These records are from CDER's historical file of information previously disclosed under the Freedom of Information Act (FOIA) for this drug approval and are being posted as is. They have not been previously posted on Drugs@FDA because of the quality (e.g., readability) of some of the records. The documents were redacted before amendments to FOIA required that the volume of redacted information be identified and/or the FOIA exemption be cited. These are the best available copies.

2014
Astelin

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-114

NOV - 1 1996

Wallace Laboratories
Division of Carter-Wallace, Inc.
Half Acre Road
Box 1001
Cranbury, New Jersey 08512-0181

Attention: George R. Hemsworth, Ph.D.
Director, Regulatory Affairs

Dear Dr. Hemsworth:

Please refer to your March 26, 1991, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Astelin (azelastine hydrochloride) Nasal Spray.

We acknowledge receipt of your amendments dated June 25, October 25, and December 19, 1991, February 28, April 22, May 1, June 10, July 5, September 28, October 23, November 2 and 20, and December 18 and 21, 1992, January 7, February 19 and 24, May 7, August 6 and 18, and September 9, 1993, April 6, June 29, and October 28, 1994, June 30, July 7, August 31, September 22 and 29, 1995, and May 13 and 22, June 7, July 10 and 19, August 20, September 18, 27, and 30, and October 9 and 31, 1996.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for the treatment of the symptoms of seasonal allergic rhinitis, such as rhinorrhea, sneezing, and nasal pruritus, in adults and children 12 years and older, as recommended in the draft labeling submitted on October 31, 1996. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the October 31, 1996, draft physician labeling and the September 27, 1996, final printed carton and container labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 16 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this

submission should be designated "FPL for approved NDA 20-114." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you of your Phase 4 commitments specified in your submission dated October 9, 1996. These commitments, and their associated schedules for completion, are listed below.

1

2.

Protocols, data, and final reports related to the Phase 4 commitments should be submitted to this NDA as correspondence. For administrative purposes, all submissions, including supplements, relating to these Phase 4 commitments must be clearly labeled "Phase 4 Commitments." In addition, we request that each annual report to this NDA include a section that summarizes the status of each Phase 4 commitment, identifying each submission and its related commitment. If you feel the situation has changed and the data the Phase 4 study was designed to provide are no longer necessary, fully explain why you believe you should be released from the commitment. All annual reports to this NDA should include an update on Phase 4 studies until you are notified that we consider all commitments to be satisfactorily fulfilled or canceled.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Gretchen Strange
Project Manager
(301) 827-1058

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-114 Trade (generic) names Astelin (azelastine hydrochloride)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

X 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
X (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: the sponsor intends

Signature of Preparer

Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

MEMORANDUM

DATE: October 11, 1996

TO: NDA 20-114

FROM: John K. Jenkins, M.D. 10/11/96
Director, Division of Pulmonary Drug Products HFD-570

SUBJECT: Overview of NDA Review Issues

Please refer to the previous Overview of NDA Review Issues dated December 14, 1995. This memorandum will only cover issues that remained unresolved at that time.

Administrative
The sponsor received an approvable letter on December 29, 1995 which listed CMC and labeling deficiencies. The sponsor resubmitted the NDA on May 14, 1996 and the current regulatory (non-User Fee) due date is November 10, 1996.

Clinical
The NDA was considered approvable at the time of the December 29, 1996 AE letter from a clinical standpoint for the treatment of seasonal allergic rhinitis at a dose of 2 sprays per nostril BID with labeling revisions. The sponsor has not reported any additional clinical studies to the NDA since that action was taken. A safety update was recently submitted by the sponsor and is under review by Dr. Honig.

Assuming the review of the latest safety update does not uncover any significant new safety concerns, azelastine nasal spray is considered clinically approvable for the treatment of seasonal allergic rhinitis at a dose of 2 sprays per nostril BID with labeling as reflected in the draft labeling submitted by the sponsor on September 27, 1996.

Preclinical
No new preclinical data has been submitted to the NDA since the last action letter.

Azelastine nasal spray is considered approvable from a preclinical standpoint with labeling as reflected in the draft labeling submitted by the sponsor on September 27, 1996.

CMC
The sponsor has adequately addressed the CMC deficiencies listed in the last action letter. The sponsor has made CMC commitments which will be included in the action letter.

Azelastine nasal spray is considered approvable from a CMC standpoint with labeling as reflected in the draft package insert and draft carton and container labels submitted on September 27, 1996.

Biopharmaceutics

No new biopharmacuetics data has been submitted to the NDA since the last action letter. Azelastine nasal spray is considered approvable from a biopharmaceutics standpoint with labeling as reflected in the draft labeling submitted by the sponsor on September 27, 1996.

Data Verification

No new data verification issues have arisen since the last action letter was issued.

Labeling

The draft package insert and the draft carton and container labeling submitted by the sponsor on September 27, 1996 have been reviewed by the appropriate disciplines and adequately summarizes the information contained in the NDA on which the approval action is based.

Conclusion

There are no outstanding review issues from any discipline and the application should be APPROVED with labeling as reflected in the submission of September 27, 1996. The sponsor will be reminded in the approval letter of two CMC commitments which they have made to the Division.

cc:
NDA 20-114
HFD-570 Division Files
HFD-570/Jenkins
HFD-570/Strange
HFD-570/Himmel
HFD-570/Honig

MEMORANDUM

DATE: December 14, 1995

TO: NDA 20-114

FROM: John K. Jenkins, M.D.
Director, Division of Pulmonary Drug Products HFD-570

SUBJECT: Overview of NDA Review Issues

Administrative

NDA 20-114 for azelastine nasal spray was originally submitted by Wallace Laboratories on March 26, 1991. A NOT APPROVABLE letter was issued on February 18, 1992 and contained primarily CMC deficiencies. A second NOT APPROVABLE letter was issued on February 16, 1994 and contained clinical and CMC (by reference to a January 13, 1994 IR letter) deficiencies. The NDA was presented for discussion at a Pulmonary and Allergy Drugs Advisory Committee (PADAC) meeting on November 17, 1995. The current regulatory (non-User Fee) due date is December 30, 1995.

Clinical

The proposed indication for azelastine nasal spray in this NDA is allergic rhinitis. In support of this indication, the sponsor submitted three multicenter, randomized, double-blind, placebo and active-controlled, two to four week trials of azelastine nasal spray at doses of 2 sprays per nostril QD and 2 sprays per nostril BID in adults and children age 12 and older with seasonal allergic rhinitis. In addition the sponsor submitted two, randomized, double-blind, placebo and active-controlled trials of two days duration ("day in park" design) to assess the onset of action of azelastine nasal spray at doses of 1 spray per nostril BID, 2 sprays per nostril BID, and 2 sprays per nostril QD. The three long term trials consistently demonstrated that azelastine nasal spray at a dose of 2 sprays per nostril BID was more effective than placebo (although less effective than the concurrent active control of chlorpheniramine). While there were numerical trends favoring azelastine nasal spray 2 sprays per nostril QD versus placebo, statistically significant effects were not consistently observed. The two short term trials demonstrated a rapid onset of action following a single dose and confirmed the efficacy of both 2 sprays per nostril BID and 2 sprays per nostril QD throughout the respective dosing interval. It is unclear why the efficacy results observed for 2 sprays per nostril QD in the short term studies was not confirmed in the long term trials, however, the standard for approval of agents for seasonal allergic rhinitis is demonstrated efficacy in trials of at least two weeks duration. The sponsor did not submit any adequate and well controlled trials of azelastine nasal spray in patients with perennial allergic rhinitis. The PADAC recommended approval of azelastine nasal spray for the patients with seasonal allergic rhinitis at a dose of 2 sprays per nostril BID at the November 17, 1995 meeting and did not suggest that additional efficacy studies were required for this indication.

The sponsor has proposed that azelastine nasal spray be approved for use at either 2 sprays per nostril QD or BID. There appears to be adequate data as described above to support the BID dosing regimen, however, inadequate data has been presented to support the QD dosing regimen.

The safety database for azelastine nasal spray includes a total of 391 patients who received azelastine nasal spray at a dose of 2 sprays per nostril BID for up to 8 weeks duration in U.S. clinical trials. In addition, data is available from over 1200 patients exposed to azelastine nasal spray (generally at a dose of 1 spray per nostril BID) for up to two years (approximately 160 patients exposed for > 169 days) in European clinical trials. This nasal spray safety database is supplemented by an extensive amount of data from patients exposed to azelastine tablets at doses of up to 4 mg per BID and higher from U.S. and foreign clinical trials in allergic rhinitis and asthma. Local adverse reactions of note for the nasal spray formulation include taste perversion, nasal burning, sneezing, and dry mouth. The vast majority of these local adverse events were of mild to moderate severity. Systemic adverse reactions are primarily limited to somnolence which was reported by 11.5% of azelastine nasal spray patients versus 5.4% of placebo patients in U.S. clinical trials. Due to the concern over the effect of other antihistamines on the ECG (i.e., QTc prolongation) the azelastine database was reviewed extensively for evidence of any effect of azelastine nasal spray or tablets on the ECG. In addition, the sponsor conducted prospective studies investigating PK/PD effects of concomitant azelastine tablets and erythromycin or ketoconazole. The tablet safety database revealed a small, statistically significant mean increase in QTc in patients treated with 4 mg BID. Review of individual ECGs from patients in the azelastine tablet database did reveal isolated episodes of QTc prolongation to potentially clinically significant levels during azelastine treatment, however, these were not associated with arrhythmias or cardiac adverse events. The nasal spray database, which included fewer baseline and treatment ECGs than the tablet database, failed to demonstrate any evidence of an effect of azelastine nasal spray on the ECG. It should be noted that the systemic exposure to azelastine (as measured by AUC) is approximately 10X less in patients treated with azelastine nasal spray at a dose of 2 sprays per nostril BID versus patients treated with 2 mg BID orally. The interaction studies with erythromycin and ketoconazole failed to demonstrate either a PK (azelastine levels could not be measured in the ketoconazole study due to ketoconazole interference with the azelastine assay) or a PD (as measured by QTc) interaction. Taken as a whole, these data support the conclusion that azelastine nasal spray at a dose of 2 sprays BID is unlikely to have a clinically significant effect on cardiac repolarization. The information regarding the effects of azelastine tablets on the ECG are reflected in the FDA revision of the draft labeling.

Azelastine nasal spray is considered clinically approvable for the treatment of seasonal allergic rhinitis at a dose of 2 sprays per nostril BID with labeling changes as indicated in the FDA revision of the draft labeling.

Preclinical

Azelastine is non-mutagenic and was not associated with any evidence of tumorigenicity in rats and mice dosed orally for two years. In oral reproduction studies in mice, azelastine has been shown to be embryotoxic, fetotoxic, and teratogenic (external and skeletal abnormalities).

Since there are not adequate and well-controlled studies in pregnant women, azelastine is classified as Pregnancy Category C.

Azelastine nasal spray is considered approvable from a preclinical standpoint with labeling changes as indicated in the FDA revision of the draft labeling.

CMC

Azelastine nasal spray is proposed for marketing as a 0.1% solution in a 100 spray metered dose pump unit. Each spray delivers 0.137 ml mean volume containing 137 mcg of azelastine hydrochloride (equivalent to 125 mg azelastine). A significant number of CMC deficiencies remain to be resolved and will be conveyed to the sponsor in the action letter.

Azelastine nasal spray is considered not approvable from a CMC standpoint; CMC deficiencies are included in the action letter. In addition, labeling revisions by the chemistry reviewer are reflected in the FDA revision of the draft labeling.

Biopharmaceutics

Azelastine is systemically absorbed after intranasal administration (approximate 40% bioavailablility) and has an elimination half-life of approximately 22 hours following intravenous administration. Plasma exposure (as measured by AUC) following intranasal azelastine at a dose of 2 sprays per nostril BID is >10X less than that following 2 mg BID orally. Azelastine is oxidatively metabolized by the cytochrome P450 system; the major metabolite, desmethylazelastine, has antihistaminic activity. The specific P450 isoforms responsible for azelastine metabolism have not been identified, however, no PK interaction was observed with erythromycin, a known CYP3A4 inhibitor. Cimetidine, a nonspecific P450 inhibitor increased azelastine serum concentrations by 65%. Following oral administration, azelastine PK parameters were not affected by age, gender, or hepatic impairment. Renal insufficiency increased Cmax and AUC by approximately 75%.

Azelastine nasal spray is considered approvable from a biopharmaceutics standpoint with labeling changes as indicated in the FDA revision of the draft labeling.

Data Verification

The Division of Scientific Investigations (DSI) completed audits at a total of 4 clinical sites from the pivotal efficacy trials. Two sites were judged NAI and two sites were judged VAI. The audit reports were reviewed by the medical officer and the deficiencies noted by the DSI investigators were considered to be minor in nature and insufficient to raise any concern regarding the integrity of the NDA database.

Labeling

The proposed tradename, Astelin, is acceptable to the Division. The draft labeling included in this package has been revised by the Division and accurately reflects the available information for azelastine nasal spray. The sponsor should submit revised package and container labeling as well as patient instructions for use for review.

Conclusion

This application is APPROVABLE, however, CMC deficiencies remain to be resolved before the application can be approved. In addition, the sponsor should resubmit revised draft labeling based on the Division's comments noted on the enclosed copy of the FDA revision of the draft labeling.

cc:
NDA 20-114
HFD-570 Division Files
HFD-570/Jenkins
HFD-570/Strange
HFD-570/Himmel
HFD-570/Honig

MEDICAL OFFICER REVIEW

NDA#:	**20-114**
PRODUCT:	**Azelastine Nasal Spray**
ROUTE:	**Intranasal**
SPONSOR:	**Wallace Laboratories**
MATERIAL REVIEWED:	**Final Safety Update (10/10/96)** **Final Proposed Labeling (9/31/96)**
DATE REVIEWED:	**October 17, 1996**
REVIEWER:	**Peter K Honig, M.D.**

Safety Update:

This safety update includes all information subsequent to that submitted to the NDA in the four-month safety update and covers the period through October 1996.

1. Data from Annual Report submitted to the IND :

This contains two foreign safety reports for the oral formulations of azelastine received in the time period from November 24, 1994 through November 30, 1995. One 42 year old female experienced elevated LFTs while taking azelastine (4 mg po BID). The subject ceased medication use before discovery of the abnormal LFTs and an alternative explanation was not completely pursued. The second case involved a 47 year old female who was given azelastine for "allergic condition." She developed Stevens-Johnson syndrome after one day of therapy. She was on multiple drug therapy at the time of diagnosis.

Reviewer comment: LFT elevations are described in the proposed product label. The diagnosis of Stevens-Johnson syndrome is not established and, because of multiple concomitant drug therapy, causality is unclear. This does not need to be represented in product labeling at this time.

2. Data from IND Safety Reports since December 1995.

Two foreign reports were submitted. The first involved a 54 year old male with asthma being treated with azelastine (2 mg po BID) in addition to other medications (theophylline, serrapeptase, sofalcone). The patient developed increased LFTs (AST peak 358/ALT peak 729) after three months of treatment with azelastine. Work-up failed to reveal any alternative infectious/toxic or organic etiology. Laboratory abnormalities began to normalize within 2 weeks of discontinuing azelastine. Further follow-up is unavailable. The second patient was a 10 year old male who experienced "anaphylactoid" symptoms (pallor, sweating, trembling, inability to swallow saliva) after the second dose of oral azelastine (0.5 mg). The complaints resolved after supportive therapy.

Reviewer comment: LFT elevations are described in the proposed product label. The second case is ill-defined as 'anaphylactoid' and causality is impossible to establish. No further action is indicated at this time.

3. Most current Safety Report from ASTA Medica AG (dated 2/23/96):

This report encompasses trials through January 1, 1996. The profile of adverse reactions is similar to the ones seen in previous U.S. and foreign clinical trials. There are no serious adverse reactions in this report for azelastine nasal spray. There were four deaths in the tablet/asthma azelastine trials (2

azelastine/1 nedocromil/1 placebo) all of which were attributable to the underlying disease condition.

Reviewer comment: The adverse events for azelastine nasal spray are comparable in frequency and characterization to those seen in previously reviewed trials. No additions or changes to the proposed product label are indicated at this time since only controlled US trials are represented in the label.

4. Adverse events from Protocol 362 previously submitted to the IND on 3/22/96:

The final report for this marketing study is not finalized; however, preliminary analysis show the same type of adverse event profile as previously seen in US controlled clinical trials. No serious or unexpected adverse events have been reported.

Reviewer comment: No further action is indicated at this time.

Overall Reviewer Conclusions on Final Safety Update: This final safety update reveals no additional safety concerns regarding azelastine nasal spray. All clinical and spontaneously reported adverse events are represented in the proposed azelastine nasal spray labeling. The application remains approvable from a clinical safety perspective.

Final Proposed Draft Labeling (Package Insert):

The sponsor has submitted final draft labeling which is modified in accordance with previously determined Division requirements.

Reviewer comment: This labeling is acceptable; however, minor modifications may be required pending review by the Office Director and after consultation with DDMAC regarding proposed promotional claims.

Peter K Honig, MD
Medical Officer

cc:

NDA20-114/Division file
MO/Honig/
CSO/Strange

MEDICAL OFFICER REVIEW

MAY 16 1996

NDA:	**NDA #20-114 (Astelin NS)**
REVIEWER:	**Peter K Honig, MD**
PRODUCT:	**Azelastine Nasal Spray**
SPONSOR:	**Wallace Laboratories**
MATERIAL REVIEWED:	**Meeting request submission dated 5/8/96**
DATE REVIEWED:	**May 15, 1996**
DATE REVISED:	**May , 1996**

Background:

Dr. Alberto Rosenberg of Wallace Laboratories contacted this reviewer by phone on April 17, 1996 to discuss the potential for changing the proposed adult (> 12 years) dosing instructions for azelastine nasal spray. He also wanted to discuss the requirements for a pediatric indication for the product. I informed him that these proposals should be submitted in writing for review. The remainder of this review will describe the proposals as contained in the submission of May 8, 1996.

Part I: Supplement to azelastine nasal spray dosing.

The sponsor makes the argument that azelastine is approved in Europe at doses of 1 spray/nostril twice daily; however, they indicate that these studies were not placebo controlled. Furthermore, the sponsor cites Protocol 258 (Study 32) which investigated azelastine at a dose of 1 spray/nostril twice daily and showed an overall response of 32% improvement from baseline versus 18% for placebo. This was significant at the $p=0.06$ level; however, the sponsor claims that the placebo response was greater that usually seen in this type of trial. In fact, the sponsor states that it was not a true placebo control since it was placebo vehicle which may itself ameliorate symptomatology. The sponsor essentially argues that this is not necessarily a fair comparison. In this light, the sponsor proposes that the dosing recommendations be changed in the label to reflect a titration strategy. That is, patients should be started out at 2 sprays/nostril twice daily (a dose that is approvable) and back-titrated to 1 spray/nostril bid.

Reviewer comment on Part 1: The study to which the sponsor is referring is one of two "in the park" dose ranging studies that were used to select dosing regimens for the 'pivotal' Phase III trials. In this study (#3C), azelastine dosed at 1 spray bid never was statistically superior to placebo at the $p<0.05$ level for TSC (total symptom complex- see MOR of NDA 20-114 dated 7/19/93. TSC was defined as the sum of rhinorrhea, sniffles, itchy nose, nose blows, sneezes, watery eyes, itchy

eyes/ears, itchy throat, dry nose, cough and postnasal drip). The major symptom complex (MSC) included only rhinorrhea, sniffles, itchy nose, nose blows, sneezes and watery eyes. Again, azelastine dosed at 1 spray bid was never statistically superior to placebo at any timepoint (including endpoint). Azelastine dosed at either 2 sprays QAM or 2 sprays BID as well as the active control (chlorpheniramine 12 mg po bid) was consistently statistically superior to placebo.

In any case, this trial is not sufficient to support an efficacy claim of any dose of azelastine. This would require a minimum two week trial versus placebo for the claim of seasonal allergic rhinitis. These trials were conducted in support of azelastine nasal spray and a dose of 2 puffs/nostril bid was considered to be clinically approvable by the Division as well as the Pulmonary-Allergy Drugs Advisory Committee (November 17, 1995).

The sponsor is proposing a dosing recommendation that has not been adequately studied and, as such, is unacceptable. The use of uncontrolled European study data in support of this proposal is also not acceptable.

Part II: Pediatric usage for azelastine nasal spray

The sponsor proposes that azelastine nasal spray has adequate existing information to support a pediatric indication (ages >6) at a dose of 1 spray/nostril bid with a titration to 2 twice daily if no response is seen. According to the sponsor, this is based on the fact that this dose/indication is extant in Europe and there exists a considerable safety database to support the claim.

Reviewer comment: The sponsor must submit adequate justification to support their contention that a dose of 1 spray/nostril bid in children is safe and effective. For orally administered products, pharmacokinetic data may serve to link the adult efficacy data to a pediatric indication and help select the appropriate dose for children. In the case of a topical product, adequate and well-controlled clinical trial efficacy data and sufficient safety data is required. If a titration indication is sought, the trial should be designed to support that claim.

The European safety database that the sponsor proposes to submit in support of a pediatric indication is described in insufficient detail to make an assessment of its adequacy. More detail on durations of exposure (ie. long term safety) should be provided. Furthermore, quantification of common (ie. >1%) adverse events in the pediatric population should be derived from placebo controlled clinical trials.

Reviewer recommendations:

The above reviewer comments should be forwarded to the sponsor. At this point a meeting with the sponsor is not necessary; however, if after reviewing our comments, the sponsor still requests a meeting, it may be scheduled.

Peter K Honig, MD
Medical Officer

John K. Jenkins, MD
Division Director, DPDP 5/16/96

cc:

HFD-155/NDA 20-114/Division File
/MO- Honig
/CSO- Strange

MEDICAL OFFICER REVIEW

SEP 12 1995

NDA:	**NDA #20-114 (Astelin NS)**
REVIEWER:	**Peter K Honig, MD**
PRODUCT:	**Azelastine Nasal Spray**
SPONSOR:	**Wallace Laboratories** submission dated 6/30/95
MATERIAL REVIEWED:	**Response to Nonapprovable Letter of February 23, 1994**
DATE REVIEWED:	**August 23, 1995**
DATE REVISED:	**September 12, 1995**

INTRODUCTION:

The failure of the sponsor to present, in satisfactory fashion, the cardiac safety data for this new molecular entity was a significant concern and the major thrust of the Non-Approvable letter sent to the sponsor on February 23, 1994. Subsequently, the sponsor submitted partial responses to the NA letter in which the requested reanalyses of the cardiac/ECG database were performed, submitted and reviewed. The conclusions of the review were that there was a small mean effect on cardiac repolarization which should be reflected in product labeling. Furthermore, there was no pharmacokinetic or pharmacodynamic interaction with erythromycin (Study 278)and there was no cardiac pharmacodynamic effect noted in the ketoconazole interaction study (Study 279). Therefore, from a cardiac safety viewpoint, the application is Approvable.

The following review will concern the remaining issues which were detailed in the NA letter. The format of this review will restate the NA issue followed by the sponsor response and a reviewer comment. Since it was requested that the sponsor submit a complete document (ie. all NA points included), the cardiac issues will be repeated. These questions will be noted as "previously reviewed". For example, FDA Question 1 has several subsections. Several have been previously reviewed and will be noted as such.

The second section of this document will review the most recent Safety Update. The format of this section will be similar to the original Medical Officer Review of the ISS from the NDA.

FDA Question 1: At present, a full risk-benefit assessment for azelastine is not possible. In preclinical studies, azelastine has been shown to have antifibrillatory and calcium channel blocking activity and the finding of a mean QTC increase in subjects taking azelastine versus subjects taking placebo suggests potential for cardiotoxicity in humans. The fact that no correlation between concentration and effect has been demonstrated suggest the presence of unmeasured cardiotoxic metabolites and/or metabolic outliers in the population. The following information is required to allow such an assessment.

a. The requested reanalysis of the "enriched database" including placebo comparisons and sensitivity analyses.

Sponsor response: The sponsor has previously submitted the requested information in the partial response dated November 1, 1994.

Reviewer comment: The sponsor conducted an adequate reanalysis of the enriched database as requested in the NA letter. A complete review of this response was conducted and signed off on May 17, 1995.

b. Because of demonstrated in vitro activity on cardiac calcium and sodium channels, the above analyses should also be performed on PR and QRS intervals from the ECGs in the "enriched database."

Sponsor response: It was agreed at the FDA-Wallace meeting on July 27, 1994 that analyses of the PR and QRS intervals would need to be done only on the drug interaction studies.

Reviewer comment: This indeed was the agreement reached at the industry meeting.

c. In vivo interaction studies as planned for erythromycin and ketoconazole should include ECG assessments of PR, QRS, QTc and qualitative T-U wave morphologies. High quality copies of ECGs obtained during these studies should be included in the submission.

Sponsor response and reviewer comment: This information was previously submitted in the partial response and found to be acceptable. Notably, there were no PK data available for the ketoconazole interaction because of interference with the azelastine assay by ketoconazole metabolites. There were no significant ECG effects noted in either interaction study.

d. A dose escalation study, including both males and females, to steady-state for daily doses up to 24 mg with ECG assessments should be performed.

Sponsor response: It was agreed at the meeting on July 27, 1994 that the above study would not be required for the azelastine nasal spray.

Reviewer comment: This was the agreement reached at the meeting. This dose escalation study would not be required for NDA 20-114.

e. A summary of the population variability of azelastine metabolism should be provided. This should include presentations of histograms by dose of azelastine,

desmethylazelastine, the sum and ratios of the two moieties (Cmax and AUC) after single and multiple dosing. In addition, please identify any phenotypic subpopulations of azelastine metabolizers. The effects of gender on metabolism should be evaluated as well.

Sponsor response: In response to this request for information, the sponsor cites the results of study 13 in which 3 multiple doses (2 BID, 4 BID and 8 BID) and a 4 mg single oral dose were investigated. This study was previously submitted to the NDA. From this study, the sponsor submitted a series of frequency histograms looking at AUC, Cmax and Cmin for all of the doses. These data are summarized in the table below.

Azelastine

Dose	AUCtau (ng*hr/mL)		Cmin (ng/mL)		Cmax (ng/mL)	
	Median	Range	Median	Range	Median	Range
2 mg BID	25	15-145	1.5	0.5-12.5	2.5	1.5-13.5
4 mg BID	50	30-210	3	1-17	5	3-19
8 mg BID	140	100-380	10	6-30	14	10-34
4 mg Single	30	15-120	-	-	1.5	0.5-3.5

Desmethylazelastine

Dose	AUCtau (ng*hr/mL)		Cmin (ng/mL)		Cmax (ng/mL)	
	Median	Range	Median	Range	Median	Range
2 mg BID	16	10-46	1.2	0.8-3.8	1.8	1-4.2
4 mg BID	30	20-60	2.5	1.5-4.5	2.5	2-5.5
8 mg BID	85	55-105	5.5	3.5-7.5	8	5-10
4 mg Single	35	20-55	-	-	0.3	0.2-0.6

Azelastine + Desmethylazelastine (Sum of Moieties)

Dose	AUCtau (ng*hr/mL)		Cmin (ng/mL)		Cmax (ng/mL)	
	Median	Range	Median	Range	Median	Range
2 mg BID	55	30-205	3	1-15	5	3-17
4 mg BID	70	40-250	7	4-19	7	4-25
8 mg BID	205	135-450	14	10-34	21	13-41
4 mg Single	70	30-150	-	-	2.0	1.0-4.0

Desmethylazelastine/Azelastine Ratios

Dose	AUCtau (ng*hr/mL)		Cmin (ng/mL)		Cmax (ng/mL)	
	Median	Range	Median	Range	Median	Range
2 mg BID	10	2-16	0.8	0.2-1.4	0.8	0.2-1.6
4 mg BID	6	2-12	0.6	0.2-1.2	0.6	0.2-1.2
8 mg BID	6	4-10	0.8	0.2-1.0	0.6	0.2-1.0
4 mg Single	missing	missing	-	-	1.5	0.5-3.0

No data are currently available that identify a phenotypic subpopulation regarding the human metabolic disposition of azelastine. Preliminary data provided by the FDA regarding the characterization of the inhibitory spectrum of azelastine utilizing in vitro microsomal test systems suggested that azelastine may be a substrate for the p450 3A4 enzyme; however, the negative erythromycin-azelastine interaction study suggests that the metabolism of azelastine may not be mediated significantly by CYP3A4.

Two of the 12 subjects enrolled in the erythromycin interaction study were characterized as poor metabolizers of dextromethorphan (CYP2D6). The observed PK values for these subjects were within the population variability noted in the study summarized in the above tables.

Reviewer comment: The purpose of this question was to elucidate the population variability of the drug so that information regarding this feature may be accurately communicated in the label. This was thought to be important possibly for potential cardiac repolarization effects (not so important after review of complete ECG database) but remains relevant for other concentration responsive adverse events such as taste alteration and somnolence. In this light, it appears clear that the oral tablet has wide population variability in AUC and Cmax for the parent azelastine (up to 10 fold) and the major metabolite desmethylazelastine (up to 5 fold). This information should probably be reflected in the CLINICAL PHARMACOLOGY section of the product label. Unfortunately, no such detailed PK information is available for the nasal spray formulation.

Regarding the metabolism of azelastine, initial in vitro studies indicated that CYP3A4 may be responsible for oxidative biotransformation of azelastine. Personal communication with Dr. Jerry Collins indicates that this is probably in error and due to too high substrate concentrations in the in vitro system. It appears more likely that one of the CYP2C enzymes mediates the biotransformation in vivo. Therefore, it is not unexpected that clinical poor metabolizers of dextromethorphan do not exhibit differential pharmacokinetics of azelastine. While it would be nice to include detailed information about the

cytochorome(s) responsible for the metabolism of azelastine, it appears that this information is uncorroborated and work remains to be done.

Overall, this response is acceptable. This response has also been referreo to the Biopharm reviewer for additional comments.

f. If the aforementioned studies are suggestive of a cardiac effect, the following studies may be required.

-in vitro potassium channel studies

-full characterization of the metabolism of azelastine including metabolites specific to the nasal route of administration.

Sponsor response: There is no indication that azelastine, desmethylazelastine or any other identified or unidentified metabolite has a cardiac effect. Assessment of steady-state azelastine and desmethylazelastine concentrations after oral and nasal administration demonstrate lower concentrations of both after nasal application. The relative proportion of the metabolite to the parent was similar regardless of route of administration. Any other metabolite that could be formed is not altering the relative disposition of the parent and its metabolite. This suggests that there is no metabolite that may be specific to the nasal route of administration.

Reviewer comment: The FDA question was predicated on the finding of an effect of azelastine on cardiac electrophysiology. The additional arguments provided by the sponsor are supportive but not conclusive regarding differential metabolism specific to the nasal route of administration. The ECG information submitted by the sponsor is comforting in that, although there may be a small dose-related effect, cardiotoxicity does not appear to be a major concern. In this light, the additional studies are not required.

g. It was shown in vitro that salicylate caused a four-fold increase in the unbound fraction in plasma of the active metabolite. The impact of such an interaction in vivo needs to be investigated. In the absence of enough information of the clearance of this metabolite, it is difficult to predict whether the unbound concentration of desmethylazelastine will increase or remain constant. Studies utilizing the tablet formulation may address this issue.

Sponsor response and reviewer comment: This issue was raised by the Biopharmaceutics reviewer and should be addressed by the reviewer from that discipline.

h. The influence of gender on azelastine kinetics has not been addressed. Please re-analyze existing data or plan a new study to investigate gender effect.

Sponsor response: The sponsor answers this question by resubmitting data from

oral dosing studies that were previously presented in the NDA. Information is presented from Studies 183 and 20 after single- and multiple-dose oral 4 mg doses, respectively.

Dosing (4 mg)	AUC0-∞		Cmax (ng/mL)		Half-life (hrs)		Clearance (L/hr/kg)	
	♂	♀	♂	♀	♂	♀	♂	♀
Single ♂ = 4 ♀ = 11	84.7 ± 48.8	65.4 ± 31.3	N/A	N/A	20.2	19.1	1.18 ± 0.65	0.93 ± 0.55
BIDx14d ♂ = 6 ♀ = 6	51.9 ± 23.3	55.5 ± 41.2	5.1 ± 2.2	5.7 ± 3.9	N/A	N/A	3.31 ± 1.09	3.06 ± 1.64

These data support the conclusion that gender does not influence the pharmacokinetics of azelastine.

Reviewer comment: Both these studies are very small. The intersubject variability dwarfs any potential or underlying intergroup difference in pharmacokinetics. There are no evident mean differences between sexes; however, the possibility of a type II error remains. There may be a small difference that is not detected. Since other highly first pass cleared drugs like azelastine (such as nifedipine, terfenadine, etc.) do not exhibit gender-differential pharmacokinetics, there is no reason to suspect that azelastine would be any different. This response is acceptable.

2. Safety data, with particular emphasis on local toxicity, in at least 200 subjects who have received the 2 sprays per nostril BID of azelastine for at least 6-12 months must be submitted.

Sponsor response: Wallace states they are uncertain why these numbers are required since:

-Study #25 studied 30 subjects for 28 days with nasal examinations including objective measurements (color, wetness, and mucosal thickness along the septum and inferior turbinate) and subjective assessments (changes from baseline examination and nasal status in general). 10 subjects were randomized to receive each dose of azelastine (1, 2, or 3 sprays per nostril BID or placebo). Nasal examinations were performed frequently during the study and at follow-up visit.

-Study #29 studied PAR in 56 subjects for 2 months with safety exams including evaluations of nasal secretions, turbinate size and color, nasal cytology, and nasal airflow conducted at 2 week intervals and at follow-up during the study.

There was no evidence of local toxicity observed in either of the above studies.

Reviewer comment: The aforementioned safety data has been submitted previously and reviewed (see MOR of NDA 20-114 dated July 19, 1993). No specific local toxicities were noted in this clinical database. Furthermore, there were no signs of irritation to the epithelial lining of the nasal cavity in rats and dogs who received intranasal azelastine for six months.

Furthermore, the previously presented and reviewed European database includes long-term safety data from 150 subjects exposed to azelastine nasal spray (1 spray/nostril BID) for at least 22 weeks (with 35 subjects receiving it from 267 to 752 days), as shown in the table below.

Indication	Number Subjects	1-28 days	29-56 days	57-168 days	169-752 days
SAR	722	590	128	4	0
PAR	370	19	153	47	151
Mixed AR	64	29	33	2	0
Challenge	75	75	0	0	0
Totals	1231	713	314	53	151

Remember that only a small number had specific evaluations of local safety (as described above).

The sponsor conducted an examination of the frequently occurring adverse reactions (≥1%) that revealed the incidence of these particular adverse reactions did not increase with increasing duration of exposure (see table below).

WHO Term	0-56 Days Exposure (n = 869)	57-180 Days Exposure (n = 98)	> 180 Days Exposure (n = 104)
Taste Perversion	7.1	9.2	1.9
Local Irritation	5.4	6.1	3.8
Rhinitis	3.5	3.1	2.9
Headache	2.4	1.0	0.0
Fatigue	2.2	0.0	0.0
Nausea	1.7	3.1	0.0
Epistaxis	1.6	1.0	1.0
Pharyngitis	0.9	1.0	1.0

Finally, the sponsor alludes to the pre-NDA meeting of February 1990 at which time the FDA concerns were not raised. Systemic safety issues have been previously adequately addressed with data garnered from the long-term asthma trials. The sponsor also offers to obtain any additional local safety data in postmarketing trials.

Reviewer comment: While it is reassuring that toxicity (particularly local effects such as local irritation, epistaxis and pharyngitis) do not appear to increase with cumulative dosing, it should be noted that the majority of the longer term safety data (table above) is at a lower dose than may be approved in the US. The sponsor does not meet the requirements set forth in the FDA question. However, as previously stated, preclinical toxicity studies do not indicate that a particular concern is warranted. Furthermore, although the clinical studies looking at local effects are small in size, they did evaluate for potential effects in a comprehensive and exhaustive manner without demonstrating any adverse effects. Finally, the clinical trials did elicit adverse effects (local symptoms) such as irritation, epistaxis, rhinitis and pharyngitis that can be accurately reflected in the label. In my opinion, this question is adequately answered and no further sponsor action is required prior to approval. No postmarketing studies are required.

3. Please submit adverse event data with the inclusion of all intercurrent illnesses as adverse events. These data should include incidence in short-term (≤2 days duration) and long-term trials separately, for all rhinitis trials, asthma trials, combined rhinitis and asthma trials, and all US exposure. Additionally, the data should be analyzed by dose as was done in the ISS. Demographic analyses of the data looking at gender, race, and age should be done as well.

Sponsor response: This data was submitted to the FDA with the appropriate NDAs. Intercurrent illness is and always has been considered an adverse experience and reported as such. Adverse experiences for purposes of presentation in NDA 20--114 was defined as follows in the ISS: "A treatment-emergent adverse experience was defined as an adverse experience (including intercurrent illnesses and/or injuries) that occurred following randomization to double-blind treatment and which was not present prior to the double-blind treatment period and/or an adverse experience which occurred during the baseline period but worsened in severity and/or increased in frequency following randomization to double-blind treatment."

The sponsor resubmitted the appropriate (previously submitted) tables of information requested by FDA.

Reviewer comment: Although unbeknownst to the original medical reviewer at the time, these data have been previously reviewed as intercurrent illness were

included as adverse events in the NDA. This response is, therefore, acceptable.

4. Please submit any ECG data which you may have in subjects treated with the nasal spray formulation. If this database is large, an analysis of cardiac intervals in treated subjects vs. controls should be done as has been requested for the tablet formulation.

Sponsor response: All available ECG data from subjects treated with the nasal solution have been submitted to the Agency with NDA 20-114 or with the "enriched database." In study 25, ECGs were only done "off-therapy" at baseline and follow-up. In study 29, subjects (azelastine = 69; placebo = 36) had an ECG done at baseline and on the last day of the double-blind treatment. Since "on-therapy" azelastine and placebo databases are small and the total daily dose of azelastine used was 1.06 mg, an analysis of cardiac intervals vs controls does not seem warranted.

Reviewer comment: The nasal spray formulation ECG data was submitted, analyzed and reviewed as part of the "enriched database." Since the worst-case scenario (high oral doses) has been analyzed and found to be relatively free of ECG effects and there is no evidence of differential, administration-site specific metabolism, further analyses are not required. This response is acceptable.

5. The NDA submission fails to include listings of the twice daily scores ascribed by the subjects to each of the symptoms that they were asked to evaluate. Please submit these data for studies #26 and #31. In addition, please describe how the daily data were combined into a weekly score and how the different symptoms were combined into the total, major, and revised symptom complexes so that we may verify your calculations from individual symptoms scores to weekly symptom and symptom complex scores. In addition, your method for handling missing data in these calculations should be described.

Reviewer note: Initially, this response was incomplete due to a page omission. After a telephone call to Dr. Hemsworth of Wallace Regulatory Affairs, the sponsor submitted the complete narrative response and is summarized as follows.

Sponsor response: Subject listings of the twice daily individual symptoms scores for Studies #26 and #31 were submitted to the NDA on December 2, 1993.

The rules for combining daily symptom data into a weekly score and rules for calculating weekly Total and Major Symptom Complexes, including handling of missing data, are applicable for tablet as well as nasal spray formulations. For Studies #26 and #31, nine individual symptoms (nose blows, sneezes, runny nose, itchy nose, watery eyes, itchy eyes/ears/throat/palate, cough, post-nasal drip, and stuffiness) were scored twice daily (AM and PM) by subject using diary cards.

These scores were averaged to form visit scores upon which all analyses were based. At each visit, the mean of all AM data and the mean of all PM data since the previous visit were calculated. The visit score was defined to be the mean of the two means (AM and PM).

The Total, Major, or Revised Symptom complex visit scores were defined as the sum of the scores for specified symptoms. The first five individual symptoms in the above list were summed to for the Major Symptom Complex. The Total Symptom Complex consisted of all symptoms except stuffiness. The Revised Symptom Complex was determined by summing the scores for itchy nose, postnasal drip, watery eyes, and itchy eyes/ears/throat.

The Total, Major, or Revised Symptom complex visit scores were defined as the mean of all non-missing days since the previous visit. For calculating any Symptom Complex score, any missing symptom was assigned the mean of all available symptoms prior to summation. For any given response variable, if a subject had no baseline data, neither improvement nor percent improvement from baseline could be calculated and those subjects were omitted from the analysis. Also, if a subject had no data beyond the baseline visit, the subject was necessarily omitted from the analysis.

Reviewer comment: This response adequately restates the rules used to calculate the composite and mean (weekly visit) scores contained in the application. The number of missing days allowed before the subject was prematurely discontinued secondary to non-compliance with study requirements was not stated in the response but was elucidated in the study protocols. The requested line listings have been previously submitted to the NDA (and have been resubmitted, as requested). No further information or narrative explanations are required at this time.

6. For studies #26 and #31, please provide us with information regarding the number of subject days with no symptom score for each symptom by treatment arm and by week. For trials where both AM and PM data were collected, these data should be depicted separately. In addition, we would like to have the missing patient day data depicted by outcome for each treatment arm.

Sponsor response:
Part I: The number of subjects that participated in these trials were 247 (#26) and 251 (#31). There were very few subject days with missing symptoms as shown in tables below.

STUDY 26			Number of Subject Days			
Symptom	Time	AM or PM	2 sprays/QD	2 Sprays BID	CTM	Placebo
Sneezes	Baseline	AM	1	1	0	1
		PM	0	0	2	0
	Week 1	AM	2	1	0	1
		PM	3	1	1	1
	Week 2	AM	0	2	0	0
		PM	2	0	1	0
Nose Blows	Baseline	AM	1	1	0	1
		PM	0	0	2	0
	Week 1	AM	2	1	0	1
		PM	3	1	1	1
	Week 2	AM	0	2	0	0
		PM	2	0	1	0
Congestion	Baseline	AM	1	1	0	1
		PM	0	0	1	0
	Week 1	AM	2	1	0	1
		PM	3	1	1	1
	Week 2	AM	1	2	0	0
		PM	3	0	4	0
Itchy Nose	Baseline	AM	1	1	0	1
		PM	1	0	1	0
	Week 1	AM	2	1	0	1
		PM	3	1	2	1
	Week 2	AM	0	2	0	0
		PM	2	1	0	0
Runny Nose	Baseline	AM	1	1	0	1
		PM	0	1	1	0
	Week 1	AM	2	1	0	1
		PM	3	2	2	1
	Week 2	AM	0	2	0	0
		PM	2	1	0	2

Post Nasal Drip	Baseline	AM	1	1	0	1
		PM	0	0	1	0
	Week 1	AM	2	1	0	1
		PM	3	1	1	1
	Week 2	AM	1	2	1	0
		PM	3	0	1	0
Watery Eyes	Baseline	AM	1	1	0	1
		PM	1	0	1	0
	Week 1	AM	2	1	0	1
		PM	4	1	1	1
	Week 2	AM	0	2	0	0
		PM	3	1	0	0
Itchy Eyes, Ears, Throat or Palate	Baseline	AM	1	1	0	2
		PM	0	0	1	1
	Week 1	AM	2	1	0	1
		PM	3	1	1	2
	Week 2	AM	0	2	0	0
		PM	2	0	0	1
Cough	Baseline	AM	1	1	0	1
		PM	0	0	1	0
	Week 1	AM	2	1	0	1
		PM	3	1	1	1
	Week 2	AM	0	2	0	0
		PM	2	0	0	0

STUDY 31			Number of Subject Days			
Symptom	Time	AM or PM	2 sprays/QD	2 Sprys BID	CTM	Placebo
Sneezes	Baseline	AM	0	1	0	0
		PM	1	1	0	1
	Week 1	AM	0	0	0	0
		PM	0	0	0	1
	Week 2	AM	0	0	0	0
		PM	1	0	1	0
Nose Blows	Baseline	AM	0	1	0	0
		PM	1	1	0	1
	Week 1	AM	0	0	0	0
		PM	0	0	0	1
	Week 2	AM	0	0	0	0
		PM	1	0	1	0
Congestion	Baseline	AM	0	0	0	C
		PM	1	0	0	1
	Week 1	AM	0	0	0	0
		PM	0	2	0	2
	Week 2	AM	0	0	0	0
		PM	1	0	1	0
Itchy Nose	Baseline	AM	2	0	0	0
		PM	0	0	0	1
	Week 1	AM	0	0	0	0
		PM	0	0	0	1
	Week 2	AM	0	1	0	0
		PM	1	0	1	0
Runny Nose	Baseline	AM	0	0	0	0
		PM	0	2	0	1
	Week 1	AM	0	0	0	0
		PM	2	0	0	1
	Week 2	AM	0	0	0	0
		PM	0	0	1	0

Post Nasal Drip	Baseline	AM	0	0	0	0
		PM	0	0	0	1
	Week 1	AM	0	0	0	0
		PM	0	0	0	1
	Week 2	AM	0	0	0	0
		PM	1	0	2	0
Watery Eyes	Baseline	AM	1	0	0	0
		PM	0	3	2	2
	Week 1	AM	0	0	0	0
		PM	0	0	0	2
	Week 2	AM	0	0	0	0
		PM	2	1	2	2
Itchy Eyes, Ears, Throat or Palate	Baseline	AM	1	0	0	0
		PM	0	1	0	1
	Week 1	AM	0	0	0	0
		PM	0	0	0	1
	Week 2	AM	0	0	0	0
		PM	3	0	1	0
Cough	Baseline	AM	1	0	0	0
		PM	0	0	0	1
	Week 1	AM	0	0	0	0
		PM	0	0	0	1
	Week 2	AM	0	0	0	0
		PM	1	0	1	0

Reviewer comment to Part i: This is an adequate response. The missing data are few and evenly distributed.

Sponsor response (cont'd):

Part 2: There were very few subjects with missing data; these occurred on isolated days and were distributed about equally over all treatment groups. As a result, inclusion of these subjects had essentially no effect on the analysis of the weekly means, which were based on averages over all nonmissing days since the previous visit.

Reviewer comment: The sponsor presents tables showing the mean weekly responses by symptom for individuals who had missing data. These few subjects are relatively evenly distributed across treatment arms (as can be inferred from tables above) and is unlikely to contribute any bias/direction to inferences reached. This response is adequate and no further information or analyses are required.

7. Please comment on the lack of efficacy seen during the first half of the dosing interval in the q day azelastine group in Study #26.

Sponsor response: The table below lists the mean numerical improvements from baseline bye week for the Total Symptom Complex of the four treatment groups in the morning, evening and morning/evening combined.

	AM				PM				AM/PM			
Rx Group	Week 1	Week 2	Over-all	Endpt	Week 1	Week 2	Over-all	Endpt	Week 1	Week 2	Over-all	Endpt
Azel 2 QD	2.00	3.28	2.59	3.18	2.39	3.68	2.99	3.59	2.20	3.48	2.79	3.39
Azel 2 BID	3.87*	4.67#	4.36*	4.84*	4.34*	4.88*	4.67*	4.99*	4.11*	4.78*	4.51*	4.92*
CTM	4.10*	5.13*	4.50*	4.89*	5.01*	6.05*	5.38*	5.75*	4.55*	5.59*	4.94*	5.32*
Pbo	0.88	2.23	1.44	2.01	1.14	2.36	1.57	1.99	1.01	2.30	1.50	2.00

*Indicates significance at $p<0.05$; # indicates significance at $0.05<x<0.10$.

Although statistically significant demonstration of efficacy was not achieved in the QD nasal spray group, this regimen demonstrated persistent clinical activity as evidenced by consistent numerical improvements in the primary efficacy variable. Failure of the QD group to achieve statistical significance in the first half of the dosing interval (as reflected in the PM diary scores) is likely a consequence of the dosage regimen and not the dose per se. As with many other drugs, QD dosing often results in a lower nadir of drug activity prior to each subsequent dose which could result in lower efficacy scores at the observation periods and more variability in results when compared to more frequent dosing.

Reviewer comment: The sponsor contention is logical; however, it is not completely supported by data presented by the sponsor. If this is indeed the reason, it would have been more appropriate for the sponsor to present the variability data to support the hypothesis. Nevertheless, the efficacy of the BID regimen is supported in reproducible fashion in the two trials and remains the Approvable dose/regimen. The efficacy of the QD regimen is less well supported by this trial. While, it is true that the AM score for the QD regimen is numerically

superior to placebo, the magnitude of the response for this composite variable is considerably less than the BID regimen and not statistically different from placebo for AM and PM evaluations at all timepoints shown in the table above.

8. We are unclear on how to interpret table #27 in Study #26. Weeks 1 and 2 appear to be repeated a number of times with different values.

Sponsor response: Subheadings for Table 27 were inadvertently eliminated in the final output. A correctly labelled table is provided below.

Secretions- Quantity

	Week 1				Week 2			
Regimen	Improved	No Δ	Worse	p Value	Improved	No Δ	Worse	p Value
Azel QD	38%	45%	17%	.619	27%	57%	16%	.895
Azel BID	32%	52%	16%	.923	33%	49%	18%	.617
CTM	32%	50%	18%	.937	42%	47%	12%	.121
Pbo	34%	47%	19%	-	29%	51%	20%	-

Secretions- Consistency

	Week 1				Week 2			
Regimen	Improved	No Δ	Worse	p Value	Improved	No Δ	Worse	p Value
Azel QD	25%	52%	23%	.433	21%	59%	20%	.038
Azel BID	13%	78%	10%	.427	26%	52%	21%	.074
CTM	29%	55%	16%	.942	28%	55%	17%	.204
Pbo	31%	51%	19%	-	35%	58%	7%	-

Secretions- Color

	Week 1				Week 2			
Regimen	Improved	No Δ	Worse	p Value	Improved	No Δ	Worse	p Value
Azel QD	22%	63%	15%	.751	16%	73%	11%	.143
Azel BID	10%	83%	8%	.369	23%	61%	16%	.209
CTM	31%	56%	13%	.515	32%	55%	13%	.789
Pbo	24%	63%	14%	-	33%	56%	11%	-

Turbinate Mucosal Size

	Week 1				Week 2			
Regimen	Improved	No Δ	Worse	p Value	Improved	No Δ	Worse	p Value
Azel QD	32%	53%	15%	.327	41%	45%	14%	.418
Azel BID	44%	44%	11%	.019	49%	38%	13%	.120
CTM	44%	40%	16%	.080	68%	25%	7%	.001
Pbo	22%	61%	17%	-	33%	51%	16%	-

Turbinate Mucosal Color

	Week 1				Week 2			
	Improved	No Δ	Worse	p Value	Improved	No Δ	Worse	p Value
Azel QD	40%	43%	17%	.528	50%	38%	13%	.115
Azel BID	48%	38%	14%	.131	43%	44%	13%	.267
CTM	34%	45%	21%	.839	58%	33%	8%	.008
Pbo	27%	61%	12%	-	33%	51%	16%	-

Reviewer comment: These tables are now clear. No further information/analyses are required and this response is acceptable.

9. For Study #31, please provide pollen count data on a center-by-center basis.

Sponsor response: For all four centers, the daily aeroallergen counts were high, ranging from over 100-10,000/cu.m. on the vast majority of days. For individual pollens, cedar pollen counts, which usually accounted for the majority of pollen, were generally moderate to high (>100 cu.m.) throughout the study periods.

Reviewer comment: All pollen counts (by individual allergen) were provided for all four centers. Allergens were present and inclusive of all study dates. This response is acceptable.

10. Please submit the case report forms for the 8 azelastine treated subjects in Study #26 who were discontinued prematurely.

Sponsor response: These are provided in Attachments 1-8 (Volume 32).

Reviewer comment: Each CRF is discussed briefly. The first six patients were randomized to once a day azelastine.

CRF/Subject 12: This was a 42 yo white male who was noncompliant with study medications in the second week of the study secondary to lack of therapeutic

response. There is a crossed out entry indicating that the patient may have also discontinued because of epistaxis.

CRF/Subject 43: This was a 24 yo white male who took medication as directed for seven days. The patient discontinued on Day 7 secondary to nosebleed. Notably, the patient did not appear to be experiencing any benefit from azelastine therapy at the time of discontinuation.

CRF/Subject 73: This was a 26 yo black male who was prematurely discontinued after six days secondary to medication non-compliance.

CRF/Subject 181: This was a 25 yo white male who was prematurely discontinued after 11 days secondary to adverse event ("the spray tasted like raw medicine")

CRF/Subject 210: This was a 43 yo white male who was lost to follow-up after visit 2. He did not return for visit 3 and did not return medication.

CRF/Subject 250: This was a 34 yo white female who discontinued medication after 7 days due to therapeutic failure. Patient also noted two episodes of epistaxis during single-blind (placebo) phase of trial which did not result in medication discontinuation.

CRF/Subject 37: This was a 43 yo white male who prematurely discontinued secondary to severe nosebleed lasting 20 minutes. This event occurred on the 7th day of treatment with azelastine BID.

CRF/Subject 183: This was a 37 yo white male was discontinued from the trial by the investigator after 7 days secondary to non-compliance with azelastine BID.

These numbers are in accordance with the reasons for premature discontinuation discussed in the original medical officer review. Furthermore, as noted in the original review, these numbers are very small and unlikely to have a significant effect on the outcome of the trial.

11. Please submit the CRFs for the 5 azelastine treated subjects in Study #31 who were discontinued prematurely.

Sponsor response: The CRFs are provided in Attachments 9-13 (Volume 33).

Reviewer comment: *Each CRF is discussed briefly. All patients were randomized to BID azelastine.*

CRF/Subject 17: This was a 12 yo white male due to medication non-compliance after 8 days on study.

CRF/Subject 95: This was a 53 yo white female who discontinued secondary to treatment failure after 9 days. The patient also noted intermittent complaints of mild headache and conjunctivitis during the study.

CRF/Subject 31: This was a 34 yo white male who discontinued the study due to the adverse event of intermittent dizziness on Day 8 of study medication. Notably, patient also complained of mild dizziness on the second day of the single-blind study period.

CRF/Subject 223: This was a 47 yo white female who discontinued medication secondary to increased blood pressure after two days of study medication. Patient returned to investigator 2 days later at which time it was back to normal. Patient has history of borderline HTN and BP reading on admission and follow-up was in the 140/80-90 range.

CRF/Subject 264: This was a 35 yo white female who was instructed by investigator to discontinue medication after 8 days of study medication secondary to inappropriate enrollment (insufficient symptom scores).

The information garnered from review of these CRFs in is accordance with the observations made in the initial MOR. No further information or clarification is required.

12. Please submit case report forms for the 15 azelastine treated subjects in Study #33 who were discontinued prematurely.

Sponsor response: The CRFs for these subjects is provided in Attachments 14-28 (Volumes 33, 34, 35).

Reviewer comment: The following are 7 CRFs from the azelastine QD group.

CRF/Subject 26: This was a 29 yo Asian male who was discontinued from study secondary to medication non-compliance after 6 days of double-blind medication.

CRF/Subject 45: This was a 40 yo black female who was discontinued secondary to acute left eye conjunctivitis with accompanying left auricular lymphadenopathy (concurrent illnesses) after 4 days of double-blind medication.

CRF/Subject 99: This was a 32 yo white female who discontinued after 18 days of double-blind medication secondary to severe allergic dermatologic reaction to

TMP-SMX requiring systemic steroid therapy. Septra given by another physician for urinary tract infection.

CRF/Subject 100: This was a 23 yo white female who stopped taking double-blind medication after 19 days secondary to travel commitments. Patient was previously documented to be compliant with study medications and requirements.

CRF/Subject 132: This was a 15 yo white male who was prematurely discontinued from study in first week of double-blind portion of study secondary to medication non-compliance.

CRF/Subject 149: This was a 28 yo white female who discontinued secondary to moderate dizziness and mild drowsiness after 8 days of double-blind medication.

CRF/Subject 153: This was a 43 yo white male who discontinued secondary to moderate dizziness, moderate lightheadedness and severe parathesia in hands after 4 days of double-blind medication.

The following are 8 CRFs from the azelastine BID group:

CRF/Subject 91: This was a 29 yo Hispanic male who discontinued after 14 days of azelastine secondary to treatment failure. This patient did not have any adverse reactions or concurrent illnesses.

CRF/Subject 148: This was a 34 yo white female who was instructed to discontinued azelastine after 4 days secondary to "uncontrolled diabetes." Patient had long history of Type I DM requiring insulin. There is no documentation of pre-study glucose control. Glucose was 424 (348 on repeat) at time of discontinuation.

CRF/Subject 170: This was a 18 yo white male who had acute appendicitis requiring appendectomy in fourth week of azelastine treatment.

CRF/Subject 209: This was a 18 yo white male who was discontinued from the study after 8 days of azelastine secondary to protocol violation (use of proscribed oral decongestant).

CRF/Subject 214: This was a 34 yo white female who was discontinued from the study after 18 days secondary to medication non-compliance.

CRF/Subject 235: This was a 19 yo white female who was lost to follow-up in second week of study. Patient never returned; however, patient did note adverse event of severe bad taste immediately after starting double-blind (azelastine)

period.

CRF/Subject 246: This was a 33 yo white female who was dropped from study after 19 days of azelastine because she was moving away from study area. Patient was tolerating the drug well without adverse effects.

CRF/Subject 255: This was a 22 yo white female who discontinued secondary to moderate "sinusitis" after 17 days of azelastine therapy. The patient had increased, colored nasal discharge requiring treatment with oral antibiotics. Patient fully recovered after 7 days course of cefaclor.

The information garnered from review of these CRFs in is accordance with the observations made in the initial MOR. No further information or clarification is required.

13. For Study #33, please comment on the differences in efficacy seen for the AM vs PM data based on the total symptom complex as well as individual symptoms.

Sponsor response: The table below lists mean improvements from baseline of the Total Symptom Complex for the four treatment groups in the morning and evening for the weekly, overall, and endpoint (week 2, week 4) data.

	AM							PM						
Rx Group	Wk 1	Wk 2	Wk 3	Wk 4	OV	EPW2	EPW4	Wk 1	Wk 2	Wk 3	Wk 4	OV	EPW2	EPW4
Az QD	2.79	3.78	4.75	4.52	3.68	3.56	4.19	3.51#	4.86	5.55*	5.36	4.44	4.33	5.05#
Az BID	3.46	4.49	5.00#	6.46*	4.43	4.25	5.29#	4.33*	5.33	5.38*	6.64*	5.02*	5.08	5.45#
CTM	4.74*	5.79*	6.26*	6.51*	5.80*	5.78*	6.52*	5.66*	6.36*	6.81*	6.94*	6.43*	6.37*	6.96*
Pbo	2.05	3.69	3.13	3.63	2.89	3.39	3.22	2.35	4.19	3.29	4.01	3.13	3.76	3.39

*Indicates significant at $p<0.05$; # indicates significant at $p<0.10$

Although the mean improvement of symptoms based on Total Symptom complex was less in the morning than in the evening in the azelastine groups, clinical efficacy was still superior to placebo. Importantly, a similar observation was also noted in the CTM positive control group as demonstrated by the lower mean AM and PM severity scores, and consistently smaller difference in mean improvements versus placebo in the AM than the PM data. Individual symptoms also showed generally less improvement in the AM than in the PM in the two azelastine groups as well as in the positive control treatment group. Less symptom improvement in the morning versus the evening is not unexpected given the nature and inherent diurnal or circadian symptom severity in allergic rhinitis.

Reviewer comment: While it is true that there is a numerically larger effect for the PM than the AM scores, statistical significance is maintained for both in the active control (CTM) group. The same pattern is seen for both azelastine and placebo groups; however, consistent statistical significance is not maintained for the azelastine treatment groups. The problem with the azelastine QD treatment arm has been previously discussed (see Question 7 regarding Study #26). The morning lack of efficacy with the BID azelastine group may be due to the smaller overall treatment effect of the drug versus chlorpheniramine. This is a consistent pattern that was previously seen with the pivotal study #26 (see table below).

Study #26

	AM				PM				AM/PM			
Rx Group	Week 1	Week 2	Over-all	Endpt	Week 1	Week 2	Over-all	Endpt	Week 1	Week 2	Over-all	Endpt
Azel 2 QD	2.00	3.28	2.59	3.18	2.39	3.68	2.99	3.59	2.20	3.48	2.79	3.39
Azel 2 BID	3.87*	4.67#	4.36*	4.84*	4.34*	4.88*	4.67*	4.99*	4.11*	4.78*	4.51*	4.92*
CTM	4.10*	5.13*	4.50*	4.89*	5.01*	6.05*	5.38*	5.75*	4.55*	5.59*	4.94*	5.32*
Pbo	0.88	2.23	1.44	2.01	1.14	2.36	1.57	1.99	1.01	2.30	1.50	2.00

*Indicates significance at $p<0.05$, # indicates significance at $0.05<x<0.10$.

Analysis of individual symptoms for Study #33 follow a similar pattern. This response is adequate and no further information or analyses are required.

14. Please delineate what the treatment emergent ECG changes were during the final week of Study #29.

Sponsor response: ECGs were done at the screening visit and at the end of the 8-week double-blind treatment period (Visit 7). Follow-up ECGs were to be done 1 week after completing the double-blind phase should the investigator deem any treatment emergent changes to be clinically significant. Of the 15/81 subjects who were reported to have treatment emergent ECG finding, 11/53 were in the azelastine nasal spray group and 4/28 were in the placebo nasal spray group. These abnormalities are summarized in the table below.

Clinical Study Number	Subject Number	Treatment Group	Week 8 ECG Findings	General Comments
89122	12	Azelastine Spray	Sinus Bradycardia	Baseline HR = 46
89122	18		ST elevation	ST also elevated at baseline
89122	28		ST elevation	ST also elevated at baseline
89122	30		Sinus arrhythmia	No sinus arrhythmia at baseline
89122	48		Low voltage-chest	Also present at baseline
89122	49		Sinus arrhythmia	Also present at baseline
89123	89		Sinus arrhythmia	Also present at baseline
89123	93		Sinus arrhythmia	Also present at baseline
89123	103		Sinus arrhythmia*	*
89123	105		Sinus arrhythmia	Not present at baseline
89123	111		Sinus arrhythmia	Not present at baseline
89122	29	Placebo	ST elevation	ST also elevated at baseline
89122	40		Sinus arrhythmia	Also present at baseline
89123	95		Sinus arrhythmia	Also present at baseline
89123	96		Sinus arrhythmia	Also present at baseline

*ECG taken after 2 weeks of treatment. Subject prematurely d/c'd due to adverse reaction (not cardiac).

Importantly, the investigators did not consider any of these ECG changes to be clinically significant and, therefore, no follow-up ECGs were done at Visit 8.

Reviewer comment: None of these events was clinically significant and/or present at baseline during drug free period. This respo..se is adequate and no further information/analyses are required.

15. Please report the p values for the comparison of adverse events occurring in the "all azelastine" group versus placebo in Table #410 of the ISS.

Sponsor response: A table that contains the patient counts for adverse events

occurring at ≥1% categorized according to relationship to study drug is provided. The sponsor categorizes the AE by likelihood of the relationship (probably, possibly, both). The only statistically significant ($p<0.05$) differences between azelastine and placebo were for taste perversion. This table is reproduced below. Events are listed without judgement of causality.

Cumulative Incidence Rates (≥1%) of Treatment-Emergent AEs in Short Term SAR Studies

	Azelastine n=309		Placebo n=125		
Adverse Event	Raw Number	Rate	Raw Number	Rate	p Value
Headache	70	23	16	13	**0.023**
Somnolence	55	18	13	10	**0.059**
Taste Perver	45	15	0	0	**0.0001**
Dizziness	15	5	3	2	0.299
Dry Mouth	12	4	2	2	0.368
Nausea	11	4	0	0	**0.037**
Pharyngitis	10	3	1	1	0.190
Fatigue	9	3	1	1	0.294
Nasal Burning	8	3	1	1	0.457
Nervousness	6	2	1	1	0.679
Pruritus	4	1	3	2	0.416
Rhinitis	4	1	0	0	0.582
Conjunctivitis	3	1	0	0	0.560
Throat Burn	3	1	0	0	0.560
Dyspepsia	2	<1	3	2	0.146
Injury	2	<1	3	2	0.146
Inc Sputum	1	<1	2	2	0.200

Reviewer comment: When one analyzes the date without regard to assignment of causality, more than taste perversion is statistically different between azelastine and placebo groups. Headache and nausea are significantly different and somnolence exhibits a trend toward statistical difference. Furthermore, although no individual symptom of local irritation attains statistical significance, the sum of these symptoms (pharyngitis, nasal burning and throat burning) are likely to be statistically different from placebo (21 events versus 2 events). The sponsor has

been asked to repopulate this table (with statistical comparisons) including the additional patients from the 'newer' trials discussed in the second section of this review (Safety Update)

16. Please submit case report forms of the azelastine treated subjects with elevated ALT reported as adverse events.

Sponsor response: The CRFs are provided in Attachments 29-31.

Reviewer comment: The three CRFs are reviewed and summarized below.

CRF/Study 31/Subject 257: This was a 17 yo white male who had no previous medical history/conditions except for SAR requiring occasional treatment with Seldane and Tavist-D. Screening physical examination and LFTs were normal (AST = 17, ALT = 12). LFTs were also normal at time of randomization (AST = 21, ALT = 14). After completion of azelastine treatment, AST was 135 and ALT was 43. The patient remained completely asymptomatic and reported no adverse events except for local tendonitis which was treated with ibuprofen. This was repeated one month later and LFTs normalized to 19/10. No other workup was attempted.

CRF/Study 29/Subject 110: This was a 5 [illegible] white male who had a previous recent medical history of bilateral corneal transplants. Screening physical examination and LFTs were normal (AST = 23, ALT = 42). Post-study ALT was elevated at 62 while AST remained normal at 32). Follow-up ALT remained elevated (71) one week after completing the study. Follow-up LFTs had normalized after repeat testing one month later (AST = 29). Patient remained completely asymptomatic, took no concomitant medication and offered no complaints of adverse events throughout the study.

CRF/Study 32/Subject 270: This was a 30 yo white male who had a previous medical history of nephrolithiasis. He had a normal screening physical and slightly abnormal laboratory evaluation with elevated ALT (AST = 29, ALT = 56). The patient was randomized to azelastine and completed the trial without adverse events. The post-study LFTs were abnormal (AST = 84, ALT = 200). Repeat LFT testing one month later revealed normalization of the transaminases to pre-study values (AST = 26, ALT = 57).

Overall impression: These CRFs confirm treatment-emergent transaminase elevations in two patients which normalized after discontinuation of azelastine. No other etiologies were identified. The third case is less clear since the patient had baseline transaminase abnormalities which worsened while on azelastine. Treatment-emergent transaminase elevations should be reflected in product

labeling.

17. Please report the p values for the comparison of incidence rates of adverse events in male versus female subjects in the azelastine treated subjects and the placebo group.

Sponsor response: To compare the two sex groups with respect to incidence rates of frequently reported (≥1%) treatment-emergent adverse events for azelastine alone and for placebo alone would not be appropriate since the principal comparisons in all azelastine trials were between azelastine and placebo. The test for treatment-by-sex interactions provides the answer to the question of interest. If there is a significant treatment-by-sex interaction, separate analyses for male and female subjects would be appropriate. Statistically significant ($p<0.05$) treatment-by-sex interactions were found only for taste perversion, dry mouth and fatigue.

Reviewer comment: Inspection of the treatment-by-sex interaction table (Table 17.1, Volume 1- Page 71) provided by the sponsor confirms the conclusions reached by the sponsor. However, although statistical significance is not reached for other listed AEs, women have an across-the-board higher incidence of AEs than men. This is a pattern that is reproduced across most clinical trials and the underlying reasons are left to speculation. If such information is to be included in the labeling, it should probably be included as a qualitative statement such as: "In controlled clinical trials, women report higher incidence of treatment related adverse events such as taste perversion, dry mouth and fatigue than men." As per the original MOR, sex-specific efficacy effects were not presented.

18. Case report forms for circled subjects on the following scatterplots should be submitted.

Sponsor response: For the AST scatterplot, the CRFs are contained in Attachments 33-35.

Reviewer comment: Each CRF is reviewed and commented upon below.

CRF/Study 31/Subject 142: This was a 65 yo white male with a distant medical history of colectomy for diverticulitis. He had a normal intake physical exam and laboratory evaluation (AST= 18, ALT= 38). Post-study LFTs were AST= 56, ALT= 53. Follow-up repeat testing after one week revealed normalized values at AST= 18, ALT=21. The patient successfully completed the study without adverse event (except minor headache treated with aspirin).

CRF/Study 31/Subject 236: This was a 24 yo Asian male without previous

medical history. He had normal physical examination and laboratories on screening (AST= 26, ALT= 41). Post-study LFTs were noted as abnormal (AST= 50, ALT= 75) which normalized after repeat testing one week later (24/30). This patient successfully completed the study without adverse event.

CRF/Study 32/Subject 320: This was a 33 yo white female with history of appendectomy and three Caesarian sections in the past. Her past medical history is also remarkable for hypothyroidism diagnosed 5 years before study entry requiring daily synthroid therapy. Her screening LFTs were normal (AST= 35, ALT= 40). This was a single dose study and she completed the study. Post-study LFTs were AST= 54/ALT= 76 which normalized after two days on repeat testing. The patient offered adverse event complaints of taste perversion.

CRF/Study 31/Subject 1: This was a 29 yo white male without significant previous medical history and normal screening physical exam. The subject was noted to have abnormal screening LFTs (AST= 41, ALT 72). Post-study LFTs were elevated (AST= 62/ALT= 87) which were repeated one week later. These labs indicated a normalization of the AST (39) and a persistent elevation of the ALT (54) to pre-study range.

Overall impression: The first two CRFs confirm a treatment-emergent transaminase elevation that should be reflected in product labeling (see labeling review). The second two CRFs are less convincing as attributable to azelastine.

For the BUN scatterplot, the CRF is contained in Attachment 36.

CRF/Study 33/Subject 41: This was a 44 yo white male who had a pre-study BUN of 21 (Cr= 1.1). The post-study BUN was 29 (Cr= 0.9). Follow-up repeat BUN was 18 one week later. All other laboratories were unchanged.

Overall impression: The laboratories are unchanged. No action is indicated.

For the LDH scatterplot (placebo), the CRFs are contained in Attachment 37-38.

CRF/Study 31/Subject 146: This was a 55 yo white female who had a normal screening physical and laboratory examination (LDH= 150). Post-study LDH was elevated at 298. Other laboratories remained normal. Follow-up LDH was performed one week later and found to be normal at 136. The patient remained asymptomatic during the study and there was no evidence of hemolysis in the abnormal LDH sample.

CRF/Study 32/Subject 130: This was a 26 yo white male without significant past medical history who had a normal screening physical/LDH= 178. Screening ALT

was noted to be elevated at 58 (repeat screen ALT=98). Post-study (single dose study) laboratories indicated an elevated LDH at 310 and ALT at 79. All normalized within one week on repeat testing.

Overall impression: These patients were receiving placebo.

For the LDH scatterplot (azelastine), the CRFs are contained in Attachments 39-40.

CRF/Study 31/Subject 24: This was a 32 yo white female who had a normal screening history, physical and laboratory evaluation (LDH= 154). Post-study LDH was 287; however, there was evidence of hemolysis (increased potassium. and bilirubin). Repeat testing (one week later) revealed normal potassium, bilirubin and LDH.

CRF/Study 30/Subject 114: This was a 58 yo Hispanic male who had normal screening history and physical. Screening laboratories included abnormal BUN (26), creatinine (2.2), alkaline phosphatase (284) and albumin (2.5). LDH at screening was normal (207). Post-study (single-dose) abnormal labs had normalized; however, LDH was now abnormal at 264. No follow-up was performed.

Overall impression: There is scant evidence for an adequate causality assessment of these LDH abnormalities.

For the ALT scatterplot (azelastine), the CRFs are contained in Attachments 41 and 31.

CRF/Study 31/Subject 164: This was a 52 yo white female with a distant history of an appendectomy and hysterectomy who had a normal screening physical and laboratory evaluation (AST 27/ALT 39). The subject had elevated transaminases after completion of the study (AST= 70/ALT= 139). Repeat testing one week later revealed normalized LFTs (16/13). The patient remained asymptomatic throughout the study and offered no complaints of adverse events.

CRF/Study 32/Subject 270: This CRF was previously reviewed (see Question 16).

Overall impression: These CRFs confirm treatment-emergent transaminase elevations. Treatment-emergent transaminase elevations should be reflected in product labeling. LDH and BUN effects need not be necessarily included in product labeling.

19. Are any of the differences between azelastine and placebo treated subjects

for out of normal range lab values statistically significant for subjects < age 18?

Sponsor response: Incidence rates of laboratory abnormalities for high and low abnormal values for subjects under age 18 with normal baseline values were evaluated. Comparison of the incidence rates to those of the placebo group showed that none of the treatment differences was statistically significant.

Reviewer comment: Examination of the table provided by the sponsor (Table 19.1, Volume 1- Page 80) indicates that the numbers of laboratory abnormalities in subjects under 18 was exceedingly small and there were no numerical or statistical differences between the azelastine and placebo treatment groups.

20. Are any of the differences between males and females in incidence of low CO2, cholesterol or glucose, or high chloride or cholesterol values statistically significant?

Sponsor response: There were no statistically significant treatment-by-sex interactions for the incidence of any of the above parameters.

Reviewer comment: There were no numerical or statistical differences between males and females treated with azelastine for these parameters (Table 20.1, Volume 1- Page 86).

21. Are any of the differences by weight or race in incidence of out of range laboratory values statistically significant?

Sponsor response: Except for two isolated cases, there were no statistically significant treatment-by-weight or treatment-by-race interactions for the incidence of out of range lab values. The two isolated cases included treatment-by-weight interaction for low specific gravity and treatment-by-race interaction for high LDH in azelastine treated subjects.

Reviewer comment: In both instances the numbers of subjects in each cell are exceedingly small and the statistically significant difference is, most likely spurious. For low specific gravity (by weight), there were no subjects in the < 110 lb group; 16 in the 110-170 lb group; and 10 in the > 170 lb group. For high LDH there were 6 subjects in the white group and 3 in the other group. These numbers are too small for inferential deductions. No further action or analyses are indicated.

22. The following CRFs of subjects with abnormal lab values should be submitted:

Sponsor response: The requested CRFs are provided in Attachments 31, 37, 42-

47. For subject #248 (Study #30), the pre and post-treatment alkaline phosphatase levels were 100 and 97, respectively, both of which are normal. There was a typographical error in the database in which 987 was printed at the post-treatment level, instead of the correct value of 97 which appears in the CRF.

Reviewer comment: The requested CRFs are reviewed below.

CRF/Study 31/Subject 139: This was a 35 yo white female who had a normal screening history/physical examination. The patient had elevated screening transaminase values (AST = 57/ALT = 131) which remained abnormal on repeat pre-test labs (AST = 51/ALT = 115). These remained abnormal in the post-study lab evaluation (AST = 46/ALT = 106).

CRF/Study 32/Subject 270: This CRF has been previously reviewed (see Question 16).

CRF/Study 33/Subject 116: This was a 39 yo white female with a history of tubal ligation and nephrolithiasis. The patient had a high WBC count (15.1) on screening. Patient developed an abscessed tooth during the course of the trial requiring PCN therapy. WBC subsequently decreased and was 8.3 on the post-study evaluation.

CRF/Study 33/Subject 261: This was a 46 yo white male with an unremarkable past medical history. This patient had repeatedly elevated triglyceride levels at screening (693), post-study (676) and follow-up (260, 848). Patient also had intermittent elevations in total cholesterol. He had one fasting triglyceride level which was 179. This patient most likely has a combined hyperlipidemia unrelated to azelastine therapy.

CRF/Study 26/Subject 172: This was a 29 yo white male who had an unremarkable past medical history. This patient had intermittently elevated triglyceride levels at screening (468/841), post-study (221). The patient had a normal fasting triglyceride level during the study (122). The patient most likely has a hyperlipidemia unrelated to azelastine therapy.

CRF/Study 31/Subject 164: This CRF has been previously reviewed (see Question 18).

CRF/Study 31/Subject 193: This was a 43 yo white male who had an unremarkable past medical history and screening physical examination. Screening labs were abnormal for elevated ALT (84), cholesterol (260) and triglycerides (594). These remained elevated at the post-study evaluation (ALT = 165, chol = 244, TG = 619) and remained elevated at a subsequent follow-up

examination.

Overall reviewer impression: As described previously, treatment-emergent transaminase elevations should be reflected in product labeling. The cases of high serum lipids and increased WBC have alternative explanations and are unlikely related to azelastine therapy.

23. Please identify the specific lab abnormalities that are reported on pages 2-3 of table 493.

Sponsor response: Subheadings for Table 493 were inadvertently eliminated in the final output. These subheadings were for Total Bilirubin >2.5 and Triglycerides >750.

Reviewer comment: Page 2 only has placebo patients with TB> 2.5 and the azelatine patients contained on page 3 (with elevated TGs) have been previously identified. No further information is required and this response is adequate.

24. According to our calculations, the updated European safety database should include data on 608 azelastine subjects (205 additional subjects, 35 subjects from the uncontrolled PAR study, 1 subject from the extension study, 182 subjects in the initial database of controlled trials and 185 subjects in uncontrolled trials) and 76 placebo subjects (8 in initial database and 68 in the update), yet your updated safety summary contains data on 553 azelastine subjects and 55 placebo subjects. Please explain this discrepancy.

Sponsor response: There is no discrepancy. The initial database includes 367 azelastine-treated subjects (182 in controlled trials and 185 in uncontrolled trials) and 8 placebo-treated subjects. The updated European safety database adds a total of 206 azelastine-treated subjects, of whom 35 subjects from the uncontrolled PAR study and one subject from the extension study were exposed to azelastine nasal spray. Note, these latter 36 subjects are included in the additional 206 azelastine-treated subjects. Also included in the updated European safety database are 76 placebo-treated subjects (8 from original report and 68 in update).

Therefore, the total updated database contains information on 573 azelastine-treated and 76 placebo treated subjects. Of these, 553 azelastine-treated and 55 placebo-treated subjects were in multiple dose studies. The remaining 20 azelastine-treated and 21 placebo-treated subjects were in single-dose trials.

Reviewer comment: This explanation resolves the apparent discrepancy. No further information/analyses are required. Of note, the European database (ASTA Medica) has subsequently been enlarged. The enlarged databased and the new

trials are reviewed in the second section of this review (Safety Update)

25. Were there any differences between azelastine and placebo in incidence of adverse events in the updated European safety summary statistically significant?

Sponsor response: The only adverse event for which there was a statistically significant difference ($p<0.05$) between azelastine and placebo was headache which occurred significantly less frequently with azelastine than with placebo.

Reviewer comment: This response is adequate. A revised analysis of the above question based on the additional studies/enlarged database in the Safety Update has been requested of the sponsor.

26. Please provide additional clinical information and CRFs for subjects who experienced the following adverse events (taken from table 451): dizziness .4%, palpitations .2%, and allergic reaction .2%.

Sponsor response: The referenced adverse events involved a total of 4 subjects: two with dizziness, one with palpitations, and one with an allergic reaction. The CRFs are provided in Attachments 48-51.

Reviewer comment: The CRFs are reviewed below.

CRF/Study 217/Subject 32: This was a 26 yo female who reported mild flushing and mild lightheadedness 30 minutes after each histamine challenge on Day 1 of azelastine dosing. Each symptom spontaneously resolved within 20 minutes and there was no reoccurrence at subsequent visits.

CRF/Study 212/Subject 65: This was a 32 yo male who reported dizziness, faintness, stomach pains and weakness. The subject prematurely discontinued the study secondary to treatment failure.

CRF/Study 37/Subject 72: This was a 19 yo male who reported palpitations, nervousness and insomnia early in the course of the six week study. The patient continued the study and the palpitations resolved. No ECG was performed during symptomatic periods.

CRF/Study 211/Subject 97: This was a 29 yo male who developed allergic conjunctivitis 4 weeks into a six week trial. The adverse event spontaneously resolved while continuing azelastine.

Overall impressions: These adverse events are difficult to interpret. They most likely represent intercurrent illnesses unrelated to study drug.

27 Please clarify what the difference is between tables 451 and 455 in the ISS.

Sponsor response: ASTA Medica considers adverse reactions to be possibly or probably drug-related and therefore adverse drug reactions. They consider adverse events to be unrelated to study drug and therefore not adverse drug reactions. Table 451 lists adverse events and reactions, whereas Table 455 only lists adverse reactions.

Reviewer comment: This response clarifies the format of the presentation in the ISS; however, for labeling purposes, treatment-emergent events are not considered with regard to causality.

28. CRFs for the seven subjects who discontinued prematurely from European trials should be submitted.

Sponsor response: The requested CRFs are provided in Attachments 52-58.

Reviewer comment: The CRFs are reviewed and commented upon below.

CRF/Study 2606/Subject 10: This was a 25 yo female who prematurely discontinued secondary to headaches and tiredness.

CRF/Study2606/Subject 222: This was a 42 yo male who prematurely discontinued due to "poor tolerability". Further explanation is not available.

CRF/Study2611/Subject 241: This was a 29 yo female who prematurely discontinued secondary to severe irritation of nasal mucosa.

CRF/Study 2611/Subject 75: This was a 63 yo female who prematurely discontinued secondary to unpleasant taste and nasal mucosal burning.

CRF/Study 2611/Subject 86: This was a 62 yo male who prematurely discontinued secondary to loss to follow-up.

CRF/Study2611/Subject 175: This was a 34 yo male who prematurely discontinued secondary to exaggerated nasal itching and sneezing. The relationship to the azelastine spray (temporal and causal) is difficult to determine from the CRF.

CRF/Study 2611/Subject 180: This was an 18 yo male who prematurely discontinued secondary to sneezing attacks precipitated by the azelastine spray.
CRF/Study

Overall impression: It appears clear that the azelastine nasal spray is associated with exaggerated sneezing attacks, irritation to nasal mucosal linings, fatigue, headaches and taste perversions. This information should be reflected in product labeling.

29. Please list the symptom scores of the 52 subjects with insufficient symptoms, state the reason that the 4 subjects failed to meet inclusion/exclusion criteria, explain why 3 subjects were not randomized because of too severe disease (no upper limit on symptom scores is listed in the protocol), and state what the intercurrent illness, adverse events, and unknown reasons were in the other subjects which precluded randomization to Study #33.

Sponsor response: Of the four subjects who failed to meet inclusion/exclusion criteria, one had a history of asthma, two had abnormal laboratory values prestudy, and one refused to abide by the contraceptive stipulations.

Three subjects were not randomized because of too severe disease. For these subjects, their rhinitis symptoms were so severe that they required prohibited concomitant medication(s) and, therefore, were disqualified.

Of the four subjects that were not randomized due to intercurrent illness, two had strep throat, one had acute bronchitis and one had sinusitis.

One subject was not randomized due to adverse experiences (rash, nausea, and headache) in the baseline period.

One of the two subjects that were not randomized due to unknown reasons was inadvertently included as an unrandomized subject when, in fact, he was randomized to treatment. The other subject was categorized erroneously as unknown. Upon further examination, this subject (#58) was not randomized due to insufficient symptom scores. Therefore, this subject's scores are included with the 52 other subjects mentioned above, making a total of 53 subjects not randomized due to insufficient symptom scores.

Reviewer comment: The sponsor has submitted the requested symptom score listings and adequately defended the other reasons for patient exclusions. This response is adequate and no further information/analysis is required.

30. Please list the symptom scores of the 43 subjects with insufficient symptoms, state the reason that the 6 subjects failed to meet inclusion/exclusion criteria, explain why 9 subjects were not randomized because of too severe disease, and state what the intercurrent illness, adverse events and unspecified reasons were in subjects which precluded randomization in Study #31.

Sponsor response: All six subjects who failed to meet inclusion/exclusion criteria had abnormal laboratory values prestudy. Nine subjects were not randomized because of too severe disease. For these subjects, their rhinitis symptoms were

so severe that they required prohibited concomitant medication(s) and, therefore, they were disqualified. One subject was not randomized due to an adverse experience (fungal infection of right arm/right face) in the baseline period. The one subject not randomized due to intercurrent illness had influenza. Eight subjects had unspecified reasons according to subject accession logs. Upon CRF examination, five of the subjects had insufficient symptom scores, Three others were too symptomatic and could not tolerate their symptoms during the single-blind period of the study.

Reviewer comment: The sponsor has submitted the requested symptom score listings and adequately defended the other reasons for patient exclusions. This response is adequate and no further information/analysis is required.

31. For Study #26, please list the symptom scores of the 35 subjects with insufficient symptoms, state the reason that the 11 subjects failed to meet inclusion/exclusion criteria, explain why 5 subjects were not randomized because of too severe disease, and state what the intercurrent illness and adverse events were in two subjects, each which precluded randomization.

Sponsor response: Of the 11 subjects who failed to meet inclusion/exclusion criteria, eight had abnormal laboratory values prestudy, two refused to abide by contraceptive stipulations, and one had a history of seizures which as discovered postscreening. Five subjects were not randomized because of too severe disease. For these subjects, their rhinitis symptoms were so severe that they required prohibited concomitant medications(s) and, therefore, they were disqualified. Of the two subjects not randomized due to adverse experiences, one had drowsiness and the other had dry eyes and was tired. Of the two subjects that were not randomized due to intercurrent illness, one had a sore throat and the other had sinusitis.

Reviewer comment: The sponsor has submitted the requested symptom score listings and adequately defended the other reasons for patient exclusions. This response is adequate and no further information/analysis is required.

32. Case report forms for any subject that withdrew prematurely from a US allergic rhinitis trial in NDA 20-114 or due to an adverse event which has not yet been requested or submitted should now be submitted (as a separate item) along with a tabulation of the reason for premature withdrawal by patient number.

Sponsor response: Volume 70 of this submission contain additional US-study CRFs originally submitted with the June 1994 Safety Update. Volumes 80-91 of the submission contain CRFs not previously documented.

Reviewer comment: The aforementioned CRFs are summarized and commented upon below.

The following eight CRFs are from patients who prematurely withdrew from Trial 255: Placebo-controlled evaluation of the effectiveness and safety of Astelin NS as adjunctive therapy to astelin tablets in the management of seasonal allergic rhinitis. It cannot be determined whether these patients were receiving the azelastine nasal spray or placebo; however, all patients were receiving azelastine tablets.

CRF/Subject 487: This was a 31 yo Oriental male with unremarkable past medical history and normal screening physical and laboratory examinations. Patient discontinued therapy after seven days secondary to viral gastroenteritis (diarrhea, stomach cramps). Exit physical and laboratories were normal. This was appropriately characterized as an intercurrent illness.

CRF/Subject 570: This was a 13 yo Oriental female with unremarkable past medical history and normal screening physical and laboratory examinations. Patient discontinued therapy after seven days secondary to sore throat which began one day after starting double-blind portion of trial and persisted for two weeks after discontinuing all medications. This was characterized as an intercurrent illness. Exit physical examination was normal without throat findings. This patient may have been misclassified; however, it is difficult to attribute the AE to drug. No further information is required.

CRF/Subject 14: This was a 53 yo white female with unremarkable past medical history and normal screening physical and laboratory examinations. Patient discontinued on Day 1 of single-blind portion of trial secondary to inability to comply with study scheduling demands. It appears that this CRF is appropriately classified and no further information is required.

CRF/Subject 58: This was a 17 yo white female with unremarkable past medical history and normal screening physical and laboratory examinations. Patient discontinued on Day 4 of single-blind portion of study secondary to the intercurrent illness of viral gastroenteritis which resolved 5 days after discontinuing drug. It appears that this CRF is appropriately classified and no further information is required.

CRF/Subject 114: This was a 45 yo white female with unremarkable past medical history and normal screening physical and laboratory examinations. Patient discontinued on Day 4 of single-blind portion of study secondary to onset of canker sores in mouth (also noted on exit physical examination). Patient also noted "itchiness" on hands which appears to be dyshidrotic eczema. This case

was classified as a failure to qualify; however, it could also have been classified as intercurrent illness. In any case, no further information is required.

CRF/Subject 185: This was a 30 yo white female with unremarkable past medical history and normal screening physical and laboratory examinations. The patient discontinued on Day 6 of single-blind portion of study secondary to viral gastroenteritis (nausea/vomiting/diarrhea). It appears that this CRF is appropriately classified and no further information is required.

CRF/Subject 229: This was a 15 yo white male with unremarkable past medical history and normal screening physical and laboratory examinations. Patient discontinued before dosing secondary to confirmation of diagnosis of fractured vertebrae secondary to sports injury which occurred before patient was screening for trial. This is unrelated to study drug and it appears that this CRF is appropriately classified and no further information is required.

CRF/Subject 233: This was a 13 yo white female with unremarkable past medical history and normal screening physical and laboratory examinations. Patient discontinued on Day 7 of single-blind portion of trial secondary to sore throat. No further information is required.

Overall impression: Many of these subjects were prematurely discontinued secondary to bona fide intercurrent illnesses. No further information is required and the sponsor response is adequate.

33. Regarding Study #32, it is unclear what the statement on page 08 9003 which states that the incidence of elevated SGPT (ALT) in all subjects was 13% and in at risk subject 8% is based on since, according to table #35 which reports the data on subjects with baseline normal values, the incidence of high ALT in the q day azelastine group was 6% not 8% and according to table #36 which reports lab data on all subjects regardless of baseline value, the incidence of high ALT is 11.11% not 13%.

Sponsor response: The incidence rates, as reported in the tables, are correct. The rates reported in the narrative (page 08 9003) is, as you noted, incorrect.

Reviewer comment: This response is adequate.

34. Regarding Study #32, please provide a list of the ALT values above normal in this trial, broken down by subject. This will allow us to ascertain if there are any outliers responsible for the greater incidence of high ALT in subject who received azelastine once a day.

Sponsor response: The requested table is provided.

Reviewer comment: This table indicates that there are 5 patients in the azelastine q day group who had a higher "on-study" ALT than in the screening phase of the study. This is versus 1 in the azelastine BID group, 2 in the CTM group and 1 in the placebo group. Of note, for clinically significant on-study ALT elevations (ie doubling from baseline), the breakdown is 2 (q day), 1 (BID), 1 CTM and 0 placebo. This appears to indicate that "outliers" are not disproportionately distributed. No further information is required.

35. To get a better understanding of the degree of glucose elevation in the >60 age group, please submit the individual glucose values at baseline, during the trials and at follow-up for subjects over 60 years of age who received azelastine.

Sponsor response: A list of glucose values at baseline, during the trials and at follow-up for subjects >60 who received azelastine is provided. It should be noted that protocols did not mandate that glucose samples be obtained under fasting conditions.

Reviewer comment: In all the azelastine studies, there were six patients who had "on-study" glucose elevations (1 azelastine q day, 2 azelastine BID, 1 CTM and 2 placebo). These elevations are, for the most part, relatively small (largest is 191, most in 135-160 range) and equally distributed. No further information is required and this response is adequate.

36. You must establish a link between the formulation and the spray pump system used in the clinical study and the final TBM formulation and spray pump system.

Sponsor response: This information, though previously submitted in February 1992, is contained in Volume 42, Attachment 66 of this submission.

Reviewer comment: This information will be reviewed by the chemistry reviewer.

37. In vitro studies examining the stability/compatibility of azelastine Hcl nasal spray with drug products that may be administered concomitantly via the same route of administration are recommended.

Sponsor response: As stated by the FDA, the above is a recommendation that does not impact on the approvability of this application.

Reviewer comment: The sponsor is correct in pointing out that the comment was a recommendation. This issue may serve as a discussion point at the advisory

committee meeting.

This concludes the Not Approvable questions/issues posed in the azelastine nasal spray letter. We also asked that the sponsor address the safety issues posed in the NDA. These start with question #6 of the NA letter and are reviewed below.

Tablet Questions

6. Regarding the 44 yo male in the response to comment #8, please contact the investigator and attempt to obtain any additional lab tests, ECGs and serum levels of azelastine and its metabolite.

Sponsor response: There is no further information available for this subject.

Reviewer comment: This response is adequate.

7. Regarding the last subject on Table 6 of the submission of February 11, 1993, the ECGs that have been submitted as part of the CRFs have not been read and are not labeled with regard to timing relative to the adverse event. Please label the ECGs and resubmit them along with an interpretation of the ECGs.

Sponsor response: This subject was a 37 yo female reporting bradycardia as part of Japanese postmarketing surveillance. No ECGs or laboratory tests were performed. The ECGs related to the previous subject in the table (an 83 yo female) and are included in Volume 43, Attachment 2.

Reviewer comment: ECG interpretations are provided. This patient had similar symptoms and ECG findings after discontinuation of medicines. It is also noted that the patients symptoms responded to "digestive medications." This response is adequate.

8. Regarding Subject #338 in study #240L, we note that at the start of the open-label period the subject ALT was elevated. Had this subject been enrolled in the double-blind therapy? If so, did the subject receive azelastine and, if so, what were her liver function tests over the course of double-blind therapy?

Sponsor response: This subject, a 50 yo female, was enrolled in double-blind therapy during study #24 and randomized to receive theophylline 300 mg bid during the double-blind portion of the study.

Reviewer comment: As noted, this subject did not receive azelastine during double-blind portion of trial. Review of the CRF indicates that the patient had an

ALT of 94 on study screen and remained persistently elevated throughout the trial (69, 95 on follow-up, 71 on second follow-up). Patient was referred to private physician for further follow-up. It appears that this patient had pre-existing LFT problems. This response is adequate. No further information is required.

9. Regarding Subject #46 in Study #97, had the subject been on azelastine between April 1988 and August 1988.

Sponsor response: No. This patient was randomized to placebo during the double-blind portion of study #97.

Reviewer comment: This response is adequate.

10. Regarding subject #83 in Study #97, please indicate whether this subject received azelastine from December 1987 through March 1988.

Sponsor response: This subject did not receive azelastine during the double-blind portion of the study (dates given above).

Reviewer comment: This response is adequate.

11. Regarding subject #241 in Study #23, please submit the values for cardiac intervals for baseline and on-study visits.

Sponsor response: Subject #241 received azelastine 8 mg BID. The requested ECG intervals are given below.

	PR	QRS	RR	QT	QTc
Baseline	.140	.070	.971	.383	.389
Week 5	.140	.070	1.001	.481	.481

Reviewer comment: The week 5 ECG is of very poor technical quality (ie motion artifact so baseline is very hard to determine). However, there does appear to be some morphological repolarization changes associated with the prolonged QTc noted above (ie. T-U notching). This ECG has previously been considered in the ECG database and it has been evaluated relative to placebo-dosed patients. Nevertheless, this patient exhibited altered cardiac repolarization (qualitative and quantitative) while on oral azelastine therapy. This should be reflected in product labeling (see labeling review).

12. Regarding subject #17 in Study #126, please submit better quality copies of

the subject's ECGs as well as their interpretation.

Sponsor response: The requested copies are submitted in Volume 44, Tab 7a.

The cardiologist interpretation of the ECG are noted below.

Date	HR	PR	QRS	QT	QTc	Interpret
3/1/85	88	.13	.06	.360	.430	WNL
4/19/85	107	.13	.08	.320	.427	SI Tachy
5/23/85	107	.14	.06	.310	.414	SI Tachy

Reviewer comment: This response is adequate.

13. Please submit an English translation of the CRF for Subject #17 in Study #126.

Sponsor response: The requested CRF is submitted in Volume 45, Tab 8a.

Reviewer comment: This patient completed the trial. The patient experience prolonged episode of increased SOB secondary to URI. It was also noted that patient had abnormal cardiac repolarization on screening ECG which was not noted on any on-study ECGs. This response is adequate.

14. Regarding subject #148 in Study #24, please have the intervals on this subject's ECG measure by hand by a cardiologist and interpreted.

Sponsor response: This subject receiving azelastine 4 mg bid with concomitant theophylline. The ECG were interpreted by an independent cardiologist and the intervals are summarized in the table below.

Visit	HR	PR	QRS	QT	QTc
3	97	.160	.070	.400	.508
4- 4hr p dose 8hr p dose	67 88	.160 .150	.080 .070	.430 .380	.453* .460
5	68	.150	.080	.420	.447*
7	100	.150	.080	.410	.473*
19	80	.150	.080	.405	.467*

*Indicates presence of U wave.

The consulting cardiologist, Dr. Joel Morganroth, believes that this patient had a congenitally prolonged QT syndrome.

Reviewer comment: I concur with Dr. Morganroth. This patient had a prolonged QTc at baseline (508) which did not change with azelastine therapy.

15. Regarding subject #17 in Study #194, the computer readings of the ECGs in this subject's CRF were different from the narrative description of the QT/QTC intervals for this subject. Please specify the ECGs upon which you based your report. In addition, please indicate if azelastine levels were measured.

Sponsor response: The initial ECG values cited machine calculated values. The narrative description were based on hand calculated ECG values of the same ECGs performed by Dr. Joel Morganroth. There were no drug levels measured in this subject.

Reviewer comment: This response is acceptable.

16. With regard to the pharmacokinetics of azelastine, please comment on the relative potency of the metabolite and the parent compound as well as comment on the activity of the other proposed metabolites of azelastine. In addition please describe what information you have concerning the specific microsomal enzymes are involved in the metabolism of azelastine.

Sponsor response:

16a. Regarding the potency of the identified and proposed metabolites....

	Allergic Histamine Release IC50	Ca Ionophore Induced Histamine Release	Inhibition of HETE formation at 20 uM	Inhibition of LTB4 Synthesis at 20 uM	Inhibition of LTC4 Formation IC50
Azelastine	4.6 uM	2.7 uM	16 +/- 6	7.5 +/- 1.5	21.2 uM
Desmethyast	3.9 uM	0.8 uM	35 +/- 7	85.8 +/- 7.7	16.4 uM

Therefore, overall the metabolite possesses a comparable potency to the parent compound. Other metabolites that have been identified are not produced in humans. Nevertheless, they were all found to be weaker than azelastine or desmethylazelastine as determined by their binding constants.

16b. Regarding the specific microsomal systems involved in the metabolism of azelastine.

This has been previously addressed in Question 1e of the nasal spray NA letter. Suffice to say, in vitro and in vivo studies indicate that azelastine will not interfere (or be interfered by) with the metabolism of 3A4 substrates.

Reviewer comment: This response is acceptable. The specific cytochrome(s) responsible for the biotransformation of azelastine remains to be identified.

17. Please explain why the mean Cmax and tmax data in Study #8 for the parent compound when administered IV has been omitted. Please supply this information.

Sponsor response: When a single dose is administered IV, the Cmax and Tmax correspond to time = 0. However, no adequate sample can be taken at time = 0. The time of first sampling after IV administration was 0.17 hours at which time the Cmax was 5.3 ng/mL. No metabolite was detectable at this time.

Reviewer comment: This response is acceptable.

18. The following information should be submitted on the subjects circled on the scatterplots taken from the NDA:

-Dose and duration of drug
-Values of lab test in each subject over the course of the trial
-Identify whether the subject was symptomatic (N/V/abd pain/hepatitis/changes in olfaction/jaundice/etc.)
-Indicate whether or not these changes reverted to normal
-Values of drug levels (if available)
-Listings of concomitant medications
-CRFs

Sponsor response: The sponsor has provided all the requested information in Table 16.1 (Volume 46, Page 26-49). Azelastine levels were not present for the majority of the patients. For those patients with available levels (Sub 160, Study 185; Sub 24, Study 58; Sub 51, Study 97; Sub 35, Study 185; Sub 49, Study 185; Sub 163, Study 185), the parent and metabolite values were consistent with the expected population concentrations of the moieties. Elevation of liver enzymes was reported as an adverse event for one patient (Subject 49, Study 185) who was a 20 yo white male receiving azelastine 2 mg BID from 11/26 to 12/3. The subject had minimally elevated LFTS which increased after one week of azelastine (AST 53 to 178; ALT 63 to 335; LDH 239 to 288). These returned to pre-drug levels after one week. This patient was given the final diagnosis of asymptomatic hepatitis which, in the opinion of the investigator, was present prior to the study. The remainder of the subjects were also completely asymptomatic.

Reviewer comment: This response is acceptable. LFT elevation will be reflected in product labeling.

19. Because the change from baseline vs time graphs included in the NDA depict time points over the course of the studies where the differences between azelastine and placebo may be statistically significant, please calculate the change from baseline to each timepoint at which AST, ALT, alkaline phosphatase, total bilirubin and LDH were measured and the statistical significance of the difference between azelastine and placebo treated subjects should be reported for both rhinitis and asthma trials. In addition, to ascertain whether there are outliers at each of these timepoints who experienced significant elevations, scatterplots similar to those included in the NDA should be constructed for each time point. . Outliers will have to be evaluated for clinical significance as discussed above.

Sponsor response: Data were evaluated separately for the following groups:

-Subjects exposed in short-term controlled SAR trials
-Subjects exposed in long-term controlled SAR and PAR trials
-All subjects exposed in multiple-dose controlled asthma trials

For each group, subjects 18 years and above and subjects 18 years and below were evaluated separately. Changes from baseline to each timepoint and to last on-therapy value. Changes for azelastine-treated subjects were compared to the placebo treated subjects by ANOVA. The number of subjects at each timepoint depends upon the number of subjects who had blood analyses at the designated timepoint.

The results of these analyses are shown in table 17.1 (Volume 46, Page 50). Statistically significant differences between the treatment groups are occasionally observed. For alkaline phosphatase, statistically significant differences are observed at Week 2 for subjects under 18 in long-term SAR/PAR trials (-14 U/L for azelatine versus +8 U/L for placebo). Statistically significant changes from baseline for total bilirubin are observed at Weeks 1, 16, 28 and 40 for subjects over 18 in asthma trials (-0.02, -0.02, 0.01 and 0.01 U/L, respectively for the azelastine group). For LDH, statistically significant differences are observed at Week 8 (0.97 U/L) for subjects 18 years and older in asthma trials. For ALT, statistically significant differences were seen at Weeks 2, 4 and endpoint (2.39, 3.68 and 1.68 U/L, respectively) for subjects >18 in long-term SAR/PAR trials, and at Weeks 1 and 4 (5.41 and 4.97, respectively) in subjects >18 and at Week 4 (2.41) in subjects <18 in asthma trials. For AST, statistically significant differences are observed at Weeks 2 and 4 and endpoint (0.50, 1.90 and 0.49 U/L, respectively) in subjects >18 and at Week 8 (-3.86 U/L) in subjects <18 in long-term SAR/PAR trials, and at Weeks 4 and 8 (2.89 and 1.69 U/L, respectively) in subjects >18 in asthma trials. None of the above mean changes are related to dose or exposure.

Table 17.3 (Volume 46, Page 85) lists the outliers (3x upper limit of normal

at any time during the trial) for AST/ALT/Total Bili/alkaline phosphatase and LDH and clinical data summaries for these patients are provided in Table 17.4. The distribution of these outliers is summarized in the table below.

	Short Term SAR Trials		Long Term SAR/PAR Trials		Mult Dose Asthma Trials	
	Azelastine	Placebo	Azelastine	Placebo	Azelastine	Placebo
AST	-	1	-	1	13	9
ALT	-	2	4	-	19	10
Tot Bili	2	-	3	-	3	1
Alk Phos	-	-	-	-	6	8
LDH	-	-	1	-	2	1

Scatterplots for these parameters are also provided and inspection of these plots reveals a similar distribution of data points around the line of identity.

Reviewer comment: By and large, the mean changes are sporadic, small and bidirectional. Outlier analysis reveals that several outliers (as defined above) were due to baseline elevations and/or database entry errors. Several cases deserve mention and are briefly described below.

-Subject 30/Study 68 (azelastine 2 mg BID): This 24 yo white male had elevated LFTs at baseline (AST = 58) which increased to 106 at visit 4. Patient also had elevations of ALT (Max = 188 at Visit 4) which remained elevated at study end (93). Patient followed-up with personal physician but no further information was available. LFT elevation was reported as adverse event in the NDA.

-Subject 241/Study 23 (azelastine 8 mg BID): This 37 yo white male had elevated LFTs at Week 9 of open-label portion of asthma trial (ALT = 493, AST = 135, LDH = 239). All labs normalized one month after medication discontinuation. Patient remained completely asymptomatic and hepatitis/mononucleosis workup was negative. LFT elevation was reported as adverse event in the NDA.

-Subject 151/Study 23 (azelastine 4 mg BID): This 43 yo white female had maximally elevated LFTs at the endpoint of the 12 week asthma study (ALT = 142/AST = 99). Both labs normalized after two weeks of drug withdrawal. Patient remained asymptomatic but had "tender" liver on exit physical. LFT elevation was reported as adverse event in the NDA. Patient was subsequently lost to follow-up.

-Subject 32/Study 98 (azelastine 4 mg BID): This 45 yo white female had maximally elevated LFTs (ALT = 91/AST = 44) on Visit 8 after normal baseline labs. Labs normalized after one week. Patient remained asymptomatic. LFTs elevations were reported in the NDA.

Although these LFT laboratory elevations occurred at oral doses and systemic exposures higher than those expected from the nasal spray formulation, LFT elevations should be included in the product labeling (see labeling review).

20. In the analysis requested above, for timepoints at which a statistically significant difference between azelastine and placebo subjects is demonstrated, please comment on whether the change from baseline to that timepoint increases in a dose dependent manner.

Sponsor response: None of the significant changes noted above were dose-dependent.

Reviewer comment: This response is acceptable. As previously noted, the changes were generally small, bidirectional and sporadic. Furthermore, there was no evidence of dose-dependent changes in these parameters. As noted in the table above, the proportion of outliers was greater in the higher dosing groups; however, these were relatively equally distributed between azelastine and placebo treatment groups.

21. Please comment on the overall shape of the change from baseline versus week in study curves. In specific, for AST and LDH (asthma studies), the change from baseline rises until 30 and 16 weeks, respectively, at which time it changes direction and decreases. Is this change in direction due to a decrease in AST and LDH in the same subjects or did subjects with elevated levels withdraw from the trial at that point? An endpoint analysis of change from baseline over time may address this issue.

Sponsor response: An LOCF analysis for these two laboratory parameters was performed for the multiple-dose asthma studies and is summarized below.

	AST (mean change from baseline)			LDH (mean change from baseline)		
Timepoint	Azelastine	Placebo	p value	Azelastine	Placebo	p value
Week 1	1.75	-0.51	.14	-1.27	-2.88	.72
Week 2	1.87	-0.14	.15	-0.66	-1.83	.78
Week 3	1.81	-0.30	.13	-0.86	-2.80	.64
Week 4	2.30	0.31	.03	-0.31	1.33	.55
Week 8	1.87	-0.44	.02	-0.05	-3.04	.18
Week 12	1.91	0.25	.10	0.38	-0.06	.84
Week 16	1.82	0.20	.10	0.18	0.01	.94
Week 28	1.45	0.39	.29	2.03	1.82	.95

Week 40	1.33	0.47	.39	2.05	2.52	.88
Endpoint	1.15	0.44	.50	1.76	2.21	.89

This indicates that the small mean increase in AST in the azelastine group is seen by 2 weeks and remains stable with long-term treatment. The changes in LDH are small, similar to placebo, with no directional trend.

Reviewer comment: This response is adequate. No further information/analyses are required.

22. With regard to Figure VIII.H.50 in the NDA, please provide the following additional information

a. An explanation for the difference in change from baseline to Weeks 30-42 between azelastine and placebo treated subjects.

Sponsor response: This has to do with the number of subjects who exceed the "threshold" at each timepoint. Specifically, at Week 42, there were 9 subjects in the azelastine group who had changes in TGs (>80 mg/dL) versus 4 at week 30. In the placebo arm, there were 2 at week 42 versus 4 at week 30. This results in a higher group mean change for the azelastine group and a lower group mean change for the placebo group at Week 42 versus Week 30. The other subjects had changes of similar magnitude at each of the two timepoints.

Reviewer comment: This response is acceptable.

b. Identify outliers in this dataset by providing a scatterplot of change from baseline to Week 42 (and beyond if the data is available).

Sponsor response: These scatterplots are provided in Volume 47, Pages 274-277. Outliers (for triglycerides) are identified.

Reviewer comment: This response is acceptable.

c. Additional clinical information regarding any outliers including their TG values as well as follow-up data to determine if the effect was reversible should be submitted.

Sponsor response: This information is provided in Tables 20.1 and 20.2 (Volume 46, Pages 169-172).

Reviewer comment: Examination of these tables indicates that there is neither a consistency in the magnitude, numbers of patients or direction of the changes

from baseline over the course of the trials. This response is acceptable.

d. The statistical significance on this graph and whether there was dose-related response.

Sponsor response: The difference in the mean changes between azelastine and placebo groups in not statistically significant.

Reviewer comment: This response is acceptable.

23. To further address the issue of changes in TG values, we would like you to assess whether there is a relationship between change in TG values and weight change. One way in which this could be done would be to assess change in TG levels in subjects who experienced a significant weight increase versus those who did not.

Sponsor response: This analysis was carried out examining the relationship between those patients who had a significant weight increase (>5%) and TG levels. Azelastine versus placebo was compared in the long-term SAR/PAR studies and the multiple dose asthma studies separately. The following results were noted:
Rhinitis studies: Only 7 azelastine subjects and no placebo subjects had significant weight increases, and thus the results could not be evaluated as planned.

Asthma studies: For subjects 18 years and older, the mean TG changes were 20 mg/dL for the group with a non-significant weight increase and 35 mg/dL for the group with a significant weight increase. However, this group difference of 15 mg/dL was similar to that of the placebo subjects, who showed a mean TG change of 3 for the non-significant weight group and 15 mg/dL for the significant weight group. This difference was not statistically significant (p=.964). Similar non-significant trends were seen for subjects less than 18 years of age.

Reviewer comment: This response is acceptable. There does not appear to be a correlation between weight increase and TG levels.

24. Please comment on the trend toward a significant increased incidence of palpitations in treated subjects in the asthma trials.

Sponsor response: In the azelastine Safety Summary for all US multiple-dose asthma studies, the incidences of palpitations were given as 1.0% for azelastine subjects and 0.2% for placebo subjects. In the ISS, information was available from 626 more azelastine subjects and 438 more placebo subjects. The reported

incidences for palpitations were 0.8% for azelastine and 0.5% for placebo. This difference was not statistically significant (p = 0.46).

Reviewer comment: This response is acceptable. No further information or analyses are required.

25. Please provide graphs depicting mean change from baseline versus weeks in study for BUN, creatinine and uric acid for both asthma and rhinitis trials.

Sponsor response: The mean changes versus time are shown in Volume 47, Pages 279-282. The mean changes in the azelastine group are small, similar to placebo and support the conclusion that azelastine treatment does not effect these parameters.

Reviewer comment: The sponsor has submitted the requested graphs and appropriately interpreted the results. No further information is required. This response is adequate.

26. With regard to neutrophil and lymphocyte counts, please submit the following information:

a. Reanalyze and present the change from baseline to endpoint comparison between treated and placebo subjects in both asthma and rhinitis trials using the absolute values of neutrophils and lymphocytes.

Sponsor response: The absolute change from baseline to last on-therapy valued was computed for each subject. Data were evaluated separately for the following groups of subjects:

-Short term SAR trials
-Long-term controlled SAR/PAR trials
-Multiple-dose asthma trials

Subjects 18 and older and subjects 18 and your were analyzed separately. Except for one occurrence of a statistically significant difference (p = 0.046; for PMN's in subjects 18 and over in short term SAR trials), there were no statistically significant findings.

b. Using absolute values, scatterplots for both lymphocytes and neutrophils for pre versus post-treatment values in the rhinitis and asthma trials should be submitted.

Sponsor response: These scatterplots are submitted in Volume 47. Visual inspection of these plots reveals a similar distribution of the datapoints around the line of identity.

c. To assess changes from baseline over the course of the trial, a graph using absolute values and depicting change from baseline to each timepoint at which values were measured in the trials versus weeks in the study should be submitted.

Sponsor response: The suggested/requested graphs are submitted in Volume 47, Pages 311-318. The mean changes in the azelastine an d placebo groups are generally small for both parameters.

d. Specific information regarding the outlier in the rhinitis trials who experienced a post-treatment PMN values of close to 0% should be submitted. This should include a listing of all hematologic values over the course of the trial and at follow-up, a list of concomitant medications used, a discussion of the clinical circumstances associated with the decrease in PMN count (infections, clinical workup, etc) as well as an explanation and the subject's CRF. Similar information should be submitted regarding the subjects in the placebo group who also experianced a post-treatment values close to 0%.

Sponsor response: This value of close to 0% for the patient in question represented a transcription error. The actual value is 54% (baseline was 52%).

Reviewer comment for response a-d: These responses are adequate. No further information is required.

27. Please submit scatterplots for RBCs and monocytes for pre- versus post-treatment values in rhinitis and asthma trials as well as graphs of change from baseline versus weeks in study for these parameters.

Sponsor response: The requested scatterplots are submitted in Volume 47, Pages 319-338. Comparison of these plots reveals a similar distribution of the datapoints around the line of identity. There are also graphs comparing azelastine to placebo for changes in RBCs and monocytes over time (Volume 47, Page 339-343). These changes in both parameters are small and similar in magnitude. There is only one occurrence of a statistically significant difference between azelastine and placebo groups (monocytes at Week 1 for long term SAR/PAR for subject >18 years old).

Reviewer comment: This response is adequate. There does not appear to be an effect of azelastine on these hematologic parameters.

28. With regard to pulse rate, please submit scatterplots of pre- versus post-treatment pulse rate for the asthma and rhinitis trials with separate plots for the long and short term rhinitis trials. In addition, graphs depicting change in pulse rate from baseline versus weeks in trial should also be submitted for both asthma and rhinitis trials. The data should be evaluated for statistically significant

differences between treated and placebo subjects at each timepoint, both for the overall azelastine groups as well as by dose. For those timepoint at which a significant difference is noted, additional scatterplots should be submitted.

Sponsor response: Data were evaluated as per the above analyses. Comparisons of the plots for the azelastine and placebo groups reveals a similar distribution of the datapoints around the line of identity. The summary statistics for the changes in pulse rate (by study type) from baseline at each timepoint and endpoint in Table 34.1.

Long-term SAR/PAR Trials (mean change from baseline)

	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Endpoint
Azelatine	1.27*	1.18*	0.56	0.34	2.02	1.33	0.79*
Placebo	-0.33	-0.19	-0.29	-0.81	-0.26	-1.15	-0.66

*Indicates statistically significant difference

Multiple-Dose Asthma Trials (mean change from baseline)

	< 1 Week	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10
Azelatine	0.13	1.57*	0.81	0.15*	1.71*	-0.17*	1.80*
Placebo	-0.21	-0.53	-4.38	-1.12	-0.70	-1.67	-0.60

*Indicates statistically significant difference

Multiple-Dose Asthma Trials (mean change from baseline)

	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 32
Azelatine	0.21*	2.10*	-0.55	-0.04	-0.77	-2.24	-0.63
Placebo	-1.17	-1.57	-1.29	-1.12	-1.09	-2.15	-1.30

*Indicates statistically significant difference

Multiple Dose Asthma Trials (mean change from baseline)

	Week 36	Week 40	Week 44	Week 48	Endpoint
Azelatine	-0.17	-0.81	-0.18	0.24	0.70
Placebo	0.01	-2.66	-2.72	-2.87	-0.21

*Indicates statistically significant difference

There is no evidence that the mean changes during azelastine treatment are dose related.

Reviewer comment: The mean changes in the azelastine and placebo groups are small, variable in direction and of similar (absolute) magnitude. There is little evidence to support the hypothesis that azelastine has an effect on pulse rate. This response is acceptable.

