allergic rhinitis, tension headaches, and hypokalemia on no medications was hospitalized for depression [redacted] after randomization to the olopatadine treatment group. Daily medication for depression was later added. The patient discontinued from the trial 9 days after discharge from the hospital.

2) A 17 year-old woman with asthma, intermittent herpes simplex, overactive bladder, and history of allergy to sulfa had a nonserious adverse event of depression assessed as

"moderate" in severity 4 days after randomization to olopatadine. She was hospitalized and treated for major depression on [redacted] Daily medication for depression was added. The subject continued in the trial.

Surgical/medical procedure occurred in two subjects in the olopatadine treatment group (knee replacement and cholecystectomy) but not in the vehicle group. A serious abdominal adverse event (appendicitis and intestinal obstruction) occurred in one subject each in the olopatadine treatment group and one subject in the vehicle control group. Other events were various in nature.

Table 41. C-05-69: Serious adverse events

Treatment	Sex/Age	Coded AE	Onset day	Intensity	Duration	Outcome*	D/c due to AE
Olopatadine 0.6%	F/49	Uterine Fibroid Enlarge	110	Moderate	2d	Resolved w/Tx	N
	F/72	Carcinoma Lung	5	Severe	N/A	Continuing w/Tx	Y
	F/40	Depression	11	Moderate	4d	Resolved w/Tx	N
	F/17	Depression	20	Severe	3d	Resolved w/Tx	N
	M/42	Appendicitis	138	Severe	11h	Resolved w/Tx	N
	F/38	Obstruction Intestinal	103	Severe	4h	Resolved w/Tx	N
	F/40	Embolism	78	Severe	N/A	Continuing w/Tx	N
			86	Severe	N/A	Continuing w/Tx	N
			98	Severe	N/A	Continuing w/Tx	Y
	M/14	Injury Accidental	101	Severe	1d	Resolved w/Tx	N
	F/65	Surgical/Medical Proc [knee replacement]	82	Severe	4d	Resolved w/Tx	N
	M/59	Surgical/Medical Proc [cholecystectomy]	137	Moderate	6d	Resolved w/Tx	N
Vehicle	F/32	Uterine Disorder	153	Severe	57d	Resolved w/Tx	N
	F/43	Uterine Fibroid Enlarged	41	Moderate	34	Resolved w/Tx	N
	F/38	Pneumothorax	64**	Severe	6d	Resolved w/Tx	N
	M/47	Appendicitis	178	Severe	2d	Resolved w/Tx	N
	F/44	GI Disorder	113**	Severe	4d	Resolved w/Tx	N
	M/64	Headache	167	Severe	1d	Resolved w/Tx	N
	F/52	Injury Accidental	57**	Severe	12d	Resolved w/Tx	N

*Tx = Treatment; **Occurred intermittently
[Source: Alcon Table 12.3.1.2.-1]

Three subjects experienced serious adverse events subsequent to the data cutoff date for the submission. In the olopatadine treatment group two subjects experienced serious adverse events: 1) a subject had a bicycle accident and experienced multiple trauma, and 2) a subject experience dehydration. In the vehicle treatment group a subject experienced fecal impaction after surgery. These events do not contribute to a pattern of toxicity.

Reviewer comment: Two subjects in the trial, both in the olopatadine treatment group, experienced depression requiring hospitalization. One subject had a history of depression and the other did not. The incidence of depression overall was similar between the two treatment groups at 6 months (olopatadine group 4 subjects; vehicle control, 5 subjects) and it is possible that these serious events represent chance occurrences. Depression should be monitored postmarketing in patients exposed to olopatadine.

Discontinuations due to an adverse event

Table 42 is a summary of the adverse events resulting in discontinuation. Two subjects discontinued due to the occurrence of nasal ulceration, both in the olopatadine treatment group. The events were classified as mild and moderate in severity. Otherwise, discontinuations do not show a pattern of concern.

Table 42. C-05-69: Adverse events resulting in discontinuation

	Olopatadine 0.6% N =445	Vehicle N =445
Patients withdrawing because of adverse events	22 (4.9%)	16 (3.6%)
All adverse events resulting in withdrawal	30	20
Adverse event		
Rhinitis	3	1
Sinusitis	4	4
Epistaxis	3	1
Taste perversion	2	0
Ulcer nasal	2	0
Allergy	1	1
Carcinoma lung	1	0
Dermatitis	1	0
Dyspepsia	1	0
Embolism	1	0
Erythema multiforme	1	0
Headache	1	2
Laryngismus	1	0
Myalgia	1	0
Pain	1	0
Pneumonia	1	0
Pruritus	1	0
Multiple sclerosis	1	0
Surgical/medical procedure	1	0
Weight increase	1	0
Anxiety	0	1
Asthma	0	2
Discomfort nasal	0	2
Dizziness	0	2
Insomnia	0	1
Nasal septum disorder (deviated septum)	0	1
Nausea	0	1
Palpitations	0	1

[source: AE01.jmp]

Adverse events

Nasal ulceration and taste perversion (commonly described as a bitter taste) were adverse events that occurred notably more frequently among the active treatment group than the vehicle control group (Table 43). Rhinitis occurred frequently, and at a similar incidence and distribution of severity in both treatment groups. Nasal ulceration was coded as a result of the nasal examination, discussed in a subsequent section. The majority of the infections were upper respiratory tract illnesses; other infections were of various kinds.