29. Please submit scatterplots (in similar format to above) for systolic and diastolic blood pressure.

Sponsor response: The requested scatterplots and week-by-week comparisons are provided. Comparison of the scatterplots reveals a similar distribution of datapoints around the line of identity for both treatment groups for both BP parameters. There are isolated occurrences of statistically significant differences between the treatment groups in the week-by-week analyses. The mean changes in all groups are small and similar in magnitude. There is no evidence of an azelastine dose-related effect on systolic or diastolic blood pressure.

Reviewer comment: This response is adequate. There is no evidence of an effect of azelastine on systolic or diastolic blood pressure.

30. Please submit scatterplots from pre- versus post-treatment weight in the rhinitis and asthma trials.

Sponsor response: Scatterplots of pre- versus post-treatment changes in body weight are shown in Figure 36.1 (Volume 47, Page 415-417).

Reviewer comment: Analysis of these scatterplots reveals a very tight regression with few, if any, significant outliers. This response is adequate and no further information/analyses are required.

This concludes the additional responses requested from the Allergic Rhinitis azelatine tablet NDA The following section contains the review of the Safety Update #2 which contains information accumulated since the June 30, 1993 submission of the Safety Update submitted in support of NDA.

SAFETY UPDATE (Containing all additional information since June 30, 1992).

Reviewer comment: The format of this section of the review will be similar to the original MOR of the ISS for NDA 20-114. This will allow for ease in comparison of safety data.

Extent of Exposure:

Since the original review, there have been two additional controlled clinical trials (#254 and 256) in subjects with allergic rhinitis involving the nasal spray formulation that have resulted in 182 additional exposures to azelastine nasal solution (2 sprays BID) , 80 to positive control (Vancenase AQ) and 183 to placebo. Thus, to date, 2142 subjects have participated in controlled US clinical studies of azelastine nasal solution with 1087 exposed to the azelastine nasal

solution, 393 to positive controls and 662 to placebo. The two recent studies were only 2 day "park" studies. Therefore, the long-term US azelastine nasal spray exposure is unchanged.

There have been a total of 30 European clinical trials of azelastine nasal solution. These involved 1526 azelastine nasal spray treated subjects, 927 positive control treated subjects and 336 placebo treated subjects. The duration and extent of exposures for these additional patients has been commented on previously (see Question #2 of the 20-114 NA questions).

Since the submission of NDA there have been 4 additional US clinical pharmacology studies (#278, 279, 282 and 283) involving a total of 72 healthy subjects. These crossover studies resulted in 237 additional exposures to azelastine (one week of 4 mg BID). Overall, 351 subjects participated in the clinical pharmacology studies resulting in 880 azelastine exposures, 71 positive-control exposures and 77 placebo exposures.

Since the submission of NDA there have been two additional US controlled clinical studies (#280, 281) in subjects with asthma. These were 13 week steroid-sparing trials that have recently been completed (but not submitted) and resulted in 216 azelastine exposures (4 mg BID) and 212 placebo exposures. To date, 6185 subjects have participated in studies of the azelastine oral formulations (3145 to azelastine, 1255 to one of two positive controls (albuterol or theophylline) and 1993 to placebo).

Since the last update, there have been additional European clinical studies (tablet, 4 mg BID) involving 452 patients. There have been four asthma studies (#284, 286, 289, 292) and four dermatology studies (#285, 288, 290, 293). This raises the total number of persons exposed in Europe to 2208 azelastine, 822 positive control, 826 placebo.

Additional US Clinical Experience

Clinical Pharmacology Studies:

Studies #278 and #279: These studies have been previously reviewed. They were open-label three period crossover studies investigating the interaction potential of erythromycin and ketoconazole with azelastine (4 mg BID). 12 subjects were enrolled in each study. There were no significant ECG findings in either study. Erythromycin did not raise azelastine plasma levels. Ketoconazole interfered with the azelastine assay and a pharmacokinetic interaction could not be determined.

Study #282: This was a four-period cross over bioavailability study (four 1 mg tablets, one 4 mg tablet, two 2 mg tablets, 4 mg solution involving 24 normal healthy subjects (12 male, 12 female). The study medications were generally well tolerated with no dropouts or serious adverse events.

Study #283: This was an open-label four period crossover bioavailability study similar to the one above involving 24 normal healthy subjects (12 male, 12 female). The study medications were generally well tolerated with no dropouts or serious adverse events. There were no clinically significant laboratory abnormalities in any of the aforementioned four studies.

Clinical Research Studies:

Nasal Spray Formulation:

Study #254: This was a randomized double-blind, parallel-group, placebo-controlled 2-day park study in subjects with SAR. 103 subjects were randomized to each treatment arm. There were no premature discontinuations due to adverse experience or intercurrent illness. Adverse events occurring more frequently in the azelastine arm included: rash (4.9% vs 2.0 %), taste perversion (6.8% vs 0%), nasal burning and paroxysmal sneezing (1.9% vs 0%).

Study #256: This was a randomized double-blind, parallel-group, placebo- and active (Vancenase AQ) controlled 2-day park study in subjects with SAR. 80 subjects were randomized to each treatment arm. There were no premature discontinuations due to adverse experience or intercurrent illness. Adverse events occurring more frequently in the azelastine arm included: taste perversion (azelastine 6.8%, vancenase 1.3%, placebo 1.2%), nasal burning (azelastine 3.8%, vancenase 1.3%, placebo 2.5%), dry mouth (azelastine 3.8%, vancenase 2.5%, placebo 0%), headache (azelastine 6.8%, vancenase 1.3%, placebo 0%), and paroxysmal sneezing (1.3% vs 0% vs 0%).

Oral Formulation:

Studies #280 and 281: These were identical 13 week inhaled steroid sparing trials using 4 mg azelastine BID (216 subjects) versus placebo (212 subjects). The most commonly reported azelastine-associated AEs in both studies included: taste perversion (40% and 32%), increased appetite/weight increase (29% and 21%), fatigue/somnolence (12% and 10%). Twenty four subjects discontinued from study 280 due to AE (20 azelastine/4 placebo). 12 of the azelastine discontinuations were due to taste perversion. Thirteen subjects discontinued from study 280 due to AE (13 azelastine/0 placebo). 6 of the azelastine discontinuations were due to taste perversion. There were no clinically significant

laboratory changes in either study.

Combined Nasal Solution and Tablet Study:

Study #255: This was a two day park study attempting to evaluate the adjunctive efficacy of azelastine nasal spray in patient taking open label azelastine tablets. 116 were randomized to active spray and 117 to placebo solution. In subjects who received the azelastine nasal solution, the most common AEs included taste perversion, headache and nasal burning.

Additional European Experience:

Nasal Spray Formulation:

Data from four placebo-controlled clinical trials (#294, 295, 296 and 297) involving 251 azelastine treated subjects have been added to the ASTA Medica safety report. In multiple-dose studies, AEs that occurred with an incidence of ≥1% in the combined azelastine-treated population are shown in the table below. The AEs from the new studies have been integrated into this table. Note also that the European studies also involve an "ultra-low" dose of azelastine (.28 mg/day which is equivalent to 1 spray/nostril/QDay). This has not been studied in the US and efficacy data for this strength/schedule has not been reviewed.

WHO Term	Az 1 puff/nostril/day n = 53	Az 1 puff/nostril/BID n = 1292	Az 2 puffs/nostril/BID n = 137	Placebo n = 303
Taste Perversion	3.8	5.8	7.3	0.7
Local Reaction	1.9	4.7	2.2	0.7
Headache	3.8	4.6	1.5	8.6
Rhinitis	0.0	3.5	5.1	6.6
Pharyngitis	0.0	2.2	2.9	1.7
Fatigue	1.9	2.2	0.7	0.7
Nausea	1.9	1.9	2.9	0.0
Epistaxis	0.0	1.8	2.2	3.3
Flu-like symptoms	0.0	0.9	1.5	2.6
Dyspnea	1.9	0.5	0.7	0.0
Sinusitis	0.0	0.5	1.5	0.7
Parosmia	1.9	0.2	0.0	0.0

Reviewer comment: The incidence of AEs in the European experience is best compared to the AEs seen in the US multiple-dose controlled clinical trials noted in

the table below (from original MOR, page 68).

Event	Azelastine	Positive Control	Placebo
Headache	18.1	12.8	12.9
Taste Perversion	15.4	-	0.3
Somnolence	12.0	16.9	5.7
Pharyngitis	3.2	5.8	1.9
Nasal Burning	3.0	0.3	1.9
Dizziness	2.9	2.6	1.6
Dry Mouth	2.9	4.5	1.9
Nausea	2.9	1.0	0.6
Epistaxis	2.3	1.9	1.6
Rhinitis	2.3	2.2	0.9
Fatigue	2.0	3.2	1.3
Myalgia	1.6	0.6	0
Paroxysmal Sneezing	1.4	0.3	0
Nervousness	1.3	0.6	0.6

Reviewer comment (cont'd): The relative percentages of these adverse reactions are consistent between the two tables. Some differences exist; however, this may be due to study design (ie. the manner in which adverse events were collected in the European trials) and nomenclature. For example, the European database refers to "local reactions" and "flu-like syndrome" which may be captured in the original table as "nasal burning" and "myalgia", respectively. For labeling purposes, I have asked Wallace (Hemsworth) to prepare a 1% table integrating all clinical trials AEs. This is to be presented separately (US/Foreign) as well as integrated and involved controlled clinical trials of all duration. Statistical comparisons of AEs across treatment arms will be provided.
Of note, less frequent adverse events (ie < 1%) appear to occur in similar numbers in the European and U.S. clinical databases.

Oral Formulation:

Asthma Studies: Compared to the ISS, 70 additional subjects with bronchial asthma received azelastine (4 mg BID) in four multiple-dose studies (#284, 286, 289, 292). The adverse event profile from these studies was similar to that previously noted.

Dermatologic Studies: Safety data from four multiple-dose dermatologic studies (#285, 288, 290, 293) involving 119 azelastine-treated subjects (1-2 mg BID) have been added. Again, the adverse event profile from these studies was similar to that previously noted. There were also two studies conducted investigating azelastine efficacy in rhinoconjunctivitis in a total of 128 patients. The single dose study (#301) had no adverse events noted. The multiple dose study had an adverse event profile similar to those previously noted.

Dropouts Due to Adverse Experiences of Intercurrent Illness:

US Experience:

In the 'new' US trials, a total of 47 subjects discontinued prematurely due to AEs or intercurrent illnesses. Taste perversion (19) and weight gain (12) were the most common adverse experiences for which subjects discontinued prematurely. These patients were all receiving azelastine 4 mg BID +/- another drug (ie. ketoconazole, etc.).

Reviewer comment: The CRFs for these patients have been submitted in Volumes 80-91 and have been reviewed in detail (see Question #32 above). Review of these CRFs reveals appropriate characterization of the reason for dropout; however, frequently it is difficult to assign a primary reason for dropout as some CRFs contain multiple simultaneously occurring AEs which were all characterized as leading to premature discontinuation. For example, Subject 102 in Trial #280 was receiving azelastine 4 mg BID and dropped out for "dizziness, sleepiness, and bad taste in mouth." Nevertheless, all these AEs were captured from the CRFs and no new (previously undescribed) adverse events were noted.

Nasal Spray Formulation:

From the additional nasal spray trials (previously described), five additional patients prematurely discontinued secondary to treatment intolerability. Four of these patients were receiving azelastine nasal spray and dropout was attributable to taste perversion and/or nasal burning.

Reviewer comment: These CRFs have been reviewed and the reasons for premature dropout have been appropriately categorized. In addition to integrating the adverse event profile across study site, I have also asked the sponsor to analyze the reasons for dropout by treatment arm for the nasal spray studies. This should integrate the additional European nasal spray studies and compare incidences across treatment arms.

Serious Adverse Experiences:

There have been no additional deaths or serious/unexpected adverse experiences from any azelastine formulation in any study site (Europe, Japan or US).

Vital Sign and Laboratory Data: The additional information/studies provided in the Safety Update do not change or modify conclusions reached in the previous MOR or in the first part of this review.

Demographics of Adverse Events/Laboratory Abnormalities/Vital Sign Data:

There were no notable differences in the incidence of any abnormalities of the above safety parameters based on subject demographics (ie. race, sex, weight, age) in the 'new' studies provided in the Safety Update.

Overall Reviewer Comments on Safety Update:

The additional safety information provided in the Safety Update does not alter the previously formulated conclusions based on the original MOR and the sponsor responses to the questions contained in the NA letter and answered/reviewed earlier in this document.

For labeling purposes, the sponsor has been asked to address issues of adverse event/premature dropout incidence as follows.

This document has been faxed to the sponsor as an information request.

MEMORANDUM

TO: George Hemsworth, PhD.
Wallace Laboratories

FROM: Peter K Honig, MD
Medical Reviewer

RE: NDA 20-114

DATE: August 22, 1995

This is to clarify the requested analyses discussed during our telephone conversation of earlier today.

For studies involving the azelastine nasal spray, please present

the following analyses/tables to facilitate our labeling review.

1. A >1% table of adverse events reported during the controlled trials of azelastine nasal spray. For comparative purposes, this should be presented as the U.S. and European (ASTA Medica) experiences separately and together (integrated). I realize that this may be difficult due to differing terminologies (eg. nasal burning vs local irritation) but please try your best. Statistical comparisons between treatment arms for adverse events should also be included. Adverse events from active control studies should also be included in the table; however, the statistical comparisons should be versus placebo. Clinical studies (blinded to the nasal spray) of all duration should be included; however, you may wish to present a comparison short studies (≤2 days) to longer studies to better characterize the time course (onset) of adverse events.

2. The same type of analysis should be conducted for premature discontinuations from clinical trials involving azelastine nasal spray.

Thank you for your attention to this matter. This information should greatly expedite the labeling review process. If any further information requests arise, I will be sure to notify you in similar fashion.

OVERALL REVIEWER CONCLUSIONS
(Based on sponsor responses to NA questions and Safety Update):

Based on the sponsor responses to the NA letter, NDA 20-114 is Approvable from a clinical standpoint. The Safety Update has provided additional information on the incidence of adverse events. For this reason, additional information/analyses on the incidences of adverse events in US/European trials involving the nasal spray formulation has been requested. This will facilitate the labeling review which will be contained in a separate document. The sponsor is in the process of modifying the proposed product label. This revised document will be submitted for review in the very near future (it should be here by the time this document is signed off).

Several issues contained in this submission need to be addressed by other members of the azelastine review team.

-Biopharm reviewer is to consult on Response 1e (population variability of azelastine) and to respond to 1g (in vitro salicylate-protein binding interaction with azelatine).
-Chemistry reviewer needs to address the sponsor response concerning the link between the formulation/pump device used in the clinical studies and

the TBM formulation/pump device (Question 36).

Several clinical/labeling issues remain to be resolved.

a. It appears that LFT elevation and subacute hepatitis may occur sporadically in patients exposed to azelastine. Whether the latter is extent of exposure dependent (these cases appeared in patients exposed to the oral tablet) or route of administration may be a question for the PADAC.

b. A similar question arises when one considers the cardiac effects of azelastine. The nasal spray has a favorable cardiac safety profile; however, there is evidence that, at higher doses (i.e. oral >4 mg BID), azelastine has a small mean effect on cardiac repolarization of 3-7 milliseconds and outliers with clinically significant ECG repolarization changes exist (see Question #11). Whether to include this in the nasal spray label (and where) may also be a suitable question for the PADAC.

c. The efficacy of the once-a-day (qAM) regimen of azelastine is not reproduced in two studies. The numerical magnitude of the effect of this regimen is considerably less than the BID regimen and never statistically superior to placebo in Study 26 (by Total Symptom Scores or for individual scores). Similarly, in Study 31, the qD regimen is numerically inferior to the BID regimen and sporadically statistically superior to placebo for Total Symptom Complex (never after Week 1). The physician's global assessment in this study also only supported the BID regimen. Thus, one pivotal study demonstrates sporadic efficacy of the QAM regimen versus placebo and the other demonstrates no statistically signficant efficacy. In any case, the 'approavability' of the once-a-day regimen based on one "positive" trial is another issue that may be considered by the PADAC.

d. It appears that, for whatever reason, there may evidence sex-specific adverse event reporting in the clinical trials. As stated in the review, a statement such as: "In controlled clinical trials, females report higher incidence of azelastine-related events such as taste perversion, dry mouth and fatigue." might be included in the product label. I am in favor of a qualitative statement (as above) because this phenomenon of differential reporting by sex is frequently seen in clinical trials and the reasons are unclear. It appears that there is no pharmacokinetic differences between men and women that could easily explain the phenomenon.

The DSI audits have been reviewed and reveal no discrepancies that warrant

further action or call into question the integrity of the data presented in the NDA 20-114.

The sponsor has been notified that their proposed product name, Astelin NS, is unacceptable. They have informed us that a new product name will be proposed.

Peter K Honig, MD
Medical Officer

Martin H. Himmel, MD
Medical Group Leader

cc:

HFD-155/NDA 20-114/Division File
/MO- Honig/Himmel
/CSO- Strange

MEDICAL OFFICER REVIEW

NDA:	**NDA #20-114 (Astelin NS)**
REVIEWER:	**Peter K Honig, MD**
PRODUCT:	**Azelastine Nasal Spray**
SPONSOR:	**Wallace Laboratories**
MATERIAL REVIEWED:	**DSI Audits of Pivotal Clinical Studies (#26 and #31)**
DATE:	**July 12, 1995**

DSI conducted audits of studies 26 and 31 (2 sites each). The DSI findings are summarized below.

Study #26:

A. Investigator: Storms
Inspector: Smith

8/66 subject charts were audited. There were no discrepancies between CRFs and source documents noted. There were two minor administrative issues/protocol deviations.

1. The CRF copies maintained by the investigator did not include copies of the labels from bottles of study drug dispensed to subjects during the study as required by the protocol.

2. There were no records available documenting the storage temperature of the freezer used to store azelastine plasma samples.

DSI Impressions: NAI

Reviewer comment: These are relatively minor problems that do not relate to data integrity or missing/incomplete safety data. No further action is required.

B. Investigator: Grossman
Inspector: Meyering

7/46 subject charts were audited. There were two discrepancies between CRFs and source documents noted. These involve efficacy parameters as shown below.

1. For patient #175 (visit 2), rhinitis efficacy parameters in CRF (rhinorrhea/congestion both mild to moderate) were not identical to symptom scores reported in patient notes (both severe).

2. For patient #193 (visit 2), the CRF scoring for mucosal edema was 2 (moderate) while it was scored as mild in the patient notes.

There were also some administrative/protocol deviations noted.

1. Examinations of each patient throughout the study were performed by different Physician's Assistants (4) contrary to protocol specifications.

2. There was no evidence of a protocol-mandated follow-up of an abnormally high glucose (283) at the final visit for patient #187.

DSI Impressions: VAI-2

Reviewer comment: Although there was evidence of efficacy data discrepancies, these were relatively minor and did not include missed/inaccurate safety data. Sloppiness in efficacy data transcription would tend to work against the sponsor and is, therefore, of less importance than "uncaptured" or inaccurate safety data. In this light, no further action is required.

Study #31:

A. Investigator: Kraemer
Inspector: Olson

7/48 subject charts were audited. There were no discrepancies between CRFs and source documents noted. Similarly, there were no administrative issues/protocol deviations noted.

DSI Impressions: NAI

Reviewer comment: No further action is required.

B. Investigator: Ratner
Inspector: Martinez

9/78 subject charts were audited. There were no discrepancies between CRFs and source documents noted. Similarly, there were no administrative issues/protocol deviations noted.

DSI Impressions: NAI

Reviewer comment: No further action is required.

OVERALL COMMENTS AND RECOMMENDATIONS:

The DSI audits reveal no discrepancies that warrant further action or call into question the integrity of the data presented in the NDA 20-114.

Peter K Honig, MD
Medical Officer

MAY 17 1995

MEDICAL OFFICER REVIEW

NDA#:	**20-114**
DRUG:	**AZELASTINE NASAL SOLUTION**
REVIEWER:	**PETER HONIG, M.D.**
CDER STAMP DATE:	**NOVEMBER 1, 1994**
DATE OF REVIEW:	**FEBRUARY 15, 1995**
DATE REVISED:	**MAY 17, 1995**
SPONSOR:	**WALLACE LABORATORIES**
MATERIAL REVIEWED:	**CLINICAL RESPONSE TO NOT APPROVABLE LETTER OF FEBRUARY 16, 1994 REGARDING CARDIAC SAFETY**

PREVIOUS PERTINENT SUBMISSIONS:

SEPTEMBER 2, 1993 AMENDMENT OF ORIGINAL ECG REPORT
SEPTEMBER 9, 1993 SUBMISSION OF ABNORMAL ECG ANALYSIS
APRIL 6, 1994 SUBMISSION OF ENRICHED CARDIAC DATABASE
JUNE 29, 1994 SUBMISSION OF ENRICHED CARDIAC DATABASE AND AZELASTINE-INHIBITOR INTERACTION STUDIES

BACKGROUND AND REVIEW OF PREVIOUS CARDIAC DATA:

A retrospective evaluation of the electrocardiographic data obtained during the conduct of clinical trials on azelastine in the treatment of allergic rhinitis (NDAS# 114) and asthma (NDA) was submitted in September 1992. An amendment to this submission in which additional subjects are included in the analysis was submitted on September 2, 1993.

An second post-hoc analysis of an "enriched" sample of electrocardiograms obtained during the conduct of the clinical trials was requested. The ECGs to be included in this analysis were clarified in an FDA-sponsor meeting in April 1993 and submitted on September 9, 1993. This was to be an analysis of all subject ECGs read as abnormal for any reason and ECGs from subjects who withdrew from studies regardless of reason. Both analyses were reviewed and are briefly summarized below.

Effect of single doses on QTc:

Treatment with 2 mg azelastine resulted in a mean 17.4 msec decrease in QTc interval compared to mean 1.8 msec mean increase in the placebo group (p=

0.01). Single doses of 4, 8, 12 and 16 mg azelastine resulted in mean increases in QTc ranging from 2.3 to 7.2 milliseconds. No proportional relationship of dose to mean QTc was evident.

Effect of multiple doses (steady-state) on QTc:

Treatment with azelastine 4 mg bid results in a 6.0 msec mean increase compared to a 2.5 msec decrease for placebo ($p = 0.001$). Treatment with 8 mg bid also resulted in a statistically significant mean increase of 9.5 msecs. The 2 and 6 mg dosing groups had mean increases in QTc of 3.8 and 1.7 msecs; however, this did not reach statistical significance.

The single dose studies do not have enough women in the treatment groups to allow meaningful comparisons (Table 19/Appendix). The multiple dose asthma studies reveal interesting comparisons. All azelastine treatment groups had larger mean increases for females compared to males. The placebo treatment revealed females to have larger decreases in QTc from baseline (Table 20/Appendix). This trend is duplicated for the 2 mg azelastine treatment group in the small numbers of subjects participating in the multiple dose allergic rhinitis trial.

Plasma azelastine and desmethylazelastine determinations were performed in five of the eight studies. No significant correlation coefficients were observed between the changes in the QTc and plasma azelastine (Table 28) or plasma desmethylazelastine levels (Table 28A) for any treatment group.

Reviewer comment: The report suggested that azelastine has an effect on cardiac repolarization across a population. The fact that no consistent dose-effect relationship is found may be due to small numbers of patients with differing metabolic capacities. The presence of pharmacokinetic and pharmacodynamic outliers heightens the concern over subgroups running into trouble with cardiac arrhythmias with this drug. Generally, the numbers involved in subgroup analyses are small and allow for limited statistical power; however, several interesting hypotheses may be generated. The finding of an enhanced effect on QTc change in women and the existing knowledge of hormonal influences on metabolic oxidative capacity of cytochrome P4503A4 (the cytochrome responsible for azelastine demethylation) is intriguing. The submission of September 9, 1993 was unsatisfactory in that no analysis or comparison to a control population was performed. The data and analyses of this "enriched" database were descriptive, submitted as tabulations, and did not contribute to the overall risk-benefit assessment of azelastine.

INTRODUCTION TO CURRENT SUBMISSION:

This submission is in support of NDA 20-114 which is for azelastine nasal solution for the treatment of seasonal allergic rhinitis. NDA

are not referenced or supported by this submission. Furthermore, there are further CMC "not approvable" issues to which the sponsor has not yet responded. The format of this review will be to restate the questions/issues posed in the not-approvable letter and the sponsor responses. Reviewer comments and questions will follow the sponsor response.

FDA Question 1: At present, a full risk-benefit assessment for azelastine is not possible. In preclinical studies, azelastine has been shown to have antifibrillatory and calcium channel blocking activity and the finding of a mean QTc increase in subjects taking azelastine versus subjects taking placebo suggests potential for cardiotoxicity in humans. The fact that no correlation between concentration (parent or metabolite) and effect (Qtc prolongation) has been demonstrated may suggest the presence of unmeasured cardiotoxic metabolites and/or metabolic outliers in the population. The following information is required to allow such an assessment.

1a. The "enriched database" submission of September 9, 199 is inadequate. No analyses other than that of ECG outliers were provided. The database must be reexamined with inclusion of comparable data from subjects receiving placebo during the clinical studies. The maximum change in Qtc from baseline should be determined for subjects with an abnormal ECG or who discontinued participation prematurely in placebo-controlled, single- and multiple-dose allergic rhinitis and asthma studies and compared between azelastine- and placebo-treated groups. Maximum change in Qtc should be based on evaluation of all ECGs (not just abnormal ECG) for each subject while he/she is on active treatment and identification of the ECG on which the Qtc is most prolonged. This evaluation may be made using lead II; however, all ECGs on which there is a 10% or greater prolongation in Qtc should be evaluated by a cardiology consultant for changes in T-U wave morphology. The data for single-and multiple dose trials should be evaluated separately, and the analysis should include assessment of dose-related effects, age-related effects, gender related effects, and duration-of-treatment effects. In addition to evaluating the mean and percent change from baseline, the data should describe the range of Qtc prolongation seen. An analysis should also be preformed comparing active treatment to placebo with regard to subjects with <10% increase in Qtc from baseline, 10%-15%, 15%-20%, and >20% increase over baseline. Because of possible diurnal effects on Qtc, the analysis should include a description of how the ECGs included in the analysis compare in the two groups with regard to the time they were collected. Finally, if serum drug concentrations are available, an analysis of change in Qtc by drug level (parent and metabolite) should be performed.

Sponsor response to 1a: The sponsor refers to the FDA-Wallace meeting of July 27, 1994 in which certain agreements were reached with regard to the reanalyses

of the enriched databases. Subsequent to the meeting, the following information on these enriched databases were to be provided:

- Maximum Qtc change from baseline in azelastine vs placebo groups.
- Consulting cardiologist evaluation of all ECGs which had a 10% or greater prolongation in QTc.
- Mean change, percent change, mean maximum change and percent mean maximum change in CTc for single and multiple dose trials with analysis of dose-, age-, gender- and duration of treatment effects.
- Sensitivity analysis comparing active vs placebo for the number of subjects with <10%, 10-15%, 15-20% and >20% increase in mean and maximum change from baseline.
- Description of how ECGs in two groups compare with regard to time of collection.
- When available, analysis of changes in QTc by drug level (P and M).

In addition, the full reports for the two drug interaction studies (ketoconazole and erythromycin) were to be included.

The enriched database consisted of baseline (pretreatment) ECGs and all on-therapy ECGs from azelastine and placebo treated subjects who i) had a "abnormal" on-therapy ECG or ii) prematurely discontinued clinical trial participation, regardless of reason. As in the prior sponsor-ECG analyses, the studies were grouped and analyzed as follows:

- Single/initial dose azelastine/placebo tablet (Studies 22, 23, 24, 35, 188 and 192).
- Multiple dose azelastine/placebo tablet (Studies 23, 24, 55, 56, 67, 68, 95, 97, 98, 187, 189, 190, 192, and 194).
- Multiple dose azelastine/placebo nasal spray (Study 29).

For all analyses, the response parameters included i) maximum on-therapy QTc and ii) mean on-therapy QTc. In several studies, only one on-therapy ECG was performed and, therefore, this is equivalent to the maximum on-therapy QTc. The above were analyzed as change and percent change from baseline by ANOVA. The data was also analyzed by race (white, non-white), sex (male, female),age (<40, >40) and duration of exposure (<3 months, >3 months). Sensitivity analyses were also performed (i.e. changes from baseline of <10%, 10-15%, 15-20% and >20%) using chi-square. Finally, for studies in which plasma concentration data were available (Studies 22, 23, 24, 97, 188, and 189), maximum QTc changes were analyzed vs parent, metabolite and metabolite/parent ratio by rank correlation analyses.

Results:

ECG data from 1268 subjects were available (860 azelastine, 408 placebo) was contained in the "enriched" database. 926 subjects had both a pre-treatment and on-therapy ECG required for analysis. The demographics by group are shown below.

Single/Initial Dose Group

Demo	Az 2 mg n=3	Az 4 mg n=180	Az 6 mg n=37	Az 8 mg n=5	Az 12 mg n=3	Placebo n= 165	Totals n=393
Male Female	3 0	110 70	28 9	5 0	3 0	109 56	258 135
Age-Mean ± SEM	35±9.1	35±1.2	42±1.9	28±4.6	27±9.0	35±1.1	35±0.7
Age <18 18-40 <40-60 >60*	0 2 1 0	30 85 57 8	1 14 21 1	0 4 1 0	1 1 1 0	21 95 40 9	53 201 121 18
Race W Black Other*	2 0 1	157 11 12	34 1 2	4 1 0	2 1 0	140 11 14	339 25 29

*Because n were small, for analysis purposes age was categorized at <40 and >40 and race was categorized as white or non-white.

Multiple Dose Group

Demo	Az<1 mg n=53	Az 2 mg n=75	Az 4 mg n=248	Az 6 mg n=35	Az 8 mg n=12	Placebo n=237	Totals n=660
Male Female	42 11	51 24	155 93	26 9	8 4	156 81	438 222
Age-Mean ± SEM	30±1.2	37±1.4	34±1.0	38±2.6	38±3.0	34±0.9	34±0.6
Age <18 18-40 <40-60 >60*	4 44 5 0	1 44 29 1	45 119 72 12	6 11 17 1	1 7 4 0	35 136 58 8	92 361 185 22
Race W Black Other*	51 2 0	67 5 3	222 8 18	30 2 3	12 0 0	207 18 12	589 35 36

*Because n were small, for analysis purposes age was categorized at <40 and >40 and race was categorized as white or non-white.

Nasal Spray Study Group:

Demographic	Az 2 mg Spray n=23	Placebo Spray n=13	Totals n=36
Sex Male Female	9 14	6 7	15 21
Age- Mean ± SEM	25±2.0	25±3.4	25±1.7
Age- <18 18-40 >40	6 15 2	4 8 1	10 23 3
Race- White Black	22 1	13 0	35 1

Mean Change and Percent Mean Change in QTc Analyses:

Single/Initial Dose Group Analysis:

	Change in QTc		Percent Change in QTc	
Treatment Arm	Mean Change	p Value*	Mean % Change	p Value*
2 mg (n=3)	-7.18	.77	-1.99	.69
4 mg (n=180)	0.68	.34	0.45	.30
6 mg (n=37)	11.65	**.008**	3.17	**.006**
8 mg (n=5)	-2.64	.98	-0.48	.965
12 mg (n=3)	-26.76	.14	-6.26	.149
Placebo (n=165)	-2.29	-	-0.34	-

*vs Placebo

Multiple-Dose Group Analysis:

	Change in QTc		Percent Change in QTc	
Treatment Arm	Mean Change	p Value*	Mean % Change	p Value*
<1 mg (n=53)	4.22	.50	1.17	.59
2 mg (n=75)	1.36	.96	.58	.95
4 mg (n=248)	7.22	**.017**	2.01	**.02**
6 mg (n=35)	5.20	.44	1.55	.44
8 mg (n=12)	3.57	.79	1.27	.74
Placebo (n=237)	1.53	-	.63	-

*vs Placebo

Multiple-Dose Azelastine Nasal Spray Group:

	Change in QTc		Percent Change in QTc	
Treatment	Mean Change	p Value	Mean % Change	p Value
2 spray/12h (23)	2.70	.76	0.87	.71
Placebo (n=13)	-0.27	-	-0.05	-

Mean Maximum Change and Percent Mean Maximum Change in QTc Analyses:

Multiple-Dose Group Analysis:

	Change in QTc		Percent Change in QTc	
Treatment Arm	Mean Change	p Value*	Mean % Change	p Value*
<1 mg (n=53)	5.68	.18	1.56	.16
2 mg (n=75)	2.20	**.015**	.80	**.02**
4 mg (n=248)	20.80	**.001**	5.36	**.001**
6 mg (n=35)	16.60	.35	4.35	.353
8 mg (n=12)	11.77	.99	3.17	.981
Placebo (n=237)	11.66	-	3.12	-

*vs Placebo

Sensitivity Analyses by Percent Increase in Mean Change from Baseline:

Single/Initial Dose Group:

	<10%		10-15%		15-20%		>20%			
Rx	N	%	N	%	N	%	N	%	Total	pvalue
2 mg	3	100	0	0	0	0	0	0	3	.98
4 mg	167	93	9	5	1	<1	3	2	180	.81
6 mg	31	84	3	8	2	5	1	3	37	.06
8 mg	4	80	1	20	0	0	0	0	5	.44
12 mg	3	100	0	0	0	0	0	0	3	.98
Pbo	156	95	7	4	1	<1	1	<1	165	-
Total	364	93	20	5	4	1	5	1	393	-

Multiple-Dose Group:

	<10%		10-15%		15-20%		>20%			
Rx	N	%	N	%	N	%	N	%	Total	pvalue
<1mg	50	94	3	6	0	0	0	0	53	.70
2 mg	69	92	4	5	2	3	0	0	75	.62
4 mg	227	92	12	5	7	3	2	<1	248	.25
6 mg	32	91	2	6	0	0	1	3	35	.36
8 mg	11	92	0	0	1	8	0	0	12	.20
Pbo	213	90	20	8	3	1	1	<1	237	-
Total	602	91	41	6	13	2	4	<1	660	-

Multiple-Dose Nasal Spray:

	<10%		10-15%		15-20%		>20%			
Rx	N	%	N	%	N	%	N	%	Total	pvalue
Spray	21	91	2	9	0	0	0	0	23	.27
Pbo	13	100	0	0	0	0	0	0	13	-
Totals	34	94	2	6	0	0	0	0	36	-

Sensitivity Analyses by Percent Increase in Mean Maximum Change from Baseline:

Multiple-Dose Group Analysis:

	<10%		10-15%		15-20%		>20%			
Rx	N	%	N	%	N	%	N	%	Total	pvalue
<1mg	50	94	2	4	1	2	0	0	53	.22
2 mg	68	91	4	5	3	4	0	0	75	.27
4 mg	199	80	25	10	15	6	9	4	248	.48
6 mg	30	86	2	6	2	6	1	3	35	.75
8 mg	11	92	0	0	1	8	0	0	12	.49
Pbo	198	84	25	11	8	3	6	3	237	-
Total	556	84	58	9	30	5	16	2	660	-

Reviewer comment: The analysis of the "enriched" database confirms that there appears to be a small effect of azelastine on cardiac repolarization. In fact, 4 mg azelastine in multiple dose studies is statistically significantly different from placebo for mean change/mean percent change and mean maximum change/mean percent maximum change. This was noted in the September 2, 1993 submission and is confirmed here. The fact that there does is no evidence of a dose-related effect on QTc may be attributable to the relatively small numbers of subjects treated with higher doses (6 mg and above). It is important that the magnitudes of the mean changes are small and there are dramatic outliers in repolarization effects as noted in the sensitivity analyses. The sensitivity analysis revealed a balanced distribution in >10% mean change from baseline in the multiple dose studies (10% (24/237) all doses of azelastine vs 8% (34/423) placebo. Consulting cardiologist reading of those ECGs did not reveal any significant morphological (qualitative) changes indicating altered cardiac repolarization. The small mean

cardiac effects at higher doses and the fact that the nasal spray formulation will allow for limited systemic exposure allows for a relatively high therapeutic index for this drug. In fact, pharmacokinetic studies indicate that the absolute bioavailability of the nasal spray is about 40%. To put the systemic AUC and Cmax exposures of the spray into perspective, a direct comparison between the steady-state PK parameters achieved after 2 sprays per nostril BID vs oral 2 mg tablet BID is included below.

Parameter	*2 sprays per nostril BID*	*2 mg tablet po BID*
*AUC (ng*hr/ml)*	*3.18*	*40.1*
Cmax (ng/ml)	*.307*	*3.89*

This indicates that there is considerable PK margin for the nasal spray formulation when considering safety data from the tablet formulations.

Subgroup Analyses:

Gender:

Single/Initial Dose Group- Mean Change Analyses:

	Males		Females	
Treatment	N	Mean %Change	N	Mean %Change
2 mg	3	-1.99	0	-
4 mg	110	.47	70	.41
6 mg	28	4.07	9	.35
8 mg	5	-.48	0	-
12 mg	3	-6.26	0	-
Placebo	109	-0.21	56	-.60

*Treatment by sex interaction p value = 0.448

Multiple Dose Group:

	Males		Females	
Treatment	N	Mean %Change	N	Mean %Change
< 1 mg	42	.97	11	1.92
2 mg	51	-.03	24	1.87
4 mg	155	1.63	93	2.64
6 mg	26	1.10	9	2.87
8 mg	8	.52	4	2.79
Placebo	156	.49	81	0.91

*Treatment by sex interaction p value = 0.968

Multiple-Dose Nasal Spray Group:

	Males		Females	
Treatment	N	Mean % Change	N	Mean % Change
Spray	9	-.49	14	1.74
Placebo	6	.91	7	-.87

*Treatment by sex interaction p value = 0.422

Reviewer comment: The sponsor also provided mean change analyses which yielded similar results. Percent change was presented above because it incorporates differing baselines in the comparisons.

Single/Initial Dose Group- Mean Maximum Change Analyses:
Multiple Dose Group:

	Males		Females	
Treatment	N	Mean Max %Change	N	Mean Max %Change
< 1 mg	42	1.46	11	1.92
2 mg	51	.24	24	2.00
4 mg	155	5.07	93	5.85
6 mg	26	4.06	9	5.20
8 mg	8	1.75	4	6.02
Placebo	156	2.95	81	3.45

*Treatment by sex interaction p value = 0.963

Reviewer comment: The sponsor also provided mean maximum change analyses which yielded similar results. Percent change was presented above because it incorporates differing baselines in the comparisons.

More importantly, these analyses indicate that there does not appear to be a gender mediated interaction with regard to azelastine's effect on cardiac repolarization. In the September 2, 1993 submission, there was a suggestion of a dose-related differential effect on cardiac repolarization (females > males). This hypothesis was based on unplanned subset analyses of small numbers of subjects and the finding is not confirmed or supported by the present analyses.

Age and Race Subgroup Analyses:

Reviewer comment: There were no meaningful or statistically significant age or race related interactions for mean or maximum change QTc parameters. For treatment groups which had adequate numbers of subjects for analysis (e.g. 4 mg single and multiple dose), there were minimal to no differences in absolute and percent changes from baseline versus placebo.

Duration of Exposure Analyses:

Multiple-Dose Study Group:

	Initial Dose		< 1 Month		1-3 Months		> 3 Months	
Rx	N	Max % Change	N	Max % Change	N	Max % Change	N	Max % Change
< 1mg	0	-	46	0.85	7	6.23	0	-
2 mg	0	-	54	0.55	21	1.46	0	-
4 mg	84	1.42	109	6.54	79	2.91	35	6.21
6 mg	28	3.00	12	1.52	7	1.88	7	10.99
8 mg	0	-	8	4.30	4	0.93	0	-
Pbo	107	0.70	107	2.37	53	3.80	35	4.13

*Overall Duration of Exposure Interaction p value = 0.005.

Reviewer comment: Although the overall p value for this interaction is significant, there is no clinically significant meaning that can be ascribed to this analysis. Firstly, many of the cells have very small numbers which allow for spurious conclusions. For active treatment cells that have substantial numbers of subjects (e.g. 4 mg azelastine), there is minimal numerical difference from placebo. Secondly, there is no biologically or pharmacokinetically plausible reason to

suggest that duration of treatment or cumulative dose would contribute to azelastine-mediated cardiac repolarization changes.

Association Between QTc Change and Drug Plasma Levels:

There were no significant correlations between mean azelastine concentrations and mean maximum change in QTc for any dosing level. Similarly, there was no correlation between QTc and metabolite/parent azelastine ratios. There was, however, a significant correlation between metabolite and mean maximum QTc for the 4 mg multiple dose arm only.

Reviewer comment: We have already concluded that there is a small mean azelastine effect on QTc. Therefore a correlation between metabolite concentration and this effect should not be surprising. The fact that a significant correlation was only found for the 4 mg dose is probably due to the fact that the other dosing groups had relatively small numbers of subjects and the overall QTc effect is quite small. As stated previously, for the nasal spray application, the small mean cardiac effect at higher oral doses and the fact that the nasal spray formulation will allow for limited systemic exposure allows for a relatively high therapeutic index for this drug.

Analysis of Diurnal Variations:

By and large, the timing of the on-study ECGs was specified with regard to dosing. Therefore, there was not adequate variability with regard to diurnal timing to allow for meaningful analysis of diurnal variability.

Overall Reviewer Comment on Enriched Database Analyses: The sponsor has conducted the FDA-suggested analyses of this database. There is no reason to suspect that the criteria for building this database for this analysis would result in data that would be more sensitive than the previously presented, original database analysis in detecting QTc effects of azelastine. Nevertheless, this set of enriched database analyses confirm that there is a small azelastine repolarization effect. The fact that this does not appear to be dose related speaks to the weak azelastine effect on an inherently highly variable parameter (QTc). This conclusion is also supported by the plasma concentration correlation analyses in which a statistically significant correlation was only found for the treatment group which had large numbers of subjects (4 mg multiple dose). As stated previously, for the nasal spray application, the small mean cardiac effect at higher oral doses, the lack of an outlier population, and the fact that the nasal spray formulation will allow for limited systemic exposure allows for a high therapeutic index for this drug and a relatively high comfort level in approving this drug.

FDA Question 1b. Because of demonstrated *in vitro* activity on cardiac calcium and sodium channels, the above analysis should also be performed on PR and QRS intervals from the electrocardiograms in the "enriched database."

Sponsor response to 1b: It was agreed at the FDA-Wallace meeting on July 27, 1994 that analyses of the PR and QRS intervals would need to be done only on the drug interaction studies and not on the "enriched" or "Morganroth Report" databases.

Reviewer comment: This indeed was the agreement reached at the July 27, 1994 industry meeting.

FDA Question 1c. *In vivo* interaction studies as planned for erythromycin and ketoconazole should include ECG assessments of PR, QRS, QT (quantitative) and T-U wave morphologies (qualitative). High quality copies of ECGs obtained during these studies should be included in the submission. Studies utilizing the tablet formulation may address this issue.

Sponsor response to 1c. The two interaction studies (erythromycin #278 and ketoconazole #279) were conducted with azelastine tablets (4 mg BID). Both studies were of identical design which is summarized below.

Both were open-label, three-period studies designed to evaluate the ECGs of subjects prior to receiving drug (baseline, Study Day 1), after receiving azelastine and potential inhibitor (each given as monotherapy and also given jointly), and with inhibitor added to an established regimen of azelastine. Both study populations consisted of 12 healthy adult males. In period I (on Study Day 1), subjects underwent multiple ECG recordings prior to initiation of a 14 day regimen of azelastine (4 mg BID). On the morning of Day 14, multiple blood samples were obtained to characterize the steady-state PK parameters of azelastine and metabolite. Serial ECGs (as per Day 1) were also performed. Pharmacokinetic sampling included pre-dose and 0.5, 1, 2, 4, 6, 8, 10 and 12 hours post dosing. The subjects were then randomized to one of two parallel treatment groups (8 inhibitor [ketoconazole 200 BID or erythromycin 500 TID]; 4 placebo) for 7 days. Daily pre-dose AM safety ECGs and plasma samples were obtained from Days 14-21. On Day 21, repeat plasma and ECG sampling was performed out to 96 hours post AM dosing. No drugs were ingested during the washout period from Days 22 to 42. On Study Day 43 (Period III), all subjects ingested inhibitor (ketoconazole or erythromycin) as monotherapy for 7 days. Serial ECGs were repeated on Study Day 49 (as per previous ECG profiles). Clinical laboratories (CBC, chemistries, U/A, HIV, HbsAg, and urine toxicology) were performed at pretreatment, at the end of Period I, at the beginning of Period III and at the exit visit (2 weeks after completion of Period III).

ECGs interval measurements were performed in a blinded fashion using a digitizing pad. QT duration was measured from three complexes using the earliest beginning of the QRS complex to the end of the longest T wave in any of the three leads. QT was corrected for rate (QTc) using Fridericia's formula (QT/cube root of RR)

Reviewer comment on protocol(s) and study design(s): Both study protocols were reviewed prospectively and comments were forwarded to the sponsor. The sponsor incorporated all FDA suggestions.

Results (Ketoconzole Interaction Study):

Twelve healthy males (age 19 to 39 years) were enrolled. Three subjects did not complete the study. Subject 8 entered Period II and was randomized to ketoconazole + azelastine. No ECG abnormalities were noted on Days 14-19; however, the subject withdrew consent on Day 21 and refused full exit procedures. The subject stated he was unable to tolerate study procedures (PK sampling). Subject 10 was lost to follow-up after failing to return for Study Day 25 procedures. All but the last (96 hour) PK sample was obtained for Period II (placebo + azelastine). Subject 11 withdrew after completing Period II (ketoconazole + azelastine) after experiencing small erythematous spots on the bridge of his nose which was resolving as Period II was ending. The subject, however, declined to participate in Period III (ketoconazole monotherapy).

Laboratory abnormalities were observed but were generally transient in nature, resolved after repeat testing, and were not clinically significant. Similarly, constitutional adverse events were observed. Notably, six subjects reported taste perversion which is an adverse event previously noted and frequently seen with azelastine treatment.

Pharmacokinetics: Because ketoconazole metabolites co-eluted with azelastine and metabolite on the analytic HPLC, the pharmacokinetics of azelastine/metabolite could not be determined during Period II (azelastine ± ketoconazole). Nevertheless, the pharmacokinetics of azelastine, when administered alone during Period I, exhibited the expected steady-state pharmacokinetic properties (i.e. Azelastine Cmax 8.28 ng/ml, AUC 79.74 ng*hr/ml; Desmethylazelastine Cmax 3.80 ng/ml, AUC 40.88 ng*hr/ml).

Reviewer comment: The ketoconazole interference with the clinical azelastine assay is surprising in that there was no suggestion of potential for interference during assay development and validation. If there is a suggestion of ECG effect in the pharmacodynamic analysis, the sponsor should develop another assay which would allow for quantification of azelastine/metabolite. This would be important because ketoconazole is generally recognized as the most potent in vivo inhibitor of P4503A4 and the maximum magnitude of azelastine metabolic inhibition would

be important to quantify with regard to addressing the relative clinical impact of other potential inhibitors. If there is no ECG effect (as shown below), the question is moot.

ECG Results:

PR and QRS Intervals:

			Baseline	Period I	Period II	
Measures	Treatment	N	Mean#	Mean	Mean	p Value*
Mean PR (msec)	Az + Keto	7	158.8	159.2	161.8	0.35
	Az + Pbo	4	158.9	164.5	166.2	-
Mean QRS (msec)	Az + Keto	7	80.9	78.0	79.68	0.57
	Az + Pbo	4	88.0	86.8	87.5	-

#Mean calculated as average of ECGs over study day.
*Comparison of Period II groups with baseline as covariate.
Similarly, there was no clinical or significant effect of ketoconazole therapy on PR or QRS intervals.

Reviewer comment: Because azelastine has been show to have sodium and calcium channel activity in preclinical in vitro studies, it was felt to be important to investigate the drug effect on relevant ECG intervals. There does not appear to be any clinically significant effect on PR (calcium channel mediated) or QRS (fast sodium channel mediated) intervals.

QT/QTc Intervals:

			Baseline	Period I	Period II	
Measures	Treatment	N	Mean	Mean	Mean	p Value*
Mean QTc# (msec)	Az + Keto	7	379.8	382.7	382.1	.71
	Az + Pbo	4	381.5	388.3	388.9	-
$AUC_{0\text{-}12}$ QTc (msec)	Az + Keto	7	4551.7	4588.9	4566.4	.45
	Az + Pbo	4	4546.4	4660.7	4669.1	-

#Mean calculated as average of ECGs over study day.
*Comparison of Period II groups with baseline as covariate.
Similarly, there was no clinical or significant effect of ketoconazole therapy on QTc intervals.

Sensitivity analyses were also performed on QTc data sorted by study period as shown below.

Treatment	N	≤0%	>0-5%	>5-10%	>10%	≥500 msec
Az alone	12	5(42%)	6(50%)	1(8%)	0(0%)	0(0%)
Az + Keto	7	3(43%)	3(43%)	1(14%)	0(0%)	0(0%)
Az + Pbo	4	1(25%)	2(50%)	1(25%)	0(0%)	0(0%)
Keto alone	9	3(33%)	6(67%)	0(0%)	0(0%)	0(0%)

T-U Wave Morphologies: There were no qualitative changes from baseline in the T-U wave complex in any on-study ECGs.

Reviewer comment: There is no additive or synergistic pharmacodynamic cardiac repolarization effect of azelastine and ketoconazole. There appears to be a small effect of azelastine alone on QTc duration (3-7 msecs) in the small cohorts of patients studied. There were no correlations between this effect and measured drug levels for reasons previously elucidated in the "enriched" database analysis (i.e. small mean treatment effect + small numbers of patients studied in the interaction study).

Erythromycin Interaction Study:

Twelve healthy males (age 21 to 34 years) were enrolled. All twelve subjects completed the study.

Laboratory abnormalities were observed but were generally transient in nature, resolved after repeat testing, and were not clinically significant. Similarly, constitutional adverse events were observed. Notably, seven subjects reported taste perversion and six reported somnolence which are both adverse events previously noted and frequently seen with azelastine treatment.

Pharmacokinetics:

	Period I (Day 14); N = 14 Azelastine 4 mg BID Alone		Period II (Day 21); N = 4 Azelastine + Placebo		Period II (Day 21); N = 8 Azelastine + Erythromycin	
Parameter	Azelastine	Desmethaz	Azelastine	Desmethaz	Azelastine	Desmethaz
Cmax (ng/ml)	5.57 ±2.7	2.87 ±1.1	6.92 ±5.3	2.59 ±1.1	5.36 ±2.6	2.45 ±0.4
tmax(hr)	5.0 ±2.2	4.5 ±3.3	3.0 ±1.2	4.5 ±1.0	4.8 ±1.8	6.5 ±1.8
AUCt (ng*hr/ml)	48.4 ±24	28.3 ±9.4	58.9 ±44	27.8 ±11.6	49.7 ±24	25.9 ±5.7

Reviewer comment: There is no pharmacokinetic interaction between azelastine and erythromycin. This is somewhat surprising in that azelastine is a putative substrate of P4503A4 and erythromycin has been shown to inhibit the metabolism of other P4503A4 substrates (e.g. terfenadine).

ECG Results:

PR and QRS Intervals:

			Baseline	Period I	Period II	
Measures	Treatment	N	Mean	Mean	Mean	p Value*
Mean PR# (msec)	Az + Ery	8	154.6	159.3	161.1	0.007
	Az + Pbo	4	149.7	141.4	135.8	-
Mean QRS# (msec)	Az + Ery	8	82.7	82.5	83.6	0.55
	Az + Pbo	4	77.6	77.6	79.3	-

#Mean calculated as average of ECGs over study day.
*Comparison of Period II groups with baseline as covariate.
Similarly, there was no clinical or significant effect of erythromycin therapy on PR or QRS intervals.

Reviewer comment: Because azelastine has been show to have sodium and calcium channel activity in preclinical in vitro studies, it was felt to be important to investigate the drug effect on relevant ECG intervals. Although there is statistical difference between cohorts for PR interval, there does not appear to be any clinically significant effect on PR (calcium channel mediated) or QRS (fast sodium channel mediated) intervals. This finding is due to a spurious mean decrease in the azelastine + placebo arm rather than a meaningful increase in the azelastine + erythromycin arm. This contention is supported by an analysis of the mean PR intervals between baseline and Day 14 for all patients (mean baseline PR = 153, n = 12; mean end of Period I PR = 153, n = 12: p = 0.69).

QT/QTc Intervals:

Measures	Treatment	N	Baseline Mean	Period I Mean	Period II Mean	p Value*
Mean QTc# (msec)	Az + Ery	8	377.9	371.3	378.1	0.61
	Az + Pbo	4	375.3	378.5	385.1	-
AUC_{0-12} QTc (msec)	Az + Ery	8	4403.3	4430.8	4500.7	0.865
	Az + Pbo	4	4484.5	4539.8	4597.9	-

#Mean calculated as average of ECGs over study day.
*Comparison of Period II groups with baseline as covariate.
Similarly, there was no clinical or significant effect of erythromycin therapy on QTc intervals.

Sensitivity analyses were also performed on QTc data sorted by study period as shown below.

Treatment	N	≤0%	>0-5%	>5-10%	>10%	≥500 msec
Az alone	12	5(42%)	6(50%)	1(8%)	0(0%)	0(0%)
Az + Ery	8	2(25%)	4(50%)	2(25%)	0(0%)	0(0%)
Az + Pbo	4	1(25%)	3(75%)	0(0%)	0(0%)	0(0%)
Ery alone	12	8(67%)	4(33%)	0(0%)	0(0%)	0(0%)

T-U Wave Morphologies: There were no qualitative changes from baseline in the T-U wave complex in any on-study ECGs.

Reviewer comment: There is no additive or synergistic pharmacodynamic cardiac repolarization effect of azelastine and erythromycin. There is suggestion of a small effect of azelastine alone on QTc duration (3-7 msecs) in the small cohorts of patients studied. There were no correlations between this effect and measured drug levels for reasons previously elucidated in the "enriched" database analysis (i.e. small mean treatment effect + small numbers of patients studied in the interaction study).

FDA Question 1d. A dose escalation study, including both males and females, to steady state for daily doses up to 24 mg (12 mg BID) should be performed. This may be done utilizing either a crossover or a sequential parallel-group design, but should include pharmacokinetic and ECG pharmacodynamic assessments (see item 1c) at regular intervals throughout the trial and repeated at appropriate points during the dosing interval.

Sponsor response to 1d: It was agreed at the meeting on July 27, 1994 that the above requested study would not be required for the azelastine nasal spray NDA. The available data with oral azelastine doses up to 8 mg BID, which represents a 16-fold multiple of the highest recommended nasal spray dosage, was agreed to be sufficient.

Reviewer comment: This was the agreement reached at the meeting. The dose escalation study is not required for NDA 20-114.

Overall Reviewer Comment and Regulatory Recommendation:

This submission supports the sponsor assertion that azelastine nasal spray has a favorable cardiac safety profile. It is complete, well-analyzed, and in accordance with agreements made with the Division. There is evidence that azelastine, at higher oral doses (i.e. >4 mg bid) has a small mean effect on cardiac repolarization of about 3-7 milliseconds. Outliers are not disproportionately represented in the azelastine treatment groups. The small effect on cardiac repolarization occurs at exposures much higher than those achievable with nasal spray dosing further supporting the safety of the nasal spray. The conclusions reached from the analysis of this "enriched" database do not differ substantively from the analyses contained in the original "Morganroth Report." The small mean effect should, however, be reflected in product labeling.

There is no pharmacokinetic or pharmacodynamic interaction with erythromycin and there is no pharmacodynamic interaction with ketoconazole. These findings should be reflected in product labeling.

From a cardiac safety viewpoint, this application is "approvable."

Peter K Honig, M.D.
Medical Officer

Martin H. Himmel, M.D.
Supervisory Medical Officer

Appendix

Table 19
Difference Between Males and Females With Respect to Change in QTc (in msec)
Single-Dose Asthma (Group I)

	MALE		FEMALE		
TREATMENT	N	MEAN	N	MEAN	DIFFERENCE*
AZELASTINE 2MG	12	-21.8	2	8.5	-30.3
AZELASTINE 4MG	38	5.2	8	-11.7	16.9
AZELASTINE 8MG	10	7.2			
AZELASTINE 12MG	12	3.3	1	-15.0	18.3
AZELASTINE 16MG	13	6.5			
PLACEBO	39	0.8	1	38.0	-37.2

Table 20
Difference Between Males and Females With Respect to Change in QTc (in msec)
Multiple-Dose Asthma (Group II)

	MALE		FEMALE		
TREATMENT	N	MEAN	N	MEAN	DIFFERENCE*
AZELASTINE 2MG	24	1.7	14	7.7	-6.0
AZELASTINE 4MG	233	4.9	111	8.3	-3.4
AZELASTINE 6MG	34	-2.6	12	13.7	-16.3
AZELASTINE 8MG	33	3.5	7	37.6	-34.1
PLACEBO	236	-0.3	94	-7.9	7.6

Table 21
Difference Between Males and Females With Respect to Change in QTc (in msec)
Multiple Dose Rhinitis (Group III)

	MALE		FEMALE		
TREATMENT	N	MEAN	N	MEAN	DIFFERENCE*
AZELASTINE 1MG	33	2.0	27	1.2	0.8
AZELASTINE 2MG	34	1.1	43	10.9	-9.8
PLACEBO	26	1.6	34	-2.0	3.6

-Hillig

MEMORANDUM

Date: October 20, 1993

From: Martin H. Himmel, M.D. - Medical Officer

Through: Gregory P. Burke, M.D., Ph.D. - Division Director GPBurke 10/21/93

To: NDA# 20-114

Subject: Non-approval letter

The following comments should be included in the clinical portion of the non-approval letter for this NDA as reasons for not approving the NDA:

Safety Issues:

1. At present, a full risk-benefit assessment for azelastine is not possible. In pre-clinical studies azelastine has been shown to have antifibrillatory and calcium channel blocking activity and the finding of a mean QTc increase in subjects taking azelastine vs subjects taking placebo suggests potential for cardiotoxicity in humans. The fact that no correlation between concentration (azelastine or desmethylazelastine) and effect (QTc prolongation) has been demonstrated may suggest the presence of unmeasured cardiotoxic metabolites and/or metabolic outliers in the population. The following information is required to allow such an assessment:

   A. *In vitro* K^+ channel studies investigating the electrophysiologic effect of azelastine, desmethylazelastine, the combination and any other azelastine metabolites required in Comment #2 on cardiac repolarization.

   B. Full characterization of the metabolism of azelastine and identification of all metabolites, <u>including metabolites specific to the nasal route of administration</u>. *In vitro* microsomal and/or liver slices from humans are needed. Such experiments should include drug metabolism studies with imidazole antifungals, macrolide antibiotics and H2 antagonists. Such *in vitro* studies should also include, but not limited to, evaluation of azelastine metabolism using anti P4503A4 antibodies to investigate the presence of minor or shunt metabolic oxidative pathways for the biotransformation of azelastine.

   C. The "enriched database" submission of September 9, 1993 is inadequate. No analyses other than that of electrocardiographic outliers were provided.

The database must be reexamined with inclusion of comparable data from patients receiving placebo during the clinical studies. The maximum change in QTc from baseline should be determined for subjects with an abnormal ECG or who discontinued participation prematurely in placebo controlled single and multiple dose allergic rhinitis and asthma studies and compared between azelastine and placebo treated groups. Maximum change in QTc should be based on evaluation of all ECGs (not just the abnormal ECG) for each subject while they are on active treatment and determination of the ECG on which the QTc is most prolonged. This evaluation may be made using lead II; however, all ECGs on which there is a 10% or greater prolongation in QTc should be evaluated by a cardiology consultant for changes in T-U wave morphology. The data for single and multiple dose trials should be evaluated separately and the analysis should include assessment of dose related effects, age related effects, gender related effects and duration of treatment effects. In addition to evaluating the mean and percent change from baseline, the data should describe the range of QTc prolongation seen. An analysis should also be performed comparing active treatment to placebo with regard to subjects with <10% increase in QTc from baseline, 10-15%, 15-20% and >20% increase over baseline. Because of possible diurnal effects on QTc, the analysis should include a description of how the ECGs included in the analysis compare in the two groups with regard to the time they were collected. Finally, if serum drug concentrations are available, an analysis of change in QTc by drug level (azelastine and desmethylazelastine) should be performed.

D. Because of demonstrated *in vitro* activity on cardiac calcium and sodium channels, the above analysis should also be performed on PR and QRS intervals from the electrocardiograms in the "enriched database."

E. *In vivo* interaction studies as planned for erythromycin and ketoconazole should include ECG assessments of PR, QRS, QT (quantitative) and T-U wave morphologies (qualitative). High quality copies of ECGs obtained during these studies should be included in the submission.

F. A summary of the population variability of azelastine metabolism should be provided. This should include presentations of histograms by dose of azelastine, desmethylazelastine, the sum and ratios of the two moieties (Cmax and AUC) after single and multiple (steady-state) dosing.

2. Safety data, with particular emphasis on local toxicity, in at least 200 subjects who have received the 2 sprays per nostril bid of azelastine for at least 6-12 months should be submitted.

3. Please submit adverse event data with the inclusion of all intercurrent illnesses

as adverse events. This data should include incidence in short term ($\leq$2 days duration) and long term trials separately, for all rhinitis trials, asthma trials, combined rhinitis and asthma trials and all US exposure. In addition, as was done in the integrated safety summary, the data should be broken down by dose and demographic analyses of the data should be done as well. This information can be submitted with the next safety update.

4. Please submit any ECG data which you may have in subjects treated with the nasal spray formulation. If this data base is large, an analysis of cardiac intervals in treated subjects v.s. controls should be done as has been requested for the tablet formulation.

Efficacy Issues:

1. The NDA submission fails to include listings of the twice daily scores ascribed by the subjects to each of the symptoms that they were asked to evaluate. Please submit this data for studies #26 and #31. In addition, please describe how the daily data was combined into a weekly score and how the different symptoms were combined into the total, major and revised symptom complexes so that we may verify your calculations from individual symptom scores to weekly symptom and symptom complex scores. In addition, your method for handling missing data in these calculations should be described.

2. For studies #26 and #31 please provide us with information regarding the number of subject days with no symptom score for each symptom by treatment arm and by week. For trials where both AM and PM data was collected, this data should be depicted separately. The following table provides an example of the format of the data which we are requesting:

Study # - Symptom -Number of subject days with no score reported				
Time	2 sprays qd	2 sprays bid	Pos Control	Placebo
Week 1 AM				
Week 1 PM				
Week 2 AM				
Week 2 PM				

In addition, we would also like to have the missing patient day data depicted by

outcome for each treatment arm, as in the following example:

Study # - Symptom -Treatment arm-Number of subject days with no score reported		
Time	Subjects with an improvement in mean weekly symptom score from baseline	Subjects with a decrease in mean weekly symptom score from baseline
Week 1 AM		
Week 1 PM		
Week 2 AM		
Week 2 PM		

The following are additional comments which have been previously conveyed to the sponsor by fax and should be included in the non-approvable letter:

1. Please comment on the lack of efficacy seen during the first half of the dosing interval in the 4 day azelastine group in study #26.

2. We are unclear on how to interpret table #27 in study #26. Weeks 1 and 2 appear to be repeated a number of times with different values.

3. For study #31, please provide pollen count data on a center by center basis.

4. Please submit case report forms for the 8 azelastine treated subjects in study #26 who were discontinued prematurely.

5. Please submit case report forms for the 5 azelastine treated subjects in study #31 who were discontinued prematurely.

6. Please submit case report forms for the 15 azelastine treated subjects in study #33 who were discontinued prematurely.

7. For study #33, please comment on the differences in efficacy seen for the AM v.s. PM data based on the total symptom complex as well as individual symptoms.

8. Please delineate what the treatment emergent ECG changes were during the final week of study #29.

9. Please report the P values for the comparison of adverse events occurring in the "All Azelastine" group v.s. placebo in Table #410 of the integrated safety summary.

10. Please submit case report forms of the azelastine treated subjects with elevated SGPT reported as adverse events.

11. Please report the P values for the comparison of incidence rates of adverse events in male v.s. female subjects in the azelastine treated subjects and the placebo group.

12. Case report forms for circled subjects on the following scatter plots should be submitted:

Scatter plots were faxed to sponsor on August 10, 1993

13. Are any of the differences between azelastine and placebo treated subjects for out of normal range lab values statistically significant for subjects under age 18?

14. Are any of the differences between males and females in incidence of low CO2, cholesterol or glucose or high chloride or cholesterol values statistically significant?

15. Are any of the differences by weight or race in incidence of out of range lab values statistically significant?

16. The following case report forms of subjects with abnormal lab values should be submitted:

Subject #	Protocol #	Dose of Azelastine
139	272	2 spray bid
270	281	2 spray q day
116	282	2 spray q day
261	282	2 spray q day
172	283	2 spray bid
164	272	2 spray bid
193	272	2 spray bid
248	258	? (elevated alkaline phosphatase)

17. Please identify the specific lab abnormalities that are reported on pages 2-3 of table 493.

18. According to our calculations, the updated European safety data base should

include data on 608 azelastine subjects (205 additional subjects, 35 subjects from the uncontrolled PAR study, 1 subject from the extension study, 182 subjects in the initial data base of controlled trials and 185 subjects in uncontrolled trials) and 76 placebo subjects (8 in the initial data base and 68 in the update), yet your updated safety summary contains data on 553 azelastine subjects and 55 placebo subjects. Please explain this discrepancy.

19. Were any of the differences between azelastine and placebo in incidence of adverse events in the updated European safety summary statistically significant?

20. Please provide additional clinical information and case report forms for subjects who experienced the following adverse events (taken from table 451): dizziness .4%, palpitations .2% and allergic reaction .2%.

21. Please clarify what the difference is between tables 451 and 455 in the integrated safety summary.

22. Case report forms for the 7 subjects who discontinued prematurely from European trials should be submitted.

23. Please list the symptom scores of the 52 subjects with insufficient symptoms, state the reason that the 4 subjects failed to meet inclusion/exclusion criteria, explain why 3 subjects were not randomized because of too sever disease (no upper limit on symptom scores is listed in the protocol), and state what the intercurrent illness, adverse events and unknown reasons were in the other subjects which precluded randomization to trial #33.

24. Please list the symptom scores of the 43 subjects with insufficient symptoms, state the reason that the 6 subjects failed to meet inclusion/exclusion criteria, explain why 9 subjects were not randomized because of too sever disease (no upper limit on symptom scores is listed in the protocol), and state what the intercurrent illness, adverse events and unspecified reasons were in subjects which precluded randomization to study #31.

25. For study #26, please list the symptom scores of the 35 subjects with insufficient symptoms, state the reason that the 11 subjects failed to meet inclusion/exclusion criteria, explain why 5 subjects were not randomized because of too sever disease (no upper limit on symptom scores is listed in the protocol), and state what the intercurrent illness and adverse events were in two subjects each which precluded randomization.

26. Case report forms for any subject that withdrew prematurely from a US allergic rhinitis trial in NDA 20-114 or due to an adverse event which has not yet been requested or submitted should now be submitted (as a separate item) along

with a tabulation of the reason for premature withdrawal by patient number.

27. Regarding study #32, it is unclear what the statement on page 08 9003 which states that the incidence of elevated SGPT in all subjects was 13% and in at risk subjects 8% is based on since according to table #35, which reports the data on subjects with normal baseline values, the incidence of high SGPT in the q day azelastine group was 6.00% not 8.0% and according to table #36, which reports lab data on all subjects regardless of baseline value, the incidence of high SGPT is 11.11% not 13%.

28. Regarding study #32, please provide a list of the SGPT values above normal in this trial, broken down by subject. This will allow us to ascertain if there are any outliers responsible for the greater incidence of high SGPT in subjects who received azelastine once a day.

29. To get a better understanding of the degree of glucose elevation in the >60 age group, please submit the individual glucose values at baseline, during the trials and at follow-up for subjects over 60 years of age who received azelastine.

cc:
NDA#20-114
HFD-155/Div File
HFD-155/Div Dir/Burke
HFD-155/Reviewers/Himmel/Honig/Chun/Ng
HFD-713/Gebert
HFD-155/CSO/Schumaker/Riley

MEDICAL OFFICER REVIEW

NDA#:	**20-114/**
DRUG:	**AZELASTINE**
REVIEWER:	**PETER HONIG, M.D.**
DATE OF REVIEW:	**OCTOBER 1, 1993**
SPONSOR:	**WALLACE LABORATORIES**
MATERIAL REVIEWED:	**SEPTEMBER 2, 1993 AMENDMENT OF ORIGINAL ECG REPORT** **SEPTEMBER 9, 1993 SUBMISSION OF ABNORMAL ECG ANALYSIS**

INTRODUCTION:

A retrospective evaluation of the electrocardiographic data obtained during the conduct of clinical trials on azelastine in the treatment of allergic rhinitis (NDAS# 114, (NDA# was submitted in September 1992. An amendment to this submission in which additional subjects are included in the analysis was submitted on September 2, 1993.

An second post-hoc analysis of an "enriched" sample of electrocardiograms obtained during the conduct of the clinical trials was requested. The ECGs to be included in this analysis were clarified in an FDA-sponsor meeting in April 1993 and submitted on September 9, 1993. This was to be an analysis of all subject ECGs read as abnormal for any reason and ECGs from subjects who withdrew from studies regardless of reason. Both analyses are reviewed below. An appendix contains the pharmacology reviews of cardiac ion channel and electrophysiologic properties of azelastine.

September 2, 1993 submission:

Materials and Methods:

Subject ECGs were included in this analysis if pretreatment baselines had been obtained and on-therapy tracings obtained at time corresponding to peak drug concentrations (4-8 hours after dosing) were retrievable. Eight azelastine trials met these criterion. Only technically satisfactory tracings at both points were included in the analysis. Six of the clinical trials were multiple dose asthma studies involving dosages generally two times higher (4 mg bid) than the maximum recommended dosage for allergic rhinitis (2 mg bid) with the exception of one dose-ranging trial in which 2 to 8 mg were studied. One of the trials was a single-dose ranging trial evaluating dosages to 16 mg. Tables 1 and 2 summarize the trials included in the analysis as well as the doses administered and the times when the electrocardiograms were obtained. Suitable original ECGs for 1078 subjects (673 azelastine, 405 placebo) were available for QT interval evaluation.

Subject demographics, study status, and recording dates were

entered into a database separately by an independent consultant upon receipt of the electrocardiograms from Wallace Laboratories. Each tracing was randomly coded and ECG analysts were blinded to subject identity and drug status during R-R and QT interval measurements. Three artifact-free consecutive cardiac cycles were measured for their average R-R and QT values and QTc was calculated using Bazett's formula.

(#194).

The primary measure for determining the effect of azelastine on QT intervals was change in QTc from pretreatment to on-treatment evaluation. These results were analyzed by ANOVA incorporating treatment as the main effect in the model. A secondary analysis was performed on direction (increase or decrease) of the QTc change. These directions were categorized into one of three groups: A. Decrease by 10% or more, B. No change (<10% in either direction) or C. Increase by 10% or more. These categorical variables were analyzed by Cochran-Mantel-Haenszel or Fisher's Exact tests as appropriate. Subjects with >10% increases in QTc were further subdivided into those subjects with 10-15% increase, 15-20% increase or >20% increase.

Subgroup analyses in *post hoc* stratified samples were also performed investigating gender and age effects.

In studies #22, 23, 24 188 and 189 plasma was obtained simultaneously with ECGs. The effect of azelastine and desmethylazelastine concentrations on change in QTc was investigated by testing using Spearman Correlation Coefficients.

Results

Effect of single doses on QTc:

As can be seen from Table 4, treatment with 2 mg azelastine resulted in a mean 17.4 msec decrease in QTc interval compared to mean 1.8 msec mean increase in the placebo group (p= 0.01). Single doses of 4, 8, 12 and 16 mg azelastine resulted in mean increases in QTc ranging from 2.3 to 7.2 milliseconds. No proportional relationship of dose to mean QTc is evident. Table 7 presents the direction of change in QTc after dosing in these studies. None of the dosing levels was different from placebo.

The sensitivity analysis of those patients with predetermined percent changes from baseline did not reveal any differences between any azelastine dosing group and placebo Tables 10, 13).

Effect of multiple doses (steady-state) on QTc:

Table 5 summarizes the mean changes in QTc from baseline to on-therapy. Treatment with azelastine 4 mg bid results in a 6.0 msec mean increase compared to a 2.5 msec decrease for placebo ($p = 0.001$). Treatment with 8 mg bid also resulted in a statistically significant mean increase of 9.5 msecs. The 2 and 6 mg dosing groups had mean increases in QTc of 3.8 and 1.7 msecs; however, this did not reach statistical significance.

The direction of change analysis revealed a statistically significant number of patients increased their QTc intervals from baseline after dosing at 4 mg bid (Table 8). A trend in this direction was also seen in the 2 mg bid treatment group; however, no such trends were found for the 6 and 8 mg groups.

The sensitivity analysis provided no statistically significant results although trends toward >10% prolongation in QTc from baseline were seen for all azelastine treatment groups as well as placebo (Table 11). Subanalyses of these effects revealed small numbers of patients in all treatment arms having >15% or >20% increases in QTc from baseline. One subject receiving 8 mg azelastine and 3 subjects receiving placebo had QTc changes greater than +20% (Table 14).

Subanalyses of age and gender effects:
Many of these analyses are problematic and difficult to interpret due to small numbers in the predefined strata.

Gender:
The single dose studies do not have enough women in the treatment groups to allow meaningful comparisons (Table 19). The multiple dose asthma studies reveal interesting comparisons. All azelastine treatment groups had larger mean increases for females compared to males. The placebo treatment revealed females to have larger decreases in QTc from baseline (Table 20). This trend is duplicated for the 2 mg azelastine treatment group in the small numbers of subjects participating in the multiple dose allergic rhinitis trial (Table 21).

Age:
Analogous to the analyses for gender, the single dose studies do not allow meaningful comparisons (Table 22); however, the multiple dose (Table 23) demonstrate an enhanced effect of azelastine on subjects over 50 years of age. Many of the cells have small numbers which may make comparisons of means and any analysis of age-dose-QTc relationships problematic.

Age-Gender:
These interaction analyses are complicated by very small numbers and very difficult to interpret in the light of such limited power.

Evaluation of plasma drug levels and QTc intervals:

Plasma azelastine and desmethylazelastine determinations were performed in five of the eight studies. No significant correlation coefficients were observed between the changes in the QTc and plasma azelastine (Table 28) or plasma desmethylazelastine levels (Table 28A) for any treatment group. Scatterplots (Figures 1 and 2) which plot change in QTc and corresponding azelastine and desmethylazelastine concentrations by dose are provided. Of note, 2 outliers are identified in Figure 1. Both of these subjects received azelastine at 8 mg bid. Both subjects had relatively low plasma desmethylazelastine/azelastine ratios (0.11 and 0.12 vs a population ration of 0.50). Both had clinically significant prolongations in on-treatment QTc (481 and 469 milliseconds).

Reviewer comment:

This study clearly shows that azelastine has an effect on cardiac repolarization across a population. The fact that no consistent dose-effect relationship is found may be due to small numbers of patients with differing metabolic capacities. The presence of pharmacokinetic and pharmacodynamic outliers heightens the concern over subgroups running into trouble with cardiac arrhythmias with this drug. Generally, the numbers involved in subgroup analyses are small and allow for limited statistical power; however, several interesting hypotheses may be generated. First, the fact no correlation is established between parent or metabolite concentrations raises the question of an unmeasured cardioactive metabolite. Second, the finding of an enhanced effect on QTc change in women and the existing knowledge of hormonal influences on metabolic oxidative capacity of cytochrome P4503A4 (the cytochrome responsible for azelastine demethylation) is intriguing.

It would be very interesting to see a histogram plot of Cmax and AUC ratios of parent and metabolite to allow appreciation of the population variability in the biotransformation of this substrate. A subanalysis of pharmacokinetic outliers and their electrocardiograms (if available) may be revealing. At the very least, a more complete understanding of azelastine metabolism is required.

Table 1
Number of Subjects Included in Electrocardiographic QT Interval Analysis

Study No.	Number Randomized*	Azelastine Treatment Groups							Placebo	Total
		1 mg	2 mg	4 mg	6 mg	8 mg	12 mg	16 mg		
	150	–	14	12	–	10	13	13	13	75
	254	–	40	44	46	40	–	–	37	207
	286	–	–	72	–	–	–	–	69	141
	91	–	–	34	–	–	–	–	25	59
	406	–	–	112	–	–	–	–	113	225
	268	–	–	57	–	–	–	–	56	113
	66	–	–	29	–	–	–	–	30	59
	279	70	67	–	–	–	–	–	62	199
Total		70	121	360	46	50	13	13	405	1078

*Includes all azelastine groups, positive control (if applicable) and placebo.

Source: Data on File, Wallace Laboratories

Table 2
Summary of Electrocardiogram Evaluations During Double-Blind Treatment

Protocol	ECG Obtained	ECG Selected for Analysis
	- prior to randomization - 4* and 8* hours postdose	- prior to randomization - 4 hours postdose*
	- prior to randomization - 4 hours postdose at 4* and 12* weeks	- prior to randomization - 4 weeks*
	- prior to randomization - 4 hours postdose after the first dose* and 2*, 4*, 16*, 28*, and 40* weeks	- prior to randomization - 4 weeks*
	- prior to randomization - 2 and 4 hours after first study dose and 2 weeks of therapy	- prior to randomization - 4 hours after first study dose - 4-hour ECG at 2 weeks
	- prior to randomization - 4 to 8 hours postdose at 4, 8, and 12 weeks	- prior to randomization - 4 weeks
	- prior to randomization - 4 hours postdose after the first dose* and 2*, 4*, 16*, 28*, and 40* weeks	- prior to randomization - 4 weeks*
	- prior to randomization - 4 hours postdose at 12* weeks	- prior to randomization - 12 weeks*
	- prior to randomization - 4-8 hours postdose at 2 weeks	- prior to randomization - 2 weeks

*Simultaneous [illegible] samples drawn

Table 4

Mean Change in QTc

Following the Single or First Dose of Double-Blind Treatment

(Group I)

TREATMENT	N	PRETREATMENT MEAN QTc (MSEC)	MEAN CHANGE IN QTc (MSEC)	P-VALUE
	16	416.4	-17.6	0.810
	46	385.6	2.3	0.923
	18	402.4	7.2	0.516
	13	393.8	1.9	0.983
	13	392.0	8.5	0.535
PLACEBO	38	385.7	1.8	

Table 7

Direction of the Change in QTc

Following the Single or First Dose of Double-Blind Treatment

(Group I)

TREATMENT	DECREASE* N (%)	NO CHANGE N (%)	INCREASE* N (%)	TOTAL	P-VALUE
	10 (71%)	0	4 (29%)	14	0.168
	22 (48%)	1 (2%)	23 (50%)	46	0.655
	5 (50%)	0	5 (50%)	10	1.000
	8 (62%)	0	5 (38%)	13	0.472
	5 (38%)	0	8 (62%)	13	0.472
PLACEBO	19 (50%)	0	19 (50%)	38	

Table 10

Direction of the Change in QTc

Following the Single or First Dose of Double-Blind Treatment

(Group I)

TREATMENT	DECREASE ≥10%	DECREASE <10% INCREASE <10%	INCREASE ≥10%	p-VALUE
	N (%)	N (%)	N (%)	
ASELASTINE 2 MG	2 (14%)	12 (86%)	0	0.203
ASELASTINE 4 MG	1 (2%)	43 (93%)	2 (4%)	0.971
ASELASTINE 8 MG	0	9 (90%)	1 (10%)	0.759
ASELASTINE 12 MG	0	12 (92%)	1 (8%)	0.683
ASELASTINE 16 MG	0	13 (100%)	0	0.580
PLACEBO	1 (3%)	35 (92%)	2 (5%)	

Table 13

Direction of the Change in QTc

Following the Single or First Dose of Double-Blind Treatment

(Group I)

TREATMENT	DECREASE ≥10%	DECREASE <10%	INCREASE <10%	INCREASE ≥10% <15%	INCREASE ≥15% <20%	INCREASE ≥20%
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ASELASTINE 2 MG	2 (14%)	8 (57%)	4 (29%)	0	0	0
ASELASTINE 4 MG	1 (2%)	22 (48%)	21 (46%)	2 (4%)	0	0
ASELASTINE 8 MG	0	5 (50%)	4 (40%)	1 (10%)	0	0
ASELASTINE 12 MG	0	8 (62%)	4 (31%)	0	1 (8%)	0
ASELASTINE 16 MG	0	5 (38%)	8 (62%)	0	0	0
PLACEBO	1 (3%)	18 (47%)	17 (45%)	1 (3%)	1 (3%)	0

Table 5

Mean Change in QTc During Double-Blind Treatment

Combined Mulupie-Dose (Group II)

TREATMENT	N	PRETREATMENT MEAN QTc (MSEC)	MEAN CHANGE IN QTc (MSEC)	P-VALUE
AZELASTINE 2MG	40	407.5	3.0	0.228
AZELASTINE 4MG	144	405.6	6.0	0.001
AZELASTINE 6MG	46	406.9	1.7	0.393
AZELASTINE 8MG	40	403.0	9.5	0.022
PLACEBO	330	407.2	-2.5	

Table 8

Direction of the Change in QTc During Double-Blind Treatment

Combined Mulupie-Dos (Group II)

TREATMENT	DECREASE* N (%)	NO CHANGE N (%)	INCREASE* N (%)	TOTAL	P-VALUE
AZELASTINE 2 MG	16 (40%)	6	24 (60%)	40	0.115
AZELASTINE 4 MG	133 (38%)	6 (2%)	205 (60%)	344	0.002
AZELASTINE 6 MG	21 (46%)	2 (4%)	23 (50%)	46	0.414
AZELASTINE 8 MG	19 (48%)	1 (3%)	20 (50%)	40	0.7[illegible]
PLACEBO	179 (54%)	7 (2%)	144 (44%)	330	

Table 11

Direction of the Change in QTc During Double-Blind Treatment

Combined Multiple-Dose (Group II)

TREATMENT	DECREASE ≥10% n (%)	DECREASE <10% INCREASE <10% n (%)	INCREASE ≥10% n (%)	P-VALUE
ASELASTINE 2 MG	2 (5%)	34 (85%)	4 (10%)	0.992
ASELASTINE 4 MG	7 (2%)	306 (89%)	31 (9%)	0.868
ASELASTINE 6 MG	4 (9%)	35 (76%)	7 (15%)	0.261
ASELASTINE 8 MG	1 (3%)	33 (83%)	6 (15%)	0.433
PLACEBO	17 (5%)	282 (85%)	33 (9%)	

Table 14

Direction of the Change in QTc During Double-Blind Treatment

Multiple-Dose (Group II)

TREATMENT	DECREASE ≥10% n (%)	DECREASE <10% n (%)	INCREASE <10% n (%)	INCREASE ≥10% <15% n (%)	INCREASE ≥15% <20% n (%)	INCREASE ≥20% n (%)
ASELASTINE 2 MG		14 (35%)	20 (50%)	3 (8%)	3 (3%)	0
ASELASTINE 4 MG	7 (2%)	132 (38%)	174 (51%)	26 (8%)	5 (1%)	0
ASELASTINE 6 MG	4 (9%)	19 (41%)	16 (35%)	5 (11%)	2 (4%)	0
ASELASTINE 8 MG	1 (3%)	10 (40%)	14 (35%)	3 (5%)	3 (8%)	1 (3%)
PLACEBO	17 (5%)	169 (51%)	113 (34%)	32 (7%)	6 (2%)	3 (1%)

Table 6

Mean Change in QTc During Double-Blind Treatment

Rhinitis Multiple-Dose Trial (Group III)

TREATMENT	N	PRETREATMENT MEAN QTc (MSEC)	MEAN CHANGE IN QTc (MSEC)	P-VALUE
AZELASTINE 1MG	70	411.1	3.6	0.570
AZELASTINE 2MG	67	404.8	7.4	0.068
PLACEBO	62	408.3	-0.7	

Table 9

Direction of the Change in QTc During Double-Blind Treatment

Multiple-Dose Rhinitis Trial (Group III)

TREATMENT	DECREASE* N (%)	NO CHANGE N (%)	INCREASE* N (%)	TOTAL	P-VALUE
AZELASTINE 1 MG	33 (47%)	2 (3%)	35 (50%)	70	0.270
AZELASTINE 2 MG	25 (37%)	0	42 (63%)	67	0.029
PLACEBO	35 (56%)	0	27 (44%)	62	

Table 12

Direction of the Change in QTc During Double-Blind Treatment

Multiple-Dose Rhinitis Trial (Group III)

TREATMENT	DECREASE ≥10% N (%)	DECREASE <10% INCREASE <10% N (%)	INCREASE ≥10% N (%)	P-VALUE
AZELASTINE 1 MG	2 (3%)	63 (90%)	5 (7%)	0.530
AZELASTINE 2 MG	1 (1%)	68 (90%)	6 (8%)	0.403
PLACEBO	1 (3%)	30 (86%)	2 (5%)	

Table 15

Direction of the Change in QTc During Double-Blind Treatment

Multiple-Dose Rhinitis Trial (Group III)

TREATMENT	DECREASE ≥10% N (%)	DECREASE <10% N (%)	INCREASE <10% N (%)	INCREASE ≥10% <15% N (%)	INCREASE ≥15% <20% N (%)	INCREASE ≥20% N (%)
AZELASTINE 1 MG	2 (3%)	33 (47%)	30 (43%)	4 (6%)	1 (1%)	0
AZELASTINE 2 MG	1 (1%)	24 (34%)	36 (51%)	5 (7%)	1 (1%)	0
PLACEBO	1 (3%)	16 (55%)	11 (38%)	1 (3%)	1 (3%)	0

Table 19

Difference Between Males and Females With Respect to Change in QTc (in msec)

Single-Dov (Group I)

	MALE		FEMALE		
TREATMENT	N	MEAN	N	MEAN	DIFFERENCE*
AZELASTINE 2MG	12	-21.8	2	8.5	-30.3
AZELASTINE 4MG	38	5.2	8	-11.7	16.9
AZELASTINE 8MG	16	7.2			
AZELASTINE 12MG	12	3.3	1	-15.0	18.3
AZELASTINE 16MG	13	6.5			
PLACEBO	37	0.8	1	38.0	-37.2

Table 20

Difference Between Males and Females With Respect to Change in QTc (in msec)

Mulupie-Dose (Group II)

	MALE		FEMALE		
TREATMENT	N	MEAN	N	MEAN	DIFFERENCE*
AZELASTINE 2MG	26	1.7	14	7.7	-6.0
AZELASTINE 4MG	233	4.9	111	8.3	-3.4
AZELASTINE 6MG	36	-2.6	13	13.7	-16.3
AZELASTINE 8MG	33	3.5	7	37.6	-34.1
PLACEBO	236	-0.3	94	-7.9	7.6

Table 21

Difference Between Males and Females With Respect to Change in QTc (in msec)

Multiple-Dose Rhinius (Group III)

	MALE		FEMALE		
TREATMENT	N	MEAN	N	MEAN	DIFFERENCE*
AZELASTINE 1MG	33	1.6	57	1.3	0.8
AZELASTINE 2MG	24	1.1	63	10.9	-9.8
PLACEBO	38	1.0	34	-2.8	3.8

Table 22

Mean Change in QTc (in msec) by Age Group

Single-Dose (Group II)

	AGE GROUP							
	≤20 YEARS		>20, ≤35 YEARS		>35, ≤50 YEARS		>50 YEARS	
	N	MEAN	N	MEAN	N	MEAN	N	MEAN
TREATMENT								
AZELASTINE 2MG	5	-13.0	7	-17.0	2	-32.0	1	-6.0
AZELASTINE 4MG	13	9.5	17	1.9	12	-2.0	4	-7.2
AZELASTINE 8MG	4	12.2	6	3.0				
AZELASTINE 12MG	9	1.2	2	20.0	3	-9.0		
AZELASTINE 16MG	9	0.0	3	0.0	2	12.0		
PLACEBO	11	-4.7	26	0.0	9	15.4	2	-16.5

Table 24

Mean Change in QTc (in msec) by Age Group

Multiple-Dose Rhinitis (Group III)

	AGE GROUP							
	≤20 YEARS		>20, ≤35 YEARS		>35, ≤50 YEARS		>50 YEARS	
	N	MEAN	N	MEAN	N	MEAN	N	MEAN
TREATMENT								
AZELASTINE [illegible]MG	12	-9.0	33	3.0	23	5.9	6	-5.5
AZELASTINE 2MG	30	10.9	36	0.6	37	7.8	4	-12.2
PLACEBO	9	6.1	34	-0.0	26	-3.7	5	-6.0

Table 23

Mean Change in QTc (in msec) by Age Group

Multiple-Dose (Group II)

	AGE GROUP							
	≤20 YEARS		>20, ≤35 YEARS		>35, ≤50 YEARS		>50 YEARS	
	N	MEAN	N	MEAN	N	MEAN	N	MEAN
TREATMENT								
AZELASTINE 2MG	11	3.1	23	-0.7	8	-2.6	8	18.0
AZELASTINE 4MG	1[illegible]3	0.0	185	0.2	86	6.3	40	11.3
AZELASTINE 6MG	21	2.9	10	-24.0	7	6.1	8	20.7
AZELASTINE 8MG	14	0.0	13	-1.3	11	33.0	3	10.4
PLACEBO	120	-0.4	107	3.3	71	-11.5	30	-6.0

Table 28

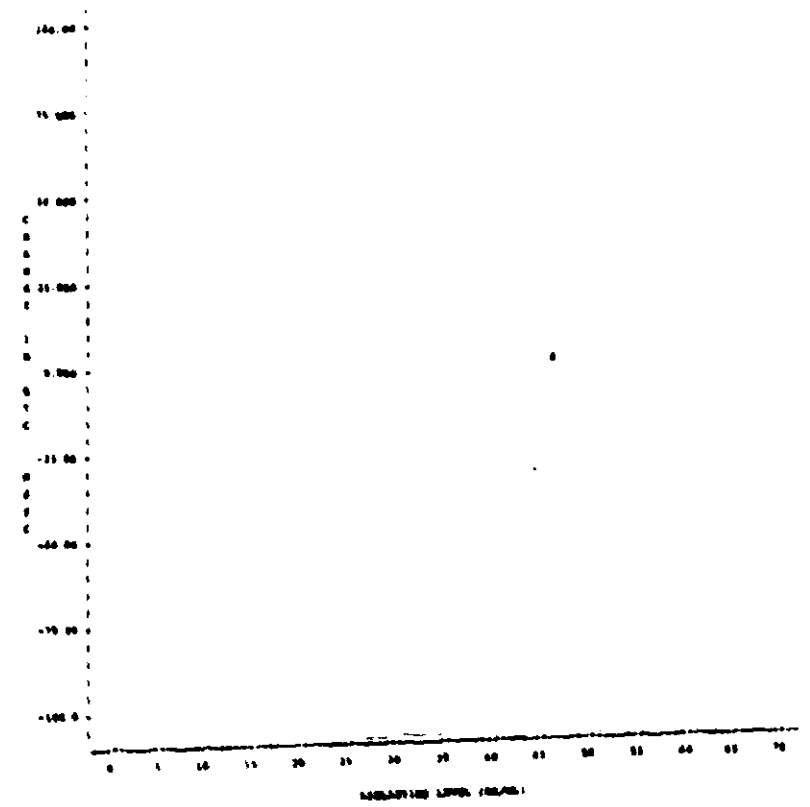
Association Between Azelastine Plasma Levels (ng/mL) and Change in QTc (msec) by Treatment by Study

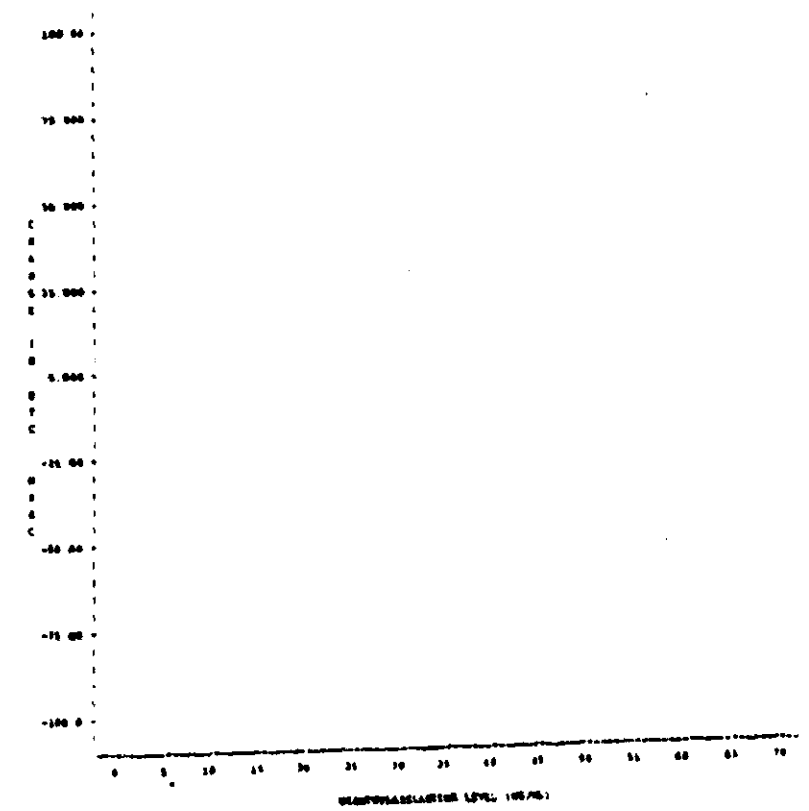
[illegible]	[illegible]	N	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Association Between Desmethylazelastine Plasma Levels (ng/mL) and Change in QTc (msec) by Treatment by Study

[illegible]	[illegible]	N	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Aztiastune ECG Report





September 9, 1993 submission:

Materials and Methods:

ECGs read as abnormal or ECGs from subjects who prematurely withdrew from clinical trials were identified. Overall, 2438 ECGs from 860 subjects were available for analysis. ECGs from 14 subjects (7 abnormals, 7 dropouts) could not be located. Subjects ECGs were categorized into one of four groups.

- Group 1: Abnormal on-therapy ECGs. (452 ECGs from 282 subjects).
- Group 2: Premature discontinuations with normal ECGs (1195 ECGs from 440 subjects).
- Group 3: Premature discontinuations with at least one abnormal on-therapy ECG (519 ECGs from 138 subjects).
- Group 4: Separate listing of ECGs from subjects with QTc interval >500 msec and/or presence of significant U-wave. 10 subjects fulfilling these criteria were identified and reviewed in detail.

Reviewer Comment:

The report is submitted as a tabulation of those subjects who met the above pre-defined criteria. No controls (placebo) were included for comparison. The database does not include the previously identified abnormalities (when existing) in the electrocardiograms. No corresponding plasma concentrations of azelastine/desmethylazelastine (when available) were included. Finally, no analysis of any type was submitted. Possible analyses would have included sensitivity analyses (10% increase or decrease from baseline) if controls could have been identified.

Since no formal analysis is possible, I attempted to categorize subjects with normal pre-treatment repolarization (QTc <440 msec) who had "abnormal" prolonged QTc while on-therapy. 440 milliseconds was arbitrarily chosen as a number that predicts an increased risk of sudden-death in populations.

Study #	Subject #	Dose	QTc(max)	Change from baseline
Group 1:				
95	019			
	023			
	069			
23	085			
	169			
	254			
24	157			
	239			
	364			

187

188

97

190

98

22
68
19

Group 2: All premature dropouts without "abnormal ECGs"

Study #	Subject #	Dose	QTc(max)	Change from baseline

23

24

187

188

190
58

67

Group 3: Premature withdrawals with abnormal ECGs

Study #	Subject #	Dose	QTc(max)	Change from baseline
23				
24				
187				
188				
190				
67				

It should be emphasized that the above tabulation is descriptive only and no comparisons can be made with placebo treatment arms. The change in QTc should be viewed in the

context of known intrasubject variability in QTc which, in some studies, may be up to 70 milliseconds over a 24 hour period.

The sponsor also had individual analyses of those patients with QTc >500 and/or significant U-waves at any time during the study. These cases were reviewed by the Wallace consultant, Joel Morganroth M.D., and are summarized below.

1. Subject #241 from Study #23 was a 35 year old male who received 8 mg azelastine. Prominent U waves were noted at week 4 and were attributed to artifact by Dr. Morganroth.

Reviewer comment: The baseline ECG is within normal limits with a QTc of 438 msecs. A week 5 ECG (obtained at Cmax) shows large U waves with a notching of the T wave in the lateral precordial leads (see copy). The corrected QT interval is well over 500 msecs by my calculation. No azelastine concentrations are given.

2. Subject #367 from Study #24 was a 33 year old female who received 4mg bid azelastine during open label extension of double-blind treatment period and had a QTc of 509 msecs. Baseline QTc was read as 459 msecs. Serum potassiums were noted to be low at the time of the longest QTc (3.3-3.5).

Reviewer comment: No baseline ECG is provided for my analysis. The follow-up electrocardiograms reveal marked abnormalities in T-U wave morphologies including diminished amplitudes of T waves and ST depression. Both of these findings are consistent with drug effects or hypokalemia. No azelastine concentration data is provided.

3. Subject #148 from study #24 was a 15 year old male who received 4mg bid azelastine. Baseline ECG revealed QTc of .457 msec. On-therapy QTc ranged from 496-516 msec. Off-therapy follow-up QTc was 465 msec. Patient was thought to have congenitally prolonged QT.

Reviewer comment: I agree that patient had abnormal baseline cardiac repolarization which was exacerbated and exaggerated with azelastine therapy. Large U waves with T wave notching are evident on therapy (see copy). These resolved with withdrawal of azelastine.

4. Subject #018 was a 76 year old female with numerous concomitant medications. Baseline QTc was read as 475 msecs. Patient received one azelastine dose and ECG recorded at Cmax revealed a QTc of 491 msec. A follow-up (drug-free) QTc was 506 msecs.

Reviewer comment: The baseline ECG obtained from this patient demonstrates evidence of ischemic heart disease and possibility of remote myocardial infarction. The QT interval is prolonged; however, the on-therapy ECG is not different with regard to T-U

segment morphology.

5. Subject #199 from Study #198 was a 48 year old female who received 4mg bid azelastine. Consultant read baseline QTc as 426 msecs and on study QTc(max) of 503 msec.

Reviewer comment: The correction of the QT intervals in this patient is complicated by rapid heart rates (>100/min). It is well established that correction formulas are less accurate at extremes of heart rate. By my calculation the baseline QTc interval is also prolonged at 498 msecs. Analysis of on-study ECGs reveals no quantitative or qualitative differences from baseline.

6. Subject #121 from Study #97 was a 22 year old female who had a baseline QTc of 500 msecs. No on therapy ECG was performed and patient was prematurely discontinued for administrative reasons.

Reviewer comment: I disagree that baseline QTc was as prolonged as stated. By my calculation, the QTc was 445 msecs.

7. Subject #337 from Study #97 was a 33 year old female who received open-label azelastine at 4 mg bid. Baseline QTc was read as 500 msecs. On-study ECG (week 24) had QTc of 462 msecs.

Reviewer comment: The ventricular rates (R-R intervals) in all these tracings make calculation of the QTc interval problematic. The baseline QTc interval is prolonged; however, I disagree that the on-study QTc are quantitatively less.

8. Subject #359 from Study #190 was a 15 year old male who received 4mg bid azelastine. Baseline QTc was 425-453 and maximum on-study QTc was read as 520 msecs.

Reviewer comment: I disagree that the pre-treatment ECG were as low as interpreted. Again, rate (bradycardia) makes QT correction problematic; however, I calculated baseline QTc as 480 mseconds. There are no morphological changes characteristic of drug induced repolarization abnormalities noted in on-therapy ECGs.

9. Subject #601 from Study #190 was a 61 year old female who received 4 mg bid azelastine. Baseline and screening visit QTc were 460 and 500 msecs. On therapy QTcs ranged from 417 to 521 mseconds.

Reviewer comment: Patient has evidence of diffuse myocardial ischemia. T waves are difficult to identify and calculation of a QT interval is made problematic due to frequent PVCs (bigeminy). Of note, Visit 7 ECG is probably from another patient as all T wave inversions are reversed and ectopy is resolved. Subsequent ECGs are consistent with baseline morphologies.

10. Subject 3017 from Study #194 was a 40 year old female who received 1 mg azelastine bid for 2 weeks. Baseline QTc was read as 447 and on-therapy QTc was read as 506 msecs. A follow-up ECG was determined to have a QTc of 471 msecs.

Reviewer comment: I agree that the baseline ECG is morphologically normal with a QTc of 447. I calculate the QTc of the on-therapy ECG to be prolonged at 518 msecs with evidence of dampening of the T wave amplitude. The follow-up ECG had a QTc of 471 msec; however, T waves were morphologically similar to baseline. No azelastine concentrations were provided. Potassium levels are unavailable due to hemolyzed sample.

Conclusion:

Conclusions from the information presented in this report are not warranted. The analyses of the individual case reports may support a drug effect on cardiac repolarization in some of the cases; however, no azelastine/metabolite concentrations are provided. If an effect on QT intervals exists for azelastine, the prospective crossover drug-interaction studies should provide the best information.

Peter Honig, M.D.
Medical Reviewer

10/6/93

11/20/93

2 Pages

Purged

Appendix

B. Influence on the Cardiovascular and Respiratory Systems

In addition to two studies with dogs submitted in NDA studies in this submission further explored the cardiac effects of azelastine (Vol 5, p 423 - 509): 1) anti-arrhythmic or antifibrillatory activity in cats and effect on rabbit purkinje fibers; 2) effects on QT intervals (4-studies in anesthetized pigs); 3) Ca^{2+} ion inhibitory action in airway smooth muscle (3 articles)

I. Cardiovascular system - dogs, cats and domestic pigs

a) Two studies with dogs for Cardiac Effects of Azelastine Hydrochloride (from NDA submitted March 1991)

1) Effects of Azelastine on Local Myocardial Ischemia Induced by Intermittent Occlusion of LAD branches in Thoracotomised Dogs, vol 17, p 05 2642

In a model of repeated coronary occlusions (thoracotomised dog, 5/dose), azelastine in doses of 1 and 2 mg/kg intravenously improved local myocardial conditions.

There were clear reduction of ST-segment elevation (up to 68%) in epicardial ECG lead mediated by reduction in contractility (-15 dp/dt) and heart rate (-15 to -20%) at 45 min, both lowering the oxygen demand of the underperfused tissue. There was a decrease in both systolic and diastolic arterial blood pressure (-11%) which lasted for 15 min and coronary blood flow through LAD was also reduced (by 10% initially) independently of the occlusions. Cardiac output was reduced to much lesser extent.

The reduction of ST-segment elevation was less after the dose of 2 mg/kg azelastine. The maximal effect was reached 45 min postaplication with a reduction of 46%. (Table 1)

More pronounced changes were seen in hemodynamics: hypotension for about 30 min, left ventricular dp/dt max was reduced, heart rate (15%) and cardiac output. (Table 2 and 3)

The observed effects could be explained by Ca^{2+} channel blocking and/or local anesthetic properties of azelastine.

S-T Segment Elevation (mV)

		Initial value	Minutes after application 5	25	45	65	85	105	125	145	165	185
Azelastine 1.0 mg/kg i.v.	x	6.1	3.8	3.0	2.0	2.7	3.5	3.4	4.4	3.8	3.0	4.0
	sd	±3.4	±2.2	±1.6	±1.6	±3.3	±2.4	±2.1	±3.7	±2.1	±2.3	±2.9
	Δ%		-40	-52	-68	-57	-44	-46	-30	-46	-52	-37
Azelastine 2.0 mg/kg i.v.	x	8.9	7.3	6.8	4.8*	4.7	5.4	6.0	5.9	6.1	6.2	5.7
	sd	±5.8	±3.6	±3.0	±3.5	±3.6	±3.3	±3.5	±4.4	±4.0	±4.0	±4.5
	Δ%		-17	-23	-46	-47	-39	-32	-34	-31	-29	-36
Control (saline)	x	7.7	7.9	7.3	7.2	7.4	6.7	6.9	6.9	7.3	6.6	6.5
	sd	±4.7	±4.1	±4.6	±4.6	±5.0	±4.6	±5.3	±5.5	±5.6	±5.0	±4.4
	Δ%		+3	-5	-6	-4	-13	-10	-10	-5	-14	-16

Table 1: Effect of azelastine (1 and 2 mg/kg i.v.) on epicardial ST-Segment elevation (mV) after 5 minutes of occlusion of LAD (reperfusion 20 min). Control experiments with application of 5 ml saline.

Arterial Blood Pressure and Heart Rate

Azelastine 1.0 mg/kg intravenously		Initial value	Minutes after application 5	25	45	65	85	105	125	145	165	185
Arterial blood pressure systolic (mmHg)	x	115	103	107*	108	107	105	103	103	105	105	100
	sd	±17	±21	±13	±13	±18	±13	±16	±15	±18	±4	±5
	Δ%		-11	-7	-6	-8	-9	-11	-11	-9	-9	-14
Arterial blood pressure diastolic (mmHg)	x	81	72*	75	76	75	74	74	71	72	72	68
	sd	±16	±15	±8	±8	±10	±10	±13	±14	±9	±9	±11
	Δ%		-11	-7	-5	-2	-8	-8	-12	-11	-11	-16
Mean arterial blood pressure (mmHg)	x	92	87	87	87	85	84	82	81	84	82	77
	sd	±16	±15	±11	±12	±9	±13	±16	±17	±11	±8	±8
	Δ%		-5	-5	-6	-8	-9	-11	-12	-9	-11	-17
Heart rate (1/min)	x	150	136**	128**	127**	126**	125**	122**	121**	119**	119**	118**
	sd	±20	±24	±23	±22	±23	±22	±23	±24	±23	±22	±20
	%		-10	-15	-16	-16	-17	-19	-20	-21	-21	-22

Table 2: Effects of azelastine (1.0 mg/kg i.v.) on arterial blood pressures and heart rate in anesthetized, thoracotomized dogs (n=5).

Values (x), standard deviation (sd) and changes compared to initial values (Δ%)
Calculation of significance according to t-test for paired values
* : p lesser 0.05 - ** : p lesser 0.01

Cardiac Output, Contractility, EDLVP

Azelastine 1.0 mg/kg intravenously		Initial values	Minutes after application 5	25	45	65	85	105	125	145	165	185
Blood flow Aorta ascend.	x	3.35	3.30	3.26	3.18	3.08*	3.20	3.08	3.18	3.24	3.19	3.16
	sd	±1.46	±1.46	±1.45	±1.29	±1.33	±1.55	±1.41	±1.20	±0.97	±0.80	±0.80
(l/min)	Δ%		-2	-3	-8	-8	-5	-8	-5	-3	-5	-6
Contractility (dp/dt max)	x	2710	2320**	2350**	2308*	2250*	2270*	2230*	2280	2260	2230	2220
	sd	±713	±757	±663	±649	±690	±823	±790	±767	±658	±591	±512
(mHg/sec)	Δ%		-14	-13	-15	-17	-16	-18	-16	-17	-18	-18
Enddiast.left ventr.pressure (EDLVP)	x	5.2	6.4	6.2*	6.4**	6.5**	6.8*	6.2	6.1	6.2	5.7	6.0
	sd	±1.5	±1.1	±1.9	±1.5	±1.4	±1.3	±1.9	±1.9	±2.2	±1.8	±1.7
(mHg)	Δ%		+23	+19	+23	+26	+31	+20	+18	+20	+10	+16
Blood flow left cor.art.desc.	x	41.7	39.4	37.6	38.2	38.2	39.4	38.2	37.0	36.2	35.8	33.9
	sd	±21.8	±24.1	±23.5	±22.1	±22.4	±27.5	±27.1	±25.3	±22.5	±18.2	±17.7
(ml/min)	Δ%		-6	-10	-8	-8	-6	-8	-11	-13	-14	-19

Table 3: Effects of azelastine (1.0 mg/kg i.v.) on cardiac output, contractility, EDLVP and coronary blood flow in anesthetized, thoracotomized dogs (n=5).

Means (x), standard deviations(sd) and changes compared to initial values (Δ%).
Calculation of significance according to t-test for paired values
* : p lesser 0.05 - ** : p lesser 0.01

2) Subacute Toxicity Study in Beagle Dogs of Azelastine Hydrochloride administered orally and daily for five weeks , (vol 30, P 05 6392)

Azelastine was administered orally and daily for 5 weeks to beagle dogs (4/group for 0, 5, 20 and 6/group for 40 and 60 mkd) with doses of 5, 20, 40 and 60 mg/kg/day.

1 One male dog in the 20 mg/kg/day group and all dogs in the 40 and 60 mg/kg/day groups died.

2. Regarding the general appearance, dogs treated with the doses of 20 mg/kg/day and higher exhibited restlessness, excitement, and tonic-clonic convulsion.

3. For cardiac effects, there were prolongation of QT and QRS intervals at ≥40 mg/kg/day but QT prolongation only at 20 mkd. In addition, localized myocardial degeneration in the heart was detected visually and adipose cell infiltration in the interstitial tissue of the myocardium was detected histopathologically among the dogs given 40 mg/kg/day and more. Subacute endocarditis was observed in 1/4 animal in 5 mg/kg/day.

Table 6-1. Five-week subacute toxicity studies of AZT in beagle dogs. Blood pressure, respiratory rate, and electrocardiogram (1).

Group	Animal No.	Blood Pressure (mmHg) Weeks Pre	1	4	Respiratory Rate (times/min) Weeks Pre	1	4	Heart Rate (beat/min) Weeks Pre	1	4
Control	B-5336	170	170	165	44	33	32	140	150	116
	B-5341	150	140	165	48	49	43	126	130	132
	B-5348	150	140	130	28	28	30	109	116	114
	B-5351	165	165	160	44	42	38	131	117	94
5 mg/kg	B-5331	150	160	150	32	36	44	106	123	97
	B-5333	125	120	133	36	28	36	165	112	111
	B-5346	150	165	140	48	31	42	129	123	118
	B-5352	130	140	155	28	22	28	136	124	136
20 mg/kg	B-5332	150	165	140	25	19	28	147	104	95
	B-5339	155	155	155	30	28	10	117	109	97
	B-5343	130	145	150	24	29	33	106	127	154
	B-5344	150	155	140	34	23	54	117	115	119
40 mg/kg	B-5334	130	D	D	27	D	D	128	D	D
	B-5335	160	D	D	40	D	D	117	D	D
	B-5340	155	D	D	45	D	D	120	D	D
	B-5349	150	D	D	36	D	D	107	D	D
	B-5353	150	155	D	20	18	D	144	108	D
	B-5354	155	D	D	16	D	D	126	D	D
60 mg/kg	B-5337	155	D	D	34	D	D	123	D	D
	B-5338	140	D	D	28	D	D	123	D	D
	B-5342	160	D	D	48	D	D	132	D	D
	B-5345	140	130	D	26	31	D	124	94	D
	B-5347	165	D	D	32	D	D	128	D	D
	B-5350	155	D	D	34	D	D	154	D	D

Table 6-2. Five-week subacute toxicity studies of AZT in beagle dogs. Blood pressure, respiratory rate, and electrocardiogram (2).

Group	Animal No.	Interval PQ (msec) Weeks Pre	1	4	QRS (msec) Weeks Pre	1	4	QT (msec) Weeks Pre	1	4	Amplitude R (mV) Weeks Pre	1	4	S (mV) Weeks Pre	1	4	T (mV) Weeks Pre	1	4
Control	B-5336	87	75	89	45	46	45	194	192	211	4.4	3.9	3.8	1.4	1.4	1.7	1.1	0.8	0.7
	B-5341	102	90	99	41	41	42	194	185	212	4.8	4.1	4.6	1.3	1.2	1.4	0.4	0.1	0.3
	B-5348	109	104	107	49	48	50	195	204	205	4.7	3.9	4.9	0.1	0.2	0.5	0.6	0.2	0.4
	B-5351	113	111	102	43	47	47	202	213	219	3.9	3.4	3.5	0.8	0.7	0.6	0.7	0.6	0.6
5 mg/kg	B-5331	105	109	123	43	49	47	213	202	220	2.5	2.4	2.2	1.0	1.0	0.9	0.4	0.3	0.4
	B-5333	94	105	111	39	45	40	180	207	209	3.2	2.7	2.9	1.6	1.1	0.9	0.9	1.0	0.6
	B-5346	100	108	113	47	47	47	184	188	205	3.9	3.6	3.9	0.5	0.5	0.6	0.5	0.1	0.4
	B-5352	102	105	111	44	45	48	202	194	190	5.0	4.3	4.7	0.7	0.5	0.9	0.3	0.1	0.2
20 mg/kg	B-5332	102	99	113	45	47	53	190	214	210	3.8	3.6	3.6	1.4	1.6	2.4	0.7	0.7	1.6
	B-5339	96	98	107	47	46	44	190	222	233	3.2	3.2	2.6	0.6	0.8	1.1	0.6	0.5	0.7
	B-5343	87	100	98	40	41	39	177	190	192	3.6	3.3	3.0	1.2	1.2	1.1	1.4	1.2	1.0
	B-5344	99	101	104	43	43	47	188	215	212	4.6	4.1	4.2	0.5	0.6	0.5	0.8	0.7	0.6
40 mg/kg	B-5334	94	D	D	44	D	D	192	D	D	3.4	D	D	1.4	D	D	0.6	D	D
	B-5335	90	D	D	45	D	D	206	D	D	3.8	D	D	2.2	D	D	0.9	D	D
	B-5340	128	D	D	42	D	D	200	D	D	3.3	D	D	0.6	D	D	0.8	D	D
	B-5349	127	D	D	39	D	D	199	D	D	4.1	D	D	0.8	D	D	1.0	D	D
	B-5353	118	116	D	43	51	D	199	221	D	4.2	4.0	D	1.9	2.2	D	0.9	0.7	D
	B-5354	99	D	D	43	D	D	193	D	D	4.2	D	D	2.2	D	D	1.0	D	D
60 mg/kg	B-5337	140	D	D	40	D	D	190	D	D	4.2	D	D	1.0	D	D	1.0	D	D
	B-5338	111	D	D	41	D	D	190	D	D	4.3	D	D	0.9	D	D	0.5	D	D
	B-5342	91	D	D	41	D	D	177	D	D	4.2	D	D	0.3	D	D	0.7	D	D
	B-5345	108	121	D	45	50	D	187	224	D	3.9	3.7	D	0.5	0.8	D	0.6	1.2	D
	B-5347	95	D	D	44	D	D	197	D	D	3.4	D	D	0.4	D	D	0.4	D	D
	B-5350	95	D	D	45	D	D	171	D	D	3.5	D	D	0.8	D	D	0.4	D	D

b) **Atrial and ventricular antiarrhythmic - antifibrillatory activity of azelastine (A comparison with quinidine in cats)**

Alterations in the susceptibility to cardiac arrhythmia induced by azelastine and quinidine were determined by measuring the electrical threshold for fibrillation in 36 chloralose/urethan anesthetized cats.

Intravenous injection of azelastine (0.5 to 5 mg/kg or 1-10 µmol/kg) to cats resulted in a significant increase in the atrial and ventricular electrical threshold for fibrilloflutter. The magnitude of this action was larger and duration longer than that exhibited by therapeutically meaningful doses of quinidine (2-6 mg/kg). Azelastine has a marked antiarrhythmic- antifibrillatory potency: in atrium about 4 times, in ventricle about 3 times of activity of quinidine, Class 1a antiarrhythmic drug. (Figure 1-4)

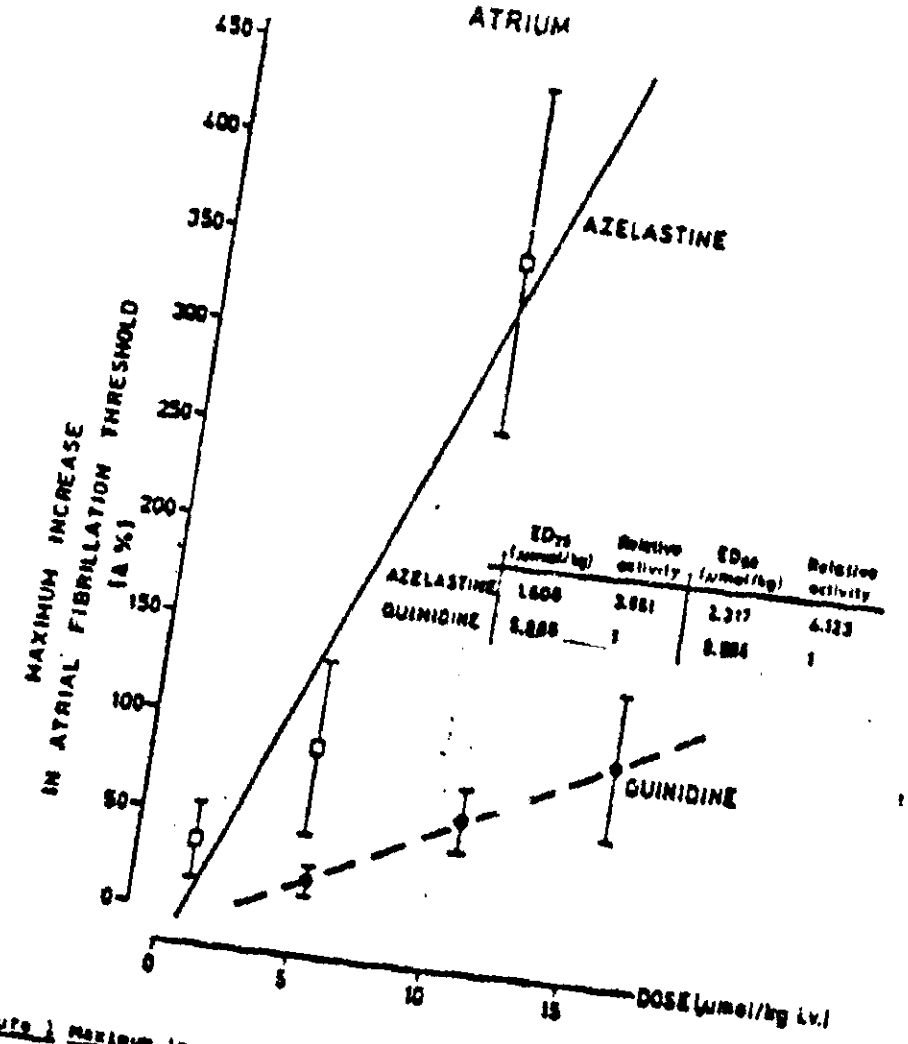
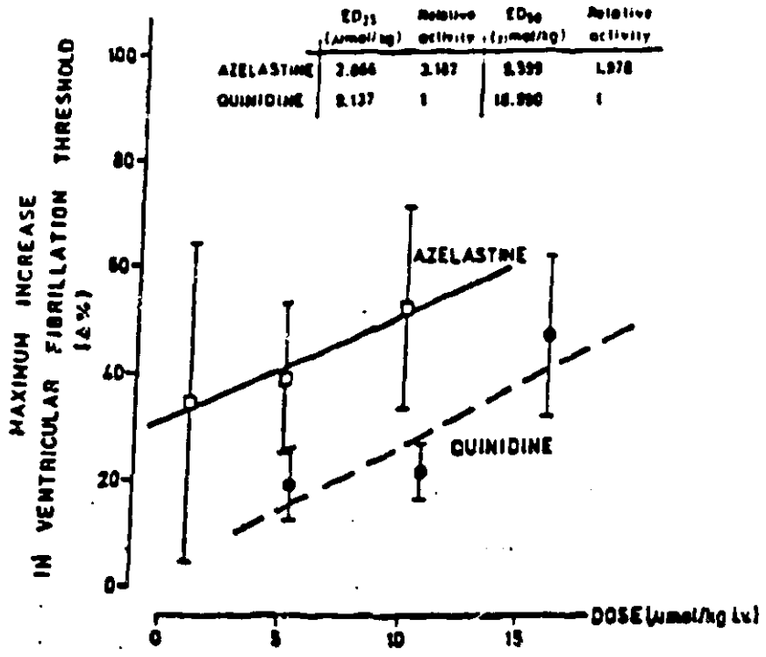


Figure 1 Maximum increase in the electrical threshold for atrial fibrillo-flutter after administration of azelastine or quinidine to cats. Mean values ± S.E.M.; n = number of experiments/animals/. ED_{25} and ED_{50} are the doses required to produce 25 and 50 % increase in the threshold.



	ED_{25} (µmol/kg)	Relative activity	ED_{50} (µmol/kg)	Relative activity
AZELASTINE	2.866	3.167	8.599	1.978
QUINIDINE	9.137	1	16.990	1

Figure 3 Maximum increase in the electrical threshold for ventricular fibrillo-flutter after administration of azelastine or quinidine to cats. Mean values ± S.E.M.; number of experiments /animals/. ED_{25} and ED_{50} are the doses required to produce 25 and 50 % increase in the threshold.

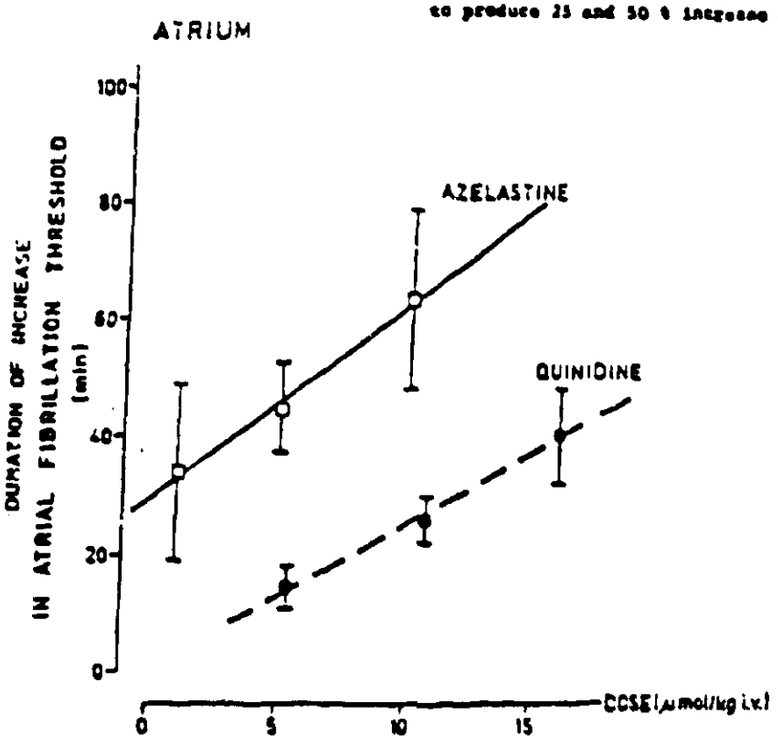


Figure 3 Duration of increase in the atrial fibrillo-flutter threshold after administration of azelastine or quinidine to cats. Mean values ± S.E.M.; n = number of experiments /animals/

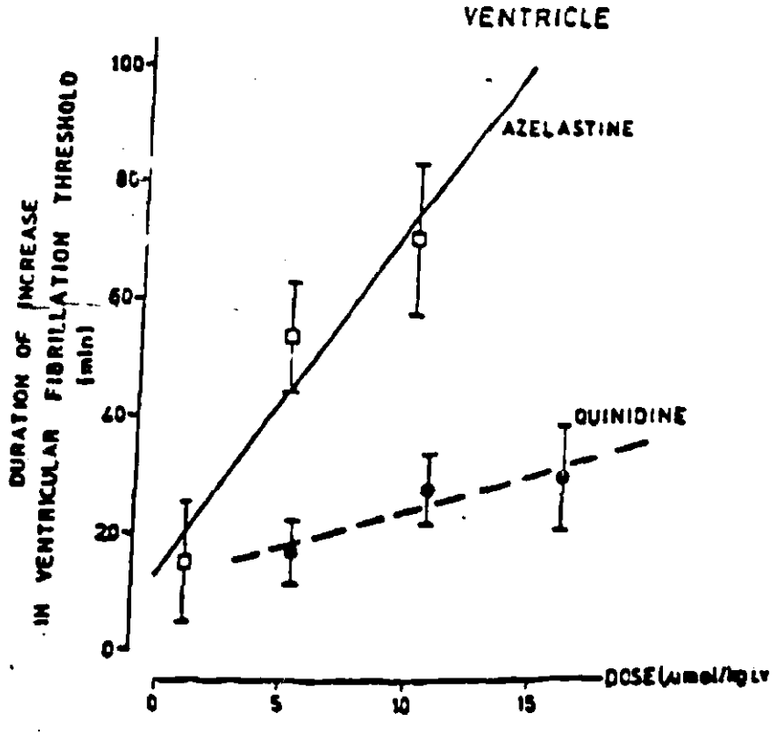


Figure 4 Duration of increase in the ventricular fibrillo-flutter threshold after administration of azelastine or quinidine to cats. Mean values ± S.E.M.; n = number of experiments /animals/.

c) Four studies with anesthetized pigs:

1) Influence of azelastine on QT-interval in anaesthetized young domestic pigs following local (intranasal) and systemic (intravenous) administration (vol 6, p05 438- #253)

Nasal administration of azelastine (0.2 mg/animal) did not influence heart rate or QT duration.

Intravenous infusion in high dosage - 0.03 mg/kg for 90 min - giving a total dose of 2.7 mg/kg reduced heart rate to a minor extent(≤7%) without changing QT or QTc (Table 1-2). In three of the infusion experiments azelastine and desmethyl-azelastine plasma level was estimated to reach values higher than 640 ng/ml far above maximal levels reached in humans under clinical conditions (3-10 ng/ml).

Time	Infused	Plasma levels
15 min	0.45 mg/	423 ± 60 ng/ml
45 min	1.35 mg/	
75 min	2.25 mg/	640 ng/ml

It was concluded that azel in anesthetized young domestic pigs (n= 18) when istered intranasally (200 µg/animal) or intravenously (2.7 mg/kg for 90 min) did not induce significant changes in QT-intervals.

Table 1: QT-duration (msec) and heart rate (1/min) during continous intravenous infusion of azelastine (0.03 mg/kg x min) for 90 min (total dose: 2.7 mg/kg) in anaesthetized domestic pigs. (+ estimation of plasma levels of azelastine by RIA).

Experiment	Control		30 min		60 min		90 min	
	QT	HR	QT	HR	QT	HR	QT	HR
60/88+	320	77	310	74	340	71	360	71
61/88+	290	96	270	96	290	103	290	99
62/88+	290	90	320	76	360	71	360	68
31/88	290	103	285	96	290	96	290	99
35/88	295	67	290	65	295	77	290	87
36/88	295	58	295	59	295	61	292	59
37/88	290	76	295	68	295	63	300	60
79/88	220	111	210	99	240	90	270	90
82/88	300	85	320	75	340	68	320	68
84/88	250	96	250	92	230	105	180	145
89/88	290	100	310	89	310	88	310	91
91/88	280	95	280	84	280	75	270	82
mean	284	87	286	81	297	81	294	85
SEM	7	1	9	1	11	1	13	2
t			0.497	4.649	1.897	2.118	0.998	0.501

Table 2: QT-duration (rate-corrected) and plasma level (ng/ml) during continous intravenous infusion of azelastine (0.03 mg/kg x min) for 90 min (total dose: 2.7 mg/kg) in anaesthetized domestic pigs. (+ estimation of plasma levels of azelastine by RIA).

Experiment	Control	15	30	45	60	75	90	min
	QTc	PL	QTc	PL	QTc	PL	QTc	
60/88+	363	506	344	>640	370	>640	392	
61/88+	367	307	341	539	380	>640	373	
62/88+	355	457	360	>640	392	>640	383	
31/88	380		361		367		373	
35/88	312		302		334		349	
36/88	290		292		297		289	
37/88	326		314		302		300	
79/88	299		270		294		330	
82/88	357		358		362		341	
84/88	316		310		304		280	
89/88	374		378		375		382	
91/88	352		331		313		316	
mean	341		330		341		342	
SEM	9		9		11		11	
t			3.114		0.014		0.187	

Table 5: QTc (heart rate corrected QT-duration) following intranasal instillation of azelastine (0.1 mg/nostril) in anaesthetized domestic pigs

	Ausgangswert	30 min	60 min	90 min
	380	392	405	416
	377	390	400	390
	450	446	417	393
	357	349	331	313
	386	391	389	392
	425	394	416	407
mean	396	394	393	385
SEM	14	13	13	37
t		0.323	0.285	0.734

21 The cardiovascular effects of azelastine after intraduodenal administration in anesthetized pigs (with particular regard to the QT-interval), vol 6, p05453 -f254

The effects of azelastine and terfenadine after intraduodenal administration on the cardiovascular system of anesthetized pigs (2/group) were investigated. When the azelastine was administered at doses of 1 mg/kg id (10 times clinical dose), only minor, non significant and clinically not relevant hemodynamic effects were observed. Blood pressure, heart rate and left ventricular contractility were slowly decreasing throughout the study period of 3 hours.

On the contrary, terfenadine in the dose of 17 mg/kg (10 times clinical dose) showed a significant fall in blood pressure; heart rate and contractility were also diminished throughout the experiment.

No arrhythmias were observed with both test compounds. At the end of experiments heart rate was about 17% under baseline values. Therefore, the calculated RR-interval increased up to a maximum of +21% and +20%, respectively. The measured QT-segment was prolonged by administration of azelastine by 12% and 14% by terfenadine. (QTs 428 to 480 azelastine; 340 to 388 terfenadine) However, the heart rate corrected QT-interval was constant for both drugs.

Minutes after administration	Azelastine			Terfenadine		
	RR interval	QT interval	QT_c corrected	RR interval	QT interval	QT_c corrected
0	546	428	579	420	340	538
15	577	431	567	432	347	528
30	600	451	582	432	349	531
45	618	456	580	455	358	531
60	645	467	581	448	357	533
75	638	473	592	438	357	539
90	645	471	586	426	346	530
120	652	472	585	469	370	540
150	645	475	591	504	389	548
180	659	480 12%	591	504	388 17%	546

Table 3: The effects following intraduodenal administration of 1 mg/kg azelastine or 17 mg/kg terfenadine on RR- and QT-intervals of anesthetized pigs (n=2). Data represent mean values in ms.

3) <u>The effects of azelastine after intraduodenal administration on cardiovascular functions in the anesthetized pig (vol 6, p05467- #255</u>

The effect of azelastine on cardiovascular functions of anesthetized pigs (3/group) was investigated.

The dosage of 1 mg/kg showed no change of any hemodynamic parameter. The dosage of 3 mg/kg produced a fall of arterial as well as of pulmonary blood pressure. This hypotensive effect was not considered significant. The highest dosage of 10 mg/kg (100 x clinical dose of 0.1 mg/kg) caused a general cardiodepressive state: hypotensive effect, decrease of heart rate and left ventricular contractility.

Therefore, it was concluded that azelastine at clinical dose is a safe drug in the cardiovascular system.

4) <u>The effects of azelastine and salbutamol alone and in combination after intraduodenal administration on cardiovascular functions in the anesthetized pig. (vol 6, p05 482- #256</u>

The effect of azelastine and salbutamol alone and in combination on cardiovascular functions of anesthetized pigs (3/group) was investigated.

Azelastine (1 mg/kg, id) alone caused no changes in hemodynamic parameters. In contrast, salbutamol (2 mg/kg, id) caused a significant fall of blood pressure, a significant increase of heart rate, cardiac output and left ventricular contractility. The combination of azelastine and salbutamol demonstrated the effect only related to salbutamol, but none effect by azelastine. Salbutamol acted via stimulation of beta-2-receptors (effect on blood pressure); probably the positive inotropic effect was induced by the unspecific mode of action, that means additional stimulation of beta-1-receptors. The doses of the two test compounds were nearly 20 times higher than those for therapeutic use in patients using the combination of 4 mg azelastine plus 8 mg salbutamol.

In conclusion, intraduodenal administration of azelastine caused no changes in hemodynamic parameters for 3 hours unlike salbutamol. Administering the combination of azelastine and salbutamol, only the effect of salbutamol and no effect related to azelastine were observed.

Summary of The effect of azelastine HCl on cardiovascular functions in anaesthetized domestic pigs:

Azelastine HCl Dose	Route	Results
Study 1		
200 µg/animal	Intranasal	No significant change
2.7 mg/kg	i.v. (90 min)	No significant changes in QT-duration
Study 2		
1 mg/kg	i.d.	Minor decrease in blood pressure, heart rate and left ventricular contractility
Terfenadine 17 mg/kg	i.d.	Significant fall in blood pressure, heart rate and contractility
Both compounds:		QTc-interval was constant No arrhythmias
Study 3		
1 mg/kg	i.d.	No change in hemodynamic parameter
3 mg/kg	i.d.	Fall in systemic arterial and pulmonary blood pressure
10 mg/kg	i.d.	Caused general cardiodepressive state: ↓ BP, HR & left ventricular contractility
Study 4		
1 mg/kg	i.d.	No effect
Salbutamol 2 mg/kg	i.d.	Significant ↓ BP; ↑ HR, CO, left ventricular contractility
Azelastine + Salbutamol	i.d.	Same as Salbutamol effects

Conclusion:

No hemodynamic effects in pigs at 10 times (1 mg/kg) the clinical dose of 0.11 mg/kg

II. Effect on electrical activity - rabbit, guniea pig

Effect of azelastine on intracellular potentials of rabbit purkinje fibers (Classification of azelastine as an antiarrhythmic agent)- Project No. A-05610 (vol.6, p05 497 #257)

Electro-pharmacological effects of azelastine at the cellular level were analyzed in rabbit purkinje fibers (n=16) using microelectrodes.

Azelastine in a dose of 0.5 μM reduced the maximum rate of depolarization (V_{max} i.e. dv/dt_{max}) and the action potential amplitude (APA) of rabbit purkinje fibers, without affecting the resting membrane potential (RP). At the same time there was a very considerable prolongation of the action potential duration, particularly at the late stages of repolarization (APD_{50-90}). The plateau-phase of the action potential was shortened in the presence of azelastine.

This reduction in V_{max} without any change in the resting membrane potential indicates that in Purkinje fibers the drug inhibits the fast inward (depolarizing) sodium current. The decrease in V_{max} induced by azelastine is associated with a prolongation of terminal phases of repolarization (APD_{50-90}), and a concentration-dependent, marked lengthening of the effective refractory period were observed. Such a cardiac electro-pharmacological pattern is also a property of typical of antiarrhythmic agent such as quinidine.

Table 1

Effects of azelastine on parameters of intracellular potentials recorded from rabbit Purkinje fibers

	n	APA (mV)	RP (mV)	APD_{50} (ms)	APD_{70} (ms)	APD_{90} (ms)	V_{max} (V/s)
CONTROL	16	109.6 ±4.1	-78.4 ±2.6	201.1 ±9.2	229.6 ±10.0	252.0 ±13.1	423.2 ±51.0
AZELASTINE 0.5 μmol/l	16	99.0 ±4.7	-77.2 ±3.0	245.2* ±7.4	303.6* ±8.7	351.4* ±21.3	309.3* ±36.7
WASH 90 min	16	104.0* ±3.4	-77.0 ±3.5	189.5 ±17.9	239.0 ±10.2	284.8* ±12.5	351.1* ±40.6

APA: action potential amplitude; RP: resting membrane potential

APD_{50}, APD_{70}, APD_{90}: action potential duration at 50, 70 and 90% repolarization level;

V_{max}: maximum rate of depolarization.

Mean values ± S.E.M.; n = number of experiments (animals).

* $P < 0.01$

Azelastine effects on electrical and mechanical activities of guinea pig papillary muscles. Paschalis-Adam Molyvdas et al. European Journal of Pharmacology: 164 (1989) 547-553

The effects of azelastine on both normal fast action potentials (Aps) and slow Aps were studied using conventional microelectrode techniques in guinea pig papillary muscles.

In cardiac and smooth muscle cells, contraction is partly dependent on mobilization of Ca^{2+} from the intracellular stores (sarcoplasmic reticulum, SR). Ca^{2+} release from the SR is triggered by sudden increase of myoplasmic ionic calcium due to Ca^{2+} entry through voltage- and time-dependent Ca^{2+} slow channels during excitation.
In cardiac cells, Ca^{2+} influx occurs during the plateau component of the action potential, which can be studied in preparations in which the fast Na^{+} channels are inactivated by partial depolarization (to about -40 mV) by elevated $[K]_o$ (e.g. 25 mM). The slow APs and accompanying contractions are blocked by agents that inhibit the slow channels.

The results show that azelastine (10^{-5}-10^{-4} M) affects the fast Aps (Fig 4) and slow Aps and contractions of guinea pig papillary muscle (Figure 2).

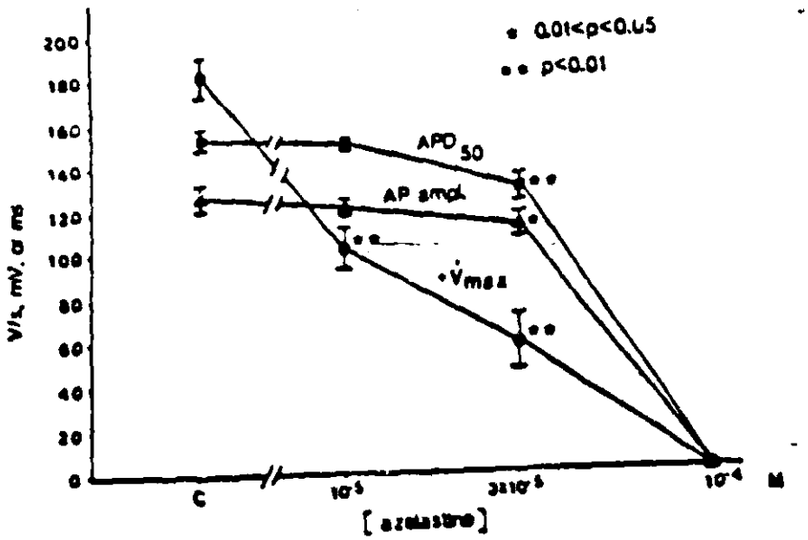


Fig. 4. Summary of the effects of cumulative concentrations of azelastine on the parameters of the fast action potentials (APs) of guinea pig papillary muscles. The parameters of the fast APs presented are AP amplitude, $\dot{V}_{max}$, and AP duration at 50% repolarization (APD_{50}). Data are presented as means ± S.E. (n = 4). Statistical significance from the control value is indicated by * $0.01 < P < 0.05$ and ** $P < 0.01$.

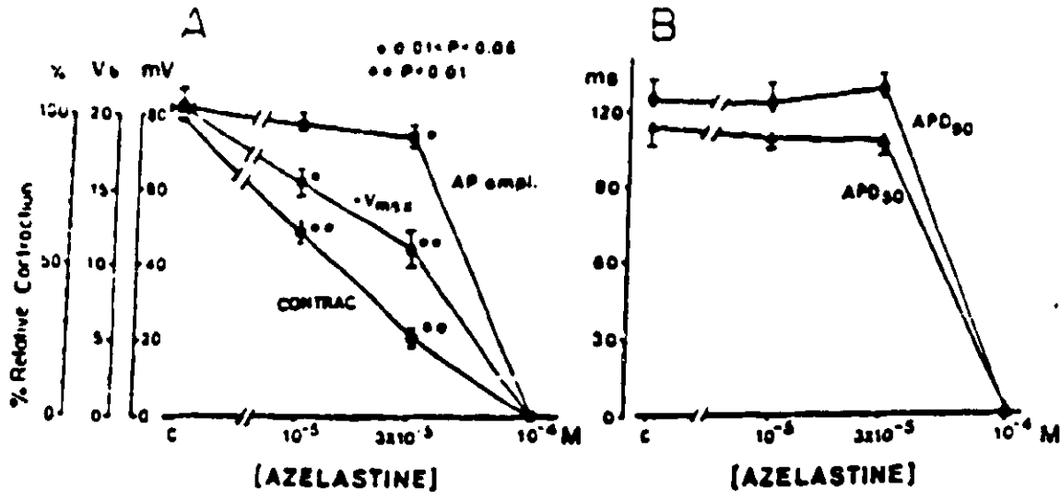


Fig. 2 Summary of the effects of cumulative concentrations of azelastine on various parameters of the isoproterenol (10^{-7} M)-induced slow APs and contractions of guinea pig papillary muscles. (A) Effect of azelastine concentration on slow AP amplitude, $+V_{max}$ and contraction. (B) Effect of azelastine concentration on duration of the slow APs at 50% repolarization (APD_{50}) and at 90% repolarization (APD_{90}). Data are presented as means ± S.E. (n = 5). Statistical significance from the control value is indicated by * $0.01 < P < 0.05$ and ** $P < 0.01$.

It was concluded that azelastine, in cardiac muscle at concentrations of 10^{-5}-10^{-4} M, inhibits the slow Ca^{2+} channels and the fast Na^{+} channels. The drug may also accumulate inside the cell and exert a prolonged inhibitory effect, possibly on the Ca^{2+} release from the intracellular stores and/or the Ca^{2+} sensitivity of the contractile proteins.

3. Effect on airway smooth muscle - rabbit, dog and human

Three published articles:

1) Aizawa,H. et al.: Effects of azelastine on vagal neuroeffector transmission in canine and human airway smooth muscle. J Allergy Clin Immunol 86:171-176 (Aug) 1990 (vol 5, p05 291 - #243)

Azelastine (10^{-4} to 10^{-6} mol/L) markedly decreased the contractile response of human bronchial and dog tracheal muscle strips to electrical field stimulation in a dose-dependent manner without changing resting membrane potential.

This indicate that azelastine inhibits the acetylcholine release from the vagal nerve terminals by interfering Ca^{2+} influx into the mast cells.

2) Richards,I.S. et al.: Azelastine and desmethylazelastine supress acetylcholine-induced contraction and depolarization in human airway smooth muscle. Eur J Pharmacol 186(2-3):331-334 (Sep 21) 1990 (vol 5, p05 297 - #244)

The effects of azelastine and desmethylazelastine on the in vitro electromechanical response of human airway smooth muscle during cholinergic stimulation were examined by measuring membrane potential and isometric force using an intracellular microelctrode and a microforce transducer.

Desmethylazelastine significantly suppressed acetylcholine-induced depolarization and contraction at 10^{-4} M, whereas azelastine produced similar results at 10^{-4} M.

3) Senn,N., Jeanclos,E. Garay,R.: Action of azelastine on intracellular Ca^{2+} in cultured airway smooth muscle. Eur J Pharmacol 205:29-34, 1991 (vol 5, p05 317 - #245)

Azelastine was tested for Ca^{2+} antagonistic properties in cultured rabbit airway smooth muscle, vascular smooth muscle and cardiocytes.

In airway smooth muscle cells, the basal cytosolic free calcium content was 195 ± 72 nM. These basal values were decreased by azelastine with an IC_{50} value of 1.1×10^{-4} M.

Endothelin-1 (10^{-7} M) induced a rapid increase in free cytosolic calcium up to 806 ± 314 nM, which returned to normal levels in 3-5 min. This was fully blocked by azelastine in a concentration-dependent manner, with an IC_{50} value of 6.7×10^{-5} M.

Azelastine fully blocked histamine-induced calcium mobilization ($IC_{50} = 7 \times 10^{-5}$ M).

In cultured vascular smooth muscle cells and cardiocytes, azelastine was unable to decrease the basal cytosolic free calcium content or inhibit agonist-induced calcium mobilization. Therefore, at therapeutic levels, a specific, mild inhibition of calcium mobilization in airway smooth muscle may be one component of the antiasthmatic action of azelastine.

Summary of Cardiac Effects

In general, azelastine hydrochloride in therapeutic dose ranges did not show any appreciable pharmacological effects on the cardiovascular (including ECG) system of anesthetized rats, dogs, cats and domestic pigs.

In anesthetized young domestic pigs, administration of azelastine Hcl (200 µg/animal) by the nasal and intravenous (2.7 mg/kg during 90 min) routes produced no significant changes in QT duration.

Azelastine HCl (1 mg/kg, i.d.) did not exert any significant effect on cardiovascular parameters in domestic pigs. However, intraduodenal administration of salbutamol(2 mg/kg) produced a significant decrease in blood pressure and significant increase in heart rate, cardiac output and left ventricular contractility. The combination of azelastine Hcl and salbutamol produced cardiovascular effects identical to those of salbutamol alone.

Azelastine hydrochloride (1 mg/kg, i.v.) in dogs showed only minor effects; blood pressure fall, reduced heart rate and decreased left ventricular contractility throughout the three hour study period.

At 1 mg/kg, i.v. azelastine Hcl exerted long lasting reduction of ST segment elevation in dogs undergoing repeated coronary occlusion. It also produced a nondose-related inhibition of arrhythmias induced in rats by coronary artery occlusion.

Orally, ECG changes, prolonged Q-T intervals at 20 mg/kg and prolonged QRS and QT intervals were observed at ≥40 mg/kg in a 5-week oral toxicity study in dogs. In addition, localized myocardial degeneration in the heart and adipose cell infiltration in the interstitial tissue of the myocardium have been noted at 40 and 60 mg/kg, respectively. However, doses above 20 mg/kg/day orally was toxic and lethal to the dogs. Azelastine hydrochloride was irritant to vessels at all dose levels when administered intravenously to dogs.

In chloralose/urethane-anesthetized cats, intravenous injection of azelastine Hcl (0.5-5 mg/kg) resulted in significant increase in the atrial and ventricular electrical thresholds for fibrilloflutter. The magnitudes of these actions were greater than those exhibited by therapeutically meaningful doses of quinidine (2 to 6 mg/kg).

Azelastine HCl has a marked antiarrhythmic-antifibrillatory potency, in the atrium about four times and in the ventricle about three times the activity of quinidine.

Azelastine HCl increased the electrical threshold for fibrilloflutter in anesthetized cats (0.5 to 5 mg/kg,i.v.); reduced the maximum rate of depolarization and action potential (AP) amplitude of rabbit purkinje fibers without affecting the resting membrane potential. It also prolonged the AP, particularly the APC_{50-90} (the late stages of repolarization), showing antiarrhythmic property. In guinea pig papillary muscles, azelastine HCl inhibits the slow Ca^{2+} channels and the fast Na^{+} channels. Azelastine HCl may also accumulate inside the cell and exert a prolonged inhibitory effect, possibly on the Ca^{2+} release from the intracellular stores and/or the Ca^{2+} sensitivity of the contractile proteins.

Effects of azelastine HCl on animal and human airway smooth muscle were tested:

a) Azelastine (10^{-8} to 10^{-4} mol/L) markedly decreased the contractile response of human bronchial and dog tracheal muscle strips to electrical field stimulation in a dose-dependent manner without changing resting membrane potential. This indicate that azelastine inhibits the acetylcholine release from the vagal nerve terminals by interfering Ca^{2+} influx into the mast cells.

b) Desmethylazelastine significantly suppressed acetylcholine-induced depolarization and contraction of human airway smooth muscle at 10^{-6} M, whereas azelastine produced similar results at 10^{-4} M.

c) Azelastine was tested for Ca^{2+} antagonistic properties in cultured rabbit airway smooth muscle, vascular smooth muscle and cardiocytes.

In airway smooth muscle cells, the basal cytosolic free calcium content (195 ± 72 nM) was decreased by azelastine with an IC_{50} value of 1.1×10^{-4} M and blocked endothelin-1 (10^{-7} M) induced increase in free cytosolic calcium and histamine-induced calcium mobilization in a concentration-dependent manner, with an IC_{50} value of 6.7×10^{-5} M and 7×10^{-5} M, respectively.

C. Anti-Inflammatory Activity

1. Effect on calcium pyrophosphate-induced pleurisy - mouse

Calcium pyrophosphate (CaPP)-induced pleurisy in mice is an acute non-specific inflammatory condition. It is primarily mediated by synthesis nd release of IL-1. Azelastine HCl or dexamethasone (5μM/kg, i.p. or p.o.,-30 min) produced a pronounced inhibition of CaPP-induced exudate volume and infiltration of inflammatory cells in the pleural cavity at two- to six-hour time intervals.

The chemotactic activity of pleural exudate on rat T-cells was inhibited by azelastine Hcl and dexamethasone. Both the drugs also inhibited IL-1 release in pleural exudate and leukocyte chemotactic activity. Azelastine Hcl also inhibited zymosan-treated serum-induced PMN chemotaxis.

2. Effect on PAF-induced chemotaxis - human eosinophils

Azelastine HCl, ketotifen (3-300 Nm), tranilast (0.1-10 μM), and dexamethasone (0.01-1 μM) did not influence PAF-induced eosinophil chemotaxis. Aminophylline (20-200 μg/ml) and isoproterenol (10-100 Nm) significantly suppressed chemotactic responses.

3. Effect on IL-1ß-induced neutrophil infiltration-mouse ear

Azelastine Hcl (20 mg/kg, 24 and 2 h) did not influence IL-1ß-induced PMN influx in mouse ear. Human recombinant IL-1ß (150 U) was injected s.c. into the left ear and sacrificed to determine myeloperoxidate (MPO) activity which is a marker enzyme for PMNs.

D. Pharmacology of Metabolites and Isomers of Azelastine HCl

The pharmacological profile of azelastine HCl's enantiomers has been summarized in a report. Azelastine HCl is a racemic mixture of d and l enantiomers. The pharmacological activities of the racemic mixture and each of the optical isomers have been evaluated in a few pharmacological models of immediate allergic reactions. Although the order of potency of these compounds varied throughout these studies depending on the model system, dose and time intervals used, the sponsor states that overall the d or l isomer offers no advantage over the racemate with respect to pharmacological activities.

Policy

8/6/93

MEDICAL OFFICER NDA REVIEW

DATE REVIEWED: June 22, 1993, Revised July 19, 1993
NDA# 20-114
REVIEWER: Martin H. Himmel, M.D.
PRODUCT: Azelastine Hydrochloride
CATEGORY of DRUG: antihistamine
ROUTE of ADMINISTRATION: intranasal spray
SPONSOR: Wallace Labs
DATE RECEIVED: FDA 3/26/91
REVIEWER 5/1/91
MATERIAL REVIEWED: Submission of March 26, 1991, December 19, 1991 and February 19, 1993
PREVIOUS PERTINENT SUBMISSIONS: See MOR for the tablet formulation of this drug. Efficacy data is reviewed in the MOR of 5/20/93 and safety data is in the MOR of 2/24/93

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Introduction

Azelastine hydrochloride nasal spray, which will be marketed as Astelin N.S., is a 0.1% nasal spray solution administered via a pump spray bottle which delivers 0.13ml (.13mg of azelastine) per spray. The proposed labelling indicates that the sponsor is looking for an indication of allergic rhinitis in adults, and that the proposed clinical dosage is two sprays q day and bid.

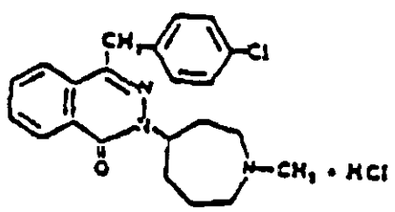
Chemistry

Chemical Name: (±)-(2H)-Phthalazinone, 4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-monohydrochloride

Molecular Formula: $C_{22}H_{24}ClN_3O$ HCL

Molecular Weight: 381.90/418.37 (base/hydrochloride)

Structural Formula:



At this point, it is important to note that the sponsor has used a number of spray pumps in the development of this product. Whereas studies #25 and 30 (study #25 is a pharmacology/safety trial and study #30 is a dose ranging trial) were conducted using a Pfeiffer pump, which delivers .12mg per spray, the other dose ranging trial (study #32) and all the pivotal efficacy trials were conducted using the Valois A pump which delivers .137mg per actuation. The importar . issue here, however, is that the sponsor intends to market a final drug product using a Valois B pump. The difference between the two Valois pumps is that the A pump (regarding which there were problems of drug leakage) uses a butyl rubber 3/522 sealing gasket with a polyethylene spring support and the Valois B pump uses a PEV-1 sealing gasket and a polypropylene or polyethylene spring support. According to the reviewing chemist (Dr. Ng) both sealing gaskets and spring supports have the same physical shape and the difference is only what they are

made of. The following is a comparison of the in vitro characteristics of the two Valois pumps, based on what is currently available in the NDA:

Parameter	Valois A (used in pivotal trials)	Valois B (to be marketed)
Physical Differences	butyl rubber 3/522 sealing gasket and polyethylene spring support	PEV-1 sealing gasket and polypropylene or polyethylene spring support
Mean Delivered Volume as percent of labelled dose (137ul/actuation)	98.5%	100.5%
Droplet Size Distribution	D50% = 50 micron	D50% = 49 micron

No data is provided regarding plume geometry. According to the reviewing chemist, the data provided regarding the Valois B pump is inadequate to characterize the pump. Additional information will be requested regarding droplet size distribution at a number of different points as well as plume geometry information.

Comment: The difference between the two pumps in mean delivered volume is not great and, in fact, would fall within the specs of the to be marketed pump of 90-110%. In addition, the fact that the physical shape of the sealing gaskets and springs are the same is somewhat reassuring regarding efficacy, however, there is currently inadequate data to make a comparison of the two pumps regarding parameters such as droplet size distribution and plume geometry. I have asked the chemists to request the information that they are seeking for both the Valois A and B pumps so that a comparison of these in vitro parameters can be made and a determination can then be made regarding whether the pivotal trials will support use of the to be marketed pump. In addition, the use of a sealing gasket and spring made of materials not used in the clinical trials could be problematic if the excipient profile of the two pumps differ. Whereas all excipients seen with pump A will have been evaluated for safety in the clinical trials, the same is not true for pump B. Therefore, chemistry has been asked to compare the excipient profile of the two pumps, following which a determination of the safety of excipients seen with pump B but not A will have to be made.

Pre-Clinical

ADME:

When administered orally, Tmax is 1-2 hours with dose proportionality up to 30mg/kg in rats and 60mg/kg in mice. In the dog, the volume of distribution was approximately 20 times the body weight. There is evidence of placental transfer as well as low levels of transfer to the brain in rodents. High first pass effect is noted in lab animals.

As in the human, there are a number of proposed metabolites with desmethylazelastine being the major one. Qualitatively, inter-species differences in the major metabolites has been shown, which, according to the pharmacology reviewer, may account for differences in toxicity seen among the different species. Based on effects on antipyrine, azelastine is not considered an enzyme inducer. In the rat, azelastine is 53-57% protein bound, which is less than the degree seen in humans.

The major route of excretion is biliary, with no signs of drug accumulation with repetitive dosing. The terminal half life for elimination of azelastine and its metabolites is 4-8 hours.

No pharmacokinetic data specific to the intranasal route of delivery is available.

Toxicology:

As per the pharmacologist's review of the pre-clinical data, major findings in the animal studies included elevated levels of alkaline phosphatase, SGOT and SGPT as well as reversible fatty changes in the liver and hepatocellular hypertrophy at oral doses of 30mg/kg/dy. Renal cortical tubular epithelium degeneration was seen in one 6 month dog study, however no changes in BUN, creatinine or specific gravity were seen.

In the dog, intravenous doses of 2-10mg/kg of azelastine resulted in dose dependent decreases in blood pressure, with both increases and decreases in heart rate noted. At 1mg/kg IV, reduction of induced ST segment elevation was noted.

Oral doses of 20mg/kg prolonged QT intervals and at 40 and 60mg/kg localized myocardial degeneration and adipose cell infiltration of the interstitial tissue of the heart were seen, respectively. Doses above 20mg/kg/dy in the dog were lethal.

At all dose levels, intravenous administration of azelastine was an irritant to vessels.

When administered intranasally to rats and dogs for six months duration, there were no systemic signs of toxicity nor were there signs of irritation to the epithelial lining of the nasal cavity.

Mutagenicity:

No mutagenic effects using the AMES test, DNA repair test, mouse lymphoma forward mutation assay, mouse micronucleus test or rat chromosomal aberration test were noted.

Carcinogenicity:

The conclusion of the reviewing pharmacologist regarding rat and mice carcinogenicity trials is that there was adequate exposure of each of these species to azelastine administered orally and that these studies support classifying azelastine as a non-carcinogen.

Reproduction:

The pharmacology review of this data concluded that at doses up to 3mg/kg, which is 37 times the clinical dose (there is no pharmacokinetic data available in the rat to compare exposure between rats and humans, however, using data from the mouse a 3mg/kg dose results in an approximately 15 fold greater exposure, based on AUC, than the 2mg bid dose in humans), there were no signs of maternal toxicity, reduced fertility, fetotoxicity or teratogenicity. At 30mg/kg adult rats showed systemic toxicity and there were reduced fetal weights, signs of skeletal anomalies and retarded ossification. At 68.6mg/kg azelastine was teratogenic, fetotoxic and maternally toxic.

Extent of Nasal Spray Exposure

A total of 1464 subjects participated in controlled clinical trials involving azelastine nasal spray. Of these, 144 participated in "clinical pharmacology" trials (105 subjects had perennial allergic rhinitis and 39 were normal volunteers) and 1320 participated in "clinical research" trials. All subjects participating in clinical research trials had seasonal allergic rhinitis. Of the 1464 subjects, 789 received azelastine, 313 received positive controls and 362 received placebo.

In studies conducted in Europe, 367 subjects were treated with azelastine in both controlled and uncontrolled trial (182 in controlled and 185 in uncontrolled trials), 181 subjects received positive controls and 8 subjects received placebo.

The following three tables summarize the duration of exposure in the US clinical pharmacology and clinical research trials as well as the European studies:

Azelastine Safety Summary (U.S. Studies)
Nasal Spray Formulation
Duration of Clinical Exposure to Treatment, by Study Type and Treatment
Clinical Pharmacology

Study Type	Treatment	Number of Subjects Exposed by Duration					Total
		0–10 days	18–29 days	32–38 days	53–59 days	60–64 days	
Perennial Allergic Rhinitis	2 sprays q12h	6	1	2	58	2	69
	placebo	1	0	0	34	1	36
Normal	1 spray qd/ q12h	0	10	0	0	0	10
	2 sprays qd/ q12h	0	10	0	0	0	10
	3 sprays qd/ q12h	0	10	0	0	0	10
	placebo	0	9	0	0	0	9
Total		7	40	2	92	3	144

Azelastine Safety Summary (U.S. Studies)
Nasal Spray Formulation
Duration of Clinical Exposure to Treatment, by Treatment
Clinical Research

Study Type	Treatment	Number of Subjects Exposed by Duration					
		Up to 1 Week	>1 to 2 Weeks	>2 to 4 Weeks	>4 to 8 Weeks	Unknown	Total
Controlled	Az 1 spray q12h	54	0	0	0	0	54
	Az 2 sprays qd	131	104	71	7	1	314
	Az 2 sprays q12h	137	106	74	5	0	322
	Chlor 12 mg q12h	130	102	74	7	0	313
	Placebo	139	101	66	8	3	317
Total		591	413	285	27	4	1320

Azelastine Safety Summary (Foreign Studies - European)
Nasal Spray Formulation
Duration of Clinical Exposure to Treatment, by Study Type and Treatment

Study Type	Treatment	Number of Subjects Exposed by Duration							
		Up to 1 Week	>1 to 2 Weeks	>2 to 4 Weeks	>4 to 8 Weeks	>8 to 22 Weeks	>22 Weeks	Unknown	Total
Controlled	Az 1 spray qd	0	26	0	0	0	0	0	26
	Az 1 spray bid	0	5	15	135	0	0	1	156
	Terfenadine	0	9	11	137	0	0	6	163
	Budesonide	0	18	0	0	0	0	0	18
	Placebo	0	8	0	0	0	0	0	8
Uncontrolled	Az 1 spray bid	0	0	1	7	26	149	2	185
Total		0	66	27	279	26	149	9	556

Demographics

The following table, taken from the NDA, depicts the demographic breakdown of the subjects enrolled in the US clinical pharmacology trials:

Study Type	Sex		Race			Age	Weight
	Male	Female	White	Black	Other	Range (years)	Range (lbs.)
Normal	100%	0%	87%	10%	3%	19-40	140-198
Perennial Allergic Rhinitis	42%	58%	96%	2%	2%	11-54	76-286

For the controlled clinical research trials, the following is the breakdown of subjects by sex and race for each of the treatment arms (percentages are the

percent of subjects in that treatment arm):

Treatment Group	Sex		Race		
	Male	Female	White	Black	Other
Az 1 spray q 12h	39%	61%	89%	2%	9%
Az 2 sprays qd	54%	46%	90%	5%	5%
Az 2 sprays q 12h	55%	45%	88%	4%	8%
Chlor 12mg q 12h	51%	49%	89%	4%	6%
Placebo	53%	47%	91%	5%	4%

The following two tables depict the breakdown of subjects in the controlled clinical research trials by age range and weight:

Treatment Group	Age Range			
	< 18	18 - 40	41 - 60	> 60
Az 1 spray q 12h	30%	59%	15%	0%
Az 2 sprays qd	17%	63%	20%	.6%
Az 2 sprays q 12h	16%	60%	22%	3%
Chlor 12mg q 12h	18%	61%	18%	2%
Placebo	19%	60%	20%	2%

Treatment Group	Weight (lbs)		
	Under 110	110-170	Over 170
Az 1 spray q 12h	9%	67%	24%
Az 2 sprays qd	5%	60%	35%
Az 2 sprays q 12h	6%	54%	41%
Chlor 12mg q 12h	7%	59%	34%
Placebo	6%	60%	34%

The following two tables depict the demographics of the foreign studies:

Azelastine Safety Summary (Foreign Studies)
Nasal Spray Formulation
Demographic Characteristics (Sex) by Study Type and Treatment

Study Type	Treatment Group	Number of Subjects Exposed by Sex		
		Female	Male	Total
Controlled	Az 1 spray qd	14	12	26
	Az 1 spray bid	72	84	156
	Budesonide	6	12	18
	Terfenadine	82	101	183
	Placebo	3	6	9
Uncontrolled	Az 1 spray bid	89	100	189
Total		341	315	556

Azelastine Safety Summary (Foreign Studies)
Nasal Spray Formulation
Demographic Characteristics (Age Range) by Study Type and Treatment

Study Type	Treatment Group	Number of Subjects Exposed by Age Range				
		< 30	30 to 40	40 to 60	> 60	Total
Controlled	Az 1 spray qd	8	10	16	8	26
	Az 1 spray bid	10	116	35	5	156
	Budesonide	0	0	18	0	18
	Placebo	0	3	6	0	9
	Terfenadine	15	123	20	5	163
Uncontrolled	Az 1 spray bid	0	107	53	17	185
Total		33	366	130	27	556

Comment: **The demographic data presented above indicates that while there is a good mix of males and females in the trials, there are few non-white subjects and few subjects above the age of 60. In addition, there is little data on the usage of azelastine nasal spray at a dose of two sprays per nostril bid beyond a duration of four weeks.**

Pharmacokinetics

Study #25 (pharmacology/safety trial)

This is a double blind, placebo controlled, randomized, parallel trial of the safety of .1% azelastine nasal spray administered at a dose of 1, 2 or 3 sprays per nostril (.12mg/spray, Pfeiffer pump) bid for 29 days. 10 subjects were randomized to receive each dose of azelastine and an additional 9 subjects received placebo.

In addition to baseline and weekly physical exams and lab tests, nasal status exams were performed at screening, predose, .25, 4, 6 and 8 hours post dose on study day 1 and predose and .25 hours postdose on study days 2, 4, 6, 8, 11, 15, 18, 22, 25, 29, 30, 31 and 36. Subjects were also told to fast for 10 hours prior to dosing until 4 hours postdose on study days 1, 8, 15, 22 and 29 for pharmacokinetic assessment of azelastine and desmethylazelastine levels.

Results:

STUDY DAY 1			
SPRAYS PER NOSTRIL	T_{max} (h)	C_{max} (pg/ml)	AUC
1 spray	2.14	130.36	2166.47
2 sprays	2.67	196.67	16671.85
3 sprays	2.11	251.71	6579.93
STUDY DAY 29			
1 spray	2.25	264.13	2692.23
2 sprays	2.50	306.81	3180.28
3 sprays	2.05	1195.15	11418.52

Comment: **Following discussion of the data in the table above with the reviewer from biopharm it was felt that the AUC value for 2 sprays per nostril on day 1 may be an error. As can be seen on the following table, this value appears quite**

aberrant when compared with the AUC values for 2 sprays per nostril on days 8, 15, 22 and 29:

Summary of Means and Standard Deviations of
Azelastine Pharmacokinetic Parameters for
Study Days 1, 8, 15, 22 and 29 After Administration of
One, Two or Three Sprays Per Nostril of Azelastine Hydrochloride Nasal Spray

1 Spray Each Nostril				2 Sprays Each Nostril				3 Sprays Each Nostril			
Study Day	AUCn (pg·h/mL)	Cmax (pg/mL)	Tmax (h)	Study Day	AUCn (pg·h/mL)	Cmax (pg/mL)	Tmax (h)	Study Day	AUCn (pg·h/mL)	Cmax (pg/mL)	Tmax (h)
Study Day 1											
Mean	2166.47[a]	130.36	2.14	Mean	16671.85	196.87	2.67	Mean	6579.93[a]	251.71	2.11
SD	687.30	37.87	1.35	SD	18651.67	117.47	1.32	SD	3197.78	178.46	1.62
n	4	7	7	n	5	8	9	n	8	9	9
Study Day 8											
Mean	1874.38[ab]	223.48[ab]	3.23	Mean	4143.29[a]	402.00[a]	3.33	Mean	8635.93[a]	876.50[a]	2.18
SD	801.05	87.51	2.26	SD	1777.51	172.97	2.17	SD	7127.65	681.41	1.63
n	10	10	10	n	10	10	10	n	10	10	10
Study Day 15											
Mean	2302.85[a]	297.17[a]	1.66	Mean	3082.22[a]	334.72[a]	3.00	Mean	10350.10[ab]	1089.85[ab]	1.93
SD	1139.10	133.48	1.34	SD	1365.07	150.14	2.11	SD	7253.28	716.39	2.24
n	10	10	10	n	10	10	10	n	10	10	10
Study Day 22											
Mean	2612.64[a]	289.06[a]	4.40	Mean	3183.60[a]	311.01[a]	3.13	Mean	9654.53[ab]	976.59[ab]	1.75
SD	1219.67	117.36	4.08	SD	1163.32	117.66	2.57	SD	6438.91	636.97	1.35
n	10	10	10	n	10	10	10	n	10	10	10
Study Day 29											
Mean	2692.23[a]	264.13[a]	2.25	Mean	3180.28[a]	306.01[a]	2.50	Mean	11416.52[ab]	1195.15[ab]	2.05
SD	1571.01	146.46	2.08	SD	1276.76	121.77	1.43	SD	8942.83	863.69	1.75
n	9	10	10	n	10	10	10	n	10	10	10

a indicates comparison of 1 spray versus 2 sprays is significantly different ($p \leq 0.05$)
b indicates comparison of 1 spray versus 3 sprays is significantly different ($p \leq 0.05$)
c indicates comparison of 2 sprays versus 3 sprays is significantly different ($p \leq 0.05$)
On Study Days 1 and 29 each subject received a single dose; on Study Days 2-28 each subject received doses b.i.d.

Beginning with the third sampling period, day 15, C_{max} and AUC were not significantly different between the 1 and 2 sprays per nostrils doses, however, both groups were significantly different from the three sprays per nostril group.

Because desmethylazelastine concentrations were below the limit of quantitation, pharmacokinetic analysis of this metabolite was not possible.

Based on an across studies comparison of AUC, the absolute bioavailabilty of

azelastine nasal spray when administered at a dose of .24-.48mg (each spray using the Valois pump delivers .13mg) is 40% (range 28-52%) with reference to an intravenous dose of 4.5mg (absolute bioavailability of the tablet is 82%).

As is demonstrated on the following two graphs of the pharmacokinetic data from this trial, the kinetics of this drug do not appear linear:

Figure 1

PLOT OF AUC VS. DOSE FOR AZELASTINE

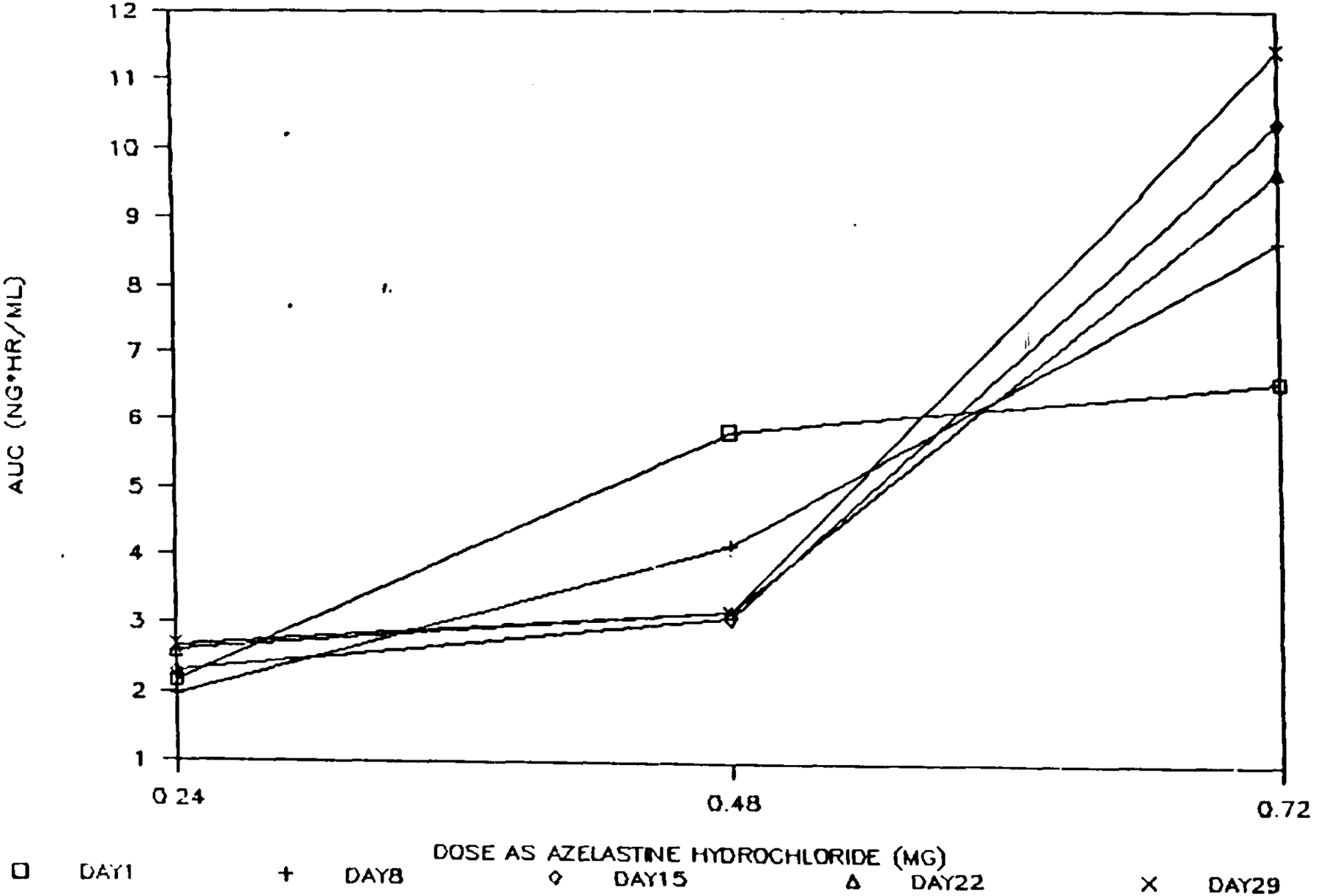
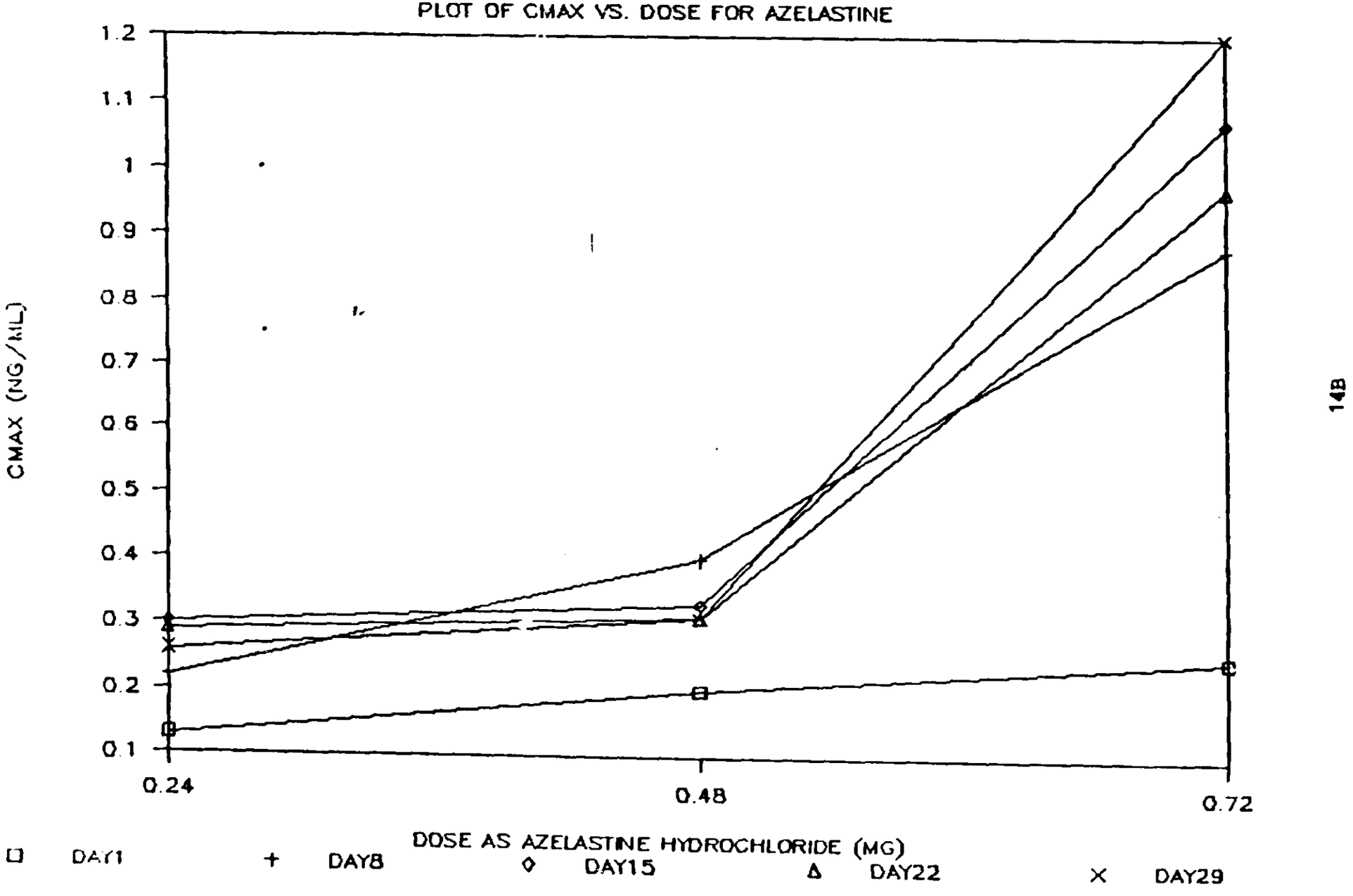


Figure II


PLOT OF CMAX VS. DOSE FOR AZELASTINE
CMAX (NG/ML)
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.24
0.48
0.72
DOSE AS AZELASTINE HYDROCHLORIDE (MG)
DAY1
DAY8
DAY15
DAY22
DAY29

With regard to nasal examination, three parameters were evaluated during the examination: color, wetness and mucosal thickness. A subject was considered to have a change from baseline if one of the three parameters was changed. In this trial all treatment groups had a similar rate of change from baseline.

The most frequent adverse events that were reported include headache (4), altered taste (4) and epistaxis (2). One of the subjects with epistaxis was on placebo. All reports of altered taste occurred in the one spray per nostril group whereas no adverse events were reported in the three sprays per nostril group. No serious adverse events or lab changes were reported.

No significant abnormalities on physical exam, vital signs or ECG were reported.

Comment: **To put the systemic AUC and Cmax of azelastine spray into perspective, its worthwhile comparing these parameters for the spray v.s. the oral tablet. In making this comparison, the AUC and Cmax for the 2 sprays per nostril bid will be compared with the AUC and Cmax for 2mg bid, both at steady state. One must recognize that the nasal spray pump used in the pharmacokinetic trial is not the to be marketed pump, but rather it is a Pfeiffer pump which delivers .12mg of drug per spray (the to be marketed pump is a Valois which delivers .137mg per spray). The reason the comparison is made with the 2mg dose is because that is the lowest dose for which pharmacokinetic data is reported.**

Parameter	2 sprays per nostril bid	2mg p.o bid
AUC (ng x hr/ml)	3.18	40.1
Cmax (ng/ml)	.307	3.89

Assuming that the kinetics of the tablet formulation is linear (based on single dose data it appears to be) the difference in AUC and Cmax between the nasal spray and the lowest clinical tablet dose of .5mg is 3.18 v.s. 10 (a 3 fold difference) and .31 v.s. .97 (again a 3 fold difference). This indicates that the same safety considerations that apply to the oral formulation may be relevant to the spray formulation. In addition, the sponsor has not characterized the metabolite profile for the nasal route of administration, neither local metabolites nor systemic. This last point should be addressed by the sponsor.

Pharmacodynamics (studies 43-46)

The effect of azelastine on histamine concentration and TAME esterase activity in nasal lavage fluid after antigen challenge was studied in 12 subjects who received 2mg bid p.o. of drug for one week. Compared to placebo, a statistically significant decrease in TAME esterase activity was noted following the first dose of

azelastine. Clinically, antigen induced sneezing and the rated severity of antigen induced itchy nose and throat was significantly decreased in the treated group vs placebo.

In another double-blind, crossover trial the effect of 4mg bid p.o. of azelastine administered for 3 1/2 days on antigen induced skin test reactivity was assessed. Significant inhibition of skin wheal responses to antigen dilutions of .01 to 100 times the threshold dose (the minimal dose of antigen eliciting a wheal equal to or greater than 10mm and 2.5 times greater than the diameter elicited by buffered saline) were noted after both the first and last dose and persisted for a week after azelastine was discontinued. Inhibition of wheal response to histamine and codeine was also noted after the last dose.

Another study was performed using the skin chamber technique to assess for neutrophil accumulation. Skin wheal response was also evaluated in this study in which 12 atopic subjects were treated with 4mg bid p.o. of azelastine administered for 3.5-4.5 days. After the administration of 7 doses of azelastine a statistically significant decrease in wheal response to multiple doses of antigen as well as to histamine and codeine was noted. No effect on histamine concentration in the skin chamber was noted and the assay for granulocyte accumulation was not interpretable.

The sponsor also reports that the drug has an IC_{50} of ex vivo histamine secretion by basophils and lung mast cells of .01-100 uM. In addition, the IC_{50} for inhibition of superoxide anion generation from human neutrophils and eosinophils is .9 - 3.0 uM.

Dose Ranging Trials

Study #30:

Protocol:

This study, which evaluated azelastine administered using the Pfeiffer pump, is a double blind, placebo and active controlled, randomized, multicenter, two day study conducted in a park setting in which 1 spray per nostril q12hr, 2 sprays per nostril q12hr and two sprays per nostril q dy were evaluated. The positive control in this trial was Chlortrimeton Repetab 12 mg q 12 hours.

The subjects included in this trial were to be between the ages of 12-65 and have a history of seasonal allergic rhinitis requiring pharmacological therapy for each of the previous two years. They also had to have demonstrable allergy to one of the common seasonal allergens based on skin testing, done either within the past year

or at screening. Subjects with asthma, but off chronic anti-asthma therapy for at least the previous 24 months or subjects with only exercise induced asthma were also permitted to be enrolled in the trial. Subjects included in the trial must have not used intranasal steroids within the previous 14 days or oral steroids within 30 days. Intranasal cromolyn, opticrom, calcium channel blockers, beta blockers or MAO inhibitors may not have been used within the previous 14 days and astemizole or reserpine had to have been discontinued within 60 days.

Subjects who met the screening criteria were seen on the first double blind day and prior to treatment were asked to rate their symptoms on an hourly basis for three hours. The following symptoms were evaluated:

1. stuffy nose (left and right separately):

    Stuffy nose was evaluated on a scale of 0-4

2. nose blows
3. sneezes

    Nose blows and sneezes were evaluated on a scale of 0-8

4. itchy nose (left and right separately)
5. runny nose (left and right separately)
6. sniffles
7. postnasal drip
8. dry nose
9. watery eyes
10. itchy eyes/ears
11. itchy throat
12. cough
13. other

    Symptoms 4-13 were evaluated on a scale of 0-5

Comment: **The inclusion of symptoms being rated on different scales into one symptom complex is valid if this was done with the intention of weighting the importance of the different symptoms, however, the sponsor has not indicated in the study protocols or the NDA that this was their intention.**

Subjects were randomized into the trial if the total for the three hourly evaluations of nose blows, sneezes, itchy nose, runny nose, sniffles, postnasal drip, dry nose, watery eyes, itchy eyes/ears, itchy throat and cough was 12 or greater.

Subjects who were randomized into the trial received their first dose at 10:00 AM

following which the above listed symptoms were evaluated hourly, in the park, for 6 hours. Subject then returned home and symptoms were again evaluated at 8, 10 and 12 hours after the first dose. The second dose was administered at 10:00 PM and symptoms were again evaluated in the park the next morning at 10, 11 and 12 hours after the second dose. The final dose was administered at 10:00 AM of the second study day and symptoms were once again evaluated for 6 hours, on an hourly basis, following the final dose. At the completion of the trial a subject global response rating was also done.

The primary endpoints in this trial were the major symptom complex (runny nose, sniffles, itchy nose, nose blows, sneezes and watery eyes) and the total symptom complex (runny nose, sniffles, itchy nose, nose blows, sneezes, watery eyes, itchy eyes/ears, itchy throat, dry nose, cough and postnasal drip). Secondary endpoints include the total symptom complex with stuffiness, change in individual symptoms and subject global evaluations.

In analyzing the symptom score data the sponsor divided the data into the following 4 evaluation periods:

1. Period #1: the first 6 hourly evaluations after dose #1
2. Period #2: evaluations at 8, 10 and 12 hours post dose #1 (note that these evaluations were not performed in the park)
3. Period #3: evaluations at 10, 11 and 12 hours after dose #2 (note that for the q day arm, these evaluations were 22, 23 and 24 hours post dose)
4. Period #4: the 6 hourly evaluations after dose #3

The individual symptom scores for each of the four periods represents the mean of the hourly scores measured during that period. The analysis of change from baseline was described as being an ANOVA analysis including the factors of treatment, investigator and treatment by center interaction.

Results:

The study was conducted by Dr. Eli O. Meltzer in San Diego, California and Dr. John Weiler in Iowa City, Iowa between August 16, 1989 and October 19, 1989. 292 subjects were screened for participation in the trial and 264 were randomized.

Three subjects (one in each of the two sprays/nostril groups and one in the placebo group) did not complete the trial due to intercurrent illnesses and two (in the one spray per nostril group) did not complete the trial due to administrative reasons. The intercurrent illnesses were a fractured toe, migraine headache and gastroenteritis. All 264 randomized subjects were included in the efficacy analysis.

The sponsor states that demographic characteristics were comparable in all

treatment groups. In addition, with regard to the total and major symptom complexes there were no significant differences between the groups at baseline and there was no significant treatment by center interaction.

Regarding percent change from baseline for the total symptom complex, the group treated with two sprays q12hr demonstrated a statistically significant difference from placebo for periods 1-4 and the group treated once a day demonstrated significant differences from placebo for periods 2-4. There were no statistically significant differences between the group that received 1 spray per nostril q12hr and placebo. Regarding absolute improvement from baseline, the data is somewhat different since the only significant difference between azelastine and placebo was seen in the 2 sprays per nostril q day group during periods 2 and 4. Overall (this represents the mean for all 4 periods) both of the two spray per nostril groups were significantly different from placebo based on percent change from baseline, however, for the absolute change only the 2 sprays q day group was significant. The data for the major symptom complex are similar except for period 1, during which there were no significant difference from placebo.

Percent Improvement and Improvement from Baseline in
Total Symptom Complex Severity Scores by Treatment and Evaluation Period
for Both Centers

				IMPROVEMENT			PERCENT IMPROVEMENT		
PERIOD	TREATMENT	N	BASE LINE	MEAN	SEM	P-VALUE	MEAN	SEM	P-VALUE
1	AZEL 1 SPRAY Q12H	54	15.94	6.59	0.93	0.4581	38.00	4.76	0.0931
	AZEL 2 SPRAYS Q.D.	54	16.30	6.39	0.91	0.5039	35.40	4.38	0.1762
	AZEL 2 SPRAYS Q12H	54	15.42	6.52	0.85	0.4771	39.56	4.17	0.0465
	CHLOR 12 MG Q12H	52	15.54	6.62	1.01	0.4083	37.58	4.79	0.0909
	PLACEBO	50	16.23	5.56	0.86	.	26.24	5.96	.
2	AZEL 1 SPRAY Q12H	54	15.94	4.20	0.88	0.9597	28.02	5.34	0.1174
	AZEL 2 SPRAYS Q.D.	53	16.39	7.37	0.92	0.0223	42.02	4.14	0.0017
	AZEL 2 SPRAYS Q12H	53	15.10	5.15	0.87	0.4639	36.41	5.56	0.0126
	CHLOR 12 MG Q12H	52	15.54	6.20	0.89	0.2313	40.57	5.32	0.0028
	PLACEBO	49	16.23	4.32	1.29	.	13.41	9.48	.
3	AZEL 1 SPRAY Q12H	53	16.10	3.18	0.88	0.9237	18.04	5.47	0.2202
	AZEL 2 SPRAYS Q.D.	53	16.39	5.67	0.85	0.0893	27.81	5.12	0.0178
	AZEL 2 SPRAYS Q12H	53	15.10	4.21	0.79	0.4785	24.65	5.05	0.0376
	CHLOR 12 MG Q12H	52	15.54	5.47	0.99	0.0866	29.94	6.41	0.0065
	PLACEBO	49	16.23	3.38	1.16	.	6.90	8.83	.
4	AZEL 1 SPRAY Q12H	53	16.10	6.69	1.03	0.3380	42.74	5.78	0.0552
	AZEL 2 SPRAYS Q.D.	53	16.39	9.80	0.92	0.0034	56.51	3.83	0.0005
	AZEL 2 SPRAYS Q12H	53	15.10	7.27	0.86	0.1734	49.13	5.29	0.0063
	CHLOR 12 MG Q12H	52	15.54	8.81	1.08	0.0160	52.81	5.43	0.0013
	PLACEBO	49	16.23	5.12	1.37	.	24.40	9.35	.
OVERALL	AZEL 1 SPRAY Q12H	54	15.94	5.15	0.75	0.7004	31.66	4.29	0.0679
	AZEL 2 SPRAYS Q.D.	54	16.30	7.22	0.80	0.0414	40.04	3.66	0.0025
	AZEL 2 SPRAYS Q12H	54	15.42	6.01	0.80	0.2776	37.93	4.16	0.0060
	CHLOR 12 MG Q12H	52	15.54	6.77	0.87	0.0780	40.22	4.21	0.0018
	PLACEBO	50	16.23	4.64	1.10	.	18.49	7.39	.
END-POINT	AZEL 1 SPRAY Q12H	54	15.94	6.60	1.01	0.4005	42.48	5.68	0.0646
	AZEL 2 SPRAYS Q.D.	54	16.30	9.65	0.92	0.0053	55.72	3.85	0.0008
	AZEL 2 SPRAYS Q12H	54	15.42	7.56	0.89	0.1428	49.36	5.21	0.0063
	CHLOR 12 MG Q12H	52	15.54	8.81	1.08	0.0191	52.81	5.43	0.0015
	PLACEBO	50	16.23	5.23	1.35	.	25.21	9.20	

OVERALL IS THE AVERAGE OF PERIODS 1,2,3 AND 4

Percent Improvement and Improvement from Baseline in Major Symptom Complex Severity Scores by Treatment and Evaluation Period for Both Centers

				IMPROVEMENT			PERCENT IMPROVEMENT		
PERIOD	TREATMENT	N	BASE LINE	MEAN	SEM	P-VALUE	MEAN	SEM	P-VALUE
1	AZEL 1 SPRAY Q12H	54	10.27	4.78	0.67	0.3385	33.72	11.58	0.5159
	AZEL 2 SPRAYS Q.D.	54	10.35	4.53	0.65	0.4562	40.29	5.06	0.1606
	AZEL 2 SPRAYS Q12H	54	9.66	4.55	0.62	0.4751	41.78	4.88	0.1240
	CHLOR 12 MG Q12H	52	9.83	4.78	0.67	0.3089	42.64	4.96	0.1020
	PLACEBO	50	9.73	3.84	0.67	.	26.03	7.62	.
2	AZEL 1 SPRAY Q12H	54	10.27	3.03	0.66	0.4579	25.15	7.75	0.0600
	AZEL 2 SPRAYS Q.D.	53	10.42	4.94	0.67	0.0095	46.39	4.77	0.0002
	AZEL 2 SPRAYS Q12H	53	9.37	3.44	0.60	0.2591	34.46	6.81	0.0050
	CHLOR 12 MG Q12H	52	9.83	4.39	0.64	0.0385	43.53	6.25	0.0006
	PLACEBO	49	9.68	2.28	0.87	.	2.44	13.70	.
3	AZEL 1 SPRAY Q12H	53	10.35	2.27	0.65	0.5255	11.08	11.71	0.1893
	AZEL 2 SPRAYS Q.D.	53	10.42	3.81	0.64	0.0288	27.22	6.96	0.0076
	AZEL 2 SPRAYS Q12H	53	9.37	2.65	0.56	0.3053	19.79	6.49	0.0360
	CHLOR 12 MG Q12H	52	9.83	3.86	0.69	0.0201	30.49	7.52	0.0030
	PLACEBO	49	9.68	1.74	0.77	.	-6.03	12.17	.
4	AZEL 1 SPRAY Q12H	53	10.35	4.30	0.79	0.2262	32.08	14.18	0.4445
	AZEL 2 SPRAYS Q.D.	53	10.42	6.63	0.67	0.0012	61.71	4.58	0.0017
	AZEL 2 SPRAYS Q12H	53	9.37	4.72	0.60	0.1116	49.76	5.80	0.0298
	CHLOR 12 MG Q12H	52	9.83	5.80	0.77	0.0101	54.55	6.38	0.0075
	PLACEBO	49	9.68	2.91	0.95	.	19.58	10.72	.
OVERALL	AZEL 1 SPRAY Q12H	54	10.27	3.59	0.56	0.3737	25.73	10.50	0.2037
	AZEL 2 SPRAYS Q.D.	54	10.35	4.93	0.58	0.0173	43.63	4.45	0.0021
	AZEL 2 SPRAYS Q12H	54	9.66	4.05	0.58	0.1711	37.52	4.97	0.0138
	CHLOR 12 MG Q12H	52	9.83	4.71	0.60	0.0304	42.80	4.61	0.0026
	PLACEBO	50	9.73	2.79	0.74	.	11.49	9.72	.
END-POINT	AZEL 1 SPRAY Q12H	54	10.27	4.25	0.78	0.2862	32.05	13.92	0.4678
	AZEL 2 SPRAYS Q.D.	54	10.35	6.54	0.66	0.0021	61.05	4.54	0.0022
	AZEL 2 SPRAYS Q12H	54	9.66	4.98	0.64	0.0899	50.25	5.71	0.0241
	CHLOR 12 MG Q12H	52	9.83	5.80	0.77	0.0136	54.55	6.38	0.0084
	PLACEBO	50	9.73	3.02	0.93	.	20.61	10.56	.

OVERALL IS THE AVERAGE OF PERIODS 1,2,3 AND 4

Comment: These data don't clearly demonstrate an effect from the first dose until period #2, which occurred 8-12 hours after the dose (and was assessed at home). Based on percent change from baseline, both dosing regimens in which 2 sprays per nostril were administered were significantly more efficacious than placebo, however there does not appear to be a dose related effect between the 2 two spray per nostril regimens. While both regimens appear more efficacious than 1 spray per nostril q 12 hrs, the significance of this difference is not clear since the difference, particularly for the total symptom complex, appears small.

The following is the individual symptom data:

Nose blows: the only significant difference between treatment and placebo was seen in the 2 sprays per nostril q day group during period 4. The effect was not dose related.

Sneezes: the only significant difference between azelastine and placebo was seen in the 2 sprays per nostril q day group during period 4. The effect was not dose related.

Itchy nose: trends or statistical significance when compared to placebo was seen for both two spray per nostril regimens during periods 1-4. The effect does not appear dose related.

Improvement from Baseline in Itchy Nose

PERIOD	TREATMENT	N	MEAN	SEM	P-VALUE*
BASELINE	AZEL 1 Q12H	54	1.70	0.14	0.8592
	AZEL 2 Q.D.	54	1.86	0.14	0.5365
	AZEL 2 Q12H	54	1.80	0.14	0.7439
	CHLOR 12 Q12H	52	1.70	0.13	0.9619
	PLACEBO	50	1.72	0.13	.
1	AZEL 1 Q12H	54	0.79	0.12	0.1658
	AZEL 2 Q.D.	54	0.90	0.13	0.0383
	AZEL 2 Q12H	54	0.92	0.13	0.0381
	CHLOR 12 Q12H	52	0.78	0.13	0.1517
	PLACEBO	50	0.52	0.13	.
2	AZEL 1 Q12H	54	0.53	0.12	0.6291
	AZEL 2 Q.D.	53	0.92	0.12	0.0137
	AZEL 2 Q12H	53	0.79	0.13	0.0691
	CHLOR 12 Q12H	52	0.64	0.14	0.2597
	PLACEBO	49	0.41	0.17	.
3	AZEL 1 Q12H	53	0.37	0.14	0.4714
	AZEL 2 Q.D.	53	0.64	0.11	0.0273
	AZEL 2 Q12H	53	0.55	0.11	0.0879
	CHLOR 12 Q12H	52	0.54	0.12	0.0861
	PLACEBO	49	0.22	0.15	.
4	AZEL 1 Q12H	53	0.71	0.15	0.1770
	AZEL 2 Q.D.	53	1.16	0.11	0.0004
	AZEL 2 Q12H	53	0.86	0.12	0.0298
	CHLOR 12 Q12H	52	0.94	0.14	0.0054
	PLACEBO	49	0.40	0.17	.

* COMPARING TO PLACEBO

Runny nose: only the 2 spray per nostril once a day group was significantly different from placebo during periods 2-4. Once again, the effect is not dose related.

Sniffles: only the 2 spray per nostril once a day group was significantly different from placebo during periods 2-4. Once again, the effect is not dose related.

Post nasal drip: only the 2 spray per nostril once a day group was significantly different from placebo during periods 2 and 4. The effect is not dose related.

Watery eyes. there were no significant differences from placebo although a trend was seen for the 2 spray/nostril q day group during periods 2 and 4. Effect was not dose related.

Itchy eye/ears: once again there were no significant differences from placebo although there were some trends, however, the effect was not dose related.

Itchy throat: no significant differences from placebo.

Regarding the global assessment, all three treatment groups, as well as the active control were significantly different from placebo . More treated subjects than placebo controls reported an improvement.

Data is also presented regarding efficacy at each hour that symptoms were assessed. The data in the two tables below is based on percent improvement for both the total and major symptom complexes.

Mean Percent Improvement from Baseline in Total Symptom Complexes
by Evaluation Time – Both Investigators Combined

EVALUATION TIME (HOURS)	AZ. 1S B.I.D. (N= 34) MEAN	P-VALUE*	AZ. 2S Q.D. (N= 34) MEAN	P-VALUE*	AZ. 2S B.I.D. (N= 34) MEAN	P-VALUE*	CHLOR. (N= 32) MEAN	P-VALUE*	PLAC. (N= 30) MEAN
1	4.0	0.343	-16.7	0.384	-10.2	0.859	-0.04	0.489	-7.4
2	29.9	0.469	25.4	0.704	25.4	0.638	26.0	0.680	22.1
3	44.4	0.022	46.6	0.010	48.1	0.007	47.1	0.009	26.0
4	51.1	0.198	40.8	0.325	57.1	0.038	46.6	0.316	41.1
5	50.9	0.174	53.2	0.079	61.6	0.004	54.6	0.048	41.0
6	47.7	0.099	55.0	0.010	55.4	0.008	49.1	0.069	34.7
8	31.7	0.030	47.9	<0.001	38.2	0.004	43.6	0.001	10.3
10	34.6	0.034	41.4	0.005	41.5	0.006	42.0	0.005	12.9
12	17.8	0.904	36.7	0.052	29.5	0.218	36.1	0.063	17.0
22	9.7	0.461	21.1	0.053	11.2	0.370	22.7	0.030	2.2
23	20.8	0.138	29.6	0.019	26.2	0.036	32.6	0.006	5.7
24	23.6	0.246	32.8	0.024	34.6	0.005	34.5	0.010	12.7
25	34.3	0.143	43.3	0.012	37.4	0.050	48.4	0.001	20.8
26	38.1	0.076	50.2	0.004	50.5	0.003	45.4	0.009	20.1
27	41.8	0.086	56.6	0.002	42.8	0.059	49.3	0.010	21.2
28	44.2	0.147	65.7	<0.001	53.4	0.015	55.6	0.007	28.6
29	49.8	0.045	62.5	0.002	54.7	0.016	58.1	0.004	30.7
30	47.1	0.039	60.8	0.001	55.8	0.002	56.6	0.001	25.7

* COMPARING TO PLACEBO

Mean Percent Improvement from Baseline in Major Symptom Complexes by Evaluation Time – Both Investigators Combined

EVALUATION TIME (HOUR)	AZ. 15 B.I.D. (N= 54)		AZ. 28 Q.D. (N= 54)		AZ. 28 B.I.D. (N= 54)		CHLOR. (N= 52)		PLAC. (N= 53)
	MEAN	P-VALUE*	MEAN	P-VALUE*	MEAN	P-VALUE*	MEAN	P-VALUE*	MEAN
1	-3.5	0.546	-15.9	0.866	-15.0	0.978	-1.0	0.353	-13.7
2	26.4	0.647	29.6	0.421	30.0	0.386	26.2	0.630	18.3
3	41.1	0.176	52.1	0.029	49.4	0.055	52.1	0.031	22.7
4	48.8	0.916	54.9	0.581	60.2	0.313	56.4	0.474	48.7
	45.2	0.948	58.5	0.126	66.1	0.025	63.2	0.041	43.3
	44.3	0.566	62.5	0.034	59.9	0.058	58.8	0.062	36.2
8	28.2	0.038	51.6	<0.001	35.1	0.009	49.0	<0.001	-0.6
10	32.1	0.030	44.0	0.003	45.8	0.002	43.3	0.004	-1.8
12	15.2	0.651	43.5	0.005	28.5	0.128	38.3	0.020	9.7
22	-0.8	0.345	16.7	0.026	-0.2	0.307	21.4	0.010	-14.9
23	20.6	0.056	29.6	0.007	24.7	0.021	34.4	0.002	-2.3
24	13.4	0.390	35.4	0.019	34.9	0.018	35.7	0.015	-0.9
25	25.9	0.698	45.4	0.032	33.6	0.208	51.9	0.006	18.5
26	29.1	0.637	54.9	0.015	53.8	0.018	48.0	0.043	19.7
27	33.5	0.164	60.3	0.001	42.3	0.241	51.0	0.007	10.6
28	31.9	0.816	69.2	0.004	52.8	0.076	55.8	0.042	26.0
2:	35.9	0.796	70.5	0.015	58.4	0.080	60.7	0.050	28.5
30	36.7	0.187	70.0	<0.001	57.7	0.004	59.9	0.002	14.2

COMPARING TO PLACEBO

Comment: These two tables demonstrate that by three hours post dosing, a significant percent improvement from baseline v.s. placebo is seen for both 2 spray per nostril groups. The statistical significance of the data fluctuates over the course of the trial, however of the three dosing regimens, the 2 prays per nostril regimens appear to be significantly different from placebo more often than the one spray per nostril dose. In addressing the issue of end of doing interval efficacy, the time point to focus on is at 22-24 hours after the first dose since that time point is the end of the dosing interval for all three azelastine regimens and the assessments occurred in the park. At that time point, the one spray per nostril group was not significantly different from placebo based on either the total or major symptom complex. However, both the 2 spray per nostril regimens were significantly different from placebo based on both the total and major symptom complexes. This may be an important issue if the pivotal trials are not adequately designed to address efficacy at the end of the dosing interval.

As outlined in NDA the Total and Major symptom complexes have a number of design problems. These include:

A. The symptoms included in these complexes are measured on different numerical scales
B. Certain symtoms, such as dry nose are not appropriate to be included in a symptom complex.
C. Its unclear what specific symptoms are driving the efficacy seen at the end of the dosing interval.

Overall, while this study does demonstrate efficacy following the first dose of azelastine nasal spray, the data is somewhat difficult to interpret because a clear dose related effect was not seen. In fact, one could argue that the once a day dosing regimen was the most efficacious of the three regimens.

Safety:

There were two treatment emergent physical examination abnormalities, a fractured toe in one subject and moderately severe rhinitis in a second subject who received 2 sprays q 12 hours. None of the vital sign or weight changes were significantly different from placebo.The only adverse experience to occur significantly more often in treated subjects v.s. placebo was headache, which occurred at a rate of 35.2% in the 2 spray per nostril bid group and 16% in the placebo group, P=.026. While there were some statistically significant differences between azelastine treated subjects and placebo regarding change from baseline in direct bilirubin, phosphorous and monocytes, these differences were not clinically significant.

Study #32

The protocol for this dose ranging trial is the same as for study #30, described above, except that an extra efficacy assessment is included at 11 hours after the first dose and only the 2 sprays per nostril q day and bid regimens were studied.

The study was conducted by Dr. Eli Meltzer in San Diego, California, Dr. Robert Dockhorn in Lenexa, Kansas and Dr. John Weiler in Iowa City, Iowa. The valois A pump was used and the study was conducted from 4/21/90 through 5/20/90.

Results:

349 subjects were screened and 294 qualified for randomization. Of these, 4 subjects did not complete the double blind period. 1 placebo subject withdrew due to treatment failure, one subject in the q day regimen withdrew due to intercurrent illness (otitis media and externa) and two subjects in the q 12 hours azelastine group withdrew due to administrative reasons. All 294 subjects were included in the efficacy analysis.

Regarding the demographics of the treatment groups, there was a statistically significant difference among the groups for age, but not for race, sex, weight or height. The mean age ranged among the four treatment groups from 24.7 to 30.3

For the total symptom complex, both azelastine groups demonstrated significant differences from placebo for both absolute and percent change from baseline during periods 2-4. During period 1 the q day regimen was not significantly different from placebo based on percent improvement from baseline. Over the course of the study, the q 12hr regimen does appear to be more efficacious on this endpoint than q day, although the difference between the two is probably not statistically significant (comparison between the q 12hr regimen and q day is not reported by the sponsor). For the major symptom complex, whereas the q 12hour regimen is significantly different from placebo at all time points for both absolute and percent change from baseline, the q day regimen is not significant for percent change from baseline for periods 1-3, although the absolute change from baseline is significantly different from placebo at all time points.

Regarding individual symptoms, both regimens demonstrated significant differences from placebo at various time points for nose blows, sneezes, itchy nose, itchy eyes/ears an itchy throat. Of note, the q day regimen did not appear to have much of an effect on runny nose and sniffles.

Comment: **The data from this study suggest that the q 12 hour regimen may be more efficacious than the q day regimen, however, the differences between the groups appear small.**

Regarding the global assessment, only the q day regimen was significantly *different from* placebo.

The following two tables depict the hourly assessments over the course of the trial:

Mean Percent Improvement from Baseline in Total Symptom Complex Severity Scores by Evaluation Time for All Centers

EVALUATION TIME	AZEL 2SPRY QD			AZEL 2SPRY Q12H			CHLOR 12 MG Q12H			PLACEBO	
	N	MEAN	P-VALUE*	N	MEAN	P-VALUE*	N	MEAN	P-VALUE*	N	MEAN
Study Hr 1	71	-1.5	0.554	74	0.3	0.345	72	3.1	0.056	75	3.8
Study Hr 2	71	30.3	0.366	74	37.6	0.025	72	32.7	0.973	75	19.9
Study Hr 3	71	36.0	0.335	74	45.3	0.019	72	33.7	0.536	75	28.0
Study Hr 4	71	49.3	0.068	74	51.9	<0.001	72	36.0	0.175	75	36.3
Study Hr 5	71	51.5	0.004	74	54.7	<0.001	72	41.7	0.136	75	39.5
Study Hr 6	71	52.2	0.029	74	56.3	0.002	72	39.1	0.932	75	34.3
Study Hr 8	71	46.1	0.026	74	49.6	0.010	72	33.3	0.595	75	24.3
Study Hr 10	71	42.7	0.050	74	46.8	0.035	72	36.6	0.287	75	24.4
Study Hr 11	71	48.1	0.022	74	47.4	0.019	72	38.9	0.150	75	24.4
Study Hr 12	71	46.3	0.023	74	39.7	0.058	72	36.5	0.185	75	20.5
Study Hr 22	70	24.2	0.029	74	33.3	0.001	72	20.3	0.011	75	1.8
Study Hr 23	70	24.5	0.033	74	35.6	0.002	72	20.9	0.026	75	9.5
Study Hr 24	70	27.2	0.015	74	34.6	<0.001	72	25.8	0.077	75	5.3
Study Hr 25	70	33.5	0.139	74	36.7	0.013	72	36.6	0.067	75	19.4
Study Hr 26	70	48.6	0.011	74	51.4	0.002	72	44.7	0.031	75	26.6
Study Hr 27	70	53.1	0.013	74	54.4	0.006	72	46.7	0.073	75	29.0
Study Hr 28	70	56.2	0.039	74	57.5	0.015	72	51.3	0.130	74	39.1
Study Hr 29	70	53.7	0.003	74	53.6	0.002	72	54.8	0.013	74	36.4
Study Hr 30	70	52.7	0.017	74	53.1	0.014	72	50.1	0.045	74	34.6

* COMPARING TO PLACEBO

Mean Percent Improvement from Baseline in Major Symptom Complex Severity Scores by Evaluation Time for All Centers

EVALUATION TIME	AZEL 2SPRY QD			AZEL 2SPRY Q12H			CHLOR 12 MG Q12H			PLACEBO	
	N	MEAN	P-VALUE*	N	MEAN	P-VALUE*	N	MEAN	P-VALUE*	N	MEAN
Study Hr 1	71	-6.4	0.560	74	11.0	0.241	72	6.1	0.013	75	0.3
Study Hr 2	71	31.6	0.350	74	39.0	0.048	72	32.3	0.423	75	32.6
Study Hr 3	71	35.4	0.359	74	45.6	0.061	72	37.6	0.362	75	37.3
Study Hr 4	71	54.0	0.804	74	54.6	0.001	72	44.1	0.079	75	38.3
Study Hr 5	71	56.0	0.627	74	58.7	0.004	72	46.8	0.208	75	35.6
Study Hr 6	71	66.7	0.489	74	68.8	0.065	72	61.2	0.971	75	60.4
Study Hr 8	71	64.0	0.247	74	69.8	0.035	72	57.1	0.486	75	57.6
Study Hr 10	71	68.9	0.163	74	68.7	0.043	72	63.3	0.387	75	51.4
Study Hr 11	71	65.4	0.165	74	68.3	0.048	72	66.5	0.160	75	58.6
Study Hr 12	71	55.1	0.612	74	64.3	0.046	72	61.5	0.138	75	52.5
Study Hr 22	70	18.9	0.005	74	32.5	0.001	72	32.8	0.003	75	-0.3
Study Hr 23	70	20.7	0.260	74	34.8	0.005	72	31.5	0.022	75	8.5
Study Hr 24	70	33.0	0.066	74	33.8	0.002	72	25.0	0.033	75	4.3
Study Hr 25	70	38.3	0.080	74	33.6	0.026	72	37.6	0.018	75	12.3
Study Hr 26	70	49.7	0.013	74	49.7	0.005	72	48.8	0.009	75	23.3
Study Hr 27	70	53.6	0.015	74	56.2	0.009	72	52.2	0.032	75	27.6
Study Hr 28	70	58.8	0.030	74	57.1	0.026	72	56.7	0.046	74	38.3
Study Hr 29	70	60.5	0.006	74	59.1	0.001	72	58.8	0.005	74	36.8
Study Hr 30	70	56.4	0.010	74	49.5	0.055	72	51.4	0.043	74	31.9

* COMPARING TO PLACEBO

Comment: For the total symptom complex, the data demonstrate significant differences from placebo at the end of the dosing interval (hours 22-24) for both azelastine regimens, however, the once a day regimen was not significantly different from placebo based on the major symptom complex.

Safety:

There were no clinically significant treatment emergent changes in physical exam. Regarding vital signs, in the q day regimen change from baseline in systolic blood pressure was significantly greater than placebo (4.01 v.s..05). A similar difference between the bid group and placebo was not seen. Both taste perversion and somnolence occurred significantly more often in azelastine treated subjects v.s. placebo. These effects were not dose related.

Regarding labs, the incidence of high SGPT in subjects receiving azelastine once daily was significantly greater than in placebo treated subjects regardless of baseline value, 13% v.s. 1.8% ($P \leq .046$). The sponsor reports that similarly when only subjects with normal baseline values were analyzed, the incidence of high SGPT in subjects treated with azelastine once a day v.s. placebo was 8.0% v.s. 0.0%, $P \leq .046$. In addition, the change from baseline for uric acid in the bid group v.s. placebo was significantly different, however, the actual difference between the two groups was small.

Comment: Regarding the reported high SGPT values, it is unclear what this statement in the NDA is based on (it can be found on page 08 9003) since according to table #35, which reports the data on subjects with normal baseline values, the incidence of high SGPT in the q day azelastine group was 6.00% not 8.0% and according to table #36, which reports lab data on all subjects regardless of baseline value, the incidence of high SGPT is 11.11% not 13%. The values for the placebo group do appear to be correct. In evaluating this difference between the treated and placebo group it is important to note that in the azelastine bid group the incidence of high SGPT was 1.63% in subjects with a normal baseline value and 1.61% in all subjects. The mean baseline SGPT in the azelastine q day group was 23.13 and at follow-up it was 28.35. This change from baseline was statistically significant, although the change compared to the change in the placebo group was not significant. Subjects in the placebo group had a mean value at baseline of 21.000 and at follow-up, 21.6316. For comparison sake, in the azelastine bid group the mean baseline value was 23.677 and at follow-up 24.4189. The lack of a dose related effect and the small change from baseline to follow-up is reassuring, however, these are mean values and they do not explain the statistically significant increased incidence in elevated SGPT in the once a day group. To better quantify how high any outliers may have been and determine if additional information regarding some of these subjects is needed, the sponsor

should provide a list of the SGPT values above normal in this trial, broken down by subject.

Pivotal Efficacy Trials

Study #26

Protocol:

This study, which evaluated azelastine administered using the Valois A pump, is a double blind, placebo and active controlled, randomized, multicenter, two week study in which 2 sprays per nostril q12hr and two sprays per nostril q dy were evaluated. The positive control in this trial was Chlortrimeton Repetab 12 mg q 12 hours.

The subjects included in this trial were to be above 12 years of age and have a history of seasonal allergic rhinitis requiring pharmacological therapy for each of the previous two years. They also had to have demonstrable allergy to one of the common seasonal allergens based on skin testing, performed either within the past year or at screening. Subjects with asthma, but off chronic anti-asthma therapy for at least the previous 24 months or subjects with only exercise induced asthma were also permitted to be enrolled in the trial. Subjects included in the trial must have not used intranasal steroids within the previous 14 days or oral steroids within 30 days. Intranasal cromolyn, opticrom, calcium channel blockers, beta blockers or MAO inhibitors may not have been used within the previous 14 days and astemizole had to have been discontinued within 60 days. Finally, antihistamines or decongestants had to be discontinued within 48 hours prior to baseline.

No antiasthma medications or antirhinitis medications or antibiotics were permitted until after the double blind treatment period was completed.

Of note, with regard to usage of the nasal spray, investigators were instructed to prime the nasal spray pump 6 times before dispensing it to subjects, and subjects were instructed not to prime the pump before use.

Drug was to be administered at 8AM and 8PM (subjects in the q day regimen received active drug in the morning) and symptom diary cards were to completed twice a day at the time of dosing. The symptoms that were assessed in this trial included nose blows, sneezes, runny nose/sniffles, itchy nose, watery eyes, itchy eyes/ears/throat/palate, cough, postnasal drip and stuffiness. All were assessed on a 0-5 scale and evaluated symptoms over the course of the previous day or night.

At clinic visits investigators were to assess the symptoms of sneezing, runny nose, nasal itching, eye symptoms and nasal blockage on a 100mm analogue scale.

For inclusion into the trial the sum of the AM and PM scores for sneezes, runny nose/sniffles, nose blows, itchy nose and watery eyes had to be at least 10 on any 4 days of the baseline week at least one of these symptoms had to be of at least moderate intensity on each of the four days.

The subjects in this trial were seen in the clinic on a weekly basis. At the clinic visits, in addition to the physician assessment of symptoms, a physician and patient global score was performed in which they both rated the change from baseline on a 5 point scale. Nasal examinations were also performed at the clinic visits. Based on these nasal examinations the quantity, consistency and color of nasal secretions were rated on a 0-3 scale.

Pollen counts were to be collected during the trial.

The weekly total and major symptom scores were arrived at by summing the individual symptoms which comprise these complexes and arriving at an AM and PM score for each day (the major Symptom Complex was defined as including runny nose/sniffles, itchy nose, nose blows, sneezes and watery eyes. The total Symptom Complex included these symptoms as well as itchy eyes/ears/throat/palate, cough and postnasal drip). A weekly mean for the separate AM and PM scores was then taken and the weekly mean is the mean of the weekly AM and PM scores. An overall analysis was also done which included the mean of all the post baseline values and an endpoint analysis was done which included the last value for each subject. Both the total and major symptom complexes were analyzed using an ANOVA analysis which included baseline as a covariate. The data are expressed as absolute and percent change from baseline.

In addition, the Agency had asked the sponsor to reanalyze their data with the AM and PM scores separated, as well as combined. A revised total symptom complex was also asked for in which sneezes, cough and nose blows were pulled out of the complex. This request was actually based on the manner in which the tablet studies were conducted, in which sneezes and nose blows were assessed on a different symptom scale than the other symptoms. In addition, it was felt that nose blows and cough are probably not appropriate symptoms to assess and nose blows and sneezes are difficult to quantify over the course of a day (which is how the these symptoms were to be scored). Therefore, in presenting the data from this study, the sponsor's initial total and major symptom complex will be presented and differences between those symptom complexes and the revised complex will be described. In addition, efficacy regarding individual symptoms will be reported.

The primary analysis is an intent to treat analysis. Change from baseline for the

symptom complexes was compared between placebo and each treatment group by t-test using the mean square error from the analysis of covariance. The sponsor reports that the analysis initially incorporated terms for treatment, investigators, baseline and treatment by center interaction, however, because no significant treatment by center interaction was found, this term was dropped from the model. Individual symptoms were analyzed in a similar manner.

For the tables that will be presented in this review, in which P values are reported for mean or percent change from baseline, these P values are for the comparison of change from baseline in the treated group v.s. placebo.

The method of randomization used was a computer generated random code balanced in blocks of 8. This description was not included in the actual protocol, only in the protocol cover sheet. Blinding was accomplished by providing subjects with three bottles of medication per week. Two of these bottles contained either azelastine nasal spray or spray placebo and one bottle contained either Chlor-trimeton tablets or tablet placebo. The bottles were labelled with the patient's number, protocol number, bottle number and dosing instructions. A tear off part of the label which included the same information was to be included in the case report forms. The tear off portion of the label also had a sealed panel which contained the identity, strength, quantity and lot number of the medication in the bottle. Subjects in the azelastine 2 spray q day group received azelastine spray and placebo tablets in the AM and placebo spray and placebo tablets in the PM. Subjects in the azelastine 2 spray bid group received azelastine spray in the AM and PM and placebo tablets in the AM and PM. Subjects in the Chlor-trimeton group received placebo spray in the AM and PM and Chlor-trimeton tablets in the AM and PM. Finally, subjects in the placebo group received placebo spray and tablets in the AM and PM.

This study was conducted from 5/11/90 through 8/1/90 by Dr. William Strorms (Colorado), Dr. Philip Halverson (Minnesota), Dr. Jay Grossman (New York), Dr. David Pearlman (Colorado) and Dr. Paul Chervinsky (Massachusetts).

Results:

307 subjects were screened for entry into the trial and 60 did not qualify. The reasons given for lack of qualification include: insufficient symptom scores (35), failure to meet inclusion/exclusion criteria (11), treatment failure/too symptomatic (5), noncompliance (3), intercurrent illness (2), ADR (2) and lost to follow-up (2).

Comment: **To ensure compliance with the protocol, the sponsor should list the symptom scores of the 35 subjects with insufficient symptoms, state the reason that the 11 subjects failed to meet inclusion/exclusion criteria, explain why 5**

subjects were not randomized because of too sever disease (no upper limit on symptom scores is listed in the protocol), and state what the intercurrent illness and adverse events were in two subjects each which precluded randomization.

247 subjects age 12-69 were randomized to this trial and 230 completed double-blind treatment. 6 subjects in the azelastine q day group withdrew prematurely, as did 2 subjects in the azelastine bid group, 7 subjects in the placebo group and 2 subjects in the positive control group. 3 azelastine-treated subjects withdrew prematurely due to adverse events (epistaxis in two subjects and altered taste in one). There were 2 withdrawals due to treatment failure in the 2 spray q day group, none in the bid azelastine group and 2 in the placebo group. Of the 247 subjects randomized, 245 were included in the efficacy analysis. 2 subjects were lost to follow-up.

Comment: **The small number of subjects who withdrew due to treatment failure is not (2 in the azelastine q day and placebo groups, 0 in the bid group) is not likely to have a significant effect on the outcome of the trial. In addition, overall the number of premature withdrawals was small in the azelastine bid group and, although it was somewhat greater in the q day group the number in the placebo group was similar. Therefore, it does not seem likely that premature withdrawals and their distribution would play a significant role in the outcome of this trial.**

Demographics:

The study population was 89% white and 55% male. Subjects' ages ranged from 12 to 69 years and their weight ranged from 89 to 277lbs.

	Azel 2 spray q dy	Azel 2 spray bid	Chlorpheneramine	Placebo
Male	57.4%	61.9%	48.4%	52.5%
White	80.3%	88.9%	93.5%	91.8%
Age	30.8	32.7	33.7	29.9
Height	66.5in.	67.2in.	67.1in.	67.4in.
Weight	154.0lbs	166.5lbs	154.1lbs	163.2lbs

The four treatment arms were not statistically significantly different based on demographic characteristics (sex, race, age, height or weight) and did not significantly differ based on baseline total and major symptom scores.

Efficacy:

TOTAL SYMPTOM COMPLEX - AM			
Visit	Treatment	Change From Baseline (P Value)	Percent Change From Baseline (P Value)
Week 1	Az 2 sprays qd	2.00 (0.3595)	3.90 (0.7728)
	Az 2 spray bid	3.87 (0.0030)	23.92 (0.0026)
	Chlorpheneramine	4.10 (0.0002)	27.65 (0.0001)
	Placebo	0.88	0.20
Week 2	Az 2 sprays qd	3.28 (0.6135)	10.73 (0.8605)
	Az 2 spray bid	4.67 (0.0826)	28.09 (0.0511)
	Chlorpheneramine	5.13 (0.0022)	33.94 (0.0023)
	Placebo	2.23	10.47
Overall	Az 2 sprays qd	2.49 (0.3935)	7.13 (0.8816)
	Az 2 spray bid	4.36 (0.0058)	26.46 (0.0045)
	Chlorpheneramine	4.50 (0.0003)	30.04 (0.0003)
	Placebo	1.44	4.39

TOTAL SYMPTOM COMPLEX - PM			
Visit	Treatment	Change From Baseline (P Value)	Percent Change From Baseline (P Value)
Week 1	Az 2 sprays qd	2.39 (0.2777)	8.74 (0.3499)
	Az 2 spray bid	4.34 (0.0009)	23.22 (0.0010)
	Chlorpheneramine	5.01 (0.0001)	33.00 (0.0001)
	Placebo	1.14	1.75
Week 2	Az 2 sprays qd	3.68 (0.3956)	16.42 (0.3379)
	Az 2 spray bid	4.88 (0.0465)	26.05 (.0242)
	Chlorpheneramine	6.05 (0.0003)	38.85 (0.0001)
	Placebo	2.36	8.01
Overall	Az 2 sprays qd	2.99 (0.2330)	12.40 (0.2562)
	Az 2 spray bid	4.67 (0.0022)	24.92 (0.0017)
	Chlorpheneramine	5.38 (0.0001)	34.92 (0.0001)
	Placebo	1.57	3.90

Regarding the major symptom complex, for which the sponsor has only submitted

the data with AM and PM combined, the results look similar to what is presented above. The bid regimen was significantly different from placebo at all time points as was the positive control, however, the once a day regimen did not demonstrate any significant differences from placebo.

The following were the AM and PM data for the bid regimen (the once a day regimen was not significantly different from placebo) using the revised symptom complex:

REVISED TOTAL SYMPTOM COMPLEX - AM			
Visit	Treatment	Change From Baseline (P Value)	Percent Change From Baseline (P Value)
Week 1	Az 2 spray bid	2.08 (0.0036)	26.45 (0.0009)
	Placebo	0.40	-9.34
Week 2	Az 2 spray bid	2.42 (0.1066)	29.88 (0.0464)
	Placebo	1.10	10.26
Overall	Az 2 spray bid	2.30 (0.0068)	28.65 (0.0011)
	Placebo	0.68	-1.08

REVISED TOTAL SYMPTOM COMPLEX - PM			
Visit	Treatment	Change From Baseline (P Value)	Percent Change From Baseline (P Value)
Week 1	Az 2 spray bid	2.22 (0.0020)	25.65 (0.0012)
	Placebo	0.51	1.64
Week 2	Az 2 spray bid	2.52 (0.0536)	29.64 (0.0913)
	Placebo	1.04	3.09
Overall	Az 2 spray bid	2.40 (0.0030)	27.92 (0.0037)
	Placebo	0.68	-0.24

Comment: Based on the total symptom complex as originally defined by the sponsor, the bid regimen appears to work during both weeks of the trial. Although the absolute change from baseline for the AM assessment was not statistically significant v.s. placebo during week 2, the percent change from baseline at the same time point was significant. In addition, the absolute change at that time point is greater than the improvement seen during week 1. Regarding the revised symptom complex, the bid regimen also appears to work during the first week of the trial, however, while the AM percent change from baseline is significant at week 2, the PM assessment of percent change at this time point is not (although

here the absolute change from baseline does show a trend towards significance, P=.0536). The actual values for both absolute and percent improvement for the second week, however, were greater than those seen during week 1. Using the overall assessment of the two study weeks, either symptom complex suggests efficacy. Additionally, for the q day regimen one would expect to at least see efficacy during the first 12 hours after dosing (which would be reflected by the PM assessment), yet this is not apparent form these data. Possibly the bid regimen must be given on a continuous basis for efficacy to be demonstrable, however, the sponsor should address this question. Both the initial and the revised total symptom scores do support efficacy for the bid regimen.

The following are the results of the individual symptom data:

Sneezes:

The q day regimen was not significantly different from placebo at any time point.

SNEEZES - AM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray bid	0.43 (0.0242)
	Placebo	0.05
Week 2	Az 2 spray bid	0.58 (0.0746)
	Placebo	0.21
Overall	Az 2 spray bid	0.51 (0.0159)
	Placebo	0.11

SNEEZES - PM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray bid	0.50 (0.0020)
	Placebo	0.05
Week 2	Az 2 spray bid	0.55 (0.1811)
	Placebo	0.31
Overall	Az 2 spray bid	0.53 (0.0080)
	Placebo	0.14

Runny Nose/Sniffles:

The q day regimen was not significantly different from placebo at any time point.

RUNNY NOSE/SNIFFLES-AM		
Visit	**Treatment**	**Change From Baseline (P Value)**
Week 1	Az 2 spray bid	0.74 (0.0035)
	Placebo	0.20
Week 2	Az 2 spray bid	0.92 (0.0257)
	Placebo	0.44
Overall	Az 2 spray bid	0.84 (0.0023)
	Placebo	0.29

RUNNY NOSE/SNIFFLES - PM		
Visit	**Treatment**	**Change From Baseline (P Value)**
Week 1	Az 2 spray bid	0.86 (0.0002)
	Placebo	0.23
Week 2	Az 2 spray bid	0.94 (0.0149)
	Placebo	0.48
Overall	Az 2 spray bid	0.91 (0.0005)
	Placebo	0.31

Itchy nose:

The q day regimen was not significantly different from placebo at any time point.

ITCHY NOSE-AM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray bid	0.60 (0.0067)
	Placebo	0.12
Week 2	Az 2 spray bid	0.71 (0.1492)
	Placebo	0.36
Overall	Az 2 spray bid	0.67 (0.0084)
	Placebo	0.19

ITCHY NOSE - PM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray bid	0.57 (0.0121)
	Placebo	0.14
Week 2	Az 2 spray bid	0.75 (0.0401)
	Placebo	0.33
Overall	Az 2 spray bid	0.66 (0.0037)
	Placebo	0.17

Watery Eyes:

The q day regimen was not significantly different from placebo at any time point.

WATERY EYES-AM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray bid	0.49 (0.0433)
	Placebo	0.11
Week 2	Az 2 spray bid	0.55 (0.2092)
	Placebo	0.21
Overall	Az 2 spray bid	0.52 (0.0612)
	Placebo	0.16

WATERY EYES-PM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray bid	0.56 (0.0219)
	Placebo	0.20
Week 2	Az 2 spray bid	0.57 (0.1837)
	Placebo	0.27
Overall	Az 2 spray bid	0.56 (0.0361)
	Placebo	0.23

Itchy eyes/ears/throat or palate:

ITCHY EYES/EARS/THROAT OR PALATE-AM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.43 (0.1447)
	Az 2 spray bid	0.67 (0.0031)
	Placebo	.05
Week 2	Az 2 spray qd	0.65 (0.1521)
	Az 2 spray bid	0.75 (0.0471)
	Placebo	.22
Overall	Az 2 spray qd	0.54 (0.1008)
	Az 2 spray bid	0.72 (0.0037)
	Placebo	.13

ITCHY EYES/EARS/THROAT OR PALATE-PM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.47 (0.0917)
	Az 2 spray bid	0.66 (0.0012)
	Placebo	.04
Week 2	Az 2 spray qd	0.67 (0.1509)
	Az 2 spray bid	0.57 (0.0829)
	Placebo	.21

ITCHY EYES/EARS/THROAT OR PALATE-PM		
Visit	Treatment	Change From Baseline (P Value)
Overall	Az 2 spray qd	0.56 (0.0756)
	Az 2 spray bid	0.68 (0.0039)
	Placebo	.12

Postnasal Drip:

A trend toward significance was seen for the bid regimen during the first week (P = .0792) and for the overall analysis (P = .0664) based on the PM data. The bid regimen was not significantly different from placebo based on the AM data and the once a day regimen did not significantly differ from placebo for either the AM or PM assessments.

Nose Blows:

A trend toward significance was seen for the bid regimen during the first week (P = .0268) and for the overall analysis (P = .0590) based on the PM data. The bid regimen was not significantly different from placebo based on the AM data and the once a day regimen did not significantly differ from placebo for either the AM or PM assessments.

Stuffy Nose:

The q day regimen was not significantly different from placebo at any time point.

STUFFY NOSE-AM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray bid	0.50 (0.0084)
	Placebo	-0.04
Week 2	Az 2 spray bid	0.54 (0.5049)
	Placebo	0.22
Overall	Az 2 spray bid	0.53 (0.0363)
	Placebo	0.05

STUFFY NOSE-PM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray bid	0.68 (0.0006)
	Placebo	-0.01
Week 2	Az 2 spray bid	0.74 (0.0665)
	Placebo	0.16
Overall	Az 2 spray bid	0.72 (0.0018)
	Placebo	0.03

Comment: Regarding the evaluation of the individual symptoms, the once a day regimen does not significantly differ from placebo and therefore cannot be considered efficacious. Regarding the bid regimen, runny nose/sniffles and itchy eyes/ears/throat/palate were significantly different from placebo for the entire duration of the study based on both the AM and PM assessments. Considering that the study was probably not powered, in terms of patient numbers, to demonstrate significance on individual symptoms, these effects are quite significant. Effects on itchy nose, sneezing and watery eyes were also seen for both weeks of the trial, although the difference from placebo was not statistically significant at a number of the week two assessments, however, at these week two time points, improvements from baseline were sustained and, in fact, were greater than week 1. Of concern is the inconsistency seen in this study between efficacy during the first 12 hours after the q day drug is administered and the bid regimen. One would expect that if bid dosing works, the drug should work during the first 12 hours after the drug is administered once a day, unless repetitive dosing on a bid basis is needed to obtain efficacy. Therefore, while this study can be considered an adequate study to support the efficacy of the bid regimen, the sponsor should be asked to address the question of lack of efficacy during the first 12 hours after the q day spray is administered.

Both doses of the drug do appear to have an effect on stuffiness. While this may be attributable to the administration of liquid into the nose, this wouldn't account for the difference from placebo. Finally, the effects seen on watery eyes may indicate that some of the drug's efficacy is via systemic absorption.

Physician assessment of individual symptoms:

Total symptom complex: the q day regimen was significantly different from placebo only during week 2, whereas the bid regimen significantly differed from placebo during week 1. Chlorpheneramine was significantly different

from placebo both weeks.

Runny nose: there were no significant differences between azelastine and placebo at any time point.

Nasal itching: a trend toward significance was seen for the bid regimen during the first week but not the second. The q day regimen did not significantly differ from placebo.

Sneezing: both regimens were significantly different from placebo during both weeks of the trial.

Nasal blockage: Neither regimen was significantly different from placebo.

Eye symptoms: the bid regimen was significantly different from placebo at week 2.

Comment: **The investigator assessments, which were done at each of the weekly visits, do not demonstrate a consistent pattern of efficacy. However, the patient symptoms scores should be relied upon more heavily than the physician assessment because they were identified as the primary efficacy parameter, they may be more accurate than physician assessments and they are measured more frequently.**

Both the patient and investigator global evaluations support the efficacy of the bid regimen.