Table 43. C-05-69: Subjects with events at 2% or greater and at an incidence greater than vehicle

COSTART term	Olopatadine 0.6% n=445	Vehicle n=445
Nasal		
Rhinitis	104 (23.4)	103 (23.1)
Ulcer nasal	39 (8.8)	26 (5.8)
Pharyngitis	35 (7.9)	30 (6.7)
Body as a whole		
Infection	67 (15.1)	65 (14.6)
Digestive system		
Diarrhea	11 (2.5)	6 (1.3)
Dyspepsia	9 (2)	6 (1.3)
GI disorder	9 (2)	7 (1.6)
Cough increased	16 (3.6)	14 (3.1)
Bronchitis	15 (3.4)	10 (2.2)
Special senses		
Taste perversion	29 (6.5)	3 (0.7)
Conjunctivitis	10 (2.2)	4 (0.9)
Urogenital system		
Urinary tract infection	9 (2)	6 (1.3)

[Source: Alcon Table 12.2.3.2.-2]

Nasal ulceration was graded as "mild" in 91% (42/46) events in the olopatadine group and 85% of the vehicle group events (28/30); the other events were graded "moderate." Nasal ulceration was an event that came from the objective evaluation (see discussion of the nasal examination below).

Among all adverse events, the following were also notable:

- Epistaxis occurred frequently, and at a higher rate in the vehicle control group (olopatadine, 86 subjects (19.3%); vehicle control, 104 subjects (23.4%)). In the previous 12-month safety trial C-01-92, the rates of epistaxis in the olopatadine and vehicle control groups were 19% and 12%, respectively. The reason for the increase in epistaxis in the vehicle group in the current trial is not clear. Most of the events of epistaxis in either treatment group in the current trial were of mild severity (122/129 events in the olopatadine group and 147/152 events in the vehicle control group); the others were of moderate severity.
- One subject in the olopatadine treatment group experienced a liver function abnormality (mild severity). Examination of adverse events showed no other liver adverse events.
- One subject in the olopatadine treatment group experienced somnolence as an adverse event. This event was not reported in the vehicle control group.

Adverse events generally did not show a concerning pattern with respect to sex. Comparison of adverse events by age is complicated by the small numbers of subjects 12-17, at least 65 year old compared to those 18-64 years old. Similarly, comparisons among the racial groups is complicated by the small numbers of subjects who were not Caucasians. There was no notable pattern of events occurring at the extremes of age, nor were patterns of events notably different among the racial subgroups.

One subject on olopatadine experienced an event called "anaphylaxis." The subject developed throat tightness after exposure to horseradish smell. The subject had a history of allergy to horseradish. The event was judged to be of moderate intensity, resolved with treatment with albuterol, and olopatadine administration was not interrupted.

Nasal examination

The nasal examination was conducted at each clinic visit. If an "anatomic abnormality," "blood in the nose," or "possible ulceration" were found on an initial examination (Section A), a second, more detailed examination (Section B) was performed. Findings in Section B were recorded in the case report form under Section A headings.

Table 44 shows results in Section A expressed as the number of subjects with the events listed during the 6 months of the trial. Bleeding and "possible ulceration" occurred in a moderate number of subjects.

Table 44. C-05-69: Section A nasal examination: Numbers of subjects with nasal examination findings on at least one occasion (n, % of subjects)

	Olopatadine 0.6% n=438	**Vehicle n=438**
Evidence of Infection*	18 (4.1)	12 (2.7)
Anatomic abnormalities**	5 (1.1)	0
Possible ulcerations	67 (15)	61 (13.9)
Bleeding	67 (15)	87 (20)

*Section B was not required to be done for this finding, but an adverse event form was filled out for it
**Swelling of the turbinates due to allergic rhinitis (n=2) and nasal polyps (n=3). See also Section B findings
[Source: Alcon Table 12.5.1.-3]

Table 45 shows Section B findings among the subjects with anatomic abnormalities, possible ulcerations, or bleeding on section A examination (note that the table shows percents of treatment groups who had a Section B evaluation, not percents of the overall treatment group). Epithelial erosions of Grades 1 and 2 occurred more frequently in active-treated subjects. There was no erosion of grade 3 nor were there any nasal septal perforations.