Regarding the change from baseline based on nasal examination, there do appear to be some statistically significant difference from placebo, however Table 27, which describes this data is not adequately labelled to interpret all of these effects. The sponsor should be asked to clarify table 27.

Safety:

The only clinically significant treatment emergent physical exam abnormalities that were noted included bilaterally injected eyes and posterior pharynx and tonsillar erythema, both in the 2 spray q day treatment groups.

Although there were some statistically significant differences from placebo in vital sign changes from baseline, these differences were not clinically significant.

Regarding adverse events, the only event which occurred significantly more often in azelastine treated subjects v.s. placebo was taste perversion. This occurred at a rate of 8.19% in the q day group, 20.63% in the bid group and 0% in placebo

treated subjects. The difference between the bid group and placebo was significant, P<.001. Somnolence also occurred more often in the q day and bid treated subjects (4.91% and 7.93%, respectively) than placebo (0%), however, this difference was not statistically significant. The difference in the incidence of local symptoms between treated subjects and placebo was small (only about 1-2 subjects).

Regarding lab tests, 15.2% of subjects in the q day azelastine group with normal glucose at baseline had an elevated level v.s. 2.1% of placebo subjects. 30% of all subjects in the q day group had a low urine specific gravity v.s. 10.2% of placebo subjects, P $\leq$ .026. Although there were some statistically significant differences between treated subjects and placebo regarding change from baseline in lab parameters, these differences were not clinically significant.

Study #31

The protocol for this study is the same as for study 26 described above.

The study was conducted between 1/4/90 and 2/23/90 at four centers in Texas.

Comment: **Since January and February are not typical allergy seasons (although they may be in Texas) the sponsor should provide the pollen count data on a center by center basis.**

335 subjects were screened for inclusion into the trial and 251 subjects were randomized.The reasons for lack of inclusion of 84 subjects include: insufficient symptom scores (43), lost to follow-up (10), failure to meet inclusion/exclusion criteria (6), treatment failure/too symptomatic (9), protocol violation (6), adverse event (1), intercurrent illness (1) and unspecified (8).

Comment: **To ensure compliance with the protocol, the sponsor should list the symptom scores of the 43 subjects with insufficient symptoms, state the reason that the 6 subjects failed to meet inclusion/exclusion criteria, explain why 9 subjects were not randomized because of too sever disease (no upper limit on symptom scores is listed in the protocol), and state what the intercurrent illness, adverse events and unspecified reasons were in subjects which precluded randomization to study #31.**

5 subjects in the bid group and 7 subjects in the placebo group discontinued from the trial prematurely. All subjects randomized to the azelastine once a day group completed double blind therapy. Two of the premature withdrawals in the azelastine group were due to adverse events (dizziness and increased blood pressure) and 1 was due to treatment failure. In the placebo group there were

three premature withdrawals due to treatment failure and one due to an adverse event (dizziness).

Comment: **As with trial #26, the overall number of premature withdrawals is small. In addition, the distribution of premature withdrawal due to treatment failure appears balanced, with 0 in the azelastine q day group, 1 in the azelastine bid group and 3 in the placebo group. Therefore, it doesn't appear likely that the distribution of premature withdrawals would play a significant role in the outcome of this trial.**

Results:

Demographics:

The study population was 97% white and 55% male. Subjects' ages ranged from 12 to 71 years and their weight ranged from 79 to 280lbs.

	Azel 2 spray qday	Azel 2 spray bid	Chlorpheneramine	Placebo
Male	46.8%	68.3%	51.6%	51.6%
White	95.2%	96.8%	98.4%	96.9%
Age	35.4	38.8	38.5	39.0
Height	66.5in.	67.8in.	67.3in.	67.8in.
Weight	158.7lbs	175.5lbs	160.8lbs	163.5lbs

There were no statistically significant differences between treatment groups with regard to sex, height or race. The mean weight at baseline in the azelastine bid group (175.5 pounds) was statistically significantly higher than in the other treatment groups (158.7, 160.8 and 163.5 pounds).

Efficacy Data:

The efficacy analysis includes data on 249 subjects. One placebo subjects was lost to follow up and one subject in the chlorpheneramine group withdrew prior to receiving any double blind treatment.

The sponsor states that at baseline the mean values for individual symptoms were statistically comparable across treatment groups.

TOTAL SYMPTOM COMPLEX - AM			
Visit	Treatment	Change From Baseline (P Value)	Percent Change From Baseline (P Value)
Week 1	Az 2 sprays qd	3.50 (0.0338)	18.07 (0.0350)
	Az 2 spray bid	5.15 (0.0003)	26.29 (0.0003)
	Chlorpheneramine	5.97 (0.0001)	30.08 (0.0001)
	Placebo	1.40	2.58
Week 2	Az 2 sprays qd	4.93 (0.4012)	26.97 (0.1950)
	Az 2 spray bid	6.48 (0.0405)	33.68 (0.0233)
	Chlorpheneramine	7.47 (0.0014)	38.67 (0.0016)
	Placebo	4.05	19.04
Overall	Az 2 sprays qd	4.21 (0.0628)	21.52 (0.0369)
	Az 2 spray bid	5.69 (0.0013)	29.38 (0.0008)
	Chlorpheneramine	6.60 (0.0001)	33.71 (0.0001)
	Placebo	2.44	9.38

TOTAL SYMPTOM COMPLEX - PM			
Visit	Treatment	Change From Baseline (P Value)	Percent Change From Baseline (P Value)
Week 1	Az 2 sprays qd	4.48 (0.0452)	21.72 (0.0239)
	Az 2 spray bid	5.80 (0.0025)	27.70 (0.0018)
	Chlorpheneramine	6.66 (0.0001)	34.76 (0.0001)
	Placebo	2.93	9.45
Week 2	Az 2 sprays qd	5.41 (0.5681)	28.82 (0.3760)
	Az 2 spray bid	6.99 (0.0896)	32.80 (.1732)
	Chlorpheneramine	7.96 (0.0035)	40.81 (0.0066)
	Placebo	5.40	24.44
Overall	Az 2 sprays qd	4.95 (0.1176)	25.27 (0.0525)
	Az 2 spray bid	6.33 (0.0074)	29.77 (0.0095)
	Chlorpheneramine	7.20 (0.0001)	37.09 (0.0001)
	Placebo	3.89	15.19

The results for the major symptom complex, as initially defined by the sponsor, are as follows (the data is presented for the combined AM and PM):

MAJOR SYMPTOM COMPLEX			
Visit	Treatment	Change From Baseline (P Value)	Percent Change From Baseline (P Value)
Week 1	Az 2 sprays qd	2.70 (0.0320)	19.50 (0.0284)
	Az 2 spray bid	3.82 (0.0003)	29.48 (0.0002)
	Chlorpheneramine	4.64 (0.0001)	34.87 (0.0001)
	Placebo	0.49	6.70
Week 2	Az 2 sprays qd	3.38 (0.6642)	26.58 (0.4832)
	Az 2 spray bid	4.59 (0.0675)	35.63 (0.0388)
	Chlorpheneramine	5.45 (0.0012)	40.90 (0.0027)
	Placebo	3.16	22.71
Overall	Az 2 sprays qd	3.04 (0.1049)	23.04 (0.0710)
	Az 2 spray bid	4.10 (0.0023)	31.82 (0.0010)
	Chlorpheneramine	4.97 (0.0001)	37.33 (0.0001)
	Placebo	2.07	13.16

Finally, with regard to symptom complexes, the following are the data based on the revised symptom complex, as requested by the Agency:

REVISED TOTAL SYMPTOM COMPLEX - AM			
Visit	Treatment	Change From Baseline (P Value)	Percent Change From Baseline (P Value)
Week 1	Az 2 sprays qd	1.94 (0.0711)	18.77 (0.0131)
	Az 2 spray bid	2.55 (0.0012)	28.56 (0.0002)
	Chlorpheneramine	2.98 (0.0001)	29.86 (0.0001)
	Placebo	0.92	-3.58
Week 2	Az 2 sprays qd	2.57 (0.9549)	29.29 (0.1296)
	Az 2 spray bid	3.32 (0.1397)	37.06 (0.0253)
	Chlorpheneramine	3.75 (0.0238)	39.00 (0.0146)
	Placebo	2.59	11.38

REVISED TOTAL SYMPTOM COMPLEX - AM			
Visit	Treatment	Change From Baseline (P Value)	Percent Change From Baseline (P Value)
Overall	Az 2 sprays qd	2.28 (0.2385)	24.03 (0.0253)
	Az 2 spray bid	2.87 (0.0072)	32.09 (0.0013)
	Chlorpheneramine	3.31 (0.0006)	33.76 (0.0007)
	Placebo	1.58	1.85

REVISED TOTAL SYMPTOM COMPLEX - PM			
Visit	Treatment	Change From Baseline (P Value)	Percent Change From Baseline (P Value)
Week 1	Az 2 sprays qd	2.18 (0.1140)	21.33 (0.0662)
	Az 2 spray bid	2.74 (0.0054)	29.28 (0.0026)
	Chlorpheneramine	3.35 (0.0002)	34.38 (0.0002)
	Placebo	1.42	8.83
Week 2	Az 2 sprays qd	2.74 (0.8393)	30.69 (0.6206)
	Az 2 spray bid	3.43 (0.1179)	35.89 (0.2245)
	Chlorpheneramine	3.99 (0.0114)	40.85 (0.0557)
	Placebo	2.80	28.12
Overall	Az 2 sprays qd	2.46 (0.2654)	26.01 (0.1146)
	Az 2 spray bid	3.05 (0.0145)	31.79 (0.0125)
	Chlorpher ramine	3.63 (0.0006)	36.98 (0.0013)
	Placebo	1.97	15.83

Comment: Statistically significant differences from placebo in total symptom complex scores are seen for the bid regimen during week one on both AM and PM assessments and during week 2 on only the AM assessment. However, even though statistically significant differences from placebo are not apparent at week 2 PM analysis, this appears to be more likely due to improvement in the placebo group rather than loss of efficacy in treated subjects. In fact, both the absolute and percent change from baseline during week 2 was greater than week 1 and significance is seen for the overall analysis. For the q day regimen, statistically significant differences from placebo are seen at week 1 both for AM and PM, however, not at all at week 2. The lack of statistical significance at week 2 again seems to be more related to placebo improvement rather than loss of efficacy in

treated subjects. A similar effect is seen for the major symptom complex.

Regarding the revised complex, the bid regimen is significant v.s. placebo during week 1 but not week 2. Again, this appears to be more likely due to improvement in placebo rather than loss of efficacy. However, the q day regimen is not significantly different from placebo during either week 1 or 2 based on the PM assessment. Therefore, while azelastine does not appear as efficacious as chlorpheneramine based on these data, the total and major symptom complexes do support efficacy for both regimens, whereas the revised complex only supports the bid regimen.

Sneezes:

SNEEZES-AM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.42 (0.0403)
	Az 2 spray bid	0.74 (0.0001)
	Placebo	.05
Week 2	Az 2 spray qd	0.63 (0.1046)
	Az 2 spray bid	0.82 (0.0073)
	Placebo	.34
Overall	Az 2 spray qd	0.53 (0.0303)
	Az 2 spray bid	0.77 (0.0002)
	Placebo	.17

SNEEZES-PM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.66 (0.0280)
	Az 2 spray bid	0.92 (0.0005)
	Placebo	.40
Week 2	Az 2 spray qd	0.70 (0.3072)
	Az 2 spray bid	0.93 (0.0669)
	Placebo	.66

SNEEZES-PM		
Visit	Treatment	Change From Baseline (P Value)
Overall	Az 2 spray qd	0.68 (0.0683)
	Az 2 spray bid	0.91 (0.0030)
	Placebo	.50

Comment: **These data show statistically significant differences or trends between both doses of azelastine and placebo at week one and overall and for the bid regimen at week two as well. Although the q day regimen is no longer significantly different from placebo at week two), improvement from baseline does increase from week one to week two. In addition, these data demonstrate a dose related effect on efficacy. Therefore, the data supports the efficacy of both doses of azelastine for this symptom.**

Stuffy Nose:

There were no statistically significant differences (or trends) between either dose of azelastine and placebo.

Runny Nose/Sniffles:

RUNNY NOSE/SNIFFLES-AM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.51 (0.0386)
	Az 2 spray bid	0.80 (0.0004)
	Placebo	.17
Week 2	Az 2 spray qd	0.70 (0.2226)
	Az 2 spray bid	1.00 (0.0076)
	Placebo	.47
Overall	Az 2 spray qd	0.60 (0.0452)
	Az 2 spray bid	0.87 (0.0006)
	Placebo	.29

RUNNY NOSE/SNIFFLES-PM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.66 (0.0454)
	Az 2 spray bid	0.85 (0.0007)
	Placebo	.36
Week 2	Az 2 spray qd	0.79 (0.7024)
	Az 2 spray bid	1.06 (0.0446)
	Placebo	.74
Overall	Az 2 spray qd	0.72 (0.1480)
	Az 2 spray bid	0.94 (0.0022)
	Placebo	.51

Comment: As with the symptom complex and sneezing, this data supports the efficacy of both doses because even though significant differences from placebo were not maintained through week two for the q day regimen, this appears to be due to large improvements in the placebo group, rather than loss of efficacy among treated subjects.

Itchy Nose:

ITCHY NOSE-AM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.50 (0.2634)
	Az 2 spray bid	0.70 (0.0042)
	Placebo	.25
Week 2	Az 2 spray qd	0.62 (0.5667)
	Az 2 spray bid	0.81 (0.3192)
	Placebo	.65
Overall	Az 2 spray qd	0.56 (0.6619)
	Az 2 spray bid	0.74 (0.0350)
	Placebo	.41

ITCHY NOSE-PM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.49 (0.2968)
	Az 2 spray bid	0.69 (0.0051)
	Placebo	.32
Week 2	Az 2 spray qd	0.67 (0.7361)
	Az 2 spray bid	0.75 (0.4877)
	Placebo	.73
Overall	Az 2 spray qd	0.58 (0.5873)
	Az 2 spray bid	0.72 (0.0417)
	Placebo	.49

Comment: **These data support the efficacy of the bid regimen for this symptom.**

Watery Eyes:

WATERY EYES-AM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.45 (0.1091)
	Az 2 spray bid	0.66 (0.0016)
	Placebo	.19
Week 2	Az 2 spray qd	0.57 (0.4980)
	Az 2 spray bid	0.92 (0.1374)
	Placebo	.64
Overall	Az 2 spray qd	0.51 (0.4427)
	Az 2 spray bid	0.78 (0.0055)
	Placebo	.37

WATERY EYES-PM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.56 (0.1246)
	Az 2 spray bid	0.78 (0.0038)
	Placebo	.23
Week 2	Az 2 spray qd	0.59 (0.5283)
	Az 2 spray bid	0.99 (0.0885)
	Placebo	.72
Overall	Az 2 spray qd	0.58 (0.5347)
	Az 2 spray bid	0.88 (0.0080)
	Placebo	.49

Comment: **As with itchy nose, these data only support the efficacy of the bid regimen for this symptom.**

Itchy eyes/ears/throat/palate:

The data is similar to that of watery eyes and itchy nose where significance is only seen for the bid regimen v.s. placebo.

Regarding postnasal drip, the data is somewhat better in that a significant difference v.s. placebo is seen for the q day regimen based on the AM assessment during week 1. The statistical significance is not sustained to week two, although the clinical effect appears to be. However, based on the PM assessment there were no significant differences between the q day regimen and placebo. Therefore, this data is supportive of the bid regimen but not q day.

There were no significant differences between treatment and placebo regarding cough.

Regarding the investigator's assessment of allergic rhinitis symptoms, there were trends toward significant differences between the bid regimen and placebo for the total symptom complex and runny nose for both weeks, itchy nose for week one and eye symptoms for week two.

The physician's global assessment supports the efficacy of the bid regimen with significantly more subjects considered improved for both weeks one and two, as well as the overall assessment. There were no significant differences between the

q day regimen and placebo on the physician's global assessment. The patient's global assessment demonstrated differences between both azelastine groups and placebo for week one, however not for week two or the overall assessment.

Regarding nasal examinations, although there were some scattered differences between treated and control subjects, this assessment did not demonstrate differences between treatment and placebo.

Comment: **Although the global assessments appear to provide support for only the bid regimen, the symptom complexes, as well as the individual symptom data in this trial, support the efficacy of both the q day and bid azelastine regimens. Both regimens appear to improve the symptom complexes as well as sneezes and runny nose/sniffles. In addition, efficacy was also seen for the bid regimen for the revised complex, itchy nose, watery eyes, itchy eyes/ears/throat/palate and postnasal drip.**

Safety:

None of the treatment emergent physical exam abnormalities appear clinically significant. In addition, there were no statistically significant differences between azelastine treated subjects and those on placebo with regard to changes in vital signs.

One subject on azelastine discontinued prematurely due dizziness and a second withdrew prematurely due to increase in blood pressure.

None of the adverse events that were reported occurred significantly more often in azelastine treated subjects than placebo controls. The incidence of local adverse reactions was low and they did not occur in more than 1-2 subjects.

Regarding lab values, the incidence of elevated SGPT and LDH was significantly greater in the bid azelastine group than placebo. For SGPT the incidence was 35% in the treated subjects and 7% in the placebo group (it was 20% in subjects receiving azelastine q day). The incidence of elevated LDH was 17% in the bid azelastine group and 4% in the placebo group (it was 6% in the azelastine q day group). The P value for both of these differences was $\leq .026$. In addition, the incidence of low BUN values was significantly greater in the azelastine q day group v.s. placebo, 24% v.s. 9%, $P = .019$.

When change from baseline to endpoint was examined, there were statistically significant differences between azelastine treated subjects and placebo for bicarbonate, albumin, triglycerides and banded neutrophils. However, the change from baseline to endpoint for all parameters except triglycerides was small. For triglycerides subjects in the azelastine q day group experienced an 18mg/dl decrease in triglycerides and subjects in the bid group experienced a 27mg/dl drop

v.s. a 17mg/dl increase in the placebo group.

Study #33

The protocol used for this trial was the same as for studies # 26 and 31 described above, except that the double blind period in this trial was four weeks, rather than two weeks as in studies 26 and 31.

The study was conducted between 4/16/90 and 7/31/90 at the following 5 centers:

Dr. Bruce Prenner - San Diego, California
Dr. Michael Kraemer - Spokane, Washington
Dr. Craig LaForce - Raleigh, North Carolina
Dr. Theodore Chu - San Jose, California
Dr. Robert Dockhorn, Prairie Village, Kansas

337 subjects were screened for inclusion into the trial and 264 subjects were randomized. The reasons given for not randomizing 73 subjects include: insufficient symptom score (52), lost to follow-up (5), failure to meet inclusion/exclusion criteria (4), intercurrent illness (4), too symptomatic (3), unknown (2), adverse events (1), non-compliance (1) and exceeded site enrollment (1).

Comment: **To ensure compliance with the protocol, the sponsor should list the symptom scores of the 52 subjects with insufficient symptoms, state the reason that the 4 subjects failed to meet inclusion/exclusion criteria, explain why 3 subjects were not randomized because of too sever disease (no upper limit on symptom scores is listed in the protocol), and state what the intercurrent illness, adverse events and unknown reasons were in the other subjects which precluded randomization.**

7 subjects in the azelastine q day group, 3 subjects in the azelastine bid group and 13 subjects in the placebo group discontinued from the trial prematurely. There were also 2 premature discontinuations from the chlorpheneramine group. Of all the premature discontinuations, only one in the azelastine bid group and one in the placebo group were due to treatment failure. In addition, two subjects each in the azelastine q day group and the chlorpheneramine group discontinued prematurely due to adverse events. There were also two premature withdrawals in the azelastine q day group due to intercurrent illnesses and 3 in the bid group. Adverse

events or intercurrent illnesses which resulted in premature withdrawal from the trials included: conjunctivitis, lymphadenopathy, allergic reaction, dizziness, somnolence, lightheadedness, numbness of face, feet and hands, parasthesias, uncontrolled diabetes mellitus, appendicitis and sinusitis.

Comment: **Case report forms of the azelastine treated subjects who discontinued prematurely should be submitted. The distribution of premature withdrawals due to treatment failure appears balanced, as does the overall number of premature withdrawals.**

Results:

Demographics:

The study population was 82% white and 58% male. Subjects' ages ranged from 12 to 69 years and their weight ranged from 72 to 267lbs.

	Azel 2 spray qday	Azel 2 spray bid	Chlorpheneramine	Placebo
Male	62.1%	45.5%	66.2%	58.2%
White	87.9%	80.3%	80.0%	80.6%
Age	30.5	28.2	31.1	31.1
Height	67.7in.	66.9in.	68.0in.	67.1in.
Weight	158.2lbs	161.2lbs	163.2lbs	155.8lbs

There were no statistically significant differences between treatment groups with regard to sex, age, height, weight or race.

Efficacy Data:

263 of the 264 subjects who were randomized were included in the efficacy analysis. One subject in the placebo group was lost to follow-up.

TOTAL SYMPTOM COMPLEX - AM			
Visit	Treatment	Change From Baseline (P Value)	Percent Change From Baseline (P Value)
Week 1	Az 2 sprays qd	2.79 (0.3419)	14.70 (0.3504)
	Az 2 spray bid	3.46 (0.1123)	18.73 (0.0956)
	Chlorpheneramine	4.74 (0.0013)	28.95 (0.0003)
	Placebo	2.05	10.10
Week 2	Az 2 sprays qd	3.78 (0.8653)	20.59 (0.8813)
	Az 2 spray bid	4.49 (0.4258)	24.89 (0.2737)
	Chlorpheneramine	5.79 (0.0319)	33.34 (0.0132)
	Placebo	3.69	18.18
Week 3	Az 2 sprays qd	4.75 (0.1337)	21.57 (0.3414)
	Az 2 spray bid	5.00 (0.0890)	29.06 (0.0454)
	Chlorpheneramine	6.26 (0.0038)	37.24 (0.0015)
	Placebo	3.13	14.54
Week 4	Az 2 sprays qd	4.52 (0.3577)	19.53 (0.8558)
	Az 2 spray bid	6.46 (0.0231)	35.99 (0.0251)
	Chlorpheneramine	6.51 (0.0099)	37.38 (0.0096)
	Placebo	3.63	18.69
Overall	Az 2 sprays qd	3.68 (0.3383)	17.66 (0.5278)
	Az 2 spray bid	4.43 (0.1088)	24.42 (0.0719)
	Chlorpheneramine	5.80 (0.0008)	34.15 (0.0003)
	Placebo	2.89	14.30

TOTAL SYMPTOM COMPLEX - PM			
Visit	Treatment	Change From Baseline (P Value)	Percent Change From Baseline (P Value)
Week 1	Az 2 sprays qd	3.51 (0.0966)	17.39 (0.1485)
	Az 2 spray bid	4.33 (0.0187)	22.15 (0.0229)
	Chlorpheneramine	5.66 (0.0001)	32.40 (0.0001)
	Placebo	2.35	10.39

Week 2	Az 2 sprays qd	4.66 (0.4158)	23.68 (0.4671)
	Az 2 spray bid	5.33 (0.2031)	27.39 (0.2246)
	Chlorpheneramine	6.36 (0.0243)	33.91 (0.0289)
	Placebo	4.19	19.74
Week 3	Az 2 sprays qd	5.55 (0.0277)	25.02 (0.1464)
	Az 2 spray bid	5.38 (0.0532)	28.89 (.0531)
	Chlorpheneramine	6.81 (0.0018)	37.02 (0.0027)
	Placebo	3.29	14.21
Week 4	Az 2 sprays qd	5.36 (0.1063)	22.49 (0.3915)
	Az 2 spray bid	6.64 (0.0314)	33.80 (0.0441)
	Chlorpheneramine	6.94 (0.0103)	37.21 (0.0108)
	Placebo	4.01	17.51
Overall	Az 2 sprays qd	4.44 (0.0776)	19.96 (0.2757)
	Az 2 spray bid	5.02 (0.0409)	25.61 (0.0592)
	Chlorpheneramine	6.43 (0.0003)	35.18 (0.0006)
	Placebo	3.13	14.07

Comment: **The AM data presented above do not support the efficacy of either dose of azelastine, whereas the positive control does seem quite efficacious v.s. placebo. The PM data does look somewhat better, at least for the bid regimen. Statistically significant differences from placebo are seen during the first, third and fourth week of the trial for the bid regimen v.s. placebo. Even during the second week, when the difference from placebo is not statistically significant, the percent and absolute improvement over baseline is greater than during the previous week. The discrepancy between the AM and PM data does make it questionable as to whether the total symptom complex supports efficacy for either dose. The sponsor should be asked to comment on these differences.**

Statistically significant differences between azelastine treated subjects and placebo were not seen, based on the revised symptom complex, until week four of the trial, at which time some differences between the bid regimen and placebo were noted. The data from the major symptom complex is similar to that of the PM total

symptom complex described above and supports efficacy for the bid regimen but not the once a day regimen (the major symptom complex was not divided into AM and PM data).

Runny nose/sniffles:

RUNNY NOSE/SNIFFLES-AM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.40 (0.5409)
	Az 2 spray bid	0.53 (0.1707)
	Chlorpheneramine	0.79 (0.0007)
	Placebo	0.29
Week 2	Az 2 spray qd	0.56 (0.5606)
	Az 2 spray bid	0.75 (0.7445)
	Chlorpheneramine	1.01 (0.0251)
	Placebo	0.63
Week 3	Az 2 spray qd	0.70 (0.3559)
	Az 2 spray bid	0.86 (0.1089)
	Chlorpheneramine	1.05 (0.0045)
	Placebo	0.50
Week 4	Az 2 spray qd	0.72 (0.7295)
	Az 2 spray bid	0.99 (0.4978)
	Chlorpheneramine	1.12 (0.0755)
	Placebo	0.78
Overall	Az 2 spray qd	0.55 (0.9573)
	Az 2 spray bid	0.71 (0.3620)
	Chlorpheneramine	0.98 (0.0018)
	Placebo	0.51

RUNNY NOSE/SNIFFLES-PM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.58 (0.0191)
	Az 2 spray bid	0.74 (0.0022)
	Chlorpheneramine	0.0001
	Placebo	.26
Week 2	Az 2 spray qd	0.67 (0.4501)
	Az 2 spray bid	0.86 (0.1399)
	Chlorpheneramine	1.06 (0.0034)
	Placebo	0.58
Week 3	Az 2 spray qd	0.85 (0.0542)
	Az 2 spray bid	0.98 (0.0274)
	Chlorpheneramine	1.10 (0.0019)
	Placebo	0.49
Week 4	Az 2 spray qd	0.88 (0.3886)
	Az 2 spray bid	1.05 (0.3121)
	Chlorpheneramine	1.09 (0.1036)
	Placebo	.77
Overall	Az 2 spray qd	0.69 (0.0991)
	Az 2 spray bid	0.83 (0.0378)
	Chlorpheneramine	1.03 (0.0002)
	Placebo	0.45

There were no statistically significant differences between either the bid or q day regimen and placebo on the AM assessment, whereas the positive control did significantly differ from placebo on this assessment.

Comment: **Despite the fact that the difference between azelastine treated subjects and placebo (for both azelastine regimens) was significant only during the first week of the trial, subjects in both azelastine regimens continued to improve each week and the effects were dose related, based on the PM assessment. This would suggest efficacy on this symptom, however the lack of a difference between azelastine treated subjects and placebo on the AM assessment raises doubts about the efficacy on runny nose.**

Sneezes:

SNEEZES - AM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.36 (0.3062)
	Az 2 spray bid	0.51 (0.0309)
	Chlorpheneramine	0.74 (0.0006)
	Placebo	.11
Week 2	Az 2 spray qd	0.45 (0.9037)
	Az 2 spray bid	0.57 (0.3110)
	Chlorpheneramine	0.85 (0.0135)
	Placebo	0.33
Week 3	Az 2 spray qd	0.63 (0.2048)
	Az 2 spray bid	0.83 (0.0768)
	Chlorpheneramine	1.00 (0.0004)
	Placebo	0.24
Week 4	Az 2 spray qd	0.60 (0.8469)
	Az 2 spray bid	0.85 (0.1281)
	Chlorpheneramine	0.99 (0.0375)
	Placebo	.47
Overall	Az 2 spray qd	0.46 (0.3927)
	Az 2 spray bid	0.62 (0.0290)
	Chlorpheneramine	0.89 (0.0001)
	Placebo	0.24

SNEEZES - PM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.44 (0.0524)
	Az 2 spray bid	0.66 (0.0006)
	Chlorpheneramine	0.80 (0.0001)
	Placebo	0.15
Week 2	Az 2 spray qd	0.60 (0.5762)
	Az 2 spray bid	0.69 (0.2199)
	Chlorpheneramine	0.90 (0.0177)
	Placebo	0.44
Week 3	Az 2 spray qd	0.70 (0.0752)
	Az 2 spray bid	0.73 (0.0281)
	Chlorpheneramine	0.99 (0.0005)
	Placebo	0.29
Week 4	Az 2 spray qd	0.66 (0.7753)
	Az 2 spray bid	0.92 (0.0928)
	Chlorpheneramine	1.02 (0.0314)
	Placebo	0.55
Overall	Az 2 spray qd	0.56 (0.0944)
	Az 2 spray bid	0.73 (0.0046)
	Chlorpheneramine	0.93 (0.0001)
	Placebo	0.29

Comment: The data presented above supports the efficacy of the bid regimen, however, because of the inconsistency between the AM and PM data for the q day regimen, efficacy for azelastine when administered once a day is not supported by this data.

Itchy nose:

Itchy Nose-PM		
Visit	Treatment	Change From Baseline (P Value)
Week 1	Az 2 spray qd	0.58 (0.1698)
	Az 2 spray bid	0.70 (0.0398)
	Placebo	.42
Week 2	Az 2 spray qd	0.74 (0.1663)
	Az 2 spray bid	0.77 (0.1352)
	Placebo	0.54
Week 3	Az 2 spray qd	0.83 (0.0138)
	Az 2 spray bid	0.75 (0.0452)
	Placebo	0.41
Week 4	Az 2 spray qd	0.76 (0.1046)
	Az 2 spray bid	0.89 (0.0396)
	Placebo	.48
Overall	Az 2 spray qd	0.69 (0.0758)
	Az 2 spray bid	0.76 (0.0321)
	Placebo	0.46

On the AM assessment there were no significant differences between azelastine treated subjects and placebo during the first two weeks of the trial. For weeks three and four, there were strong trends for the bid regimen, however, there were still no significant improvements in the q day regimen.

Comment: **Because of the lack of efficacy on the AM assessment, even though the PM assessments supports the efficacy of the bid regimen, as a whole the data does not demonstrate efficacy for azelastine regarding this symptom.**

Watery eyes:

For both the AM and PM assessment there were no significant differences, or trend towards significance, for either the bid or the q day regimen when compared with placebo

Itchy eyes/ears/throat or palate:

For both the AM and PM assessment there were no significant differences (or trends) during the first three weeks of the trial between azelastine treated subjects and those receiving placebo.

Post nasal drip:

For both the AM and PM assessments there were no significant differences, or trend towards significance, for either the bid or the q day regimen when compared with placebo

Cough:

For both the AM and PM assessment there were no significant differences (or trends) during the first three weeks of the trial between azelastine treated subjects and those receiving placebo.

Stuffy nose:

There were no significant differences, or trends towards significance, at any time point for azelastine treated subjects v.s. controls.

Comment: **Overall, this study only appears to demonstrate efficacy for the bid regimen on the symptom of sneezing. Because of discrepancies between the AM and PM data, efficacy regarding other symptoms or the symptom complexes cannot be concluded on the basis of this study. Therefore, this study does not support the efficacy of either dosing regimen for the indication of seasonal allergic rhinitis.**

Safety:

None of the treatment emergent physical exam abnormalities appear to be of a serious nature. Although there were some scattered significant differences in vital signs between treated subjects and those receiving placebo, the differences are not clinically significant. The only statistically significant difference in adverse events between azelastine treated subjects and placebo was for taste perversion. The incidence in both the q day regimen (31.8%) and the bid regimen (30.3%) was significant v.s. placebo (1.49%), $P<.001$.

There were no statistically significant increases in azelastine treated subjects in the incidence of abnormally high or low lab values. Although there were some statistically significant differences between azelastine and placebo subjects regarding lab changes from baseline to weeks 2, 4 and follow-up, the changes from baseline are small and do not appear to be clinically significant.

Additional Clinical Trials

1. Study #29 (safety trial): This is a two center, double-blind, parallel, randomized, placebo controlled trial of the safety of 2 sprays/nostril (.13mg/spray) bid of .1% azelastine solution administered for 8 weeks to subjects with perennial allergic rhinitis. Safety was assessed based on reports of adverse events and monitoring for changes in vital signs, body weight, physical exam, ECG and lab tests. Nasal exams, nasal cytology and nasal airflow rates were also assessed. 105 subjects age 11-54 were included in the trial.

Results:

All 105 subjects who were randomized are included in the analysis. 4 subjects in the azelastine group discontinued therapy prematurely due to intercurrent illness (poison oak, asthma, URI and strep pharyngitis) and 4 subjects discontinued prematurely due to adverse events. 2 subjects withdrew from the trial due to altered taste, vomiting and gagging, 1 subject withdrew due to nervousness and 1 subject who withdrew was complaining of frequent urination, racing heart, loss of taste, drowsiness, erotic dreams and a feeling of weightlessness. All adverse events resolved after therapy was withdrawn. In addition to the subjects who discontinued prematurely, one subject with bloody mucus and tiredness was lost to follow up.

There were no treatment emergent abnormalities on physical exam. There were no significant differences between treated and control subjects with regard to change in vital signs or weight from baseline. The mean changes in vital signs was also not clinically significant. Only one treated subject experienced a weight increase $\geq$ 5% of baseline body weight.

With regard to the incidence of adverse events, only taste perversion occurred statistically significantly more often in the treated subjects than in the control group, 31.88% vs 2.77% respectively. The only serious adverse event was somnolence in a subject who drives a vehicle for a living and was, therefore, discontinued from the trial. There were no significant differences between treatment and control subjects with regard to change in lab values from baseline. None of the mean changes in lab values were clinically significant, however, clinically significant lab abnormalities were reported in three treated subjects. In one subject WBC (13,400/mm^3) and neutrophil count (78%) were elevated and lymphocyte count (14%) was depressed. Similar abnormalities were noted in this subject prior to treatment. A second subject had a low WBC (3200/mm^3) which returned to normal at re-testing and a third subject had an elevated SGPT (71 U/L) which also returned to normal when the test was repeated.

The sponsor does report that there were a number of treatment emergent ECG

changes during the final week of the trial but doesn't specify what these changes were.

With regard to nasal exam, there were no significant differences between treatment groups. There were also no significant differences with regard to mean change from baseline in cell counts or in mean airflow rate at each visit. Use of backup medications was similar in the two groups, however, the acceptability rating of the drug was significantly greater for placebo than azelastine, 97.14% vs 62.12% ($P < .001$), respectively.

2. Study #34: This was a randomized, double blind trial of 1 spray q day of azelastine v.s. placebo in 16 subjects in Germany with allergic rhinitis. No statistical comparisons of efficacy data are reported. Adverse reactions included tiredness and hyposmia in one treated subject and tiredness in a placebo subject.

3. Study #35: This was an open label, budesonide controlled, randomized trial of 1 spray per nostril q day administered for two weeks to 36 subjects in Germany. No statistical analysis of efficacy is presented. Adverse events included unpleasant taste in two azelastine treated subjects.

4. Study #36: This was a double blind, randomized trial of azelastine nasal spray (1 spray per nostril bid) v.s. terfenadine (60mg bid) administered for 6 weeks to 167 subjects with seasonal allergic rhinitis at 8 centers in Germany. The sponsor states that there were statistically significant improvements from baseline on total symptom scores for both treatment arms and "no relevant differences" between the two treatments. There were no deaths during the trial. Two azelastine treated subjects discontinued therapy prematurely due to headaches in one subject and abdominal pain, redness and swelling of the throat and breathing difficulties attributed to "psychological state" in the other.

5. Study #37: This was a double blind, randomized trial of azelastine (1 spray per nostril bid) v.s. terfenadine (60mg bid) administered for 6 weeks to 100 subjects with seasonal allergic rhinitis in Germany. As in study #36, there were no significant efficacy differences between the two treatment arms. There were no deaths or premature withdrawals.

6. Study #38: This was an open, uncontrolled trial of 1 spray per nostril bid of azelastine administered for 6 months to 185 subjects in Germany with perennial allergic rhinitis.There were no deaths or serious adverse events in the trial. Adverse events included: application site reactions (itching or burning) in 12 subjects, taste perversion in 11 subjects, rhinitis in 5 subjects, nausea in 3 subjects, parasomia, thirst, epistaxis and pharyngitis in 1 subject each. Four subjects discontinued prematurely due to application site reactions and one due to taste perversion.

7. Study #39: This was a double blind, randomized trial of azelastine (1 spray per nostril bid) v.s. terfenadine (60mg bid) administered for 6 weeks to 52 subjects in Germany with perennial allergic rhinitis. No significant difference between the two treatments was seen. There were no deaths, premature withdrawals or adverse events reported.

Overall Efficacy Comments

The data from the pivotal trials that was presented above supports the efficacy of the twice a day azelastine nasal spray regimen, but not the once a day regimen (assuming that the questions to be sent to the sponsor are adequately answered). Study #26 demonstrates the efficacy of bid administration of azelastine nasal spray to subjects with seasonal allergic rhinitis on the total and revised symptom complexes, runny nose/sniffles, itchy eyes/ears/throat/palate, itchy nose, sneezes and watery eyes. Efficacy was not demonstrated for the once a day regimen. In fact, efficacy was not even seen during the first 12 hours after administration of azelastine. Study #31 demonstrates the effectiveness of both dosing regimens on improving the total and major symptom complexes, sneezing and runny nose. The bid regimen also demonstrated improvement on the revised complex, itchy nose, watery eyes, itchy eyes/ears/throat and palate and post nasal drip. Improvement from baseline is dose related. Regarding efficacy at the end of the dosing interval, Study #30 supports this for both the bid and q day regimen, although the duration of this trial was only 1.5 days. In addition, the efficacy seen for the q day regimen in Study #31 supports efficacy at the end of the dosing interval for the bid regimen. The third pivotal efficacy study, however, only demonstrated efficacy for the bid regimen on the symptom of sneezing. For other symptoms there were discrepancies between AM and PM data which precludes the usefulness of this study to support either dosing regimen.

Integrated Safety Summary

Extent of Exposure:

1320 subjects were enrolled in clinical research trials of the nasal spray and 144 subjects in two pharmacology trials. Of these, 789 subjects were exposed to azelastine, 313 to positive controls and 362 to placebo. The doses of azelastine that were studied in the clinical research trials include 1 spray per nostril q12 hr, 2 sprays per nostril qd and 2 sprays per nostril q12 hours. In the clinical research trials 322 subjects were treated with azelastine for less than one week, 210 subjects were treated for 1-2 weeks, 145 subjects received azelastine for 2-4 weeks and 12 subjects were treated for 4-8 weeks.

556 subjects were enrolled in foreign studies and of these 367 received azelastine nasal spray. Most subjects in the foreign trials were treated for 4-8 weeks.

Safety data from the two pharmacology trials is included in the description of these trials described elsewhere in this review. In the research trials there were no deaths and no serious and unexpected adverse events.

Adverse events:

Adverse events which occurred statistically significantly more often in subjects treated with azelastine vs placebo include headache (18.1% vs 12.9%), somnolence (12.0% vs 5.7%), taste perversion (15.4% vs .3%) and nausea (2.9% vs .6%). Of these taste perversion and possibly somnolence demonstrated a dose related effect:

Adverse Event	Az 1 spray q 12h	Az 2 sprays qd	Az 2 sprays q 12h	Placebo
Headache	29.6%	18.5%	15.8%	12.9%
Somnolence	5.6%	12.7%	12.4%	5.7%
Taste Perversion	9.3%	14.6%	17.1%	0.3%
Nausea	1.9%	3.5%	2.5%	0.6%

Local adverse events include:

Event	azelastine	placebo
pharyngitis	3.2%	1.9%
nasal burning	3.0%	1.9%
dry mouth	2.9%	1.9%
epistaxis	2.3%	1.6%
rhinitis	2.0%	1.3%
paroxysmal sneezing	1.4%	0%
throat burning	.9%	0%

Of these adverse events, the difference between active treatment and placebo is not reported as statistically significant and only pharyngitis occurred in a dose related manner.

With regard to duration of exposure, taste perversion, rhinitis and myalgia were more common with increasing duration of exposure, however, these and all other adverse events first occurred more often during the first week of therapy.

When data from short term trials (2 days duration) is reported separately, adverse events which occurred at least 2% more often in treated subjects than controls include headache (22.7% vs 12.8%), somnolence (17.8% vs 10.4%), taste perversion (14.6% vs 0%), dizziness (4.9% vs 2.4%), dry mouth (3.9% vs 1.6%), nausea (3.6% vs 0%), pharyngitis (3.2% vs .8%) and fatigue (2.9% vs .8%). Taste perversion, somnolence and possibly nausea occurred in a dose related manner. In long term trials taste perversion (16% vs .5%), somnolence (7.3% vs 2.6%), paroxysmal sneezing (2.6% vs 0%) and myalgias (2.4% vs 0%) occurred more often in treated subjects than in those receiving placebo by at least 2%.

For all controlled trials, the only adverse events which may be considered cardiac related were dizziness (2.9% in azelastine subjects, 2.6% in the positive control group and 1.6% in the placebo group), hypertension (.1% in the azelastine group and 0% in the positive control and placebo groups) and palpitations (.1% in azelastine subjects and .3% in the placebo group). These adverse events did not occur in a dose related manner. Adverse events which may be considered hepatic related included abdominal pain (.4% in the azelastine group, .3% in the positive control group and .9% in the placebo group) and SGPT increased (.1% in the azelastine group and 0% in the placebo group).

15 subjects who were receiving azelastine in controlled research trials discontinued their trial prematurely due to an adverse event or intercurrent illness. 7 of the subjects discontinued due to adverse events and 8 discontinued due to intercurrent illnesses. Of the 7 subjects with adverse events, 3 experienced dizziness, 2

experienced epistaxis and somnolence, and taste perversion and hypertension occurred in one subject each.

ADVERSE EVENTS WHICH OCCURRED AT A RATE OF ≥ 1%			
Adverse Event	**Azelastine**	**Positive Control**	**Placebo**
Headache	18.1%*	12.8%	12.9%
Taste Perversion	15.4%*		.3%
Somnolence	12.0%*	16.9%	5.7%
Pharyngitis	3.2%	5.8%	1.9%
Nasal Burning	3.0%	.3%	1.9%
Dizziness	2.9%	2.6%	1.6%
Dry Mouth	2.9%	4.5%	1.9%
Nausea	2.9%*	1.0%	.6%
Epistaxis	2.3%	1.9%	1.6%
Rhinitis	2.3%	2.2%	.9%
Fatigue	2.0%	3.2%	1.3%
Myalgia	1.6%	.6%	0%
Sneezing, Paroxysmal	1.4%	.3%	0%
Nervousness	1.3%	.6%	.6%

* Statistically significant v.s. placebo

Demographics of Adverse Events:

Age:

Adverse events did not occur more often in subjects under the age of 18 or older than 60 than in subjects between those ages.

Gender:

The incidence of many of the adverse events was greater in females than in males.

The adverse events with the greatest difference between the two groups were headache (22.7% vs 14.1%), taste perversion (20.8% vs 10.6%) and somnolence (14.6% vs 9.8%). Although the incidence of these adverse events in the placebo groups was greater in female subjects v.s. males, the difference was not as great as in the treated subjects. The sponsor should be asked whether the difference between males and females in the azelastine treated group for any of the adverse events is statistically significant, and if it is, whether the difference between males and females in the placebo group is also significant.

Race:

There were no notable differences between whites and non-whites with regard to incidence of adverse events.

Weight:

There were also no notable differences in the incidence of adverse events based on weight.

Vital Signs:

Compared to placebo controls changes from baseline in blood pressure (systolic or diastolic) or pulse rate were not clinically or statistically significant. There were also no clinically and statistically significant differences between the groups with regard to change from baseline in body weight or in the incidence of abnormal blood pressure, pulse or body weight.

Laboratory Tests:

In controlled US trials there were no significant differences between treated and placebo subjects with regard to the incidence of out of normal range lab values. There were also no statistically significant differences in change from baseline to endpoint between the two groups for any lab test in which the change was greater in the treated subjects than placebo (there were some labs in which the change from baseline in the placebo group was greater than in the treated group). There was a statistically significant greater decrease from baseline in BUN in the placebo group than in treated subjects, .53 vs .01 respectively. None of the changes from baseline in treated subjects appears to be clinically significant.

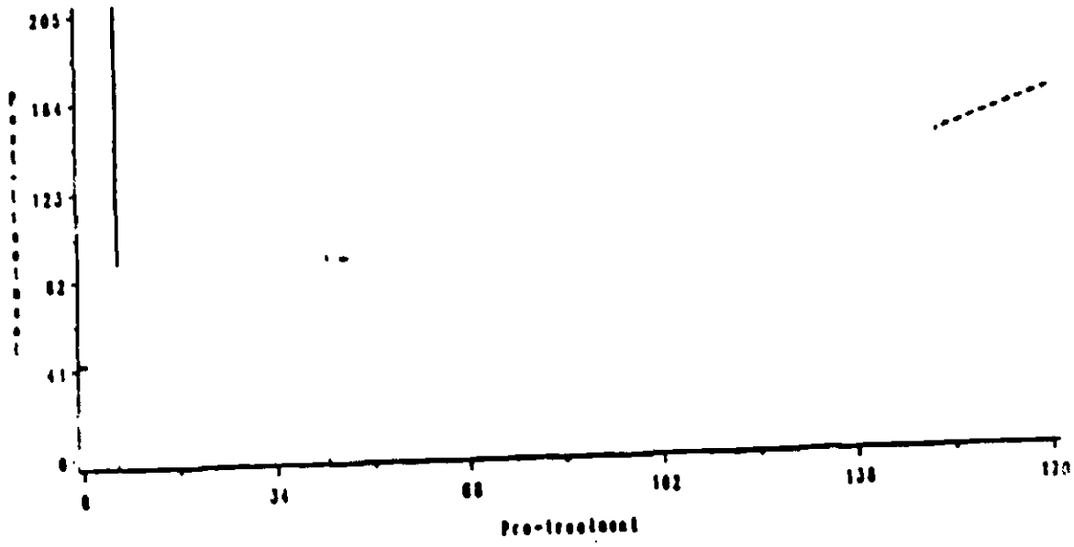
Although there were no dose related effects on change from baseline, the incidence of elevated SGPT and chloride did appear dose related (however, this was not significantly different from placebo).

The scatter plots on the following pages depict the changes from baseline to

endpoint for the azelastine and placebo groups for a number of labs assessed. The points that are circled represent outliers that the sponsor should identify and submit case report forms for:

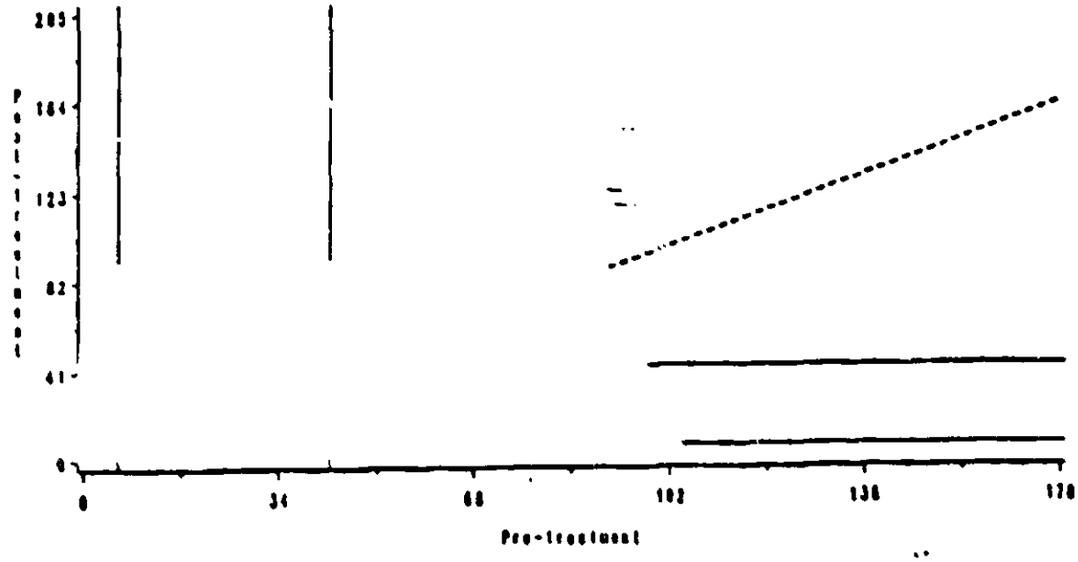
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

ALT (SGPT) U/L
Treatment = All Azelastine



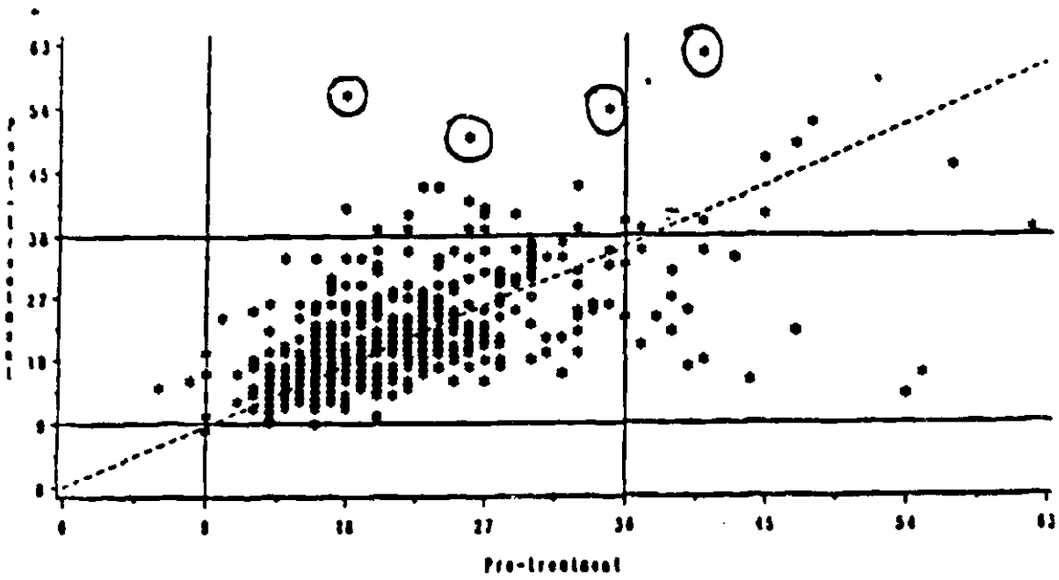
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

ALT (SGPT) U/L
Treatment = Placebo



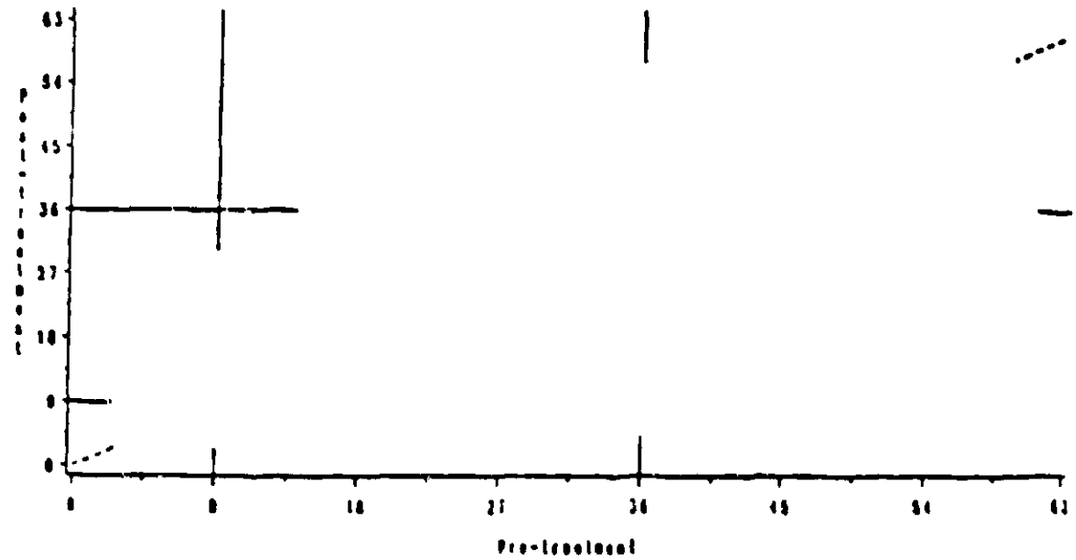
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

AST (SGOT) U/L
Treatment = All Azelastine



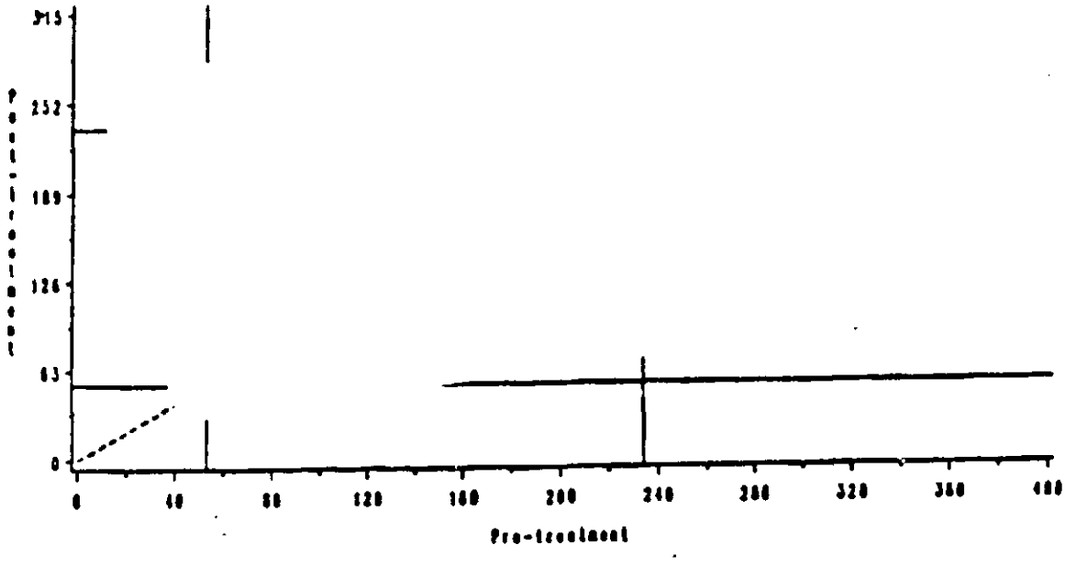
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

AST (SGOT) U/L
Treatment = Placebo



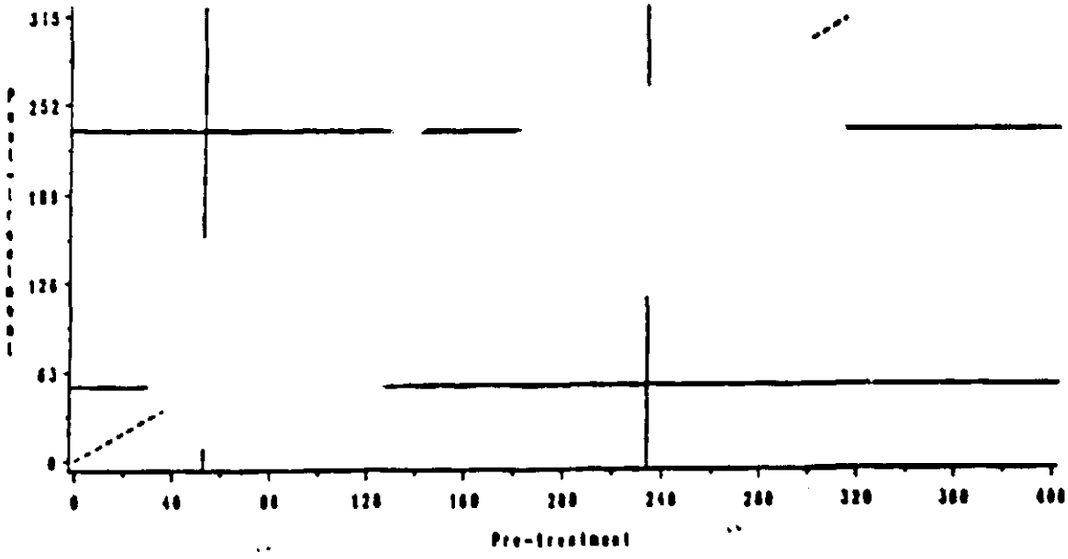
Controlled Nasal Spray
Scatter Plot - Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

LDH U/L
Treatment = All Azelastine



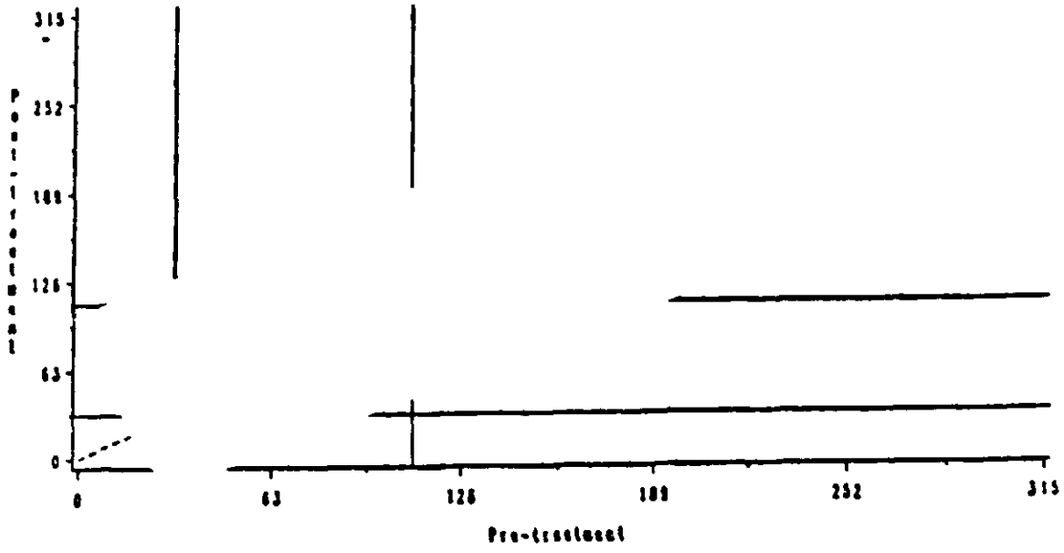
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

LDH U/L
Treatment = Placebo



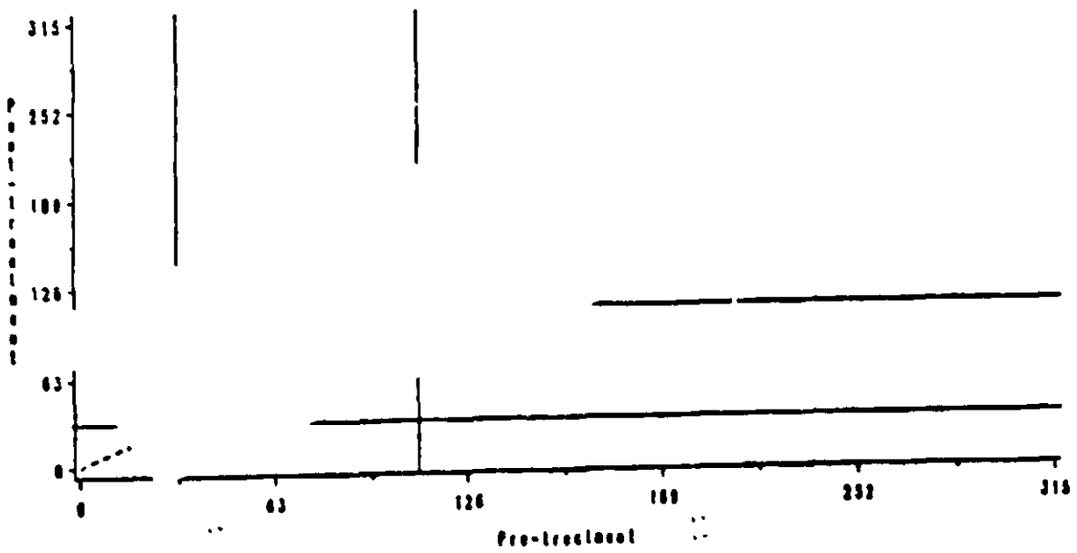
Controlled Nasal Spray
Scatter Plot - Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

Alkaline Phosphatase U/L
Treatment = All Azelastine



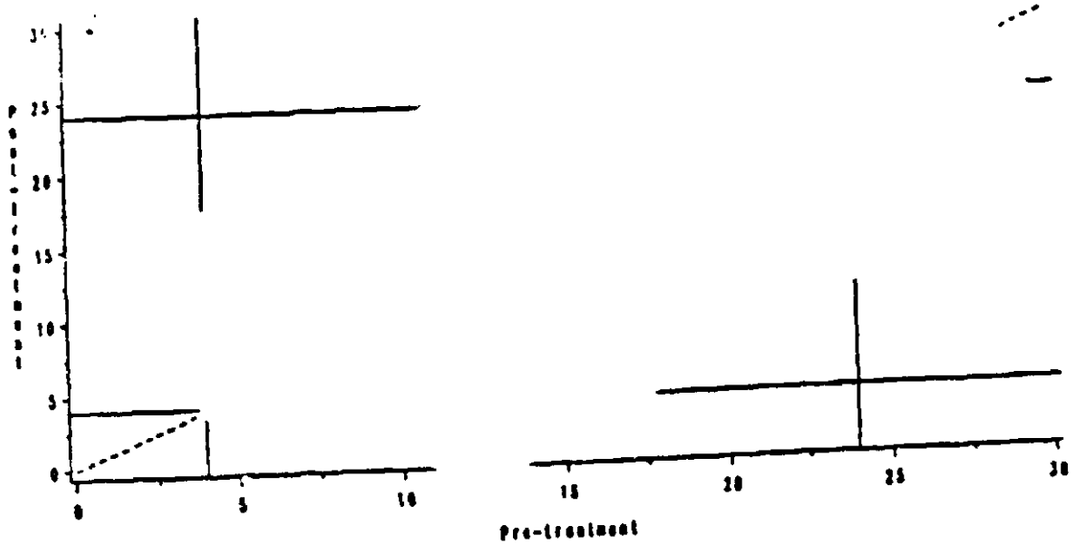
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

Alkaline Phosphatase U/L
Treatment = Placebo



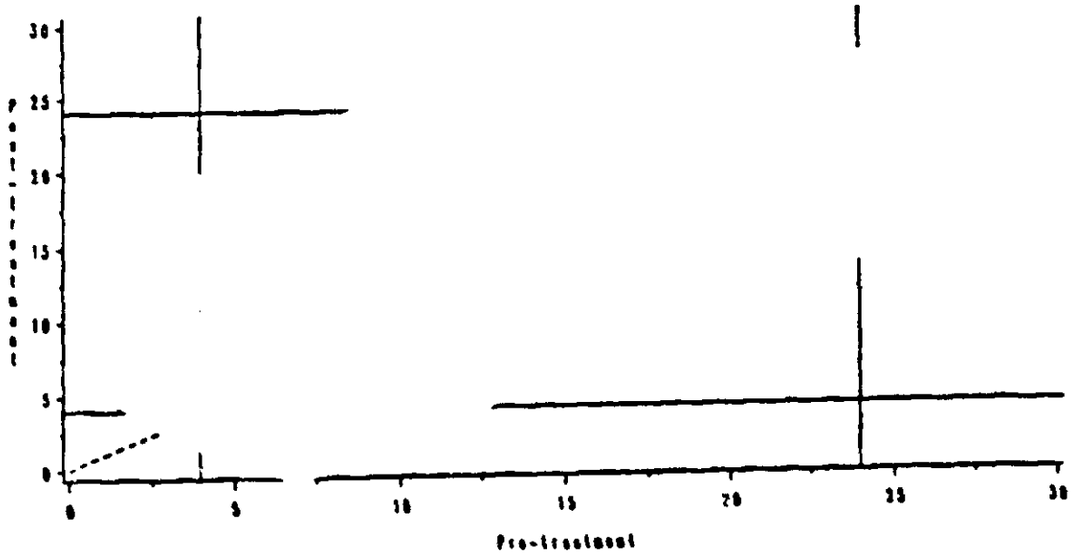
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End of Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

BUN mg/dL
Treatment = All Azelastine



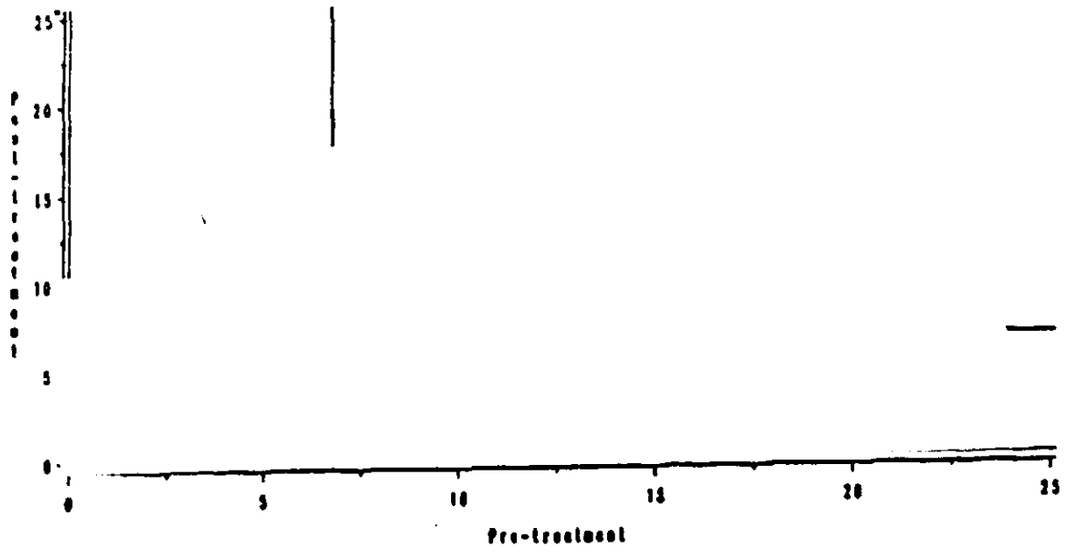
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

BUN mg/dL
Treatment = Placebo



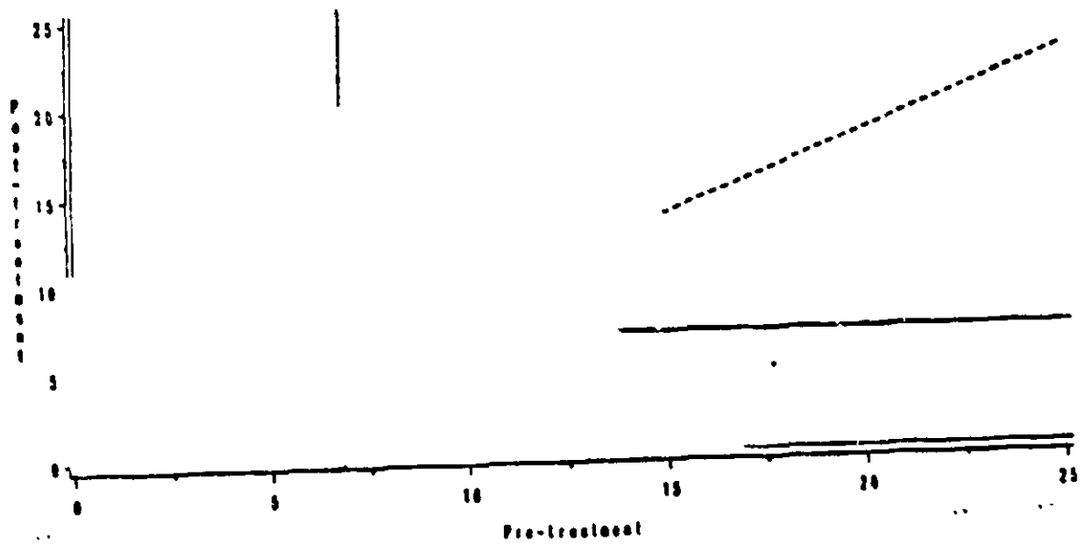
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

Eosinophils %
Treatment = All Azelastine



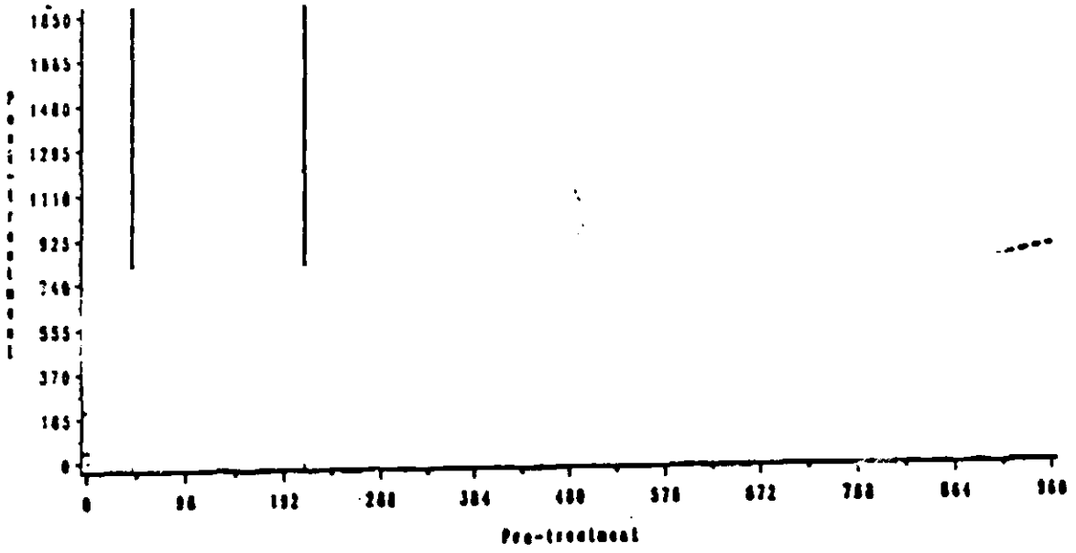
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

Eosinophils %
Treatment = Placebo



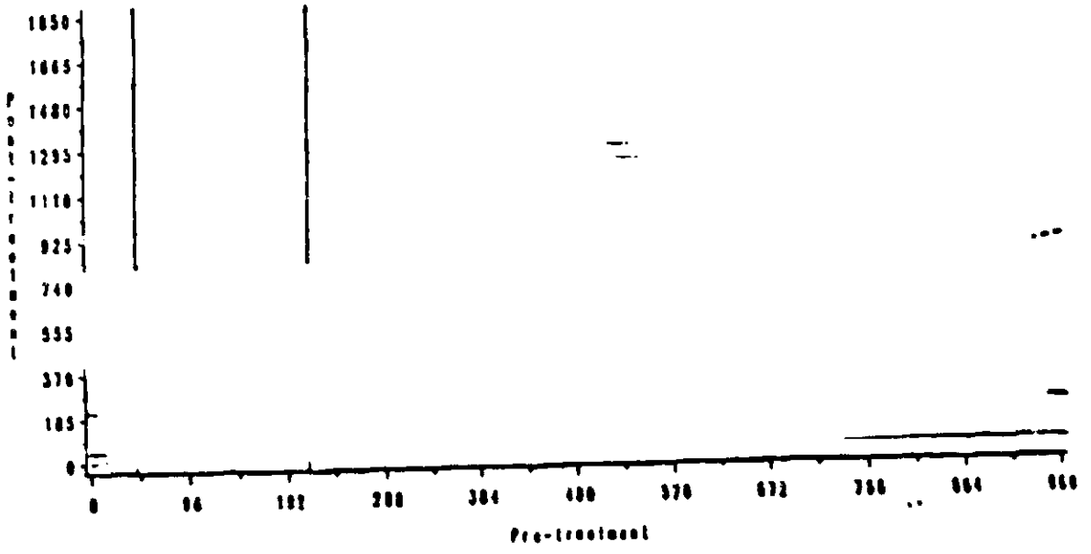
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

Triglycerides mg/dL
Treatment = All Azelastine



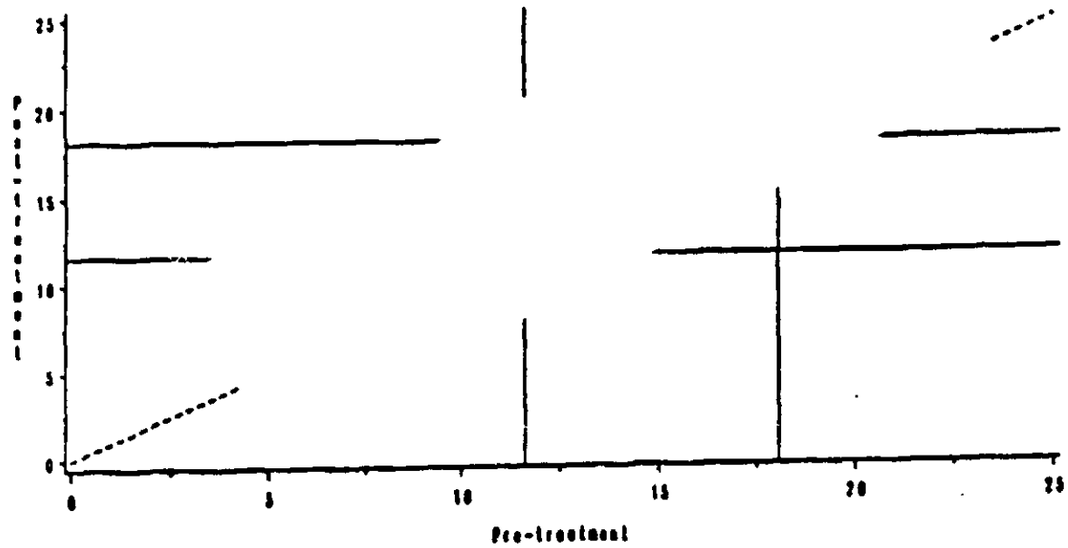
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

Triglycerides mg/dL
Treatment = Placebo



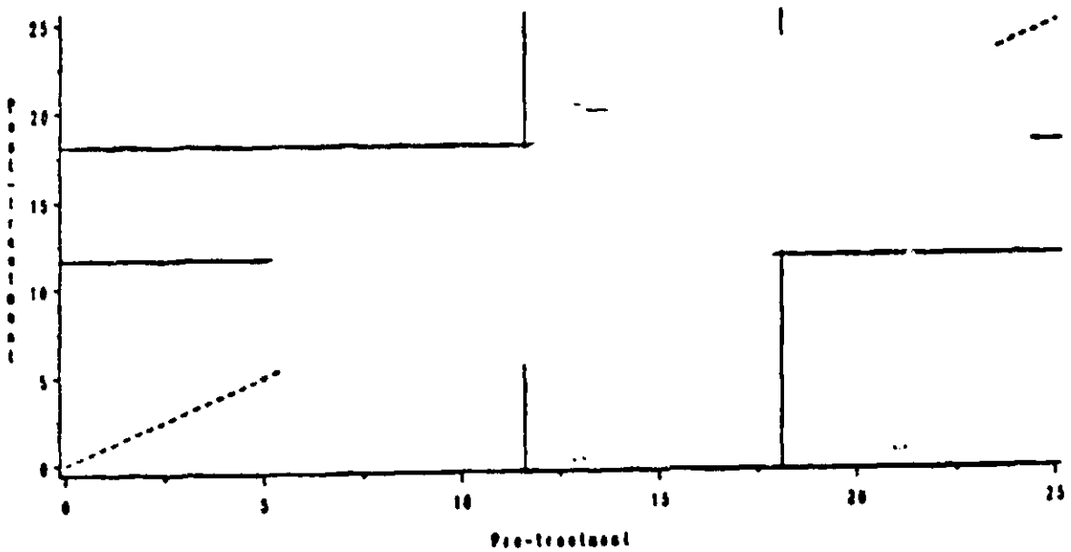
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

Hemoglobin g/dL
Treatment = All Azelastine



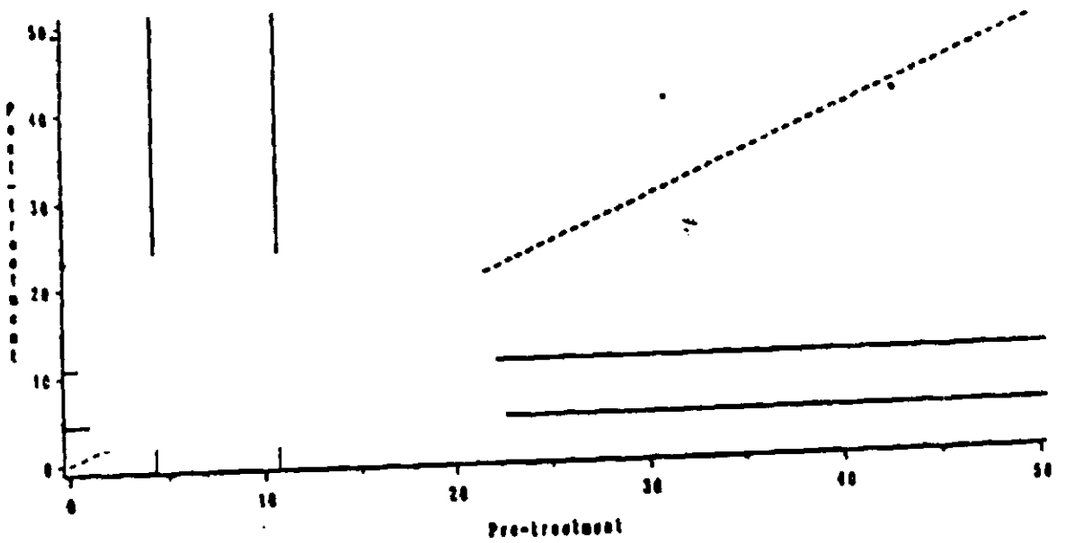
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

Hemoglobin g/dL
Treatment = Placebo



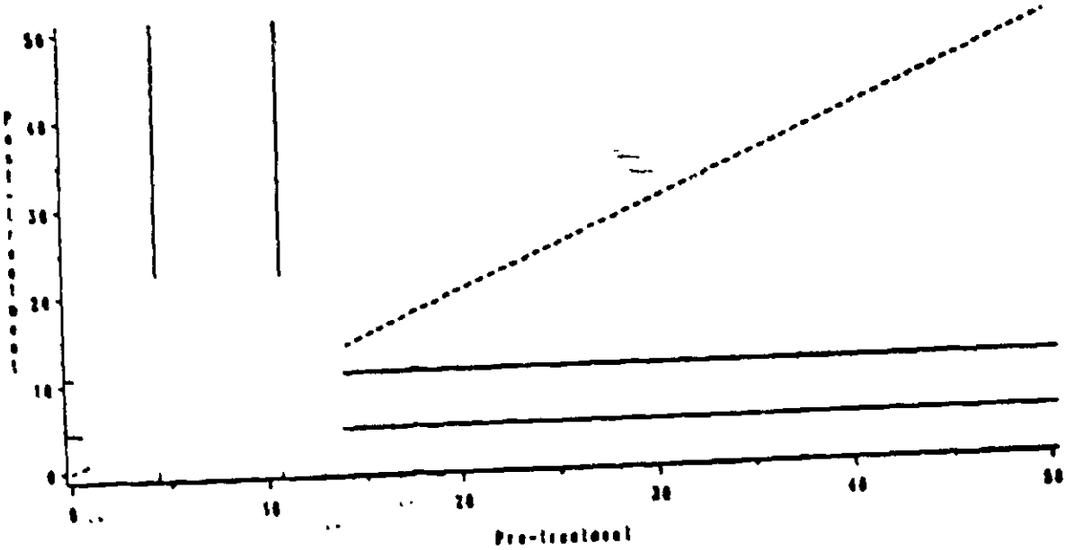
Controlled Nasal Spray
Scatter Plot - Pretreatment vs. End of Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

WBC x 10^3/mcL
Treatment = Azelastine



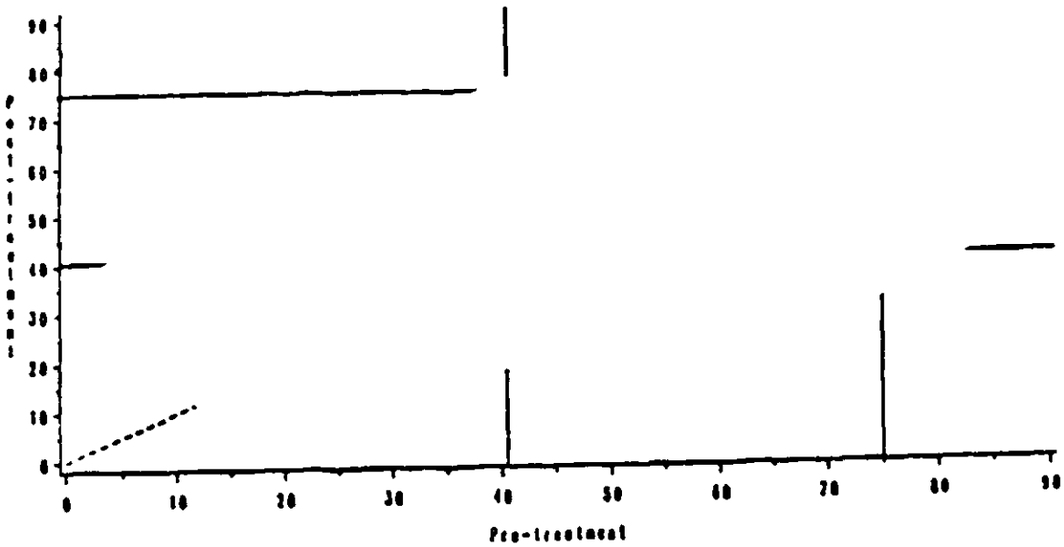
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

WBC x 10^3/mcL
Treatment = Placebo



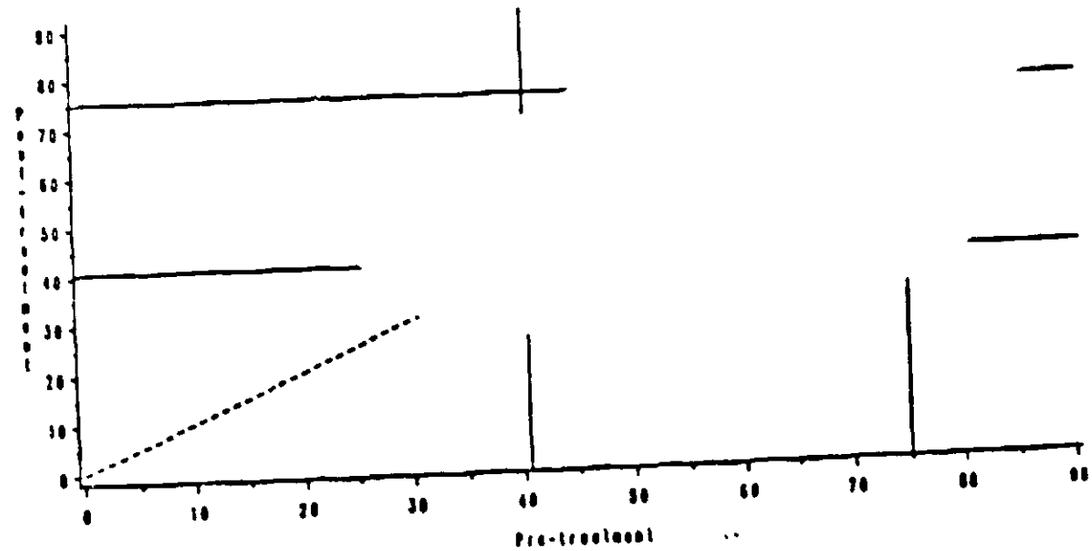
Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

Neutrophils %
Treatment = Azelastine



Controlled Nasal Spray
Scatter Plot – Pretreatment vs. End-of-Treatment Laboratory Values
(Horizontal and Vertical Lines Indicate Normal Ranges)

Neutrophils %
Treatment = Placebo



Regarding incidence of out of range lab values as a function of duration of exposure, the incidence of elevated uric acid and triglyceride levels increased with increasing duration of exposure as did the incidence of low cholesterol levels. Similar effects of duration of exposure were noted in the placebo group.

Of note, ECG's were not done during the pivotal efficacy trials and there is no ECG data reported in the integrated safety summary for the nasal spray.

Demographics of Lab Value Changes:

Age: (<18, 18-60, >60 years)

Since there were only 11 subjects in the greater than 60 age group, a meaningful comparison of incidence of out of range labs between subjects in this group and subjects age 18-60 is difficult to make. With regard to change from baseline, the only lab parameter for which the difference between the two groups is clinically significant was glucose. The older group experienced a mean increase in glucose of 30.67mg/dl vs an increase of 2.62 in subjects age 18-60. A similar difference was not noted in the placebo group. With regard to subjects under age 18, the incidence of high out of range values for glucose (6.2% vs 0%), eosinophils (10.2% vs 6.5%) and basophils (2.7% vs 0%) was greater in treated subjects than controls. The incidence of low out of range values for glucose (6.2% vs 0%), red blood cells (8% vs 4%) and hematocrit (7.1% vs 4%) was also greater in treated subjects than controls. There were no clinically significant changes in lab values from baseline to follow-up.

Comment: **The differences between treated and placebo subjects for incidence of high or low lab values is somewhat greater in the under 18 population v.s the difference seen in subjects age 18-60. Because these difference are larger, the sponsor should report whether any of the differences in out of normal range lab values in subjects under age 18 is statistically significant. In addition, to get a better understanding of the degree of glucose elevation in the >60 age group, the sponsor should report the individual glucose values at baseline, during the trials and at follow-up for subjects over 60 years of age who received azelastine.**

Gender:

Lab values for which the incidence of out of normal range alues was greater in females than males and in which a similar relationship was not noted in the placebo group include:

Lab Parameter	Females	Males
Low CO_2 values	3.6%	0%

High chloride values	3.6%	1.1%
Low cholesterol values	4.8%	3.8%
High cholesterol values	5.6%	3.0%
Low glucose values	4.2%	1.0%

Comment: **Since similar differences between the genders were not noted in the placebo group, the sponsor should identify whether the differences listed above were statistically significant.**

There were no clinically significant differences between males and females in change from baseline that were not also noted in the placebo group.

Weight:

For this analysis subjects were categorized into one of three different weight groups: <110 pounds, 110-170 pounds and >170 pounds. The incidence of high values of SGPT was greater in the upper and lower weight group than in subjects weighing 110-170 pounds. In the lower weight group the incidence was 5.3% vs 2.4% in the middle weight group and 6.7% in subjects weighing more than 170 pounds. In the placebo group the incidence of high values of SGPT was 0%, .8% and 5.7% for subjects weighing <110, 110-170 and >170 pounds, respectively. Similarly, the incidence of high uric acid levels was greater in the <110 pound (5.3%) and >170 pound (2.3%) groups than the 110-170 pound group (0.7%). The incidence of low values of CO_2, cholesterol, glucose, RBC, hematocrit, monocytes, chloride and glucose was greater in the group weighing <110 than in the other groups. The sponsor does not report that any of these differences were statistically significant.

With regard to change from baseline, in the lower weight group the mean decrease in platelet count was 25.29 x 10^3 /mcl vs a decrease of 1.82 and 3.13 x 10^3 in the two upper weight groups. Placebo subjects in the <110 pound weight group experienced a mean decrease from baseline of 9.08 x 10^3/mcl.

Race:

The incidence of out of range values, both low and high values, was elevated in the non-white subjects vs white subjects for a number of lab tests. For some of these labs the difference was not noted in the placebo group, however, the differences do not appear to be large and the non-white group had considerably fewer subjects (54) than the white group (479).

There were no withdrawals from any nasal spray trial due to abnormal labs.

Foreign data:

The sponsor states in the integrated summary of safety that in addition to the 556 subjects enrolled in European trials that were listed in the "Extent of Exposure" section above, an additional 445 subjects (205 received azelastine spray, 46 received azelastine tablets, 126 received positive controls and 68 received placebo) in 6 recently completed trials, as well as 35 subjects from an uncontrolled perennial rhinitis trial and one subject from an extension study are also included in the European safety data base. As described in the comments to the sponsor below, there are some discrepancies between the number of subjects that the updated safety report should include and the number actually included.

The following adverse events were reported in the azelastine group at a rate of 1% or greater:

Event	Azelastine	Placebo
Taste Perversion	6.5%	1.8%
Application Site Reactions	4.5%	3.6%
Headache	4.0%	10.9%
Rhinitis	2.9%	7.3%
Nausea	2.2%	0.0%
Pharyngitis	2.0%	0.0%
Bronchitis	1.6%	0.0%
Influenza Like Symptoms	1.6%	0.0%
Epistaxis	1.4%	3.6%
Fatigue	1.1%	1.8%
Viral Infection	1.1%	0.0%
Flushing	1.1%	3.6%

No deaths were reported in the European nasal spray studies. 7 subjects in these trial discontinued prematurely; 5 due to unspecified application site reactions, 1 due to rhinitis and taste perversion and 1 due to abdominal pain, dyspnea and pharyngitis.

Comment: **The sponsor should state whether any of the differences between azelastine and placebo treated subjects in incidence of adverse events is statistically significant. In addition, among the adverse events occurring at a rate of less than 1% are: dizziness (.4%), palpitations (.2%) and allergic reaction (.2%). The sponsor should be asked to provide additional information and case report**

forms regarding these adverse events. Case report forms of the 7 subjects who discontinued prematurely should also be submitted.

There are no lab data reported from the European trials.

Overall Comments on Safety Data: With regard to adverse events, effects which appear related to azelastine therapy, based on statistically significant differences from the placebo group, include headache, somnolence, taste perversion and nausea. Additional confirmation of the relationship between taste perversion and somnolence and drug use is provided by the dose response relationship for these two adverse events. The incidence of local adverse events at the site of drug administration did not significantly differ between treated subjects and controls (although this doesn't ensure the safety of inactive ingredients or extractables, which are also present in the placebo, the incidence rates are low and most events were considered mild to moderate [nasal burning 19/21 azelastine, 6/6 placebo; epistaxis 14/16 azelastine, 5/5 placebo; paroxysmal sneezing 9/10 azelastine; throat burning 6/6 azelastine]). With regard to duration of exposure, all adverse events were more often first reported during the first week of exposure. This suggests that despite the increased prevalence of certain adverse events with increased duration of exposure, which is expected, longer term exposure, at least up to 8 weeks, does not result in increased drug toxicity. None of the adverse events that were reported in the US trials were of such a serious nature which would preclude the clinical use of this drug, however, as noted above, the possibility of adverse effects from the Valois B pump which were not seen with the Valois A pump used in clinical trials does exist and warrants a careful comparison of the excipient profile from the two pumps.

With regard to the demographic analysis, only a comparison of the incidence of adverse events in male vs females revealed notable differences between the two groups. The sponsor will be asked to comment on whether these differences were statistically significant.

With regard to effects of the drug on labs, there were no significant differences between the treated and placebo groups, although the incidence of elevated SGPT and chloride, while not significantly different between the treatment arms was dose related. This effect on SGPT may be of importance because statistically significant effects were seen in a number of individual trials. In study #32 the incidence of high SGPT was greater in the azelastine q day group v.s. placebo (although a similar difference was not seen for the bid group;additional information to quantify this effect is to be requested of the sponsor) and in study #31 the incidence of elevated SGPT and LDH was greater in the bid group than placebo.

Regarding demographic analyses of effects on lab values, although a meaningful analysis of effects in subjects older than 60 years is difficult because of the small

size of this group, an increase of 30.67mg/dl in glucose from baseline was noted in this age group. The incidence of out of range lab values for a number of labs was greater in subjects younger than 18 than subjects 18-60. Again, the sponsor should comment on whether any of these differences were statistically significant.

With regard to differences based on gender, although the two groups did not differ in change from baseline, there were differences with regard to incidence of out of range lab values. The sponsor should comment on whether these differences were statistically significant. They should also comment on whether any of the differences noted by weight or race were statistically significant. The ability to make a meaningful comparison of the incidence of out of range lab values between the <110 pound group and other weight groups may be limited by the fact that this weight group only included at most 19 subjects and for some lab tests data was based on even fewer subjects.

Data is also presented on the following 10 azelastine treated subjects who experienced clinically significant elevations of lab values:

LIVER ENZYMES
CRITERIA: 3 X ULN OR OVER
SUBJECTS 18 AND OVER

PROTOCOL	TREATMENT	CENTER	SUBJECT	AGE	SEX	RACE	VISIT	SGOT	SGPT	LDH	ALK. PHOS.	COMMENT
258	AZ 1 SPRAY Q12H	89017	248	18	MALE	WHITE	SCREENING	33	37	173	100	DATA ERROR*
							END OF STUDY	31	34	165	987*	
	AZ 2 SPRAYS Q12H	89117	8	27	MALE	WHITE	SCREENING	151*	67	188	91	
							WEEK 2	28	30	137	59	
							FOLLOW-UP	38	31	125	65	
272	AZ 2 SPRAYS Q12H	89118	125	51	MALE	WHITE	SCREENING	37	165*	196	68	
							WEEK 2	39	93	142	66	
							FOLLOW-UP	32	57	171	68	
272	AZ 2 SPRAYS Q12H	89119	139	35	FEMALE	WHITE	SCREENING	57	131*	168	127	
							WEEK 2	46	106*	160	131	
							FOLLOW-UP	44	103*	152	119	
272	AZ 2 SPRAYS Q12H	89119	144	56	FEMALE	WHITE	SCREENING	27	39	175	96	NOT CLINICALLY SIGNIFICANT
							WEEK 2	70	189*	193	100	
							FOLLOW-UP	16	13	151	91	
272	AZ 2 SPRAYS Q12H	89119	193	44	MALE	WHITE	SCREENING	39	84	200	97	NOT CLINICALLY SIGNIFICANT
							WEEK 2	31	135*	145	88	
							FOLLOW-UP	38	105	169	82	
281	AZ 2 SPRAYS QD	90053	210	28	MALE	WHITE	SCREENING	29	56	134	109	PROBABLY NOT RELATED TO AZELASTINE
							END OF STUDY	84	300*	182	132	

PROTOCOL	TREATMENT	CENTER	SUBJECT	AGE	SEX	RACE	VISIT	LAB VALUE
282	AZ 2 SPRAYS QD	90057	316	38	FEMALE	WHITE		629
							SCREENING	311
							WEEK 2	261
							WEEK 6	616
							FOLLOW-UP	1008*
282	AZ 2 SPRAYS QD	90058	261	62	MALE	WHITE	SCREENING	693
							1 WEEK BASELINE	179
							WEEK 2	676
							WEEK 6	260
							FOLLOW-UP	948*
281	AZ 2 SPRAYS Q12H	90063	172	28	MALE	WHITE	SCREENING	468
							1 WEEK BASELINE	861*
							WEEK 2	132
							FOLLOW-UP	221

The sponsor should identify the abnormal lab tests in the last three subjects in the table. In addition, case report forms for all subjects except those with an abnormal value only at baseline should be submitted.

Finally, the cardiac issues which were addressed in the NDA review for NDA; . . . have a bearing on this NDA as well because the dose to be administered, .52mg bid with a 40% bioavailability is not that much lower than the lowest oral dose of .5mg bid and the occurrence of somnolence with this formulation does indicate the presence of systemic drug effects.

6 Pages

Purged

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Comments: This labelling will be reviewed in detail in a subsequent review, however, two points should be noted. The first is that although all clinical studies were done in subjects with seasonal allergic rhinitis, the proposed labelling states an indication of "allergic rhinitis". To this reviewer, the indication of allergic rhinitis includes both the short term usage seen in seasonal allergic rhinitis, as well as long term usage associated with perennial allergic rhinitis. While the underlying pathophysiology for both diseases may be similar, the longer term usage that would be expected in patients with perennial allergic rhinitis should be supported by longer

term efficacy data (8-12 weeks) and longer term safety data. The efficacy data included in this NDA consists of two 2 week studies and one 4 week study, however, the 4 week trial does not support the efficacy of either dosing regimen. Therefore, efficacy data of an adequate duration to support the usage of azelastine nasal spray beyond 2 weeks does not exist. Regarding safety, in US trials there have been 63 subjects who have received azelastine 2 sprays per nostril bid longer than 4 weeks and none in the European data base. Therefore, there does not appear to be adequate efficacy or safety data to support long term usage (beyond 2 weeks) of azelastine nasal spray. The second issue is the paragraph which discusses activities requiring mental alertness. This section of the package insert suggests that the drug does not result in impairment of mental alertness. However, as presented above, somnolence is an adverse event of this drug which occurs in significantly more treated subjects than those who receive placebo. In addition, diminished sedation of azelastine relative to a single 100mg dose of diphenhydramine hydrochloride provides no reassurance that the drug is not sedating. Finally, as has been discussed in a previous advisory committee meeting, the clinical relevance of the tests used in these CNS studies is questionable, particularly since in this NDA and in the NDA for the tablet formulation the drug does result in dose related somnolence.

Comments to be Faxed to Sponsor

1. Please comment on the lack of efficacy seen during the first half of the dosing interval in the q day azelastine group in study #26.

2. We are unclear on how to interpret table #27 in study #26. Weeks 1 and 2 appear to be repeated a number of times with different values.

3. For study #31, please provide pollen count data on a center by center basis.

4. Please submit case report forms for the 8 azelastine treated subjects in study #26 who were discontinued prematurely.

5. Please submit case report forms for the 5 azelastine treated subjects in study #31 who were discontinued prematurely.

6. Please submit case report forms for the 15 azelastine treated subjects in study #33 who were discontinued prematurely.

7. For study #33, please comment on the differences in efficacy seen for the AM v.s. PM data based on the total symptom complex as well as individual symptoms.

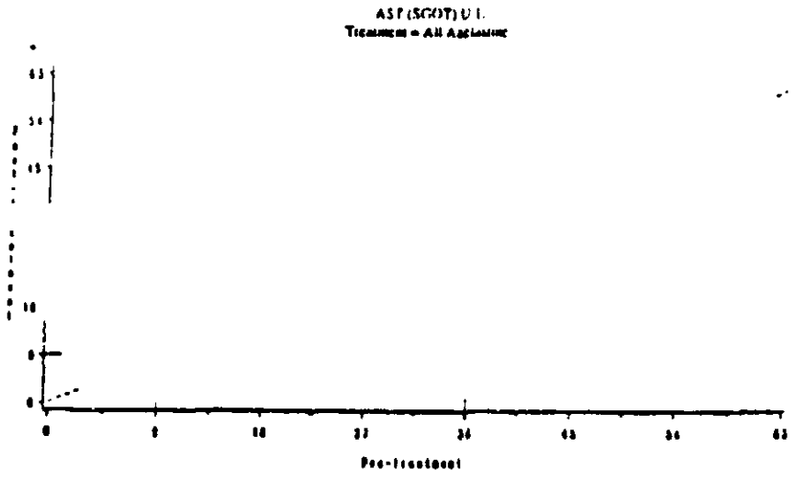
8. Please delineate what the treatment emergent ECG changes were during the final week of study #29.

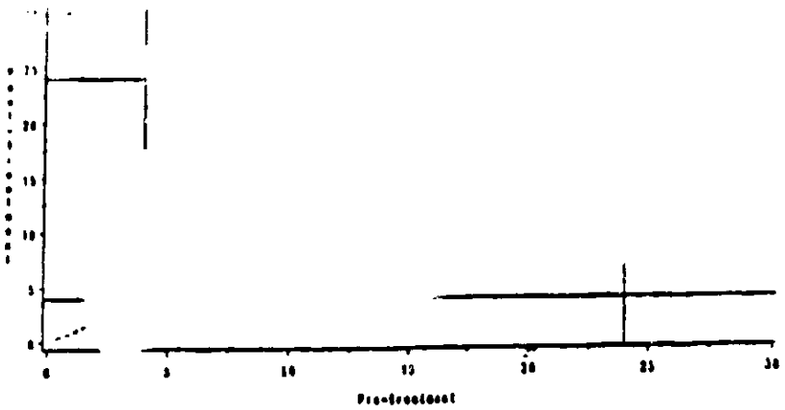
9. Please report the P values for the comparison of adverse events occurring in the "All Azelastine" group v.s. placebo in Table #410 of the integrated safety summary.

10. Please submit case report forms of the azelastine treated subjects with elevated SGPT reported as adverse events.

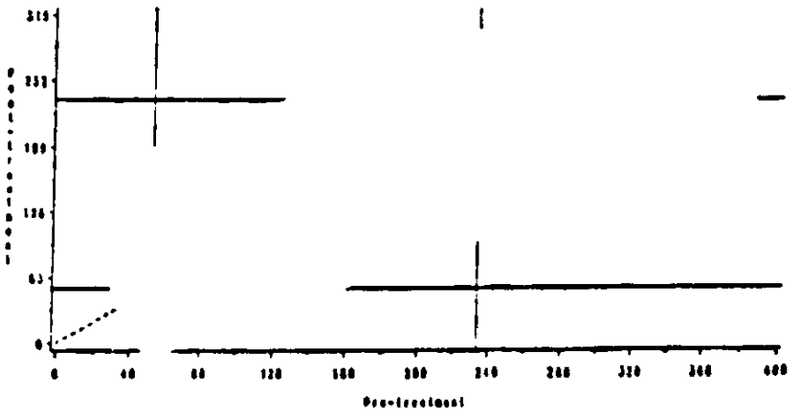
11. Please report the P values for the comparison of incidence rates of adverse events in male v.s. female subjects in the azelastine treated subjects and the placebo group.

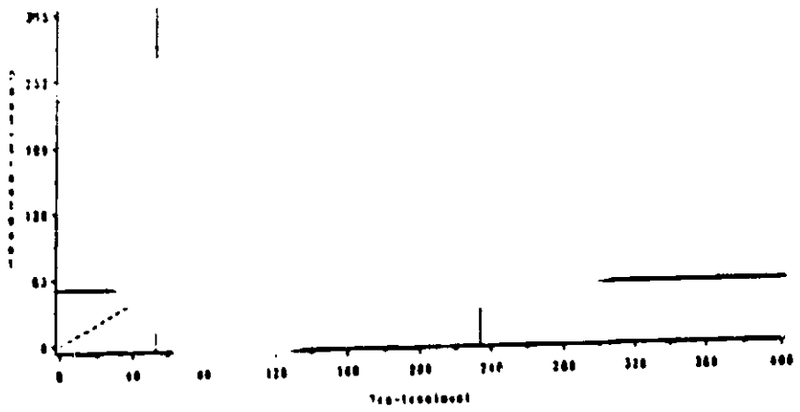
12. Case report forms for circled subjects on the following scatter plots should be submitted:

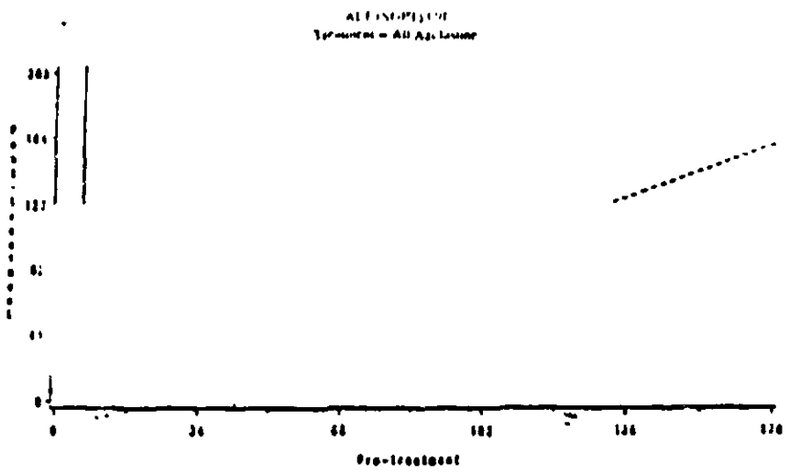




LDH U/L
Treatment = Placebo







13. Are any of the differences between azelastine and placebo treated subjects for out of normal range lab values statistically significant for subjects under age 18?

14. Are any of the differences between males and females in incidence of low CO2, cholesterol or glucose or high chloride or cholesterol values statistically significant?

15. Are any of the differences by weight or race in incidence of out of range lab values statistically significant?

16. The following case report forms of subjects with abnormal lab values should be submitted:

Subject #	Protocol #	Dose of Azelastine
139	272	2 spray bid
270	281	2 spray q day
116	282	2 spray q day
261	282	2 spray q day
172	283	2 spray bid
164	272	2 spray bid
193	272	2 spray bid
248	258	? (elevated alkaline phosphatase)

17. Please identify the specific lab abnormalities that are reported on pages 2-3 of table 493.

18. According to our calculations, the updated European safety data base should include data on 608 azelastine subjects (205 additional subjects, 35 subjects from the uncontrolled PAR study, 1 subject from the extension study, 182 subjects in

the initial data base of controlled trials and 185 subjects in uncontrolled trials) and 76 placebo subjects (8 in the initial data base and 68 in the update), yet your updated safety summary contains data on 553 azelastine subjects and 55 placebo subjects. Please explain this discrepancy.

19. Were any of the differences between azelastine and placebo in incidence of adverse events in the updated European safety summary statistically significant?

20. Please provide additional clinical information and case report forms for subjects who experienced the following adverse events (taken from table 451): dizziness .4%, palpitations .2% and allergic reaction .2%.

21. Please clarify what the difference is between tables 451 and 455 in the integrated safety summary.

22. Case report forms for the 7 subjects who discontinued prematurely from European trials should be submitted.

23. Please list the symptom scores of the 52 subjects with insufficient symptoms, state the reason that the 4 subjects failed to meet inclusion/exclusion criteria, explain why 3 subjects were not randomized because of too sever disease (no upper limit on symptom scores is listed in the protocol), and state what the intercurrent illness, adverse events and unknown reasons were in the other subjects which precluded randomization to trial #33.

24. Please list the symptom scores of the 43 subjects with insufficient symptoms, state the reason that the 6 subjects failed to meet inclusion/exclusion criteria, explain why 9 subjects were not randomized because of too sever disease (no upper limit on symptom scores is listed in the protocol), and state what the intercurrent illness, adverse events and unspecified reasons were in subjects which precluded randomization to study #31.

25. For study #26, please list the symptom scores of the 35 subjects with insufficient symptoms, state the reason that the 11 subjects failed to meet inclusion/exclusion criteria, explain why 5 subjects were not randomized because of too sever disease (no upper limit on symptom scores is listed in the protocol), and state what the intercurrent illness and adverse events were in two subjects each which precluded randomization.

Study #26 - Runny Nose - Number of Subject Days with no Score Reported (if 2 subjects didn't report scores on the same day, that would be two subject days)				
Time	Azel q day	Azel bid	Positive Control	Placebo
Week 1-AM				
Week 1-PM				
Week 2-AM				
Week 2-PM				

Martin H. Himmel, MD
Medical Officer

7/30/93

9 Burke MD
8/6/93

cc:

NDA# 20-114
HFD-155/Div File
HFD-155/Div Director/Burke
HFD-155/Medical Officer/Himmel/Honig
HFD-155/CSO/Riley
HFD-155/Pharmacology/Chun
HFD-155/Chemistry/Ng
HFD-710/Gebert

MEMORANDUM

Date: January 13, 1992

From: Martin H. Himmel, M.D.

To: NDA File - NDA #20-114

Subject: Text of Clinical Section of Non-Approvable Letter (see Memo dated 8/27/91)

Because of a number of ambiguities regarding the materials and methods used in the clinical trials based on chemistry tests conducted by the sponsor, the recommended text for the clinical portion of the non-approvable letter (see memo dated 8/27/91) should be amended. The new text should be:

Please indicate which pump was used in each batch of drug product used in each clinical trial. Since the differences between the pumps affect both volume of drug delivered and potency, this issue must be clarified before a review of the clinical trials can be initiated so that the relevance of the individual trials to the final drug product can be determined. In addition, we have the following specific questions regarding patient use of the pump in the clinical trials:

1. Because the NDA is somewhat unclear regarding the number of times the pump must be primed after non-use (it was primed 4 times in a number of tests, the label claims that 5-6 primings are needed, method TS-444-01 requires 30 strokes to obtain a fine mist and the Priming test required 20 strokes) the specific instructions given to subjects in clinical trials must be stated. In addition, please explain what methods were used to evaluate compliance with the recommended use of the pump.

2. Because the delivered drug volume diminishes after 90 actuations of the pump, please clarify the number of times subjects in the trials were expected to actuate an individual pump prior to its being replaced and any specific instructions that they may have received with regard to diminished pump output.

3. Please clarify instructions that were given to subjects with regard to the fact that the first actuation of the pump contains a different drug concentration than subsequent actuations.

4. Since the pump was noted to have a loss of potency over time, please clarify the time from manufacture to

clinical use of the pumps used in the clinical trials and what the expected potency would be based on elapsed time.

5. Please clarify whether the leakage and evaporation of drug which was noted in study SS #4679 was noted in any of the lots used in the clinical trials. If so, please elaborate on how this may effect drug potency and delivery and how it was evaluated in the trials.

Martin H. Himmel

Martin H. Himmel, M.D.
Medical Officer

cc:

NDA #20-114
HFD-150/Div File
HFD-150/Group Leader/Leonard
HFD-150/Medical Officer/Himmel
HFD-151/Schumaker
HFD-150/Chemistry/Look

1/29/92

2.1

MEMORANDUM

DATE: 8/21/91, Revised 8/27/91

TO: NDA File

FROM: Martin H. Himmel, M.D.
Medical Officer

SUBJECT: Azelastine Nasal Spray-Review of Clinical Trials-Nasal Spray Pump

The initial studies of this drug were conducted using a pump of drug per actuation. In subsequent clinical trials, two different types of pumps, each of which delivers of drug per actuation, replaced the . The difference between these two pumps (designated pumps "A" and "B") is that pump "A" was associated with a loss of potency due to absorption of the active ingredient by the sealing gasket. The final marketed product for which this NDA was submitted will be manufactured using pump "B". Although the batch numbers used in each clinical trial have been submitted, the NDA does not indicate which pump ( ) was used in each batch of drug product used in each clinical trial. Since the differences between the pumps affect both volume of drug delivered and potency, this issue must be clarified before a review of the clinical trials can be initiated so that the relevance of the individual trials to the final drug product can be determined. This NDA is not approvable from the chemistry point of view.

RECOMMENDED TEXT FOR NON-APPROVABLE LETTER (clinical):

Please indicate which pump ( ) was used in each batch of drug product used in each clinical trial. Since the differences between the pumps affect both volume of drug delivered and potency, this issue must be clarified before a review of the clinical trials can be initiated so that the relevance of the individual trials to the final drug product can be determined.

Martin H. Himmel

Martin H. Himmel, M.D.
Medical Officer

cc:

NDA #20-114
HFD-150/Div File

MAR 6 1993

MEDICAL OFFICER REVIEW

DATE REVIEWED: January 21, 1993, Revised February 24, 1993
NDA# 20-115
REVIEWER: Martin H. Himmel, M.D.
PRODUCT: Azelastine tablets for allergic rhinitis
CATEGORY of DRUG: antihistamine
ROUTE of ADMINISTRATION: oral
SPONSOR: Wallace Laboratories
MATERIAL REVIEWED: This review will discuss the integrated safety summary included in the initial NDA as well as the following amendments that have been submitted since the initial filing date (March 26, 1991):

1. Amendment of January 29, 1992 - case report forms.
2. Amendment of July 31, 1991 - response to Division fax of 7/19/91 and case report forms of 10 subjects who experienced syncope.
3. Amendment of April 15, 1992 - case report forms of 6 subjects who experienced syncope.
4. Amendment of May 7, 1992 - study report of study #18 - tolerability and pharmacokinetics in volunteers over age 65 and the study report for the antipyrine study.
5. Amendment of January 14, 1992 - case report forms and P values for adverse events occurring at a rate $\geq$ 2% in the integrated safety summary.
6. Amendment of April 22, 1992 - clarification of a discrepancy in patient numbers and clarification of an ECG.
7. Amendment of August 8, 1991 - correspondence from the sponsor.
8. Amendment of August 24, 1992 - questions from the sponsor regarding case report forms for the asthma NDA.
9. Amendment of April 16, 1992 - case report forms.
10. Amendment of August 15, 1991 - ECG's of subjects with sinus bradycardia and efficacy data regarding investigator's assessment of global changes.
11. Amendment of December 16, 1991 - correspondence stating that the integrated safety summary update will be withheld.
12. Amendment of December 9, 1991 - case report form of a subject with cardiac arrhythmia.
13. Amendment of September 8, 1992 - clarification of a number of specific adverse events; initial QT data; case report forms of 13 subjects identified by the sponsor as having a prolonged QT interval.
14. Amendment of December 18, 1992 - case report forms regarding two deaths in European trails and a subject with A-V block; information regarding gender differences in adverse events and statistically significant adverse events in the European/Japanese data.
15. Amendment of September 28, 1992 - updated integrated safety summary.
16. Amendment of February 11, 1993 - response to safety questions conveyed to the sponsor by phone and fax.

Additional amendments have been submitted which refer to efficacy data; these will be referred to in the review of the efficacy data.

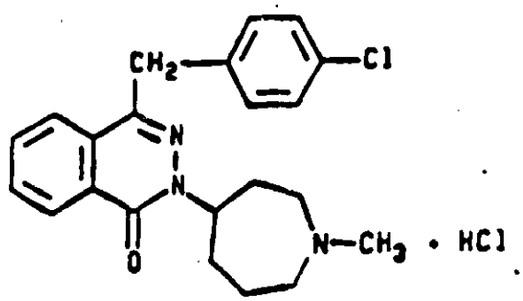
CHEMISTRY:

Chemical Name: (±)-(2H)-Phthalazinone, 4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-monohydrochloride

Molecular Formula: $C_{22}H_{24}ClN_3O$ HCL

Molecular Weight: 381.90/418.37 (base/hydrochloride)

Structural Formula:



PRE-CLINICAL:

ADME:

Tmax 1-2 hours with dose proportionality up to 30mg/kg in rats and 60mg/kg in mice. In the dog, the volume of distribution was approximately 20 times the body weight. There is evidence of placental transfer as well as low levels of transfer to the brain in rodents. High first pass effect is noted in lab animals.

As in the human, there are a number of proposed metabolites with desmethylazelastine being the major one. Qualitatively, inter-species differences in the major metabolites has been shown, which, according to the pharmacology reviewer, may account for differences in toxicity seen among the different species.Based on effects on antipyrine, Azelastine is not considered an enzyme inducer. In the rat, Azelastine is 53-57% protein bound, which is less than the degree seen in humans.

The major route of excretion is biliary, with no signs of drug accumulation with

repetitive dosing. The terminal half life for elimination of Azelastine and its metabolites is 4-8 hours.

Toxicology:

As per the pharmacologist's review of the pre-clinical data, major findings in the animal studies included elevated levels of alkaline phosphatase, SGOT and SGPT as well as reversible fatty changes in the liver and hepatocellular hypertrophy at oral doses of 30mg/kg/dy. Renal cortical tubular epithelium degeneration was seen in one 6 month dog study, however no changes in BUN, creatinine or specific gravity were seen.