Table 45. C-05-69: Section B nasal examination: Numbers of subjects with nasal examination findings on at least one occasion (n, % of subjects with a Section B evaluation)

	Olopatadine 0.6% n=103	Vehicle n=110
Redness/irritation	70 (68)	57 (52)
Nasal bleeding	59 (57)	77 (70)
Epithelial erosion		
Grade 1	37 (36)	27 (25)
Grade 2	4[1] (4)	1[2] (1)
Grade 3	0	0
Nasal perforation	0	0
Intranasal mass[3]	4 (4)	1 (1)

[1] Severity: 3 mild, one moderate
[2] Severity: mild
[3] Described as polypoid changes (n=1, active group) or polyps
[Source: Alcon Tables 12.5.1.-4, 12.5.1.-5, 12.5.1.-7]

Alcon presented by-visit information regarding the nasal examinations among those subjects with Grade 2 erosions. Two subjects in the olopatadine treatment group had a Grade 2 erosion at two consecutive visits; in one of these subjects nasal examination at subsequent visits revealed Grade 1 erosion and in the other, subsequent evaluation showed no reportable finding on Section B examination. Two other subjects on olopatadine had a Grade 2 epithelial erosion that was followed by no reportable finding at the next visit. Upon request, Alcon submitted a

tabulation of selected olopatadine diary use information for subjects who had epithelial erosions. Subjects did not tend to discontinue medication upon the occurrence of these events.

Contribution of nasal examination to adverse event terms

The nasal examination was one source of adverse events. In response to a request from FDA, Alcon summarized the adverse events that resulted from the nasal examination Sections A and B (Table 46). The adverse event term nasal ulceration derived solely from the nasal examination; for the other events, the nasal examination was one component, but not the sole source, of recorded adverse events.

Table 46. C-05-69: Adverse event terms from the nasal examination

Adverse Event (Nasal exam finding)	Olopatadine 0.6% N = 445	Vehicle N = 445
Sinusitis (Evidence of Infection)	18 (4.1%)	12 (2.7%)
Neoplasm[1] (Significant Anatomic Abnormality)	4 (0.9%)	1 (0.2%)
Rhinitis (Possible Ulceration of the Mucosa)	65 (14.6%)	57 (12.8%)
Nasal ulceration (Possible Ulceration of the Mucosa)	39 (8.8%)	26 (5.8%)
Nasal septum perforation	0	0
Epistaxis (Blood in the Nose)	67 (15.1%)	88 (19.8%)

[1]Described as intranasal mass (n=1, active group) or polyps
[Source: Alcon January 10, 2008 response to FDA request]

Alcon performed a by-subject analysis (not shown here) of the occurrence over time of nasal irritation, epistaxis, and nasal ulceration. As epistaxis occurred in more subjects than did nasal ulceration, it is not surprising that the occurrence of epistaxis did not predict the subsequent occurrence of nasal ulceration. In addition, nasal ulceration occurred without the prior occurrence of epistaxis in some subjects.

Events that can occur with antihistamine and anticholinergic drugs

Table 47 shows the incidence of adverse events that are associated with antihistamine and anticholinergic drugs. They occurred infrequently in either treatment group.

Table 47. C-05-69: Incidence of adverse events associated with antihistamine and anticholinergic drugs

COSTART term	Olopatadine 0.6% n=445	Vehicle n=445
Dyspepsia	9 (2)	6 (1.3)
Nausea	5 (1.1)	9 (2)
Fatigue	4 (0.9)	4 (0.9)
Somnolence	1 (0.2)	0
Constipation	2 (0.4)	4 (0.9)
Dry mouth	4 (0.9)	3 (0.7)
Weight increase	5 (1.1)	0
Urinary retention	0	0

[Source: Alcon Table 14.3.1.3.1.-1]

Vital signs

Pulse and blood pressure were recorded at monthly visits after the subject had been seated quietly for 5 minutes. Three subjects in the active group and 1 in the vehicle control group experienced tachycardia as an adverse event, all of which were "mild" in severity and resolved without treatment. Review of group statistics by treatment visit, including shifts from baseline, did not show a notable pattern for either treatment group.

Thirteen subjects in the olopatadine treatment group and 15 in the vehicle control group experienced what was considered a clinically relevant increase in blood pressure. Most of the events were of mild severity and the overall severity was balanced between treatment groups. Review of the data tabulation did not reveal a notable difference in clinical features of the events. Group statistics showed slight decreases in systolic and diastolic blood pressure from baseline to the 6 month time point (for example, mean decreases in systolic blood pressure in the olopatadine and vehicle control groups of approximately 3 and 2 mm Hg, respectively, and mean decreases in diastolic blood pressure of 1.7 mm Hg, vehicle, 2.1 mm Hg, respectively) that were not clinically different between the treatment groups.

Concomitant medications

Review of changes in medications occurring during the trial did not reveal concerns in addition to those manifested by review of adverse events.

10.1.2.3 Summary of C-05-69

Clinical trial C-05-69 was adequately conducted for a reasonable interpretation of its results. In this randomized, double-blind trial of subjects with perennial allergic rhinitis the symptom questionnaire results, collected at 30 days of treatment, were substantially the same as the 12-month results from the previously submitted trial of the previous, povidone-containing formulation. This result, in combination with drug levels obtained in a subset of subjects, is sufficient evidence for exposure to allow an interpretation of safety. No death occurred, and serious adverse events did not occur in a concerning pattern. Discontinuations for adverse events were infrequent. There were no reports of nasal septal perforations. Nasal septal ulceration, which occurred in 8.8% of olopatadine and 5.8% of vehicle control subjects, was mostly of mild severity. Epistaxis occurred frequently in both groups (19.3% in the olopatadine group and

23.4% in the vehicle control group). The pattern of adverse events and results of the nasal examination conducted monthly over the course of the 6 months do not raise toxicity concerns that would be a barrier to approval.

10.1.3 Additional Reports of Clinical Trials (Povidone-containing Formulation)

Alcon submits reports of three clinical trials (see Table 2) of olopatadine 0.6% nasal spray containing povidone. This review will describe the notable features of the designs and findings of the trials briefly.

C-04-70

Alcon's "Safety and Efficacy Study of Olopatadine Hydrochloride Nasal Spray 665 mcg versus Olopatadine Hydrochloride Nasal Spray Vehicle versus Astelin in Treatment of Seasonal Allergic Rhinitis" was a multicenter trial of randomized, double-blind treatment for 16 days of subjects at least 12 years of age with seasonal allergic rhinitis. The design of the trial was similar to that of the pivotal efficacy trials C-02-10 and C-02-37 submitted in the original NDA. The objective of the trial was to assess efficacy and safety. It was conducted between May 11, 2005 and October 19, 2005.

Alcon attests that the trial was conducted according to Good Clinical Practice, and that no investigator reported a conflict of financial interest.

Procedures

Table 48 shows the procedures in the trial, which were similar to those in the prior seasonal allergic rhinitis efficacy trials.

Screening (Visit 1) procedures included assessment for eligibility, a medical and medication history, a physical and nasal examination, a skin prick test was followed by treatment with olopatadine vehicle during a 4-14-day run-in period. Eligibility for randomization at visit 2 included the presence of symptoms (with a total nasal symptom score of at least 36 from any 3 of the 4 calendar days immediately preceding visit 2) and an acceptable nasal examination. Trial personnel called the subject at 7 days after randomization to assess adherence to treatment and diary completion, medication changes, and adverse events. The final clinic visit was 16 days after randomization; notable procedures at this visit included assessment of adverse events, diary symptom information, and a nasal examination.

Blood tests (hematology and serum chemistry) were not required.

Table 48. C-04-70: Procedures

	Visit 1 Screening	Visit 2 Randomization	Visit 3 Telephone call	Visit 4 or Early Exit
	4-14 days		Day 7±1	Day 16 (+7)
Consent form	X			
Inclusion/Exclusion	X	X		
Pregnancy test (urine) if applicable	X	X		X
Medical and medication history	X			
Allergic Rhinitis Symptoms history	X			X
Skin prick or intradermal test if not done in last 5 yrs.	X			
Physical examination	X			X
Nasal examination	X	X		X
12-lead ECG	X			
Blood pressure and pulse	X	X		X
Review changes in medical history and concomitant medications		X	X	X
Adverse events	X	X	X	X
Weigh and dispense/Collect Study medication	X	X		X
Administer dose at study site	X	X		
Dispense diary/medical problems log with tions	X	X		
and Allergy Visual Analog Scale		X		X
ent Satisfaction Questionnaire for Medications				X
Determine TNSS based on Daily Compliance Report		X		
Review Medical Problems Log		X	X	X
Review Status Summary report for subject compliance			X	X
Complete Screening Exit/Randomization form		X		
Complete Exit form				X

[Source: Alcon Table 9.1.-1]

Subjects

Subjects were to have seasonal allergic rhinitis and be without concurrent medical conditions that might interfere with evaluation of the medication. Notable medical eligibility criteria were:

Inclusion

- 2-year history of nonrecalcitrant spring or fall allergic rhinitis
- Allergy to a current prevalent seasonal allergen of the area (positive case history and positive skin prick or intradermal test or both)
- Washout of prohibited medications
- Sum of AM and PM reflective total nasal symptom scores of at least 36 for 3 complete calendar days out of the 4 prior to randomization
- Absence of significant anatomic abnormalities, infection, bleeding, and mucosal ulcerations on nasal examination prior to administration of test article at visits 1 and 2

Exclusion

- Concurrent disease such as rhinitis medicamentosa or large obstructive nasal polyps,
- Any other nasal anatomic deformity on nasal examination at visit 1 or 2 that would interfere with participation, or history or evidence of nasolacrimal drainage system dysfunction
- Systemic or ocular disorder (other than allergic conjunctivitis) that would interfere with evaluation of study medication

- History of severe, unstable, or uncontrolled cardiovascular, hepatic, renal, or other disease or illness that would interfere with the study
- Current chronic sinusitis or acute sinusitis within 30 days of visit 1
- Respiratory tract infection within 14 days of visit 1
- Asthma, except mild intermittent asthma
- Congestion that would interfere with administration of nasal drugs
- Use of prohibited medications
- Non-responsive to antihistamines for seasonal allergic rhinitis
- Chronic or intermittent use of oral, intramuscular, intravenous, or dermal potent or super-potent topical corticosteroids
- Chronic use of long-acting antihistamines (for reasons other than allergic rhinitis) or medications that would affect assessment of effectiveness
- History of or ongoing clinically relevant electrolyte abnormalities
- Use of anti-allergy immunotherapy within the past 2 years
- Hypersensitivity to study drug or any component
- Clinically relevant ECG abnormalities at visit 1, and QTcB values or >450 msec for males and 470 msec for females
- Current or use within 14 days of any drugs that may prolong the QT interval
- Planned travel outside the study area for more than 48 hours during the study period.
- Clinically relevant abnormal vital signs at visit 1 or visit 2 (normal ranges in protocol: systolic blood pressure 95-160 mm Hg, diastolic blood pressure 55-90 mm Hg, and pulse 50-100 bpm).
- Bottle weight at visit 2 outside the acceptable range

Prohibited medications and washout periods

Table 49 shows prohibited medications and their washout periods. They are similar to those in the pivotal efficacy trials.

Table 49. C-04-70: Prohibited medications

Drug	Washout prior to visit 1
Anti-allergy immunotherapy in the previous two years	Last 2 years
Systemic corticosteroids (oral, parenteral, intravenous, rectal)	30 days
Inhaled or ocular corticosteroids	30 days
Nasal corticosteriods	14 days
Nasal or inhaled ipratroprium bromide (or atropine) nedocromil or sodium cromolyn	14 days
Leukotriene pathway modifiers and systemic and topical anticholinergics	14 days
Systemic antibiotics (except those used to treat acne)	14 days
Systemic antifungal agents	14 days
Loratadine, desloratidine, and levocabastine	14 days
Chlorpheniramine, clemastine fumarate, brompheniramine maleate, hydroxyzine, hydroxyzine pamoate, azatadine maleate, azelastine 0.1 % nasal spray, cetirizine HCL, fexofenadine HCL	7 days
Ocular anti-allergy medications including lodoxamide, olopatadine	7 days
Topical nasal decongestants	7 days
Diphenhydramine, promethazine HCl, cyproheptadine HCl, triprolidine HCl, acrivastine	3 days
Oral decongestants, such as pseudoephedrine, all over-the-counter cold/cough and sleep aids without a component listed above	3 days
NSAIDS (as-needed use)	3 days
Aspirin (except low dose for cardiac prophylaxis)	3 days
Nasal and/or ocular saline	1 day
Antiarrhythmic agents	
Class IA: Disopyramide, procainamide HCl, Quinidine Sulfate	14 days
Class IC: Flecainide, Propafenone	14 days
Class III: Amiodarone, Bretylium, Dofetilide, Ibutilide Fumerate, N-acetylprocainamide, Sotalol HCl	14 days
Herbals	
St. Johns Wort, Ma Huang, Ginkgo Biloba and/or any herbal with the potential to relieve allergy symptoms	7 days

[Source: Alcon Table 9.3.1.-1]

Treatment

Treatment consisted of 2 sprays in each nostril twice daily of olopatadine HCl Nasal Spray 0.6% (formulation containing povidone [redacted]), olopatadine vehicle placebo (formulation containing povidone [redacted]), or azelastine HCl nasal spray 0.1%.

Analysis

The primary efficacy test was the percent change from baseline in the Total Nasal Symptom Score, defined as the average of the morning and evening reflective severity scores.