In the dog, intravenous doses of 2-10mg/kg of Azelastine resulted in dose dependent decreases in blood pressure, with both increases and decreases in heart rate noted. At 1mg/kg IV, reduction of induced ST segment elevation was noted.

Oral doses of 20mg/kg prolonged QT intervals and at 40 and 60mg/kg localized myocardial degeneration and adipose cell infiltration of the interstitial tissue of the heart were seen, respectively. Doses above 20mg/kg/dy in the dog were lethal.

At all dose levels, intravenous administration of Azelastine was an irritant to vessels.

Mutagenicity:

No mutagenic effects using the AMES test, DNA repair test, mouse lymphoma forward mutation assay, mouse micronucleus test or rat chromosomal aberration test were noted.

Carcinogenicity:

In female mice at high doses a positive dose response relationship was noted for bone osteosarcoma and spleen lymphosarcoma. These were within the historical control ranges. In rats, a positive dose response relationship was noted for skin sebaceous adenomas.

The pharmacologist's conclusions based on these studies is that Azelastine is not carcinogenic, however, based on discussion at the CAC, further pharmacokinetic data in the mouse was requested to ensure that adequate doses of drug were used in the mouse study. A final conclusion regarding the mouse carcinogenicity study will be made based on the results of this additional data.

Reproduction:

The pharmacology review of this data concluded that at doses up to 3mg/kg, which is 37 times the clinical dose, there were no signs of maternal toxicity, reduced fertility, fetotoxicity or teratogenicity. At 30mg/kg adult rats showed systemic toxicity and there were reduced fetal weights, signs of skeletal anomalies and retarded ossification. At 68.6mg/kg Azelastine was teratogenic, fetotoxic and maternally toxic.

PHARMACOKINETICS:

Azelastine is a phthalizone derivative which exists as a hydrochloride salt and contains a racemic mixture. Regarding pharmacologic activity, the sponsor states that the order of potency for the mixture and the two individual enantiomers varies in studies using pharmacological models of immediate allergic responses. Neither individual enantiomer is thought to offer an advantage over the mixture. The following is a summary of the US ADME studies reported in this NDA:

I. Study #1

A.

B. open-label ADME trial - single (fasting) dose - 4.4mg solution

C. 6 healthy male subjects - age 19-37 years (all completed trial)

D. results

1. absorption
   a. nearly completely absorbed
   b. lag time of 1/2 hour before the start of absorption
   c. less than 10% of dose appeared in feces unchanged
2. distribution
   a. no indication of a second or third compartment
3. metabolism
   a. highly metabolized
   b. 3 metabolites definitely present and an additional two possibly present
      (1) metabolite profile similar in urine, feces and plasma
      (2) probable metabolites include desmethylazelastine, 7-oxoazelastine and 2-oxoazelastine
      (3) possible metabolites include 6-hydroxyazelastine and 7-hydroxyazelastine
4. elimination
   a. 24% of dose recovered in urine and 75% in feces
   b. mean $T_{1/2}$ in plasma was 17 hours
   c. $T_{1/2}$ of desmethylazelastine in urine was 47 hours

E. adverse events

1. none reported

II. Study #8

B. intravenous 4.5mg dose and oral 8.8mg single dose
C. open-label, randomized, two period crossover design
D. results

1. azelastine

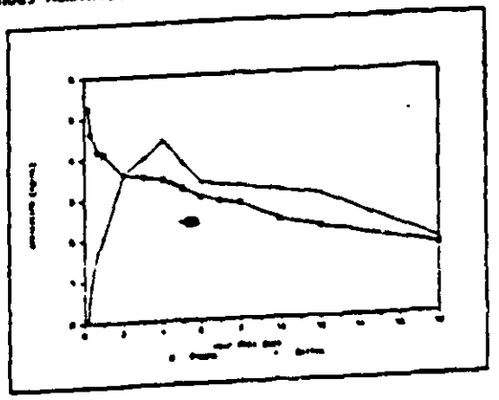
Variable	IV Dose (mean)	PO Dose (mean)
Cmax		5.884ng/ml
Tmax		5.3hr
AUC	204 h*ng/ml	167h*ng/ml
Vss/kg	14502ml/kg	14489ml/kg
terminal elimination half-life	22.43hr	21.88hr

2. desmethylazelastine

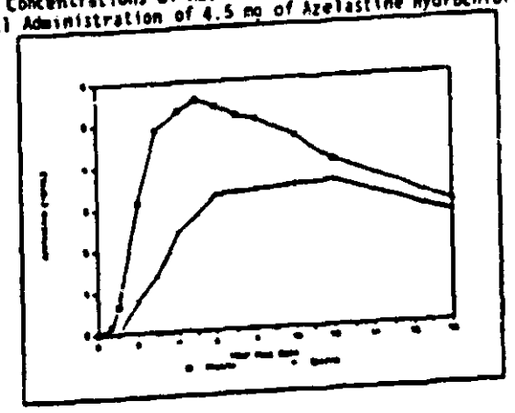
Variable	IV Dose (mean)	PO Dose (mean)
Cmax	.656ng/ml	.874ng/ml
Tmax	34.5h	20.5hr
AUC	67.4h*ng/ml	85.7h*ng/ml
terminal elimination half-life	54.13h	54.22h

Saliva samples were also collected and measured for the presence of Azelastine. The following are the results of saliva v.s. plasma levels of Azelastine when administered intravenously and orally.

Means of Concentrations of Azelastine in Saliva and Plasma Following Intravenous Administration of 4.5 mg of Azelastine Hydrochloride



Means of Concentrations of Azelastine in Plasma and Saliva Following Oral Administration of 4.5 mg of Azelastine Hydrochloride



III. Study #13

A.

B. fasting single (4.4mg tablet) and multiple dose (2.2, 4.4 and 8.8mg tablet bid x 7 days)

C. open-label crossover design - 18 healthy males - 20-40 years of age (all completed the study)

D. results

1. azelastine - steady state pharmacokinetics

PARAMETER	2.2mg	4.4mg	8.8mg
C_{min} (ng/ml)	2.76	5.23	10.81
C_{max} (ng/ml)	3.89	8.02	16.84
AUC_{tau} (ngxhr/ml)	40.10	80.20	168.21
Cl (L/min)	1.18	1.18	0.91
T_{max} (hr)	5.3	5.8	5.3

a. there was a statistically significant difference in plasma concentration between AM and PM suggesting diurnal variation

Comment: Biopharm should elaborate on this diurnal variation in drug levels because the clinical data will need to be evaluated to determine if the diurnal variation has clinical significance.

b. the sponsor reports that AUC and Cmax increased linearly in response to dose

c. single dose pharmacokinetics (4.4mg)

(1) AUC = 50.4 ngxhr/ml

(2) C_{max} = 1.71 ng/ml

(3) T_{max} = 5.8 hr

(4) $T_{1/2}$ = 20.7 hr

d. there was some evidence of drug accumulation with chronic dosing

2. desmethylazelastine-steady state pharmacokinetics

PARAMETER	2.2mg	4.4mg	8.8mg
C_{min} (ng/ml)	1.59	2.86	6.08
C_{max} (ng/ml)	1.86	3.47	7.51
AUC_{ss} (ngxhr/ml)	20.16	37.71	80.79
T_{max} (hr)	6.8	6.8	6.7

a. less pronounced diurnal variation

b. single dose (4.4mg) pharmacokinetics

(1) AUC = 33.7 ngxhr/ml

(2) C_{max} = 0.37 ng/ml

(3) t_{max} = 21.8 hr

(4) mean $T_{1/2}$ = 50.2 hours

E. adverse events

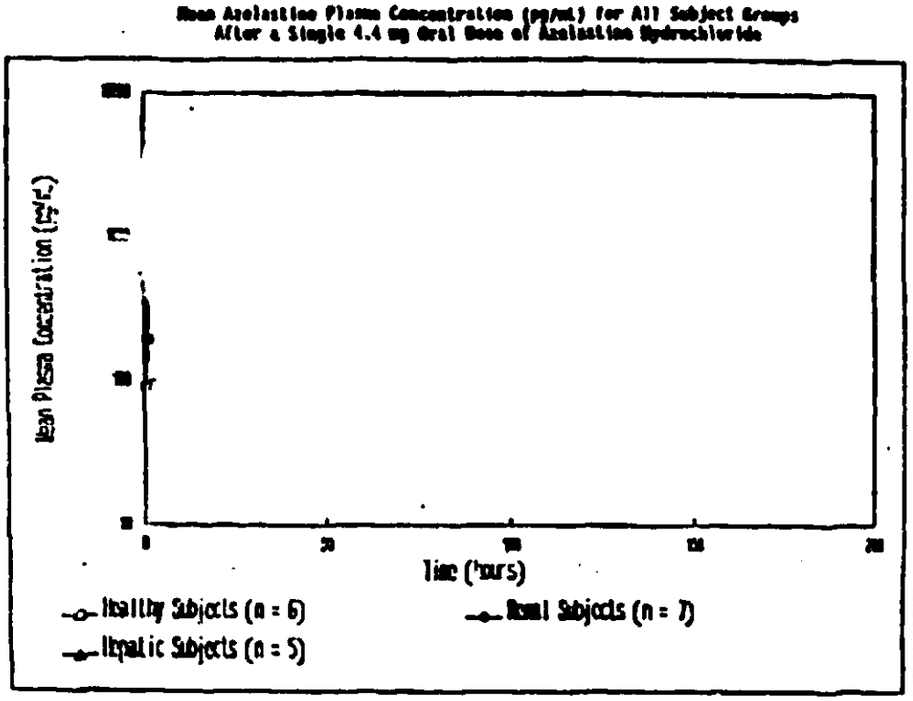
1. included clinically significant elevated LFT's in two subjects (returned to normal in one, the other was lost to follow-up), elevated WBC in one subjects and depressed WBC in a second (attributed to intercurrent infection), altered taste, tiredness, epistaxis and headaches

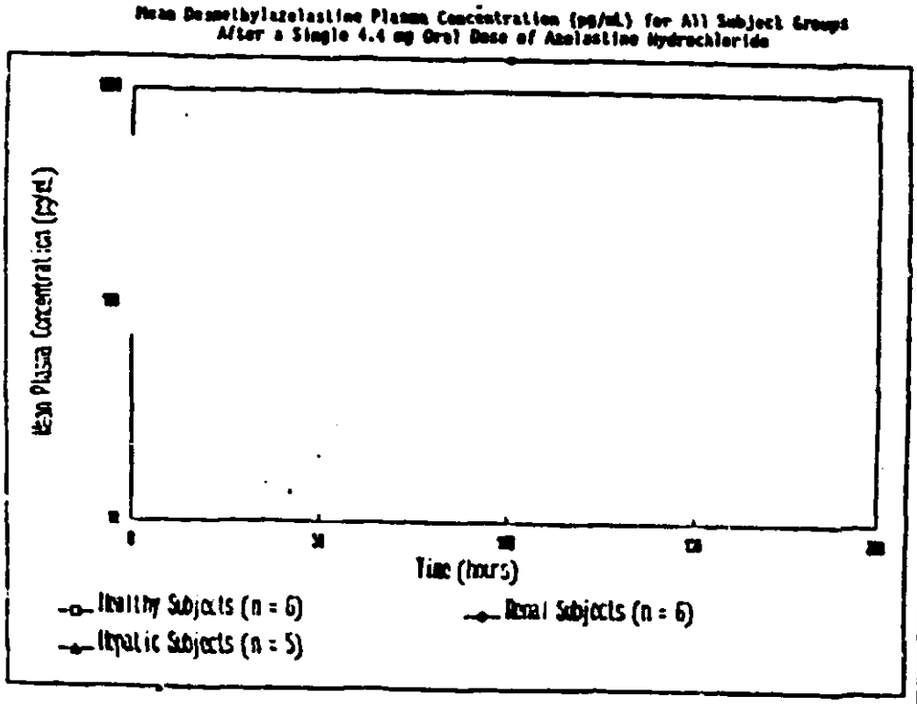
A number of trials were conducted to assess the drug's pharmacokinetics under certain specific circumstances. The sponsor reports that absorption and bioavailability were not affected by administration with a standard meal, compared to after a 10 hour fast. When the drug was administered in conjunction with an antacid, T_{max} was slightly lower (4.3hr vs 5.4hr) compared to ingestion without the antacid. In subjects over 65 years of age, single dose AUC was noted to be 1.5-2 times higher than in younger subjects, although steady state pharmacokinetics in the two populations was similar.

Comment: There was one subject in the trial of subjects over age 65 who experienced ECG changes. Although the changes were attributed to discontinuation of Digitalis use, the sponsor should describe the ECG changes that were noted and elaborate on the timing of the abnormality relative to Azelastine administration and Digitalis discontinuation. In addition, they should submit the subject's case report forms.

When the drug was administered to subjects with renal and hepatic impairment it was noted that C_{max} was significantly greater in the renal subjects vs healthy

volunteers. Regarding the metabolite desmethylazelastine, AUC and C_{max} were significantly elevated compared with healthy volunteers. No significant difference was noted between subjects with hepatic impairment and normal subjects.





Based on antipyrine testing the drug was not noted to induce hepatic anzymes. Although no effect of co-administration with ranitidine was noted, cimetidine was associated with a questionable effect on C_{max} and AUC.

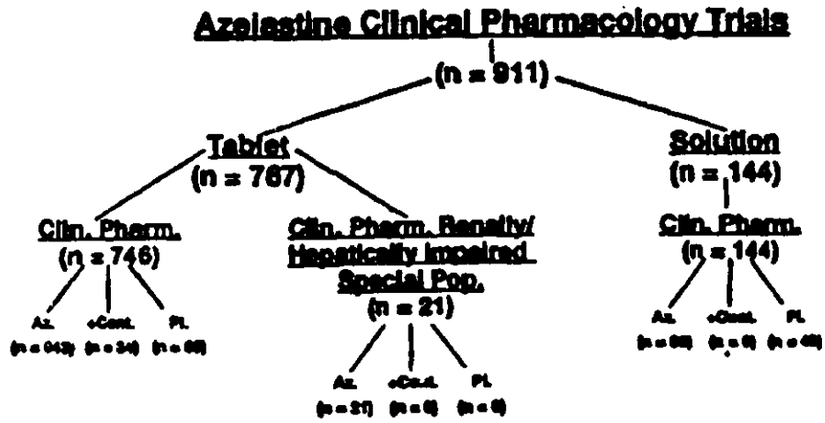
		Without Cimetidine*	With Cimetidine*	Without Ranitidine*	With Ranitidine*
Cmax, obs	ng/ml	5.42 ± 3.03 (12)	8.98 ± 5.96 (11)	7.83 ± 4.06 (11)	8.88 ± 3.75 (10)
Tmax, obs	h	3.42 ± 0.52 (12)	4.40 ± 1.88 (11)	3.91 ± 1.6 (11)	4.35 ± 2.00 (10)
AUC 0-12	ng•h/ml	53.74 ± 31.83 (12)	88.81 ± 50.78 (11)	80.88 ± 43.55 (11)	88.22 ± 40.43 (10)
t½ term	h	-	24.73 ± 8.90 (11)	-	22.38 ± 8.22 (10)
I.F. AUC 0-12		-	1.56 ± 0.22 (11)	-	1.88 ± 0.11 (10)

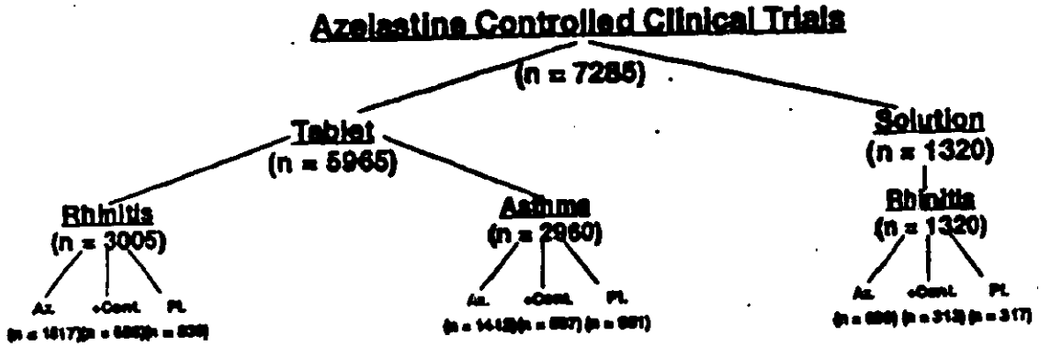
Finally, the sponsor states that based on data from an asthma trial, there does not appear to be an interaction between theophylline and Azelastine resulting in increased Azelastine or desmethylazelastine levels.

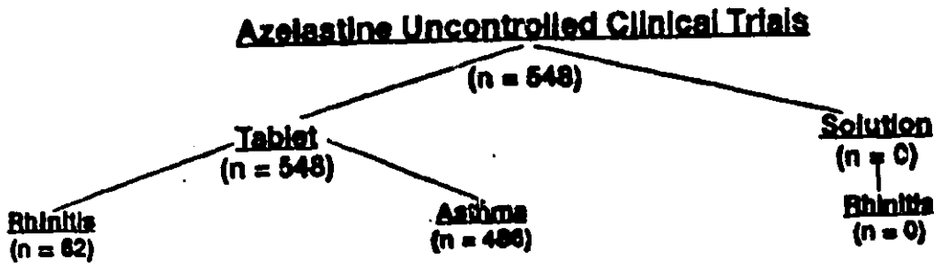
In summary, the drug has a $T_{1/2}$ of 17-20 hours. Plasma levels, which are linear and dose-proportional, appear within 1-2 hours of dosing and reach a C_{max} in 4-6 hours. The drug is greater than 80% bioavailable, is extensively metabolized (less than 10% of a dose appears unchanged in the feces) and is approximately 88% bound to plasma proteins. Azelastine has an active metabolite, desmethylazelastine, which the sponsor reports does not accumulate with chronic dosing. This metabolite has a half life of about 50 hours with a Tmax of 6-7 hours. When Azelastine was studied in a number of special populations, the bioavailability of the drug does not appear to be affected by fed v.s. fasted state, use of antacids, hepatic impairment or co-administration with Ranitidine. Co-administration with Cimetidine did result in an increase in pharmacokinetic parameters. At steady state pharmacokinetics in subjects older and younger than age 65 appeared similar although in the single dose study AUC was lower in younger subjects.

INTEGRATED SAFETY SUMMARY:

The following flow charts depict the number of subjects treated for each of the different indications:







Pharmacokinetic trials:

224 subjects were treated in single and multiple dose clinical pharmacology trials performed in the US. In these trials the most common adverse events were taste perversion (85), fatigue (40) and somnolence (27). Serious adverse events included AV block in a subject who received an 8mg single dose, convulsions in a 28 year old male on day 2 of a 4mg single dose capsule/solution trial and syncope in 4 subjects. 3 of the subjects who experienced syncope received an 8mg single dose and 1 received a 4mg single dose.

Comment: **The subject who experienced AV block was a 19 year old male who initially received 4.4mg of Azelastine intravenously followed two weeks later by 8.8mg orally. The AV block which this subject experienced was first degree with reported PR intervals two weeks after the IV infusion and one week after oral dosing of .24 sec. The sponsor reports that on taking a closer look at the baseline ECG it too appears prolonged to .23sec. To this reviewer, neither the baseline nor the follow-up ECG's appear to have a prolonged PR interval, however, since this adverse event is not serious, it need not be pursued further.**

With regard to the subjects who experienced syncope, all cases occurred within one minute of blood drawing and three were attributed by the investigator to a vasovagal episode related to blood drawing, whereas in the fourth case a reason for syncope was not stated. Three of the episodes occurred two hours after dosing and one occurred three hours after dosing. In three of the subjects there were no clinically significant changes between pre and post study labs and ECG's whereas one subject had a new first degree heart block on an ECG performed post study.

Allergic Rhinitis Trials:

Doses of <.5mg bid to 4mg bid were studied in controlled US trials in subjects with either seasonal or perennial allergic rhinitis. These studies included 1255 subjects who received Azelastine, 525 subjects who received positive controls and 708 subjects who received placebo. Of these, 74 subjects did not complete their trial due to adverse experiences and one subject experienced a serious and unexpected adverse event.

Of the 74 subjects who did not complete the trial, 39 subjects received Azelastine. The reasons for early withdrawal included: somnolence (10), hypertension (1), palpitations (1), abdominal pain (1), nausea (1), increased SGOT (1), increased SGPT(1), tooth disorder (1), vomiting (1), weight increase (1), generalized edema (1), thirst (1), arthralgia (1), myalgia (1), dizziness (1), hypokinesia (1), dry mouth

(3), depression (1), nervousness (2), bronchospasm (2), pharyngitis (1), rhinitis (1), sinusitis (3), URI (6), earache (2), otitis media (1), taste perversion (11), allergic reaction (1) and fatigue (3). Intercurrent illnesses which resulted in premature discontinuation from the trials included sinusitis, earache, bronchospasm, URI, taste perversion, tooth disorder, otitis media and pharyngitis.

Comment: **To ensure that adverse events in subjects who withdrew prematurely are not missed, the sponsor should be asked to list the adverse events which occurred in subjects who withdrew prematurely due to reasons other than an adverse event.**

The subject who experienced a serious and unexpected adverse event was a 35 year old female who received one dose of 2mg of Azelastine and approximately 3 hours later experienced sudden onset of nausea, vomiting and acute right flank pain. The subject was subsequently hospitalized and her workup revealed an elevated white blood cell count with bands, fever, an ovarian cyst and a uterine fibroid tumor. Possible etiologies for her symptoms included a ruptured ovarian cyst, the fibroid tumor and cholecystitis. The subject discharged herself from the hospital before the workup was completed and a definitive diagnosis was not made.

The sponsor also reports one case of an arrhythmia in a 50 year old subject who had been taking Azelastine for 3 weeks and felt dizzy. An ECG done at the time by her physician employer demonstrated an irregular rhythm. The case report does not include the ECG or the specific rhythm that was seen. The subject continued taking Azelastine for another week until the conclusion of the trial, at which time her ECG and vital signs were normal. The subject's ECG at baseline was normal sinus rhythm at a rate of 80 bpm and a QT interval of .36. At the conclusion of the trial the ECG demonstrated a normal sinus rhythm at a rate of 98 bpm and a QT interval of .32.

Adverse events which occurred statistically significantly more often in the Azelastine treated subjects than in the placebo group included somnolence (12% vs 4%, P=.001) and taste perversion (12% vs 0.4%, P=.001). Trends towards statistical significance were noted for dry mouth (5 vs 3%, P=.093) and fatigue (2 vs 1%, P=.083). Taste perversion and rhinitis occurred more often in the Azelastine group than among subjects receiving a positive control, with P values of .001 and .050, respectively.

Adverse events in which the incidence differed between Azelastine and placebo by 1% or greater included: somnolence (12.2% vs 4.4%, positive control = 14.1%), taste perversion (12% vs .4%, positive control = 2.7%), dry mouth (4.5% vs 3%, positive control = 5.7%) and fatigue (2.3% vs 1.1%, positive control = 2.3%).

The only adverse event for which a dose related response was noted was taste perversion.

Exclusion of short term trials (less than one week in duration) from the analysis resulted in the demonstration of a dose response relationship for somnolence and fatigue in addition to taste perversion. All other adverse event data remained the same.

The incidence of all adverse events was highest in the first week of use with the incidence decreasing with increasing duration of use.

When the perennial and seasonal allergic rhinitis data were examined separately, the adverse event data was similar to what was noted above, however in the perennial allergic rhinitis studies fatigue now also occurred statistically significantly more often in the Azelastine group than with placebo.

ADVERSE EVENTS OCCURRING AT A RATE OF $\geq$ 1% IN LONG TERM RHINITIS TRIALS			
Adverse Event	Azelastine	Positive Control	Placebo
Headache	26.1%	22.4%	34.7%
Taste Perversion	15.7%	2.8%	.4%
Somnolence	14.6%	15.8%	4.1%
Pharyngitis	6.1%	4.7%	6.5%
Dry Mouth	5.7%	6.1%	3.4%
URI	3.8%	4.7%	6.3%
Fatigue	3.5%	3.2%	1.4%
Epistaxis	3.0%	2.4%	3.5%
initis	2.9%	.8%	3.9%
Nausea	2.2%	2.1%	1.9%
Dizziness	2.1%	2.9%	2.6%
Dyspepsia	2.0%	1.8%	2.1%
Nervousness	2.0%	2.4%	1.4%
Coughing	1.8%	2.4%	2.6%
Diarrhea	1.8%	1.6%	1.4%
Influenza Like Syndrome	1.8%	2.1%	1.2%
Insomnia	1.8%	1.8%	1.2%
Myalgia	1.8%	3.2%	2.1%

ADVERSE EVENTS OCCURRING AT A RATE OF ≥ 1% IN LONG TERM RHINITIS TRIALS			
Adverse Event	Azelastine	Positive Control	Placebo
Earache	1.3%	1.1%	.9%
Appetite Increased	1.2%		.4%
Bronchospasm	1.2%	1.6%	.7%
Fever	1.0%	.5%	1.1%
Injury	1.0%	1.3%	1.2%
Rash	1.0%	.8%	.4%
Sinusitis	1.0%	1.6%	1.4%
Weight Gain	1.0%	.5%	.4%
Malaise	1.0%	1.3%	.9%

The following are the rates of adverse events which may be considered cardiac in nature:

Adverse Event	Azelastine	Positive Control	Placebo
dizziness	2.1%	2.9%	2.6%
chest pain	.5%	.8%	.4%
arrhythmia	.1%	0%	0%
tachycardia	0%	0%	.2%
palpitations	.1%	.5%	0%

The following are the hepatic related adverse events reported in the NDA:

Adverse Event	Azelastine	Positive Control	Placebo
SGPT increased	.4%	.3%	.5%
bilirubinemia	.1%	0%	0%
enzyme abnormality	.1%	0%	0%
LDH increased	.1%	0%	0%
SGOT increased	.1%	.5%	.2%

Comment: Based on the safety data from the rhinitis studies, adverse events which could be attributed to the drug, based on the demonstration of a significant difference from placebo, include somnolence and taste perversion. Taste perversion was also noted to occur in a dose related manner. Fatigue may also be considered attributable to Azelastine because it occurred significantly more often in treated subjects with perennial rhinitis than in controls. There does not appear to be a relationship between duration of therapy and incidence of adverse events. Specific information regarding the cardiac and hepatic adverse events reported above will be requested of the sponsor.

Based on the amendment of February 11, of the 9 cases of bronchospasm reported above, 6 occurred in subjects with a prior history of asthma. Of the three subjects with no prior history of asthma, 1 case occurred at 1mg bid and 2 occurred at 2mg bid. The investigator did not feel that the event was drug related, although the basis for the diagnosis was unknown in two of the cases. In one subjects bronchospasm was associated with chest cold and flu-like symptoms.

Asthma Trials:

Doses of 2-16mg were studied in single dose asthma trials and doses of 1-8mg bid were evaluated in multiple dose asthma trials. The controlled US trials included 970 subjects who received Azelastine, 26 subjects received Azelastine and theophylline, 395 subjects received positive controls and 599 subjects received placebo. 84 subjects did not complete a trial due to adverse events and there was one death.

The subject who died was a 57 year old Mexican-American female with a history of asthma and hypertension who received 4mg bid of Azelastine for 259 days. While on a visit to Mexico she experienced chest pain and sudden death. The submission states that for unknown reasons the subject had been treated with Inderal while in Mexico. The treating physician in Mexico attributed the subject's death to myocardial infarction. The investigator adds that the use of Inderal in this subject with asthma may have contributed to her demise. No additional information is available and no post-mortem examination was performed.

Five serious and unexpected adverse events were reported during the asthma trials:

1. meningococcal meningitis: 21 year old male receiving 4mg bid of Azelastine x 8 days
2. venostasis retinopathy of unknown etiology: 57 year old female received 4mg bid of Azelastine and Theo-Dur 400mg x 259 days
3. lung nodule (surgical pathology benign): 37 year old male received Azelastine 6mg bid x 366 days
4. psychotic episode: 23 year old male received Azelastine 4mg bid x 1 day. The subject had a history of familial problems and possibly alcohol use as well.
5. overdose: 18 year old male who was the son of a subject in a trial overdosed on Azelastine and theophylline in a suicide attempt. No complications were reported.

Of the 84 subjects who withdrew prematurely, 45 were in the Azelastine treatment arm. Reasons for premature withdrawal in the Azelastine arm include: abnormal ECG (1), hypertension (2), rash (1), dyspepsia (1), gastritis (1), hepatitis (1), nausea (1), SGOT increased (2), SGPT increased (2), vomiting (1), appetite increased (3), generalized edema (1), facial edema (1), weight increase (8), myalgia (1), convulsions (1), dizziness (2), headache (1), meningitis (1), somnolence (10), anxiety (1), depression (3), emotional lability (2), insomnia (2), nervousness (2), pharyngitis (1), rhinitis (1), URI (2), taste perversion (13), renal pain (1), UTI (1), chest pain (1), fatigue (2), influenza like symptoms (1) and injury (1). Intercurrent illnesses which resulted in premature withdrawal included: hepatitis, influenza like symptoms, meningitis, emotional lability, URI and pharyngitis.

The case reports also demonstrate that subject #148 in study #24 experienced a prolonged QT interval on a number of ECG's collected during the course of the trial. The subject's baseline ECG, which was considered normal, showed a heart rate of 96 and a QT/QT_c of .392/.502. Over the course of the trial the QT ranged from .412 to .434 and the QT_c ranged from .460 to .520 (the ECG with a QT_c of .520 was considered within normal limits). No associated clinical adverse events are reported in this subject.

The sponsor reports that in the single dose asthma trials, only the incidence of taste perversion (35.3%), somnolence (27.2%), dizziness (3.8%), nervousness (2.7%) and fatigue (2.2%) exceeded the rate in placebo subjects by 2% or more. Taste perversion and somnolence occurred in a dose related manner. Two subjects who were enrolled in single dose trials of 4 and 16mg of Azelastine experienced syncope. In one subject the episode occurred 5 hours after dosing in association with a venipuncture procedure. The case report forms attribute the episode to a vagal response. The second subject had a history of hypoglycemic induced syncope in the past and so this event, which occurred 13 hours post dosing, was attributed to the same etiology.

In the multiple dose studies adverse events which occurred significantly more often in the Azelastine group than placebo include taste perversion (38% vs 4%, P < .001), somnolence (20% vs 5%, P <.001), rhinitis (9% vs 5%, P < .001), fatigue (7% vs 4%, P=.039), dry mouth (6% vs 2%, P=.002), bronchospasm (5% vs 2%, P=.013), weight increase (5% vs 2%, P=.031) and appetite increase (3% vs 1%, P=.005). A trend towards an increased incidence was noted for palpitations (1% vs .2%, P=.097).

Syncope occurred in 3 subjects (.4%) on 4mg bid of active drug and 1 placebo subject (.2%). One of the subjects on active treatment experienced numerous episodes of syncope associated with coughing and chest pain beginning at week 9 of a 13 week trial. No clinically significant changes were noted on ECG or laboratory tests. Following completion of the trial is was learned that the subject had a history of cough induced syncope dating back to two years prior to the trial. A neurology workup determined that the subject also had a history of head trauma and seizures. It was concluded that the subject had cough related syncope and a seizure disorder, the threshold of which may have been lowered by the use of theophylline and possibly the study drug as well. The three other subjects experienced syncope at the time of blood drawing. In two subjects the event occurred 4 hours after dosing; in a third subject the timing of the event relative to dosing is unknown. One subject on active treatment developed first degree heart block during the trial.

The following are the incidences in the combined allergic rhinitis/asthma trials of adverse events which could be interpreted as having a cardiac relationship:

Adverse Event	Azelastine	Positive Controls	AZ 4mg/Theo	Placebo
dizziness	3.2%	3.7%	7.7%	3.9%
chest pain	1%	.9%	3.8%	.6%
palpitations	.4%	1.1%	7.7%	.1%
syncope	.1%	0%	0%	.1%
tachycardia	.1%	.3%	0%	.2%
arrhythmia	.1%	0%	0%	0%

None of the adverse events listed above occurred in the Azelastine treated subjects in a dose related manner.

Comment: The concern with potential cardiac related effects is related to concern about effects of antihistamines on the ECG, and in particular on the QT interval. This issue is addressed elsewhere in this review, however the sponsor should be requested to submit a listing of the nature and etiology of the chest pain in the 21 subjects in whom this event was reported. In addition, they should identify the

specific arrhythmias seen in the .1% of treated subjects.

The amendment of February 11, 1993 includes information regarding this adverse event. There was one case of chest pain in the .5mg group, 2 cases in the 1mg group, 6 cases in the 2mg group, 8 cases in the 4mg group and one case at 8mg. The following is the data reported by the sponsor concerning these subjects:

Dose	Study#/ Subject#	Age/Sex	AE name	Etiology	Comments
.5mg BID	55/424	33/F	chest pain	unknown	ECG reported as normal. No prior history.
1mg BID	56/64	32/F	chest pain	unknown	ECG reported as normal.No prior history.
1mg BID	186 81 (asthma)	31/M	chest tightness	related to PFT's an exercise challenge	
2mg BID	23/44 (asthma)	37/M	chest congestion	Intercurrent illness. "Fluid buildup and increase asthma symptoms"	Started after double-blind medication was stopped.
2mg BID	23/167 (asthma)	32/M	chest pain	Associated with ingestion of MSG	Prior history of occurrence with MSG.
2mg BID	23/149 (asthma)	42/M	pain in chest	asthma	history of pain with asthma and overuse of inhaler
2mg BID	23/153 (asthma)	52/F	chest tightness	unknown	began 5 days after last dose of double blind medicine
2mg BID	27/70	22/M	chest pain	unknown	ECG showed sinus bradycardia. URI with cough developed day after pains.
2mg BID	65/316	64/M	chest tightness	weight lifting	occure with coughing, lifting or moving
4mg BID	186/153 (asthma)	33/M	chest tightness	exercise	"prior history"
4mg BID	23/190 (asthma)	23/M	heaviness in chest	exacerbation of asthma	"prior history"
4mg BID	23/145 (asthma)	45/M	chest pain	associated with cough	"prior history"
4mg BID	24/28 (asthma)	13/M	chest pain	possible pleurisy	ECG-normal
4mg BID	24/43 (asthma)	24/M	hot/cold sensation in chest	? stress	ECG normal. Also reported palpitations and PVC's
4mg BID	24/155 (asthma)	33/F	chest pain	asthma	present at study entry; prior history
4mg BID	24/360	54/M	pain in right side of chest	hiatal hernia	prior history

Dose	Study#/ Subject#	Age/Sex	AE name	Etiology	Comments
4mg BID	97/117 (asthma)	32/M	congested chest	possibly related to other ex	concurrent sore throat and earache
8mg bid	23/197 (asthma)	197/20M	chest tightness	asthma	prior history;began one day after completing double blind medications

Regarding this response, the sponsor should answer a number of questions:

1. **When they state that the ECG was normal, are they referring to a post chest pain ECG?**
2. **When they state "prior history" does that indicate that the subject has a prior history of chest pain?**
3. **When they state that symptoms occurred after double-blind therapy was discontinued, were these subjects on any open label therapy?**
4. **The results of a follow-up ECG, taken after the complaint of chest pain, should be reported for all treated subjects included in Table 2**
5. **The NDA identifies 21 treated subjects who experienced chest pain. Data on the three subjects not included in this amendment should also be submitted.**

Also noted is one report of a patient with transient ST segment and T wave changes on ECG. The investigator attributed the ECG changes in this subject (study 23, subject #254), a 46 year old female, to stress. Myocarditis is also listed a cause for the ECG changes in this subject. An ECG performed at follow-up was normal. The sponsor should be asked to submit the case report for this subject as well as describe the basis for the diagnosis of myocarditis.

With regard to potential effects of antihistamines on liver function tests, the following adverse events reported in the combined allergic rhinitis/asthma trials relate to this issue:

Adverse Event	Azelastine	Positive Controls	AZ 4mg/Theo	Placebo
SGPT increased	.4%	0%	.4%	.4%
enzyme abnormality	.1%	0%	0%	0%
LDH increased	.1%	.1%	0%	.2%
SGOT increased	.1%	.2%	0%	.1%
bilirubinemia	1 subject	1 subject	0	0

Comment:

The list of adverse events that may be associated with Azelastine is somewhat more extensive for asthma patients and includes taste perversion, somnolence, rhinitis, fatigue, dry mouth, bronchospasm, weight increase and appetite increase.

With regard to serious adverse events, one subject died in Mexico shortly after she was started on a beta blocker. The physician in Mexico attributed the death to myocardial infarction possibly based on the fact that the subject experienced chest pain shortly before her demise, however, there is no additional data available to corroborate the cause of death. In addition, the reason for starting the beta blocker is also unknown. Of note, the subject's baseline ECG demonstrated a right bundle branch block with a QT/QTc of 372/414msec. Four months later, the subject's ECG (this ECG is her last one in the study and was performed three months before her demise) demonstrated a right bundle branch block with a QT/QTc of 440/471msec. This represents an increase in QTc of 57msec, or 13.8% above baseline.

Regarding the subject reported above with a prolonged QT interval on ECG, the interpretation of the ECG's performed on this subject is not consistent with regard to the criteria being used for considering the QT interval prolonged. For example, on January 27th an ECG demonstrated a heart rate of 87 and a QT/QTc of .396/.482. This ECG was labelled as showing prolongation of the QT interval. Four hours later another ECG demonstrated a heart rate of 92 with a higher QT/QTc of .417/.520. This ECG was considered normal. Therefore, the sponsor was requested to provide additional information concerning the cardiac workup of this subject as well as information on any other subjects with prolonged QT intervals. In the amendment of 9/8/92 the sponsor reports that the subject was evaluated by a cardiologist. The evaluation stated that the subject's QTc was prolonged at baseline and that there was also evidence of prolonged QTc on a holter monitor performed one week after discontinuation of Azelastine. The cardiologist concluded that the subject had prolonged QT syndrome. The sponsor also submitted the following table which they state describes the subjects who had prolonged QT intervals.

Subjects with Reported Prolonged QT Interval

Study Number	Subject Number	Treatment Group	Visit Number	Comment	QT (msec)	QTc (msec)	Reported as Adverse Experience	Comments
67	189	Azelastine 2 mg	• 1	(pretreatment)	340	371	no	Normal ECG
			• 4	(4 weeks treatment)	400	371	no	Sinus bradycardia 47/min.
194	17	Azelastine 1 mg	2	(pretreatment)	404	404	no	———
			• 4	(2 weeks treatment)	436	494	yes	Asymptomatic
			5	(1 week posttreatment)	416	478	no	Asymptomatic
24	148	Azel. 4 mg/dose 800/400 mg	• 4	(4 h after the 1st dose)	427	478	no	Repeated
			4	(8h after the 1st dose)	386	482	no	Asymptomatic
			6	(2 weeks treatment)	434	460	no	Asymptomatic
			• F/U	(1 week after treatment)	412	496	yes	Cardiology Consult–QT Prolongation Syndrome
24	159	Azelastine 4 mg	3	(pretreatment)	360	430	no	Normal ECG
			4	(4 h after the 1st dose)	446	468	no	Normal ECG
			• 6	(2 weeks treatment)	442	470	no	Asymptomatic
			• 7	(3 weeks treatment)	445	488	no	Asymptomatic
			F/U	(1 week after treatment)	413	464	no	Normal ECG
24	231	Azelastine 4 mg	3	(pretreatment)	391	462	no	Normal ECG
			• 4	(4 h after the 1st dose)	434	497	no	Asymptomatic
			6	(2 weeks treatment)	398	459	no	Normal ECG
			7	(3 weeks treatment)	410	461	no	Normal ECG
			• 10	(6 weeks treatment)	430	496	no	Asymptomatic
			• 13	(9 weeks treatment)	411	424	no	Normal ECG
			16	(12 weeks treatment)	438	430	no	Normal ECG
			F/U	(1 week after treatment)	424	420	no	Normal ECG

*QT prolongation reported on ECG

Subjects with Reported Prolonged QT Interval

Study Number	Subject Number	Treatment Group	Visit Number	Comment	QT (msec)	QTc (msec)	Reported as Adverse Experience	Comments
24 OL	70	Azelastine 2 mg	2	(1 week treatment)	360	403	no	One PVC
		Azelastine 4 mg	3	(2 weeks treatment)	400	408	no	rare PVC no change
		Azelastine 6 mg	6	(3 months treatment)	380	405	no	Frequent PVCs – Asymptomatic
		Azelastine 6 mg	7	(1 month treatment)	412	481	no	PVC
			• F/U	(2 weeks after treatment)	440	480	yes	Rare PVC
			F/U	(1 year after treatment)	370	441	—	Rare PVC
187	234	Azelastine 6 mg	1	(pretreatment)	360	412	no	Normal ECG
			3	(1 month treatment)	340	412	no	FLAT T-Waves V_5 V_6 – not clinically significant
			7	(4 months treatment)	380	460	no	Normal ECG
			• F/U	(2 weeks after treatment)	392	463	no	Asymptomatic
187	236	Azelastine 6 mg	1	pretreatment	360	384	no	Normal ECG
			3	(1 month treatment)	368	433	no	Normal ECG
			7	(5 months treatment)	420	455	no	Normal ECG
			• F/U	(2 weeks after treatment)	384	460	no	Asymptomatic
187 OL	203	Azelastine 6 mg	1	(pretreatment)	412	441	no	Normal ECG
			• 5	(4 months treatment)	448	484	no	Asymptomatic
			• 9	(8 months treatment)	424	781	no	Asymptomatic
			13	(1 year treatment)	372	410	no	Asymptomatic
			F/U	(2 weeks after treatment)	400	421	no	Asymptomatic
97	237	Azelastine 6 mg	• 1	(pretreatment)	380	396	no	Normal ECG
			• 8	(3 months treatment)	360	384	no	Normal ECG
			• 14	(5 months treatment)	420	454	no	Asymptomatic
			F/U	(1 week after treatment)	416	421	no	Normal ECG

*QT prolongation reported on ECG

Subjects with Reported Prolonged QT Interval

Study Number	Subject Number	Treatment Group	Visit Number	Comment	QT (msec)	QTc (msec)	Reported as Adverse Experience	Comments
190	359	Aclasine 4 mg	1	pretreatment	432	447	no	Normal ECG
			• 3	(pretreatment)	452	456	no	Sinus arrhythmia – asymptomatic
			5	(1 month treatment)	488	447	no	Sinus bradycardia – asymptomatic
			• 7	(2 months treatment)	512	501	no	Sinus bradycardia – asymptomatic
			• 9	(3 months treatment)	516	463	no	Sinus bradycardia – asymptomatic
			• F/U	(1 week after treatment)	492	474	no	Sinus bradycardia – asymptomatic
98	262	Aclasine 4 mg	1	pretreatment	360	399	no	Normal ECG
			4	(1 month treatment)	404	425	no	Normal ECG. Sinus arrhythmia, asymptomatic
			6	(2 month treatment)	428	448	no	Normal ECG. Sinus arrhythmia, asymptomatic
			• 8	(3 month treatment)	452	471	no	Sinus arrhythmia – asymptomatic
			F/U	(2 week after treatment)	380	398	no	Sinus arrhythmia – asymptomatic
98	435	Aclasine 4 mg	1	pretreatment	360	444	no	Normal ECG
			4	(1 month treatment)	424	431	no	Normal ECG
			• 6	(2 month treatment)	400	466	no	asymptomatic
			8	(3 month treatment)	404	451	no	Normal ECG
			F/U	(1 week after treatment)	408	442	no	Normal ECG. sinus arrhythmia

With regard to these 13 subjects, QTc increased by up to 320msec if the data on subject 203 is to be believed or up to 72msec if that subject is excluded. This represents an 18% increase in QTc from baseline. However, this table cannot be considered a complete report of all subjects who experienced a prolonged QT interval since the subject described above who died is not included and, even within this table there appears to be no consistency with regard to what is being considered a prolonged QT interval. For example, in subject #251 a QT/QTc of 411/424 is considered prolonged whereas 438/430 is not.

The sponsor also submitted data from a retrospective analysis of ECG data from a number of clinical trials. For this analysis the sponsor identified 7 clinical trials in

which ECG's were performed at approximately Tmax at some point in the trial. The seven trials included one single dose trial, one multiple dose rhinitis trial and five multiple dose asthma trials. The trials were divided into the following three groups:

Group I: Single-Dose - Protocol 146
(Treatment groups: Azelastine 2 mg, 4 mg, 8 mg, 12 mg, 16 mg, and Placebo)

Group II: Multiple-Dose - Protocols 149, 150, 198, 204 and 234
(Treatment groups: Azelastine 2 mg, 4 mg, 6 mg, 8 mg, and Placebo bid)

Group III: Multiple-Dose Rhinitis - Protocol 287
(Treatment groups: Azelastine 1 mg, 2 mg, and Placebo bid)

Of the 1709 subjects who had been randomized to these trials, the sponsor selected 1019 subjects who had "suitable original ECG's" for the analysis. Lead 2 of the ECG's was chosen for analysis and it was analyzed by computer for QT interval and R-R. QTc was then calculated using Bazette's formula and the treatment groups were compared versus placebo.

Regrading change in QTc from baseline, in group 2, subjects in the 4 and 8mg groups exhibited statistically significant increases versus placebo. The values were 6.2msec (P=.001) and 9.5msec (P=.029), respectively. In group 3 the 2mg dose group exhibited a mean increase of 7.4msec which was significant versus placebo, P=.048.

Significantly more subjects in the 4mg treatment arm of group 2 had an increase in QTc from baseline versus placebo, 59% versus 45% (P=.001). Similarly, in group 3 significantly more subject in the 2mg arm had an increase in QTc versus placebo, 63% vs 44% (P=.029). When the incidence of a greater than 10% change from baseline was analyzed, there were no differences among the treatment arms. Also, none of the statistically significant effects listed above occurred in a dose related manner.

Although the statistically significant effects reported above do not appear clinically significant, the study does not adequately assess the issue for the following

reasons:

1. 690 subjects, or 40% of the data base, was not analyzed because they did not have suitable ECG's. The sponsor should explain why these subjects were not included in the analysis.

2. The accuracy of the computer read ECG intervals should be verified by comparing the computer's interpretation of a selected group of ECG's with the interpretation of a cardiologist.

3. The selection of only ECG's performed at 4 hours post dosing may not be appropriate since QTc prolongation may occur at a time point later than Tmax. In addition, the drug has an active metabolite with a Tmax of 6-7 hours in multiple dose studies and 22 hours in single dose studies. Therefore, all ECG's performed on all subject should be analyzed.

Because of these weakness in the analysis, the sponsor should analyze QT/QTc data on all subjects included in controlled asthma and rhinitis trials. Single dose and multiple dose trials should be analyzed separately. For each subject, the maximum QTc at any time during treatment should be determined and the change and percent change from baseline should be analyzed for each dose versus placebo. The QTc should be measured on the lead with the longest QT interval and the method for measuring ECG intervals and calculating QTc should be standardized. Finally, the sponsor should submit the ECG's from patient #203 in study #187OL who had a reported QTc of 761.

The following comments were faxed to the sponsor on 11/5/92:

"Based on our evaluation of the integrated safety summary included in the NDA submitted on March 26, 1991 as well as the amendment of September 8, 1992, we request the following additional information to further assess for possible effects of Azelastine on the QTc interval:

1. The maximum change in QTc from baseline should be determined for all subjects in placebo controlled single and multiple dose US allergic rhinitis and asthma studies and compared between Azelastine and placebo treated groups. Maximum change in QTc should be based on evaluation of all ECG's for each subject while they are on active treatment and determination of the ECG on which the QTc is most prolonged. This evaluation may be made using lead II, however, all ECG's on which there is a 10% or greater prolongation in QTc should be evaluated by a cardiologist for changes in T wave morphology and the presence of U waves. The data for single dose and multiple dose trials should be evaluated separately and the analysis should include assessment of dose related effects, age related effects, differences between males and females and effects based on duration of treatment. In addition to evaluating the mean and percent change from baseline,

the data should describe the range of QTc prolongation seen. An analysis should also be performed comparing active treatment to placebo with regard to subjects with < 10% increase in QTc from baseline, 10-15%, 15-20% and >20% increase over baseline. Because of possible diurnal effects on QTc, the analysis should include a description of how the ECG's included in the analysis compare in the two groups with regard to the time they were collected. Finally, if serum drug levels are available, an analysis of change in QTc by drug level should be performed.

2. Please submit all ECG's that were performed on the 18 year old male who was the son of a subject in a clinical trial and who had taken an overdose of Azelastine. A discussion of the electrocardiographic findings, with particular emphasis on QTc intervals and T and U wave morphology should be included.

This comment was addressed in the amendment of 2/11/93. No ECG was done. Although a rhythm strip was measured, it was of poor quality and was uninterpretable.

3. In the submission of September 8, 1992 subject #203 (study #1870L) is reported to have a QTc interval of 761msec while on therapy. This value should be rechecked to ensure its accuracy and the case report for this subject should be submitted.

The sponsor responded to this comment in the amendment of 2/11/93. The 761 is an error. It should read 461. The subject's case report forms were submitted on 9/8/92. This subject's baseline ECG revealed a QT/QTc of 388/408 v.s. 425/461 15 months later. This represents a 13% increase from baseline.

4. Please report on cardiovascular adverse events, including palpitations, seizures and syncope that have been reported in countries in which the drug is currently marketed."

Regarding this request, the sponsor states in the amendment of 2/11/93 that there have been 12,231 Azelastine treated subjects reviewed in 6 postmarketing surveillance reports over the period 1986 -1992 based on use of the drug in Japan and South Korea and topical intranasal use in Germany and the UK. The sponsor states that of these subjects, there were 6 cardiovascular adverse events. 4 subjects experienced palpitations, 1 experienced bradycardia and 1 experienced chest discomfort. The following is a summary of these cases:

Age/Sex	Dose	Adverse Event	Comment
29/F	2mg	palpitations, drowsiness	symptoms resolved after discontinuation of drug

35/F	3mg	palpitations-described as a tightness in chest	resolved after discontinuation
?	2mg	palpitations and eruptions	
44/M	2mg	convulsions and increased heart rate on second day of therapy	symptoms disappeared after therapy discontinued
83/F	2mg	chest discomfort	MI suspected due to inverted T waves. Symptoms improved with nitroglycerin as well as digestive meds
37/F	1mg	bradycardia-pulse decreased to 50. Systolic BP decreased from 90-100 to 80	Pulse normalized 3 days after drug withdrawal

The sponsor should be asked to provide all the clinical data available, including ECG's, on the last three subjects included in this table. In addition, its unclear to this reviewer if safety information based on the 12,231 Azelastine treated subjects which was reviewed in the six Eisai postmarketing safety reports was included in the foreign data reported in the integrated safety summary. If this information was not included in the integrated safety summary, it should be submitted.

Of the other five serious adverse events (meningitis, venostasis retinopathy, psychotic episode, lung nodule and an overdose) venostasis retinopathy is a possible complication of antihistamine use due to effects on vascular smooth muscle. The physicians involved in the workup of this subject did not arrive at a conclusion regarding the etiology of this adverse event, however the long exposure prior to its occurrence (259 days) suggests that it may not be drug related. The psychotic episode did occur after only one day of therapy however this adverse event is not consistent with the adverse event profile of antihistamines. Meningitis is not a likely adverse event from antihistamine use and the subject who took the overdose was not on therapy at the time the overdose occurred. In addition the overdose was well tolerated.

Combined Multiple Dose Allergic Rhinitis and Asthma Trials:

2041 subjects received azelastine, 26 received azelastine and theophylline, 920 subjects received positive controls and 1221 subjects received placebo in double-blind, multiple dose trials which were from 2 days to one year in duration.

Adverse events which occurred statistically significantly more often in the treated group include: taste perversion (22% vs 2%, P<.001), somnolence (15% vs 5%, P<.001), dry mouth (5% vs 3%, P<.001), fatigue (4% vs 2%, P=.010), bronchospasm (2% vs 1%, P=.012), and weight increase (2% vs 1%, P=.026). A trend towards increased incidence was noted for nervousness (3% vs 2%, .098). A dose related effect was noted for both somnolence and taste perversion.

When the time of first occurrence of adverse events was examined, it appeared that most adverse events occurred during the first week of the trial with the incidence decreasing with increasing study duration.

Comment: Of the adverse events listed above that occurred significantly more often in treated subjects than controls taste perversion, somnolence and fatigue were also noted in the allergic rhinitis studies. The increase in bronchospasm, weight increase and dry mouth is probably due to the asthma studies where these events were also noted to occur significantly more often in treated subjects. Dry mouth is an expected side effect of antihistamines, whereas bronchospasm may indicate lack of efficacy or possible exacerbation of disease in asthma patients. The increased incidence of weight gain may be due to the significant increase in appetite noted in the asthma trials.

Foreign Trials:

European studies:

1756 subjects received Azelastine, 570 received positive controls and 600 subjects received placebo in 14 pharmacology trials, 5 rhinitis trials, trials and one dermatology study. The European trials also included an eight week, randomized, double-blind, positive control trial in 92 children age 6-12 years.

61 Azelastine subjects were discontinued prematurely due to drug intolerance and 3 deaths were reported, two among Azelastine subjects and one placebo subject. The two Azelastine subjects that died were receiving 4mg bid of Azelastine and had been enrolled in an study for >200 days. One subject died of status asthmaticus and the second died from a tropical viral infection. A third subject on placebo also died of status asthmaticus. There were various reasons cited for patient discontinuation, however, the only serious reasons appear to be angina pectoris in two subjects after receiving 4 and 16 days of drug therapy.

Comment: The case report forms for the two subjects who received Azelastine and died have been reviewed. One subject was a 64 year old male with hypertension and asthma who died after receiving Azelastine for approximately 9 months. The case report form only states that the subject died from an infection after a trip to

Africa. The case report form does not provide any details to support the cause of death and no ECG's are included. The second subject was a 49 year old male with asthma who received Azelastine for approximately 8 months before he died. The case report form states that the subject died due to acute status asthmaticus, however, as with the previous report, no additional information or ECG's are provided. Because of the serious nature of these adverse events, the sponsor should be asked to provide additional information regarding both subjects who died. This information should include all of the subjects' ECG's, a copy of their hospital chart for the admission during which they expired and a narrative discussion of the information upon which the cause of death is based.

In the 5 multiple dose rhinitis trials, the following adverse events occurred at a rate of $\geq$ 1%: fatigue (11.3%), taste perversion (4.0%), headache (2.4%), nervousness (2.4%), dizziness (1.6%), dry mouth (1.6%) and eye pain (1.6%). No adverse events were reported in the 16 subjects who received placebo. 12.2% of the 82 subjects who received other controls experienced fatigue and 2.4% experienced nervousness.

In multiple dose placebo controlled trials done for all three indications listed above, fatigue (8.4% vs 2.5%, P=.001), taste perversion (13.7% vs 0.6%, P<.001) and somnolence (11.1% v.s. 4.2%, P<.001) occurred significantly more often in treated subjects v.s. controls. Both taste perversion and somnolence occurred in a dose related manner. Serious adverse events included angina (.3% vs 0%), chest pain (.3% vs 0%) and dyspnea (.1% vs 0%).

Adverse events reported in the trial of subjects age 6-12 included bitter taste, increased and decreased appetite, vomiting, weight gain, nausea, fatigue, tiredness, sleepiness, headache and urticaria. Three subjects discontinued early due to the following adverse events: bitter taste and nausea, dermatitis and urticaria.

The sponsor does not report whether any of the adverse events in the European trials occurred statistically significantly more often in treated subjects than controls.

Adverse events which occurred in the European trials and could be considered cardiac in nature include:

Event	Azulastine	Placebo
angina pectoris	.3%	0%
chest pain	.3%	0%
palpitations	0%	.3%
heart disorder	0%	.6%
tachycardia	.1%	0%

There were numerous Azelastine treated subjects who discontinued prematurely from clinical trials. Often the reason listed was somnolence and taste perversion. The only serious reasons listed were angina pectoris and chest pain.

Japanese studies:

These trials involved 1389 subjects on Azelastine, 253 subjects who received positive controls and 209 subjects on placebo. There were no deaths and 20 subjects on Azelastine discontinued early. In the multiple dose trials adverse events which occurred more often in the treatment group than among controls include: taste perversion (5.7% vs 1.5%), somnolence (6.3% vs 2.9%) and thirst (1.7% vs 0%). Taste perversion and thirst occurred in a dose related manner.

Concomitant Therapy Interactions:

The adverse event profile in subjects taking concomitant pseudoephedrine, cough/cold preparations, anti-inflammatory drugs, anti-rheumatic drugs or oral contraceptives is similar to the adverse events described above.

Demographic (combined perennial and seasonal allergic rhinitis):

Age:

For this analysis subjects were divided into four age groups, <18 years, 18-40 years, 41-60 and >60 years. The number of subjects in the two extreme age groups, <18 and >60, is small however, there does not appear to be an increased incidence in any particular adverse event in the younger or older populations.

Gender:

Many adverse events occurred more often in female subjects than male, particularly headache, somnolence, taste perversion, pharyngitis, dry mouth and nausea where the rate exceeded the rate in men by $\geq$ 2%. A similar difference in the placebo group was only noted for pharyngitis.

Race:

Although there were a few adverse events which occurred more often in "other" races combined, the difference between other races and whites was small.

Weight:

The incidence of taste perversion was 23.8% in subjects weighing less than 110

pounds vs 12.4% and 10.2% in subjects weighing 110-170lbs and >170lbs, respectively. Other differences between weight groups were small.

Comment: With regard to the adverse event of syncope, there were 10 cases reported in the integrated safety summary, 9 occurred in subjects on Azelastine and one occurred in a placebo subject. 4 of the 9 Azelastine subjects experienced syncope in single dose pharmacokinetic trials in which 8mg doses were administered to 3 subjects and a 4mg dose was administered to one subject. All four events occurred at the time of blood drawing; 3 occurred two hours after dosing and one occurred 3 hours after dosing (T_{max} is approximately 5 hours). No assessments were made at the time of the syncopal episodes to help clarify their etiology, although one subject was noted to have a new first degree heart block on a follow-up ECG. The episodes are reported to have lasted a few minutes and resolved on their own.

The sponsor's explanation that the syncopal events are due to a vasovagal response to blood drawing is reasonable since they clearly occurred at the time of a blood drawing procedure, they resolved spontaneously, the events occurred prior to T_{max} and there is no report of further problems at about 5 hours post dose. It also seems unlikely that a single dose of drug, albeit higher than the single doses to be used in allergic rhinitis, would have such an extreme effect on the CNS or cardiovascular system to result in syncope. Even though first degree heart block was subsequently noted in one subject, this is not a clinically significant abnormality and should not be considered an etiology for the adverse event. The US pharmacologic trials consisted of 547 exposures to Azelastine and 35 exposures to placebo. The rate of syncope following exposure to drug or placebo is .73% in the Azelastine group vs 0% in the placebo group. This suggests that although there were no cases in the placebo group, the incidence on drug is not much different from placebo.

Of the additional 6 syncope cases, two occurred in single dose asthma trials in which the subjects received 4 and 16mg of drug. The subject who received 4mg of Azelastine experienced syncope, again associated with blood drawing, 5 hours after being dosed whereas the other subject, who had a history of hypoglycemic induced syncope, experienced the adverse event 13 hours post dosing. The event in the second subject did not occur in conjunction with a blood drawing procedure. The sponsor attributed the event to hypoglycemia based on the subject's history, however this explanation is inadequate because a prior history of hypoglycemia dose not necessarily indicate that this event is due to the same etiology. The case report does not describe how the episode was resolved, whether the subject required medical attention or the subject's blood glucose level at the time of the episode, although the 13 hour interval between the administration of Azelastine and the occurrence of syncope and the fact that this was only a single dose study make it unlikely that the event is related to the study drug (for doses of 2, 4 and

8mg T_{max} is 5-6 hour).
Four cases of syncope were also reported in the multiple dose asthma trials, 3 in Azelastine treated subjects (4mg bid) and one in the placebo group. In three of the subjects, syncope occurred at the time of blood drawing and was attributed to a vasovagal responses. In two of these subjects the event occurred 4 hours after dosing; in a third subject the timing of the event is unknown. The sponsor reports that in one of these subjects first degree heart block developed during the trial. A review of the case report forms reveal that sinus bradycardia and sinus arrhythmia was also present however these may be completely normal findings and the ECG with AV block was taken 5 months prior to the syncopal episode.

In the fourth subject, syncope occurred almost every other day beginning at week 9 of the 13 week trial and usually occurred in conjunction with coughing and chest pain. The subject's ECG and lab tests did not vary significantly over the course of the trial and after the trial it was determined that he had a 2 year history of cough induced syncope and seizures. The investigator and sponsor attributed the subject's syncope episodes to his prior history with a possible lowering of the seizure threshold by theophylline and possible study drug. The sponsor's explanation in this case and the three others are adequate.

Over all, the incidence of syncope reported in the NDA in the pharmacokinetic (each single dose exposure is counted as a patient), single dose and multiple dose asthma trials was .6% in the Azelastine treated subjects and .2% in the placebo group. There were no cases of syncope among subjects who received positive controls. Although the incidence is a bit higher in the actively treated group the differences do not seem large and except for the subject with a history of hypoglycemia, all the events are adequately explained.

An additional 3 cases of syncope were reported in the annual report of March 24, 1992 and are described in the submission of April 15, 1992. The first subject was a 21 year old female with chronic asthma being treated with 4mg bid of Azelastine who experienced a 1 minute episode of syncope at work 2 days after starting therapy. The episode occurred 10 hours after her last azelastine dose. The submission states that the subject had not eaten all day and was under stress of being fired. Baseline ECG and a follow-up ECG one month later were normal and the subject continued in the trial for another seven months without complications. The second subject was a 16 year old male with asthma who was being treated with 4mg bid of Azelastine and experienced syncope about 6 months after randomization. The submission does not state the duration of time that elapsed between the last dose and the event. Neurological examination performed the same day and EEG performed 5 days later were normal. ECG's 1 1/2 months prior to and two weeks after the event were also normal. No etiology for the event is stated. The subject completed the trial one week later. The third case of syncope was a 50 year old male who experienced a 30 second syncopal episode associated

with coughing 2 months after being randomized to receive 4mg bid of Azelastine. ECG's performed one month prior to and two months after the event were normal. The subject continued in the trial for another 9 months without problem.

Of these adverse events, only the one associated with fasting and stress seems to be adequately explained. No reasonable explanation for syncope in the second subject is suggested although the duration of exposure prior to the episode (6 months), the negative neurologic workup and the fact that therapy continued without additional events is reassuring. Similarly, although coughing may be associated with syncope, the report does not mention if the subject had a history of cough induced syncope and no efforts were made to rule out other etiologies. Again, the duration of therapy prior to the event (2 months) and the fact that therapy was continued for another three months without event is reassuring.

With regard to the demographic analysis, the greater incidence of taste perversion and dry mouth in subjects older than 60 years is somewhat deceiving since there were only 12 subjects in this age group vs approximately 1200 subjects in the younger groups. Therefore, these higher incidences in the older group represents only 2-3 subjects and comparison with the younger groups would not be appropriate.

The demographic analysis does not reveal a particular group in which adverse events are more common although some of the groups analyzed are quite small.

LABORATORY DATA

Allergic rhinitis - U.S. trials (subjects older than 18 years):

The short term trials included 489 subjects on Azelastine, 141 on placebo and 146 on positive controls. In these trials the only statistically significant difference between the Azelastine group and placebo regarding out of normal range lab values was for triglyceride levels. 44.9% of subjects on Azelastine had a triglyceride level above normal vs 31.4% of placebo subjects, $P<.05$. The mean increase in triglyceride levels for subjects on Azelastine was 87.71mg/dl, from a baseline of 139.96mg/dl to 226.66mg/dl. In the placebo group the mean increase was 53.28mg/dl from a baseline of 129.64mg/dl to 182.92mg/dl. This was also the only lab parameter for which a significant difference between the two groups was noted regarding the incidence of exceeding the incremental delta limit of 145mg/dl (22.5% vs 14.9%, $P\leq.05$).

Labs for which the change from baseline to endpoint was significantly different in the two treatment groups and the change was either greater in the Azelastine group or in an opposite direction compared to placebo included trigiycerides (87.7

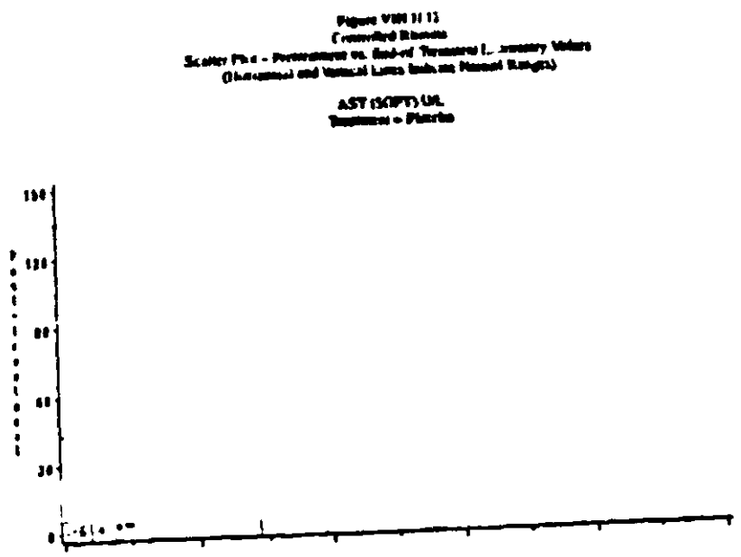
vs 53.28, P=.0095), neutrophils (-2.00% [Azelastine] vs 0.63%, P=.0099) and lymphocytes (1.30 [Azelastine] vs -1.38, P=.0041). The changes noted in neutrophil and lymphocyte levels were dose related.

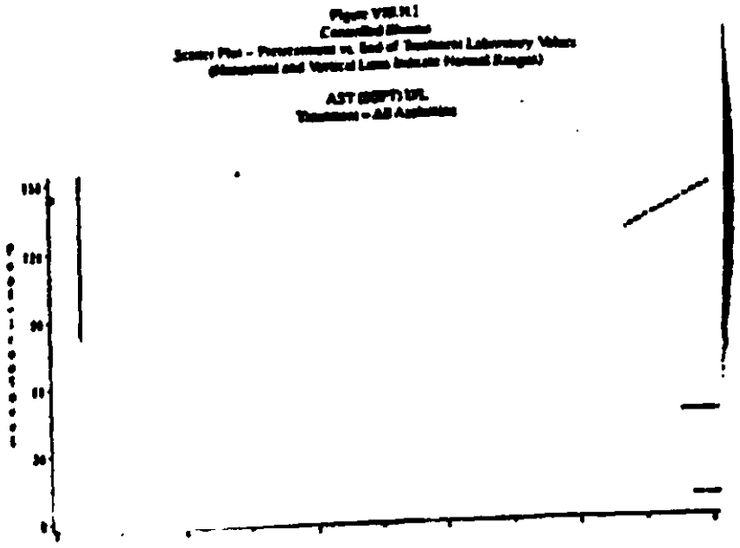
The long term trials included 766 subjects on Azelastine, 567 on placebo and 379 on positive controls. There were no lab values for which the rate of exceeding the normal range significantly differed between the two groups. In these studies the incidence of elevated triglyceride levels was 14.13% in Azelastine treated subjects vs 9.4% in placebo treated subjects. However, the change from baseline to endpoint was significantly different in the treated group vs placebo 16.4mg/dl vs 1.7mg/dl, P=.0443

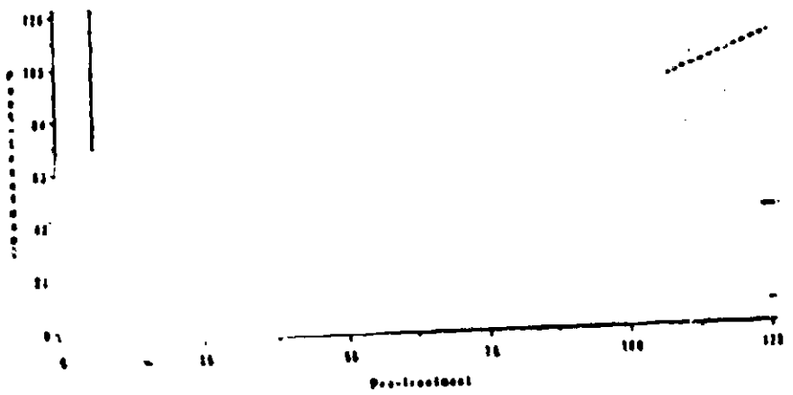
The only parameter for which there was a statistically significant difference in the incidence of exceeding the delta limit was the SGOT incremental limit (11U/L) in which 7.0% of Azelastine subjects exceeded the limit vs 3.3% of placebo subjects. Change of SGOT from baseline to endpoint was also significant different in treated subjects vs the placebo group .61 vs -1.24 (P=.0171) respectively. A trend toward a statistically significant difference in change from baseline to endpoint for SGPT was also noted (2.09 vs 0.39, P=.0791).

With regard to these lab parameters, the following pages depict scatter plots of pre-treatment v.s. post-treatment LFT's. The data is presented for both allergic rhinitis trials as well as asthma trials. Following the scatter plots are graphs depicting the time course of the change from baseline for SGOT, SGPT, alkaline phosphatase and LDH in the rhinitis and asthma studies.

SGPT







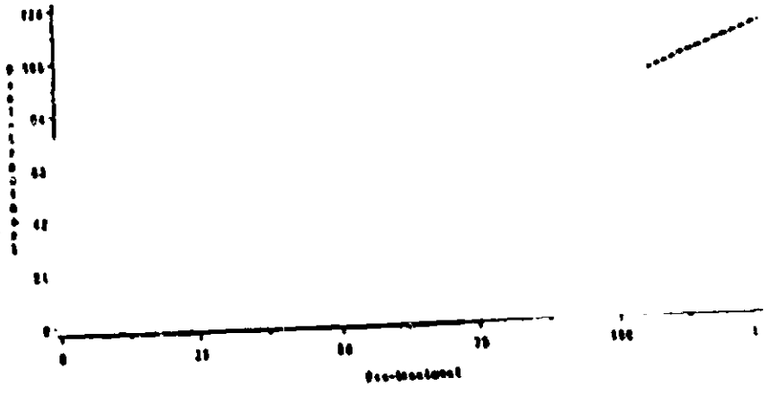


Figure VIII.H.24
Controlled Rhinitis (NDA Studies 55, 56, 67 and 68)
Lab Parameter – SGPT U/L
Subjects 18 and Older

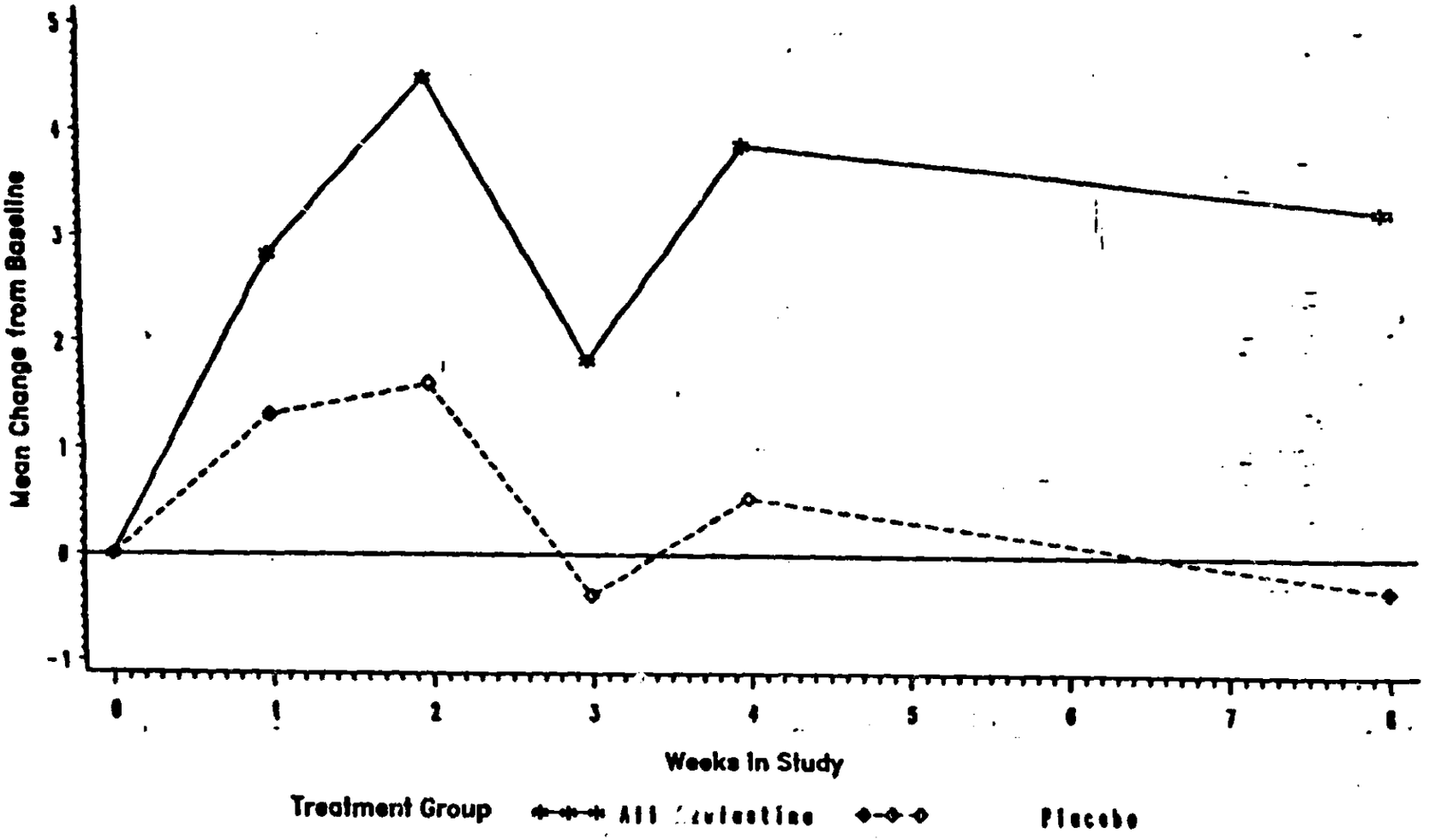
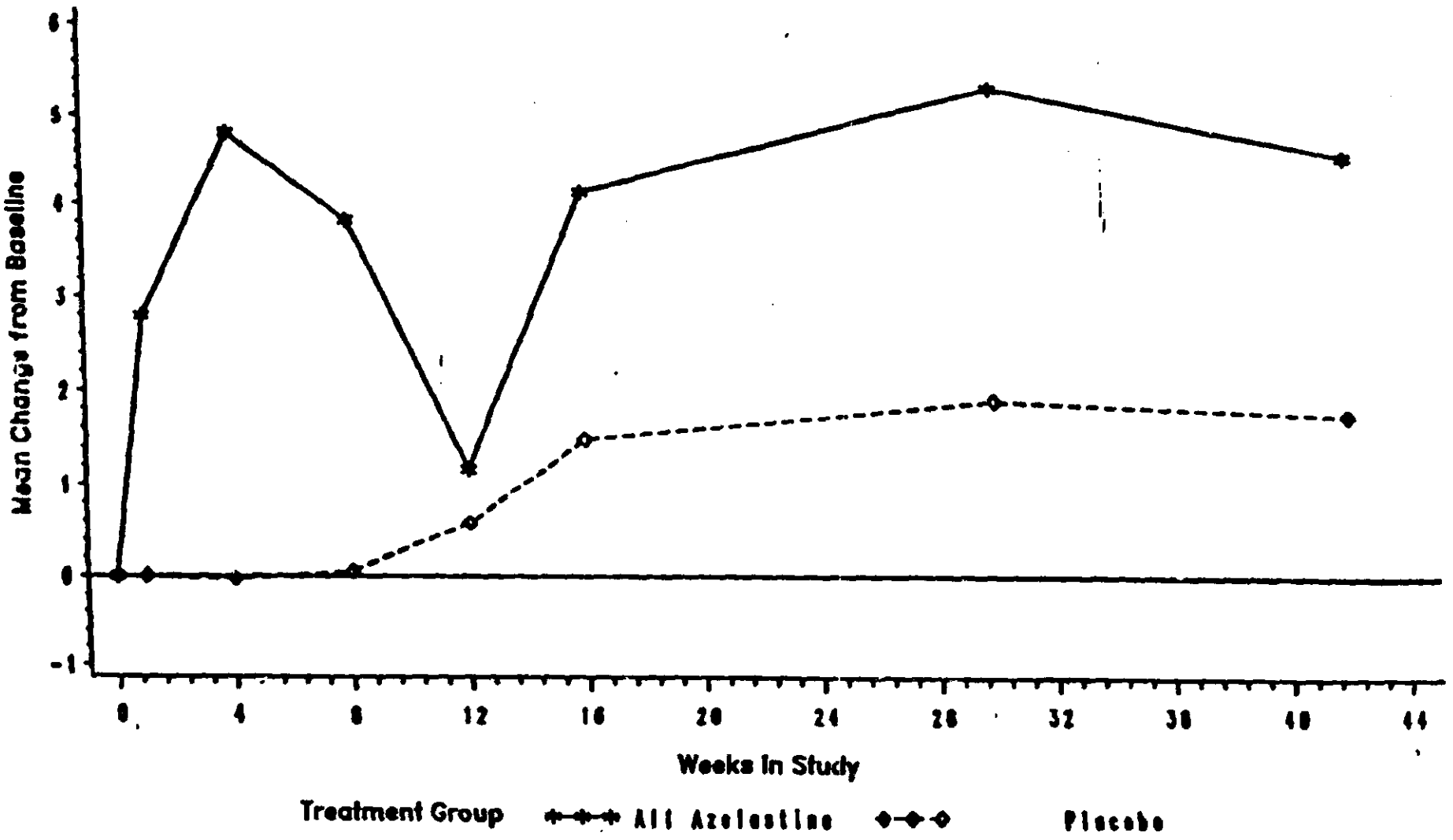
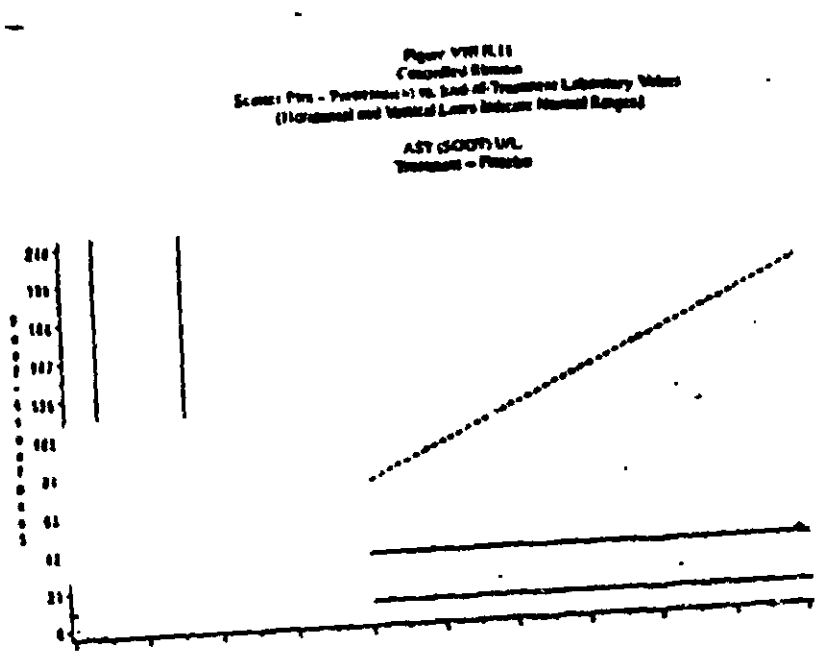
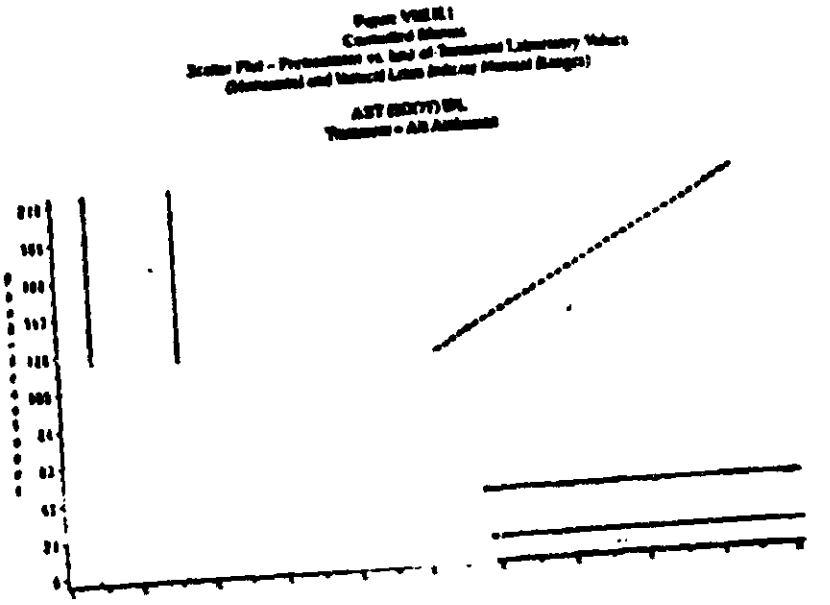
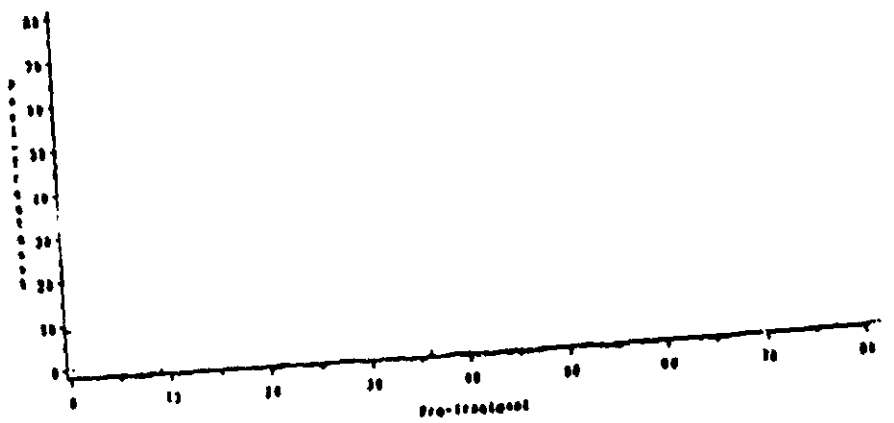


Figure VIII.H.49
Controlled Asthma (NDA Studies 23, 24, 189, 97 and 98)
Lab Parameter – SGPT U/L
Subjects 18 and Older









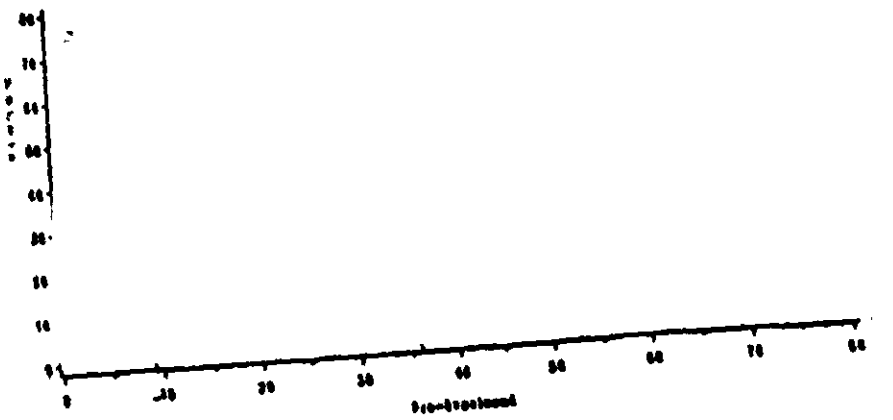


Figure VIII.H.48
Controlled Asthma (NDA Studies 23, 24, 189, 97 and 98)
Lab Parameter – SGOT U/L
Subjects 18 and Older

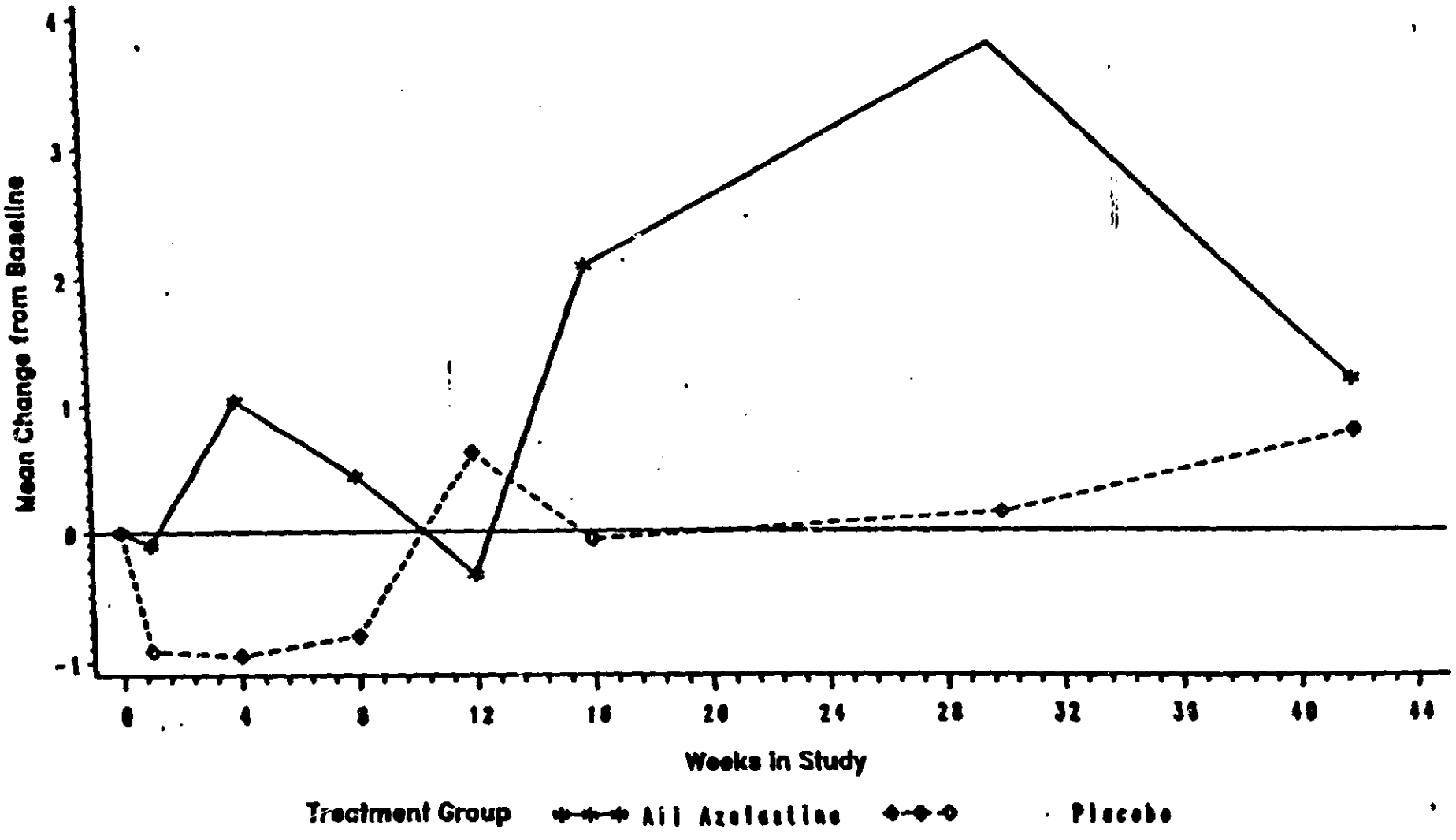
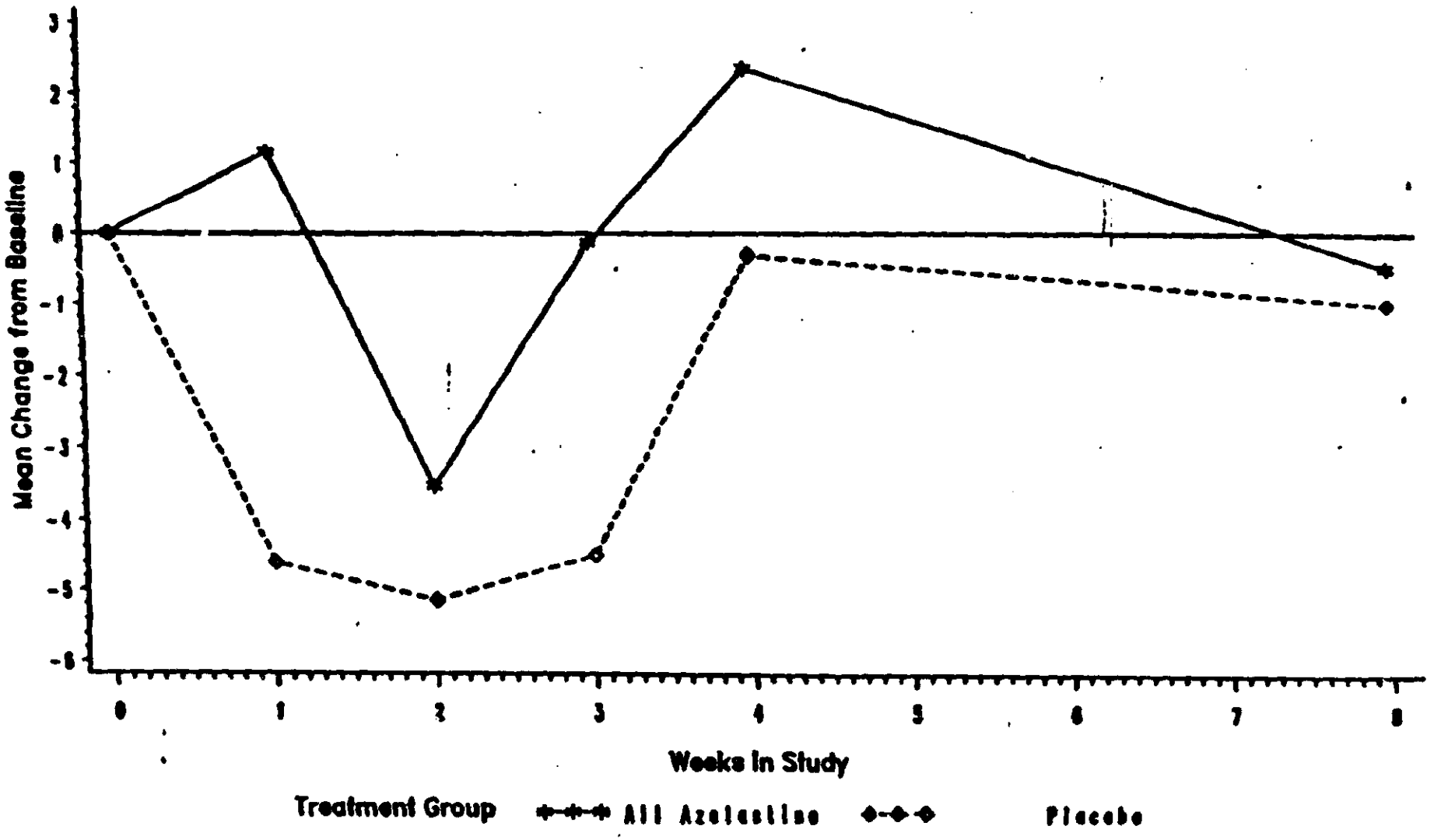
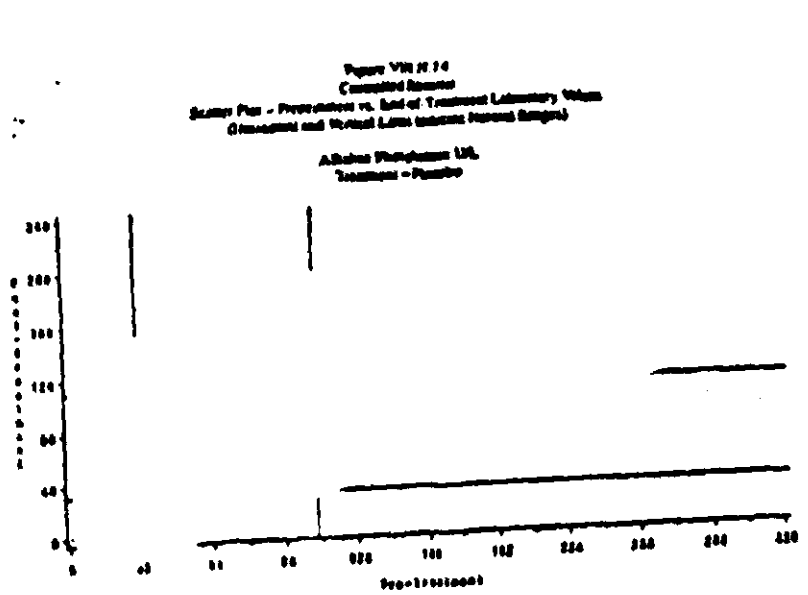
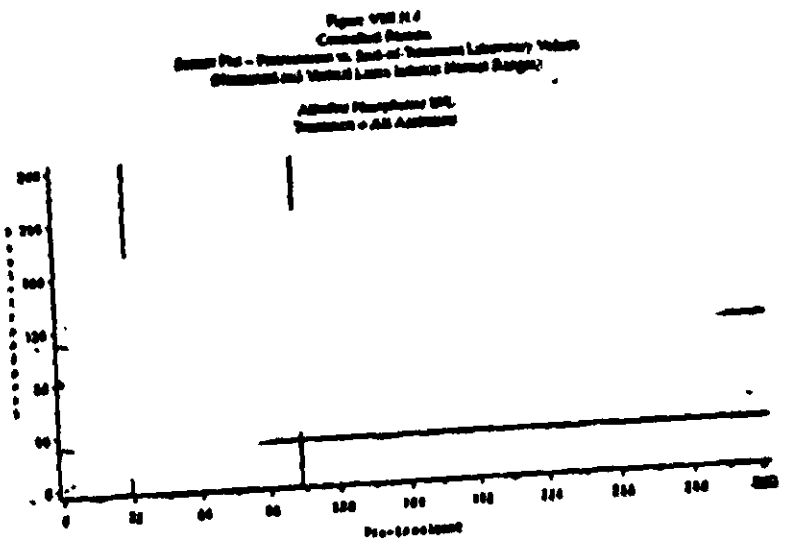


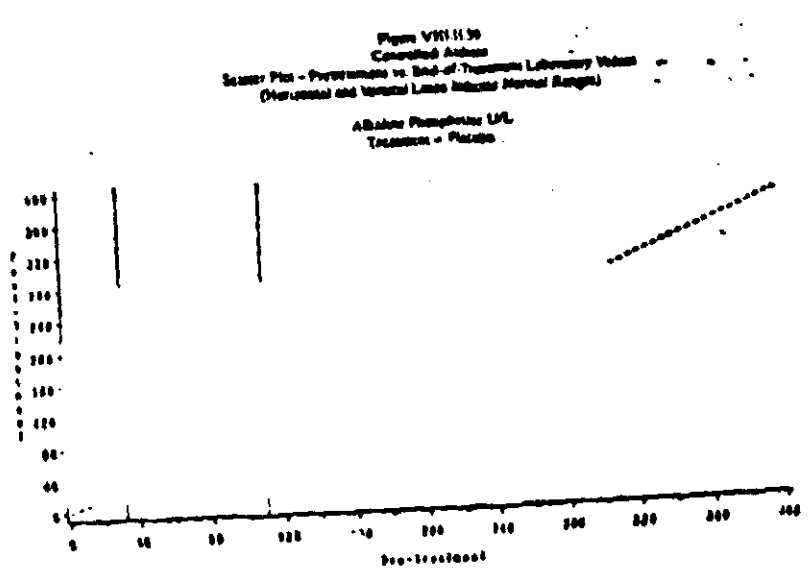
Figure VIII.H.23
Controlled Rhinitis (NDA Studies 55, 56, 67 and 68)
Lab Parameter = SGOT U/L
Subjects 18 and Older



Alkaline Phosphatase







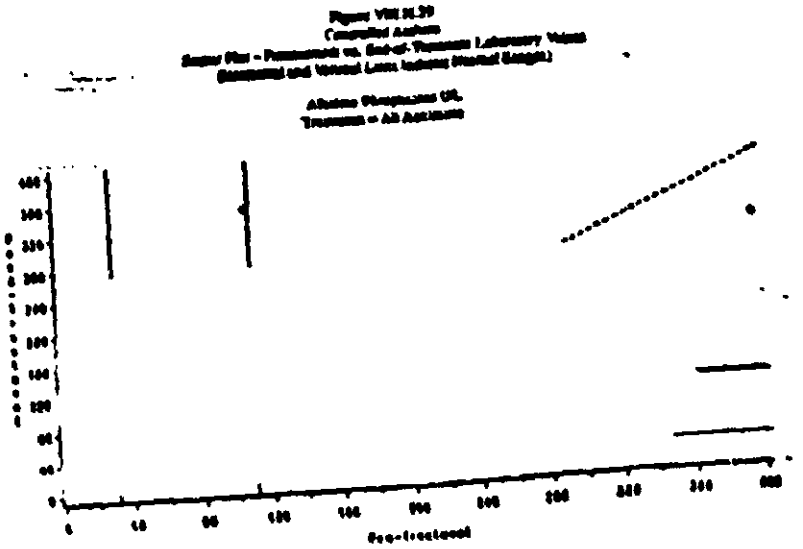


Figure VIII.H.46
Controlled Asthma (NDA Studies 23, 24, 189, 97 and 98)
Lab Parameter – Alkaline Phosphatase U/L
Subjects 18 and Older

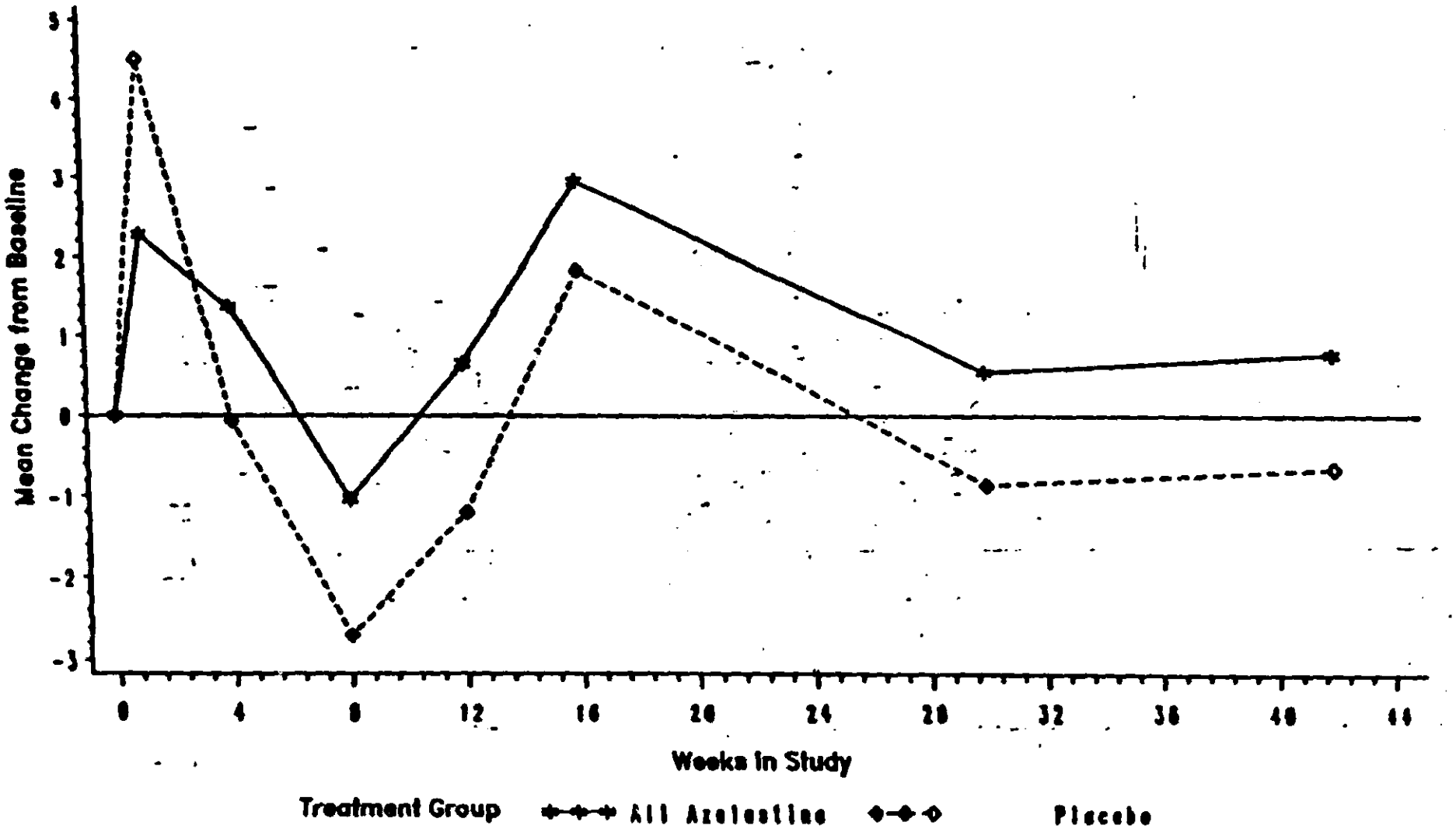
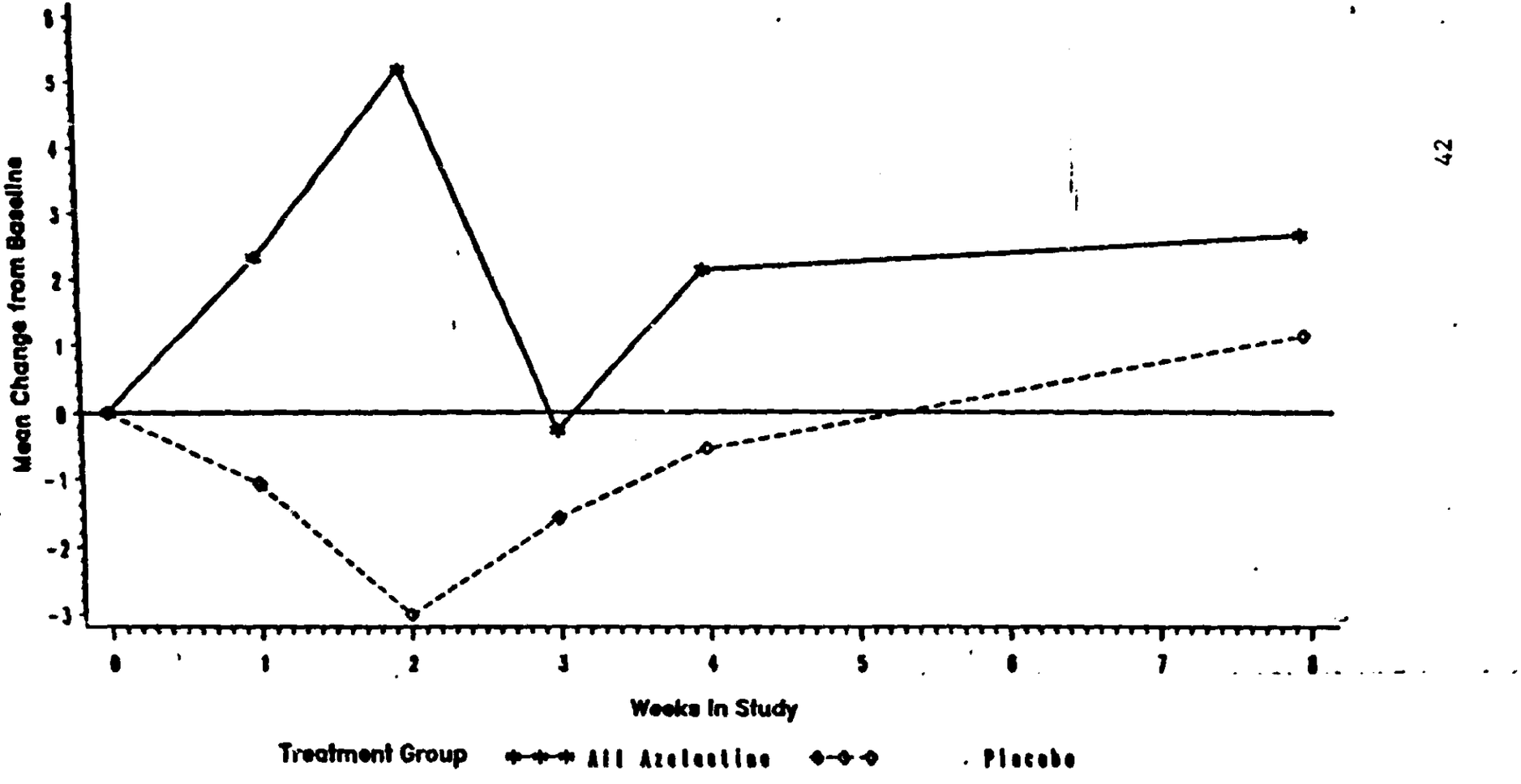
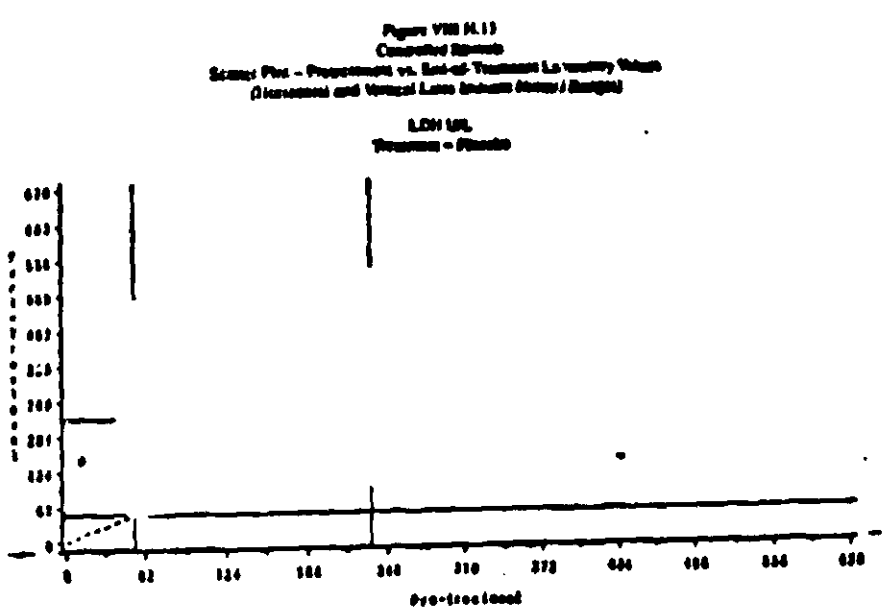
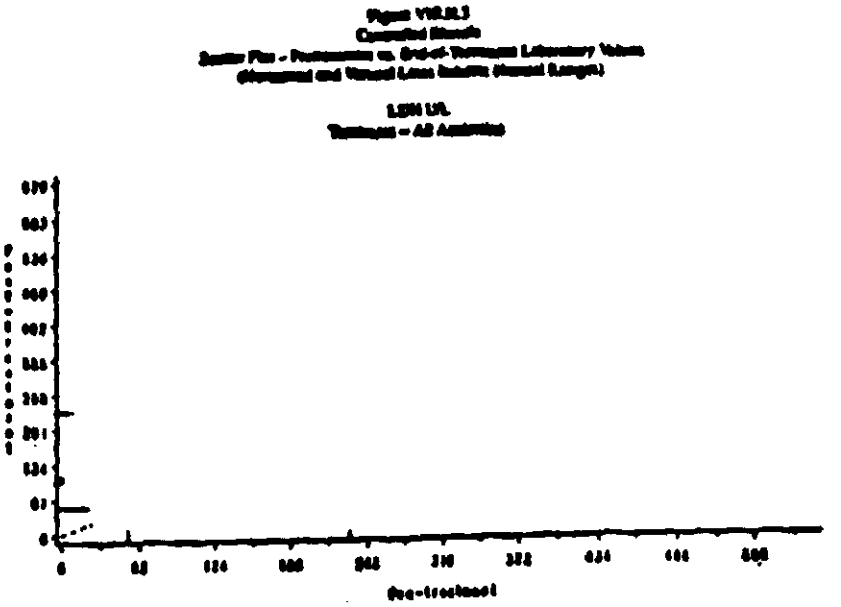
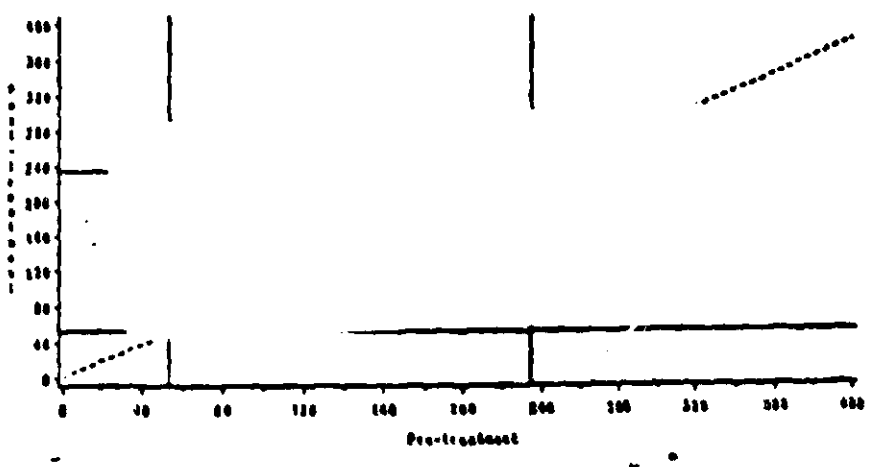


Figure VIII.H.21
Controlled Rhinitis (NDA Studies 55, 56, 67 and 68)
Lab Parameter – Alkaline Phosphatase U/L
Subjects 18 and Older




LDH U/L
Pre-treatment


LDH U/L
Pre-treatment


LDH U/L
Pre-treatment

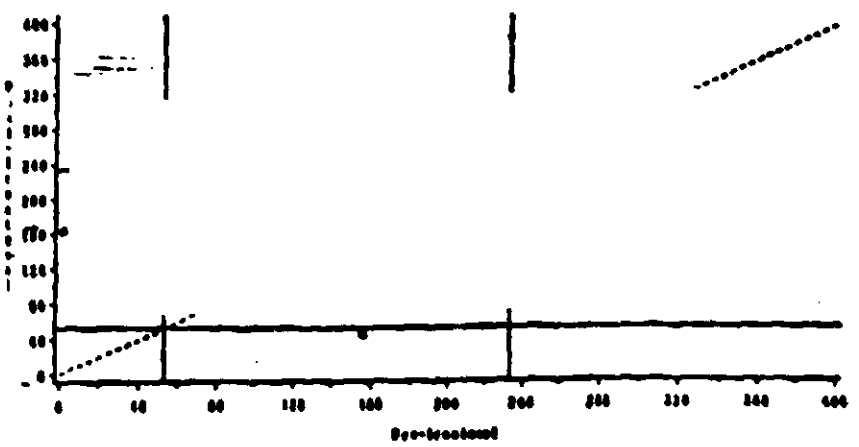

LDH U/L
Pre-treatment

Figure VIII.H.22
Controlled Rhinitis (NDA Studies 55, 56, 67 and 68)
Lab Parameter – Lactic Dehydrogenase U/L
Subjects 18 and Older

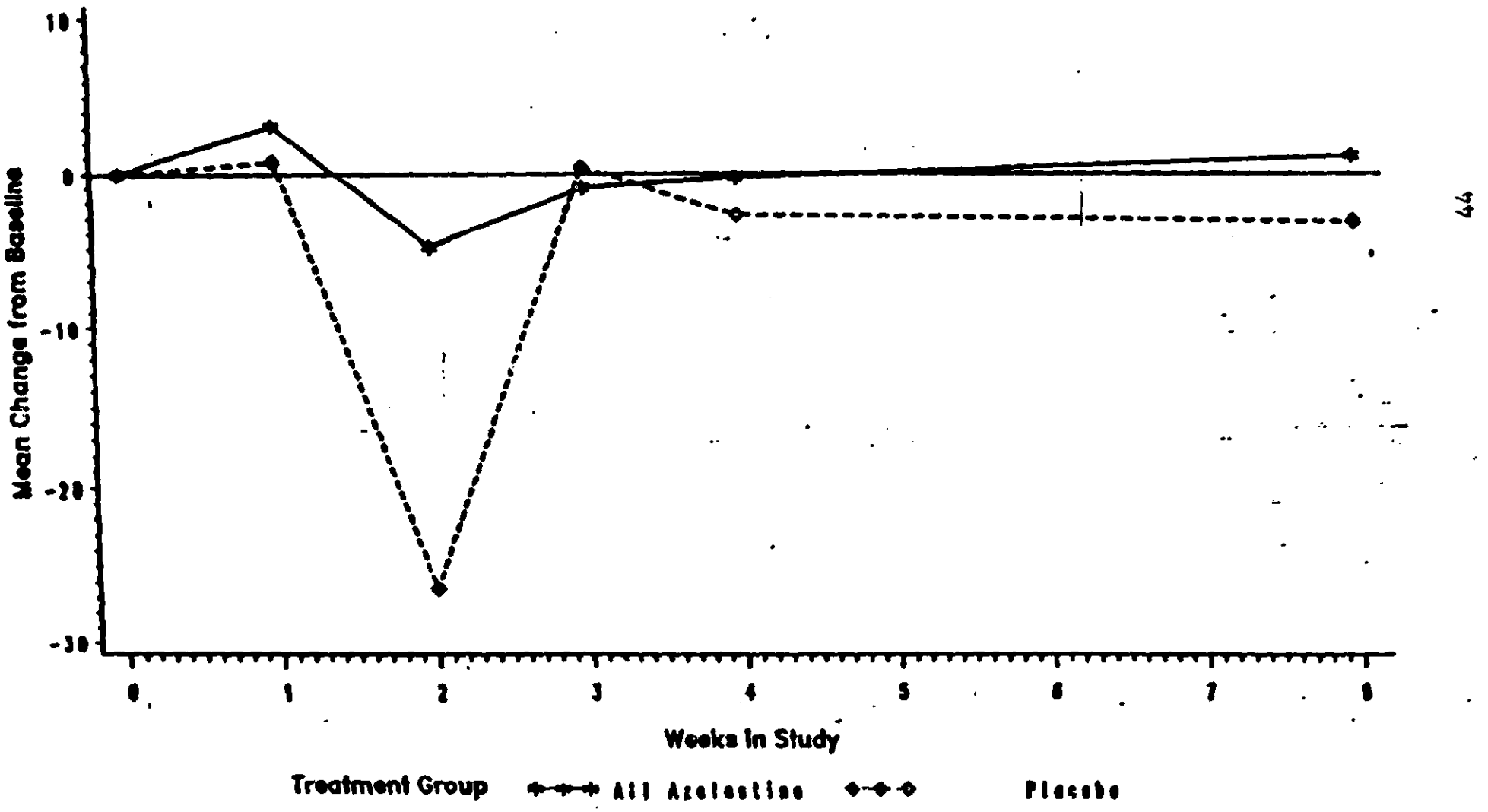
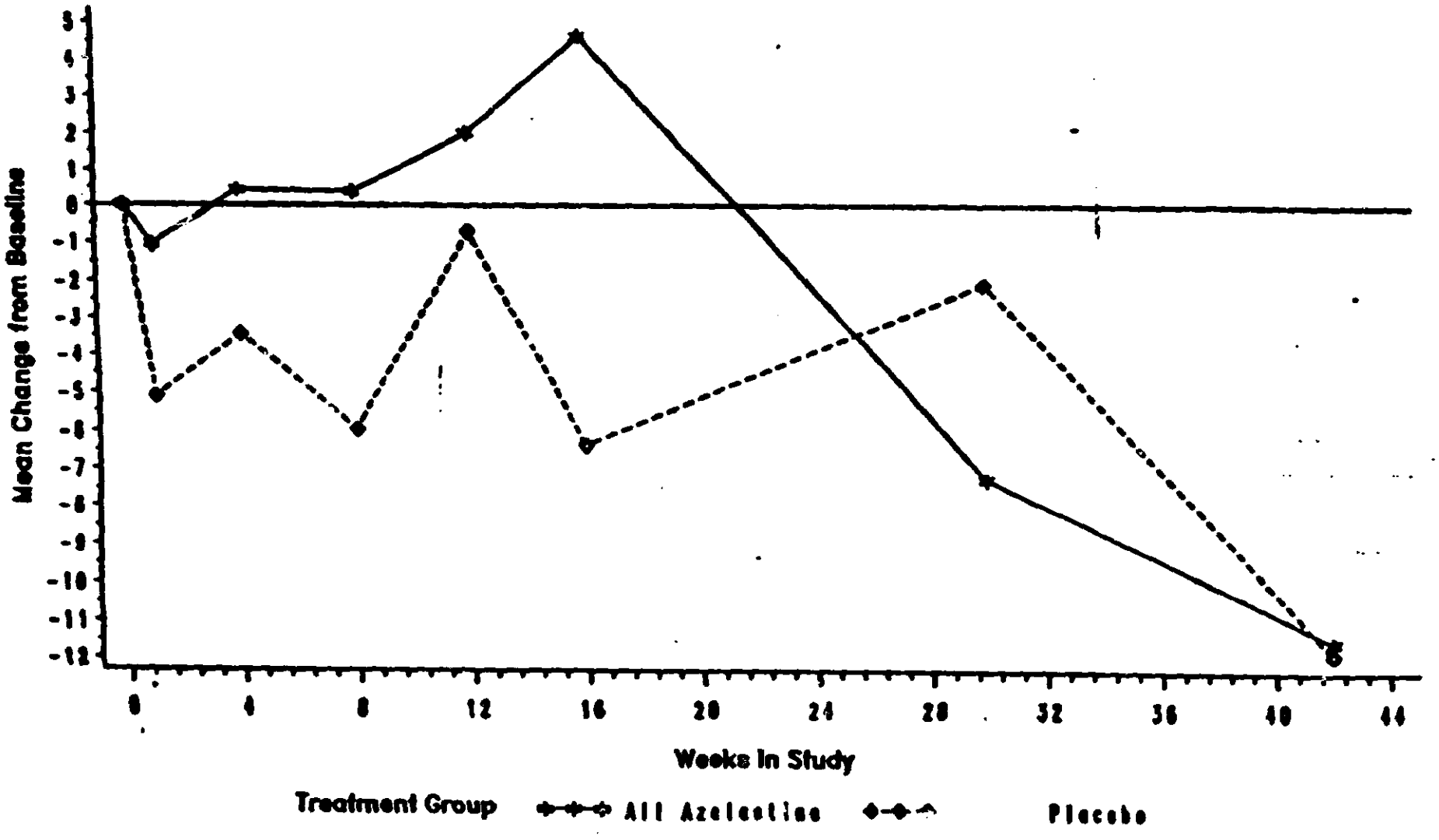
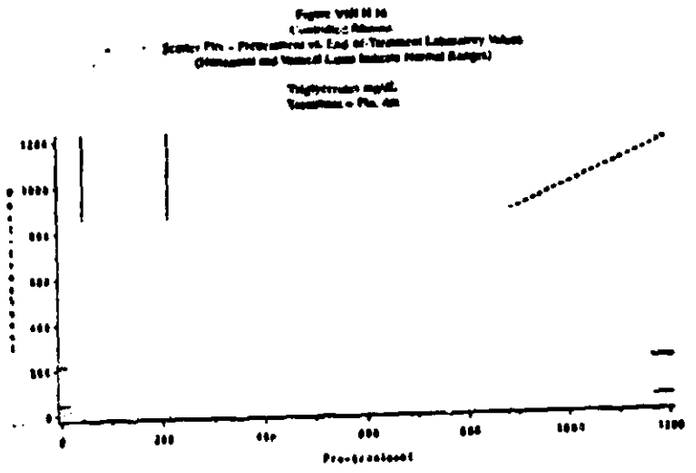


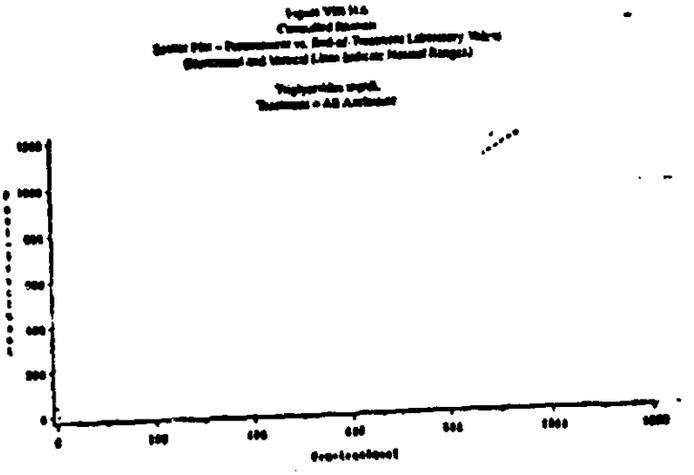
Figure VIII.H.47
Controlled Asthma (NDA Studies 23, 24, 189, 97 and 98)
Lab Parameter = Lactic Dehydrogenase U/L
Subjects 18 and Older

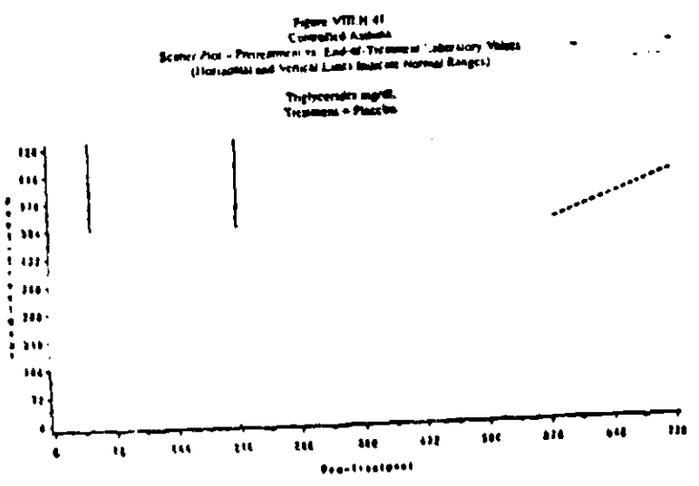


With regard to triglycerides, the follow scatter plots and time graph depict the changes in this parameter:

Triglycerides







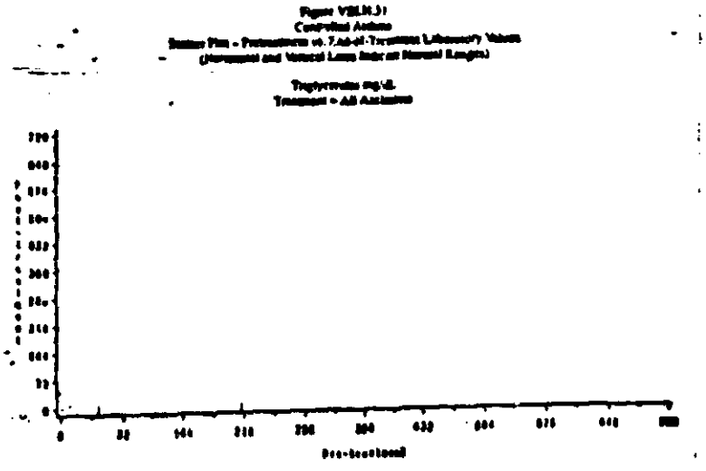


Figure VIII.H.50
Controlled Asthma (NDA Studies 23, 24, 189, 97 and 98)
Lab Parameter – Triglycerides mg/dL
Subjects 18 and Older

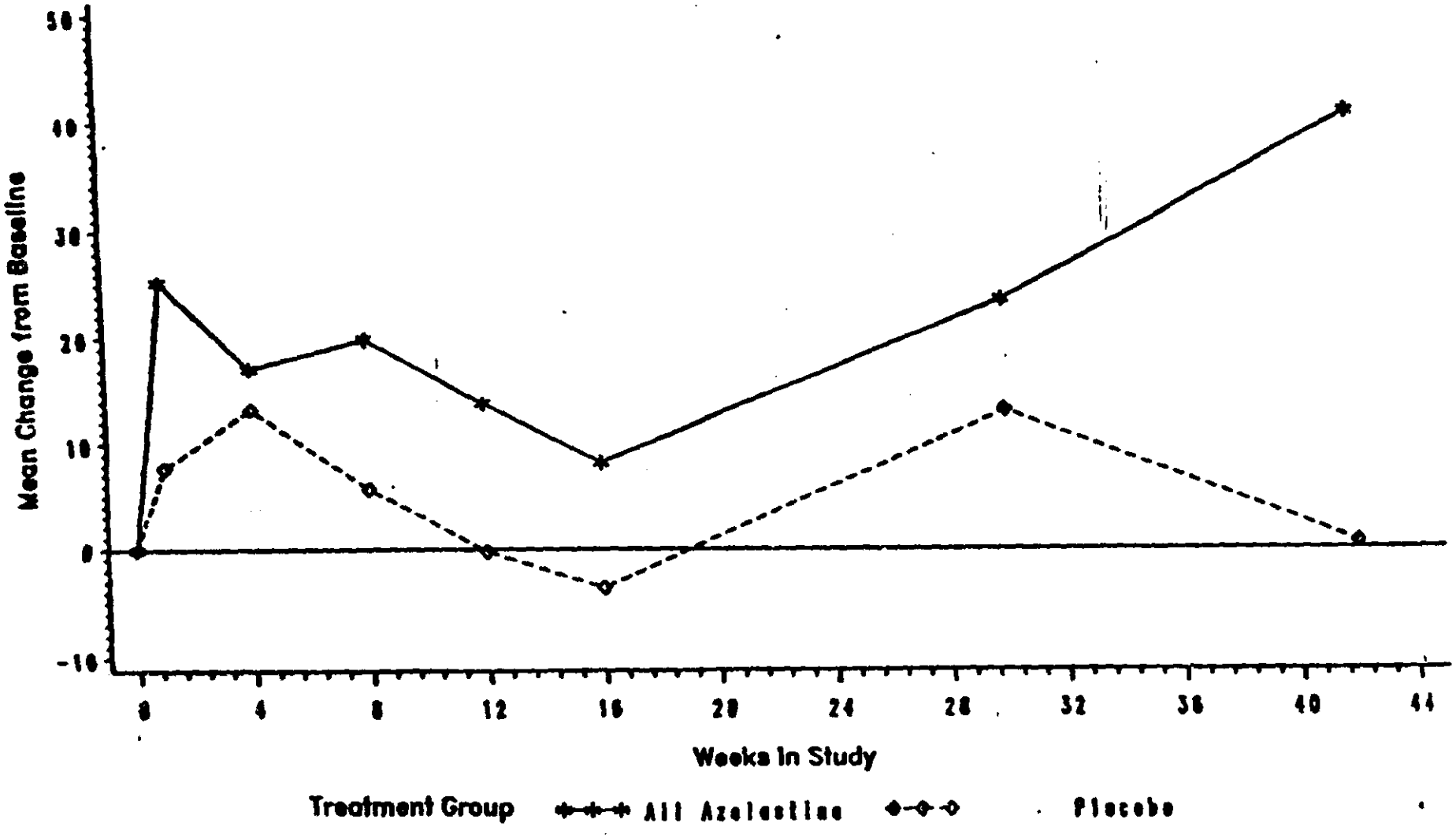
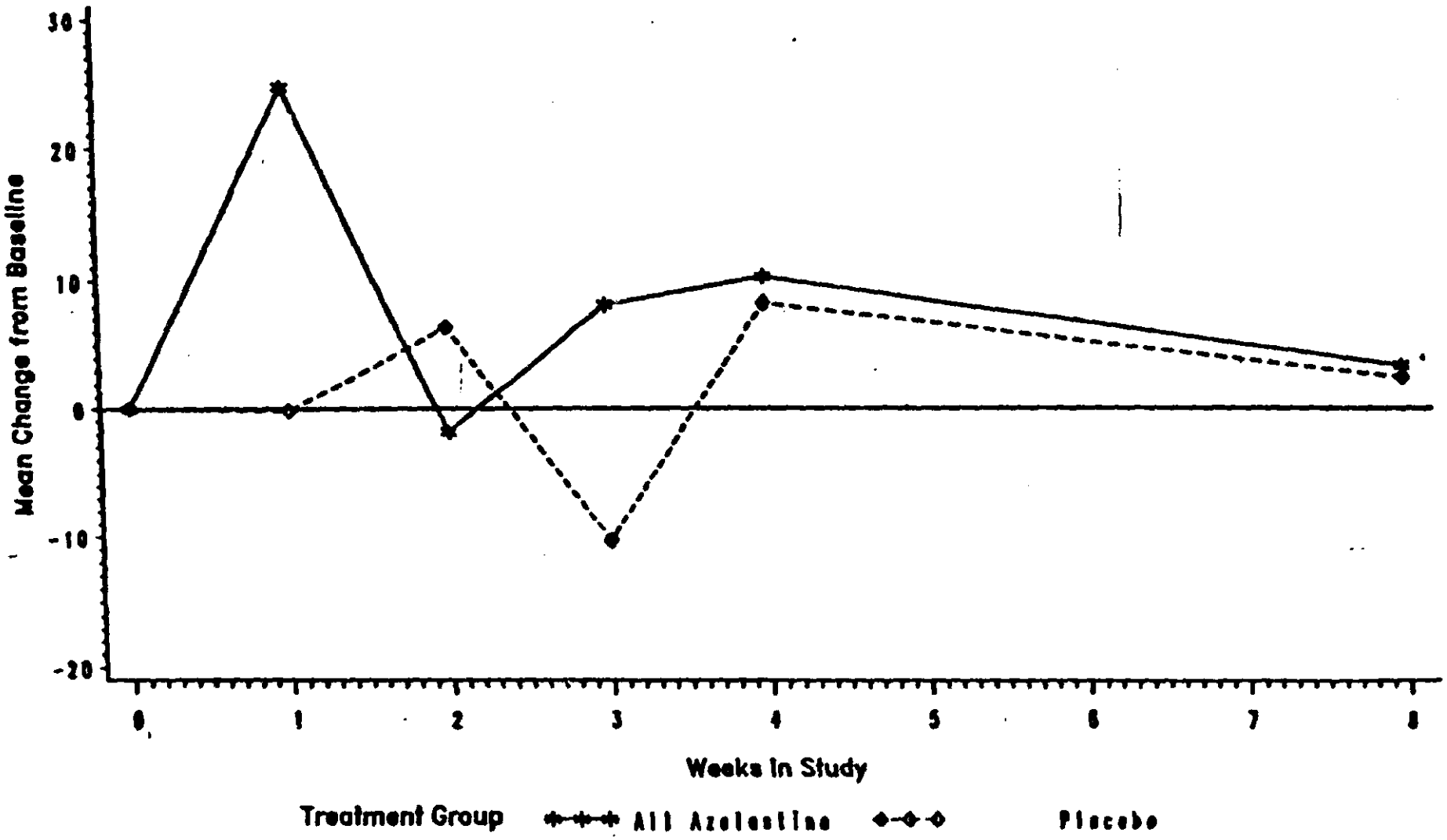


Figure VIII.H.25
Controlled Rhinitis (NDA Studies 55, 56, 67 and 68)
Lab Parameter – Triglycerides mg/dL.
Subjects 18 and Older



The sponsor reports that for the combined data from the long and short term trials, the greatest incidence of out of normal range laboratory tests for triglyceride levels was during the first week of exposure. The sponsor also states that the differences in triglyceride level changes between the long and short term studies probably reflects the fact that in the short term trials blood samples were more often obtained at a time reflecting post prandial elevations. In addition, although the differences between the treated group are statistically significant, they are not clinically significant.