Protocol modifications

Alcon made a protocol modification on September 1, 2005, after 71 subjects had entered into the screening phase of the trial. The amendment changed the wording of the eligibility criteria to include subjects with fall as well as spring allergic rhinitis, to expand the change in bottle weight ranges, to remove a reference to blue dust covers in the section on dosing compliance, and the change contact information. These changes would not have been expected to change the results of the trial, nor reflect on the overall conduct of the trial.

Results

The results of the azelastine treatment group are not relevant to the assessment of safety of olopatadine 0.6% nasal spray from this trial, and are not reported here.

Enrollment and trial subjects

Twenty-one sites enrolled 728 subjects, despite an original goal of 480 subjects. However, of the 728, 184 were judged screening failures and were not randomized, 120 of whom

were for insufficient symptoms on the diary. Of the 544 subjects analyzed for safety, 180 were in the olopatadine treatment group and 176 in the vehicle control group.

Demographics of the olopatadine and vehicle control groups were reasonably balanced and reflected a primarily Caucasian population with a majority of women, and a mean age in around 36 years old. These demographics are not notably different from those in the pivotal efficacy trials C-02-10 and C-02-37.

Table 50. C-04-70: Demographics (ITT population*)

	Olopatadin % (povidone) n=180	Vehicle n=176
Age		
Mean (yrs)	35.7	36.6
Std dev. (yrs)	12.8	13.1
Min, max (yrs)	12, 70	12, 77
Ranges (yr) (n, %)		
12 - 64 years	177 (98.3)	174 (98.9)
≥65	3 (1.7)	2 (1.1)
Sex (n,%)		
Male	52 (28.9)	61 34.7)
Female	128 (71.1)	115 (65.3)
Race (n,%)		
Caucasian	136 (75.6)	133 (75.6)
Black	19 (10.6)	18 (10.2)
Asian	2 (1.1)	2 (1.1)
Hispanic	22 (12.2)	23 (13.1)
Other	1 (0.6)	0

*Subjects who entered the treatment period
[Source: Alcon Tables 11.2.1.-1 and 11.2.1.-2]

Discontinuations and protocol deviations

Table 51 shows discontinuations for subjects from the olopatadine and vehicle control treatment groups. It shows that discontinuations from these groups were infrequent and reasonably balanced.

Table 51. C-04-70: Discontinuations

Reason for discontinuation	Olopatadine 0.6% (povidone) n=180	Vehicle n=176
Adverse event	5	5
Decision unrelated to adverse event	1	1
Treatment failure	1	-
Protocol violation	5	4
Other	-	3
Total	12	13

*Subjects who entered the treatment period
[Source: Alcon Tables 11.2.1.-1 and 11.2.1.-2]

Table 52 shows that violations of eligibility were infrequent. The number of these protocol violations in the azelastine treatment arm was similar. Review of listings of other violations indicates that their nature and number would not be expected to affect the ability of the trial to assess safety or efficacy or reflect on the integrity of the trial notably.

Table 52. C-04-70: Major protocol violations

Protocol deviation	Olopatadine 0.6% (povidone) n=180	Vehicle n=176
Inclusion criterion	3	2
Visit out of window	1	1
Exclusion criterion	9	11
Breaking of blind*	0	1
Total	13 (7.2%)	15 (8.5%)

[Source: Alcon Table 10.2.-1]
Note: Alcon Table 16.2.2.-1 notes that 1 other subject in the vehicle group had the blind broken

Trial treatment

The trial tested the same formulation of vehicle and active olopatadine nasal spray that were used in the pivotal seasonal allergic rhinitis efficacy trials C-02-10 and C-02-37.

Efficacy

FDA has not reviewed the efficacy analysis in trial C-04-70. The study is not considered to be a pivotal efficacy study in this drug development program. Results reported are consistent with Alcon's conclusion that olopatadine-treated subjects had more improvement in the reflective total nasal symptom score than vehicle-treated subjects. Based on Alcon's reported results, the difference between olopatadine and vehicle control in the percent change from baseline in reflective total nasal symptom scores in trial C-04-70 was -8.4, and the difference in the mean change in reflective TNSS scores was -0.8 points. In the previously-submitted trials C-02-37 and C-02-10, the difference from placebo for the percent change from baseline was -12.2 and -11.4, respectively, and the difference from placebo in the mean change in reflective TNSS was -1.0 and -1.1, respectively. A treatment effect supports the use of the safety information from the trial.

Safety

Exposure to study treatment was a little over 2 weeks in both the olopatadine and vehicle control groups (Table 53). This exposure is comparable to the exposure in the pivotal seasonal allergic rhinitis trials (Table 19).