Demographic Analyses - Rhinitis Studies

Age:

No significant adverse effects are reported in a subgroup of patients under age 18 years, however, there were only 30 treated subjects in this subset.

For the subset of patients older than 60 years, the mean change in triglyceride values from baseline was 135mg/dl vs 62.30 in treated subjects age 18-60, however, this data is based on only 5 subjects over 60 vs 696 subjects in the younger group.

Gender:

There was no difference based on sex with regard to the incidence of out of normal range labs. Although the sponsor reports that the incidence of elevated triglyceride levels was greater in men than in women, 37.8% vs 25.9%, a similar difference was also noted in the placebo arm, 22.9% vs 9.6%. The mean change in triglyceride levels was also greater in men than in women for both treatment arms.

Weight (<110lb, 110-170lb and ≥170lb):

The incidence of elevated triglyceride levels was greater in the upper weight group vs the lower groups, 43.8% vs 29.5% and 28.6%. This difference by weight group was not noted in the placebo arm. Similarly, triglyceride change from baseline was greater in the >170lb group than the other two groups, 81.23mg/dl vs 51.10 and 55.43mg/dl.

Race:

No differences based on race are reported.

31 Pages

Purged

Martin H. Himmel, M.D.
Medical Reviewer

cc:

NDA
HFD-150/Division File
HFD-150/Div Dir/Burke
HFD-150/Medical Reviewer/Himmel
HFD-150/Reviewers/Honig/Chun
HFD-151/CSO/Riley/Schumaker

3/6/93

Statistical Review and Evaluation

NDA #: NDA 20-114 OCT 29 1993

Applicant: Wallace Laboratories

Name of Drug: Astelin (azelastine hydrochloride) 0.1% Nasal Spray

Indication: Treatment of the symptoms of seasonal allergic rhinitis

Documents Reviewed: Volumes 1.1, 1.248-1.253, 1.262-1.266,1.273-1.279,and 1.287-1.288 dated March 26,1991; 10 unnumbered volumes dated February 19, 1993; and 3 unnumbered volumes dated August 18,1993.

The medical officer for this submission is M. Himmel, M.D. (HFD-155) with whom this review was discussed.

This review pertains to the review of 3 studies in seasonal allergic rhinitis.

I. BACKGROUND

The sponsor in the March 26, 1991 submission had combined AM and PM assessments. The sponsor was asked to provide separate analyses for the AM and PM symptom scores. These were provided in the February 19,1993 submission. The medical officer also requested a revised symptom score be provided which included only symptoms itchy nose, post-nasal drip, watery eyes, itchy eyes/ears/throat/palate (i.e. secondary symptoms specific to allergic rhinitis).

The sponsor originally analyzed improvements from baseline for the symptom scores in these studies with an analysis of covariance model using factors center and treatment and baseline assessment as covariate. The sponsor stated that center by treatment interaction was not included because it was not significant in any analysis. The submission of February 19, 1993 analyzed the improvements from baseline for the AM and PM and AM/PM combined assessments of symptoms using the same analysis of covariance model with factors treatment and center with baseline symptom score as covariate. Although the treatments did not differ significantly in mean symptoms scores at baseline, the covariate was highly significant in almost all models fit. If this covariate is not included in the model, the error variability to test whether treatments are different in improvements from baseline is too high. This reviewer requested the P-values to test treatment by center interaction be provided to verify the sponsor's omitting this term from their model and,

furthermore, requested the sponsor provide P-values to test whether all treatment groups had equal covariate slopes. The sponsor supplied these P-values in their August 18 ,1993 submission which showed that treatment by center interaction was not a problem in these studies (only 1 interaction, post-nasal drip at Week 1 in Study 31, was significant among the 10 symptoms or symptom complexes analyzed in these 3 studies). Furthermore, the results for the testing of equivalence of covariate slopes showed that it was adequate to assume that all treatments had the same slope. (Although there was significant heterogeneity in Study 31 for the revised symptom complex and stuffy nose at Week 2 only, adding treatment by baseline term to the model did not change least squares means or the P-values comparing least squares means for these two analyses.) This review will focus, therefore, on the results of this analysis of covariance model on improvements from baseline with factors treatments and center and baseline symptom score as covariate.

In this review a P-value will be stated to be significant if $P \leq 0.05$, and will be stated to be nearly significant if $0.05 < P \leq 0.10$. Nearly significance will be claimed only for the comparisons of active drug with placebo because they might reflect on the efficacy of azelastine. Nearly significance will not be claimed for comparisons between active treatments. Moreover, only significant differences will be discussed in the overall conclusions section.

II. Seasonal Allergic Rhinitis Studies

A. STUDY 26

1. Study Description

This was a 2 week, multi-center, dose response trial comparing azelastine two sprays/nostril q.d., azelastine two sprays/nostril b.i.d., placebo and oral chlorpheniramine 12 mg b.i.d. (Chlor-Trimeton Repetabs) in patients with seasonal allergic rhinitis. Treatments were masked using double dummy techniques. The azelastine q.d. dose was given at 8 AM with placebo given at 8 PM and the b.i.d. doses were given at 8 AM and 8 PM.

The patient assessed symptoms of rhinitis on a daily diary card at the time of each dosing. The assessment of nose blows and sneezes was a scale listing the number of nose blows or sneezes, a reflective assessment. [The scale used was: 0=none, 1=1-3 (mild), 2=4-6 (modest),3=7-10 (moderate), 4=11-15 (moderately severe), 5=>15 (severe). The other symptoms (itchy nose, runny nose/sniffles, post-nasal drip, watery eyes, stuffy nose, cough, itchy eyes/ears/throat/palate) were assessed on a 6-point scale:

0=<u>none</u>:symptoms were not present during any portion of day or

night,
1=mild:symptoms were present during a small part of the day or night, were barely noticeable and did not interfere in any way with activities during the day or night,
2=modest:symptoms were present during the day or night, were noticeable, but did not interfere with any activities during the day or night,
3=moderate:symptoms were present during the day or night, were somewhat bothersome and interfered slightly with activities during the day or night,
4=moderately severe:symptoms were present during the day or night, interfered significantly with activities, but did not prevent normal daytime or nighttime activities,
5=severe:symptoms were essentially continuously present during the day or night and were a constant distraction which prevented normal daytime or nighttime activities.

The sponsor averaged daily AM assessments over each week and daily PM assessments over each week and then averaged AM and PM assessments. [The first week's PM assessments did not include the first PM assessment, as it was a no medication assessment, but included the first PM assessment of the second week.] The total and revised symptom complexes were determined by summing the daily average severity scores for individual symptoms for each week.

The sponsor's protocol defined total symptom score as the primary efficacy variable. Total symptom complex included all symptoms except stuffy nose.

To enter the study the sum of the AM and PM rhinitis symptom severity scores of the Major Symptom Complex (sneezes, runny nose/sniffles, nose blows, itchy nose and watery eyes) was to be at least 10 on any four days of the baseline period and at least one of the symptoms was to be of moderate or greater intensity on each of the four days. Major symptom complex will not be discussed further in this review.

In consultation with the medical officer it was decided to focus the review for this study on the following symptoms and symptom complexes: runny nose/sniffles, sneezes, stuffy nose, revised symptom complex, and total symptom complex. The total symptom complex is still somewhat questionable because it contains some symptoms that might not be appropriate to seasonal allergic rhinitis (nose blows and cough), and nose blows and sneezes are only on the same scale as the other symptoms if one accepts the sponsor's scaling for these symptoms. The AM/PM Combined analyses will mainly be discussed because the results from the AM and PM analyses were fairly similar and since the combined analysis results represent the overall 24 hours of treatment. [Both AM and PM assessments are reflective over the time since last

treatment.] A separate table of the P-values for the azelastine q.d. comparison with placebo (AM and PM) will be provided since it might be expected that the PM results might be more favorable than the AM results.

2. Results

There were 247 patients (61 azelastine q.d.,63 azelastine b.i.d., 62 chlorpheniramine, and 61 placebo) who were randomized into the trial at 5 centers. There were 17 patients (6 azelastine q.d.,2 azelastine b.i.d.,2 chlorpheniramine, and 7 placebo) who failed to complete the study. Four patients (2 azelastine q.d., 1 azelastine b.i.d. and 1 chlorpheniramine) withdrew because of adverse experiences. Five (2 azelastine q.d.,1 chlorpheniramine, and 2 placebo) withdrew because of treatment failure. Two patients (1 azelastine q.d. and 1 placebo) were lost to follow-up without providing any effectiveness data.

The treatment groups were comparable at baseline in demographic variables and total symptom complex. The sponsor did not provide the other comparisons of treatment groups at baseline for the individual symptom assessments. [Since analyses of covariance were the method of analysis, the analyses would adjust for differences at baseline, therefore it is not important that the sponsor did not provide these analyses.]

Tables 1,2,3,4,5 contain the adjusted treatment means and P-values comparing treatments with placebo for revised symptom complex, sneezes, stuffy nose, runny nose/sniffles and total symptom complex, respectively. Azelastine q.d. was not significantly different from placebo for either week for these symptoms or symptom complexes. Both azelastine b.i.d. and chlorpheniramine were more effective than placebo at Week 1 for all these symptoms or symptom complexes. Azelastine b.i.d. was more effective than placebo at Week 2 only for runny nose/sniffles whereas chlorpheniramine was more effective than placebo for all these symptoms or symptom complexes. Azelastine b.i.d. was, however, nearly significantly different from placebo at Week 2 for revised symptom complex, sneezes and total symptom complex.

Azelastine b.i.d. was more effective than azelastine q.d. for total symptom complex , stuffy nose and runny nose/sniffles at Week 1. Chlorpheniramine was more effective than azelastine 2 spray q.d. at Weeks 1 and 2 for total symptom complex, revised symptom complex, sneezes, and runny nose/sniffles; and for stuffy nose at Week 1. Chlorpheniramine was significantly different from azelastine b.i.d. at Weeks 1 and 2 for sneezes.

Table 6 contains the P-values for the AM and PM comparisons of azelastine q.d. with placebo for this study. Although the P-values for the PM assessments are slightly lower than those of

the AM assessments, there is no evidence that the q.d. dose of azelastine is effective at even the first 12 hours after dosing. The b.i.d. dose of azelastine had similar AM and PM P-values (not shown here) and both showed efficacy.

3. Reviewer's Comments

The azelastine q.d. dose has failed to demonstrate efficacy. The azelastine b.i.d. dose has demonstrated efficacy in this study. Chlorpheniramine has shown more efficacy than either dose of azelastine in this study. It was significantly more effective than azelastine q.d. for almost all assessments and for azelastine b.i.d. for sneezes at Weeks 1 and 2.

B. STUDY 31

1. Study Description

This study was similar to Study 26. The definitions of severity assignments for the assessments were slightly modified but the changes were minor.

2. Results

There were 251 patients (62 azelastine q.d.,63 azelastine b.i.d., 62 chlorpheniramine, and 64 placebo) who were randomized into the trial at four centers. There were 15 patients (5 azelastine b.i.d., 3 chlorpheniramine, and 7 placebo) who failed to complete the study. Three patients (2 azelastine b.i.d. and 1 placebo) withdrew because of adverse experiences. Four (1 azelastine b.i.d. and 3 placebo) withdrew because of treatment failure. One subject randomized to placebo was lost to follow-up and one subject randomized to chlorpheniramine withdrew due to intercurrent illness and, therefore, no effectiveness data is available for these patients.

The treatment groups were comparable at baseline in baseline efficacy variables and in demographic variables except for weight where the azelastine b.i.d. group was on average over 10 pounds heavier than the other 3 groups. The difference in weight at baseline would have little effect on the efficacy results seen in this trial because the drug is a nasal spray.

Tables 7,8,9,10,11 contain the adjusted treatment means and P-values comparing treatments with placebo for revised symptom complex, sneezes, stuffy nose, runny nose/sniffles and total symptom complex, respectively. Azelastine q.d. was more effective than placebo for Week 1 for sneezes, runny nose/sniffles and total symptom complex. Azelastine q.d. was nearly significantly different from placebo for Week 1 for stuffy nose and revised symptom complex. Both azelastine b.i.d. and chlorpheniramine were more effective than placebo at Week 1 for revised symptom

complex, sneezes, runny nose/sniffles and total symptom complex. Chlorpheniramine was more effective than placebo at Week 1 for stuffy nose, also. Azelastine b.i.d. was more effective than placebo at Week 2 only for runny nose/sniffles and sneezes whereas chlorpheniramine was more effective than placebo for all these symptoms or symptom complexes. Azelastine b.i.d. was nearly significantly different from placebo at Week 2 for total symptom complex.

Chlorpheniramine was more effective than azelastine 2 spray q.d. at Weeks 1 and 2 for total symptom complex, revised symptom complex, sneezes, and runny nose/sniffles; and for stuffy nose at Week 2. Chlorpheniramine was more effective than azelastine b.i.d. for sneezes and stuffy nose at Week 2.

Table 12 contains the P-values for the AM and PM comparisons of azelastine q.d. with placebo for this study. The P-values for the AM and PM assessments are fairly similar. The P-values of the PM assessments were not lower as one would expect. The b.i.d. dose of azelastine had fairly similar AM and PM P-values (not shown here) and both showed efficacy except for stuffy nose.

3. Reviewer's Comments

This study showed some efficacy at Week 1 for the q.d. dose of azelastine. The b.i.d. dose of azelastine showed efficacy at both Weeks 1 and 2. Again chlorpheniramine is showing more efficacy than either dose of azelastine.

C. STUDY 33

1. Study Description

This study was similar to Study 26 except it was 4 weeks rather than 2 weeks. The definitions of severity assignments for the assessments were slightly modified from those of both Studies 26 and 31 but the changes were minor.

2. Results

There were 264 patients (66 azelastine q.d.,66 azelastine b.i.d., 65 chlorpheniramine, and 67 placebo) who were randomized into the trial in five centers. There were 30 patients (7 azelastine q.d., 8 azelastine b.i.d., 2 chlorpheniramine, and 13 placebo) who failed to complete the study. Four patients (2 azelastine q.d. and 2 chlorpheniramine) withdrew because of adverse experiences. Two (1 azelastine b.i.d. and 1 placebo) withdrew because of treatment failure. One subject in the placebo group was lost to follow-up and did not provide data to the efficacy analyses.

The treatment groups were comparable at baseline in demographic

variables and total symptom complex. The sponsor did not provide the other comparisons of treatment groups at baseline for the individual symptom assessments. [Since analyses of covariance were the method of analysis, the analyses would adjust for differences at baseline, therefore it is not important that the sponsor did not provide these analyses.]

Tables 13,14,15,16,17 contain the adjusted treatment means and P-values comparing treatments with placebo for revised symptom complex, sneezes, stuffy nose, runny nose/sniffles and total symptom complex, respectively. Azelastine q.d. was more effective than placebo only for revised symptom complex at Week 3. Azelastine q.d. was nearly significantly different from placebo for total symptom complex and sneezes at Week 3 and revised symptom complex at Week 4. Azelastine b.i.d. was more effective than placebo only for revised symptom complex at Week 4, sneezes and runny nose/sniffles at Week 1 and 3, and total symptom complex at Weeks 1 and 4. Azelastine b.i.d. was nearly significantly different from placebo for total symptom complex at Week 3 and sneezes at Week 4. Chlorpheniramine were more effective than placebo at all 4 Weeks for revised symptom complex, sneezes and total symptom complex and at Weeks 1,2 and 3 for stuffy nose and runny nose/sniffles.

Chlorpheniramine was more effective than azelastine q.d. for sneezes at all 4 weeks, for runny nose/sniffles at Weeks 1 and 2; and for total and revised symptom complex at Week 1.

Table 18 contains the P-values for the AM and PM comparisons of azelastine q.d. with placebo for this study. Although the P-values for the PM assessments are slightly lower than those of the AM assessments, there is only weak evidence that the q.d. dose of azelastine is effective at even the first 12 hours after dosing. The b.i.d. dose of azelastine had similar AM and PM P-values (not shown here).

3. Reviewer's Comments

Although a few significant differences or near significant differences were seen for the q.d. dose of azelastine compared to placebo, considering the number of comparisons done it is what might be expected from chance alone. The results for the b.i.d. dose were slightly more favorable to demonstrating efficacy but were not as convincing as was the results of Studies 26 and 31. Chlorpheniramine again showed more efficacy than the azelastine doses.

III. OVERALL CONCLUSIONS

Azelastine 2 sprays/nostril q.d. showed no significant differences from placebo for the symptoms or symptom complexes discussed in this review in Study 26, but was more effective than

placebo at Week 1 in Study 31 for sneezes, runny nose/sniffles and total symptom complex and in Study 33 for revised symptom complex at Week 3. Therefore, azelastine 2 sprays/nostril q.d. has not satisfied the requirement of two adequate and well-controlled studies demonstrating efficacy.

Azelastine 2 sprays/nostril b.i.d. was more effective than placebo in Study 26 for all the 5 symptoms or symptom complexes discussed in this review at Week 1 and for runny nose/sniffles at Week 2; in Study 31 for revised and total symptom complexes, sneezes and runny nose/sniffles at Week 1, and for runny nose/sniffles and sneezes at Week 2;and in Study 33 for revised symptom complex at Week 4, sneezes and runny nose/sniffles at Weeks 1 and 3 and for total symptom complex at Weeks 1 and 4. Azelastine 2 sprays/nostril b.i.d. has adequately demonstrated efficacy in these studies.

This reviewer believes that the superior efficacy of oral chlorpheniramine to azelastine 2 sprays/nostril b.i.d. (numerically in all studies and significantly ($P<0.05$) for sneezes at Weeks 1 and 2 in Study 26 and for sneezes and stuffy nose at Week 2 in Study 31) should be reflected in the labelling.

James R. Gebert, Ph.D.
Mathematical Statistician HFD-713

Concur: Dr. Wilson

Dr. Dubey 10-29-93

This review contains 8 pages of text and 14 pages of tables.

cc:
Orig NDA 20-114
HFD-155
HFD-155/Dr. Himmel
HFD-155/Ms. Riley
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File 1.3.2 NDA]
HFD-713/Dr. Gebert
HFD-713/Dr. Wilson
Chron

This review was typed by jrg into file AZELNASP on May 29,1993 and was modified on August 18,1993 and on October 25, 1993.

TABLE 1
STUDY 26
SYMPTOM- REVISED SYMPTOM COMPLEX AM/PM Combined
ADJUSTED MEAN IMPROVEMENTS (N)

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	1.11 (60)	2.02 (63)	2.22 (62)	0.54 (60)
WEEK 2	1.75 (59)	2.24 (61)	2.97 (60)	1.23 (55)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.233	0.002	<0.001	0.001
WEEK 2	0.343	0.067	0.002	0.013

TABLE 2
STUDY 26
SYMPTOM- SNEEZES AM/PM Combined
ADJUSTED MEAN IMPROVEMENTS (N)

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	0.25 (60)	0.44 (63)	0.74 (62)	0.07 (60)
WEEK 2	0.32 (59)	0.52 (61)	0.84 (60)	0.28 (55)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.152	0.004	<0.001	<0.001
WEEK 2	0.768	0.097	<0.001	<0.001

TABLE 3
STUDY 26
SYMPTOM- STUFFY NOSE AM/PM Combined
ADJUSTED MEAN IMPROVEMENTS (N)

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	0.25 (60)	0.54 (63)	0.61 (62)	0.08 (60)
WEEK 2	0.42 (59)	0.54 (61)	0.72 (60)	0.30 (55)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.218	0.001	<0.001	<0.001
WEEK 2	0.517	0.177	0.019	0.105

TABLE 4
STUDY 26
SYMPTOM- RUNNY NOSE/SNIFFLES AM/PM Combined
ADJUSTED MEAN IMPROVEMENTS (N)

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	0.38 (60)	0.76 (63)	0.84 (62)	0.22 (60)
WEEK 2	0.64 (59)	0.86 (61)	1.08 (60)	0.45 (55)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.296	<0.001	<0.001	<0.001
WEEK 2	0.264	0.017	<0.001	0.002

TABLE 5
STUDY 26
SYMPTOM- TOTAL SYMPTOM COMPLEX AM/PM Combined
ADJUSTED MEAN IMPROVEMENTS (N)

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	2.07 (60)	3.97 (63)	4.82 (62)	1.16 (60)
WEEK 2	3.23 (59)	4.46 (61)	6.02 (60)	2.50 (55)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.286	0.001	<0.001	<0.001
WEEK 2	0.478	0.054	0.001	0.003

TABLE 6

STUDY 26
AM AND PM P-VALUES FOR
AZELASTINE QD COMPARISON WITH PLACEBO

VARIABLE	AM P-VALUE	PM P-VALUE
TOTAL SYMPTOM COMPLEX		
WEEK 1	0.360	0.278
WEEK 2	0.614	0.396
REVISED SYMPTOM COMPLEX		
WEEK 1	0.264	0.257
WEEK 2	0.482	0.270
SNEEZES		
WEEK 1	0.408	0.071
WEEK 2	0.836	0.728
STUFFY NOSE		
WEEK 1	0.137	0.405
WEEK 2	0.765	0.376
RUNNY NOSE/SNIFFLES		
WEEK 1	0.382	0.289
WEEK 2	0.399	0.192

TABLE 7
STUDY 31
SYMPTOM- REVISED SYMPTOM COMPLEX AM/PM Combined
ADJUSTED MEAN IMPROVEMENTS (N)

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	2.04 (62)	2.72 (63)	3.22 (61)	1.09 (63)
WEEK 2	2.64 (62)	3.43 (60)	4.02 (59)	2.61 (60)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.068	0.002	<0.001	<0.001
WEEK 2	0.948	0.158	0.016	0.045

TABLE 8
STUDY 31
SYMPTOM- SNEEZES AM/PM Combined
ADJUSTED MEAN IMPROVEMENTS (N)

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	0.56 (62)	0.79 (63)	1.04 (61)	0.23 (63)
WEEK 2	0.69 (62)	0.84 (60)	1.24 (59)	0.48 (60)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.026	<0.001	<0.001	<0.001
WEEK 2	0.187	0.024	<0.001	<0.001

TABLE 9
STUDY 31
SYMPTOM- STUFFY NOSE
ADJUSTED MEAN IMPROVEMENTS (N) AM/PM Combined

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	0.41 (62)	0.38 (63)	0.61 (61)	0.13 (63)
WEEK 2	0.49 (62)	0.49 (60)	0.88 (59)	0.51 (60)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE
COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.079	0.118	0.003	0.029
WEEK 2	0.910	0.914	0.042	0.084

TABLE 10
STUDY 31
SYMPTOM- RUNNY NOSE/SNIFFLES AM/PM Combined
ADJUSTED MEAN IMPROVEMENTS (N)

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	0.60 (62)	0.80 (63)	1.01 (61)	0.28 (63)
WEEK 2	0.76 (62)	1.02 (60)	1.20 (59)	0.63 (60)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE
COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.030	<0.001	<0.001	<0.001
WEEK 2	0.422	0.022	0.001	0.004

TABLE 11
STUDY 31
SYMPTOM- TOTAL SYMPTOM COMPLEX AM/PM Combined
ADJUSTED MEAN IMPROVEMENTS (N)

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	4.14 (62)	5.31 (63)	6.41 (61)	2.07 (63)
WEEK 2	5.38 (62)	6.53 (60)	7.94 (59)	4.68 (60)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.030	0.001	<0.001	<0.001
WEEK 2	0.501	0.079	0.002	0.013

TABLE 12

STUDY 31
AM AND PM P-VALUES FOR
AZELASTINE QD COMPARISON WITH PLACEBO

VARIABLE	AM P-VALUE	PM P-VALUE
TOTAL SYMPTOM COMPLEX		
WEEK 1	0.034	0.045
WEEK 2	0.401	0.568
REVISED SYMPTOM COMPLEX		
WEEK 1	0.071	0.114
WEEK 2	0.995	0.839
SNEEZES		
WEEK 1	0.040	0.028
WEEK 2	0.105	0.307
STUFFY NOSE		
WEEK 1	0.102	0.099
WEEK 2	0.894	0.931
RUNNY [illegible]/SNIFFLES		
[illegible]EK 1	0.039	0.045
WEEK 2	0.223	0.702

TABLE 13
STUDY 33
SYMPTOM- REVISED SYMPTOM COMPLEX AM/PM Combined
ADJUSTED MEAN IMPROVEMENTS (N)

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	1.70 (66)	1.92 (66)	2.58 (65)	1.37 (66)
WEEK 2	2.35 (63)	2.51 (63)	3.00 (64)	1.96 (59)
WEEK 3	2.77 (61)	2.55 (61)	3.20 (63)	1.63 (58)
WEEK 4	2.73 (59)	3.16 (58)	3.31 (63)	1.63 (54)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.435	0.200	0.006	0.042
WEEK 2	0.459	0.297	0.046	0.245
WEEK 3	0.050	0.113	0.007	0.051
WEEK 4	0.081	0.016	0.007	0.034

TABLE 14
STUDY 33
SYMPTOM- SNEEZES AM/PM Combined
ADJUSTED MEAN IMPROVEMENTS (N)

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	0.39 (66)	0.58 (66)	0.73 (65)	0.18 (66)
WEEK 2	0.50 (63)	0.63 (63)	0.83 (64)	0.45 (59)
WEEK 3	0.62 (61)	0.69 (61)	0.96 (63)	0.35 (58)
WEEK 4	0.60 (59)	0.88 (58)	0.97 (63)	0.59 (54)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.099	0.002	<0.001	<0.001
WEEK 2	0.747	0.209	0.008	0.032
WEEK 3	0.094	0.033	<0.001	0.002
WEEK 4	0.937	0.088	0.024	0.045

TABLE 15
STUDY 33
SYMPTOM- STUFFY NOSE AM/PM Combined
ADJUSTED MEAN IMPROVEMENTS (N)

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	0.33 (66)	0.33 (66)	0.58 (65)	0.26 (66)
WEEK 2	0.52 (63)	0.48 (63)	0.77 (64)	0.44 (59)
WEEK 3	0.61 (61)	0.56 (61)	0.88 (63)	0.38 (58)
WEEK 4	0.68 (59)	0.78 (58)	0.87 (63)	0.53 (54)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.602	0.593	0.024	0.121
WEEK 2	0.626	0.820	0.040	0.148
WEEK 3	0.216	0.326	0.006	0.050
WEEK 4	0.445	0.194	0.074	0.319

TABLE 16
STUDY 33
SYMPTOM- RUNNY NOSE/SNIFFLES AM/PM Combined
ADJUSTED MEAN IMPROVEMENTS (N)

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	0.50 (66)	0.61 (66)	0.86 (65)	0.29 (66)
WEEK 2	0.64 (63)	0.77 (63)	1.03 (64)	0.63 (59)
WEEK 3	0.79 (61)	0.88 (61)	1.08 (63)	0.53 (58)
WEEK 4	0.84 (59)	0.96 (58)	1.12 (63)	0.79 (54)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.114	0.017	<0.001	<0.001
WEEK 2	0.905	0.327	0.007	0.022
WEEK 3	0.138	0.046	0.002	0.020
WEEK 4	0.778	0.372	0.081	0.298

TABLE 17
STUDY 33
SYMPTOM- TOTAL SYMPTOM COMPLEX AM/PM Combined
ADJUSTED MEAN IMPROVEMENTS (M)

	AZEL QD	AZEL BID	CHLOR	PLACEBO
WEEK 1	3.24 (66)	3.81 (66)	5.17 (65)	2.15 (66)
WEEK 2	4.32 (63)	4.87 (63)	6.02 (64)	3.84 (59)
WEEK 3	5.26 (61)	5.22 (61)	6.55 (63)	3.18 (58)
WEEK 4	5.24 (59)	6.40 (58)	6.79 (63)	3.71 (54)

P-VALUES COMPARED TO PLACEBO AND OVERALL P-VALUE COMPARING ALL TREATMENT MEANS

	AZEL QD	AZEL BID	CHLOR	All TRT
WEEK 1	0.180	0.040	<0.001	0.003
WEEK 2	0.618	0.286	0.024	0.123
WEEK 3	0.059	0.064	0.002	0.022
WEEK 4	0.199	0.025	0.009	0.044

TABLE 18

STUDY 33
AM AND PM P-VALUES FOR
AZELASTINE QD COMPARISON WITH PLACEBO

VARIABLE	AM P-VALUE	PM P-VALUE
TOTAL SYMPTOM COMPLEX		
WEEK 1	0.342	0.097
WEEK 2	0.865	0.416
WEEK 3	0.134	0.028
WEEK 4	0.358	0.106
REVISED SYMPTOM COMPLEX		
WEEK 1	0.481	0.404
WEEK 2	0.636	0.326
WEEK 3	0.121	0.022
WEEK 4	0.159	0.042
SNEEZES		
WEEK 1	0.306	0.052
WEEK 2	0.904	0.576
WEEK 3	0.205	0.075
WEEK 4	0.847	0.775
STUFFY NOSE		
WEEK 1	0.722	0.461
WEEK 2	0.544	0.725
WEEK 3	0.305	0.168
WEEK 4	0.373	0.537
RUNNY NOSE/SNIFFLES		
WEEK 1	0.541	0.019
WEEK 2	0.561	0.450
WEEK 3	0.356	0.054
WEEK 4	0.730	0.389

STRANGE

PHARMACOKINETICS/BIOPHARMACEUTICS REVIEW

NDA 20-114

ASTELIN® N.S. (AZELASTINE NASAL SOLUTION)

WALLACE LABORATORIES
DIVISION OF CARTER-WALLACE, INC.
CRANBURY, NJ 08512

SUBMISSION DATE:
30 JUNE 1995

REVIEWER:
DALE P. CONNER, PHARM.D.

TYPE OF SUBMISSION: RESPONSE TO DEFICIENCY LETTER

TITLE: Narrative responses to comments in the not approvable letter dated February 16, 1994, for nasal solution rhinitis NDA 20-114.

BACKGROUND:

There were three major biopharm deficiencies included in the not approvable letter of 16 February 1994. These comments were numbered 1.e., 1.g. and 1.h. The text is as follows:

1.e. A summary of the population variability of azelastine metabolism should be provided. This should include presentations of histograms by dose of azelastine, desmethylazelastine, the sum and ratios of the two moieties (C_{max} and AUC) after single and multiple (steady-state) dosing. In addition, please identify any phenotypic subpopulation of azelastine metabolizers. The effects of gender on metabolism should be evaluated as well.

1.g. [illegible] shown in vitro that salicylate caused a four-fold increase (from 3% to 12%) in the unbound fraction in plasma of the active metabolite, desmethylazelastine. The impact of such an interaction in vivo needs to be investigated. In the absence of enough information on the clearance of this metabolite, it is difficult to predict whether the unbound concentration of desmethylazelastine will increase (as with high-clearance drugs) or remain constant (as with low-clearance drugs). Studies utilizing the tablet formulation may address this issue.

1.h. The influence of gender on azelastine kinetics has not been addressed. Please re-analyze existing data or plan a new study to investigate gender effect.

SPONSOR'S RESPONSES TO QUESTIONS

1.e. The sponsor stated that a profile of the frequency of distribution of AUC_t, $\ln(AUC_t)$, C_{max}, $\ln(C_{max})$, t_{max}, C_{min} and $\ln(C_{min})$ for azelastine and desmethylazelastine, as well as information on oral clearance, after multiple doses of 2, 4, or 8 mg of azelastine were included in the original NDA 20,114 in Study No. 13. Copies of this information were included in the reply document (Vol. 28, Attachment X). The sponsor concluded that there was no evidence of phenotypic metabolism.

1.g. The sponsor stated that they did not expect that the change in the free concentration of desmethylazelastine would be clinically meaningful. They further stated that "the total desmethylazelastine concentration accounts for the 3% free fraction. If in vivo the presence of salicylate caused the free fraction of desmethylazelastine to increase 11%, the resultant change in concentration could not be distinguished from the variation of desmethylazelastine concentrations seen in the population".

1.h. In Study No. 183 (Vol. 39, Tab 5) a single 4 mg oral dose of azelastine was given to male and female asthmatic subjects. The mean (SD) pharmacokinetic parameters were:

	Female	Male
N	11	4
$t_{1/2}$, h	19.1	20.2
$AUC_{0-\infty}$, mg•h/ml	65.4 (31.3)	84.7 (48.8)
Cl/f, L/h/kg	1.18 (0.65)	0.93 (0.55)

In Study No. 20 (Vol. 39, Tab 6), normal healthy subjects received 4 mg bid of azelastine for 14 days. The mean (SD) pharmacokinetic parameters were:

	Female	Male
N	6	6
C_{max}, h	5.1 (2.2)	5.7 (3.9)
AUC_{τ}, mg•h/ml	51.9 (23.3)	55.5 (41.2)
T_{max}, h	3.3 (0.5)	3.5 (0.5)
Cl/f, L/h/kg	3.31 (1.09)	3.06 (1.64)

The sponsor concluded that there was no gender difference in the pharmacokinetics of azelastine.

COMMENTS

In general, the sponsor has adequately addressed the deficiencies listed above. Specific comments on their responses are:

1.e. The sponsor has provided the information requested in the comment. Consistent with the sponsors conclusion there does not seem to be any evidence of phenotypic metabolism.

1.g. The sponsor's reasoning in explaining the effect of salicylate displacement on the kinetics of azelastine is faulty, however the conclusion that a displacement interaction would have no probable clinical significance may be correct. This conclusion is based on the finding that azelastine has a large volume of distribution, probably due to extensive tissue binding. Any displacement of drug from plasma proteins would equilibrate with tissue binding sites yielding a decrease in total but no change in free concentrations.

1.h. The data that the sponsor presents is from a relatively small number of subjects but does not show any indication of a gender difference in plasma pharmacokinetics.

Mei-Ling Chen, Ph.D., Director

Dale P. Conner, Pharm.D.
Team Leader
Div. of Pharmaceutical Evaluation II

cc:
HFD-155 (Division File)
HFD-155 (Strange, CSO)
HFD-155 (Honig, MO)
HFD-427 (Mei-Ling Chen)
HFD-155 (Conner)
HFD-340 (Viswanthan)

OCT - 4 1995

NDA: 20-114

SUBMISSION DATE: March 26, 1991
October 25, 1991
October 23, 1992

GENERIC NAME: Azelastine Hydrochloride

BRAND NAME: Astelin® N.S.

ROUTE OF ADMINISTRATION: Intra-Nasal

DOSAGE FORM AND STRENGTH: Nasal Spray (0.1% w/v solution)

SPONSOR: Wallace Laboratories

INDICATIONS: Allergic Rhinitis

REVIEWER: Mohammad Hossain, Ph.D.

TYPE OF SUBMISSION: Original NME

DRUG CLASSIFICATION: 1S

SYNOPSIS:

The firm submitted several biopharmaceutic and pharmacokinetic studies conducted on azelastine hydrochloride including oral and intravenous administration of azelastine hydrochloride tablets, capsules and solutions. The absorption, distribution, metabolism and

Therefore, only studies conducted using the nasal spray and the nasal route of administration has been the primary of focus of review for this NDA (#20-114). Systemic absorption occurs following topical administration of the nasal spray.

The Division of Pulmonary Drug Products (HFD-155) has sent two "NOT APPROVABLE" letters to the sponsor (Dated: February 18, 1992 and February 16, 1993) for NDA 20,114 (Astelin® N.S.). Prior to the issuance of these two letters from the Clinical division (HFD-155), the Division of Biopharmaceutics provided valuable input to the reviewing Medical Officer (in the form of an official memorandum identifying key biopharmaceutic issues for this application) (**Appendix I**). The final review of this submission is now being completed. Because of the not approvable status of this NDA and until the application is found adequate in

other respects (clinical, pharmacology and chemistry), no labeling comments are provided in this review. However, specific biopharmaceutic issues have been identified and provided as Comments for the sponsor.

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BACKGROUND:

Azelastine hydrochloride (molecular formula $C_{22}H_{24}ClN_3O.HCl$, molecular weight 418.37) occurs as a white to off-white, almost odorless, crystalline powder with an extremely bitter taste. It is sparingly soluble in water, methanol and propylene glycol and slightly soluble in ethanol, octanol, and glycerin. It has a melting point of about 225°C and the pH of a saturated solution is between 5.0 and 5.4. The apparent pK_a value for azelastine hydrochloride is 8.4.

Azelastine hydrochloride 0.1% (w/v) solution nasal spray is intended for topical administration in the treatment of the symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus and lacrimation. The product (ASTELIN N.S.™) will be manufactured by Wallace Laboratories (division of Carter-Wallace, Inc.) in Decatur, Illinois

(subsidiary of Carter-Wallace, Inc.) in Humacao, Puerto Rico, under a product sublicense from Degussa Company, ASTA Pharma AG in Germany. In November 1990, azelastine hydrochloride nasal spray 0.1% w/v was approved in the United Kingdom for treatment of seasonal and perennial allergic rhinitis.

Recommended Dose (Sponsor's): Starting dosage for adults and children 12 years and older is 2 sprays/nostril once daily (total daily dose=0.52 mg, as azelastine hydrochloride). If needed, this may be increased to 2 sprays/nostril twice daily (total daily dose=1.04 mg, as azelastine hydrochloride).

Each azelastine hydrochloride nasal solution spray bottle contains 15 mg (1 mg/mL) of azelastine hydrochloride and is to be used with the provided metered-dose spray pump. The spray device consists of a nasal pump dispenser separate from the bottle and is supplied with a leaflet of patient instructions. The patient primes the delivery system of the pump spray bottle so that upon actuation of the unit it delivers a metered-droplet spray having a mean volume of 0.13 mL (0.13 mg azelastine hydrochloride) per spray. Each spray bottle can deliver at least 100 sprays.

SUMMARY OF BIOAVAILABILITY AND PHARMACOKINETICS:

I. BIOAVAILABILITY:

Absolute Bioavailability: The absolute bioavailability of azelastine hydrochloride for the intranasal route of administration has not been determined by the firm. The mean absolute bioavailability of azelastine hydrochloride given AM under fasting condition as a 2x4.4 mg tablet orally was about 82% (CV 24%), with reference to an IV dose of 4.5 mg (concentration of 0.15 mg/mL) of azelastine hydrochloride infused at a rate of 2 mL/min for 15 minutes (**Study 8**). However, from an across study comparison using AUC normalized for dose, the absolute bioavailability of azelastine hydrochloride when given as 0.24-0.72 mg b.i.d. intra-nasally (**Study 25**) was about 40% (%CV=25%), with reference to an I.V. dose of 4.5 mg of azelastine hydrochloride (**Study 8**).

II. PHARMACOKINETICS:

A. **Absorption:** Azelastine hydrochloride is absorbed following intranasal administration under conditions of therapeutic use. Increasing the intranasal dose of azelastine hydrochloride (i.e., 1 spray/nostril, 2 sprays/nostril and 3 sprays/nostril) results in a more than proportional increase in C_{max} and AUC_{0-t} for azelastine. However, T_{max} (range 2-3 hours) remains unaffected and is much shorter compared to the oral route of administration (T_{max} of 5 hrs) indicating rapid drug absorption from the nasal spray dosage form (**Study 8 and Study 25**).

B. **Distribution:** Following intravenous and oral dosing, azelastine exhibited a large steady-state volume of distribution (V_{ss}) of about 14.5 L/kg (**Study 8**). This is approximately 50 times the volume of total body water and indicates extensive tissue distribution and/or binding.

Using ^{14}C-azelastine and ultracentrifugation, azelastine was shown to be 88% bound to human plasma proteins (mainly to human serum albumin and alpha-amino acid glycoprotein). Azelastine binding was shown to increase with increasing concentrations of human serum albumin. Further, *in vitro* protein studies using non-labeled azelastine have shown that an average of 11% and 3% of free azelastine and free desmethylazelastine (equally active metabolite), respectively was found over the plasma concentration range of 5 to 40 ng/mL, corresponding to 89% and 97% binding of these two compounds (azelastine and desmethylazelastine, respectively) to human plasma proteins (**Study 27**). In addition, no competetive binding between azelastine and desmethylazelastine or between azelastine and theophylline were observed. In the presence of 150 μg/mL salicylic acid, amount of free azelastine and desmethylazelastine in plasma increased from 10.7% to 17.7%, and from 3% to 11%, respectively.

C. Metabolism: The metabolism of azelastine hydrochloride following the intra-nasal route of administration has not been studied. Azelastine is extensively metabolized following oral administration of azelastine hydrochloride. Co-chromatography with reference compounds indicated the probable presence of desmethylazelastine (a metabolite with equal pharmacologic activity to that of the parent drug), 2-oxoazelastine, 7-oxoazelastine, 7-acid, 2-acid, and the possible presence of 6-hydroxyazelastine and 7-hydroxyazelastine. A similar metabolic profile was observed for plasma, urine and feces. Most of the metabolites had half-lives equal to or less than that of azelastine ($T_{1/2}$ of about 22 hours). The values for all other metabolites were less than the half-life value for desmethylazelastine ($T_{1/2z}$ of about 54 hours). Urinary recovery of methylamino-carboxy-3-pentyl (7-acid metabolite), a relatively polar metabolite with a half-life of about 18-31 hours, was about 1.5 times higher than desmethylazelastine following oral and intravenous administration of azelastine hydrochloride. In plasma, however, only azelastine and desmethylazelastine were detected in measurable concentrations following intra-nasal administration (**Study 1 and 2**).

Comparison of Cmax and $AUC_{0\text{-}12hr}$ of azelastine and desmethylazelastine in plasma following multiple dose intra-nasal administration of azelastine hydrochloride, shows that desmethylazelastine is approximately 30-35% of the values observed for azelastine (**Study 25**).

D. Elimination: Following oral and intravenous administration of azelastine hydrochloride (**Study 8**), the terminal elimination half-life ($T_{1/2}$) for azelastine and desmethylazelastine was found to be about 22 hours and 54 hours, respectively. The mean plasma clearance (Cl_p) was approximately 507 mL/hr/kg and the mean renal clearance (Cl_r) was approximately 13 mL/hr/kg following oral administration. The renal clearance for both i.v. and oral route of administration is only a small fraction (2.5%) of the total body or systemic clearance suggesting extensive metabolism and/or biliary excretion. After 24 hours, total excretion amounted to 11% of dose (completely urinary excretion) following oral administration of ^{14}C-azelastine hydrochloride. After 10 days, approximately 75% and 25% of the dose was excreted in feces and urine, respectively (**Study 1 and Study 2**), with less than 10% excreted as unchanged azelastine in the feces.

III. DOSE AND DOSAGE FORM PROPORTIONALITY: The sponsor attempted to show dose proportionality between q.d and b.i.d. dosing regimens based on pre-dose and 2 hour post dose data when azelastine hydrochloride nasal spray (0.1%, 0.13 mg azelastine hydrochloride per spray) was administered as 2 sprays/nostril q.d. or 2 sprays/nostril b.i.d. for 2 weeks (**Study 26**). Mean predose and postdose azelastine values for the b.i.d. dosing regimen were 1.7 to 2.3 times greater than corresponding values obtained for the q.d. dosing regimens. Mean

predose and postdose desmethylazelastine values for the b.i.d. dosing regimen were 1.5 to 1.6 times greater than corresponding values obtained for the q.d. dosing regimens. For both dosing regimens, mean two-hour post dose desmethylazelastine concentrations were approximately equal to mean pretreatment values.

Increasing the intranasal dose of azelastine hydrochloride results in a more than proportional increase in C_{max} and $AUC_{0\text{-}12\ hr}$ for azelastine. However, the non-linear increase is evidenced at the 3 sprays/nostril b.i.d. treatment (total dose=0.72 mg of azelastine hydrochloride) which is above the maximum labeling dose (2 sprays/nostril b.i.d., total dose=0.52 mg of azelastine hydrochloride) (**Appendix II**).

IV. **SPECIAL POPULATIONS**: None performed with the nasal spray formulation.) special populations studies were performed.

V. **DRUG INTERACTIONS**: None performed with the azelastine nasal spray formulation.

VI. **PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS**: Not studied for the nasal spray dosage form.

VII. **FORMULATION**: Azelastine Hydrochloride (0.1% w/v nasal spray solution) to be delivered by a metered dose actuator using spray pump B. However, the metered dose system using the actuator and Pump B was not used in any clinical studies as conveyed by the firm in their recent NDA 20-114 amendment. The firm has submitted stability data to support Pump B in NDA 20-114.

VIII.

GENERAL COMMENTS (Need not be sent to the firm):

1. Throughout the course of the clinical trials, several changes were made in the following areas -

   (a) **Drug Delivery System** - (i) spray pump gaskets were changed due to observed potency losses in azelastine HCl and benzalkonium chloride (preservative), and (ii) two different actuators were used - the initial studies used a system which delivered (per stroke and later studies used the intended marketed system which delivered . The metered-dose system is not planned to be marketed by the firm because the volume delivered in individual actuations was highly variable. Internal testing by the firm demonstrated a mean delivery of 0.12 mg per actuation instead of 0.13 mg of azelastine hydrochloride as claimed in the label. The actuator with spray pump B is the to be marketed metered-dose system.

   (b) **Formulation** - two azelastine hydrochloride nasal solution formulations (were used in Wallace-sponsored clinical studies.

2.

3. Estimates of the half-life values for the metabolites indicated that some of the metabolites had half-lives equal to or less than that of azelastine and the values for all other metabolites were less than the half-life value for desmethylazelastine. Such slow elimination indicates the possibility of accumulation of some of the metabolites upon multiple dosing. In plasma, however, only azelastine and desmethylazelastine were detected in measurable concentrations. Comparison of Cmax and $AUC_{0\text{-}12hr}$ of azelastine and desmethylazelastine in plasma following multiple dose intra-nasal administration of azelastine hydrochloride, shows that desmethylazelastine is approximately 30-35% of the values observed for azelastine.

4. A plot of $AUC_{0\text{-}12hr}$ and C_{max} versus dose shows that increasing the intranasal dose of azelastine hydrochloride results in a more than proportional increase in C_{max} and $AUC_{0\text{-}12hr}$

for azelastine. However, the non-linear increase is evidenced at the 3 sprays/nostril b.i.d. treatment (total dose=0.72 mg of azelastine hydrochloride) which is above the maximum labeling dose (2 sprays/nostril b.i.d., total dose=0.52 mg of azelastine hydrochloride).

5. The reviewing Chemist is requested to note that multiple manufacturing sites are involved in the production of azelastine hydrochloride nasal spray. The product (ASTELIN N.S.™) will be manufactured by Wallace Laboratories (division of Carter-Wallace, Inc.) in Decatur, Illinois a (subsidiary of Carter-Wallace, Inc.) in Humacao, Puerto Rico, under a product sublicense from Degussa Company, ASTA Pharma AG in Germany.

COMMENTS TO BE SENT TO THE FIRM:

6. In Study 25, the firm attempted to characterize the pharmacokinetics (AUC, C_{max} and T_{max}) of Azelastine. They failed to characterize the major and equally active metabolite, desmethylazelastine. The firm claims that due to the large number of plasma concentrations below the limit of quantitation (BLQ), estimation of pharmacokinetic parameters for the equally active metabolite, desmethylazelastine was not performed. However, desmethylazelastine plasma concentrations for subjects in the 3 sprays/nostril group ($n \geq 5$) could easily be used to calculate similar pharmacokinetic parameters as seen for azelastine.

7. In Study 26, based on pre-dose and 2 hour post-dose data points the firm attempts to show dose proportionality. Based on Study 25, the sponsor surmised that T_{max} for azelastine is 2 hours. However, even in that study T_{max} had a range of 0.8-4 hour. So, the importance given to the 2-hr post-dose concentration value as corresponding to C_{max} values in Study 26 is not valid.

8. In view of the relatively high inter-subject variability observed in azelastine pharmacokinetic parameters (%CV=50-80%), the sponsor is encouraged to identify whether azelastine behaves as a "highly variable drug" (usually intra-subject variability of ≥30%) or whether azelastine exhibits any genetic polymorphism (e.g., poor vs extensive metabolizers).

9. The proposed labeling with regard to the Pharmacokinetics sub-section of the Clinical Pharmacology section appears to be deficient. Currently, in the draft labeling, there is no major informative pharmacokinetic data presented for the nasal spray dosage form. Descriptive pharmacokinetic information needs to be provided for azelastine nasal spray package insert.

10. A comparison of plasma concentrations (C_{min} and $Cp_{2\ hr}$ following b.i.d. administration of 2 sprays/nostril) observed in healthy male subjects (Study 25) to that observed in patients

(Study 26), shows that on an average patients have about 3.5-fold higher levels of azelastine and about 2.4-fold higher desmethylazelastine levels.

OVERALL DEFICIENCIES:

1. The firm needs to establish a link between the formulation and spray pump system used in the clinical study, and the final to be marketed formulation and spray pump system. In this regard the following *in vitro* and *in vivo* studies are recommended:

   (i) Use *in vitro* techniques to compare between the clinically tested product (Valois-Pump A) and the to be marketed product (Valois-Pump B) using the original endpoints used for testing the product (viz., delivered volume and weight tests, single actuation dose reproducibility, particle size and spray pattern), and

   (ii) Conduct a single-dose, two-way crossover study according to the proposed dosing regimen (2 sprays/nostril) and if possible, apply standard bioequivalence analysis for both the parent and the active metabolite.

2. The firm needs to identify the drug supplies/drug product used in the clinical/ biopharmaceutics studies. The sponsor proposes in the NDA that the manufacturing, packaging, labeling and control of the drug product will be performed by Wallace Laboratories (Division of Carter-Wallace, Inc.) in Decatur, Illinois and a subsidiary of Carter-Wallace, Inc. in Humacao, Puerto Rico. Since there are multiple manufacturing sites involved, it is important to ensure that the *in vitro* equivalence requirements among the two or more product manufacturing sites are in accordance with the specifications initially used to characterize the clinically tested product (as listed in item 1(i) above under "Overall Deficiencies").

3. The sponsor is requested to conduct *in vitro* biotransformation pathways studies in order to fully characterize and identify predominant P450 isozymes involved in the metabolism of azelastine and whether azelastine has any potential for enzyme inhibition or induction. Such information may allow early recognition of potential drug-drug interactions before they are observed in the patient population.

4. The sponsor is requested to conduct stability/compatibility studies on azelastine nasal spray, when it is concomitantly administered via the same route of administration with other drug products.

5. The bioavailability of azelastine and its major metabolite(s) have not been adequately characterized by the sponsor following administration of azelastine hydrochloride nasal spray. The steady-state pharmacokinetics ($AUC^{ss}_{0-\tau}$, C^{ss}_{max}, C^{ss}_{min}, T_{max}, and $T_{1/2}$) of the major, equipotent metabolite (desmethylazelastine) following administration of azelastine

hydrochloride nasal spray needs to be defined. Adequate, well-controlled studies and literature reports characterizing the pharmacokinetics (viz., bioavailability, dose proportionality, effect of gender, age and race) of azelastine and the equally active metabolite, desmethylazelastine, following intra-nasal administration of azelastine hydrochloride may need to be provided by the sponsor.

RECOMMENDATIONS:

This submission (NDA-20-114) has been reviewed by the Division of Biopharmaceutics. In order for this submission to be acceptable for meeting the Biopharmaceutics requirements, the sponsor should respond satisfactorily to all enclosed Comments as well as Deficiencies. The sponsor may re-analyze existing data, submit literature reports, and/or plan new study(ies) to address some of the issues identified by the Agency. The sponsor is requested to contact the Division of Biopharmaceutics for any assistance or clarification on the above mentioned issues.

Please convey Comments 6-10 and Deficiencies 1-5 to the firm.

M Hossain 10/4/95

Mohammad Hossain, Ph.D.
Pharmacokinetics Evaluation Branch I

First Draft initialed by Mohammad Hossain, Ph.D. M.H. 10/7/91
Second Draft initialed by Mohammad Hossain, Ph.D. M.H. 6/26/95
Drafts initialed by Raman Baweja, Ph.D. R.B. 8/18/93; 9/28/95
FT initialed by Raman Baweja, Ph.D. R. Baweja 10/4/95.

cc: NDA 20-114 (orig.), HFD-155, HFD-426 (Hossain, Baweja, Fleischer), Chron, Drug, Reviewer, and FOI (HFD-19) files.

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Division of Pulmonary Drug Products
Labeling Review

NDA 20-114	**Reviewer:** Misoon Y. Chun, Pharm.D., D.A.B.T. **Date of Submission:** 3/26/91, Revised 9/21/95 **Date of Review:** September 21, 1995
Sponsor:	Wallace Laboratories/ Division of Carter-Wallace Inc.
Drug Name:	Azelastine Hydrochloride (ASTELIN®) Nasal Solution 0.1% W/V
Proposed Dosage/ Indication:	Two sprays per nostril one to two times a day (0.52 to 1.04 mg/day) for allergic rhinitis.

Information to be Conveyed to the Sponsor: Yes

COMMENTS ON THE LABELING

As stated in the review of original submission dated March 27, 1992 on page 74, the dose levels from the animal studies were expressed only as number of times the maximum human clinical doses on a mg/kg basis throughout the labeling. Dose levels in the carcinogenicity, pregnancy category, and overdosage sections should be indicated as mg/kg/day and also be expressed as number of times the maximum recommended clinical dose on a mg/m^2 basis for allergic rhinitis.

Labeling should be revised and read as follows:

1. **Carcinogenicity, Mutagenesis and Impairment of Fertility section:** Two carcinogenicity studies in rats and mice dosed orally with azelastine hydrochloride for 24 months at doses up to 30 mg/kg/day and 25 mg/kg/day, respectively (240 and 100 times the maximum recommended clinical nasal dose on a mg/m^2 basis, respectively) revealed no evidence of tumorigenicity. Azelastine hydrochloride showed no mutagenic effects in the Ames test, DNA repair test, mouse lymphoma forward mutation assay, mouse micronucleus test or chromosomal aberration test in rat bone marrow.

   Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 30 mg/kg/day (240 times the maximum recommended clinical nasal dose on a mg/m^2 basis). However, at an oral dose of 68.6 mg/kg/day (550 times the maximum recommended clinical nasal dose on a mg/m^2 basis), the duration of estrous cycles was prolonged and copulatory activity and the number of pregnancies were decreased.

Although the implantation ratio was not affected, the numbers of corpora lutea and implantations were decreased.

2. **Pregnancy Category C:** In oral reproduction studies in mice, azelastine hydrochloride has been shown to be embryotoxic, fetotoxic and teratogenic (external and skeletal abnormalities) at an oral dose of 68.6 mg/kg/day (280 times the maximum recommended clinical nasal dose on a mg/m^2 basis).

   In rats, delayed ossification (undeveloped metacarpus) and the incidence of 14th rib were increased at an oral dose of 30 mg/kg/day (240 times the maximum recommended clinical nasal dose on a mg/m^2 basis). At 68.6 mg/kg/day (550 times the maximum recommended clinical nasal dose on a mg/m^2 basis), the resorption rate and fetal mortality were increased and fetal body weight was reduced. In pregnant rabbits, doses equal to or greater than 30 mg/kg/day (445 times the maximum clinical nasal dose on a mg/m^2 basis) caused abortion and fetotoxic effects.

   There are no adequate and well controlled clinical studies in pregnant women. Azelastine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

3. **Nonteratogenic Effects:** Delete this section.

4. **Overdosage:.....** The lowest oral LD_{50} of azelastine hydrochloride was 310 mg/kg in rats (2470 times the maximum recommended clinical nasal dose on a mg/m^2 basis), greater than 120 mg/kg in mice and guinea pigs (480 and 3000 times the maximum recommended clinical dose on a mg/m^2 basis, respectively) and 51.3 mg/kg in dogs (1400 times the maximum recommended clinical dose on a mg/m^2 basis). Single dose as high as 10 mg/kg (270 times the maximum recommended clinical dose on a mg/m^2 basis) in dogs has been well-tolerated but 20 mg/kg was lethal.

Recommendation:

The above mentioned comments on the labeling should be conveyed to the sponsor.

Misoon Y. Chun

Misoon Y. Chun, Pharm.D.,D.A.B.T.
Pharmacologist, HFD-570

cc: NDA 20-114
HFD-570/Div le
/PHor
/Gsti
/MChun,
/JSun

ised 10/25/95, 11/20/95, 11/21/95

Attachment

NOV. 22, 1995

N/A 7

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original Amendment

NDA 20-114

Reviewer: Misoon Y. Chun
Date of Submission: 11/20/92
Date of Review: 3/11/93

Sponsor: Wallace Laboratories/Division of Carter-Wallace, Inc.
Princeton, New Jersey 08540

Drug Name: Azelastine Hydrochloride (ASTELIN ®)

Submission: This submission contains the result of the study conducted in response to our request for steady state plasma areas under the curve (AUC) of azelastine and its desmethyl metabolite in mice for comparison with data from humans.

Review of the Study:

Note - Portions of this review were excerpted directly from the sponsor's submission.

"Plasma levels of azelastine and its N-desmethyl-metabolite in mice after oral ingestion of 25 mg/kg azelastine HCl for 21 days as a drug-food-admixture: ASTA-Tox-Study No. 888186."

Study facility: ASTA Medica AG (Frankfurt)
Date: July 28, 1992
GLP Requirement: Satisfactory
Dosage: 25 mg/kg A-05610 (azelastine HCl) in drug-food-admixture, orally for 21 days
Batch No.: 041071

Study Design:

The objective of the study is to determine the toxicokinetic profile of the test substance Azelastine Hydrochloride during 3 weeks of oral administration in mice to support the results of previous oncogenicity study No. 856236.

A total of 210 males and 210 females of Bor: NMRI mice were used to obtain the plasma AUC at steady state as well as the plasma elimination half-life-time.

Blood samples were taken at:

Group I (AUC group): 0, 3, 6, 9, 12, 15, 18, 21, 24 h
Group II(Decline group): 0, 3, 6, 9, 12, 15, 18, 21, 24, 36, 48, 72 h.

Sample time "0" is defined as clock time 6:00 pm for Group I and 6:00 am for Group II. On each time point 9 animals will be bled; equal amounts of the heparinized blood from 3 mice will be pooled and centrifugated for plasma.

The study protocol was modified to incorporate our suggestions discussed over the telephone on using both sexes of animals and measuring the plasma levels of both azelastine as well as N-desmethyl-azelastine.

Results:

There were no treatment-related clinical symptoms or influence on body weight gain, except slightly decreased food consumption due to the bitter taste of the test substance with corresponding decrease of the test substance.

The mean calculated doses for 3 weeks were:
males : 25.4 and 24.3 mg/kg for groups 1 and 2
females: 24.3 and 24.1 mg/kg for groups 1 and 2

The content and the homogeneity of azelastine HCl in rodent feed were documented. The content of azelastine Hcl in rodent feed was analyzed and quantified by using a peak area or height with reference to the standard calibration curve.

The mean concentrations of the homogeneity samples were found to be in the range of 74.7% to 102.3% and varied from -5% to +8% of the mean concentrations.

Pharmacokinetic Results:

The for A-05610 (Azelastine HCl) and D-17469 (N-desmethyl-azelastine HBr) had a lower limit of quantitation of 6.25 ng/ml for both analytes. The linear range of the assay was 6.25 - 800 ng/ml.

Plasma AUC for the mean concentrations was calculated using the trapezoidal rule. The steady-state plasma concentrations were calculated : C_{ss} = AUC/24 h. The elimination-half life for the decline from steady-state was determined by curve-fitting of the mean concentrations with RSTRIP 5.0 on a computer.

1. AUC-group

	Azelastine HCL		N-Desmethyl-Azelastine Hbr	
	Males	Females	Males	Females
AUC (ng.hr/ml)	12404.16	5901.44	15704.14	7176.03
C_{ss} (ng/ml)	516.84	245.89	654.34	299.00
$T_{½}$ (hr)	2.40	2.40	5.51	4.45

Steady-state plasma concentrations were found higher for D-17469 (N-desmethyl-azelastine Hbr) than for the parent drug A-05610 (Azelastine Hcl). Males exhibited approximately twice the plasma concentration of females.

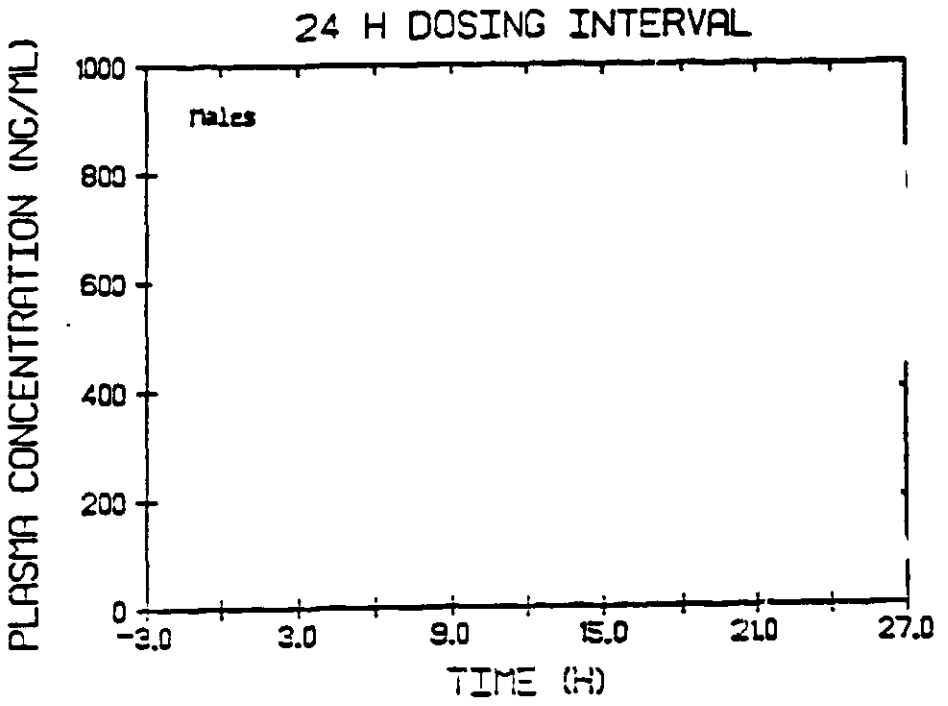


Fig. 6: Comparison of the time courses of the plasma levels during a 24 h dosing interval in male and female mice

2. Decline-group

The limit of quantitation (LOQ) was reached for Azelastine within 6-12 hours, for the metabolite D-17469 within 24-36 hours.

The terminal plasma half live times of elimination were 2.4 hours for the parent drug in both sexes and 5.51 (males) and 4.45 (females) respectively for the metabolite.

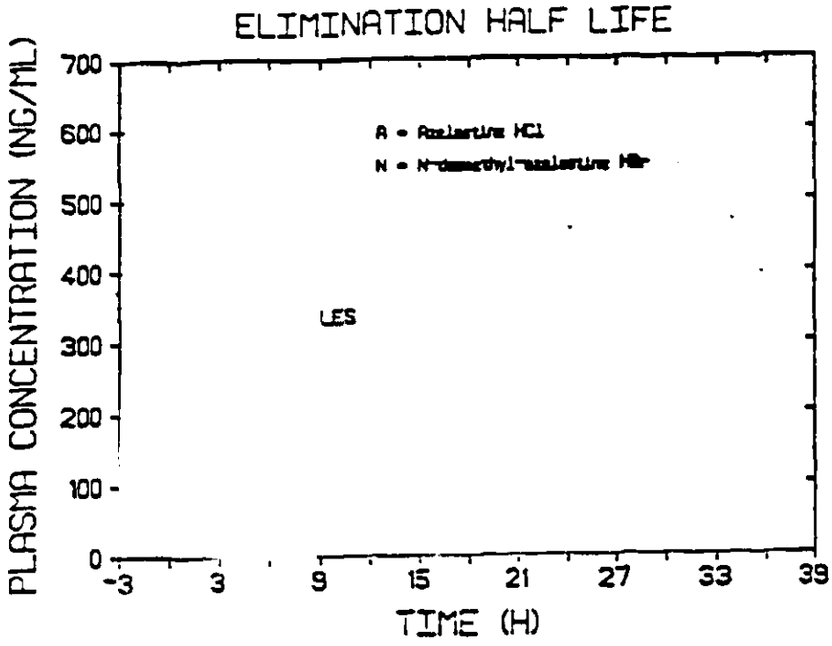


Fig. 7: Comparison of the time courses of the plasma level decline from steady state of A-05610 (azelastine HCl) and D-17469 (N-desmethyl-azelastine HBr) in male and female mice

It was concluded that 25 mg/kg (98-132 ppm in the diet) was the highest possible dose which could be administered due to the limited palatability of the test substance by the animals. Nevertheless, the plasma concentrations obtained from the animals in this study demonstrated that the sufficient test substance was taken in from the diet-admixture. The metabolite exceeded the levels of the parent, and males had higher levels than females.

Discussion:

The analytical method used for the plasma level determinations in this study was comparable to those used during the carcinogenicity study in mice and during the MTD study in mice. Drug was administered as a drug-food admixture in all three studies. The plasma concentrations attained after 25 mg/kg A-05610 in the present study was comparable to those found in the animals of the previous studies in magnitude and pattern with males showing higher plasma levels than the females.

Comparison of Pharmacokinetic data in Mice:

Plasma Level Data from 13-week MTD study in Mice (Day 86):

Doses (mg/kg) Nominal	Actual	Plasma levels (C_{ss}) (ng/ml) Azelastine HCl		Desmethyl-azelastine	
	M F	M	F	M	F
1	0.9 1.1	<50	<50	n.b.	n.b.
5	4.6 6.1	89.5	n.b.	89.4	n.b.
30	27.0 32.0	305.5	352.0	341.8	330.7
60	54.0 65.0	683.8	462.1	1459.9	872.5
120	106.0 148.0	805.2	516.5	3510.8	2453.5

(n.b. : Not detectable)

Plasma Level Data from 104-weeks CA study in Mice (Week 60):

Doses (mg/kg) Nominal	Actual**	Plasma levels (C_{ss}) (ng/ml) Azelastine HCl		Desmethyl-azelastine	
M	F	M	F	M	F
1 1.08	0.88	74.7	68.9	42.2	traces
5 4.51	6.68	162.4	92.3	139.0	58.3
25 24.8	28.2	609.8	326.2	1001.9	477.7

Pharmacokinetic Data from 3-weeks PK study in Mice:

Dose 25 mg/kg/day	Azelastine HCL		N-Desmethyl-Azelastine Hbr	
Parameters	M	F	M	F
AUC (ng.hr/ml)	12404.16	5901.44	15704.14	7176.03
C_{ss} (ng/ml)	516.84	245.89	654.34	299.00
$T_{½}$ (hr)	2.40	2.40	5.51	4.45

Pharmacokinetic parameters of Azelastine HCl

Species, Strain	Dose (mg/kg)	Route	C_{max} (ng/ml)	T_{max} (h)	$AUC_{0-\infty}$ (ng.h/ml)	$T_{\frac{1}{2}}$ (h)
Mouse, NMRI	50	p.o.	1223 (400-1700)	0.7-0.8	9765-11450	4.6-4.8
NMRI (Azelastine Hcl)	25	p.o.	516.84 (m) 245.89 (f)		12404.16 5901.44	2.40 2.40
(N-desmeth. Az)			654.34 (m) 299.00 (f)		15704.14 7176.03	5.51 4.45
Human single dose (mg)						
Azelas-tine	2.2	p.o.	1.0±0.3	4.3±1.1	17.6± 6.3	--
	4.4		1.7±0.8	5.8±0.3	50.4±30.2	20.7±3.5
	8.8		5.9±2.1	5.3±1.6	167 ± 68	21.9±3.9
	17.6		8.4±2.0	4.3±0.8	199 ± 64	--
Desmeth ylazelas tine	2.2	p.o.	0.4±0.3	7.2± 3.2	5.9± 8.4	--
	4.4		0.4±0.1	21.8±13.8	33.7±11.0	50.2±12.8
	8.8		0.9±0.1	20.5±11.2	85.7±16.2	54.2±14.8
	17.6		2.3±0.8	14.0± 9.5	105.6±31.7	--
Human bid	**Dose (mg)**	**Route**	C_{max} (ng/ml)	T_{max} (h)	$AUC_{0-\tau}$ (ng.h/ml)	**Cl (ml/min)**
Azelas-tine	2.2	p.o.	3.9±2.9	5.3±1.2	40.1±32.6	1.2± 0.6
	4.4		8.0±4.9	5.6±1.1	80.2±51.0	1.2± 0.7
	8.8		16.8±6.4	5.3±1.4	168 ± 70	0.9± 0.3
Desmeth ylazelas tine	2.2	p.o.	1.9±0.7	6.8± 3.2	20.2± 7.6	--
	4.4		3.5±0.9	6.8±2.5	37.7±10.2	--
	8.8		7.5±1.2	6.7±2.1	80.8±13.1	--

The metabolic profiles in animals as well as in humans are similar qualitatively with some quantitative inter-species differences. There were eight possible metabolites; the desmethylazelastine being the major metabolite of importance which showed pharmacological activity and measurable from the plasma.

Conclusion:

Plasma concentrations of azelastine and the metabolite in mice are nearly 2 orders of magnitude (100 times) greater than those of the humans, although in mice the elimination half-life for both analytes are shorter (1/10) than in man.

Therefore, the sponsor has concluded that the differences in plasma level exposures allows a considerable safety margin between the toxicological findings in mice and in man after oral therapeutic doses. This margin becomes even greater with regard to the plasma levels attained after multiple intranasal administration of azelastine HCl to man (1.68 mg/day resulted in C_{max} of 1.1 ng/ml A-05610 and 0.3 ng/ml D-17469 (Report No. CP-90-254, 7/2/90).

This pharmacokinetic study was conducted in response to the concerns raised at CAC meeting on November 11, 1991, regarding adequacy of the highest dose (25 mg/kg/day) used in the carcinogenicity study in mice previously. This study has shown that the mice were adequately exposed to the compound in the carcinogenicity study and demonstrated that the plasma level exposures (AUCs) in mice were in 100 fold greater than the human exposure.

In conclusion, the mouse carcinogenicity which did not show any significant neoplasm is acceptable; and therefore, azelastine HCl can be classified as non-carcinogen based on the carcinogenicity studies conducted in rats and mice.

Misoon Y. Chun

Misoon Y. Chun, Pharm.D.,DABT
Pharmacologist, HFD-150

cc: NDA 20-114,
HFD-150/Div. File
HFD-150/MHimmel
HFD-150/Mchun
HFD-400/JContrera
HFD-150/CSO

Alan Taylor 3-2293

Alan Taylor, Ph.D.
Supervisory Pharmacologist

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original Summary

NDA 20-114

Reviewer: Misoon Y. Chun, Pharm.D.
Date of Submission: 3/26/91
Date Assigned: 3/29/91
Date of Review: Started 4/9/91
Finished 11/15/91
Revised 3/27/92

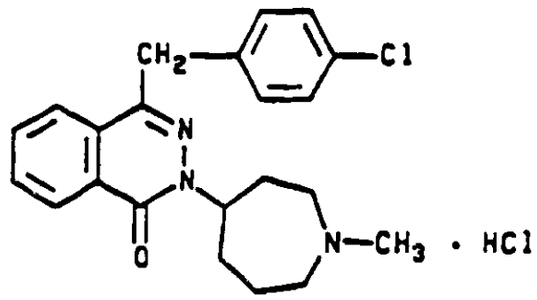
SPONSOR: Wallace Laboratories/Division of
Carter-Wallace, Inc.
Princeton, New Jersey 08540

DRUG NAME: Azelastine Hydrochloride (ASTELIN N.S.®)

Code Name : W-2979M (Wallace Lab)
A-5610 (ASTA Pharma AG)

Chemical Name: (±)-1-(2H)-Phthalazione,4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride

Chemical Structure:



- Molecular Formula - $C_{22}H_{24}ClN_3O \cdot HCl$
- Molecular Weight - 381.90/418.37 (base/hydrochloride)

CATEGORY OF DRUG: Anti-allergy

DOSAGE FORM: 0.1% Nasal Spray
(1 mg/ml, 0.13 ml/actuation)

RELATED INDS: IND IND

PROPOSED INDICATION: Allergic Rhinitis

PROPOSED DOSAGE: Two sprays per nostril one to two times a day (0.52 to 1.04 mg/day)

FORMULATIONS:

Intranasal Solution:

The nasal spray will be packaged in 15 ml high density polyethylene bottles using pumps (pump B) metered dose system which delivers azelastine hydrochloride) per spray.

NOTE: This formulation differs from the formulation used for preclinical toxicity studies only in using pumps instead of spray pumps.

PRECLINICAL DATA:

NOTE: The content and reviews of Nonclinical Pharmacology, Toxicology and Pharmacokinetic data are identical for both NDA 20-114 A copy of review for two six-month intranasal studies in animals from IND is attached in Appendix I.

Portions of this review were excerpted directly from the sponsor's submission.

Laboratories Performed the studies:

GLP Requirements: Satisfactory

Contents of the Review (Page Number):

1.	Pharmacology	(3)	3.	ADME Studies	(54)
2.	Toxicology	(16)	4.	Summary and Evaluation	(66)
	Carcinogenicity	(31)	5.	Conclusions	(75)

1. PHARMACOLOGY

The pharmacology profile of azelastine hydrochloride has been established in the following studies performed by Wallace Laboratories; Degussa company, ASTA Pharma AG of Frankfurt, West Germany; and by various commercial and university groups under sponsorship of these companies.

Pharmacology Studies conducted:

A. Primary Pharmacologic Activities (Antiallergic Effects)

a) Effect on immediate allergic responses

1) Inhibition of synthesis and release of chemical mediators

a. Histamine - Mast cells, Basophils
b. Leukotrienes - Human neutrophils, Guinea pig lung
c. Superoxide anions- Human neutrophils, Eosinophils

2) Inhibition of immediate allergic responses

a. Inhibition of passive cutaneous and peritoneal anaphylaxis - Rat, Guinea Pig
b. Inhibition of immediate allergic responses in the airways - Rat, Guinea Pig, Dog
c. Inhibition of aeroallergen induced eosionphilia in the airways - Guinea Pig

b) Effect on chemical mediator-induced responses

1) Antihistaminic activity

2) Inhibitory Activity Induced by Other Mediators

B. Other Pharmacologic Actions:

1. Neuropharmacology
2. Influence on the Cardiovascular and Respiratory Systems
3. Gastrointestinal Pharmacology
4. Urogenital Pharmacology
5. Anti-Inflammatory, antipyretic and analgesic Activities
6. Ancillary Pharmacology

C. Special Studies:

a. Drug Interactions
b. Pharmacology of Metabolites and Isomers of Azelastine
c. Mechanism of Action

A. Primary Pharmacologic Activities (Antiallergic Effects)

a) Effect on immediate allergic responses

1) Inhibition of synthesis and release of chemical mediators

a. **Histamine:** Azelastine hydrochloride inhibits allergic and nonallergic histamine secretion in the peritoneal cavity of passively sensitized rats at dose ranges of 1-10 mg/kg, i.p., and from *in vitro* rabbit and human basophils at the inhibitory concentration ranges of 1.9 - 50 μM (Table E.1., vol 2, p 114).

Table E.1
Inhibition by Azelastine HCl of Allergic and Nonallergic Histamine Secretion from Rat Peritoneal Mast Cells (RPMC) and Rabbit and Human Basophils

		IC50 (μM) Preincubation Time (Min)		
Cell Type	Stimulus	0	10	30
Allergic Histamine Secretion				
RPMC	OA + PS[a]	7.6	4.8 5.0 2.7 1.8	
Rabbit basophils	RAE[b], 10 μg/mL	2.4	1.9 4.5 5.0 5.6 5.1 5.2 1.9	3.5
Human basophils	RAE, 10 μg/mL		3.3	
Human lung mast cells	Anti-IgE, 1 μg/mL Anti-IgE, 5 μg/mL		12.0 48.0	
Nonallergic Histamine Secretion				
RPMC	Con A + PS	6.8	1.9	
	Calcium Ionophore A23187, 0.1 μg/mL	7.7	10.2 9.1 5.0 2.7	
	Compound 48/80, 0.1 μg/mL	51.0	48.0 50.0	

[a]OA or Con A + PS = 10 μg/mL of ovalbumin or concanavalin A plus 10 μg/mL of phosphatidyl serine.
[b]RAE = ragweed antigen extract.

b. **Leukotrienes:** Azelastine hydrochloride did not inhibit phospholipase A_2 (PLA_2) enzymatic activity in rabbit PMNs and allergic platelet activating factor (PAF) formation or secretion in exudate cells from the rat pleural cavity with concentrations up to 100 μM, but inhibited FMLP stimulated - arachidonic acid release in rabbit PMNs with IC50 of 20 μM by indirect mode of action.

It showed a little or no direct inhibitory activity on thromboxane B_2, 6-keto $PGF_{2\alpha}$, 5-lipoxygenase, elastase and cyclo-oxygenases; however, this compound produced inhibition of the release of arachidonic acid and the formation of 5-HETE, LTB_4, as well as LTC_4 and LTC_4/LTD_4 in various cell types. The magnitude of the inhibitory activity increased with the prolongation of preincubation time (Table E.2, vol 2, p 115).

Table E.2

Effect of Azelastine HCl on the Formation of the Products of 5-Lipoxygenase Pathway of Arachidonic Acid Metabolism

Cell Type	Preincubation Time in Minutes	Stimulus	Mediator Synthesis	IC50 (μM)
Rat mixed peritoneal cells	10	A23187 (0.2 μM)	5-HETE	35.5; 55.2
			LTB_4	42.8; 47.4
			LTC_4	21.2; 22.9; 31.7
Sonicated rat basophilic leukemia cells	5	Arachidonic acid (200 μM)	5-HETE	140
Guinea pig lung fragments	10	Ovalbumin (100 μg/mL)	LTC_4/D_4	79
	15	Ovalbumin (200 μg/mL)	LTC_4/D_4	64
	20	Ovalbumin (30 μg/mL)	LTC_4	35.2
	30	Ovalbumin (200 μg/mL)	LTC_4/D_4	47
	120	Ovalbumin (10 μg/mL)	LTC_4	14
Human mixed leukocytes	10	A23187 (1 μg/mL)	LTC_4/D_4	36.7
Human neutrophils (PMN cells)	15	A23187 (1 μM)	LTB_4	30
	15		LTC_4	40
	15	A23187 (0.3-1 μg/mL)	LTC_4/D_4	36; 33
	30			2.3
	360	A23187 (1 μM)	LTB_4/C_4	1
Human lung mast cells	10	Anti-IgE (5 μg/mL)	LTC_4	42
Passively sensitized human lung fragments	10	Rabbit anti-IgE (1:5 dilution)	LTC_4	272

c. **Superoxide anion:** Azelastine hydrochloride exerts a significant inhibitory effect on the generation of superoxide free radicals in guinea pig PMNs with IC50s of 4.1-17 μM and 23 μM in rabbit PMNs. In human neutrophils and eosinophils, azelastine hydrochloride inhibited the superoxide generation at IC50s of 0.9-3.0 μM (Table E.3, vol 2, p 116).

Table E.3

Effect of Azelastine Hydrochloride on Superoxide Anion Generation

Activator	IC50 (μM) Human Neutrophils	Human Eosinophils	GP PMNs	Rabbit PMNs
PMA (40 min)	0.9	1.8	4.1	
(120 min)	2.4	2.4		
FMLP (120 min)	2.1	3.0	17	23
Calcium Ionophore (120 min)	1.6	1.7		

2. Inhibition of immediate allergic responses

(a) Skin

Azelastine hydrochloride produced strong inhibition of 72-hour IgE-mediated homologous PCA (passive cutaneous anaphylaxis) in rats (Table E.4); azelastine HCl (5-25 mg/kg, p.o.) produced 40-80% inhibition of the 48-hour homologous PCA in rats. In guinea pigs, oral dose of 0.03-7.5 mg/kg produced dose-dependent inhibition of 48-hour homologous PCA that persisted for 48 hours.

Table E.4
Anti-PCA Activities of Azelastine Hydrochloride in IgE-Mediated, 72-Hour PCA in the Rat

Drug	Route	ID50 (mg/kg) Posttreatment Time		
		2 Hours	4 Hours	24 Hours
Azelastine Hydrochloride	p.o.	1.4	1.8	2.6

The anti-allergic activity persisted for at least 24 hours but no antihistaminic or antiserotnergic activities were detected after 24 hours (Table E.5, vol 2, p 118).

Table E.5
Anti-PCA, Antihistaminic and Antiserotonin Activities of Orally Administered Azelastine Hydrochloride in Rat Skin

	Oral ID50 (mg/kg)					
	Posttreatment Time					
Drug	2 Hours			24 Hours		
	PCA	Histamine	Serotonin	PCA	Histamine	Serotonin
Azelastine Hydrochloride	2.6	3.1	>10	3.7	>10	>10

(b) Airways

Azelastine hydrochloride provided protection against antigen, aeroallergen - induced, or leukotriene - mediated immediate allergic responses (IAR-bronchoconstriction) in the airways when administered p.o., i.v., or s.c. to sensitized rats and guinea pigs without tachyphylaxis (Table E.6, vol 2, p 119).

Table E.6
Inhibition of Immediate Allergic Response (IAR) by Azelastine Hydrochloride

Species	Test	Oral ID50 (mg/kg)
Rat	Antigen (i.v.)-induced bronchoconstriction (KR)	0.7 (2 h)*
Guinea Pig	Aeroallergen-induced IAR	0.146 (30 min) 0.139 (6 h) 0.389 (8 h)
	Leukotriene-mediated acute lung anaphylaxis (KR)	0.06 (2 h) 0.12 (24 h)
	Aeroallergen-induced acute lung anaphylaxis (PM) ($+C_{dyn}$)	0.93 (2 h)
	($+R_L$)	0.05 (2 h)

*( ) posttreatment time.
KR = Konzett-Rossler method.
PM = pulmonary mechanics technique.

In addition, azelastine hydrochloride, 1 mg/kg orally, protected against aeroallergen-induced IAR, such as decline in dynamic lung compliance ($\downarrow C_{dyn}$) and an increase in lung resistance ($\uparrow R_L$) in guinea pigs (Table E.7).

Table E.7

Protective Effects of Orally Administered Azelastine HCl and Its Optical Isomers and Metabolite on Immediate Allergic Responses (Acute Lung Anaphylaxis) in the Guinea Pig

		Mean % Inhibition ± SEM					
		Posttreatment Time					
		1 Hour		2 Hours		24 Hours	
Drug	Dose (mg/kg)	$\downarrow C_{dyn}$	$\uparrow R_L$	$\downarrow C_{dyn}$	$\uparrow R_L$	$\downarrow C_{dyn}$	$\uparrow R_L$
Azelastine HCl	1	69 ± 11*	90 ± 4*	50 ± 16*	71 ± 11	47 ± 13	70 ± 10
d Isomer	1	49 ± 13*	39 ± 7	68 ± 14*	77 ± 4*	30 ± 13	50 ± 18
l Isomer	1	66 ± 13*	77 ± 8*	57 ± 14*	67 ± 15	52 ± 15*	71 ± 7*
Desmethyl metabolite	1	45 ± 12	82 ± 5	70 ± 10*	84 ± 7*	32 ± 15	44 ± 17

N - 5-8.
*P<0.05 as compared with controls.

The major metabolite, desmethylazelastine, and the d- and l-isomers exerted similar effects (Table E.7 and E.8, vol 2, p122).

Table E.8

Protective Effects of Azelastine Hydrochloride, Its Optical Isomers and Desmethyl Metabolite on Aeroallergen-Induced Immediate Allergic Responses (Acute Lung Anaphylaxis) in the Guinea Pig

	Oral ID50 (mg/kg)	
	2 Hours Posttreatment Time	
Drug	$\downarrow C_{dyn}$	$\uparrow R_L$
Azelastine Hydrochloride	0.93	0.05
d Isomer	0.29	<0.1
l Isomer	1.24	0.79
Desmethyl metabolite	0.28	<0.1

Inhibition of Antigen-induced Contractions (in vitro):

	Azelastine HCl Dose Range/ IC_{50} (Contact time with the tissue)
Rat trachea	0.7 μM
Guinea pig ileum	0.001 - 0.1 μM
Guinea pig trachea	96 μM (30 min)
	49 μM (2 hrs)
Human bronchus	100 μM (2 hrs)

Effect on Antigen-induced Airway hyperreactivity:

Azelastine hydrochloride, when administered as an aerosol to guinea pigs, inhibited IAR regardless of the method of sensitization, day of sensitization, route of antigen challenge or time of administration (15 min before, immediately before or simultaneously with antigen challenge) as shown in Table E.9 (vol 2, p 123).

Table E.9

Effects of Aerosolized Azelastine HCl (100 Inhalations) on Immediate Allergic Responses (Acute Lung Anaphylactic Responses) in Guinea Pigs Sensitized to Ovalbumin (OA) by Three Different Methods

Method of Sensitization	Days of Sensitization	Challenge Dose of OA, Route	Conc. of Drug Solution (mg/mL)	Time of Aerosol Administration	Mean % Inhibition ± SEM $+C_{dyn}$	$+R_L$
1 mg OA plus $5x10^9$ B. pertussis cells, i.p.	14-18	0.6 mg/kg, i.v.	10	15 minutes prechallenge	89 ± 6***	97 ± 1**
10 μg OA plus 100 mg $Al(OH)_3$, i.p.	15-18	0.3 mg/kg, i.v.	1	immediately before challenge	12 ± 6	55 ± 15
			5		41 ± 24	52 ± 18
			10		89 ± 10***	96 ± 4**
			1	15 minutes prechallenge	33 ± 13	53 ± 19
			5		29 ± 13	55 ± 18
			10		57 ± 15**	71 ± 18*
	15-28	100 inhalations of aerosol (100 mg/mL)	10	immediately before, simultaneous with and 15 min before challenge	46 ± 12*	52 ± 12
					48 ± 14*	52 ± 16
					30 ± 8	49 ± 13
OA aerosol	30-43	0.6 mg/kg, i.v.	10	immediately before and 15 min before challenge	92 ± 6*	96 ± 2*
					79 ± 16*	90 ± 8*

*p<0.05; **p<0.01; ***p<0.001 as compared with controls

In guinea pigs, azelastine HCl, 1 mg/kg orally, produced dose-dependent inhibition of late phase-associated eosinophil infiltration in tracheobronchial tree and lungs; 3 mg/kg orally, two hours before aeroallergen challenge reduced viscosity of the bronchial lavage fluid during the late-phase allergic response.

b) Effect on chemical mediator-induced responses in vivo models:

1) Antihistaminic activity

a. Azelastine hydrochloride is a H_1-receptor antagonist in vivo and in vitro as shown in Table E.10 and E.11.
b. Topical application of Azelastine hydrochloride, 0.3 or 1% either in a cream or aqueous solution, inhibited (84-93%) histamine-induced whealing responses in rabbit skin.
c. Oral dose of **2 mg/kg** abolished histamine-induced reduction in nasal obstruction in dogs
d. Oral dose of **0.001-0.1 mg/kg** blocks histamine-induced shock in guinea pigs; **1 mg/kg** protective effect persisted for 18 hours.

Table E.10
In Vivo Histaminolytic Activity of Azelastine Hydrochloride

Species	Route of Histamine Admin.	Oral ID50 (µg/kg) and Posttreatment Time	
Inhibition of Wheal and Flare Response			
Rat	intradermal	1400	2 h
		2100	2 h
Guinea Pig	intradermal	16	2 h
Inhibition of Bronchospasm Response			
Guinea Pig	i.v.	17.5	5 min
		130	3 h
	aerosol inhalation	37.0	2 h
		29.2	8 h
		118	24 h
		740	48 h
		161	0.5 h
		123	4 h
		180	6 h
		178	8 h

2) Inhibitory Activity Induced by Other Mediators

Inhibition	Induced by	ID_{50}	
Bronchospasm (GP)	PAF	0.11 mg/kg	(p.o.)
		0.031 mg/kg	(i.v.)
Cutaneous reaction 40-60% rat skin	Serotonin	5-25 mg/kg	(p.o.)
		0.3-1 mg/kg	(p.o.)
Bronchospasm 11% blockade (GP)	Acetylcholine	2.15 mg/kg	(i.v.)
Intestinal spasm 19% blockade	Neostigmine	10 mg/kg	(i.v.)

In vitro studies, azelastine hydrochloride inhibited smooth muscle contractile responses to histamine as well as other mediators such as serotonin, acetylcholine, leukotrienes, Ca^{2+} and bradykinin. (Table E.11, vol 2, p 127).

Table E.11
Antagonism by Azelastine HCl of Histamine, Serotonin, Norepinephrine, Acetylcholine, Crude SRS-A, Leukotriene C_4, Leukotriene D_4, Bradykinin and Calcium in Isolated Tissue Preparations

Tissue	Spasmogen	IC50 (M)
Guinea pig ileum	Histamine dihydrochloride	6.5×10^{-9} 8.55×10^{-9} 8.6×10^{-9}
Rat stomach fundus	Serotonin creatinine sulfate	4.3×10^{-7}
Rat uterus	Serotonin creatinine sulfate	6.5×10^{-8}
Guinea pig vas deferens	L-norepinephrine bitartrate	5.3×10^{-7}
Guinea pig ileum	Acetylcholine chloride	3.1×10^{-6}
	Calcium chloride	6.05×10^{-6}
	Crude SRS-A (rat)	7.9×10^{-6}
	Leukotriene C_4	8.27×10^{-6} 7.0×10^{-6} 1.32×10^{-5}
	Leukotriene D_4	8.39×10^{-6} 1.1×10^{-5}
	Bradykinin triacetate	1.03×10^{-5}
Guinea pig trachea	Calcium chloride	9.84×10^{-6}
	Serotonin creatinine sulfate	5.64×10^{-7}

B. Other Pharmacologic Actions:

	CNS Activity	
Mouse:	depressed motor activity	≥20 mg/kg, p.o.
	potentiated pentobarbital induced hypnosis	10 mg/kg, p.o.
	no potentiation of a sub - hypnotic dose of alcohol	25 & 50 mg/kg, p.o.
	no convulsion	40 mg/kg, p.o.
Rats:	no effect on EEG	10 mg/kg, i.v.
	transient inhibition of the polysynaptic reflex potential	1-10 mg/kg, i.v.
Rabbit:	no effect on EEG	2 or 8 mg/kg, i.v.
Dogs:	CNS stimulation	10-30 mg/kg, s.c.
Monkeys:	CNS stimulation	3-6 mg/kg, i.v.
	clonic convulsions	10 mg/kg, i.v.
	Cardiovascular	
	no appreciable effect on anesthetized animals	therapeutic dose
Dog	decrease in BP and increase or decrease in heart rate	2-10 mg/kg, i.v.
	reduction of ST segment elevation	1 mg/kg, i.v.
Rat	increase in BP and heart rate	2-10 mg/kg, i.v.
Cat	decrease in BP and HR	2-10 mg/kg, i.v.
	Respiratory	
Mouse:	increase in tracheobronchial secretion	0.52 mg/kg, p.o.
Dog:	decrease mucus rigidity	eq.to human dose of 3 mg/kg, i.v.
	decrease in antigen-elevated visco-elasticity of tracheal mucus	3 mg/kg, p.o.
	Gastrointestinal	
Mouse:	no effect on gastric motility or emptying or GI transport	1-50 mg/kg/, p.o.
Rat:	increase the amplitude of gastric and duodenal contractions	1 mg/kg, i.v.
	decrease --	5 mg/kg, i.v.
	slight acceleration of gastric emptying	1-10 mg/kg, p.o.
	retard --	50 mg/kg, p.o.

no effect on intestinal motility, pancreatic and biliary secretions — 5-200 mg/kg, p.o.
no ulcerogenic effect
inhibition of gastric secretion

Urogenital

Rats: no effect on urine volume, urinary excretion of electrolytes — 0.25-25 mg/kg, p.o.
no effect on uterine movements — 3 mg/kg, i.v.

Dog: no effect on renal blood flow, glomerular filtration rate — 0.5 mg/kg, i.v.

Anti-inflammatory

GP: inhibition of minimum heterologous and homologous reverse passive Arthus reactions (RPA) — 0.1-20 mg/kg, p.o. 30 min
maximum (40%) effect on RPA — 20 mg/kg, p.o.

delayed hypersensitivity:
tuberculin reaction-no effect — 20 mg/kg, p.o.
Listeria proteolipid-inhibition — 0.214-4.64 mg/kg, sc

Ancillary

No antitussive activity in cats and GP — 1-6 mg/kg/, i.v.
Inhibition of platelet aggregation:
induced by ADP: rat, gp and rabbit
PAF: rabbit, human
thrombin: rat

No cytotoxic effects in rabbit PMN cell in vitro
No effect on blood coagulation, fibrinolytic capacity

C. Special Pharmacology Studies

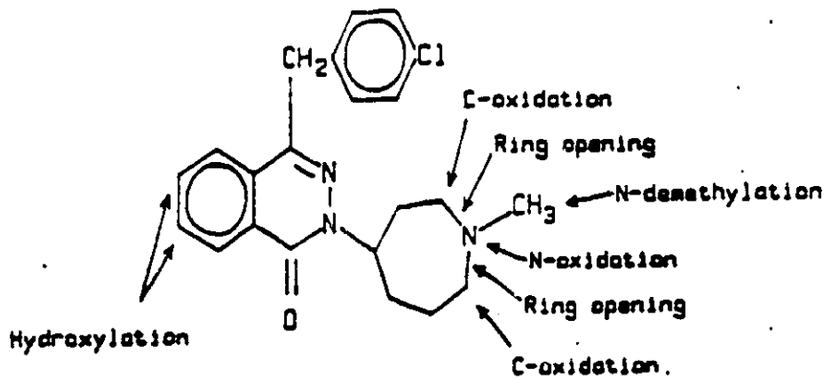
a. Drug interactions

Azelastine hydrochloride (0.1-1.0 mg/kg, i.v. or p.o.) exerted no significant interactions with DSCG (0.1-3.0 mg/kg, i.v.), prednisolone (1-30 mg/kg, p.o.), albuterol (0.001-1.0 mg/kg, p.o. and/or i.v.) or theophylline (0.1-1.0 mg/kg, p.o.) in the rat PCA model.

b. Pharmacologic profile of metabolites

Metabolism studies with [^{14}C]-azelastine hydrochloride in animals showed that it is extensively metabolized in the liver through eight different pathways as shown in Figure E.4 (vol 2, p 131). The major metabolites appear to be derived by 6-hydroxylation, C_7-oxidation, cleavage of N-C_7 and N-demethylation.

Figure E.4
Metabolic Pathways for Azelastine Hydrochloride in Animals



Desmethylazelastine (metabolite 4) has been found in the plasma of mouse, guinea pig, dog and man. It is pharmacologically similar to azelastine hydrochloride, more active than azelastine against antigen-induced decline in dynamic lung compliance and aginst pulmonary airway resistance with longer antiallergic activity (24-48 hours). Some of the pharmacological activities of the metabolites are shown in Table E.12 (vol 2, p 132).

Table E.12
Effect of Metabolites of Azelastine HCl on Allergic and Nonallergic Mediator Synthesis/Release

	IC50 (μM)				
	Allergic Histamine Secretion		Calcium Ionophore		Allergic LTC_4 Formation
Drug	Rabbit Basophils	Rat Peritoneal Mast Cells	Histamine Secretion (Rat Peritoneal Mast Cells)	LTC_4 Formation (Rat Mixed Peritoneal Cells)	(Guinea Pig Chopped Lung)
Azelastine HCl	1.9; 4.5	4.8	2.7	21.2	14.0
Desmethyl metabolite	1.2	3.9	0.8	16.4	> 50.0
6-Hydroxy metabolite	1.4	12.3	0.7	20.4	
7-Hydroxy metabolite	0.8	0.31	0.9		
6-Hydroxydesmethyl metabolite			13.2	26.6	
7-Hydroxydesmethyl metabolite			3.6	25.0	
Methylaminocarboxy-2-pentyl metabolite			> 50.0	> 50.0	
Methylaminocarboxy-3-pentyl metabolite				> 50.0	

c. Mechanism of action

Azelastine has been shown to inhibit activation of mast cells and basophils and to antagonize histamine in the nasal cavity of dog, skin of rats and airways of guinea pigs and dogs.

The precise mode of action is not yet known; however, the synthesis/secretion of mediators depends on the influx or release of Ca^{2+} from intracellular sources. It has been proposed that inhibition of Ca^{2+}/calmodulin-dependent steps in the stimulus-secretion coupling mechanisms in inflammatory cells and in stimulus-contraction coupling mechanism in smooth muscle cells by azelastine hydrochloride may be important to the mechanism of action of the drug.

Summary of Pharmacology

Azelastine hydrochloride inhibits immediate allergic reactions in the airways (bronchoconstriction) of the dog, guinea pig and rat and the skin (wheal and flare) of the rat and guinea pig. It is a potent H_1-histamine receptor antagonist and in addition has long-lasting antiallergic activity. In vitro studies showed its indirect anti-inflammatory activities:

-by preventing the activation of inflammatory cells - mast cells, basophils, eosinophils, PMNs, macrophages and monocytes

-by inhibiting the synthesis of LTB_4, LTC_4 and superoxide anion and secretion of histamine, substance P and acetylcholine

-by moderate to strong receptor antagonism to Ca^{2+}, serotonin, acetylcholine, platelet-activating factor (PAF), leukotrienes, adenosine and bradykinin in isolated tissues and/or in vivo.

Azelastine has little or no direct inhibitory effect on PLA_2, elastase, cyclo-oxygenase and 5-lipoxygenase, but interferes with the release of arachidonic acid and formation of 5-HETE, LTB_4 and LTC_4/LTD_4, by an indirect mode of action (Ca^{2+}-dependent activation/translocation).

In addition, azelastine HCl has been shown to inhibit aeroallergen-induced eosinophilia in the airways in guinea pigs; thus it seems to provide protection in both the early and late phases of allergic responses by inhibiting the synthesis and/or secretion of those chemical mediator in the airways or interfering with the action of these mediators known to be involved in immediate hypersensitivity and airway inflammatory processes.

Azelastine hydrochloride administered at high oral doses (30-50 mg/kg) to mice and rats produced little or no apparent CNS changes except depressed motor activity in mice at doses ≥ 20 mg/kg. Intravenous doses of 10 mg/kg in rats and up to 8 mg/kg in rabbits showed no effects on the spontaneous EEG and failed to prevent EEG arousal responses. However, the administration of high doses (10-30 mg/kg, s.c.) to dogs and 3-6 mg/kg i.v. to cynomolgus monkeys produced CNS stimulation and even convulsions at 10 mg/kg, i.v. in monkeys.

In general, azelastine hydrochloride in therapeutic dose ranges usually effective against allergic responses was devoid of any effects on the cardiovascular and respiratory systems of anesthetized rats, dogs and cats.