Table 53. C-04-70: Exposure (Treatment period population)

	1-6 days	7-16 days	>16 days	Mean (days)	Median (days)
Olopatadine 0.6% n=180	1 (0.6%)	86 (47.8%)	93 (51.7)	16.8	17
Vehicle n=176	3 (1.7%)	84 (47.7%)	89 (50.6)	16.5	17

[Source: Alcon Table 12.1.-4 and text]

No one died. No subject in the olopatadine or vehicle control group experienced a serious adverse event or a nasal ulcer.

Table 54 shows the adverse events resulting in discontinuation from the trial. The events did not form a concerning pattern. More than one event may have been listed as a reason for discontinuation. Five subjects discontinued for adverse events from each group shown.

Table 54. C-04-70:Adverse events resulting in discontinuation (Subjects and % of group)

Adverse events (COSTART)	Olopatadine 0.6% Povidone n=180	Vehicle n=176
Headache	2 (1.1%)	0
Pharyngitis	2 (1.1%)	0
Taste perversion	2 (1.1%)	0
Cough increased	1 (0.6%)	0
Dyspepsia	1 (0.6%)	0
Gastroenteritis	1 (0.6%)	0
Nausea	1 (0.6%)	0
Pain	1 (0.6%)	0
Pruritus	1 (0.6%)	0
Rhinitis	1 (0.6%)	0
Sneezing	1 (0.6%)	0
Sinusitis	0	2 (1.1%)
Dermatitis contact	0	1 (0.6%)
Epistaxis	0	1 (0.6%)
Arthropod bite	0	1 (0.6%)

[Source: Alcon Response to February 25, 2008 FDA Request,Table C-2]

Table 55 shows adverse events that occurred in at least 3 subjects and at an incidence greater than vehicle. Taste perversion was the most common adverse event in the olopatadine treatment group. Somnolence was reported by one subject in each treatment group.

Table 55. C-04-70: Adverse events occurring in 3 or more subjects and at an incidence greater than vehicle

Adverse events (COSTART)	Olopatadine 0.6% Povidone n=180	Vehicle n=176
Nasal		
Rhinitis	6 (3.3)	3 (1.7)
Epistaxis	4 (2.2)	2 (1.1)
Pharyngitis	3 (1.7)	2 (1.1)
Body as a whole		
Headache	7 (3.9)	6 (3.4)
Infection	3 (1.7)	1 (0.6)
Fatigue	3 (1.7)	2 (1.1)
Special senses		
Taste perversion	22 (12.2)	3 (1.7)

[Source: Alcon Table 14.3.1.3.1.-1]

Review of all adverse events with respect to subgroups of sex, age category (12-17, 18-64, and at least 65), and race showed no remarkable patterns. However, the relatively small numbers of males and the small numbers of nonCaucasians and subjects at the extremes of age of the enrolled population make comparisons problematic.

Nasal examination

Nasal examination results were reported as clinically relevant increases from baseline in nasal parameters as assessed at the final visit. In neither group were anatomic abnormalities or mucosal ulcerations reported. Infection was noted in 2 subjects in both the olopatadine and vehicle treatment groups, and bleeding was noted in 1 subject in the olopatadine and 1 in the vehicle treatment group.

Vital signs

Based on shifts from baseline to the any visit, there were no notable differences between olopatadine- and vehicle-treated subjects in pulse or systolic or diastolic blood pressure. Hypertension as an adverse event was reported for two subjects in the olopatadine group and one in the vehicle group.

Summary of the results of trial C-04-70

C-04-70 was similarly designed to the pivotal efficacy trials in seasonal allergic rhinitis and the data are adequate for an assessment of safety. Efficacy was not reviewed by FDA. No deaths or other serious adverse events occurred in the olopatadine or vehicle control groups. Taste perversion was the most common adverse event, occurring notably more frequently in the olopatadine group. The safety results of this trial add to the existing data on two-week safety for the povidone-containing formulation of olopatadine.

C-04-45

Alcon's "A Double-Masked, Vehicle-Controlled, Multiple-Dose, Safety and Pharmacokinetic Study of Olopatadine Nasal Spray 0.6% and Olopatadine Nasal Spray 0.6% Plus Degradation Products of Olopatadine, Following Intranasal Administration in Healthy Subjects" was a single-center, randomized, double-blind, 5-parallel-arm trial in healthy subjects at least 20 years old whose objective was to determine plasma pharmacokinetics and safety of olopatadine and the degradation product [redacted]. Twelve subjects were enrolled into each of 5 treatment arms (see Table 2). In each arm the dose was two 100 µl sprays per nostril twice daily for 5 days, with a single administration on day 6. Randomized treatments were olopatadine vehicle, olopatadine 0.6%, olopatadine 0.6% with [redacted] olopatadine 0.6% with [redacted], or olopatadine 0.6% with [redacted] and [redacted] (concentrations of [redacted] are expressed as percents of the olopatadine concentration). The trial was conducted between March 21, 2005 and April 8, 2005. Alcon attests that the trial was conducted according to Good Clinical Practice.