Intravenous administration of azelastine hydrochloride to rats (2 mg/kg), dogs (<1-1 mg/kg) and cats (<2-15 mg/kg) did not affect systemic blood pressure or heart rate. However, higher doses (5-10 mg/kg, depending on species tested) resulted in increase (rat) or decrease (dog, cat) in blood pressure and increase (rat, dog) or decrease (dog, cat) in heart rate. At 1 mg/kg i.v., it exerted long-lasting reduction of ST segment elevation in dogs and nondose-related arrhythmias in rats . ECG changes, prolonged Q-T intervals at 20 mg/kg and prolonged QRS and QT intervals were observed at ≥40 mg/kg in a toxicity study. In addition, localized myocardial degeneration in the heart and adipose cell infiltration in the interstitial tissue of the myocardium have been noted at 40 and 60 mg/kg, respectively, suggesting an effect of azelastine administration on the heart at very high doses.

Azelastine Hcl caused a dose-dependent increase in tracheobronchial secretion in the mouse with an ED50 of 0.52 mg/kg, p.o. and enhanced mucolytic activity in the tracheobronchial lumen of rats (ED50 = 0.33 mg/kg). It was found to decrease mucus rigidity in beagle dogs at a dose equivalent to 3 mg/kg and decreased antigen-elevated viscoelasticity of tracheal mucus in the dogs.

Oral administration of azelastine HCl of 1 to 50 mg/kg did not influence gastric motility and emptying in mice, but in rats, 1 to 10 mg/kg produced a slight acceleration of gastric emptying and retardation at 50 mg/kg. It exerted little or no effect on intestinal motility or pancreatic, biliary and salivary secretions in rats.

Summary of Pharmacologic Activities of Azelastine HCl

Pharmacological Activities	Animals/Tissue	Treatment time	Oral ID_{50}/IC_{50}
Antihistaminic activity in vitro	GP trachea		0.9-22 ng/ml
	Rat trachea		0.7-0.88 μM
Skin reaction (wheal and flare)	Rat		1.4-2.1 mg/kg
	GP		0.016 mg/kg
Broncholytic	GP		2.7 μg/kg, iv
	Dog		25.5 μg/kg,id
			4.3 μg/kg,iv
Anti-allergic (RPA)	GP		0.1-20 mg/kg
Anti-allergic activity	GP trachea		9.6×10^{-6} μM
Skin:			
Inhibition of 72-hr PCA (hour prior to antigen challenge)	Rat	2 hr	1.4 mg/kg
		4	1.8
		24	2.6
Anti-PCA effect (48-hour homologous PCA reaction)	Rat		5-25 mg/kg
	GP		0.03-7.5 mg/kg
Lung:			
Brocholytic (IgE-mediated)	Rat	2	0.7 mg/kg
Inhibition of asthma by aeroallergen	GP	1-8	0.3-1.0 mg/kg
		2	0.1 mg/kg
Inhibition of eosinophil infiltration (late phase)	GP		1 mg/kg
Mucolytic activity	GP		3 mg/kg
Anti-SRS-A (Leukotrienes)	GP ileium		3.3 μg/ml
Broncholytic	GP	2	0.063 mg/kg
Anti-Serotonin activity			
Skin reaction	Rat		5-25 mg/kg
			0.1-3 mg/kg
Anticholinergic activity (weak-broncholytic)	GP		2.15 mg/kg,i.v.
Anti-PAF activity	GP platelet		0.7-1.0 mM

2. TOXICOLOGY

Preclinical toxicology studies have been conducted by Wallace, ASTA Pharma , West Germany (G), England (E), Scotland (S), Canada (C) and Japan (J) as summarized below. (vol 22, p 05 4024)

A. Acute Toxicity
   - LD_{50}s (G,J)-mouse, rat, guinea pig and dog

B. Subchronic Toxicity
   - Rat -5 weeks(J), 6 weeks (G) and 3 months (US)
   - Neonatal Rat - 7 weeks (US)
   - Dog - 5 weeks (J) and 6 weeks (G)

   Chronic Toxicity
   - Oral Studies
     - Rat - 6 months (G,J) and 12 months (J)
     - Dog - 6 months (G,E) and 12 months (US)
   - Intranasal Studies
     - Rat - 6 months (C)
     - Dog - 6 months (S)

C. Carcinogenicity
   - Mouse - 24 months (G)
   - Rat - 24 months (US)

D. Special Studies
   - Acute Toxicity (J)
   - Maximum Tolerated Dose - Hamster (US)
   - Dermal Studies (G)
   - Ocular Studies (G)
   - In Vitro Cytotoxicity (J)
   - Combination Studies - Azelastine Hcl/d-Pseudoephedrine Hcl
     - Acute LD_{50}s - mouse and rat (US)
     - Subchronic Toxicity
       - Rat - 3 weeks and 3 months (US)
       - Dog - 3 weeks and 3 months (US)
     - Reproductive Toxicity
       - Rat - Dose Range and Segment II (US)
       - Rabbit - Dose Range and Segment II (US)

E. Reproductive Toxicity
   - Segment I - rat (G,J)
   - Segment II - mouse (J), rat (G,J) and rabbit (G,J)
   - Segment III - rat (J)
   - Multigeneration Study - rat (G)

F. Mutagenicity Studies
   - Bacterial Assays (US,J,G)
   - Mouse Lymphoma Forward Mutation Assay (US)
   - Mouse Micronucleus Test (US,J)
   - Rat Chromosomal Aberration Test (G)

A. **Acute Toxicity Studies** (vol. 22, p. 05 4027)

Species	Route	LD_{50} or range (mg/kg)+ Male	Female
Mouse	p.o.	124-143	139-156
	p.o.*	200	153
	p.o.**	180	210
	i.v.	25.4-36.5	29.3-35.5
	i.p.	56.4	42.8
	s.c.	63.0	54.2
Rat (Adult)	p.o.	310-660	417-580
	i.v.	24.6-25.9	28.5-30.3
	i.m.	143	115
	i.p.	43.2	46.6
	s.c.	66.5-90.5	59.6-80.5
Rat (21-Day)	p.o.	180	186
Guinea pig	p.o.	126	130
	i.v.	23.0	24.8
	i.m.	46.2	52.2
	s.c.	41.0	37.3
Dog	p.o.	51.3-107	51.3-153
	i.v.	11.3-17.2	13.7

\+ Based on 7 or 14 -day observation periods.
* d-Isomer
** l-Isomer The others are with racemic mixtures.

Regardless of route of administration, dose-related clinical signs seen in mice and rats included blepharoptosis, tremor, clonic and tonic convulsions, loss of righting reflex, decreased muscle tone and salivation. In guinea pigs, tremors, convulsions and irritability were often observed.

In dogs after p.o. or i.v. administration, clinical signs observed included emesis, salivation, tremor, loss of righting reflex, difficult respiration, aggressive behavior and tonic-clonic seizures.

Summary: Across the species, the sensitivity to azelastine HCl was very similar except the dogs which were slightly more sensitive. The clinical signs observed in all species were indicative of central nervous system stimulation.

B. Subchronic and Chronic Toxicity Studies (vol.2, p. 145)

1. Mouse

Strain	No.of Animals	Method of Adm.	Duration	Dosage, mg/kg/day
(MTD Study)				
NMRI	300/sex	feed	17 weeks	0, 1, 5, 30, 60,120
(Carcinogenicity Study)				
NMRI	270/sex	feed	2 years	0, 1, 5, 25

The MTD determination study and the carcinogenicity study are discussed in detail under the carcinogenicity assessment section on page 31.

2. Rat

Strain	No.of Animals	Method of Adm.	Duration	Dosage, mg/kg/day
SD-Slc	50/sex	gavage	5 weeks	0, 3, 10, 30, 100
SD/MR-1200	55/sex	feed	6 weeks	0, 10, 31.6, 100
SD-CD-1*	100/sex	gavage	7 weeks	0, 1, 5, 30
SD-CD-1	60/sex	gavage	3 months	0, 1, 30, 90
SD-CD-1+	50/sex	feed	14 weeks	0,50,100,200,400
SD/MR-1200	40/sex	feed	6 months	0, 3.16, 10, 31.6
SD	50/sex	gavage	6 months	0, 1, 3, 10, 30
SD	50/sex	gavage	1 year	0, 1, 3, 10, 30
Crl:CD(SD)BR	310/sex	feed	2 years	0, 1, 5, 30
(Carcinogenicity Study)				
Crl:CD(SD)BR	75/sex	nasal	6 months	0, 0.2, 0.4, 0.8**
SD	48/sex	i.v.	4 week	0, 1, 2.15, 4.64

* Neonatal (5-7 day old)
** Dose is mg/animal as 0.1% nasal formulation.
\+ MTD study (12 weeks on drug + 2 weeks recovery period)

Mortality and Body weight/Food consumption: Mortality was observed at the highest doses, 400 mg/kg/day when the drug was given in feed mixture (4/20) and 100 mg/kg/day when given by gavage (6/20, 2/20). The lowest dose that caused drug-related death (2/20) in 5 week study was 30 mg/kg/day by gavage which was 375 times the proposed clinical total daily dose (4 mg/day). In general, body weight gain and/or food consumption was lower than control values following the administration of azelastine Hcl in mid to high dose groups.

Hematology and Clinical chemistry parameters: Reduction in hematocrit, hemoglobin and RBCs were observed in some but not all studies and variable at doses of 30 mg/kg/day or greater. The changes were statistically significant but biologically not significant. Increases in alkaline phosphatase was seen consistently at 30 mg/kg/day or greater. Glutamic pyruvic transaminase, glutamic oxalacetic transaminase, BUN, serum cholesterol and glucose level were elevated at high doses (68.6 or 100 mg/kg/day).

Urinalysis parameters: There were increases in urine volume for female rats dosed at 30 mg/kg/day in the one-year study and the increased urinary excretion of potassium and chloride noted for the same animals. However, there was no correlation between these changes and blood urea nitrogen or creatinine determinations or the histopathological changes in the kidneys of these rats.

Organ weights: The absolute/relative liver weight and absolute kidney weight increased in the female rat at doses of 30 mg/kg/day, but the changes for kidney weight were within the normal range. The absolute/relative liver weight increased in the male rat at higher doses.

Histopathological findings: The consistent observation in mice and rats (but not in dogs) at doses of 30 mg/kg/day or greater was hepatocellular cytoplasmic vacuolation. There were sometimes nuclear displacement but no degeneration or necrosis associated with the vacuoles.

When azelastine hydrochloride was studied in **neonatal rats** given orally by gavage for 49 days, azelastine showed no toxic effects in neonatal rats at 1 and 5 mg/kg/day and slight toxicity at 30 mg/kg/day as was seen in adult rats. NOEL was considered to be 1 mg/kg/day.

Plasma drug levels: Plasma drug levels were determined after administration of azelastine hydrochloride by gavage or as a drug-feed admixture. Analysis indicate that the compound was absorbed in a dose-dependent manner in rats.

Summary of Toxicity in Rats:

Most of the changes in hematology (elevated serum AP, SGOT and SGPT) and urinary parameters (increased urine volume and potassium), liver and kidney weight increases and hepatocellular changes (cytoplasmic vacuolation) occurred at 30 mg/kg/day and higher. The target organs for toxicity were liver and kidney and the drug-induced changes appeared reversible upon drug withdrawal.

NOEL was considered to be 3 mg/kg/day in subchronic study and later increased to 10 mg/kg/day in 6-month study. NOEL for neonatal rats was 1 mg/kg/day.

3. Dog

Strain	No.of Animals	Method of Adm.	Duration	Dosage, mg/kg/day
Beagle	12/sex	capsule	5 weeks	0, 5, 20, 40, 60
Beagle	6/sex	capsule	6 weeks	0, 4.64, 10, 21.5
Beagle	12/sex	capsule	6 months	0, 4.64, 10, 21.5
Beagle	35/sex	capsule	6 months	0, 0.2, 1, 5, 10*
Beagle	21M/20F	capsule	1 year	0, 1, 3, 10
Beagle	20/sex	nasal	6 months	0,0.84,1.68,3.36**
Beagle	9/sex	i.v.	4 weeks	0, 0.464, 1, 2.15

* Dose reduced to 10 mg/kg/day after 5 days from 20 mg/kg/day.
** Dose is mg/animal as 0.1% nasal formulation.

Mortality and Body weight/Food consumption: Mortality was observed mostly at doses **20 mg/kg/day** or above when given by capsule. The lowest dose that caused drug-related death (1/10) preceded by aggression and convulsions in 1-year study was 10 mg/kg/day which was 125 times the proposed clinical total daily dose.

Sporadic emesis and salivation were observed at 3 and 10 mg/kg/day and convulsions and other CNS disturbances (tremor, paddling of limbs and snapping of jaws) observed at 10 mg/kg/day and above in 1-year study. Females were more frequently affected than males.

Body weight gain and/or food consumption was decreased following the administration of azelastine hydrochloride at doses 10 mg/kg/day in males and 3 mg/kg/day in females.

Hematology and Clinical chemistry parameters: There were no changes in hematology or clinical chemistry parameters when dogs were dosed at 10 mg/kg/day for one-year as was seen in studies with rats.

Ophthalmic evaluation: Azelastine hydrochloride did not produce any ophthalmic abnormalities in dogs.

Cardiac effects: In dogs, there were no appreciable pharmacologic effects on the cardiovascular system in therapeutic dose range; however, there were decrease in blood pressure and increase or decrease in heart rate at 2-10 mg/kg, i.v. and up to 68% reduction of ST segment elevation at 1 mg/kg, i.v. In a 5-week study, prolonged Q-T intervals in 2/4 dogs at 20 mg/kg orally at week 1 and 4, and prolonged QRS and QT intervals were observed in 40 and 60 mg/kg/day dose groups at week one after dosing.

In addition, discoloration of myocardium, increased adipose cells of myocardium have been noted at 40 and 60 mg/kg, respectively.

Histopathological findings: In a 26-week dog study, slight to moderate degeneration of renal cortical tubular epithelium was seen in animals dosed at 4.64-21.5 mg/kg/day for 13 and 26 weeks.

The distribution of the kidney changes:

	After 13 weeks	After 26 weeks
Control	1/6	1/6
4.64 mg/kg	2/2	3/6
10 mg/kg	1/2	4/6
21.5 mg/kg	0/2	1/6

However, the above findings were not conclusive since there was no dose response and no changes in blood urea nitrogen, creatinine or specific gravity to correlate the histological findings. In addition, another six-month dog study conducted at doses of 0, 0.2, 1. 5 and 20/10 mg/kg/day and a one-year dog study conducted at 0, 1, 3, and 10 mg/kg/day did not reveal similar histo-pathological lesions of the kidney.

When azelastine hydrochloride was administered intravenously to dogs, there were signs of irritation to blood vessels at all dose levels such as perivasculitis, thrombosis, fibrinoid necrosis.

There was no change in the liver such as hepatocellular cytoplasmic vacuolation as was observed in rats.

Plasma drug levels: Plasma drug levels were determined after administration of azelastine hydrochloride to dogs by capsule. Analysis indicate that the compound was absorbed in a dose-dependent manner in dogs.

Summary of Toxicity in Dogs:

NOEL for the dogs was determined to be 1 mg/kg/day from one-year toxicity study. There was minimal toxicity (sporadic emesis and salivation) observed in dogs at 3 mg/kg/day and definite toxicity (aggression and convulsions) at 10 mg/kg/day; 20 mg/kg/day was lethal. MTD was considered to be 10 mg/kg/day.

Dogs seem to be more sensitive species to azelastine hydrochloride than rats in terms of CNS effect with toni-clonic convulsions at high doses. The hepatocellular vacuolation found in rats was not observed in dog. The degeneration of renal cortical tubular epithelium was found in one 6-month study which may have been incidental. In 5-

week study, many dogs exhibited positive test for urinary proteins at ≥5 mg/kg/day without corresponding histological changes. Electron microscopic examination of the liver and kidney in other studies showed no apparent drug-related effects.

Prolongation of the QRS and QT intervals, localized myocardial degeneration in the heart detected visually, and adipose cell infiltration in the interstitial tissue of the myocardium detected histopathologically were observed among the dogs in the 40 and 60 mg/kg/day dose groups, suggesting an effect of azelastine administration on the heart. Q-T prolongation was seen in 2/4 dogs at ≥20 mg/kg orally; however, at this dose, tonic-convulsions were observed and mortality occurred (1/4) at week 5 and all animals died at ≥40 mg/kg/day after the first week.

Summary tables on toxicity parameters observed during oral multidose studies are provided (vol.2, pp. 147-158).

Table E.15
Summary of Mortality for Oral Multiple-Dose Toxicity Studies with Azelastine HCl

Species	Method of Admin.	Study Duration (Wks)	Dose (mg/kg)	Multiple of Human Dose*	No. Dead/ Total
Rat	Drug/Feed	14	400	4545	4/20
Rat	Gavage	5	100	1136	6/20
Rat	Gavage	5	30	341	2/20
			100	1136	2/20
Rat	Gavage	13	90	1023	5/30
Dog	Capsule	5	20	227	1/4
			40	455	6/6
			60	682	6/6
Dog	Capsule	26	21.5	244	2/6
Dog	Capsule	26	20	227	2/14
Dog	Capsule	52	10	114	1/10

* Assumes a maximum total daily dose of 4.4 mg/day given to a 50 kg individual; therefore, the dose would be 0.088 mg/kg.

Table E.16
Summary of Body Weight and Food Consumption Changes
During Oral Multi-Dose Toxicity Studies with Azelastine HCl

Species	Method of Admin.	Study Duration (Wks)	Dose (mg/kg)	Multiple of Human Dose	Food Consumption	Body Weight (BW)	Range (%) of Reduction in BW or BW Gain
Mouse	drug/feed	17	120	1364	decr. male	decr. male	10
Rat	drug/feed	14	50,100, 200,400	568,1136 2273,4545	decr. male & female	decr. male & female	6-64
Rat	gavage	5	100	1136	decr. male & female	decr. female	9
Rat	gavage	5	100	1136	decr. male & female	decr. male & female	9-10
Rat	drug/feed	6	100	1136	decr. female	decr. male & female	17-18
Rat	gavage	13	90	1023	NC	decr. male	8
Dog	capsule	5	40,60	455,682	decr. male & female	decr. male & female	(a)
Rat	drug/feed	26	31.6	359	decr. male & female	decr. female	6
Dog	capsule	26	21.5	244	NC	decr. male & female	5-12
Dog	capsule	26	20,10	277,114	NC	NC	0
Dog	capsule	52	10	114	NC	decr. male & female	16-63
Mouse	drug/feed	104	25	284	NC	decr. male	4
Rat	drug/feed	104	30	341	NC	decr. male	14

(a) = animals died prior to end of study.
NC = No change

Table E.18
Mean Values for Selected Hematology Parameters During Oral Multi-Dose Toxicity Studies in the Rat with Azelastine HCl

Study Duration (Wks)	Sex	Dose Level (mg/kg)	Multiple of Human Dose	HGB (g/dL)	HCT (%)	WBC (10x3/mL)	Neutro. (%)
5	M	0		NC	NC	11.2	10.8
	M	100	1136			15.1	15.6
	F	0		NC	NC	9.8	13.7
	F	100	1136			14.7	18.1
5	M	0		15.8	44.5	NC	NC
	M	30	341	16.0	45.9		
	M	100	1136	16.7	46.7		
	F	0		15.3	43.5	NC	NC
	F	30	341	14.8	42.0		
	F	100	1136	14.7	41.4		
13	M	0		14.80	40.55	NC	NC
	M	10	114	15.04	41.13		
	M	30	341	14.83	40.52		
	M	90	1023	15.17	42.03		
	F	0		14.54	39.88	NC	NC
	F	10	114	13.85	38.30		
	F	30	341	13.99*	38.47*		
	F	90	1023	13.67*	38.19*		
26	M	0		NC	47.1	NC	NC
	M	30	341		45.7*		
	F	0		NC	45.2	NC	NC
	F	30	341		43.6*		
52	M	0		NC	47.5	NC	NC
	M	30	341		47.6		
	F	0		NC	44.9	NC	NC
	F	30	341		43.0*		

NC = No change.
*$p < 0.05$ compared to control group

Table E.19
Summary of Changes in Clinical Chemistry Parameters
During Oral Multi-Dose Toxicity Studies with Azelastine HCl

Species	Method of Admin.	Study Duration (Wks)	Dose (mg/kg)	Multiple of Human Dose	Parameters
Rat	gavage	5	30	341	incr. Alk.Phos., GPT, female
			100	1136	incr. Alk.Phos. & GPT, male & female incr. Choles., female
Rat	gavage	5	10	114	incr. Alk. Phos., male
			100	1136	incr. Alk. Phos., GPT & GOT, male & female incr. Glucose, female incr. BUN, male & female
Rat	gavage	13	30	341	incr. Alk.Phos. & Choles., female
			90	1023	incr. Alk.Phos., GPT & K, male incr. Alk.Phos, BUN, K & Choles., female
Rat	drug/feed	14	50,100 200,400	568,1136 2273,4545	incr. Alk.Phos., male & female
			200,400	2273,4545	incr. GPT, male
Rat	gavage	26	30	341	incr. Alk.Phos., male decr. Cl, female
Rat	gavage	52	30	341	decr. K, female

Table E.20
Mean Values for Selected Clinical Chemistry Parameters During Oral Multi-Dose Toxicity Studies in the Rat with Azelastine HCl

Study Duration (Wks)	Sex	Dose Level (mg/kg)	Multiple of Human Dose	Alk. Phos. (IU/L)	GPT (IU/L)	GOT (IU/L)	Choles. (mg/dL)	BUN (mg/dL)	K (meq/L)	Cl (meq/L)	Glucose (mg/dL)
5	M	0		120.5	57.1	NC	57.6	NC	NC	NC	NC
	M	30	341	131.3	57.6		57.4				
	M	100	1136	174.5	70.3		69.9				
	F	0		62.8	34.6	NC	62.2	NC	NC	NC	NC
	F	30	341	78.6	44.1		72.2				
	F	100	1136	174.7	72.7		93.8				
5	M	0		140.1	61.1	110.9	NC	13.75	NC	NC	146.6
	M	10	114	163.8	61.1	122.1		14.70			144.1
	M	30	341	163.9	52.1	113.4		13.90			134.2
	M	100	1136	200.4	89.7	140.1		17.62			135.2
	F	0		88.9	30.9	87.3	NC	15.11	NC	125.5	146.9
	F	10	114	102.0	34.7	92.6		14.60		124.4	143.8
	F	30	341	92.0	36.3	91.3		14.24		124.2	144.1
	F	100	1136	175.6	58.3	153.6		21.38		120.9	128.1
13	M	0		279.4	NC	NC	80.7	16.5	4.07	NC	NC
	M	30	341	255.0			78.3	16.0	3.92		
	M	90	1023	464.7*			76.7	18.9	4.30		
	F	0		161.2	NC	NC	82.3	18.6	3.62	NC	NC
	F	30	341	199.6*			92.8	17.5	3.40		
	F	90	1023	301.2*			100.0*	20.5*	4.28*		
14	M	0		237.4	73.8	NC	NC	NC	NC	NC	NC
	M	50	568	277.0	69.8						
	M	100	1136	428.0*	83.5*						
	M	200	2273	802.8*	104.2*						
	M	400a	4545	>510.8	82.8						
	F	0		226.0	73.8	NC	NC	NC	NC	NC	NC
	F	50	568	345.6	75.6						
	F	100	1136	410.2*	79.4						
	F	200	2273	>672.0*	72.3						
	F	400a	4545	1018.5	67.8						
26	M	0		69.7	NC	NC	NC	NC	NC	124.6	NC
	M	30	341	83.3*						124.3	
	F	0		32.9	NC	NC	NC	NC	NC	126.4	NC
	F	30	341	39.4						122.7*	
52	M	0		NC	NC	NC	NC	NC	4.14	NC	NC
	M	30	341						4.32		
	F	0		NC	NC	NC	NC	NC	4.05	NC	NC
	F	30	341						3.75*		

a = Values at Week 8, all other values at Week 12.
NC = No change.
* $p < 0.05$ compared to control group

Table E.22
Mean Values for Selected Urinalysis Parameters During
Oral Multi-Dose Toxicity Studies in the Rat with Azelastine HCl

Study Duration (Wks)	Sex	Dose Level (mg/kg)	Multiple of Human Dose	Volume (mL)	mEq/23 hrs. Na	K	Cl
5	M	0		23.1	0.99	1.67	0.86
	M	30	341	29.8	1.34	1.68	0.74
	M	100	1136	22.4	1.61	1.64	1.41
	F	0		10.7	0.56	0.89	0.51
	F	30	341	17.8	0.89	0.99	0.71
	F	100	1136	17.8	1.11	1.39	1.14
5	M	0		20.9	0.53	1.69	0.57
	M	10	114	20.4	0.80	1.74	0.69
	M	30	341	28.8	0.98	1.67	0.75
	M	100	1136	29.1	1.60	1.83	1.62
	F	0		24.3	0.42	0.96	0.50
	F	10	114	27.0	0.62	0.98	0.70
	F	30	341	19.8	0.72	1.01	0.60
	F	100	1136	27.4	1.06	1.51	1.43
26	M	0		13.0	0.58	NC	NC
	M	30	341	25.2*	0.77*		
	F	0		13.1	0.58	NC	NC
	F	30	341	31.2*	0.82		
52	M	0		19.7	0.57	1.35	0.86
	M	30	341	22.9	0.83*	1.37	0.88
	F	0		17.4	0.59	0.95	0.66
	F	30	341	48.5*	1.04*	1.47*	1.04*

* $p < 0.05$ compared to control group
NC = No change.

Table E.24
Mean Values for Selected Absolute and Relative Organ Weights
During Oral Multi-Dose Studies with Azelastine HCl

Study Duration (Wks)	Species	Sex	Dose Level (mg/kg)	Multiple of Human Dose	Liver(g)		Kidney(g)		Thymus(mg)	
					Abs.	Rel.	Abs.	Rel.	Abs.	Rel.
17	Mouse	M	0		1.89	5.0	0.28	0.73	NC	NC
		M	60	682	1.87	5.0	0.28	0.74		
		M	120	1364	1.83	5.4*	0.27	0.78*		
		F	0		1.43	4.9	0.18	0.62		
		F	60	682	1.57	5.3*	0.20	0.67*		
		F	120	1364	1.64*	5.8*	0.18	0.64		
14	Rat	M	0		14.4	3.2	NC	NC	NC	NC
		M	50	568	16.3	3.9*				
		M	100	1136	18.4*	5.4*				
		M	200	2273	11.9*	5.6*				
		M	400	4545	-	-				
		F	0		9.1	3.7	NC	NC	NC	NC
		F	50	568	9.5	3.8				
		F	100	1136	10.9	4.6				
		F	200	2273	9.7	5.6*				
		F	400	4545	-	-				
5	Rat	M	0		10.6	2.8	2.72	0.71	NC	NC
		M	30	341	11.3	2.8	2.87	0.72		
		M	100	1136	13.3	3.9	2.77	0.84		
		F	0		6.6	2.9	1.59	0.70		
		F	30	341	6.8	3.1	1.65	0.74		
		F	100	1136	8.8	4.3	1.63	0.80		
5	Rat	M	0		11.1	2.8	3.03	0.77	396	0.10
		M	100	1136	12.	4.0	2.74	0.87	275	0.09
		F	0		6.4	2.7	1.71	0.73	391	0.17
		F	100	1136	8.3	4.2	1.64	0.84	258	0.13
13	Rat	M	0		15.27	3.62	NC	NC	NC	NC
		M	90	1023	19.08*	4.86*				
		F	0		9.24	3.67	NC	NC	NC	NC
		F	90	1023	12.85*	5.14*				
26	Rat	M	0		13.6	2.48	3.34	0.61	NC	NC
		M	30	341	13.9	2.62	3.27	0.62		
		F	0		7.4	2.46	1.97	0.66	NC	NC
		F	30	341	8.1*	2.68*	2.07	0.69		
52	Rat	M	0		15.1	2.37	3.57	0.56	NC	NC
		M	30	341	15.3	2.67*	3.61	0.63*		
		F	0		7.9	2.23	2.11	0.60	NC	NC
		F	30	341	9.6*	2.56*	2.46*	0.66		

* $p < 0.05$ compared to control group
NC = No change.

Table E.25
Summary of Histopathological Changes Observed During
Oral Multi-Dose Studies with Azelastine HCl

Species	Method of Admin.	Study Duration (Wks)	Dose (mg/kg)	Multiple of Human Dose	Histological Change
Mouse	drug/feed	17	60,120	682,1364	Liver- fatty infiltration & cytoplasmic vacuolation.
Rat	drug/feed	14	50,100 & 200	568,1136 2273	Liver- cytoplasmic vacuolation - males.
			100,200	1136,2273	Vacuolation - females.
Rat	gavage	5	100	1136	Liver- cloudy swelling, centrolobular; hydropic degeneration, perilobular.
Rat	gavage	13	30	341	Liver- centrolobular hypertrophy - males;
			100	1136	Liver- centrolobular hypertrophy - males & females. Increased thyroid activity - females.
Rat	gavage	7	30	341	Liver- centrolobular hypertrophy - males.
Dog	i.v.	4	0.464,1.0 2.15	5,11 24	Vessel- perivasculitis, thrombosis, fibrinoid necrosis.
Rat	gavage	26	30	341	Liver- centrolobular fatty change - males.
Rat	gavage	52	30	341	Liver- centrolobular fatty change (vacuolation) - males.
Dog	capsule	26	21.5	244	Kidney- slight to moderate degeneration of renal cortical tubular epithelium.
Rat	drug/feed	104	30	341	Liver- hepatocellular hypertrophy and centrolobular cytoplasmic vacuolation - female.

Chronic Intranasal Toxicity Studies

Species/ Strain	No.of Animals	Method of Adm.	Duration	Dosage levels* (mg/day)
Rat/ Crl:CD(SD)BR	75/sex	Intra-nasal	6 months	0, 0.2, 0.4, 0.8
Dog/ Beagle	20/sex	Intra-nasal	6 months	0, 0.84, 1.68, 3.36

* Dose is mg/animal as 0.1% nasal formulation.

In the rat study, there were no clinical findings indicative of systemic toxicity of azelastine hydrochloride and irritancy to the epithelium lining of the nasal cavity when given at doses up to 0.2 mg/rat four times a day. There were neither macroscopic tissue findings nor organ weight changes which could be attributed to the intranasal administration of azelastine hydrochloride or vehicle.

In the dog study, azelastine hydrochloride administered intranasally at dosage levels up to 3.36 mg/day for six months, did not show any toxicity except a marginal reduction in body weight gain for males and females at the highest dose level. There were no clinical or histopathological changes observed and no sign of irritation of the nasal epithelium seen.

In addition, the irritation potential of 0.2% azelastine HCl nasal spray on the mucous membrane of the rabbit eye was investigated. When 0.1 ml of such solution was instilled into the conjuctival sac of the right eye once daily for five days (the left eye served as the untreated control), diffuse reddening of the conjuctiva was observed on the first day of administration in one animal. No other changes were noted during the study; therefore, concluded that the 0.2% azelastine HCl nasal spray was not irritating to the mucous membrane of the rabbit eye.

Summary: There were no signs of significant toxicity from either studies, except a marginal decrease in body weight gain observed in dogs. The intranasal administration of azelastine hydrochloride appeared to be safe based on the two six-month intranasal studies and the irritation study.

Plasma levels of azelastine hydrochloride and its metabolite, desmethylazelastine, in both studies showed generally dose-related increases in concentrations.

NOTE: **For detailed review of these two studies, see the attached review from IND**

C. Carcinogenicity Assessment

A) MTD Studies:
1. Mouse

Strain	No.of Animals	Method of Adm.	Duration	Dosage, mg/kg/day
NMRI	12/sex/gr	feed	17 weeks*	0, 1, 5, 30, 60,120
	6/sex/gr	(recovery groups)		0, 30, 60, 120
	10/sex/gr	(plasma level study)		all doses
	Age: weanlings			

*13 weeks on drug plus a 4-week recovery period
Laboratory: Degussa-Asta, Lalle-Kunsebeck

Results:

Mortality: One female died at 5 mg/kg at on day 65
No toxic signs or behavioral change observed.

Body weight:

7-10% reduction (compared to controls) in body weight only in HD (120 mg/kg) male group during week 1-13. No significant reduction in females. However, reduction in body weight gain in males was considerable at all doses as shown below.

Sex	Groups	% Reduction of Mean Body weight Gain			
		First Wk	Last Wk	Difference	Gain rel.to
	mg/kg	Weight in grams			Control (%)
Male					
	0	27.3	39.9	12.6	0
	1	28.2	39.3	11.1	-11.9
	5	28.2	37.7	9.5	-24.6
	30	28.4	37.2	9.8	-22.2
	60	28.1	39.6	11.5	- 8.7
	120	27.6	35.8	8.2	-34.9
Female					
	0	24.2	30.4	6.2	0
	1	24.0	30.9	6.9	+11.3
	5	23.3	30.2	6.9	+11.3
	30	24.2	31.7	7.5	+20.9
	60	24.8	32.1	7.3	+17.7
	120	24.4	30.4	6.0	-3.4

Food Consumption:

There was no drug-related reduction in food consumption, but only in males, tendency to slight decrease in HD.

Hematology:

In males, at Week 14, a significant decrease of the leucocytes (WBC) was seen in animals dosed at 1(31%), 5(49%), 30(36%), 60(19%), and 120(27%) mg/kg, but not in females. These changes were not dose-dependent and within the physiological range.

Clinical Chemistry at Week 14:

		Dose groups (mg/kg)					
		0	1	5	30	60	120
AP:	M			+27%			+44%*
	F						
ALT (GPT)	M						+17%*
	F			+32%			+68%*
AST (GOT)	M						
	F		+32%	+31%		+27%	+19%
BUN	M				-16%	-15%	-14%
	F					-27%	-23%
Total Bilirubin	M				+17%	+15%	
	F				+18%		

* Statistically significant and considered drug related although they were within the physiological range and not dose related.

Organ Weights:

	Dose Group (mg/kg)	Absolute (%)	Relative (%)
Liver:	60 mg/kg	F +9.8%	F +8.8%
	120	F +16%	F +18%, M +9%
Kidney:	1 mg/kg	M +11%	M +14%
(left)	5		M +10%
	30	F +10%	M +17%, F +9%
	60		F +8%
	120		M +3.5%

Histopathology:

Kidney:

No drug-related degenerative changes were found in renal cortex and medulla. Some focal infiltrates consisting of histiocytes, lymphocytes and plasma cells are seen predominantly in the renal pelvis and cortex at all doses.

Liver:

Moderate fatty infiltration of liver cells with clear vacuolization of the cytoplasm, hepatocellular hypertrophy were seen in the high dose groups, 60 and 120 mg/kg as shown in the following page. These changes were seen slightly more in females and reversible after recovery period.

Hepatocellular Changes
(Slight, Moderate, Prominent)

Number of animals with changes/group:

Dose Groups (mg/kg)	0	1	5	30	60	120
Fatty Infiltration						
Male	7s	2s,1m	6s	1s	9s	7s,4m,1p
Female	8s	9s,1m	9s,2m	7s,4m	5s,4m,2p	1s,7m,4p
Vacuolization						
Male	1s	1s	2s	0	1s,1m	2s,8m,1p
Female	6s	2s	4s,1m	6s,1m	5s,4m	4m, 7p
Necrosis (Single cell and Focal)						
Male	5	4	5	2	7	5
Female	7	1	4	0	7	9

Number of animals examined: 12/sex/gr

Conclusion:

In this MTD study, 10% reduction on body weight was seen in only males at 120 mg/kg, but the reduction in body weight gain was greater than 10% for all treated male animals when compared to the controls.

Other signs of toxicity observed were changes in clinical chemistry parameters (AP, AST, and ALT), increased liver weight and hepatocellular changes occurring mostly at 60 and 120 mg/kg.

The sponsor suggested an MTD of below 60 mg/kg/day. We would interpret the data to support the selection of 60 mg/kg/day as an MTD in males based on the liver toxicity and body weight considerations. In females, 60 mg/kg dose was associated with liver toxicity; however, no body weight alterations were reported.

2. Rats

Strain	No.of Animals	Method of Adm.	Duration	Dosage, mg/kg/day
Sprague-Dawley, CD-1	10/sex/gr	feed	14 weeks*	0, 50, 100, 200, 400

*12 weeks on drug plus a 2-week recovery period. Interim sacrifice was done at Week 8 for 5 male and 4 female animals in 400 mg/kg group. The remaining animals were terminated at Week 14, except the rest of the high dose animals terminated at Week 10, 2 weeks after the drug was taken off.

Results:

Mortality: 4 (2M/2F) animals died at 400 mg/kg
1M died, 1F missing at 100 mg/kg
1F died at 0 mg/kg

Body weight/Food consumption:

There were significant dose-related reduction in body weight gain and in food consumption in all dosed animals.

Dose groups		% Reduction in weight gain from control Week 8	Week 12	Week 14
50 mg/kg	M	10 %	9 %	4 %
	F	3.3	7	8
100	M	23	30	14
	F	12	18	14
200	M	53	64	40
	F	30	43	29
400	M	87	NA	
	F	78	NA	

NA: Not available because the remaining animals in this group were terminated at Week 10 after being taken off the drug for 2 weeks.

Clinical Chemistry:

Alkaline phosphatase (U/l)

Dose groups		Week 8	Week 10+	Week 12	Week 14+
0 mg/kg	M			237.4	272.6
	F			226.[illegible]	236.3
50 mg/kg	M			277.0	246.4
	F			345.6	194.8
100	M			428.0*	255.8
	F			410.2*	192.5

200	M			803.8*	349.0
	F			>672.0*	267.6
400	M	>510.8	413.3	0	0
	F	1018.5	303.3	0	0

Glutamic Pyruvic Transaminase (U/l)

Dose groups		Week 8	Week 10+	Week 12	Week 14+
0 mg/kg	M			73.8	82.2
	F			73.8	94.8
50 mg/kg	M			69.8	78.4
	F			75.6	82.2
100	M			63.5*	80.3
	F			79.4	66.5
200	M			104.2*	64.2*
	F			73.3	61.6
400	M	83.8	57.8	0	0
	F	67.8	51.5	0	0

\+ After 2 weeks off drug
* Statistically significant ($p<0.05$)

Alkaline phosphatase was increased in both male and female in 400 mg/kg group at Week 8 with a downward trend at Week 10. In 100, 200 mg/kg groups at Week 12, AP was increased significantly but returned to normal after 2 weeks off drug.

Glutamic pyruvic transaminase in male rats at Week 12 was reduced at 100 mg/kg and increased at 200 mg/kg but decreased and tended toward to normal after 2 weeks off drug when compared to controls.

Organ Weights at Week 12:

	Dose Group (mg/kg) 5/sex/gr	Absolute Wt Percent increase from control	Relative Wt
Liver:	50 mg/kg	M +13%, F + 4%	M +22%, F + 3%
	100	M +28%, F +20%	M +69%, F +24%
	200	M -17%, F +11%	M +75%, F +51%

At Week 12, both absolute and relative liver weight was increased in males and females at 50 and 100 mg/kg. At 200 mg/kg, the relative liver weight was increased significantly ($p<0.05$) in males and females. However, liver weight in males was reduced at 200 mg/kg due to the reduced body weight in this group.

Histopathology:

An apparent treatment related hepatocellular hypertrophy was noted in some or all liver sections from the treated groups.

Hepatocellular Changes in Male and Female Rats

Hepatocellular cytoplasmic vacuolation:

	Male (S.R.)*		Female (S.R.)	
0	0/5		0/6	
50 mg/kg	4/5	(1-2)	0/5	
100	5/6	(2-4)	2/5	(1-3)
200	5/5	(1-3)	5/5	(1-3)
400**	5/10	(1-3)	4/10	(1-3)

Hypertrophic changes:

0	0/5		0/6	
50 mg/kg	3/5	(1)	1/5	(1)
100	5/6	(2-3)	5/5	(1-3)
200	5/5	(2-3)	5/5	(2-3)
400	7/10	(1-3)	4/10	(2)

* S.R. (Subjective Severity Rating): 1 = minimal, 2 = slight, 3 = moderate, 4 = marked

** Nine animals sacrificed after 8 weeks. Of the 8 HD rats surviving, 5 had evidence of minimal extramedullary hematopoiesis in the liver.

The above histopathological changes are indicative of enzyme induction and associated with increased liver weight and alkaline phosphatase. The data also show that the most of the changes in liver are more pronounced in male than female rats and reversible.

Conclusion:

Based on the reduction of body weight gain, liver weight changes and histopathological findings, the sponsor determined the MTD to be below 50 mg/kg in both male and female rats; our analysis suggest the MTD should be 50 mg/kg.

B) Genotoxicity:

Azelastine hydrochloride showed no mutagenic effects in the AMES test, DNA repair test, mouse lymphoma forward mutation assay, mouse micronucleus test or rat chromosomal aberration test as shown on page 53.

C) **Carcinogenicity Studies:**

Species/ Strain	No.of Animals	Method of Adm.	Duration	Dosage, mg/kg/day
Mouse/ NMRI	100/sex(C) 50/sex/gr (Degussa, Germany)	Feed	2 years	0, 1, 5, 25
Rat/ Crl:CD(SD)BR	110/sex(C) 65/sex/gr (Wallace Laboratory)	Feed	2 years	0, 1, 5, 30

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1. **Mouse**

NMRI mice (100/sex in control and 50/sex/group in drug) were treated with azelastine Hcl in a dietary admixture for 104 weeks at doses of 0, 1, 5 and 25 mg/kg/day for carcinogenicity study. In addition, there were five per sex in all groups for determination of plasma drug levels.

Study was terminated (107 weeks for males and terminated after 97 weeks for females) when the survival rate, determined separately for each sex, of control or low dose animals reached about 25%.

The MTD study (13 wk + 4 wk recovery) in mice showed liver weight increase and hepatocellular changes at 60 mg/kg/day and higher and significant increases in ALT, Alkaline Phosphatase at 120 mg/kg/day. The dose of 25 mg/kg, however, was selected to be MTD for this study based upon the intended human therapeutic dose (0.15 mg/kg) for which the MTD exceeds the clinical dose level by more than a 100 fold (this procedure is in accordance with EC-guidelines).

Results:

At Week 60, dose- related plasma drug levels were detected. Drug-induced changes were not observed in clinical signs.

Mortality:

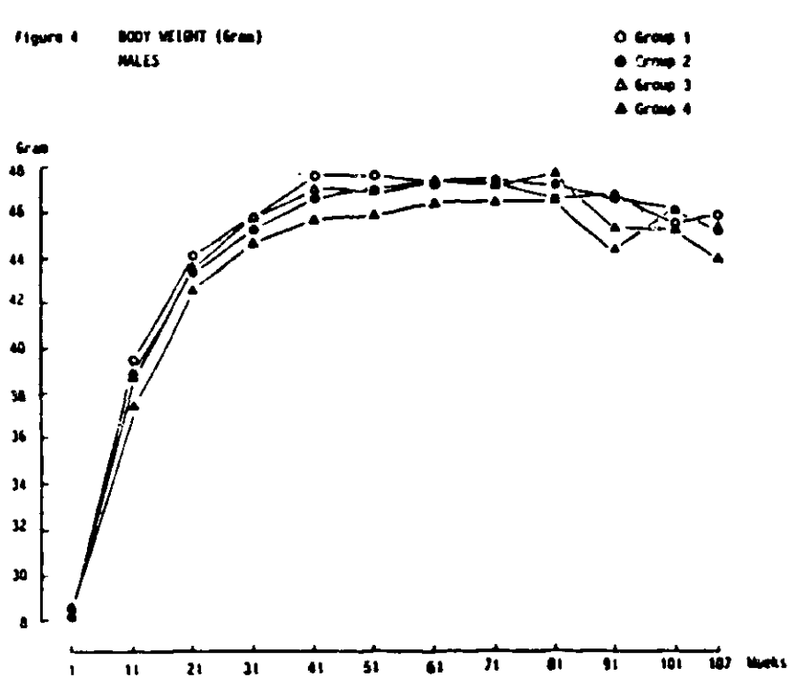
The survival rates of the treated animals were similar to that of controls.

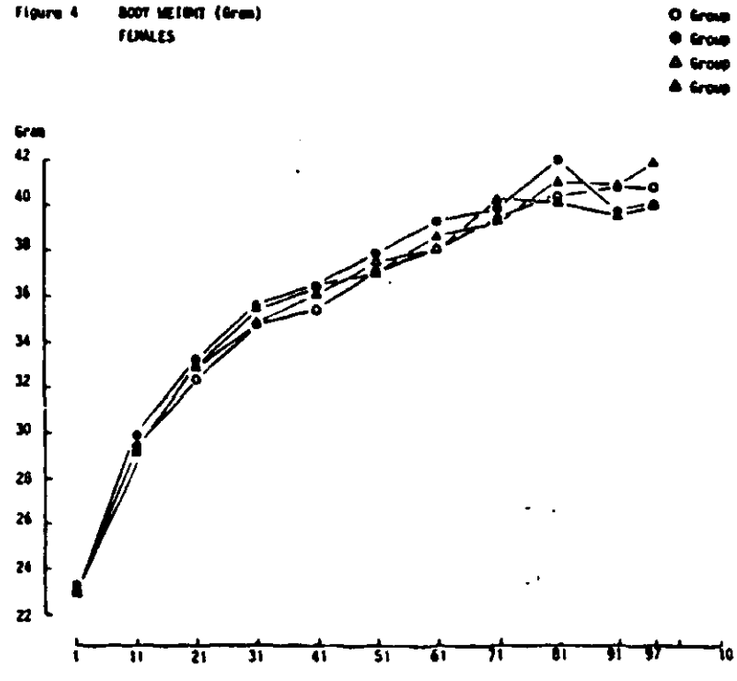
Number of animals died or killed extremis:

Group 1 - Control:	69/100 males,	74/100 females
Group 2 - 1 mg/kg:	37/50 males,	33/50 females
Group 3 - 5 mg/kg:	33/50 males,	34/50 females
Group 4 - 25 mg/kg:	39/50 males,	35/50 females

Body Weight/Food Consumptions:

Body weight gain was slightly reduced in only the high-dose males (4%) with statistical significance during weeks of 5-8, 10-19, 49, 91 and 95-99. Females showed no apparent drug-related changes in weight gain. The food consumption was slightly reduced in all dose groups.





Hematology:

There were no drug-induced changes in hematology parameters.

Pathology:

There were no drug-induced changes in numbers of palpable masses or macroscopic pathology. The relative organ weights of liver and kidneys were slightly reduced in HD males but within normal range.

Histopathology:

Non-Neoplastic changes:

There were increased incidence of non-neoplastic lesions such as ovarian tubular downgrowth, endometrial hyperplasia, cervicovaginal epithelial and stromal hyperplasia in the females and distension of mucosal glands in the trachea; however, these findings were considered spontaneous lesions in old mice. The microscopic findings in treated animals did not show any significant effects in the liver.

Neoplasms:

Neoplasms were observed in several organs with various frequencies but considered to be incidental and unrelated to treatment.

In the high dose group, significant or near significant negative dose-related trends were seen in the following: the adrenal cortical and Harderian gland tumors in males ($p<0.01$) and in combined sexes ($p<0.05$), ovarian tumors in females ($p<0.01$), the number of multiple tumors at any site in males ($p<0.05$) and in the combined sexes ($p<0.05$).

There were statistically significant (by the Division of Biometrics; exact test: p= 0.03935) positive dose-response relationship of bone-osteosarcoma and spleen-lymphosarcoma in female mice at high doses, but the incidences were within historical control ranges (osteosarcoma: 0-4.3%; lymphosarcoma: 20-46.8%) from the breeder.
(The summary of incidences of all the neoplasms are attached.)

Number of Animals with Neoplasms

Groups (mg/kg)	Control	Low	Mid	High
Total animals examined	100	50	50	50
Female Mice with Bone-osteosarcoma	0	0	0	2
Female mice with Spleen-lymphosarcoma	0	0	0	2

Pharmacokinetic data:

Plasma Level Data from 13-week MTD study in Mice (Day 86):

Doses (mg/kg) Nominal	Actual**		Plasma levels* (ng/ml) Azelastine Hcl		Desmethyl-azelastine	
	M	F	M	F	M	F
1	0.9	1.1	<50	<50	n.b.	n.b.
5	4.6	6.1	89.5	n.b.	89.4	n.b.
30	27.0	32.0	305.5	352.0	341.8	330.7
60	54.0	65.0	683.8	462.1	1459.9	872.5
120	106.0	148.0	805.2	516.5	3510.8	2453.5

n.b. : Not detectable
* : Blood samples (10/sex/gr) were taken between 8-11:30 a.m. of the days 9, 44 and 86.
** : Actual dose was calculated from the average of actual food consumption on days 1-7, 36-42, and 78-84 of the experiment.

The plasma concentrations of the metabolite are higher than the parent compound, especially in the higher dosage groups by a factor of 4, which may be due to the saturation of alternative degradation pathways. The plasma levels of both parent compound and the metabolite are lower in the females than the male animals.

Plasma Level Data from 104-weeks CA study in Mice (Week 60):

Doses (mg/kg)		Plasma levels* (ng/ml)			
Nominal	Actual**	Azelastine Hcl		Desmethyl-azelastine	
	M	F	M	F	M	F
1	1.08	0.88	74.7	68.9	42.2	traces
5	4.51	6.68	162.4	92.3	139.0	58.3
25	24.8	28.2	609.8	326.2	1001.9	477.7

* : Blood samples (5/sex/gr) were taken between 10-11:30 a.m. in the test week 60.

** : Actual dose was calculated from the average of actual food consumption in test week 59.

The sponsor stated that the above cross study comparison showed similar magnitude in plasma levels. However, the plasma levels from this study are higher in general (perhaps due to redistribution) but of similar pattern with the results in a 13-week MTD study; the plasma levels determined in the females are lower than those found in the males and showed more consistency.

When the plasma level data are compared with human data, there is a 100 fold differences in plasma levels from the 25 mg/kg dose given to mice in a diet and the clinical doses (2.2 to 8.8 mg bid) given to human. Mice showed a significantly shorter half-life than human; however, dietary dosing could maintain high plasma levels.

Conclusion:

In this study, no significant effects on survival, body weight gains, clinical symptoms, neoplastic or non-neoplastic pathology were observed in the animals. However, the study is acceptable based on the pharmacokinetic data. The highest dose used (25 mg/kg) in the study was sufficient to give animals 100 fold exposure to drug compared to human and close to 1/2 the MTD determined from 13-week study.

Statistical analysis showed that there was no increase in malignant, non-malignant or total neoplasms due to drug treatment. Azelastine HCl was considered non-carcinogenic in the study by the sponsor and we concur.

2. **Rats**

Sprague-Dawley rats, 620 male and female rats (115/sex in control and 65/sex/group in drug), were treated with azelastine Hcl in feed admixture for 104 weeks at doses of 0, 1, 5, and 30 mg/kg/day to assess the carcinogenic potential of the drug. Five rats/sex/group were sacrificed at Weeks 14, 52, 79 and at termination for liver function test (AP, SGPT,and SGOT) and histopathologic examination. Blood samples were taken from five rats/sex/group at Weeks 52 and 104 for determination of plasma drug levels.

The MTD was selected on the basis of a 90-day toxicity study in rats from which MTD was considered to be 50 mg/kg/day. However, 30 mg/kg/day was chosen to be high dose for this carcinogenicity study based on the findings in other subchronic and chronic toxicity studies. Starting at 30 mg/kg/day and higher doses, the toxicity findings were slight increases in AP, GPT, cholesterol and liver weight as well as hepatocellular hypertrophy and centrolobular fatty changes including vacuolation in those studies.

COMMENT: Although the selection of MTD at 30 mg/kg/day is acceptable based on the body weight reduction and the toxic signs shown from this CA study, the doses are not appropriately spaced. Since the plasma levels for drug was not detectable at 1 mg/kg and minimal at 5 mg/kg and no effect dose was determined to be 10 mg/kg/day from 6-month study, the results may have shown more meaningful dose-response relationship if the ½MTD and ¼MTD were used instead.

Results:

Dose-related plasma drug levels were detected in nonfasted high- and mid-dose males and females at Week 104; only in high-dose males and females at Week 52. Plasma drug levels of the low-dose groups were below the level of detection at both times which indicate that the low and mid doses were too low.

There was no drug-induced changes in mortality, food consumption or ophthalmic changes.

Body Weight:

Body-weight gain over 104 weeks was gradually reduced in the high-dose males (13.5%) with statistical significance but in high-dose females the reduction was gradual only during the first 60 weeks and the last few weeks. Body weight gain in low and mid dose groups were similar to the control groups.

% Reduction in weight gain from control in High-Dose groups
At different weeks

Weeks	13	24	50	60	80	94	99	101	103	104
Male	3.0	3.9	4.7	5.3	5.3	3.4	7.5	8.6	11.6	13.5
Female	9.8	12.0	16.2	13.6	6.8	-	6.5	10.3	12.4	12.9

Clinical chemistry:

Chemistry parameters (SGOT, SGPT and/or AP) were both increased or decreased at Weeks 14, 52, 79 and 104. Although statistically significant, they were considered not drug-related or biologically not significant by the sponsor and we concur.

Histopathology:

At termination week 104, there were slight increases in incidence of hepatocellular hypertrophy and cytoplasmic vacuolation in high-dose females as was found in previous studies in rats but there was no evidence of nodular hyperplasia or increased thyroid activity. The neoplasms found in the tissues from all groups were considered incidental or naturally occurring.

Number of Rats in High Dose Group

Liver	Week 14	Week 52	Week 79	Week 104
Hepatocellular hypertrophy (slight to minimal)	2/5M	3M, 2F*	2M, 2F*	6F
Hepatocellular cytoplasmic vacuolation (slight to moderate)	5/5M	5M, 1F	5M, 3F	11F
Nodular hyperplasia (minimal to moderate)		3F		0

* High-dose females showed evidence of increased thyroid activity up to week 79 but not at termination.

Thyroid activity was derived and subjectively rated from thyroid histology, based on relative follicular size, height of follicular epithelium, and amount of colloid in the follicles.

Organ Weights: There were no reports on organ weight changes.

Neoplasms:

Sponsor's statistical analysis by life-table methods and Chi-square tests showed that there was no increase in malignant, non-malignant or total neoplasms due to drug treatment. (The summary of incidence of neoplasms (vol. 2) are attached in the back.)

Reanalysis of the tumor data by our Division of Biometrics using the exact permutation trend test showed that there was positive dose-response relationship of skin sebaceous adenoma in male rats which is a benign "rare" tumor. However, when skin sebaceous gland adenoma is combined with ear/mastoid sebaceous gland adenoma, as is considered appropriate by the NTP (personal communication between Dr. Taylor with Dr. Eustis), sebaceous gland adenoma incidence is not statistically significant.

Number of Rats with Sebaceous gland adenoma

Groups (mg/kg)	0		1		5		30	
Sex	M	F	M	F	M	F	M	F
Number Examined	113	115	65	65	65	65	65	65
Organ:								
Skin					2	1	2	
Ear/Mastoid			1					

COMMENT:

Historical control data on skin sebaceous gland adenoma (0-0.6%) in Sprague-Dawley rat from various sources suggested that incidence here exceeded historical incidence. However, the appropriate historical data would need to include related skin tumors which might be diagnosed similarly such as basal cell epithelioma, basal cell adenoma, and trichoepithelioma. (Taylor, Eustis)

Conclusion:

Reductions in body weight and histological findings suggest that dosing was at or near the MTD and the study is acceptable. Azelastine HCl was found to be non-carcinogenic in rats under the conditions of the study.

History of Carcinogenicity Assessment:

The preliminary evaluation of the 2 year study in mice by the pharmacologist from HFD-160 (Mr. Oberlander) states that the study showed apparent increase in tumor frequency and increased mortality in high dose males during the first 1½ years with significant body weight reduction. He also noted in the high dose group, significant or near significant negative dose-related trends in adrenal cortical tumors, Harderian gland tumors, ovarian tumors and multiple tumors at any site. However, there was a higher incidence of some non-neoplastic lesions in treated mice such as distension of mucosal glands in the trachea, dose-related increase in tubular downgrowth in the ovary, stromal hyperplasia and focal squamous epithelial hyperplasia in the cervix and vagina.

The sponsor was asked to provide 1) historical control tumor data for this species and strain and 2) an explanation of the biological significance for the increased incidence of non-neoplastic lesions found in the study as well as the spontaneous incidence of these types of non-neoplastic lesions if available.

Both studies were reviewed by the Division of Biometrics at the request of the pharmacologist and several areas of concern were addressed and conveyed to the sponsor at the meeting held on June 7, 1989:

1. In the NMRI mouse carcinogenicity study our statistical branch considered the incidence of osteosarcoma and lymphosarcoma to be statistically increased in treated female mice, whereas Wallace Laboratories had not considered the findings positive. Sponsor was asked to respond to this difference in evaluation and also submit historical tumor control data in the NMRI strain as employed by the German firm that conducted this study.

2. In the Sprague-Dawley rat carcinogenicity study our biometric reviewers considered the sebaceous adenoma incidence to be statistically increased in treated male rats when analyzed by the "exact permutation trend test". It was noted that sponsor had employed a "Peto" test to evaluate the data and considered the findings negative but that our statistical branch felt that the EPTT was correct method to analyze a "rare" tumor. It was requested that sponsor submit historical tumor control data for the Sprague-Dawley rats in the facility which conducted the bioassay.

3. Sponsor was asked also to provide time tables for the occurrence of tumors in question; to respond to Mr. Oberlander's request for additional information regarding treatment related increases in several non-tumorous lesions seen in mice; and to review chronic toxicity studies for the signs of neoplasia.

In response to our request, sponsor submitted the available information on historical control data and time to tumor data in Amendment # 173, dated 10/17/89 under Ind 21,418.

The sponsor stated that they do not have any information that would support a pharmacologic effect, or predisposing hyperplastic effects on sebaceous glands, bone or the lymphoreticular system. The compound did not show any mutagenic effect, no sign of drug effects on the location at which such tumors are usually seen nor on the time to tumor; furthermore, the findings were confined to one sex.

The sponsor also stated that the frequency between the control and treatment groups of ovarian tubular downgrowth, endometrial hyperplasia, cervicovaginal epithelial and stromal hyperplasia in the female genital tract, as well as the incidence of distension of mucosal glands in the trachea were incidental and part of the spontaneous lesions in old mice.

The second review by the Division of Biometrics of May 29, 1991 stated that the skin sebaceous adenoma found in male rats shows a significant positive dose-response relationship upon reevaluation. However, the bone-osteosarcoma and spleen-lymphosarcoma found in female mice are within historical control ranges supplied by sponsor and lacking the significant dose-response relationship.

Dr. Alan Taylor, the supervisory pharmacologist, has discussed with Dr. Scott Eustis, the head of the NTP, about the sebaceous gland adenoma in rats at the most recent CAC meetings.

According to Dr. Scott Eustis, the appropriate historical incidence for this tumor type might be difficult to ascertain, because various skin tumors such as sebaceous gland adenoma, basal cell epithelioma, basal cell adenoma, or trichoepithelioma, etc. may be variably diagnosed by different pathologist. Therefore, Dr. Eustis suggested that it is appropriate to combine the skin and ear forms of this tumor type and made the incidence reported in this study statistically not-significant.

Addendum to the Carcinogenicity Evaluation:

Since the original review, the carcinogenogencity studies with Azelastine HCl have been discussed at the Carcinogenicity Assessment Committee meeting (11/19/91). CAC has recommended to conduct an additional pharmacokinetic study in mice which will provide plasma kinetic data (plasma AUCs at steady state) with the highest dose (25 mg/kg/day) used in the carcinogenicity study.

A letter from Dr. Robert Temple, dated February 18, 1992, was sent to the sponsor, wherein a study was requested to assess relative steady state plasma AUCs of azelastine and desmethylazelastine in mice for comparison with human data from a normal dosing schedule.

The sponsor has agreed to provide such data and a protocol for a pharmacokinetic study in mice was submitted in subsequent supplement, dated 2/28/92. Therefore, the final decision on the acceptability of mouse carcincgenicity study will be deferred until the final report of the pharmacokinetic study demonstrates that the relative exposure in the mouse study exceeds anticipated human exposure by a very sizeable margin.

If both mouse and rat carcinogenicity studies are acceptable, Azelastine hydrochloride will be considered non-carcinogenic in both mouse and rat from these studies.

D. Special Toxicity Studies

Total of 21 special studies with azelastine hydrochloride alone or in combination with d-pseudoephedrine hydrochloride and related compounds have been completed at various countries and by various laboratories.

Two acute toxicity studies in mice, three dermal studies in guinea pigs and rabbits, two ocular irritation studies in rabbits, and an *in vitro* cytotoxicity study have been reviewed previously and the results are summarized for this NDA. Ten studies conducted with azelastine hydrochloride in combination with d-pseudoephedrine have not been reviewed for this submission but the information from the results are included in the Drug Interaction Section of the labeling.

Summary of Special Toxicity Studies:

a) Two acute toxicity studies were conducted in mice with 4-(p-chlorobenzyl)-1-(2H)-phthalazionene, a degradation product of azelastine, and an acute intravenous study with 6-hydroxyazelastine, a metabolite of azelastine.

No toxic effects were observed with a degradation product with doses up to 500 mg/kg in mice. In the acute intravenous study in mice, the LD_{50} of the metabolite was 74 mg/kg in males and 86 mg/kg in females showing less toxicity than the parent compound.

b) Three dermal studies were conducted with azelastine hydrochloride: 1) a guinea pig sensitization study, 2) a primary dermal irritation study in the rabbit, and 3) a seven-day dermal irritation study in rabbits (in a cream and a gel formulation.

There was no drug effects seen in guinea pig sensitization study; mild erythema and edema were seen in the primary dermal irritation study up to 72 hours of observation. Both the cream and gel formulations of azelastine hydrochloride and cream vehicle were irritants to intact and abraded skin.

c) Two ocular irritation studies were conducted with a single application of a 0.5% aqueous solution and multiple application (five days) of an intranasal formulation (0.2%) of azelastine hydrochloride in the rabbit eye. Both solutions did not cause any adverse irritative effects.

d) An in vitro cytotoxicity study was conducted with BALB/c3T3 cells and azelastine hydrochloride, chlorcyclizine hydrochloride, cytosine arabinoside, mitomycin C, cycloheximide, actinomycin D and colchicine.

The toxicity of azelastine hydrochloride to the cultured cells was about the same as that of chlorcyclizine hydrochloride but much less than the toxicities of the other known cytotoxic agents tested.

e) Ten combination studies were conducted with azelastine HCl and d-pseudoephedrine HCl: two acute studies, four maximum tolerated dose studies, two three-month studies and two teratology studies. In studies of up to three months duration in the rat and dog, azelastine hydrochloride in combination with d-pseudoephedrine showed no greater toxicity than either component alone. No teratogenic effects were seen in Segment II rat and rabbit studies with the combination. (NOTE: THESE STUDIES HAVE NOT BEEN REVIEWED INDIVIDUALLY FOR THIS NDA.)

E. Reproductive Toxicity (vol. 2, P. 177-178)

Summary of Reproductive Studies with Azelastine HCl

Species	Strain	Initial Group Size and Sex	Study Type	Method of Admin.	Dose Levels (mg/kg)	Study Duration
Rat	SLC-SD	5 M/5 F	MTD*	Gavage	0, 48, 68.6, 98, 140, 200	2 wks
Rabbit	JW-NIBS	3 F	MTD	Gavage	0, 50, 70, 100 140, 200	2 wks
Rat	Sprague-Dawley	15 M/20 F	Seg I	Diet	0, 4.64, 21.5	M-51 days F-56 days
Rat	SLC-SD	24 M/24 F	Seg I	Gavage	0, 0.3, 3, 30, 68.6	M-11 wks F-21 days
Mouse	SLC-ICR	14 F	Seg II	Gavage	0, 0.3, 3, 68.6	18 days
Mouse	SLC-ICR	16 F	Seg II	Gavage	0, 30	18 days
Rat	Sprague-Dawley	10 F	Seg II	Diet	0, 4.64, 21.5	21 days
Rat	SLC-SD	18-39 F	Seg II	Gavage	0, 0.3, 3, 30, 68.6, 100	18 days
Rat	SLC-SD	10-20 F	Seg II	Gavage	0, 50	20 days
Rat	SLC-SD	8-12 F	Seg II	Gavage	0, 68.6	20 days
Rabbit	White Russian	10-20 F	Seg II	Diet	0, 4.64, 21.5, 46.4	26 days
Rabbit	JW-NIBS	10-14 F	Seg II	Gavage	0, 0.3, 30, 50	29 days
Rat	SLC-SD	24 F	Seg III	Gavage	0, 0.3, 3, 30	15 wks
Rat	BOR:WISW	24 M/24 F	Three Generation	Gavage	0, 0.3, 3, 30	29 wks

*MTD = Maximum Tolerated Dose Study

Rabbit	New Zealand White	20 F	Seg II	Gavage	0, 10, 20 200, 300
	Combination w/d-pseudoephedrine				5/100, 10/200, 20/400

Total of fourteen studies were conduced in mice, rats and rabbits to assess reproductive toxicity as listed on previous page. The following two tables (vol.2, p.179-180) list only those studies in which some positive responses were noted. Maximum tolerated doses (MTD) were determined from two 14-day studies to be 68.6 mg/kg/day for rats and 50 mg/kg/day for rabbits. Additional Segment II study in rabbits was submitted in support of the use of this drug in women of childbearing potential.

Segment I Studies:
(2-Seg I and 1-multigeneration study)

Table E.31
Summary of Reproductive Performance (Segment I) for Female Rats Receiving Azelastine HCl Orally and Sacrificed on Day 20 of Gestation

Dose (mg/kg):	0	0.3	3	30	68.6
Multiple of Human Dose:		3	34	341	780
Parameter					
Number Pregnant	20	22	18	19	6
Corpora Lutea					
Total	314	347	297	299	78
Per animal	15.7	15.8	16.5	15.7	13.0*
Implantations					
Total	282	306	267	255	66
Per animal	14.1	13.9	14.8	13.4	11.0*
Resorptions					
Total	8	17	10	16	6
Per animal	0.4	0.8	0.6	0.8	1
Resorption Rate (%)	2.8	5.6	3.7	6.3	9.1
Live Fetuses					
Total	274	289	257	238	50
Per animal	13.7	13.1	14.3	12.5	10.0
Sex ratio (M:F)	1.0	0.8	1.3	0.8	0.7
Mean Fetal Weight (g)	3.6	3.6	3.9	3.4	3.8
Number Dead	0	0	0	1	0
Abnormalities					
External	0	1	1	0	0
Visceral	0	4	2	3	1
Skeletal	19	17	30	21	5

* $p < 0.05$ compared to control group

Summary of Findings (Segment I):

Studies	Dose (mg/kg/day)	Species	Findings
1)	21.5	Rats	Increased postnatal mortality
2)	30	Rats	Reduced body weight gain
	68.6	Rats	Reduced body weight gain; Prolonged duration of the estrous cycle; Reduced copulatory activity, number pregnant, number corpora lutea and number of implantations
3)+	≤30	Rats	No significant effects except reduced fertility index in parental generation(+three generation study)

Segment I oral reproduction study of azelastine (0.3, 3, 30 & 68.6 mg/kg) in the Sprague Dawley rat showed that at 30 mg/kg or below there was reduced body weight gain and reduced fertility index on the parent animals but there was no effects on embryogenesis at 68.6 mg/kg.

Segment II Studies:

(2 in mouse, 4 in rats and 3 in rabbits)

Table E.32

Summary of Effects During Segment II Studies with Azelastine HCl

Dose (mg/kg):	0.0	0.3	3.0	30.0	50.0	68.6	100.0
Multiple of Human Dose:		3	34	341	568	780	1136
Species/Parameter							
Mouse							
Resorption rate (%)	14.1	22.2	12.6			72.3*	
Live fetuses (total)	135	131	139			35*	
Mean fetal weight (g)	1.29	1.34	1.25			0.9*	
Skeletal abnormalities (total)	15	34	27			33*	
Rat							
Corpora lutea/animal	16.1	15.6	16.3	15.9		15.8	14.5*
Resorption rate (%)	8.5	3.5	3.2	5.2		95.0*	100.0*
Live fetuses (total)	280	356	306	329		13	0
Mean fetal weight (g)	3.60	3.65	3.55	3.46		2.92*	---
Skeletal abnormalities (total)	23	26	30	55*		2	---
Rabbit							
Corpora lutea (total)	78	79		69	44*		
Implantations (total)	73	67		67	37*		
Live fetuses (total)	67	62		62	34*		
Mean fetal weight (g)	46.6	44.5		38.5*	38.2*		

* $p < 0.05$ compared to control group.

Summary of Findings (Segment II):

Studies	Dose (mg/kg/day)	Species	Findings
1)	30	Mouse	No effects
2)	68.6	Mouse	Maternal toxicity; Embryotoxicity, fetotoxicty and skeletal abnormalities (reduced ossification in proximal digits of forelimb, 5th sternebrae and sacrocaudal body; increased incidence of short tail, absent tail, cleft palate, fused, absent or branched ribs and fused vertebral arch).
3)	21.5	Rats	No effects
4)	30	Rats	Reduced fetal body weight, increased incidence of 14th rib
	68.6	Rats	Increased resorption rate and fetal mortality; Reduced fetal body weight and skeletal ossification
	100	Rats	Maternal mortality and dec number of corpora lutea
5)	50	Rats	Decreased fetal weight, delayed ossification, and increased incidence of 14th rib
6)	68.6	Rats	Decreased fetal body weight, delayed ossification and increased skeletal abnormalities in early- and mid- period groups when dams were dosed during three different periods of organogenesis (Days 7-9, 10-13 and 14-17).
7)	≤46.4	Rabbits	No effect
8)	≥30	Rabbits	Abortion, severe maternal toxicity and fetotoxic effects.
9)	≤20/400*	Rabbits	No embryotoxicity or teratogenicity; (significant reduction in maternal body weight)

* combination with d-pseudoephedrine (additional study)

In Segment II oral reproduction study of azelastine (0.3, 3, 30, 68.6 & 100 mg/kg) in mice, there were reduced body weight gain and reduced fertility index at 30 mg/kg dose and skeletal abnormalities and fetotoxicity at 68.6 mg/kg dose.

In rats, there were no adverse effects in pregnant rats at 30 mg/kg; however, there were reduced fetal weight and skeletal abnormalities in the pups at this dose. NOEL for fetuses and neonates was 3 mg/kg.

In rabbits, the maximum dose that could be given without adverse effects in either pregnant rabbit or fetus was 0.3 mg/kg in one study; in another study, although maternally toxic, no teratogenic or reproductive effects were seen up to 20 mg/kg alone or in combination with p-pseudoephedrine hydrochloride.

Segment III Study:

Study	Dose (mg/kg/day)	Species	Findings
1)	≤30	Rats	No effects on pregnancy, delivery, lactation or physical and reflex behavior of the neonates.
Three Generation Study, Oral:			
3)+	3	Rats	Decreased fertility (F_0), decreased number of corpora lutea, increased retarded ossification of cranium, reduced body wt gain in F_1 dams
	30		Decreased fertility, reduced body weight (F_0)

Summary of Reproduction Studies:

In doses ranging from 30-68.6 mg/kg/day which is 375 to 857 times the recommended maximum clinical daily dose for rhinitis (4 mg/day) caused variable maternal and fetal effects depending on the species.

At 30 mg/kg/day in rats, reduced fetal weight, skeletal abnormalities in the pups and maternal toxicity were observed occasionally. At 68.6 mg/kg, maternal and embryotoxicity, embryo and fetal lethality were observed in mice and rats. In rabbits up to 20 mg/kg dose in one study, there was no signs of embyrotoxicity or teratogenicity, although significant reduction in maternal body weight was

observed. In another study, 30 mg/kg dose in rabbits showed abortion, severe maternal toxicity and fetotoxic effects.

The maximum dose that could be given without adverse effects in Segment I and II studies was 3 mg/kg in mice, rat and rabbit and was 30 mg in rats in Segment III study. Therefore, it could be concluded that at doses up to 3 mg/kg there were no signs of maternal toxicity, reduced fertility, fetotoxicity or teratogenicity.

F. Mutagenicity Studies
(vol.2, p 182)

Table E.33
Mutagenicity Tests of Azelastine HCl

Protocol	Concentration or Dose Range	Metabolic Activation	Observed Endpoint	Effect
In Vitro Microbial Assays				
Ames Test	0.5-1000 ug/plate	+/-	Induction of base-pair substitution or frameshift mutations	Negative
Ames Test	1.47-4640 ug/plate	+/-		Negative
Ames Test	0.5-500 ug/plate	+/-		Negative
DNA Repair Test	0-1 mg/spot	-	Induction of DNA damage	Negative
In Vitro Mammalian Cell Assay				
Mouse Lymphoma Forward Mutation Assay	0.781-12.5 ug/mL	-	Induction of forward mutations at the thymidine kinase locus	Negative
	3.13-50 ug/mL	+		Negative
	18.75-100 ug/mL	+		Negative
In Vivo Mammalian Assays				
Mouse Micronucleus Test	1.75-17.5 mg/kg	+	Induction of micronuclei	Negative; mitotic depression not observed
Mouse Micronucleus Test	0.5-70 mg/kg	+	Induction of micronuclei	Negative
Rat Chromosomal Aberration Assay	50-200 mg/kg	+	Induction of structural chromosomal aberrations	Negative

Summary: Azelastine hydrochloride showed no mutagenic effects in the AMES test, DNA repair test, mouse lymphoma forward mutation assay, mouse micronucleus test or rat chromosomal aberration test.

3. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

Absorption:

The absorption of azelastine HCl in animals appeared to be rapid and almost complete with general dose linearity, the short absorption half-life (0.14-0.18 hr in mice; 0.8-1.1 hr in dogs) and the short T_{max} (1-2 hours) in all species as shown in the following tables for the pharmacokinetic parameters in various species. The fraction absorbed as determined after a single oral dose varied (<20% in dogs and 82% in humans) and was inaccurate because of the first pass-effect and biliary elimination. However, in a special duodenal absorption study in rats, 90% of the drug was absorbed after three hours.

The plasma concentrations of the metabolite (desmethyl-azelastine) are higher than the parent compound in dogs and mice, especially in the higher dosage groups by a factor of four in mice but lower in the guinea pig and rat plasma. The plasma levels of both parent compound and the metabolite were lower in the females than the male mice.

In rats and guinea pigs, blood levels of radioactivity following oral and intravenous administration of azelastine HCl showed similar absorption and decay curves during the first 8 hours. The maximum levels were observed at about 1.5 hour and 1 hour in rats and guinea pigs, respectively and declined to levels of about 1/10 and 1/7 of the maximum at 24 hour, 1/20 and 1/44 at 48 hour, respectively.

When azelastine HCl and desmethylazelastine were studied in adult and pediatric dogs, there were no biologically significant differences in bioavailability parameters of the drug between the adult and pediatric dogs or sex-related differences.

In the pediatric dogs, the AUC was about 43% higher and the C_{max} was about twice than those in the adult dogs after a single dose. However, following the multiple dosing, there was no differences in AUC among the two groups and C_{max} in pediatric but the C_{max} in adult dogs was increased by about 44%. The T_{max} was about 0.5 hour earlier in the pediatric dogs showing slightly faster rate of absorption than in the adult dogs. The elimination half-life of azelastinwe was similar in both age groups; however, $T_{\frac{1}{2}}$ of the desmethyl-azelastine was significantly longer in the adult dogs than in the pediatric dogs which may be responsible for the accumulation of the metabolite in the adult dogs.

Pharmacokinetic parameters of Azelastine HCl

(Vol.2, pp.147-218)

Single Dose:

Species, Strain	Dose (mg/kg)	Route	C_{max} (ng/ml)	T_{max} (h)	$AUC_{0-\infty}$ (ng.h/ml)	$T_{1/2}$ (h)
Mouse, NMRI	50	p.o.	1223a (400-1700d)	0.7-0.8	9765-11450	4.6-4.8
Rat, S-D	0.25	p.o.	5	2		
	0.5		18	2		
	1.0		63	0.5		7.5
	4.0		205	0.5		
	10		500	1.5		
Guinea Pig, CAMM Hartley	1	p.o.	240	1		
	1		290	1		3.0
	1		235	2		19.0
	1		119a	1		(3.0)
			17.6d	3		(4.2)
Dog, Beagle	10	i.v.	n.a.	n.a.		(2.7)
	20	p.o.(s)	20.8	1		
		p.o.(t)	21.6	2		
	1	i.v.	n.a.	n.a.	2048	14.9
		p.o.	104	0.75	1650	25.5
	2.5	p.o.	109	1.7	377	(2.3)
			203p	1.4	539p	
Human						
Azelastine	2.2*	p.o.	1.0±0.3	4.3±1.1	17.6± 6.3	--
	4.4		1.7±0.8	5.8±0.9	50.4±30.2	20.7±3.5
	8.8		5.9±2.1	5.3±1.6	167 ± 68	21.9±3.9
	17.6		3.4±2.0	4.3±0.8	199 ± 64	--
Desmethylazelastine	2.2	p.o.	0.4±0.3	7.2± 3.2	5.9± 8.4	--
	4.4		0.4±0.1	21.8±13.8	33.7±11.0	50.2±12.8
	8.8		0.9±0.1	20.5±11.2	85.7±16.2	54.2±14.8
	17.6		2.3±0.8	14.0± 9.5	105.6±31.7	--

Multidose:

Human	Dose** (mg)	Route	C_{max} (ng/ml)	T_{max} (h)	$AUC_{0-\tau}$ (ng.h/ml)	Cl (ml/min)
Azelastine	2.2	p.o.	3.9±2.9	5.3±1.2	40.1±32.6	1.2± 0.6
	4.4		8.0±4.9	5.6±1.1	80.2±51.0	1.2± 0.7
	8.8		16.8±6.4	5.3±1.4	168 ± 70	0.9± 0.3
Desmethylazelastine	2.2	p.o.	1.9±0.7	6.8± 3.2	20.2± 7.6	--
	4.4		3.5±0.9	6.8±2.5	37.7±10.2	--
	8.8		7.5±1.2	6.7±2.1	80.8±13.1	--

* Single dose (mg) s= solution
** Dose (mg) q 12h for 7 days t= tablet
$AUC_{0-\tau}$= Area under the concentration-time curve over the dosing interval
a Azelastine HCl ($T_{\frac{1}{2}}$) = elimination from
b Desmethylazelastine blood
\- Azelastine HCl Equivalents for others
p Pediatric

Plasma Levels of Azelastine HC in Multiple-Dose Animal Toxicity Studies
(Vol.2, p.184)

Species, Strain	Dose (mg/kg)	Method of Adm	Mean Drug Concentration (ng/ml) Determined	Normalized to 1 mg/kg	Time
Mouse, NMRI	5	feed	94	18.8	9,44,86 days
	30		330	11.0	
	60		665	11.1	
	120		788	6.6	
Rat, S-D	50	feed	330-560	6.6-11.2	12 weeks
	100		950-1050	9.5-10.5	
	200		1690-1730	8.5-8.7	
	400		1790-1920	4.5-4.8	
	5	feed	33-47	6.6-9.4	104 weeks
	30		515-527	17.2-17.6	
	10	gavage	120-330	12.0-33.0	13 weeks
	30		390-412	13.0-13.7	
	90		490-1620	5.4-18.0	
Rat, neonatal S-D	1	gavage	1.7-3.1	1.7-3.1	7 weeks
	5		4.6-15.2	0.9-3.0	
	30		30.5-69.8	1.0-2.3	
Dog, Beagle	1	p.o.	23-93	23-93	2,6,25,51 weeks
	3		164-248	54-83	
	10		537-1403	54-140	

In general, the plasma levels of azelastine and its metabolites increased with doses up to 60 mg/kg in mice and 30 mg/kg in rats, but not always proportionally.

Observed or Calculated Pharmacokinetic Parameters for ^{14}C Radioactivity After Dosing of 1 mg/kg [^{14}C]Azelastine HCl in Dogs (Ref. 34*)

Parameter	Units	Dosing Route		
		i.v.	p.o.	p.o. multiple
Cmax[1]	ng-equiv./mL	--	104	114
Tmax[1]	h	--	0.75	1.0
AUC$_{0-\infty}$	ng-equiv./mL.h	2048	1650	1965
Amount absorbed	% of dose	--	80	95
T 1/2 abs	h	--	1.1	0.8
T 1/2 dis	h	(1.5)	2.5	2.6
T 1/2 el	h	14.9	25.5	22.7
lag time	h	--	0.4	0.3
Vd (^{14}C)	L	143	336	30
Clearance	L/h	9.2	9.1	9.2

[1]Means of observed values
*Location: Vol. 070 p.05 18566

Distribution:

The distribution of the drug into tissues was found to be rapid ($T_{\frac{1}{2}}$ of distribution = 0.5 h in guinea pigs) and extensive since tissue concentrations of azelastine hydrochloride equivalent were much higher than the plasma concentration at peak concentration of radioactivity in rats and guinea pigs. Tissue distribution by whole-body autoradiography in rats (10 mg/kg) and guinea pigs (1 mg/kg) showed that 1-2 hour after the oral dose administration the radioactivity was distributed almost to the entire body (75%); the distribution was especially high in the digestive tract (43%), the liver, lung and kidney which was decreased considerably after six hours and almost disappeared (<2%) after 24 hours.

Specificity in tissue uptake was demonstrated in the rats and particularly in the guinea pigs where, among nonexcretory organs, high concentrations of radioactivity (desmethylazelastine as major component 62% vs azelastine 18%) were observed in the lung up to 6 hours and very low levels in the brain as shown in the Tables E.37-E.40 (vol.2 p 187-190). In addition, the volumes of distribution values (205L, 10 mg/kg; 143L, 1 mg.kg, i.v. in dogs; 9.8 L/kg in guinea pigs) were much larger than the body weight of the animals, suggesting extensive drug distribution into tissue.

Table E.37

Mean Concentrations and Amounts of [^{14}C]Azelastine HCl Equivalents in Tissues of Various Rat Organs After a Single Oral 10 mg/kg Dose or 21 Daily 10 mg/kg Oral Doses of [^{14}C]Azelastine HCl

	^{14}C Concentration as Azelastine HCl Equivalents (I[a]) or Amounts (II[b])											
	Day 1						Day 7		Day 14		Day 21	
Tissue	Hour 1		Hour 6		Hour 24		Hour 24		Hour 24		Hour 24	
	I	II	I	II	I	II	I	II	I	II	I	II
Brain	420	1.1	250	0.6	20	<0.1	40	0.1	70	0.2	60	0.1
Lung	9290	22.3	12060	28.9	400	1.0	500	1.2	1710	4.1	1350	3.2
Heart	1710	4.1	1570	3.8	80	0.2	160	0.4	500	1.2	300	0.7
Stomach	41760	100.0	3180	7.6	150	0.4	150	0.4	720	1.7	210	0.5
Sm Intestine	54210	130.0	6900	16.6	1370	3.3	410	1.0	1780	4.3	890	2.1
Lg Intestine	7430	17.8	4840	11.6	790	1.9	750	1.8	2430	5.8	1170	2.8
Liver	15210	36.5	9460	22.7	1670	4.0	2610	6.3	4430	10.6	4540	10.9
Pancreas	6760	16.2	3790	9.1	150	0.4	210	0.5	990	2.4	180	0.4
Kidney	3900	9.4	4130	9.9	340	0.8	890	2.1	2340	5.6	1650	4.0
Spleen	3750	9.0	4730	11.4	240	0.6	420	1.0	1600	3.8	1070	2.6
Adrenal	7390	17.7	5970	14.3	270	0.6	540	1.3	2320	5.6	1400	3.4
Testes	440	1.1	930	2.2	160	0.4	610	1.5	1110	2.7	800	1.9
Muscle	1700	4.1	680	1.6	40	0.1	90	0.2	250	0.6	140	0.3
Fat	2000	4.8	3030	7.3	160	0.4	350	0.8	890	2.1	190	0.5
Blood	370	0.9	300	0.7	40	0.1	40	0.1	50	0.1	40	0.1

[a]Concentration, ng/g or ng/mL
[b]Amount, μM

Table E.38

Mean Concentration or Amount of [^{14}C]Azelastine HCl Equivalents in Tissues of Various Guinea Pig Organs 24 Hours After a Single Oral Dose of 1 mg/kg [^{14}C]Azelastine HCl

	Mean Concentration (I[a]) or Amount (II[b]) of Azelastine HCl Equivalents					
	Hour 1		Hour 6		Hour 24	
Tissue	I	II	I	II	I	II
Brain	72	0.2	40	0.1	4	<0.1
Lung	2455	5.9	2424	5.8	147	0.4
Heart	458	1.1	237	0.6	27	<0.1
Stomach-Duodenum	7755	18.6	535	1.3	452	1.1
Jejunum-Ileum	6691	16.0	1520	3.6	274	0.7
Cecum-Colon	970	2.3	5425	13.0	1965	4.7
Liver	7872	18.8	2619	6.3	315	0.8
Kidney	1147	2.7	630	1.5	74	0.2
Spleen	1291	3.1	633	1.5	63	0.2
Adrenal	869	2.1	460	1.1	63	0.2
Gonad	203	0.5	171	0.4	22	<0.1
Muscle	187	0.4	180	0.4	13	<0.1
Fat	276	0.7	133	0.3	29	<0.1
Blood	217	0.5	94	0.2	9	<0.1
Trachea	269	0.6	155	0.4	17	<0.1
Eye	48	0.1	38	0.1	6	<0.1
Bile	5776	13.8	4797	11.5	600	1.4

[a]ng/g or ng/mL
[b]μM

Table E.39
Total Tissue Uptake of ^{14}C-Radioactivity, Azelastine HCl Equivalents, Expressed as AUC in Guinea Pig Tissue After a Single Oral Dose of 1 mg/kg [^{14}C]Azelastine HCl

Tissue/Organ	AUC[1] $\mu g/g.h^{-1}$	Peak Concentration $\mu g/g$	Peak Concentration μM
Bile	92.50	7.86	18.8
Liver	60.95	7.87	18.8
Lung	41.19	3.48	8.3
Adrenal	20.28	1.04	2.5
Spleen	13.44	1.52	3.6
Kidney	13.35	1.43	3.4
Heart	4.98	0.52	1.2
Muscle	3.16	0.28	0.7
Plasma	3.02	0.38	0.9
Brain	0.83	0.09	0.2
Eye	0.78	0.07	0.2

[1]AUC(0→48) calculated by trapezoidal-rule method

Table E.40

Mean Concentrations and Amounts of ^{14}C Radioactivity, Azelastine Base Equivalents and Desmethylazelastine Base Equivalents in the Blood and Lung Tissue of Guinea Pigs After a Single Oral Dose of 1 mg/kg [^{14}C]Azelastine Hydrochloride

Time h	Concentration											
	Blood						Lung					
	Total ^{14}C[1]		AZ[1]		DAZ[2]		Total ^{14}C[1]		AZ[1]		DAZ[2]	
	µg/mL	µM	µg/mL	µM	µg/mL	µM	µg/g	µM	µg/g	µM	µg/g	µM
0.5	135	0.4	75	0.2	2	<0.1	1031	2.7	735	1.9	109	0.3
1	229	0.6	119	0.3	10	<0.1	2986	7.8	1778	4.7	770	2.1
2	235	0.6	86	0.2	14	<0.1	3638	9.5	1643	4.3	1698	4.6
4	140	0.4	43	0.1	17	<0.1	4747	12.4	1312	3.4	2822	7.6
6	93	0.2	18	<0.1	17	<0.1	4323	11.3	575	1.5	2863	7.7
12	27	<0.1	4	<0.1	7	<0.1	1239	3.2	74	0.2	921	2.5
24	8	<0.1	<1	<0.1	1	<0.1	365	1.0	6	<0.1	257	0.7

[1]Azelastine base equivalents
[2]Desmethylazelastine base equivalents

Placental transfer as well as transfer into milk were shown to occur in the rat, but in both cases only a small part of the dose remained at 24 hours; less than 0.1% was found in the fetal tissues and approximately 0.2% in milk.

The ^{14}C distribution in all fetal tissues was higher than that in fetal plasma with most ^{14}C radioactivity in the lung at 0.5 and 4 hours and a tissue/plasma ratio of 10. The mean concentration of the labeled azelastine HCl in the fetal lungs was similar to that of the maternal placenta and the uterus at 0.5 hour but decreased considerably by six hours, which indicate significant placental transfer of the drug occurred initially (Table III.17), contrary to the sponsor's statement that the amount of placental transfer of azelastine and/or its metabolite was low. (vol.67, P 05 17654)

Table III.17

Mean Concentration of [^{14}C]Azelastine HCl Equivalents in Tissues of Maternal and Fetal Organs at Different Times After a 0.5 mg/kg Intravenous Dose of [^{14}C]Azelastine HCl to Pregnant Rats on Day 20 of Gestation (Ref. 22*)

	Mean Concentration ± S.D. (ng/g tissue)		
Tissue	0.25-0.75 h	3.75-4.25 h	23.75-24.25 h
Maternal			
Blood	70 ± 8	23 ± 2	2 ± 1
Plasma	45 ± 5	23 ± 2	2 ± 1
Placenta	621 ± 64	407 ± 92	45 ± 11
Uterus	454 ± 66	325 ± 86	24 ± 4
Amniotic Fluid	9 ± 3	10 ± 2	3 ± 1
Fetal			
Blood	62 ± 26	18 ± 4	< 1
Plasma	51 ± 4	19 ± 2	< 1
Brain	220 ± 26	50 ± 2	2 ± 1
Heart	207 ± 26	70 ± 5	3 ± 1
Lung	659 ± 67	178 ± 4	10 ± 3
Liver	343 ± 54	125 ± 2	7 ± 1
Kidney	230 ± 15	86 ± 7	7 ± 1
GI Tract	250 ± 16	165 ± 31	32 ± 8
Carcass	129 ± 15	42 ± 3	2 ± 1

*Location: Vol. 068 p.05 18007

Metabolism:

Metabolism, mainly through bile, is 2- or 7-oxidative opening of the perhydroazepine ring (2 isomers), N-demethylation, N-oxidation and 6- or 7-hydroxylation. Metabolic profiles for urine, feces and plasma are similar. Individual metabolite identified in excreta or plasma of the mouse, rat, guinea pig and dog are listed in Table E.42. (vol.2 p.192)

Table E.42
Metabolites of Azelastine Hydrochloride Identified in Various Species of Animals[a]

Species, Strain	Medium	Identified Metabolites
Mouse, NMRI	Plasma	Desmethyl
	Urine	Desmethyl
Rat, Donryu and Sprague-Dawley	Liver microsomes	Desmethyl, 6- and 7-hydroxy, methylaminocarboxy-2- and 3-pentyl, N-oxides
	Urine	Desmethyl, 6- and 7-hydroxy, methylaminocarboxy-2- and 3-pentyl, 7-oxo
	Feces	Desmethyl, 6- and 7-hydroxy, 6-hydroxydesmethyl, methylaminocarboxy-2-pentyl, 7-oxo
	Tissue	Desmethyl, 6-hydroxy
Guinea Pig, CAMM-Hartley	Plasma	Desmethyl
	Tissue	Desmethyl
	Urine	Desmethyl, methylaminocarboxy-2- and 3-pentyl, 6- and 7-hydroxy, 7-oxo
	Feces	Desmethyl, methylaminocarboxy-2- and 3-pentyl, 6- and 7-hydroxy, 7-oxo
	Bile	Desmethyl, methylaminocarboxy-2- and 3-pentyl
Dog, Beagle	Plasma	Desmethyl
	Urine	Desmethyl, 6- and 7-hydroxy, methylaminocarboxy-2- and 3-pentyl, N-oxides
	Feces	Desmethyl, 6-, and 7-hydroxy, methylaminocarboxy-2- and 3-pentyl, N-oxides
Humans	Urine	Desmethyl, methylaminocarboxy-2- and 3-pentyl, unknown

Amount of Azelastine and Its Identified Metabolites Excreted in 24-hour Urine and Feces (vol.67)

Species/Dose	Percent of ^{14}C Dose		
Metabolite	**Urine**	**Feces**	**Sum**
Rats/1 mg/kg, p.o. (ref.40)			
Azelastine	0.1	3.7	3.8
Desmethylazelastine	trace	trace	
6-Hydroxy and 7-Hydroxy metabolites, free	1.1	56.3	**57.4**
Glucuronides	0.1	--	0.1
7-Oxo metabolite	0.1	9.1	9.2
Total	1.4	69.1	70.5
Rats/1 mg/kg, p.o. (ref.43)			
Azelastine	0.2	4.5	4.7
Desmethylazelastine	0.2	2.9	3.1
6-Hydroxy and 7-Hydroxy metabolites, free	1.2	30.7	**31.9**
Methylaminocarboxy-3-pentyl metabolite	1.8	16.5	18.3
6-Hydroxydesmethyl metabolite	0.2	5.7	5.9
Total	3.6	60.3	63.9
Guinea Pigs/1 mg/kg, p.o. (ref.40)			
Azelastine	2.7	7.0	9.7
Desmethylazelastine	trace	trace	
6-Hydroxy and 7-Hydroxy metabolites, free	4.5	15.5	**20.0**
Glucuronides	1.5	--	1.5
7-Oxo metabolite	1.6	6.2	7.8
Total	10.3	28.7	39.0
Guinea Pigs/1 mg/kg, p.o.-48 hour (ref. 45)			
Azelastine	1.4	10.4	11.8
Desmethylazelastine	2.1	8.7	10.8
2-Acid**	--	1.3	1.3
7-Acid*	13.5	42.9	**56.4**
Total	17.0	63.3	80.3

Dogs/5 mg/kg, i.v. or p.o. (ref. 47)

Azelastine	0.46	3.96	3.52
Desmethylazelastine and N-oxide metabolite	0.52	7.65	8.17
Hydroxy Metabolites	0.80	3.24	4.04
Methylaminocarboxy-2- and 3-pentyl	3.86	43.92	47.78
Total	5.64	57.87	63.51

Urinary Recovery of Azelastine and Metabolites Following Azelastine Hydrochloride, P.O. or I.V. (% Dose ± SD)

Human (vol.2, p.229)	I.V.	P.O.	P.O./I.V.
Azelastine	2.5±1.7	2.2±1.6	0.91
Desmethylazelastine	2.6±0.6	2.9±0.7	1.10
7-Acid*	4.0±1.0	4.2±1.2	1.06
2-Acid**	1.1±0.5	1.2±0.6	1.12
Unknown metabolite	1.2±1.2	1.0±0.7	0.86
Total	11.3±2.3	11.6±2.6	1.01

* Methylaminocarboxy-3-pentyl metabolite (7-Acid)
** Methylaminocarboxy-2-pentyl metabolite (2-Acid)

In humans, the analysis of urine identified azelastine, desmethylazelastine, two carboxylic acids formed by oxidative cleavage of the seven membered ring and one unknown metabolite, which made up 11% of the dose.

Quantitative differences in metabolic profile between the rats and humans were observed. The metabolites 6- and 7-hydroxyazelastine were the major component in rat feces (50%) and urine (1.2%), whereas desmethylazelastine (less than 5% in both excreta) was the major metabolite in human.

Qualitatively, metabolic profiles were similar among animal species, but there were quantitative inter-species differences in the metabolism of the drug as shown on previous pages.

The desmethylazelastine was found in all species and was the only metabolite isolated in mice. The most common metabolites found in feces of rats and guinea pigs were 6- and 7-hydroxyazelastine and methylaminocarboxy-2- and 3-pentyl metabolites which was the major metabolite in dogs. Methylaminocarboxy -3- pentyl metabolite (7-Acid) was another major metabolite in guinea pigs and humans.

Excretion:

Excretion studies with ^{14}C-azelastine hydrochloride in animals showed that the major route of excretion of the drug and its metabolites for all species is through the feces. The amount excreted in urine varied with the species and route of administration, but almost all of the radioactivity in urine and feces was recovered in the first two days in rats, guinea pigs and dogs.

The amount of ^{14}C eliminated in the dog urine within the first 24 hours varied from 7.8-13.5% of the dose and in feces 68.7-86.3% during 55 to 120 hours after administration. Biliary excretion of ^{14}C in the rat amounted to from 50-83% of the dose with half-life of 2.2 and 7.5 hours after i.v. and p.o., respectively. About one-fifth of the biliary ^{14}C (19%) was recirculated in rats; the bile may thus serve as a temporary storage compartment for the drug and its metabolites. (Table E.41, vol.2 p.191)

In humans, ten days after oral administration approximately 24 and 75% of the radioactivity was recovered in urine and feces, respectively. The half-lives of azelastine and desmethylazelastine (and other metabolites) were in the range of 24 and 48 hours, respectively. The half-lives of other metabolites were supposed to be comparable to those of desmethylazelastine according to the sponsor (no data available).

Table E.41
Excretion of ^{14}C in Animals After a Single Dose of [^{14}C]Azelastine Hydrochloride

Species, Strain	Dose (mg/kg)	Route	Time (h)	% of ^{14}C Dose			
				Urine	Feces	Total	Bile
Rat, Donryu	1	i.v.	168	3.1	102.7	105.8	
	10	p.o.	168	10.2	88.5	98.7	
Rat, Donryu	1	i.v.	48				82.7
	1	p.o.	48				54.3
	10	p.o.	48				50.0
Guinea Pig	1	i.v.	168	37.6	69.4	107.0	
	1	p.o.	168	20.2	82.0	102.2	
Guinea Pig, CAMM-Hartley	1	p.o.	72	18.4	74.0	92.4	
	1	p.o.	48	21.7	69.3	91.0	
Dog, Beagle	1	i.v.	144	13.3	86.9	100.2	
	1	p.o.	144	8.9	100.1	109.0	

Effect on enzymes:
Effect on activity of hepatic microsomal drug-metabolizing enzymes was studied in rats. At a dose of 10 mg/kg/day, a little change was observed whereas at a dose of 50 mg/kg/day there was a slight increase in the activity of aminopyrine N-demethylase and the content of cytochrome P-450.

Protein binding:
The degree of protein binding of total radioactivity was found to be 53-57% in rats. In human, the degree of protein binding was 88% for azelastine and 97% for desmethyl-azelastine.

Summary of ADME:

The absorption of azelastine hydrochloride seems to be very rapid (T_{max} for animals 1-2 hours; for human 4-6 hours) and almost complete in laboratory animals (rat, guinea pig and dog) and humans. Plasma concentrations for both animals and humans show general dose proportionality. There were no biologically significant differences in C_{max}, T_{max} and $T\frac{1}{2}$ for azelastine and desmethylazelastine between adult and pediatric male and female dogs.

The degree of protein binding of total radioactivity was found to be 53-57% in rats. In human, the degree of protein binding was 88% for azelastine and 97% for desmethy-lazelastine.

In both laboratory animals and humans, the distribution of the drug into tissues was found to be extensive since azelastine HCl equivalent concentrations were much higher than those in circulation. In addition, the volume of distribution was much larger than the body weight, meaning azelastine hydrochloride is widely distributed to body tissues with a preferential uptake by the lung observed in two species studied, rat and guinea pig. There is clear evidence for a placental transfer, very low levels of transfer to the brain and a high first pass effect in animals and humans.

The drug is metabolized to various metabolites (eight possible metabolic pathways), desmethylazelastine being the major metabolite in human. Qualitatively, the metabolic fate of azelastine hydrochloride is similar in the mouse, rat, guinea pig, dog and human. However, there are some significant quantitative inter-species differences in the metabolism of the drug.

The desmethylazelastine, the other known pharmacologically active metabolite, was also found in trace amount in rats

The desmethylazelastine, the other known pharmacologically active metabolite, was also found in trace amount in rats and guinea pigs but the second major metabolite in guinea pigs, dogs and human and was the only metabolite isolated in mice. In the rats, the major metabolite was 6-and 7-hydroxyazelastine (which is known to be less toxic than the parent compound and not found in humans) whereas methylaminocarboxy-2- and 3-pentyl metabolites was the major metabolite in dogs, guinea pigs and in human.

Azelastine hydrochloride did not induce enzyme when tested for antipyrine half-life in low dose but slightly induced at higher dose of 50 mg/kg in rats.

The predominant route of elimination in the animals and humans was biliary excretion. In the rat, approximately 50% and 83% of the [^{14}C]azelastine Hcl doses following oral and intravenous administration, respectively, were eliminated in the bile. A significant portion (19%) of the biliary radioactivity was recirculated. The terminal half-lives for elimination of azelastine and its metabolites were 4-8 hours in mice and rats, 15-25 hours in dogs and 20-50 hours in human.

4. SUMMARY AND EVALUATION

PHARMACOLOGY

Azelastine HCl drug substance is a racemic mixture (dl). The pharmacologic activities of the individual enantiomers showed general trend d ≥ dl ≥ l isomers in several studies, although clear differentiation of the relative activities was not revealed always.

Pharmacologic studies in laboratory animals and *in vitro* model systems indicate that azelastine hydrochloride is an orally active, long-acting agent with multiple actions in both the upper and lower airway. These include inhibition of allergic reactions, interference with inflammatory processes and modulation of airways smooth muscle response.

Azelastine hydrochloride is a H_1-histamine receptor antagonist and inhibits histamine release from mast cells and basophils. In addition it inhibits the generation of other mediators of allergy such as superoxide anions and leukotrienes (B_4, C_4, and D_4). It also has the property of inhibiting contractile responses induced by adenosine, Ca^{2+}, KCl, tetramethylammonium (TEA), $CaCl_2$, serotonin, acetylcholine, leukotrienes and bradykinin in isolated tissues and/or *in vivo*.

Azelastine HCl has also been shown to inhibit aeroallergen-induced eosinophilia in the airways in guinea pigs and reduce viscosity of the bronchial lavage fluid; thus it seems to provide protection in both the early and late phases of allergic responses.

Azelastine HCl has been shown to interfere with Ca^{2+} influx into target tissues. Since Ca^{2+} is essential in the synthesis and release of chemical mediators and in their interaction at receptor sites, azelastine's ability to interfere with Ca^{2+}-dependent processes may partly be the mechanism of its broad spectrum of pharmacological activities.

Azelastine HCl protected against immediate allergic responses (i.e., broncho-constriction) in rats with oral ID_{50} of 0.7 mg/kg (antigen induced) and ID50 of >0.014 mg/kg in guinea pigs. Inhibition (40-80%) of 48-hour homologous PCA was observed at 5-25 mg/kg in rats and 0.03-7.5 mg/kg in guinea pigs orally. In guinea pigs, at 0.01-0.1 mg/kg, azelastine Hcl blocked histamine-induced shock; 1 mg/kg orally protected against aeroallergen-induced asthma and produced dose-dependent inhibition of late phase - associated eosinophil infiltration in bronchial trees; and 3 mg/kg reduced viscosity of the bronchial lavage fluid during the late-phase allergic response. In dogs, 0.026 mg/kg of azelastine intraduodenally inhibited histamine-induced bronchoconstriction and 2 mg/kg orally abolished histamine-induced reduction in nasal obstruction in dogs, showing greater sensitivity to azelastine Hcl for its pharmacologic effects.

Azelastine hydrochloride administered at high oral doses in mice and rats produced little or no apparent CNS changes except depressed motor activity in mice at doses ≥ 20 mg/kg. However, the administration of high doses (10-30 mg/kg, s.c.) to dogs and 3-6 mg/kg i.v. to cynomolgus monkeys produced CNS stimulation and even convulsions at 10 mg/kg, i.v. in monkeys.

In general, azelastine hydrochloride in therapeutic dose ranges usually effective against allergic responses was devoid of any effects on the cardiovascular and respiratory systems of anesthetized rats, dogs and cats.

Intravenous administration of azelastine hydrochloride to rats, dogs and cats did not affect systemic blood pressure or heart rate. However, higher doses (5-10 mg/kg, depending on species tested) resulted in increase or decrease in blood pressure and in heart rate.

In dogs, 1 mg/kg i.v. dose exerted long-lasting reduction of ST segment elevation. Orally, ECG changes, prolonged Q-T intervals at 20 mg/kg and prolonged QRS and QT intervals were observed at ≥40 mg/kg in one toxicity study. In addition, localized myocardial degeneration in the heart and adipose cell infiltration in the interstitial tissue of the myocardium have been noted at 40 and 60 mg/kg, respectively, suggesting an effect of azelastine administration on the heart at very high doses.

Azelastine HCl caused a dose-dependent increase in tracheobronchial secretion in the mouse with an ED50 of 0.52 mg/kg, p.o. and enhanced mucolytic activity in the tracheobronchial lumen of rats (ED50 = 0.33 mg/kg). It was found to decrease mucus rigidity in beagle dogs at a dose equivalent to 3 mg/kg and decreased antigen-elevated viscoelasticity of tracheal mucus in the dogs.

Oral administration of azelastine HCl of 1 to 50 mg/kg did not influence gastric motility and emptying in mice, but in rats, 1 to 10 mg/kg produced a slight acceleration of gastric emptying and retardation at 50 mg/kg. It exerted little or no effect on intestinal motility or pancreatic, biliary and salivary secretions in rats.

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

The absorption of azelastine hydrochloride is very rapid in animals evidenced by short T_{max} of 1-2 hours compared to human T_{max} of 4-6 hours and bioavailability is good in laboratory animals (rat, guinea pig and dog) and humans. Plasma concentrations for both animals and humans show general dose proportionality up to 30 mg/kg in rats, 60 mg/kg in mice and over the dose ranges of 2-16 mg in humans.

In both laboratory animals and humans, azelastine hydrochloride is widely distributed to body tissues with a preferential uptake by the lung observed in two species studied, rat and guinea pig. In the dog, the volume of distribution of azelastine after intravenous dosing was approximately 20 times the body weight. There is a clear evidence for a placental transfer, very low levels of transfer to the brain in rodents and a high first pass effect in animals and humans.

The drug is metabolized to various metabolites (eight possible metabolic pathways), desmethylazelastine being the major metabolite of importance. Qualitatively, the metabolic fate of azelastine hydrochloride is similar in the mouse, rat, guinea pig, dog and human. However, there are quantitative inter-species differences in the major

metabolites which may be partly responsible for different toxicity between rats and dogs. Azelastine hydrochloride is not an enzyme inducer when tested for antipyrine half-life.

The degree of protein binding of total radioactivity was found to be 53-57% in rats. In human, the degree of protein binding was 88% for azelastine and 97% for desmethyl-azelastine.

The major route of elimination in the animals and humans was biliary excretion. In the rat, approximately 50% and 80% of the [^{14}C]azelastine HCl doses following oral and intravenous administration, respectively, were eliminated in the bile. A significant portion (19%) of the biliary radioactivity was recirculated. In humans, 25 and 50% of the radioactivity was recovered in urine and feces, respectively after five days of oral administration (4 mg) and 25 and 75% after ten days. There were no signs of tissue accumulation with repeated dosing. The terminal half-lives for elimination of azelastine and its metabolite in rodents was 4-8 hours compared to 15-25 hours in dogs and 20-50 hours in human. This long half-life of the metabolite which is active pharmacologically explains the long duration of action in azelastine hydrochloride.

TOXICOLOGY

Studies evaluating the toxicity of azelastine Hcl have been conducted in a variety of animal species in Germany, Japan, the United States and England. The results from these studies adequately characterized the toxicologic profile of azelastine Hcl.

Major findings from the toxicologic evaluations included elevated serum levels of alkaline phosphatase, SGOT and SGPT and reversible fatty changes in the liver and hepatocellular hypertrophy. These findings occurred at oral doses of 30 mg/kg/day or greater which is 375 times the proposed human clinical dose of 4 mg/day (in 50 kg individual) and 30 time the dose that inhibited the bronchoconstriction in rats.

Acute Toxicity studies:

The acute toxicity of azelastine Hcl was evaluated in the mouse, rat, guinea pig and dog. The oral LD_{50}s in all species tested were greater than 124 mg/kg (1550 X) except in dogs the lowest LD_{50} was 51.3 mg/kg (641 X the maximum proposed total daily dose of 0.08 mg/kg in man for allergic rhinitis).

The 6-hydroxyazelastine, the major metabolite in rats and guinea pigs, was found to be slightly less toxic than the parent compound when tested in mice intravenously. The comparative toxicity of other metabolites have not been studied.

Across the species, the sensitivity to azelastine Hcl was very similar except the dogs which were slightly more sensitive. The clinical signs observed in all species were salivation, convulsions, irritability, tremor, loss of righting reflex and aggressive behavior which were indicative of central nervous system stimulation.

Subchronic and chronic toxicity studies:

Twenty studies were conducted to assess the toxicity and/or carcinogenicity of orally administered azelastine Hcl. In subacute and chronic studies in the rat, most of the changes in hematology (elevated serum AP, SGOT and SGPT) and urinary parameters (increased urine volume and potassium), liver and kidney weight increases and hepatocellular changes (cytoplasmic vacuolation) occurred at 30 mg/kg/day (375X the clinical dose) and higher. The target organs for toxicity were liver and kidney and the drug-induced changes appeared reversible upon drug withdrawal. However, there were no changes in kidney function parameters and histopathology to correlate the kidney weight increase and the liver changes may be adaptive response. In neonatal rats, no toxic effect of azelastine Hcl was found at 1 and 5 mg/mg and slight toxicity at 30 mg/kg was seen as in adult rats.

Dogs seem to be more sensitive species to azelastine hydrochloride than rats in terms of CNS effect as well as the antiallergic effects (ID50 = 0.026 mg/kg vs 1 mg/kg in rats). There were minimal toxicity (emesis and salivation) observed in dogs at 3 mg/kg/day and definite CNS toxicity (aggression and tonic-clonic convulsion) at ≥10 mg/kg/day (100 times the clinical dose); 20 mg/kg/day was lethal. The change in hepatic enzymes or hepatocellular vacuolation found in rats were not observed in dog at 10 mg/kg or less for one year. (The hepatic change was also observed in the mouse and rabbit at doses of 30 mg/kg.)

The degeneration of renal cortical tubular epithelium was seen at 21.5 mg/kg in one 6-month dog study but there were no dose response and no changes in blood urea nitrogen, creatinine or specific gravity to support the histological finding. Later electron microscopic examination of the liver and kidney in another study showed no apparent drug-related effects. In the rabbit study, cloudy swelling of the renal tubular epithelium was observed only in those dams that were found dead.

Cardiovascular effects in dogs:
Azelastine hydrochloride in pharmacologically effective dose ranges (0.026-3 mg/kg, p.o.) was devoid of any cardiovascular effects in anesthetized dogs.

Intravenous administration of azelastine hydrochloride to dogs (<1-1 mg/kg) did not affect systemic blood pressure or heart rate. However, higher doses (2-10 mg/kg) resulted in dose-dependent decrease in blood pressure (11%) and increase or decrease in heart rate (15-20%). At 1 mg/kg i.v., it exerted long-lasting reduction (up to 68%) of ST segment elevation in dogs. At 0.3-3 mg/kg, i.v., azelastine exerted no effect on cardiac output and stroke volume.

Orally, ECG changes, prolonged Q-T intervals at 20 mg/kg and prolonged QRS and QT intervals were observed at ≥40 mg/kg in a 5-week oral toxicity study. In addition, localized myocardial degeneration in the heart and adipose cell infiltration in the interstitial tissue of the myocardium have been noted at 40 and 60 mg/kg, respectively, suggesting an effect of azelastine administration on the heart. However, doses above 20 mg/kg/day orally was toxic and lethal to the dogs.
Azelastine hydrochloride was irritant to vessels at all dose levels when administered intravenously to dogs.

Intranasal studies:

Two six-month studies were conducted with the intranasal formulation in rats and dogs. Except a marginal decrease in body weight gain observed in dogs at highest dose level, there were no clinical findings indicative of systemic toxicity of azelastine Hcl and no signs of irritation to the epithelium lining of the nasal cavity in both species. The intranasal administration of azelastine hydrochloride up to 0.2 mg/rat four times a day (200X clinical dose) and 3.36 mg/day (20X clinical dose) to dogs appeared to be safe in these studies.

Plasma levels of azelastine hydrochloride and its metabolite, desmethylazelastine, in both intranasal studies showed generally dose-related increases in concentrations with average plasma levels of 25 ng/ml in treated rats and 105 ng/ml in treated dogs.

Mutagenicity Studies:

Azelastine hydrochloride showed no mutagenic effects in the AMES test, DNA repair test, mouse lymphoma forward mutation assay, mouse micronucleus test or rat chromosomal aberration test.

Carcinogenicity Studies:

Two 104-week carcinogenicity studies were conducted in mice and rats to assess the carcinogenic potential of azelastine hydrochloride. Statistical analysis of the results by the sponsor showed that there was no increase in malignant, non-malignant or total neoplasms due to drug treatment in both mice and rats.

When the tumor data was reanalyzed by our Division of Biometrics, there was positive dose-response relationship of bone-osteosarcoma and spleen-lymphosarcoma in female mice at high doses, but they were within historical control ranges from the breeder. In rats, there was positive dose-response relationship of skin sebaceous adenoma in male rats which is a rare tumor. However, when skin sebaceous adenoma was combined with ear/mastoid sebaceous gland adenoma (advised by NTP), the incidence became not statistically significant. The hepatic changes found were similar to those found in subchronic and chronic studies. Therefore, azelastine HCl was considered non-carcinogenic in both mice and rats.

Since the original review, these two studies have been discussed at the carcinogenicity assessment committee (CAC) and a recommendation was made to obtain further pharmacokinetics data (on plasma AUC at steady state) in mice to confirm that adequate doses were used in the carcinogenicity study to make the result valid. Therefore, the final conclusion on mouse carcinogenicity study will be deferred until such data from the sponsor is submitted and evaluated.

Reproduction Studies:

Fourteen studies were conducted in mice, rats and rabbits to assess reproductive toxicity. In doses ranging from 30-68.6 mg/kg/day which is 375 to 857 times the recommended maximum clinical daily dose caused variable maternal and fetal effects depending on the species.

At 30 mg/kg/day in rats, reduced fetal weight, minor skeletal abnormalities (retarded ossification, undeveloped metacarpus, cervical ribs, and 14 ribs) in the pups and maternal toxicity were observed occasionally. At 68.6 mg/kg, maternal and embryotoxicity in mice, increased resorptions, dead fetuses, decreased fetal weight and skeletal anomalies in rats were observed. In rabbits up to 20 mg/kg dose in one study, there was no signs of embryotoxicity or teratogenicity, although significant reduction in maternal body weight was observed. In another study, 30 mg/kg dose in rabbits showed abortion, severe maternal toxicity and retarded ossification.

The maximum dose that could be given without adverse effects in Segment I and II studies was 3 mg/kg in mice, rat and rabbit. In Segment III study in rats there was no adverse effects on duration of gestation, neonatal viability, development and behavior at 30 mg/kg.

Therefore, it could be concluded that at doses up to 3 mg/kg (37 times clinical dose), there were no signs of maternal toxicity, reduced fertility, fetotoxicity or teratogenicity. At 30 mg/kg (375 times) at which adult rats showed systemic toxicity, there were reduced fetal weights, signs of skeletal anomalies occasionally and retarded ossification in the fetus. At 68.6 mg/kg (857 times), it was teratogenic, fetotoxic and maternally toxic.

Discussion:

No observable effect level of toxicity (NOEL) for rats was considered to be 3 mg/kg/day from the subchronic study and later increased to 10 mg/kg/day (125X clinical dose) in 6-month study; NOEL for neonatal rats was 1 mg/kg/day. For dogs, NOEL was considered to be 1 mg/kg/day from one-year toxicity study. Most of the toxic signs occurred at ≥30 mg/kg/day in rats and ≥3 mg/kg/day in dogs, which is 30 times and 100 times the doses that inhibited bronchospasm in rats and dogs, respectively.