Qualified subjects were to be domiciled for up to 8 days and were to be dosed every 12 hours. Safety evaluations were to include daily evaluation of blood pressure and pulse, a nasal examination, and a review of adverse events and concomitant medications. An ECG was to be done for screening and at discharge; clinical laboratory tests were to be done at screening, the day before the first dose, and at discharge.

Sixty subjects were enrolled, with an age range of 20-77 (mean ages of the groups were from 36 to 49 years of age). Males and females were randomized approximately equally (the largest disparity in the numbers of males and females randomized to a group was 2). Approximately 43% of the trial population was Caucasian and 48% Hispanic, without remarkable disparities among the groups. Five "Blacks" were enrolled, of whom 1 was enrolled in the vehicle group, and none in the olopatadine 0.6% group.

The analytical plan called for pharmacokinetic analysis only of the 12 subjects receiving olopatadine with the [redacted] degradants, with analysis of other groups to clarify the results if needed. The pharmacokinetic analysis of this study has not been evaluated at FDA. Alcon reports that Day 6 plasma determinations showed quantifiable concentrations of olopatadine (≥0.050 ng/ml).

All 60 subjects were evaluable for the safety analysis. All subjects received 6 days of dosing. No deaths or other serious adverse events were reported in any subject in the trial. Nasal septal disorder (characterized as septal erythema) was reported for 4/12 subjects in the

olopatadine 0.6%-only group, 3/12 in the olopatadine+ group, 2/12 in the olopatadine+ and vehicle groups, and in none of the subjects in the olopatadine+ group. One clinically relevant change from baseline occurred upon nasal examination and was reported as an adverse event. Nasal bleeding was observed in a subject in the olopatadine+ treatment group. Regarding cardiovascular events, one subject, in the olopatadine+ group, experienced "tachycardia" graded as "mild" as an adverse event. Nonnasal adverse events occurred sporadically, usually in no more than 1 subject per treatment group, and in no particularly informative pattern.

The safety results from this trial do not change the understanding of the safety of olopatadine 0.6% nasal spray.

Trial C-03-49

Alcon's "Randomized, Multicenter, Crossover Study to Evaluate Sensory Attributes of Olopatadine 0.6% Nasal Spray and Astelin® in Patients with Allergic Rhinitis" was a 6-center trial of randomized, double-blind single-dose treatment of 110 subjects at least 18 years of age with seasonal allergic rhinitis, followed after a washout period of 24 hours by crossover to the alternative treatment. Treatments were 2 sprays in each nostril of olopatadine HCl Nasal Spray 0.6% (formulation containing povidone) and Astelin (azelastine HCl) Nasal Spray 137 mcg. The objective of the trial was to assess "sensory attributes including taste and aftertaste." The trial was conducted between August 29, 2005 and November 17, 2005. Alcon attests that the trial was conducted according to Good Clinical Practice.

Screening procedures included assessment of eligibility, including a nasal examination. Eligibility for randomization at visit 2 included a history of seasonal allergic rhinitis, the presence of at least one nasal allergy symptom recorded on a Symptom Severity Rating Scale (runny, itchy, or stuffy nose or sneezing), the absence of disorders that would complicate the evaluations, and an acceptable nasal examination. Changes in concomitant medications and adverse events were collected at each treatment visit and at the end of the trial, 24 hours after the second treatment was administered. Vital signs were collected for eligibility and prior to the first dose, for screening purposes. The protocol did not include the collection of laboratory test determinations or ECGs.

Six sites enrolled 110 subjects, all of whom were evaluated for safety. Subjects were predominantly Caucasian (88%), female (67%), and below the age of 65 (95%).

All subjects were exposed to both drugs. No one died, there were no other serious adverse events, and no one discontinued due to an adverse event. The adverse event that occurred at the greatest frequency in the olopatadine treatment group was headache, which occurred in 3 subjects.

The results of this trial do not signal a new safety concern for the proposed, povidone-free formulation.

Reviewer comment

FDA does not condone a clinical study to qualify potentially toxic degradants. The trial was started shortly after submitting the protocol. When the Division of Pulmonary and Allergy Products called Alcon about the trial, Alcon informed DPAP that the last of the subjects were to complete in a few days.

10.2 Line-by-Line Labeling Review

REFERENCES

None

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

/s/

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3/6/2008 03:53:52 PM
MEDICAL OFFICER

Charles Lee
3/6/2008 03:57:53 PM
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I concur.