Most of the antiallergic effects of azelastine HCl were observed at much lower doses around 1 mg/kg in both rats and guinea pigs. Azelastine HCl at 5-25 mg/kg, p.o. in rats and 0.03-7.5 mg/kg in guinea pigs showed inhibition (40-80%) of 48-hour homologous PCA. In guiniea pigs, at 0.01-0.1 mg/kg, azelastine HCl blocked histamine-induced shock; 1 mg/kg orally protected against aeroallergen-induced asthma and produced dose-dependent inhibition of late phase-associated eosinophil infiltration in bronchial trees; and 3 mg/kg reduced viscosity of the bronchial lavage fluid during the late-phase allergic response. In dogs, 0.026 mg/kg orally inhibited histamine-induced bronchoconstriction and 2 mg/kg orally abolished histamine-induced reduction in nasal obstruction in dogs, showing greater sensitivity to azelastine HCl than rats for its pharmacological effects.

The dogs and humans seem to be more sensitive species to the azelastine hydrochloride for its pharmacological effects and similar in pharmacokinetic paramethers than other species. The differences in sensitivity to CNS toxicity to azelastine HCl between rats and dogs could be explained by the differences in sensitivity to the drug pharmacologically, in major metabolic pathways and the rate of elimination in these animals.

The predominant metabolites in rats were 6- and 7-hydroxyazelastine with shorter elimination half-life of 4-8 hours in rodents in one compartment model whereas methylaminocarboxy 3- and 2-pentyl metabolite was the major metabolite in dogs with much longer elimination half-life of 15-25 hours in a two compartment model. (See pages 62-63)

The 6-hydroxyazelastine, the major metabolite in rats and guinea pigs, was found to be slightly less toxic than the parent compound when tested in mice intravenously. However, in the absence of additional comparative toxicity studies conducted with different metabolites, it is difficult to understand the reasons for the differences in CNS toxicity between these two species. In addition, the drug distribution studies were conducted only in rats and guinea pigs and found that a very little radioactivity was found in the brain and the cerebrospinal fluid, but no such information is available for dogs.

Overall, azelastine hydrochloride has shown a wide safety margins when used at the dose range proposed for allergic rhinitis (4 mg/day; 0.08 mg/kg/day). Based on rat studies, at doses ≥30 mg/kg/day which is approximately 375 times the clinical dose, the systemic toxicity in animals, maternal toxicity and minor skeletal anomalies in offsprings in animals were found. In dogs at NOEL of 1 mg/kg showed plasma AUC of 1650 ng/ml (16X) compared to the approximately 100 ng/mg from the human clinical dose of 0.9 mg/kg. Azelastine hydrochloride was found to be non- mutagenic or non- carcinogenic (pending PK data).

COMMENTS ON THE LABELING

1. **Throughout the labeling**, the dosages were expressed as number of times the maximum human clinical doses. Since the clinical doses can differ depending upon the indications and the body weight used in calculations, it is recommended that the dose be expressed as mg/kg/day (# X maximum clinical dose for rhinitis).

2. **Carcinogenicity, Mutagenesis and Impairment of Fertility section:** Again this section should be revised using the exact mg/kg dosages. According to the three generation study in rats, there was decreased fertili · and reduced body weight in parental generation at 30 mg/kg dose. Such information should be included in the first paragraph under the Impairment of Fertility section.

3. **Pregnancy Category C:** This section should be revised to show the exact dosages expressed in mg/kg/day rather than the multiples of clinical dose and the wording to reflect the findings from the reproduction studies. It is misleading to say no teratogenic effects were seen in the rat or rabbit in oral doses ranging between 30-68.6 mg/kg. According to the study results, the skeletal changes found in rats, in addition to reduced fetal weight and fetal mortality, included delayed ossification, increased incidence of 14th rib and cleft palate in mice were found in rats at these dose ranges.

4. **Nonteratogenic Effects:** There were signs of maternal toxicity in rats and rabbits starting at 30 mg/kg/day. Such information should be included.

5. CONCLUSIONS

1) The extensive preclinical studies submitted offer adequate support for the therapeutic indication (allergic rhinitis) and the safety of the proposed clinical dose of azelastine hydrochloride nasal spray.

2) Labeling should be revised as recommended above.

Misoon Y. Chun

Misoon Y. Chun, Pharm.D.
Pharmacologist, HFD-150

cc: NDA 20-114
HFD-150/Division File
HFD-150/CSO
HFD-150/MHimmel
HFD-150/MChun
HFD-150/ATaylor AJT 4-1-92
HFD-502/JWeissinger

Appendix I: Previous review of two intranasal studies (IND

Appendix II: Summary of incidences of all the neoplasms from the carcinogenicity studies

Addendum to the original review:

Since the original review, the carcinogenogencity studies with Azelastine HCl have been discussed at the Carcinogenicity Assessment Committee meeting (11/19/91). CAC has recommended to conduct an additional pharmacokinetic study in mice which will provide plasma kinetic data (plasma AUCs at steady state) with the highest dose (25 mg/kg/day) used in the carcinogenicity study.

A letter from Dr. Robert Temple, dated February 18, 1992, was sent to the sponsor, wherein a study was requested to assess relative steady state plasma AUCs of azelastine and desmethylazelastine in mice for comparison with human data from a normal dosing schedule.

The sponsor has agreed to provide such data and a protocol for a pharmacokinetic study in mice was submitted in subsequent supplement, dated 2/28/92. Therefore, the final decision on the acceptability of mouse carcinogenicity study will be deferred until the final report of the pharmacokinetic study demonstrates that the relative exposure in the mouse study exceeds anticipated human exposure by a very sizeable margin.

Appendix I: Previous review of two intranasal studies (IND

INL

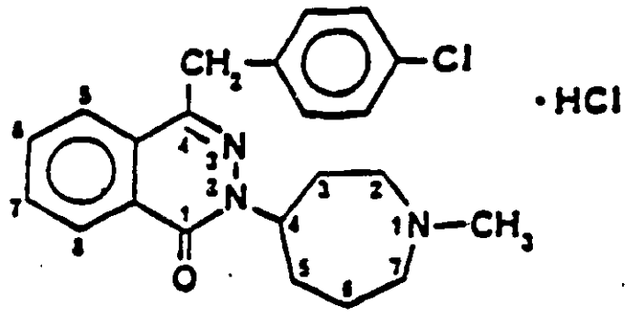
Sponsor: Wallace Laboratories/Division of Carter-Wallace, Inc.
Cranbury, NJ 08512-0181

Review #1

Date of Review: March 24, 1989

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary
Date of Receipt - February 7, 1989
IT - March 20, 1989

Drug: Azelastine Hydrochloride Nasal Spray 0.1%



Formulation: %w/v

The nasal spray, which will be packaged in 15 cc high density polyethylene bottles, will be dispensed using the Dose System which delivers hydrochloride, per spray.

Category: Antiallergy Agent - Seasonal Allergic Rhinitis

Related IND: - azelastine hydrochloride

Proposed Clinical Studies: The safety and tolerability of 0.1% azelastine nasal spray will be determined in a double-blind, placebo-controlled, randomized, parallel study in 39 healthy males, divided into 3 groups of 13 subjects, who will receive the spray at 12-hour intervals for 29 consecutive days.

In each group, 10 subjects will receive the drug. Subjects in Groups 1, 2 and 3 will be administered doses of 1, 2 and 3 sprays, respectively, into each nostril, with each spray delivering 0.14 mg of azelastine hydrochloride. On days 1 and 29 each subject will receive one dose. On days 2-28, each subject will receive 2 doses every 12 hours.

New Preclinical Studies and Testing Laboratories:

A Six-Month Intranasal Toxicity Study of
Azelastine Hydrochloride in the Albino Rat
TC-88E-7

A Six-Month Intranasal Toxicity Study of
Azelastine Hydrochloride in Dogs
ASTA Pharma Report No. A5610/7100000887

GLP Statements: Adequate

Reference is also made to preclinical data in IND (Azelastine Hydrochloride Summaries of these essentially oral studies, prepared by the sponsor, will appear in the Evaluation section of this review. Details of these studies may be found in the numerous pharmacology reviews in IND

TOXICOLOGY
A Six-Month Intranasal Toxicity Study of Azelastine Hydrochloride in the Albino Rat

Study Dates: August 31, 1987 to March 2, 1988

Test Article: Azelastine Hydrochloride (0.1%) Intranasal Solution, Batches No. 18/7 and 19/7

Per 100 ml

mg azelastine hydrochloride

The vehicle served as the placebo control.

Test System: 6-7 week old Sprague Dawley rats (Crl:CD(SD)BR(VAF)PLUS, weighing 179-240 gm (males) and 146-184 gm (females) were divided into 5 groups of 15 rats/sex/group.

Dosage Groups:

1 - Sham (air) Control	0.1 ml/nostril q.i.d.	
2 - Vehicle Control	0.1 ml/nostril q.i.d.	
3 - Azelastine Hydrochloride	0.1 ml/nostril q.d.	0.2 mg/rat/day
4 - Azelastine Hydrochloride	0.1 ml/nostril b.i.d.	0.4 mg/rat/day
5 - Azelastine Hydrochloride	0.1 ml/nostril q.i.d.	0.8 mg/rat/day

Methodology: Drug solution or vehicle was administered by intranasal administration, bilaterally, 7 days per week for 26 weeks.

Observed Effects: No apparent drug-related effects were observed.

Mortality: 2 high dose males and 1 sham control male died at various times and deaths did not appear to be drug-related.

One high dose male, which showed decreased activity, tremors and/or piloerection on days 74 to 79 was moribund (severely reduced motor activity, slight dehydration, labored breathing, moderate piloerection, moderate red/clear unilateral lacrimation and hypothermia) on day 79 and was necropsied.

One high dose male was found dead on day 159 without observed effects except slight epistaxis which had been noted frequently (76 times) between days 16-144.

One sham control male, which showed slight or moderate epistaxis on days 90-93 and 97-100, became moribund (dry dark material at inner region of both eyes, foul odor, wet fur on ventrum and moderately decreased motor activity) and died.

Body Weight: Mid dose females showed significant decreases at weeks 13 and 15 which did not appear to be drug-related.

Food Consumption: Group 2 males showed a significant increase during week 14 and Group 2 females showed a significant increase during week 18.

Ophthalmologic Exam: No apparent drug-related changes were detected.

Hematology: No apparent drug-related findings were noted. Significant differences (decreases, except for segmented neutrophils which were increased), compared to control values, were seen as follows:

Week 8	Males	rbc count	Groups 2, 3, 4, 5	D
Week 8	Females	lymphocytes	Group 3	D
Week 8	Females	seg. neutrophils	Group 4	I
Week 8	Females	rbc count	Group 3	D
Week 13	Males	rbc count	Group 2	D
Week 27	Males	lymphocytes	Group 2	D
Week 27	Females	A.P.T.T.	Group 2	D

Blood Chemistry: BUN, T. Protein, Alkaline Phosphatase, GPT, GOT, Cholesterol, Creatinine, Glucose, Sodium, Potassium, Chloride and Triglyceride values did not appear to show a drug-related effect.

Plasma Concentrations of Azelastine Hydrochloride and Desmethylazelastine:

Sponsor reported that plasma levels of azelastine hydrochloride and its metabolite, desmethylazelastine, generally increased in a dose-dependent mannner.

However, mean plasma levels of the parent compound and its metabolite were not reported. Additionally, it is noted that substantial detectable levels of azelastine hydrochloride and desmethylazelastine were found in plasma samples obtained from control animals.

Urinalysis: No apparent drug-related changes were detected.

Organ Weight: Adrenal glands, brain, heart, kidneys, liver, ovaries and testes did not appear to show any drug-related effects.

Gross/Histopathology: No apparent drug-related pathology was detected.

A Six Month Intranasal Toxicity Study of Azelastine Hydrochloride in Dogs

Study Dates: February 25 to August 28, 1987

Test Article:

Substance	Form	Batch	Amount (litres)	Expiry Date	Date Used on Study
*Azelastine hydrochloride 0.1% w/v	Clear colourless solution stored in brown glass bottles	11/7	5.5	February 1988	25 February - 14 June 1987
*Azelastine hydrochloride 0.1% w/v	Clear colourless solution stored in brown glass bottles	13/7	6.0	April 1988	15 June - 27 August 1987
Placebo solution for A5610-L/11	Clear colourless solution stored in brown glass bottles	11/3	3.5	February 1988	25 February - 22 June 1987
Placebo solution for A5610-L/11	Clear colourless solution stored in brown glass bottles	12/3	4.0	April 1988	23 June - 27 August 1987
50 Stella bottles - 30 ml capacity and 5 spray pumps	Brown glass Plastic	-	-	-	25 February - 27 August 1987

Test System: 23-28 week old beagle dogs weighing 6-10.2 kg were divided into 5 groups of 8 animals (4/sex)

Dosage Levels:

Dose Group	Test Material	Treatment Regimen: No. of Sprays/Nostril	No. of Dose Sessions	Total No. of Sprays/Day	Nominal Dose Level (mg conc. nasal)
1	0.9% NaCl	4	3	24	0
2	Placebo	4	3	24	0
3	Azelastine Hydrochloride	1	3	6	3.84
4	Azelastine Hydrochloride	2	3	12	7.68
5	Azelastine Hydrochloride	4	3	24	3.36

Methodology: One control group received 0.9% NaCl and the other control group received a placebo formulation which contained no azelastine hydrochloride but did contain sodium cyclamate. The 3 test groups received Azelastine Hydrochloride Nasal Spray 0.1% three times daily with a minimum period of one hour between administrations. To facilitate dosing, each animal's head was held (snout up) at a 30' angle and the spray applicator placed just inside each nostril. The dog's head was retained at this angle for approximately 1 minute to allow the test material to drain through the nasal passages.

Observed Effects: Signs indicating estrus were observed in the majority (7/8) of the females in Groups 1 and 2; however, the proportion of females was lower (6/12) in the drug treated groups.

Mortality: None.

Body Weight: Compared to the Group 2 control, terminal mean body weights showed dose-related decreases in low, mid and high dose males of 10%, 20% and 43%, respectively, and in low, mid and high dose females of 20%, 31% and 35%, respectively.

Food Consumption: No apparent drug-related changes were noted.

Ophthalmoscopy: No apparent drug-related changes were noted.

Respiration Rate: No apparent drug-related changes were noted.

Hematology: No apparent drug-related changes were noted. Significant findings included:

Week 7: Reduced MCHC in Group 2, 4 and 5 males.
Increased eosinophils in Group 5 females.

Week 13: Reduced lymphocytes and increased monocytes in Group 3 males.

Week 26: Reduced MCHC in Group 5 females.

Blood Chemistry: Significant changes:

Week 7: Increased LDH in Group 2 males and reduced creatinine in Group 4 females. A non-significant dose-related decrease in total bilibrubin occurred in females.

Week 13: Increased chloride values occurred in Group 2, 3, 4 and 5 males; reduced ALT in Group 2, 3, 4 and 5 females and a reduced Ca in Group 2 females.

Week 26: Reduced cholesterol in Group 4 females.

BUN, Glucose, Aspartate Aminotransferase, LDH, Na, K, T. Protein, Albumin, A/G Ratio and Phosphate showed no apparent drug-related changes.

Plasma Concentrations of Azelastine Hydrochloride and Desmethylazelastine:

Plasma levels of azelastine hydrochloride and desmethylazelastine showed dose-related increases in concentration.

Table 3: SUMMARY GROUP MEAN DETERMINED PLASMA AZELASTINE AND DESMETHYLAZELASTINE LEVELS FOR STUDY 636724

Group	Dose Level mg/dog/day	Mean Determined Concentration of Analyte Base (pg/mL) ± SE* Week 0	Week 1	Week 6	Week 13	Week 26
Desmethylazelastine						
1	0	0	0	0	0	0
3	0.84	0	290±11 (N=2)	274±6 (N=3)	264±1 (N=2)	276±7 (N=3)
4	1.68	0 **	325±39 (N=3)	434±38 (N=6)	377±40 (N=5)	402±46 (N=7)
5	3.36	0	740±147	1055±121	1023±127	1046±121
Azelastine						
1	0	0	0	0	0	0
3	0.84	0	4434±523	4378±511	7011±854	5302±450
4	1.68	0	6282±938	9706±1482	8673±1030	10185±1282
5	3.36	0	14152±1444	18182±2246	23004±4075	20964±1687

*N=8 except for: Desmethylazelastine levels which were less than 255.70 pg/mL and not included in the calculation of the mean, the N is indicated in parentheses. All values rounded to whole numbers.

**A trace amount of analyte was observed in this sample, 340.69 pg/mL, which was considered an artifact.

Urinalysis: Significant findings:

Week 7: In males there was a drug-related increase in urine volume which was significant in Group 5. Specific gravity was lower (non-significant) in Group 2-5 males compared to Group 1.

Week 13: Urine volume was higher (non-significant) in Group 2-5 males. Specific gravity was higher in Group 4 females and tended to be higher in other drug-treated female groups.

Week 26: pH values were slightly lower (non-significant) in Group 2-5 males.

Organ Weights: Absolute and covariance analsysis showed the following significant findings:

Increased prostate weights in Group 3 males and reductions in ovarian weights seen in Group 3, 4 and 5 females and in uterine weights in Groups 3 and 5.

Gross Pathology: No apparent drug-related changes were observed.

Histopathology: No apparent drug-related pathologic changes were noted.

Peribronchiolar inflammatory cell changes were detected in 1/4 males each in mid and high dose groups, in 1 each of the female control groups and 2/4 each in mid and high dose female groups.

No corpora lutea were detected in ovary sections from 2/4 females each in low and mid dose groups and from 3/4 high dose female groups, whereas all control females had corpora lutea. Similarly, 3/4 low dose, 2/4 mid dose and 3/4 high dose females had small uteri compared with control females and also showed a lesser degree of glandular development. Sponsor stated this finding indicated that the uterus was from a prepubertal animal and was described as immature. These observations correlated with the lower incidence of estrus activity in the drug-treated animals as well as the significant reductions in ovary and uterus weights.

Previous chronic oral toxicity studies did not reveal any effect on the uterus or ovaries.

IT - March 20, 1989

This toxicology information amendment provides a response to our call to the sponsor on March 13, 1989 requesting means of plasma levels of azelastine and metabolite in the six-month intranasal toxicity study of azelastine hydrochloride in the rat and an explanation for the detectable levels of drug and metabolite observed in the control animals.

The sponsor has provided a summary table (Table 1) of plasma levels for azelastine and its desmethyl metabolite including information on problems that occurred during sample collection and analysis. A total of 212 samples were analyzed for azelastine and desmethylazelastine. Out of this number, a total of 117 samples should not have contained any drug and metabolite because they originated either from animals in the two control groups or from one animal at the pretreatment interval. However, in Table 2, 8 sample analyses did show quantifiable azelastine levels which were below levels found in the drug-treated animals.

treated animals (average 25000 pg/mL) is suggestive of possible external contamination during sample collection or analysis. However, review of the laboratory records could not confirm this. One sample assay result (item 171), showing the presence of approximately 7000 pg/mL azelastine and detectable levels of desmethylazelastine, indicates a possible sample labeling error. The sponsor hypothesizes this because another sample at Week 26 from the treatment group (item 209) contained no drug or metabolite.

Although the sponsor could not identify the true cause of these descrpancies, the sponsor concluded that these findings do not affect the validity or conclusions drawn from the study. We concur.

Table 1: Summary Group Means ± Standard Error Calculations for Azelastine (AZ) and Desmethylazelastine (DES) Concentrations in Rat Plasma - Study H/R923

				Mean ± S.E. Concentration (pg/mL)									
				Week 0[a]		Week 1		Week 6		Week 13		Week 26	
GROUP	SEX	RAT NOS.	REGIMEN	DES	AZ	DES	AZ	DES	AZ	DES	AZ	DES	AZ
1	M	111-115	Control	--	No.114[b]	--	Nos.112,[c] 114	--	--	--	--	--	--
2	M	211-215	Control	--	--	--	No.214[d]	--	--	--	--	No.213[e]	No.213[e]
3	M	311-315	Drug 1X	--	--	1661 ± 272	20146 ± 781	313 ± 89	9537 ± 2047	762 ± 205[f]	22401 ± 1966[f]	825 ± 96	21332 ± 1568
4	M	411-415	Drug 2X	--	--	306 ± 237	30160 ± 3508	--[g]	--[g]	1369 ± 272	29712 ± 4630	1522 ± 75	29494 ± 3025
5	M	511-515	Drug 4X	--	--	3475 ± 301	17342 ± 1499	--[g]	--[g]	2148 ± 139	15135 ± 885	2625 ± 218[h]	14167 ± 1143
1	F	161-165	Control	--	--	--	No.161[i]	--[g]	--[g]	--	No.161[i]	--	--
2	F	261-265	Control	--	--	--	No.263[j]	--[g]	--[g]	--	--	--	--
3	F	361-365	Drug 1X	--	--	1514 ± 201	31993 ± 4095	--[g]	--[g]	553 ± 72	12569 ± 923	1513 ± 127	30365 ± 7504
4	F	461-465	Drug 2X	--	--	3233 ± 298[k]	23203 ± 3532[k]	--[g]	--[g]	3300 ± 633	34018 ± 3214	3540 ± 252	40902 ± 4159
5	F	561-565	Drug 4X	--	--	7148 ± 999	29551 ± 2130	--[g]	--[g]	5326 ± 330	28426 ± 6233	6912 ± 168[l]	27375 ± 4751

[a] Prestudy baseline designated "Week 0."

[b] Except for animal No. 114 (see Summary Table 2), all determinations were below the limit of quantitation (LOQ) for DES which is 511 pg/mL and AZ which is 569 pg/mL.

[c] All below LOQ except for animals No. 112 and No. 114 (see Summary Table 2).

[d] All below LOQ except for animal No. 214 (see Summary Table 2).

[e] All below LOQ except for animal No. 213 (see Summary Table 2).

[f] N=4; analyses for animal No. 311 was not reported due to chromatographic interferences.

[g] No analyses reported due to equipment failure.

[h] No sample received at week 26 for animal No. 514.

[i] All below LOQ except animal No. 161 (see Summary Table 2).

[j] All below LOQ except animal No. 263 (see Summary Table 2).

[k] N=6; one replacement animal was added to the study.

[l] N=1; animal No. 562 at week 26 was excluded from the group mean calculation since questionable results were found (see Summary Table 2).

Table 2: List of Control Plasma Samples Containing Azelastine and Desmethylazelastine Concentrations Greater Than the Limit of Quantitation (LOQ)

Item No.*	Sample Code		Concentration (pg/mL)	
	#/Sex	Time	Azelastine	Desmethylazelastine
4	114/M	0	1337.87	0
50	112/M	1	2295.04	<LOQ
52	114/M	1	2117.07	0
57	214/M	1	618.7	0
74	161/F	1	2626.76	<LOQ
80	263/F	1	608.99	0
139	161/F	13	700.8	0
171	213/F	26	6926.44	593.8
209**	562/F	26	<LOQ	<LOQ

*Item No. refers to the numbering in the "Sample Analysis Report" starting on p. 455 of TC-88E-7 (Appendix No. 56).

**Not a control animal.

Evaluation

This IND is for a 0.1% weight/volume nasal spray formulation of azelastine hydrochloride, a new chemical entity, which is a long-acting oral antiallergy drug (IND with histamine H_1-receptor blocking properties and with receptor blocking activity toward SRS-A, serotonin, acetylcholine and bradykinin at concentrations greater than that required to block histamine. Azelastine appears to interfere with the secretory functions of mast cells (basophils) and other leukocytes, either by cell membrane stabilization and/or by interference with calcium ion flux. Azelastine produces broncholytic activity by antagonizing the bronchoconstrictor effects of chemical mediators on the receptor sites on the target organs (e.g. airway smooth muscle). The safety and tolerability of 0.1% azelastine nasal spray will be determined in a double-blind, placebo-controlled, randomized, parallel study in 39 healthy males, divided into 3 groups of 13 subjects, who will receive the spray at 12-hour intervals for 29 consecutive days. In each group, 10 subjects will receive the drug. Subjects in Groups 1, 2 and 3 will be administered doses of 1, 2 and 3 sprays, respectively, into each nostril, with each spray deliverying 0.14 mg of azelastine hydrochloride. On days 1 and 29 each subject will receive one dose. On days 2-28, each subject will receive 2 doses every 12 hours. The maximum proposed daily intranasal dose of azelastine hydrochloride is 1.68 mg, corresponding to 0.03 mg/kg/50 kg subject.

Azelastine hydrochloride, a racemic mixture, has been studied extensively as an as a therapeutic agent for the treatment of seasonal and perennial allergic rhinitis (0.55 to 2.2 mg orally b.i.d.) and) in over 1500 subjects in the U.S. The greatest frequency of adverse reactions consisted of headache, somnolence and altered taste. The nasal spray formulation of azelastine hydrochloride is currently being evaluated in West Germany for the treatment of seasoral allergic rhinitis.

An ocular irritation study of a 0.2% azelastine hydrochloride nasal spray, administered for 5 days, in rabbits showed no significant irritation, as evaluated in our review of August 15, 1988 in IND New preclinical studies in the original submission of this IND include 6 month intranasal toxicity studies of azelastine hydrochloride in the rat and dog. Summaries of preclinical data in IND essentially oral studies, prepared by the sponsor, will follow the evaluation of the new intranasal studies. Details of these studies may be found in the numerous pharmacology reviews in IND

A 6-month subchronic intranasal toxicity study of Azelastine Hydrochloride Nasal Spray 0.1% in Sprague Dawley rats (equivalent to 0.2, 0.4 and 0.8 mg/rat of azelastine hydrochloride or approximately 1, 2 and 4 mg/kg, respectively) showed no apparent drug-related toxicity. The highest dose is about 133 times the maximum proposed daily human intranasal dose. Two high dose males and one sham control male died at various times during the study, but these deaths appeared to be unrelated to the drug. Neither the drug or vehicle seemed to be inherently irritating to the epithelium lining the nasal cavity. The greater incidence of epistaxis was attributed to trauma, associated with minor struggling of the animals during treatment. Plasma levels of azelastine hydrochloride and its metabolite, desmethylazelastine, generally showed a dose-dependent increase. Therefore, the NOEL in the rat appears to be more than 100 times the proposed human dose.

A 6-month subchronic intranasal toxicity study of Azelastine Hydrochloride Nasal Spray 0.1% in beagle dogs (equivalent to 0.84, 1.68 and 3.36 mg/dog of azelastine hydrochloride or approximately 0.1, 0.2 and 0.4 mg/kg, respectively) showed nonsignificant dose-related reductions in body weight (10-43% in males; 20-35% in females); dose-related increases in plasma concentrations of azelastine (week 26: 5302-20964 pg/ml) and desmethylazelastine (week 26: 276-1046 pg/ml), a lower incidence of estrus activity in drug-treated animals as well as significant reductions in ovary and uterus weights and a lack of corpora lutea in 50% of the low and mid dose females and 75% of the high dose females. These findings may be attributed to the immaturity of the animals. It is noted that previous chronic oral toxicity studies did not reveal any effect on the uterus or ovaries. Therefore, apa. from marginal reductions in body weight there were no apparent drug-related toxic effects in the dog up to approximately 13 times the maximum proposed daily human intranasal dose.

Pharmacologic studies in laboratory animals and <u>in vitro</u> model systems indicate that azelastine HCl is an orally active, long-acting agent with multiple actions in both the upper and lower airway. These include modulation of airways smooth muscle response, interference with inflammatory processes and inhibition of allergic reactions. Specific activities of azelastine HCl are:

- Modulation of airways smooth muscle responses
  - Inhibition of leukotriene-mediated (H_1-antihistamine-resistant) bronchospasm in the guinea pig
  - Antagonism of Ca^{2+}-, histamine-, acetylcholine-, serotonin-, bradykinin-, adenosine- and PAF-induced responses
  - Interference with antigen- and phospholipase A_2-induced airway hyperresponsiveness to cold in rat tracheal segments
- Modulation of the inflammatory response
  - Inhibition of superoxide radical generation in guinea pig polymorphonuclear leukocytes and human neutrophils and eosinophils
  - Inhibition of chemotactic responsiveness in guinea pig macrophages
- Antiallergic actions
  - Inhibition of allergic and nonallergic histamine secretion from rat peritoneal mast cells
  - Inhibition of histamine release from rabbit and human basophils and human lung mast cells
  - Interference with the synthesis and release of leukotrienes from rat peritoneal cells and guinea pig lung
  - Inhibition of allergen-induced bronchospasm in the guinea pig
  - Inhibition of IgE-dependent passive cutaneous anaphylaxis in the rat

Azelastine HCl has also been shown to interfere with Ca^{2+} influx into target tissues. Since Ca^{2+} is essential in the synthesis and release of chemical mediators and in their interaction at receptor sites, azelastine HCl's ability to interfere with Ca^{2+}-dependent processes may at least partially explain its ability to produce a beneficial effect in human airways.

Tissue distribution studies in rats and guinea pigs using radiolabeled azelastine HCl clearly demonstrate that the lungs preferentially take up the drug. Moreover, the concentration of radioactivity achieved in the lungs following administration of radiolabeled azelastine HCl is comparable to the concentrations required in vitro to inhibit mediator synthesis, release or activity.

Acute, subacute and chronic toxicity studies have been conducted with azelastine HCl in the mouse, rat, guinea pig and dog. In addition, reproductive toxicity, mutagenicity and carcinogenicity evaluations have been conducted with the drug.

Signs of toxicity in acute studies included salivation, tremor, convulsions, blepharoptosis, loss of righting reflex and aggressive behavior. In these studies, the dose that caused death in 50% of the animals tested exceeded the proposed maximum clinical daily dose (8 mg b.i.d.) by more than 100-fold.

In subacute and chronic studies in the rat, doses of azelastine equal to or greater than 85 times the proposed maximum clinical dose caused an increase in alkaline phosphatase, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase. Histopathology revealed fatty changes in the liver and/or [illegible]cellular hypertrophy. These effects were reversible upon drug [illegible]rawal. Aggression, convulsions and death were observed in dogs [illegible] doses of azelastine 50 times greater than the proposed maximum clin[illegible]se.

Two two-year oncogenic[illegible] studies have been conducted, one in the rat and one in the mouse. In neither of these studies did azelastine HCl increase the incidence of malignant or nonmalignant neoplasms or reduce the longevity of either species.

Reproductive studies conducted in the rat and teratology studies conducted in the mouse, rat and rabbit revealed that, at maternally toxic doses, azelastine HCl caused embryo and fetal mortality and resulted in skeletal abnormalities. Lower doses (1-10 times the proposed maximum clinical dose) of azelastine HCl had no significant embryotoxic or fetotoxic effects and had no effect on reproductive performance, delivery or lactation.

Azelastine HCl showed only minimal toxicity when given orally at doses 85 times greater than the proposed maximum clinical dose to pediatric rats for 49 days. The effects seen at this dose were similar in pediatric and adult rats.

Azelastine HCl showed no mutagenic activity in the Ames Salmonella/ microsome plate test, DNA repair test and the mouse lymphoma forward mutation assay and no clastogenic activity in the mouse micronucleus tes

The pharmacokinetic profile of azelastine HCl has been studied in the dog, rat and guinea pig. The drug was rapidly and almost completely absorbed. Excretion of the drug and/or its metabolites was predominantly in the feces in all species. No significant tissue accumulation was observed, but significant uptake by the lungs was seen. Placental transfer in the rat took place with equal distribution of drug and/or metabolites between the maternal and fetal circulations. The fetal tissue levels decreased with time; at 24 hours the tissue levels reflected only a small fraction of the dose.

Four metabolites of azelastine were detected in guinea pig and rat feces, bile and urine. These were identified as 6-hydroxyazelastine, 2- and 7-oxoazelastine and N-desmethylazelastine.

Azelastine is almost completely absorbed in man as well and the primary route of excretion is also through the feces. Ten days after a single radiolabeled dose of azelastine HCl, about 75% of the radioactivity was excreted in the feces and 25% was excreted in the urine.

The average elimination half-life of azelastine in man is approximately 20 hours. The drug is extensively metabolized and metabolites, some with longer elimination half-lives which average approximately 40 hours, may contribute to azelastine's long duration of clinical activity. However, once steady state was achieved, no further accumulation of the drug in plasma was observed after 12 weeks of dosing.

Plasma concentrations of azelastine increase in a linear fashion with increasing doses over the dosage range of 2-16 mg, expressed as the base, in healthy subjects. Time to maximal concentrations in plasma is approximately four to six hours after a single dose. Absorption of azelastine in the elderly does not appear to differ from that in younger subjects, although the elimination half-life of the drug is approximately twice that of younger subjects. Consequently, the area under the time-plasma concentration curve is greater in the elderly.

The absorption of azelastine is not influenced by food or concomitant administration of an antacid (Mylanta II).

Plasma protein binding of azelastine *in vitro* was estimated to be 95% while in *ex vitro* studies it ranged from 78 to 88%.

Conclusion

Preclinical data support the relative safe use of this drug in the proposed protocol.

Recommendation

Mean plasma levels of azelastine hydrochloride and its metabolite, desmethylazealastine, which were monitored in the 6-month intranasal toxicity study of Azelastine Hydrochloride Nasal Spray 0.1% in rats should be submitted.

The sponsor should explain why plasma levels of azelastine hydrochloride and desmethylazelastine were also detected in the control rats of this study.

DRAFT OF PHARMACOLOGY PORTION OF LETTER TO SPONSOR

Mean plasma levels of azelastine hydrochloride and its metabolite, desmethylazealastine, which were monitored in the 6-month intranasal toxicity study of Azelastine Hydrochloride Nasal Spray 0.1% in rats should be submitted.

Please explain why plasma levels of azelastine hydrochloride and desmethylazelastine were also detected in the control rats of this study.

Clyde G Oberlander
Pharmacologist

cc IND
HFD-160
HFD-340
Doc. Rm. 160
R/D COberlander 3/24/89
R/D Init. by JInscoe 3/27/89
Typed by COberlander 3/24/89 W#00840

Appendeix II: The summary of incidences of all the neoplasms from the carcinogenicity studies

Table E.26
Mortality Table for Mice Receiving Azelastine HCl Orally
in a Two-Year Oncogenic Study

Dose Level (mg/kg)	0	1	5	25	0	1	5	25
Sex	M	M	M	M	F	F	F	F
Number at Start of Study	100	50	50	50	100	50	50	50
Number of Survivors at 12 Mon.	97	50	50	49	91	48	49	44
(%)	(97)	(100)	(100)	(98)	(91)	(96)	(98)	(88)
15 Mon.	94	49	47	42	85	44	44	41
(%)	(94)	(98)	(94)	(84)	(85)	(88)	(88)	(82)
18 Mon.	83	40	43	34	67	32	35	34
(%)	(83)	(80)	(86)	(68)	(67)	(64)	(70)	(68)
21 Mon.	71	33	30	27	44	22	25	24
(%)	(71)	(66)	(60)	(54)	(44)	(44)	(50)	(48)
Termination (%) a	30 (30)	12 (24)	17 (34)	12 (24)	26 (26)	17 (34)	16 (32)	15 (30)

a = Males terminated at Week 107; females at Week 97.

Table E.27
Mortality Table for Rats Receiving Azelastine HCl Orally
in a Two-Year Oncogenic Study

Dose Level (mg/kg)	0	1	5	30	0	1	5	30
Sex	M	M	M	M	F	F	F	F
Number at Start of Study	115	65	65	65	115	65	65	65
Number of Survivors at 12 Mon. (%)	101 (88)	52 (80)	54 (83)	54 (83)	100 (87)	54 (83)	52 (80)	52 (80)
at 15 Mon. (%)	94 (82)	49 (75)	51 (78)	52 (80)	96 (83)	53 (82)	50 (77)	47 (72)
at 18 Mon. (%)	83 (72)	45 (69)	44 (68)	48 (74)	83 (72)	44 (68)	44 (68)	40 (62)
at 21 Mon. (%)	50 (43)	30 (46)	30 (46)	33 (51)	61 (53)	29 (45)	30 (46)	31 (48)
at 24 Mon. (%)	28 (24)	16 (25)	16 (25)	22 (34)	36 (31)	12 (18)	20 (31)	24 (37)

5 Rats/Sex/Group were sacrificed at Weeks 13, 52 and 78.

Table E.28
Summary Incidence of Neoplasms in Mice Receiving Azelastine HCl Orally in a Two-Year Oncogenic Study

Dose Level	0 mg/kg		1 mg/kg		5 mg/kg		25 mg/kg	
Sex	M	F	M	F	M	F	M	F
Number/Group	100	100	50	50	50	50	50	50
Body System								
Organ								
Neoplasm								
INTEGUMENTARY								
SKIN No. Exam.:	98	99	50	47	50	50	50	49
Adenoma	1							
Adenocarcinoma		1						
Carcinoma, squam. c.	1			1				
Metastasis, carcinoma							1	
Fibroma						1		
Fibrosarcoma	2	1		1	2	1	1	1
Sarcoma		1						
Hemangiosarcoma						1		
Retic. c. sarc.			1					
Invas. ret. c. sarc.		5		1		1		
Invas. lymphosarc.	4	1	1		1			
RESPIRATORY								
NASAL TURBINATES	96	96	50	47	50	50	50	50
Invas. ret. c. sarc.				1				
Invas. lymphosarc.	1							
TRACHEA	97	100	50	49	50	50	50	50
Invas. ret. c. sarc.		2				1		
LUNGS	99	100	50	49	50	50	50	50
Adenoma, bronchoalv.	19	11	10	8	8	1	4	5
Adenocarc., bronchalv.	8	7	9	3	10	7	8	2
Metastasis, carcinoma			1				1	1
Metastasis, sarc.			1					2
Invas. ret c. sarc.		13	1	6	3	6		5
Invas. lymphosarc.	5	16	1	11	2	8	3	9
Leukemia, metas.		1		1				

(Continued)

Table E.28 (Continued)
Summary Incidence of Neoplasms in Mice Receiving Azelastine HCl Orally in a Two-Year Oncogenic Study

Dose Level	0 mg/kg		1 mg/kg		5 mg/kg		25 mg/kg	
Sex	M	F	M	F	M	F	M	F
HEMATOPOIETIC								
SPLEEN	97	99	49	49	50	50	49	47
Ret. c. sarcoma		2	1	3	1			3
Invas. ret. c. sarc.		8		4	1	7		2
Lymphosarcoma	1							2
Invas. lymphosarc.	7	3	1	2	4	3	5	
Leukemia		1		1				
BONE MARROW	98	100	50	49	50	50	50	50
Reticulum c. sarc.							1	
Invas. ret. c. sarc.		5		2	1			
Invas. lymphosarc.	3	3		1				
Leukemia, metas.				1				
THYMUS	98	100	50	49	50	50	50	49
Retic. c. sarc.		7		2	2			3
Invas. ret. c. sarc.		7		4		5		2
Lymphosarcoma	6	13	5	7		6	4	5
Invas. lymphosarc.	4	4		4	4	1	1	5
Leukemia, metas.		1						
CERVICAL LYMPH NODE	95	98	50	49	50	47	50	48
Reticulum c. sarc.		7				2		
Invas. ret. c. sarc.		7	1	3	1	2		4
Lymphosarcoma	8	10	3	7	5	3	3	4
Invas. lymphosarc.	2	8	3	4		3	2	3
Leukemia, metas.		1		1				
MESENT. LYMPH NODE	95	94	49	49	50	47	49	47
Metas., sarcoma				1	1			
Retic. c. sarcoma		12		2	1	8		
Invas. ret. c. sarc.		8		8	1	2		5
Lymphosarcoma	13	11	4	9	6	7	5	4
Invas. lymphosarc.	2	5	3	4		5	2	3
Leukemia, metas.				1				
CIRCULATORY								
HEART	99	100	50	49	49	50	50	50
Metastasis, carc.	1							
Invas. ret. c. sarc.		9		3	2	2		4
Invas. lymphosarc.	6	4	4	6		2	2	3
Leukemia, metas.		1		1				

(Continued)

Table E.28 (Continued)
Summary Incidence of Neoplasms in Mice Receiving Azelastine HCl
Orally in a Two-Year Oncogenic Study

Dose Level	0 mg/kg		1 mg/kg		5 mg/kg		25 mg/kg	
Sex	M	F	M	F	M	F	M	F
DIGESTIVE								
LIVER	98	99	49	49	50	50	50	50
Adenoma, bile ducts		1						
Adenoma, hepatocell.	12	1	5		4		2	1
Carc., hepatocell.					1			
Metas., carcinoma							1	
Hemangioma			1				1	
Hemangiosarcoma		1		1				
Sarcoma			1					
Metastasis, sarc.		1	1					2
Reticulum c. sarc.				1				
Invas. ret. c. sarc.		18	1	10	2	9		6
Invas. lymphosarc.	13	11	4	12	4	12	4	7
Leukemia, metas.		1		1				
GALLBLADDER	85	77	44	44	43	46	35	40
Adenoma				1				
Invas. ret. c. sarc.				1				
Invas. lymphosarc.	1					1		2
PANCREAS	98	94	49	49	48	50	50	49
Carcinoma							1	
Invas. ret. c. sarc.		10		8	1	5		1
Invas. lymphosarc.	5	4	2	6	1	5	3	3
Leukemia, metas.		1		1				
SALIVARY GLANDS	98	99	49	49	50	50	50	50
Adenoma	1							
Invas. ret. c. sarc.		8	1	3		5		3
Invas. lymphosarc.	4	11	1	9	1	6	1	4
STOMACH	97	97	49	49	49	50	49	47
Adenoma	4							
Papilloma					1			
Adenocarcinoma	1							
Invas. ret. c. sarc.		4		2		3		
Invas. lymphosarc.	3	2		1				1
DUODENUM	97	88	48	46	44	48	40	43
Invas. lymphosarc.	1							
Leukemia, metas.				1				
JEJUNUM	97	87	48	46	46	47	39	44
Carcinoma	1							
Hemangioma			1					
Invas. ret. c. sarc.				2				
Invas. lymphosarc.	3	2		2		1		1

(Continued)

Table E.28 (Continued)
Summary Incidence of Neoplasms in Mice Receiving Azelastine HCl Orally in a Two-Year Oncogenic Study

Dose Level	0 mg/kg		1 mg/kg		5 mg/kg		25 mg/kg	
Sex	M	F	M	F	M	F	M	F
LARGE INTESTINE	97	91	50	47	47	47	46	46
Papilloma		1						
Carcinoma, squam. c.	1							
Leiomyosarcoma		1						
Hemangiosarcoma								1
Reticulum c. sarc.								1
Invas. ret. c. sarc.				2				
Invas. lymphosarc.		3		2		2	1	1
URINARY								
KIDNEY	99	100	50	49	50	50	50	50
Metas., carcinoma							1	
Fibroma						1		
Reticulum c. sarc.						1		
Invas. ret. c. sarc.		14		7		7		5
Invas. lymphosarc.	6	14	1	12	2	11	3	9
Leukemia, metas.		1						
URINARY BLADDER	97	95	49	49	50	50	48	50
Carcinoma								1
Carcinoma, squam. c.						1		
Fibrosarcoma					1			
Invas. ret. c. sarc.		5		3		5		5
Invas. lymphosarc.	1	4	1	6		7		4
ENDOCRINE								
ADRENAL GLANDS	97	98	49	49	49	50	49	50
Adenoma	3	2	3	1	1			
Carcinoma	3							
Adenocarcinoma	1							
Pheochromocytoma	3		1		1			
Invas. ret. c. sarc.		4		3				
Invas. lymphosarc.	4		1	1		1		
Leukemia, metas.		1						
THYROID GLANDS	91	95	50	47	48	50	48	49
Adenoma	1		1					1
Invas. ret. c. sarc.		4		1		1		
Invas. lymphosarc.	1			3		1	1	1
PARATHYROID GLANDS	21	56	37	26	36	34	32	34
Adenoma		1						
PITUITARY GLAND	72	86	40	47	42	43	47	42
Adenoma		9	1	1		4		4
Invas. ret. c. sarc.				1				

(Continued)

Table E.28 (Continued)
Summary Incidence of Neoplasms in Mice Receiving Azelastine HCl
Orally in a Two-Year Oncogenic Study

Dose Level	0 mg/kg		1 mg/kg		5 mg/kg		25 mg/kg	
Sex	M	F	M	F	M	F	M	F
REPRODUCTIVE								
TESTES	98		50		50		50	
Adenoma, Leydig c.	3		1				1	
Adenoma, tubular	1							
Metastasis, carc.					1			
Invas. lymphosarc.	1				1		1	
EPIDIDYMIDES	97		50		50		50	
Adenoma	1							
Metastasis, carc.					1			
Invas. lymphosarc.			1		1			
PROSTATE	95		47		50		48	
Invas. rat. c. sarc.					1			
Invas. lymphosarc.	4		1		2		2	
SEMINAL VESICLES	98		50		50		50	
Adenocarcinoma	1				1			
Fibroma					1			
Fibrosarcoma	1							
Invas. lymphosarc.	2		2		2		3	
PREPUTIAL GLANDS	29		14		15		20	
Adenoma	2							
Fibroma			1					
OVARIES		99		49		50		50
Adenoma		5		2		4		
Luteoma		5		2		1		
Granulosa c. tumor		2						
Sertoli c. tumor		1						
Fibroma		1						
Sarcoma		1						
Reticulum c. sarc.		1		2				2
Invas. rat. c. sarc.		4		3		2		
Invas. lymphosarc.		3						1
Leukemia, metas.		1						

(Continued)

Table E.28 (Continued)
Summary Incidence of Neoplasms in Mice Receiving Azelastine HCl
Orally in a Two-Year Oncogenic Study

Dose Level	0 mg/kg		1 mg/kg		5 mg/kg		25 mg/kg	
Sex	M	F	M	F	M	F	M	F
UTERUS		99		49		50		50
Adenoma						1		
Adenocarcinoma						1		
Fibroma								1
Hemangioma						2		
Fibrosarcoma				1				
Leiomyosarcoma				1				
Leiomyofibrosarc.		1						
Reticulum c. sarc.				2		1		
Invas. ret. c. sarc.		2		1		2		1
Invas. lymphosarc.				1				
Leukemia, metas.		1						
CERVIX/VAGINA		99		49		*50		50
Carcinoma, squam. c.								1
Fibroma		1						
Leiomyoma		1						
Leiomyofibroma		1						
Hemangioma		1						
Fibroleiomyosarc.		1						
Invas. ret. c. sarc.		2		3		2		1
Invas. lymphosarc.				1		1		
Leukemia, metas.		1						
MAMMARY GLANDS	98	92	50	42	50	48	50	48
Adenocarcinoma		1						1
Carcinoma, squam. c.				1				
Invas. ret. c. sarc.		9		5		2		
Invas. lymphosarc.		4		3				2
Leukemia, metas.		1						
NERVOUS								
BRAIN	97	98	50	48	50	50	49	47
Meningioma		1						
Invas. ret. c. sarc.		4		1		2		
Invas. lymphosarc.	2	4		2		3		2
Leukemia, metas.		1		1				
SPINAL CORD	97	93	50	48	50	50	48	48
Invas. ret. c. sarc.		1				2		
Invas. lymphosarc.		1						
PERIPHERAL NERVE	97	98	50	49	48	50	50	47
Invas. ret. c. sarc.		5						
Invas. lymphosarc.	1			1	1			

(Continued)

Table E.28 (Continued)
Summary Incidence of Neoplasms in Mice Receiving Azelastine HCl
Orally in a Two-Year Oncogenic Study

Dose Level	0 mg/kg		1 mg/kg		5 mg/kg		25 mg/kg	
Sex	M	F	M	F	M	F	M	F
SPECIAL SENSE								
EYES	97	88	48	46	48	44	47	42
Invas. ret. c. sarc.		3				1		
Invas. lymphosarc.						1		
HARDERIAN GLANDS	92	85	48	46	47	46	43	41
Adenoma	13	12	11	6	10	5	2	4
Adenocarcinoma		1	1					
Invas. ret. c. sarc.		3		1		1		
Invas. lymphosarc.	4	3				3		1
TONGUE	98	99	50	49	50	49	50	50
Invas. ret. c. sarc.		3		1		1		1
Invas. lymphosarc.		1				1		1
Leukemia, metas.		1		1				
MUSCULOSKELETAL								
SKELETAL MUSCLE	98	100	50	49	50	50	50	50
Fibrosarcoma	1							
Invas. ret. c. sarc.		9	1	3		1		
Invas. lymphosarc.	4	5	1	3	1	1		
Leukemia, metas.								
BONE	98	100	50	49	49	50	50	50
Osteosarcoma	1							2
BODY CAVITIES								
THORACIC CAVITY	25	38	11	22	10	14	9	14
Metas., carcinoma.					1			
Invas. ret. c. sarc.		8		3		1		3
Invas. lymphosarc.	11	10	3	8	4	7	7	1
ABDOMINAL CAVITY	29	40	16	27	12	23	14	18
Metas., carcinoma	1						1	
Fibrosarcoma							1	
Hemangiosarcoma		1						
Invas. ret. c. sarc.		16		9	2	7		7
Invas. lymphosarc.	12	14	4	12	1	8	6	6
Leukemia, metas.		1		1				
ALL OTHER SYSTEMS								
OTHER ORGANS/TISSUES	12	10	5	5	5	2	7	3
Adenoma	1							
Hemangioma	1	1						
Invas. ret. c. sarc.		3		1		1		
Invas. lymphosarc.	4	3		3	2	1	1	
Leukemia, metas.				1				

Table E.29
Summary Incidence of Neoplasms in Rats Receiving Azelastine HCl Orally in a Two-Year Oncogenic Study

Dose Level	Basal Diet		1 mg/kg		5 mg/kg		30 mg/kg	
Sex	M	F	M	F	M	F	M	F
Number/Group	115	115	65	65	65	65	65	65
Body System								
Organ								
Neoplasm								
INTEGUMENTARY								
SKIN								
Papilloma	2	1	1		1		2	
Trichoepithelioma								1
Sebaceous adenoma					2	1	2	
Squamous c. carc.					1			
SUBCUTIS								
Fibroma			2	2	3	3	1	
Lipoma	1				1			1
Fibrosarcoma	1	1	1		1	1		
RESPIRATORY								
NASAL CAVITY								
Papilloma		1						
Fibrosarcoma							1	
Squamous cell carcinoma, hard palate			1					
LUNG								
Carcinoma					1			
HEMATOPOIETIC								
MULTIPLE ORGANS								
Malignant lymphoma	2		1				1	1
Granulocytic sarcoma					1			
VASCULAR								
Hemangioma				1		1	1	
Hemangiosarcoma	1				1			
THYMUS								
Thymoma	1		1					

(Continued)

Table E.29 (Continued)
Summary Incidence of Neoplasms in Rats Receiving Azelastine HCl
Orally in a Two-Year Oncogenic Study

Dose Level	Basal Diet		1 mg/kg		5 mg/kg		30 mg/kg	
Sex	M	F	M	F	M	F	M	F
CIRCULATORY								
HEART								
Anitschow c. tumor				1				
DIGESTIVE								
SALIVARY GLAND								
Malignant mixed tumor							1	
LIVER								
Adenoma	2							
Carcinoma	1		1		2		2	
Cholangioma	1							
PANCREAS								
Adenocarcinoma		1						
DUODENUM								
Adenocarcinoma			1					
JEJUNUM								
Adenoma	1							
Leiomyosarcoma				1				
ILEUM								
Adenoma	1							
URINARY								
KIDNEY								
Embryonal nephroma			1					
Adenoma						1		
Carcinoma			1					
Liposarcoma					1			
Papilloma, pelvis			1					
URINARY BLADDER								
Papilloma			1					

(Continued)

Table E.29 (Continued)
Summary Incidence of Neoplasms in Rats Receiving Azelastine HCl Orally in a Two-Year Oncogenic Study

Dose Level	Basal Diet		1 mg/kg		5 mg/kg		30 mg/kg	
Sex	M	F	M	F	M	F	M	F
ENDOCRINE								
PANCREAS								
Islet cell adenoma	1	1	2	2	3		3	2
Islet cell carcinoma	2	1	1			1		
PITUITARY								
Adenoma	52	87	19	46	29	43	31	45
Carcinoma		1			1			
THYROID								
Follicular adenoma	4	1			2		3	1
Follicular adenocarcinoma	1	1	2		1	1	1	
C cell adenoma	2	5	1	1	1	1	3	2
C cell carcinoma	1		1					
ADRENAL								
Cortical adeno.	1	5				2		1
Cortical carc.		1				1	1	
Pheochromocytoma	13	2	11		7	1	5	
REPRODUCTIVE								
TESTES								
Interstitial cell adenoma	3				1		2	
OVARY								
Granulosa cell tumor								1
Thecal cell tumor						1		
UTERUS/CERVIX/VAGINA								
Endometrial stromal polyp		6		3		2		2
Adenoma						1		
Squamous cell carcinoma								1
Sarcoma				3				1

(Continued)

Table E.29 (Continued)
Summary Incidence of Neoplasms in Rats Receiving Azelastine HCl
Orally in a Two-Year Oncogenic Study

Dose Level	Basal Diet		1 mg/kg		5 mg/kg		30 mg/kg	
Sex	M	F	M	F	M	F	M	F
MAMMARY GLAND								
Fibroadenoma		22		10		12		13
Adenoma	1	6	1	8		6		6
Adenocarcinoma	1	7		6		8		7
NERVOUS								
BRAIN								
Glioma	5	1	4	1	2		1	1
Medulloblastoma					1			
Meningioma	1							1
SPECIAL SENSE								
EAR								
Sebaceous adenoma			1					
Fibroma						1		
GENERAL BODY								
HEAD								
Squam. c. carc.	1							
TAIL								
Fibrosarcoma								1
MOUTH								
Papilloma, lip			1					
BODY CAVITIES								
ABDOMINAL								
Leiomyosarcoma	1							
Fibrosarcoma						1	1	
THORACIC								
Fibrosarcoma		1						
Lipoma	1							
ALL OTHER SYSTEMS								
VARIOUS ORGANS								
Malignant fibro-histiocytoma	2	1	1	1				1
Osteosarcoma					1			

Statistical Review and Evaluation

IND #: Date: [illegible] 2 9 1989

Applicant: Wallace Laboratories

Name of Drug: Azelastine Hydrochloride

Documents Reviewed:

1. Wallace Laboratories, Response to Request for Information, October 17, 1989, Serial # 173, Volume 1 and 2.
2. Floppy diskettes submitted on Feb. 27, 1989.

Background

Two animal carcinogenicity studies (one in rats, and one in mice) included in this IND submission have been reviewed by the Division of Biometrics. In the previous review, the results of the analyses showed that there were statistically significant positive dose-response relationships in skin sebaceous adenoma in male rats ($p = 0.0331$), in bone-osteosarcoma ($p = 0.0393$) and spleen-lymphosarcoma ($p = 0.0393$) in female mice. In response to FDA's request, the sponsor has submitted the following information: (1) Time to tumor for sebaceous gland adenoma in male rats during the two-year rat carcinogenicity study with azelastine conducted by Wallace. (2) Historical control incidence rates for sebaceous gland adenoma in the male Sprague-Dawley rat. (3) Time to tumor for lymphosarcoma of the spleen and osteosarcoma in female mice during the two-year mouse carcinogenicity study with azelastine conducted by Asta Pharma. (4) Historical control incidence rates for lymphosarcoma and osteosarcoma in the female NMRI mouse. Dr. Misoon Y. Chun, HFD-150, who is the reviewing pharmacologist of this IND has requested the Division of Biometrics to decide whether the explanations submitted by the sponsor for the differences in evaluation of the statistical significance of tumor incidences in the mouse and the rat carcinogenicity studies are acceptable.

In this review, the phrase "positive dose-response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing mortality or tumor rate as dose increases.

Further Review and Analyses

(1) Skin Sebaceous adenoma in male rats.

The data submitted on computer floppy diskettes were used in the reviewer's analyses. The following animal numbers were coded with skin (tissue code = 01) sebaceous adenoma (tumor code = 8410):

Animal Number	Dose (mg/kg)	Week of Death
181	5	95
210 *	5	97
248	30	94
277	30	104

* Animal number 210 was coded with skin sebaceous adenoma on computer floppy diskettes. However, the sponsor's submission on October 17, 1989 (section B, p. 4) indicated that animal number 201 has skin sebaceous adenoma.

In addition, animal number 154 in the low-dose group was coded with ear and mastoid (tissue code = xy) sebaceous adenoma (tumor code = 8410). In the previous review, the exact permutation trend test was applied to skin sebaceous adenoma, and ear and mastoid sebaceous adenoma separately. The time intervals 0-12, 13, 14-50, 51, 52-77, 78, 79-103 weeks and terminal sacrifice were used in this method. The actual dose levels 0, 1, 5, and 30 were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the analyses showed that there was a significant positive dose-response relationship in skin sebaceous adenoma in male rats ($p = 0.033$). No significant (at 0.05 level) dose-response relationship was detected in ear and mastoid sebaceous adenoma ($p = 0.5739$), and combined skin, ear, and mastoid sebaceous adenoma ($p = 0.0607$) in male rats. The incidences of the above tumors are shown in Tables 1 and 2.

The sponsor has reanalyzed the tumor data by using the exact permutation trend test (see Table 3). The results of the analyses of skin sebaceous adenoma (distribution A) and combined skin, ear, and mastoid sebaceous adenoma (distribution B) were listed in Table 3. The whole study period as one interval instead of dividing the whole experiment into sub-intervals (time-adjusted method) was used to test the positive dose-response relationship in the tumor data. Hence, the computed p-values of sponsor's results are slightly different from those of the reviewer's results. The p-value is 0.0425 (compared to 0.033) for skin sebaceous adenoma, and 0.0818 (compared to 0.0607) for combined skin, ear, and mastoid sebaceous adenoma. However, the sponsor's reanalysis results do not change the conclusions.

The sponsor also provided the historical control incidences for sebaceous gland adenoma in the male Sprague-Dawley rat from various sources as follows:

Sources	Incidence Actual	Percent	References
Wallace	0/481	0.0	(1)
Charles River	1/806	0.1	(2)
Merck Sharp & Dohme	9/1618	0.6	(3)

(1) Wallace Toxicology Archives.

(2)

(3) Gordon, Lea: Personal communication.

Although the sponsor has listed the references, the information are not included. Historical control data can be valuable in final interpretation of the study results when used appropriately especially when the differences in incidence rates between treated and concurrent controls are small but statistically significant and can be shown to be within the anticipated historical incidence. However, before historical control data are used, the issues of possible differences in nomenclature and diagnostic criteria, sources of variability among laboratories, and dates of studies have to be addressed.

(2) Bone-osteosarcoma in female mice

The time to tumor for osteosarcoma in the female mice in the azelastine carcinogenicity study is shown below:

Animal Number	Dose (mg/kg)	Date of Obs.	Death	Days on study
470	25	6/18/85	6/28/85	513
488	25	5/7/85	6/3/85	488

The above data are consistent with the reviewer's finding. The sponsor also provided the historical control incidence of osteosarcoma in the female NMRI mice from a confidential source (Bayer AG: confidential personal communication) as follows:

Breeder	Incidence Actual	Percent	No. of Studies	Range
Winkelmann	4/239	1.7	5	0-4.3%
Firis	1/204	0.5	3	0-1.3%
Wiga	3/392	0.8	9	0-2.2%

Table 4 listed the above historical control data of individual studies from different sources. The incidence of this tumor in the high dose group (2/50 = 4%) is within the historical control range (0-4.3%) from breeder Winkelmann. However, as mentioned in the previous paragraph, before historical control data are used, the issues of possible differences in nomenclature and diagnostic criteria, sources of variability among laboratories, and dates of studies have to be addressed.

(3) Spleen-lymphosarcoma in female mice

The sponsor indicated that "since lymphosarcoma of the spleen is normally not a palpable tumor, no time to tumor can be established in this case". The sponsor also indicated that "lymphoid tumors in rodents are generally systemic tumors with extensive involvement of many organs. The assignment of a single location as the primary site is frequently impossible due to the extensive metastasis of this tumor type. .... For this reason, lymphoma/lymphosarcoma is generally analyzed as a systemic tumor

irrespective of primary site." The incidences of lymphosarcoma at any site in female mice of the azelastine carcinogenicity study were 24/100, 16/50, 14/50, and 11/50, respectively, for the 0, 1, 5, and 25 mg/kg groups. Statistical evaluation of this incidence does not indicate a treatment-related effect (p = 0.7359).

The historical control incidences of lymphosarcoma in female NMRI mice from a confidential source confidential personal communication) are provided as follows:

	Incidence			
Breeder	Actual	Percent	No. of Studies	Range
	84/245	34.3	5	20-46.8%
	89/204	43.6	3	37.5-46.6%
	124/387	32.0	9	11.1-37.5%

Table 5 listed the above historical control data of individual studies from different sources.

Summary

In the previous review, the results of the analyses showed that there were statistically significant (at 0.05 level) positive dose-response relationships in skin sebaceous adenoma in male rats (p = 0.0331), in bone-osteosarcoma (p = 0.0393) and spleen-lymphosarcoma (p = 0.0393) in female mice. Dr. Misoon Y. Chun has requested the Division of Biometrics to decide whether the explanations submitted by the sponsor for the differences in evaluation of the statistical significance of tumor incidences in the mouse and the rat carcinogenicity studies are acceptable.

An analysis incorporating the ear and mastoid sebaceous adenoma in the low dose group with the skin sebaceous adenoma in male rats is made. The exact permutation trend test reveals a p value of 0.0607. No significant positive dose-response relationship (at 0.05 significant level) in combined skin, ear, and mastoid sebaceous adenoma was detected in male rats. However, there is a significant positive dose-response relationship in skin sebaceous adenoma in male rats.

The incidence of bone-osteosarcoma in the high-dose female mice (2/50 = 4%) is within one of the historical control ranges (0-4.3%) supplied by sponsor's confidential source. However, before historical control data be used, the issues of possible differences in nomenclature and diagnostic criteria, sources of variability among laboratories, and dates of studies have to be addressed.

With regards to the spleen-lymphosarcoma in female mice, if the sponsor's statement "lymphoma/lymphosarcoma is generally analyzed as a systemic tumor irrespective of primary site" is correct, then there is no

significant positive dose-response relationship in the incide. of lymphosarcoma at any site in the female mice.

Daphne Lin, Ph.D.
Mathematical Statistician

Concur: Karl K. Lin 5/29/91
Karl K. Lin, Ph.D., Group Leader, SARB

cc: Original IND
HFD-150/Dr. Burke
HFD-150/Dr. Chun
HFD-150/Mr. Ledet
HFD-710/Chron
HFD-715/Chron (SARB)
HFD-715/Dr. Karl Lin
HFD-715/Dr. Daphne Lin
HFD-502/Dr. Weissinger
HFD-715/DRU 2.1.1, Azelastine Hydrochloride, Wallace Lab.

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Mr. Kent Johnson, Chair, (HFD-600) MPN II

FROM: Division of Oncology/Pulmonary D.P. HFD-150
Attention: Alan C. Schroeder Phone: 443-3415
Alan Schroeder 5/8/91

MCT for CPH 5-8-91

DATE: May 7, 1991

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Astelin N.S. NDA/ANDA #20-114

Established name, including dosage form: azelastine hydrochloride nasal solution.

Other trademarks by the same firm for comparison products:

Indications for use (may be a summary if proposed statement is lengthy:
for treatment of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus and lacrimation.

Initial comments from the submitter: (concerns, observations, etc.)
There does not seem to be a need for "N.S." to be a part of the trademark. In addition, in a computerized search of the FDR I did not find any marketed drug products with "N.S." in the trademark.

NOTE: **Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.**

Consult #56 (HFD-150)

Astelin N.S. Azelastine Hydrochloride Nasal Solution

A review did not reveal names which look or sound like the proposed name other than another product by the same firm, Astelin (Azelastine Hydrochloride Tablet).

Grave concerns were expressed about the addition of the suffix "N.S." to differentiate the nasal solution from the tablet. The Committee discourages the use of prefixes or suffixes that are not well recognized and which add little to the understanding of the product intended. We believe the two dosage forms can be clearly distinguished by the use of a drug name and strength, two essential parts of any medication order.

Furthermore, we have concerns that the abbreviation "N.S." is more likely to be associated with "normal saline" than with "nasal solution", particularly in a hospital setting.

The Committee finds the "N.S." portion of the proposed name to be unacceptable for the reasons cited above.

CDER Labeling and Nomenclature Committee

_____, Chair 5.31.91

OCT 11 1996

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA:	20-114	**DATE REVIEWED:**	October 10, 1996
REVIEW #:	8	**RECOMMEND ACTION:**	Approvable
REVIEWER:	Linda Ng, Ph.D.		

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	March 26, 1991	March 27, 1991	June 3, 1991
AMENDMENT	December 18, 1992	December 22, 1995	December 23, 1995
AMENDMENT	May 7, 1993	May 10, 1993	May 10, 1993
AMENDMENT	August 6, 1993	August 11, 1993	August 11, 1993
AMENDMENT N(BZ)	June 30, 1995	July 3, 1995	July 10, 1995
AMENDMENT N(BC)	August 31, 1995	September 6, 1995	
AMENDMENT N(BC)	September 22, 1995	September 25, 1995	
AMENDMENT N(AZ)	May 13, 1996	May 14, 1996	
AMENDMENT N(BC)	June 7, 1996	June 10, 1996	
AMENDMENT N(AZ)	July 10, 1996	July 12, 1996	
AMENDMENT N(BC)	August 20, 1996	August 21, 1966	
AMENDMENT N(BC)	September 18,1996	September 18, 1996	
Subject of this review:			
AMENDMENT N(BC)	September 30, 1996	October 4, 1996	
AMENDMENT N(BC)	October 9, 1996	October 10, 1996	

NAME & ADDRESS OF APPLICANT: Wallace Laboratories
Div. of Carter-Wallace, Inc.
Cranbury, New Jersey 08512

DRUG PRODUCT NAME

Proprietary:	ASTELIN® Nasal Spray, 137 mcg
Nonproprietary/Established/USAN:	azelastine hydrochloride
Code Name/#:	W-2979M, A-5610, E-0659
Chem.Type/Ther.Class:	1C

PHARMACOLOGICAL CATEGORY/INDICATION: Allergic rhinitis

DOSAGE FORM: Nasal Spray solution

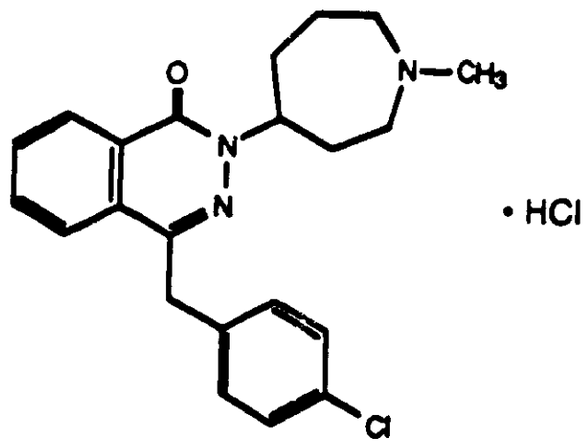
STRENGTHS: 0.1 % (w/v); 0.137 mL = 0.137 mg azelastine hydrochloride per actuation.

ROUTE OF ADMINISTRATION: Nasal; 2 actuations per nostril twice per day

DISPENSED: X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(±)-1-(2H)-Phthalazinone,4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride

$C_{22}H_{24}ClN3O•HCl$ MW 418.37



SUPPORTING DOCUMENTS:

DMF #	Holder Name	Subject	Status	Date Reviewed	Reference

RELATED DOCUMENTS :

Type	Number	Owner	Subject
IN			
IN			
ND			
ND.			

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
Environment Assessment HFD-102, P. Vincent			
Microbiology, HFD-160	8/19/91	Acceptable 2/6/92	Preservative eff. & microbial limits spec.
Pharmacology, HFD-155 (HFD-570)	5/6/93	Completed 8/11/93	Extractable issue. General policy for inhalation solutions provided.
Labeling & Nomenclature Committee	5/7/91	Completed 5/28/91	N.S. in name not acceptable. See def. 14.a, CR#2.
Biometrics	7/31/95	Completed 9/18/95	Expiration dating period
Methods Validation	10/10/96	Open	Submitted to St. Louis and Philadelphia labs.
EER	7/27/95 6/17/96 6/28/96	Acceptable 11/6/96 Acceptable 6/28/96 Acceptable 8/12/96	ASTA site replaced by new site for release - acceptable

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is approvable from the standpoint of chemistry, manufacturing and controls. Commitments summarised in submission dated October 9, 1996 are attached in appendix 6 of this review.

Linda Ng, Ph.D.
Review Chemist, HFD-570

cc: Org. NDA 20-114 & Division File.
HFD-570/LNg/10-10-96
HFD-570/GPoochikian 10/11/96
HFD-570/CSO GStrange

File. 20114H.REV
R/D by:

OCT 8 1996

DIVISION OF PULMONARY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA:	20-114	**DATE REVIEWED:**	September 25, 1996
REVIEW #:	7	**RECOMMEND ACTION:**	Not approvable
REVIEWER:	Linda Ng, Ph.D.		

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	March 26, 1991	March 27, 1991	June 3, 1991
AMENDMENT	December 18, 1992	December 22, 1995	December 23, 1995
AMENDMENT	May 7, 1993	May 10, 1993	May 10, 1993
AMENDMENT	August 6, 1993	August 11, 1993	August 11, 1993
AMENDMENT N(BZ)	June 30, 1995	July 3, 1995	July 10, 1995
AMENDMENT N(BC)	August 31, 1995	September 6, 1995	
AMENDMENT N(BC)	September 22, 1995	September 25, 1995	
AMENDMENT N(AZ)	May 13, 1996	May 14, 1996	
AMENDMENT N(BC)	June 7, 1996	June 10, 1996	
Subject of this review:			
AMENDMENT N(AZ)	July 10, 1996	July 12, 1996	
AMENDMENT N(BC)	August 20, 1996	August 21, 1966	
AMENDMENT N(BC)	September 18,1996	September 18, 1996	

NAME & ADDRESS OF APPLICANT: Wallace Laboratories
Div. of Carter-Wallace, Inc.
Cranbury, New Jersey 08512

DRUG PRODUCT NAME

Proprietary:	ASTELIN® Nasal Spray, 137 mcg
Nonproprietary/Established/USAN:	azelastine hydrochloride
Code Name/#:	W-2979M, A-5610, E-0659
Chem.Type/Ther.Class:	1C

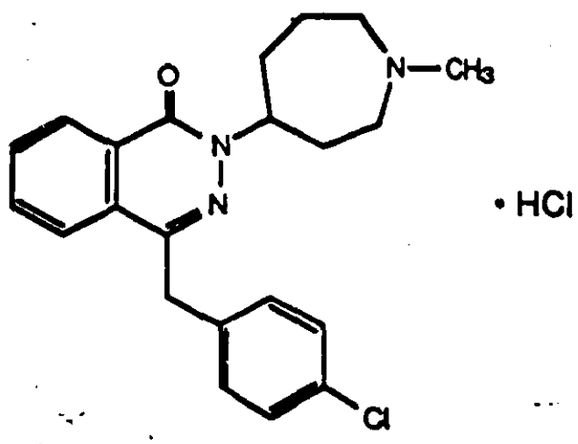
PHARMACOLOGICAL CATEGORY/INDICATION: Allergic rhinitis

DOSAGE FORM: Nasal Spray solution
STRENGTHS: 0.1 % (w/v); 0.137 mL = 0.137 mg per actuation.
ROUTE OF ADMINISTRATION: Nasal; 2 actuations per nostril twice per day
DISPENSED: X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(±)-1-(2H)-Phthalazinone,4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride

$C_{22}H_{24}ClN3O \cdot HCl$ MW 418.37



SUPPORTING DOCUMENTS:

DMF #	Holder Name	Subject	Status	Date Reviewed	Reference

RELATED DOCUMENTS :

Type	Number	Owner	Subject
IND			
IND			
NDA			
NDA			

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
Environment Assessment HFD-102, P. Vincent			
Microbiology, HFD-160	8/19/91	Acceptable 2/6/92	Preservative eff. & microbial limits spec.
Pharmacology, HFD-155 (HFD-570)	5/6/93	Completed 8/11/93	Extractable issue. General policy for inhalation solutions provided.
Labeling & Nomenclature Committee	5/7/91	Completed 5/28/91	N.S. in name not acceptable. See def. 14.a, CR#2.
Biometrics	7/31/95	Completed 9/18/95	Expiration dating period
Methods Validation		Not Requested	
EER	7/27/95 6/17/96 6/28/96	Acceptable 11/6/96 Acceptable 6/28/96 Acceptable 8/12/96	ASTA site replaced by new site for release - acceptable

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not acceptable from the standpoint of chemistry, manufacturing and controls. Deficiencies as detailed in the draft letter to applicant, chemistry portion should be forwarded via facsimile to the applicant.

The medical officer should be asked to comment on the female figure head in the immediate container and package container labels.

Linda Ng, Ph.D.
Review Chemist, HFD-570

cc: Org. NDA 20-114 & Division File.
HFD-570/LNg/9-25-96
HFD-570/GPoochikian 10/8/96
HFD-570/CSO GStrange

File: 20114G.REV
R/D by:

AUG 15 1996

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA:	20-114	**DATE REVIEWED:**	August 14, 1996
REVIEW #:	6	**RECOMMEND ACTION:**	Not approvable
REVIEWER:	Linda Ng, Ph.D.		

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	March 26, 1991	March 27, 1991	June 3, 1991
AMENDMENT	December 18, 1992	December 22, 1995	December 23, 1995
AMENDMENT	May 7, 1993	May 10, 1993	May 10, 1993
AMENDMENT	August 6, 1993	August 11, 1993	August 11, 1993
AMENDMENT N(BZ)	June 30, 1995	July 3, 1995	July 10, 1995
AMENDMENT N(BC)	August 31, 1995	September 6, 1995	
AMENDMENT N(BC)	September 22, 1995	September 25, 1995	
Subject of this review:			
AMENDMENT N(AZ)	May 13, 1996	May 14, 1996	
AMENDMENT N(BC)	June 7, 1996	June 10, 1996 (nitrosamine issue only)	

NAME & ADDRESS OF APPLICANT: Wallace Laboratories
Div. of Carter-Wallace, Inc.
Cranbury, New Jersey 08512

DRUG PRODUCT NAME

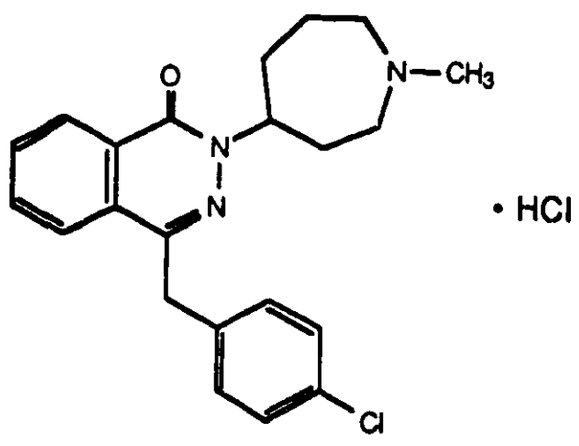
Proprietary:	ASTELIN® Nasal Spray, 137 mcg
Nonproprietary/Established/USAN:	azelastine hydrochloride
Code Name/#:	W-2979M, A-5610, E-0659
Chem.Type/Ther.Class:	1C

PHARMACOLOGICAL CATEGORY/INDICATION: Allergic rhinitis

DOSAGE FORM: Nasal Spray solution
STRENGTHS: 0.1 % (w/v); 0.137 mL = 0.137 mg per actuation.
ROUTE OF ADMINISTRATION: Nasal; 2 actuations per nostril twice per day
DISPENSED: X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(±)-1-(2H)-Phthalazinone,4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride

$C_{22}H_{24}ClN3O \cdot HCl$ MW 418.37



SUPPORTING DOCUMENTS:

DMF #	Holder Name	Subject	Status	Date Reviewed	Reference

RELATED DOCUMENTS :

Type	Number	Owner	Subject
IND			
IND			
NDA			
NDA			

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
Environment Assessment HFD-102, P. Vincent			
Microbiology, HFD-160	8/19/91	Acceptable 2/6/92	Preservative eff. & microbial limits spec.
Pharmacology, HFD-155 (HFD-570)	5/6/93	Completed 8/11/93	Extractable issue. General policy for inhalation solutions provided.
Labeling & Nomenclature Committee	5/7/91	Completed 5/28/91	N.S. in name not acceptable. See def. 14.a. CR#2.
Biometrics	7/31/95	Completed 9/18/95	Expiration dating period
Methods Validation		Not Requested	
EER	7/27/95 6/17/96 6/28/96	Acceptable 11/6/96 Acceptable 6/28/96 Open	ASTA site canceled for release testing.

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not acceptable from the standpoint of chemistry, manufacturing and controls. Deficiencies as detailed in the draft letter to applicant, chemistry portion will be conveyed via facsimile to the applicant.

Linda Ng, Ph.D.
Review Chemist HFD-570

cc: Org. NDA 20-114 & Division File.
HFD-570/LNg/7-22-96; revised 7-29-96; revised 8-14-96.
HFD-570/GPoochikian File: 20114F.REV
HFD-570/CSO GStrange CS 8/15/96 R/D by:

DEC 10 1995

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA:	20-114	**DATE REVIEWED:**	December 3, 1995
REVIEW #:	5	**RECOMMEND ACTION:**	Not approvable
REVIEWER:	Linda Ng, Ph.D.		

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	March 26, 1991	March 27, 1991	June 3, 1991
AMENDMENT	December 18, 1992	December 22, 1995	December 23, 1995
AMENDMENT	May 7, 1993	May 10, 1993	May 10, 1993
AMENDMENT	August 6, 1993	August 11, 1993	August 11, 1993
Subject of this review:			
AMENDMENT N(BZ)	June 30, 1995	July 3, 1995	July 10, 1995
AMENDMENT N(BC)	August 31, 1995	September 6, 1995	
AMENDMENT N(BC)	September 22, 1995	September 25, 1995	

NAME & ADDRESS OF APPLICANT: Wallace Laboratories
Div. of Carter-Wallace, Inc.
Cranbury, New Jersey 08512

DRUG PRODUCT NAME

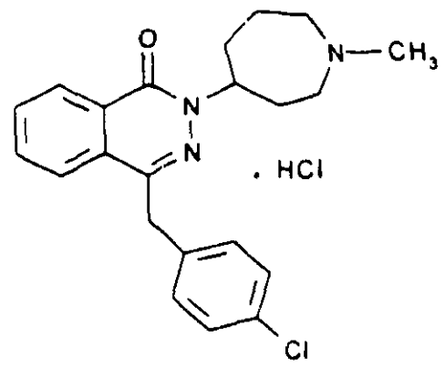
Proprietary:	ASTELIN N.S.™
Nonproprietary/Established/USAN:	azelastine hydrochloride
Code Name/#:	W-2979M, A-5610, E-0659
Chem.Type/Ther.Class:	1C

PHARMACOLOGICAL CATEGORY/INDICATION: Allergic rhinitis

DOSAGE FORM: Nasal Spray solution
STRENGTHS: 0.1 % (w/v); 0.137 mL = 0.137 mg per actuation.
ROUTE OF ADMINISTRATION: Nasal; 2 actuations per nostril per day
DISPENSED: _X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(±)-1-(2H)-Phthalazinone,4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride

$C_{22}H_{24}ClN3O•HCl$ MW 418.37



SUPPORTING DOCUMENTS:

DMF #	Holder Name	Subject	Status	Date Reviewed	Reference

RELATED DOCUMENTS :

Type	Number	Owner	Subject
IND			
IND			
NDA			mg)
NDA			

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
Environment Assessment HFD-102, P. Vincent			
Microbiology, HFD-160	8/19/91	Acceptable 2/6/92	Preservative eff. & microbial limits spec.
Pharmacology, HFD-155 (HFD-570)	5/6/93	Completed 8/11/93	Extractable issue. General policy for inhalation solutions provided.
Labeling & Nomenclature Committee	5/7/91	Completed 5/28/91	N.S. in name not acceptable. See def. 14.a, CR#2.
Biometrics	7/31/95	Completed 9/18/95	Expiration dating period
Methods Validation		Not Requested	
EER	7/27/95	Acceptable 11/6/95	Follow-up Request

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not acceptable from the standpoint of chemistry, manufacturing and controls. Deficiencies as detailed in the draft letter to applicant, chemistry portion should be promptly forwarded to the applicant.

Linda Ng, Ph.D.
Review Chemist, HFD-570

cc:
Org. NDA 20-114
HFD-570/Division File
HFD-570/GPoochikian
HFD-570/CSO Gstrange
HFD-570/LNg

F/D by: LNg/12/3/95; revised 12/8/95
R/D by:
File: 20114E.REV

OCT 27 1993

Division of Oncology and Pulmonary Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-114 **CHEM. REVIEW#:** 4 **REVIEW DATE:** October 18, 1993

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	March 26, 1991	March 27, 1991	

This review is not concerned with any particular submission by the sponsor. The review is prompted by a response by one of the DMF holders concerned with the drug substance.

NAME AND ADDRESS OF SPONSOR: Wallace Laboratories
Div. of Carter-Wallace, Inc.
Cranbury, New Jersey 08512

DRUG PRODUCT NAME:

Proprietary:	Astelin N.S.
Nonproprietary/USAN:	azelastine hydrochloride
Code Name/#:	W-2979M, A-5610, E-0659
Chem. Type/Ther. Class:	1C

PHARMACOL. CATEGORY/INDICATION: Allergic Rhinitis

DOSAGE FORM: Nasal Spray Solution

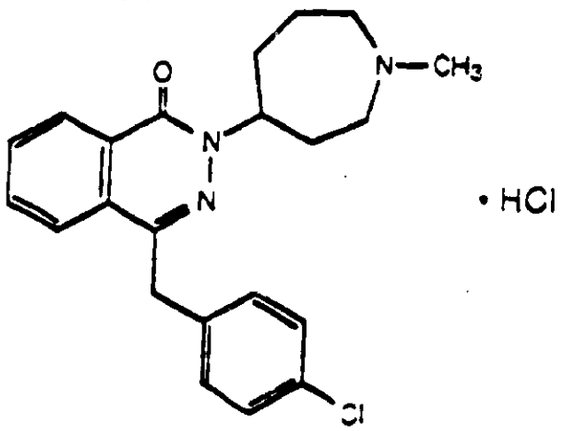
STRENGTHS: 0.1% (w/v); 0.137 mL = 0.137mg per actuation

ROUTE OF ADMINISTRATION: nasal

Rx/OTC: prescription

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:

$C_{22}H_{24}ClN3O \cdot HCl$ MW 418.37



SUPPORTING DOCUMENTS:

See chemistry review 3.

Additional comments were sent to the holder of DMF (azelastine drug substance). Reference is made to chemistry review # 3 of DMF

An amendment dated October 1, 1993 to DMF (synthesis intermediate) was reviewed (Chemistry Review 2 of DMF and a deficiency letter sent to the DMF holder.

RELATED DOCUMENTS
See chemistry review 3.

CONSULTS:
See chemistry review 3.

REMARKS/COMMENTS:

This review is an addendum to Chemistry Review 2. The deficiency contained in the attached draft letter is prompted by the response of one of the DMF holders concerned with drug substance synthesis.

CONCLUSIONS AND RECOMMENDATIONS:

The attached draft deficiency should be forwarded to the applicant by the CSO with comments from chemistry reviews # 2 and # 3.

Dale L. Koble 10/27/93
Dale L. Koble, Ph.D.
Review Chemist HFD-155

CC:
Orig. NDA
HFD-155 Division File
HFD-155/DKoble
HFD-155/GPoochikian
HFD-156/TRiley
R/D Init. by: for GP 10/27/93
doc. NDA20114.CR4

11.1

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA:	20-114	**DATE REVIEWED:**	October 5, 1993
REVIEW #:	3	**RECOMMEND ACTION:**	Not approvable

REVIEW TEAM MEMBERS: Linda Ng, Ph.D. (Drug Product)
Dale Kobla, Ph.D.(Drug Substance)

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	March 26, 1991	March 27, 1991	June 3, 1991
AMENDMENT	August 6, 1993	August 11, 1993	August 11, 1993

NAME & ADDRESS OF APPLICANT: Wallace Laboratories
Div. of Carter-Wallace, Inc.
Cranbury, New Jersey 08512

DRUG PRODUCT NAME

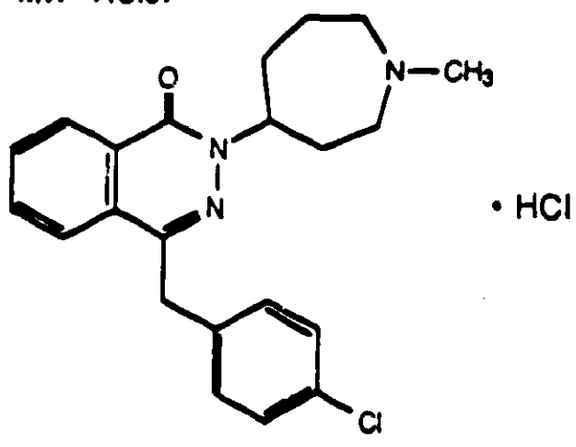
Proprietary:	ASTELIN N.S.™
Nonproprietary/Established/USAN:	azelastine hydrochloride
Code Name/#:	W-2979M, A-5610, E-0659
Chem.Type/Ther.Class:	1C

PHARMACOLOGICAL CATEGORY/INDICATION: Allergic rhinitis

DOSAGE FORM: Nasal Spray solution
STRENGTHS: 0.1 % (w/v); 0.137 mL = 0.137 mg per actuation.
ROUTE OF ADMINISTRATION: Nasal
DISPENSED: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(±)-1-(2H)-Phthalazinone,4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride

$C_{22}H_{24}ClN3O \cdot HCl$ MW 418.37



SUPPORTING DOCUMENTS:

DMF #	Holder Name	Subject	Status	Date Reviewed	Reference

RELATED DOCUMENTS :

Type	Number	Owner	Subject
IND			
IND			
NDA			
NDA			

CONSULTS:
Requests for consultation have been forwarded for environmental assessment, microbiology, pharmacology/toxicology and labeling & nomenclature committee.

CONSULT	DATE FORWARDED	STATUS	COMMENTS
Environment Assessment HFD-102, P. Vincent			
Microbiology, HFD-160	8/19/91	Acceptable 2/6/92	Preservative eff. & microbial limits spec.
Pharmacology, HFD-155	5/6/93	Completed 8/11/93	Extractable issue. General policy for inhalation solutions provided.
Labeling & Nomenclature Committee	5/7/91	Completed 5/28/91	N.S. in name not acceptable. See def. 14.a, CR#2.

REMARKS/COMMENTS:

1. Other amendments reviewed are:
   AMENDMENT December 18, 1992
   AMENDMENT May 7, 1993

2. DMFs cited as supporting this application have been found to be deficient upon review. Letters have been sent to the holders explaining the deficiencies as follows:

DMF	HOLDER	STATUS

3. The issue on extractables has been requested from the applicant and should be re-considered later as needed from DMF The pump unit is assembled by

4. Review of the environmental assessment for the NDA has been completed by Ms Christina Good on August 20, 1993. The list of dificiencies has been forwarded to the CSO, Ms. Tracy Riley to forward to the applicant. Review of the EA for the DMFs are

still outstanding (see remark #6).

In addition the following comments are noted:

Drug Substance.

5. Reference is made to question 1e in the review section below. The particle size information can be considered adequate for the purposes of NDA 20-114 (nasal solution) but should be reviewed again in consideration of .

6. A consult dated 4/15/93 for environmental assessment was sent to Phil Vincent (HFD-102) for review of information submitted on environmental assessment to DMF . and DMF (azelastine hydrochloride drug substance). The consults for the DMFs are still outstanding.

Drug Product.

All page references made in this section are from submission dated December 18, 1992.

7. The reviewing medical officer has been alerted that the final marketed pump unit (pump B) is different from that used in the clinical studies (pump A). Data for the droplet size distribution is similar for both from Attachment 32. Delivery volume has been indicated to be about 2% higher for pump B from Attachments 36 and 37. See comments in review section II.F.

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from freezing.

12. The applicant requests that "recommended expiration period is 24 months. When the product is dispensed, a new expiration date of 6 months from that date will be assigned (but not exceeding the original 24 months)". The expiration dating will be evaluated upon receipt of complete stability data.

13. The fill volume has been changed from 15 mL to 17 mL with this amendment. The applicant has been asked to clarify the target fill as it is not clear if a) the round HDPE bottle has been retained from the original application, b) the manufacturing section states a fill of 17.5 mL and c) labeling states 17.0 mL fill.

14. Since only pump B will be marketed with production scale of in Decatur, Illinois, the acceptable stability studies are 4587 (with screw cap) and 4725 (with pump B) for batch E-2270A, 5080 (with screw cap) and 5081 (with pump B) for batch 03-25b-01c. The intended batch size for commercial production is 3,300 L. Stability data (studies 4725 & 4587) for th , manufactured "scale-up" batch at Decatur, Illinois were incomplete, (i.e., missing pages?). One commercial size batch (studies 5080 and 5081) was manufactured with initial stability data submitted.

15. The applicant provided inadequate specification and limit for droplet size distribution. As noted in comments to be conveyed to the applicant, a realistic release and stability specification should be proposed for this attribute. The limit should be based on an appropriate size distribution that is scientifically supported for a nasal solution using data from batches used in pivotal clinical studies.

16. The USP preservative effectiveness data and the proposed microbial limit of 100 CFU/mL for the drug product (in-process and regulatory specifications) were approvable based on microbiological quality by Ms. Carol Vincent, Microbiology Reviewer.

17. Applicant should be reminded of their commitment to submit analytical release data of the drug product if none is submitted with the next amendment. See deficiency 13 of this review and responses to 7.i. of last review.

18. Concerning the labeling, the applicant is again advised to revise the proprietary name to: Astelin Nasal Solution from Astelin N.S.

19. The "protect from freezing" statement is included in the labeling as a precaution because of lack of visibility for the nasal solution in the opaque container. The drug product will freeze at lo temperature but will re-dissolve upon shaking.

20. Item numbers, drawings and letters of compliance for materials are provided for each component of the the pump unit. In addition, the applicant has stated: "It is understood that no change in pump component materials is permitted without agency approval (p. 38)".

21. Establishment Evaluations: for current status.

22. Methods validation will not be forwarded to the field until all issues are resolved.

23. Pharmacology has been consulted on the extractable issue. See letters from Dr. A. Taylor, dated 8/11/93 and review by Dr. M. Chun dated 7/21/93.

24. Biometrics consult will be deferred until issues on specifications, stability data, etc., have been resolved.

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not acceptable from the standpoint of chemistry, manufacturing and controls. Deficiencies as detailed in the draft letter to applicant, chemistry portion together with deficiencies from chem review #2 should be promptly forwarded to the applicant.

Linda Ng, Ph.D.
Review Chemist

cc:
Org. NDA 20-114
HFD-155/Division File
HFD-155/GPoochikian
HFD-155/CSO TRiley
HFD-155/LNg
HFD-155/DKoble
F/D by: LNg/10/5/93
R/D by: 10/7/93
File: 20228C.REV

Kelley

AUG 7 1993

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA:	20-114	**DATE REVIEWED:**	July 28, 1993
REVIEW #:	2	**RECOMMEND ACTION:**	Not approvable

REVIEW TEAM MEMBERS: Linda Ng, Ph.D. (Drug Product)
Dale Koble, Ph.D.(Drug Substance)

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	March 26, 1991	March 27, 1991	June 3, 1991
AMENDMENT	December 18, 1992	December 22, 1992	December 23, 1992
AMENDMENT	May 7, 1993	May 10, 1993	May 10, 1993

NAME & ADDRESS OF APPLICANT: Wallace Laboratories
Div. of Carter-Wallace, Inc.
Cranbury, New Jersey 08512

DRUG PRODUCT NAME

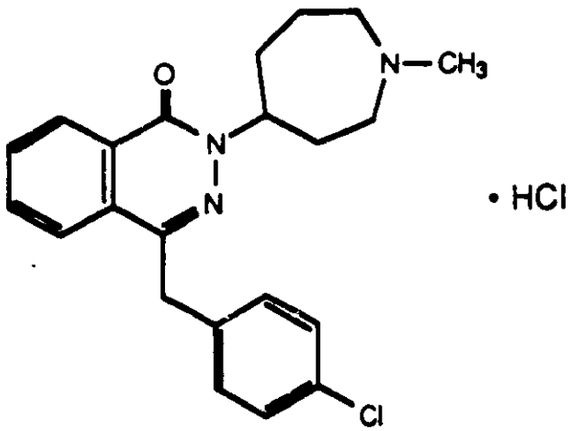
Proprietary:	ASTELIN N.S.™
Nonproprietary/Established/USAN:	azelastine hydrochloride
Code Name/#:	W-2979M, A-5610, E-0659
Chem.Type/Ther.Class:	1C

PHARMACOLOGICAL CATEGORY/INDICATION: Allergic rhinitis

DOSAGE FORM: Nasal Spray solution
STRENGTHS: 0.1 % (w/v); 0.137 mL = 0.137 mg per actuation.
ROUTE OF ADMINISTRATION: Nasal
DISPENSED: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(±)-1-(2H)-Phthalazinone,4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride

$C_{22}H_{24}ClN3O \cdot HCl$ MW 418.37



SUPPORTING DOCUMENTS:

DMF #	Holder Name	Subject	Status	Date Reviewed	Reference
					Letter sent.

RELATED DOCUMENTS :

Type	Number	Owner	Subject
IND			
IND			
NDA			
NDA			

CONSULTS:
Requests for consultation have been forwarded for environmental assessment, microbiology, pharmacology/toxicology and labeling & nomenclature committee.

CONSULT	DATE FORWARDED	STATUS	COMMENTS
Environment Assessment HFD-102, P. Vincent			
Microbiology, HFD-160	8/19/91	Acceptable 2/6/92	Preservative eff. & microbial limits spec.
Pharmacology, HFD-155	5/6/93	OPEN	Extractable issue. General policy for inhalation solutions requested.
Labeling & Nomenclature Committee	5/7/91	Completed 5/28/91	N.S. in name not acceptable. See def. 14.a, CR#2.

REMARKS/COMMENTS:

DMFs cited as supporting this application have been found to be deficient upon review. Letters have been sent to the holders explaining the deficiencies as follows:

DMF	HOLDER	STATUS

The issue on extractables has been requested from the applicant and should be re-considered later as needed from DMF The pump unit is assembled by Valois.

In addition the following comments are noted:

Drug Substance.

1. Reference is made to question 1e in the review section below. The particle size information can be considered adequate for the purposes of NDA 20-114 (nasal solution) but should be reviewed again in consideration of NDA

2. A consult dated 4/15/93 for environmental assessment was sent to Phil Vincent (HFD-102) for review of information submitted on environmental assessment to DMF . . . . . and DMF (azelastine hydrochloride drug substance). Dr. Vincent was reminded of other outstanding consults for NDA 20-114 and

Drug Product.

1. The reviewing medical officer has been alerted that the final marketed pump unit (pump B) is different from that used in the clinical studies (pump A). Data for the droplet size distribution is similar for both from Attachment 32. Delivery volume has been indicated to be about 2% higher for pump B from Attachments 36 and 37. See comments in review section II.F.

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6. The applicant requests that "recommended expiration period is 24 months. When the product is dispensed, a new expiration date of 6 months from that date will be assigned (but not exceeding the original 24 months)". The expiration dating will be evaluated upon receipt of complete stability data.

7. The fill volume has been changed from 15 mL to 17 mL with this amendment. The applicant has been asked to clarify the target fill as it is not clear if a) the round HDPE bottle has been retained from the original application, b) the manufacturing section states a fill of 17.5 mL and c) labeling states 17.0 mL fill.

8. Since only pump B will be marketed with production scale of liters in Decatur, Illinois, the acceptable stability studies are 4587 (with screw cap) and 4725 (with

pump B) for batch E-2270A, 5080 (with screw cap) and 5081 (with pump B) for batch 03-25b-01c. The intended batch size for commercial production is 3,300 L. Stability data (studies 4725 & 4587) for the 200 L (6% of 3,300 L), manufactured "scale-up" batch at Decatur, Illinois were incomplete, (i.e., missing pages?). One commercial size batch (studies 5080 and 5081) was manufactured with initial stability data submitted. Another production size batch for stability studies has been requested from the applicant.

9. The applicant provided inadequate specification and limit for droplet size distribution. As noted in comments to be conveyed to the applicant, a realistic release and stability specification should be proposed for this attribute. The limit should be based on an appropriate size distribution that is scientifically supported for a nasal solution using data from batches used in pivotal clinical studies.

10. The USP preservative effectiveness data and the proposed microbial limit of 100 CFU/mL for the drug product (in-process and regulatory specifications) were approvable based on microbiological quality by Ms. Carol Vincent, Microbiology Reviewer.

11. Applicant should be reminded of their commitment to submit analytical release data of the drug product if none is submitted with the next amendment. See deficiency 13 of this review and responses to 7.i. of last review.

12. Concerning the labeling, the applicant is again advised to revise the proprietary name to: Astelin Nasal Solution from Astelin N.S.

13. The "protect from freezing" statement is included in the labeling as a precaution because of lack of visibility for the nasal solution in the opaque container. The drug product will freeze at low temperature but will re-dissolve upon shaking.

14. Item numbers, drawings and letters of compliance for materials are provided for each component of the the pump unit. In addition, the applicant has stated: "It is understood that no change in pump component materials is permitted without agency approval (p. 38)".

15. Establishment Evaluations: See p. . of this review for current status.

16. Methods validation will not be forwarded to the field until all issues are resolved.

17. A request for updated stability studies and initiation of stability studies for another production batch have been requested per telcon of May 21, 1993. No information has been received to date.

18. Pharmacology has been consulted on the extractable issue. See letters from Dr. A. Taylor, dated 7/7/93 and review by Dr. M. Chun dated 7/21/93.

19. Biometrics consult will be deferred until issues on specifications, stability data, etc., have been resolved.

CONCLUSIONS & RECOMMENDATIONS:
The application as submitted is not acceptable from the standpoint of chemistry, manufacturing and controls. Deficiencies are detailed in the accompanying and summarized in the attached draft letter to applicant, chemistry portion. These deficiencies should be promptly forwarded to the applicant.

SECTIONS REVIEWED:

DRUG SUBSTANCE:

Dale L. Koble

Dale Koble, Ph.D.
Review Chemist

DRUG PRODUCT:

Linda Ng

Linda Ng, Ph.D.
Review Chemist

cc:
Org. NDA 20-114
HFD-155/Division File
HFD-155/GPoochikian
HFD-155/CSO TRiley
HFD-155/LNg
HFD-155/DKoble 7/28/93
F/D by: DS - DKoble 5/10/93
DP - LNg 5/26/93
Revised 7/28/93
R/D by:

Freedom of Information Copy

CHEMISTRY, MANUFACTURING AND CONTROLS

TECHNICAL SECTION

ENVIRONMENTAL ASSESSMENT

ASTELIN® (azelastine hydrochloride) Nasal Spray, 0.1% w/v

ENVIRONMENTAL ASSESSMENT
AZELASTINE HYDROCHLORIDE NASAL SOLUTION

1. **Date of Report:** Revised September 28, 1995

2. **Name of Applicant:** Wallace Laboratories
Division of Carter-Wallace, Inc.

3. **Address of Applicant:** Half Acre Road, PO Box 1001
Cranbury, New Jersey 08512

4. **Description of Proposed Action:**

The proposed action involves the medicinal agent, azelastine hydrochloride (Astelin® Nasal Spray), for which Wallace Laboratories submitted a New Drug Application (NDA) NDA 20-114 on March 26, 1991. Azelastine hydrochloride drug substance will be produced by ASTA Pharma AG,* Frankfurt, Germany. Azelastine hydrochloride produced at this facility will be subsequently used in the manufacture of 0.1% azelastine hydrochloride nasal solution at Wallace Laboratories' facility located in Decatur, Illinois.

Normal disposal of azelastine hydrochloride will be via nasal inhalation and the subsequent metabolism and excretion of the drug and its metabolites into cesspools/septic tanks and publicly and privately owned wastewater treatment plants (WWTP). Disposal may also include small amounts of unused drug by patients and returned or rejected product, containing azelastine hydrochloride, disposed in accordance with the applicable regulations.

*ASTA Pharma AG has changed the name of the company to ASTA Medica AG.

Minor amounts of azelastine hydrochloride, such as those present in equipment designed to control emissions from manufacturing operations, will be disposed of by Wallace Laboratories' Decatur facility as solid waste in a sanitary landfill or incinerated at a permitted solid waste incinerator or as discharges to a WWTP.

The Wallace Laboratories' Decatur manufacturing site is located in the city of Decatur, Illinois, in an industrial and manufacturing area. The topography of the area is flat and the climate is temperate. The Sagamon River is the receiving body of the plant effluent after treatment at the Sanitary District of Decatur WWTP.

Azelastine hydrochloride and/or certain intermediates required for its manufacture are produced by ASTA Pharma AG, Frankfurt, Germany. Certification of environmental compliance from the appropriate governmental authorities for ASTA Pharma AG, Frankfurt, Germany has been provided in Appendix A hereto.

5. **Identification of the Chemical Substances that are the Subject of the Proposed Action**

AZELASTINE HYDROCHLORIDE

Chemical Name: (±)-1-(2H)-Phthalazinone, 4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1-1H-azepin-4-yl)-,monohydrochloride

Generic Name: Azelastine Hydrochloride

Tradename: Astelin® Nasal Spray

CAS Registry Number: 79307-93-0

Physical Description: Azelastine hydrochloride is a white, almost odorless crystalline powder with a bitter taste.

Structural Formula:

Molecular Weight: 381.90/418.37, (Base/Hydrochloride)

Water Solubility:

	pH5	pH7	pH9
mean solubility mg/l	15,600	3,850	2.69

Hydrolysis: Hydrolytically stable at pH 5.00, 7.00 and 9.00 based on the aerobic biodegradation study and product stability profile.

Vapor Pressure: Estimated $<10E^{-7}$torr

Partition Coefficient:

	Concentration (M)	**Mean Kow**	**log (mean Kow)**
pH5	8.18×10^{-5}	13.1	1.12
pH5	9.69×10^{-4}	10.1	1.00
pH7	8.41×10^{-5}	54.7	1.74
pH7	9.85×10^{-4}	78.8	1.90
pH9	8.82×10^{-4}	8120	3.91
pH9	9.13×10^{-3}	7120	3.85

Dissociation Constant: 8.74 in reagent water. 8.4 in propylene glycol-water mixture.

Soil Sorption/Desorption:

A test was performed at solution: soil ratios of 5:1 with two different aqueous phases, 0.01 M $CaCl_2$ and distilled, deionized (DDI) water at an azelastine hydrochloride nominal concentration of 25.2 mg/L. The soil types were California Clay, Iowa Silty Clay Loam and Indiana Loam. A summary of these results is presented in the following table:

Soil Type	Percent Sorbed to Soil of Total Applied to Test System		Percent Desorbed (from amount sorbed to soil)	
	0.01 M $CaCl_2$	DDI Water	0.01 M $CaCl_2$	DDI Water
California	99.5	99.4	1.13	6.38
Iowa	99.5	94.3	1.09	3.31
Indiana	99.5	94.0	1.11	3.35

The results indicate that azelastine hydrochloride is strongly bound to sediments and soils.

Aerobic Biodegradation in Activated Sludge: Degradation of approximately 10-20% was observed during a 28 day study.

Photolysis: The photolytic half lives of azelastine hydrochloride in synthetic humic water and pure water was determined to be 10.1 and 15.8 days respectively.

UV Spectrum: The major absorbance for azelastine hydrochloride is 285 nm.

Microbial Inhibition:

Inhibitory concentrations of Azelastine hydrochloride determine for five microorganisms during this study.

Species	Azelastine hydrochloride MIC (mg/L as free base)
Aspergillus niger	100
Trichoderma viride	1000
Clostridium perfringens	400
Bacillus subtilis	200
Nostoc	20

Acute Aquatic Toxicity: 48 hour EC-50 for *Daphnia magna* exposed to azelastine hydrochloride was determined to be 4.4 mg A.I./L

Product Excipients: The excipients used in the formulation of this proposed action are designated as GRAS (Generally Recognized As Safe). A list of the excipients and their CAS numbers, as available, follows. Material Safety Data Sheets (MSDS) for azelastine hydrochloride and all excipients have been provided in Appendix B.

Excipient Listing

Substance	CAS Number
Hydroxypropyl Methylcellulose 2910, USP	9000-65-3
Edetate Disodium, USP	6381-92-6
Benzalkonium Chloride Solution, NF 50%	8001-54-5
Citric Acid, USP, Anhydrous	77-92-9
Dibasic Sodium Phosphate, USP, Heptahydrate	7558-79-4
Sodium Chloride, USP	7647-14-5
Purified Water, USP	7332-18-5

c. **Introduction of Substances into the Environment**

(A) Production - Manufacturing, processing, packaging and labeling of the azelastine hydrochloride will be completed by ASTA Pharma of Frankfurt, Germany. Certification of environmental compliance from the appropriate governmental authorities for ASTA Pharma, Frankfurt, Germany has been provided in Appendix A hereto.

Formulation of azelastine hydrochloride into 0.1% w/v nasal solution will be completed at the Wallace Laboratories' plant in Decatur, Illinois.

The expected increase upon current production loading in

The expected increase upon current production loading in Decatur, Illinois facility will not significantly impact production capacity, controls or emissions at the facility.

Releases of raw materials and finished product will be controlled as delineated below:

1. Control of Manufacturing Emissions

(a) Workplace Emissions

Workplace emissions are controlled via appropriate equipment design, material and product transfer procedures, operating procedures, personal protective equipment, if appropriate and particulate control devices.

(b) Atmospheric

Air emissions from the formulation processes are controlled through the use of air pollution control devices, standard operating procedures, and employee training. Substances which could be emitted through atmospheric emissions from the Wallace Laboratories' Decatur, Illinois facility are as follows:

Chemical	CAS Registry Number
Azelastine Hydrochloride	79307-93-0
Hydroxypropyl Methylcellulose 2910, USP	9000-65-3
Edetate Disodium, USP	6381-92-6
Citric Acid, USP, Anhydrous	77-92-9
Dibasic Sodium Phosphate, USP, Heptahydrate	7558-79-4
Sodium Chloride, USP	7647-14-5

Total atmospheric emissions of these materials will not be in excess of permitted levels. The air emissions from Wallace

Laboratories are regulated by the Illinois Environmental Protection Agency. The processes for the manufacture of Astelin® Nasal Spray are regulated by air permit number 87030062 which expires April 25, 2000.

(c) Aqueous

Wastewater discharges from the formulation process in the form of collected particulate matter and equipment wash waters to the WWTP are estimated to contain the following substances:

Chemical	CAS Registry Number
Azelastine Hydrochloride	79307-93-0
Hydroxypropyl Methylcellulose 2910, USP	9000-65-3
Edetate Disodium, USP	6381-92-6
Benzalkonium Chloride Solution, NF 50%	8001-54-5
Citric Acid, USP, Anhydrous	77-92-9
Dibasic Sodium Phosphate, USP, Heptahydrate	7558-79-4
Sodium Chloride, USP	7647-14-5
Purified Water, USP	7332-18-5

In addition, small amounts of final product from equipment and facilities washing are capable of being disposed of via liquid discharge to the WWTP. Wastewater discharges from Wallace Laboratories are regulated by the Sanitary District of Decatur through the wastewater permit number 265. The wastewater permit for the Decatur facility expires February 16, 1996 and is presently being evaluated for renewal.

(d) Terrestrial

Non-hazardous solid wastes, mainly comprised of returned or rejected product, raw materials and solids recovered from emissions control systems, are collected and disposed of in a permitted solid waste landfill or by incineration at a permitted solid waste incinerator. These wastes are composed of:

Chemical	CAS Registry Number
Azelastine Hydrochloride	79307-93-0
Hydroxypropyl Methylcellulose 2910, USP	9000-65-3
Edetate Disodium, USP	6381-92-6
Benzalkonium Chloride Solution, NF 50%	8001-54-5
Citric Acid, USP, Anhydrous	77-92-9
Dibasic Sodium Phosphate, USP, Heptahydrate	7558-79-4
Sodium Chloride, USP	7647-14-5
Purified Water, USP	7332-18-5

Disposal of non-hazardous solid waste is regulated by the Illinois Environmental Protection Agency. This waste classified as special waste is permitted for disposal through waste stream authorization number 942243 which expires July 21, 1999.

2. Certification of Compliance

(a) Workplace Emissions

Workplace emissions are controlled via appropriate equipment design, material and product transfer and handling procedures, personal protective equipment, if appropriate, and permitted particulate control devices.

(b) Atmospheric

Air emissions will be controlled in compliance with the Illinois Environmental Protection Act and air operating permits issued by the Illinois Environmental Protection Agency.

(c) Aqueous

Wastewater discharges will be in accordance with the discharge requirements and limitations approved by the applicable Wastewater Treatment Plant, Sanitary District of Decatur.

(d) Solid Waste

There are no hazardous wastes, as defined by 40 CFR 260-267, generated in the formulation of azelastine hydrochloride into 0.1% w/v nasal solutions. Non-hazardous solid raw material wastes will be transported to a permitted sanitary landfill and disposed in compliance with the applicable laws of Illinois. Non-hazardous liquid raw materials will be discharged to the WWTP and final products may be incinerated at a non-hazardous solid waste incinerator.

(e) General Compliance Statement

Carter-Wallace, Inc., states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emissions requirements set forth in permits, consent decrees and administrative orders applicable to the production of azelastine hydrochloride nasal solution at its Wallace Laboratories' facility in Decatur, Illinois as well as emission requirements set forth in applicable federal, state and local statues and regulations applicable to the production of

azelastine hydrochloride nasal solution at its Wallace Laboratories' facility in Decatur, Illinois.

6. B. 1. Use and Disposal

Azelastine hydrochloride (Astelin® Nasal Spray) 0.1% w/v nasal solution is used in the treatment of symptomatic seasonal and perennial allergic rhinitis. Wallace Laboratories proposes to formulate the drug substance into 0.1% nasal solution dosage forms for the treatment of seasonal and perennial allergic rhinitis.

Production of azelastine hydrochloride solutions at Wallace Laboratories' Decatur facility will be via a batch process. Good Manufacturing Practices (GMPs) are employed to minimize waste generated during the production process.

A description of the environments where the product will be used is not possible as the product usage does not target a specific localized population.

The formulation, use and disposal of azelastine hydrochloride 0.1% nasal solution will result in the release of azelastine hydrochloride to the environment from cesspools/septic tanks, wastewater treatment plants and landfill leachate, as well as from stormwater runoff. It is estimated that patient use of azelastine hydrochloride is unlikely to introduce more than 10% of the total amount of the drug administered into the environment. Normal disposal of azelastine hydrochloride will be via nasal inhalation and subsequent metabolism and excretion of the drug and its metabolites into cesspools/septic tanks and publicly and privately owned WWTP's and through discharge from

the site due to production and packaging of the product.

As a result of patient use, the maximum concentration of azelastine hydrochloride emitted into the environment, assuming the total amount of drug produced is discharged into sewage systems and is not metabolized by patients, is estimated to be 1.1×10^{-6} mg/L (ppm). The actual amount of azelastine hydrochloride discharged into the environment will be no more than 10% of this amount, since more than 90% is metabolized by patients.

7. Fate of Azelastine Hydrochloride in the Environment

A. Air

Azelastine hydrochloride, a non-volatile solid based on the vapor pressure, may be emitted as particulate matter at the Decatur facility where it is formulated into 0.1% w/v solution. The particulate emissions are controlled by the use of permitted pollution control devices.

The atmospheric compartment is not expected to be at risk by the presence of azelastine hydrochloride which is not released to the air in measurable amounts or volatilized from aquatic and/or terrestrial sources.

B. Water

The greatest emission of azelastine hydrochloride from production and use will be to wastewater. Based on the soil sorption/desorption data Azelastine hydrochloride will sorb to solids in the wastewater stream and the WWTP.

Microbial inhibition and acute toxicity to Daphnids studies were conducted and the results indicate that azelastine hydrochloride

at the estimated discharge concentrations will have no adverse effects on the WWTP's operations. Although a standard aerobic biodegradation study showed no evidence for the breakdown of azelastine hydrochloride, a study simulating the aerobic digestor of a WWTP provided evidence that azelastine hydrochloride can be biotransformed in this type of environment. Degradation of approximately 10-20% was observed during a 28 day study at sludge concentration similar to those found in WWTP. In addition, azelastine hydrochloride was demonstrated to degrade through aqueous photolysis. Half lives ranging from 10.1 days to 15.8 days were experimentally determined by exposing solution of azelastine hydrochloride to simulated sunlight. Pathways for degradation were shown to exist by both direct and indirect photolysis. Releases of azelastine hydrochloride to the WWTP as well as other environmental compartments, will be minimized by adherence to GMP's, employee training and standard operating procedures.

C. Terrestrial

Returned or rejected product forwarded to the Decatur, Illinois facility for disposal may be incinerated at a permitted solid waste incinerator. Azelastine hydrochloride, discharged to a WWTP, will highly sorb onto the sludge associated with wastewater treatment and may be disposed of at a permitted landfill or applied to land.

Azelastine hydrochloride will not hydrolyze in a neutral pH aerobic environment, although studies suggest that enzyme mechanisms exist in the environment that can extensively metabolize azelastine hydrochloride. Many natural microflora

contain enzyme systems identical to mammalian systems in several fungal species. These systems are naturally occurring and will undoubtedly degrade azelastine hydrochloride when exposed to it.

8. **Environmental Effects of Release Substances**

Given the low levels of human and environmental exposures and the toxicology data, the use and/or disposal of azelastine hydrochloride and its metabolites and documented pathways for degradation such as direct and indirect photolysis, azelastine hydrochloride is not expected to cause adverse effects upon humans, animals, plants, other organisms or the environment. Evidence suggests that azelastine hydrochloride and its metabolites do not provide any indication or mutagenicity, oncogenicity, teratology or reproductive effects.

9. **Use of Resources and Energy**

Formulation of azelastine hydrochloride solutions will be carried out at an existing facility in Decatur, Illinois. There are no plans to expand the present site or to construct new facilities. No amount of rare minerals nor raw materials derived from any source which would be considered to be endangered or threatened will be used in the production and/or formulation of azelastine hydrochloride solutions. The estimated usage of energy associated with the production of solutions at Decatur is 190,995 kilowatt-hours of electrcity and 6953 therms of gas in the fifth year of production. It is expected that there will be no adverse effects upon property listed in or eligible for listing in the National Register of Historic Places.

10. **Mitigation Measures**

No adverse impacts have been identified in relation to the formulation, use and disposal of azelastine hydrochloride solutions.

In addition to the controls exercised under Item 6 above, Wallace Laboratories will formulate azelastine hydrochloride solutions under the supervision of qualified personnel and will engage in an active maintenance program. Moreover, the Decatur facility where azelastine hydrochloride will be formulated into solution, procedures and equipment are in place to contain spills of raw materials and to prevent their introduction into the environment.

11. **Alternative to Proposed Action**

Wallace Laboratories has assessed the fate and effects of azelastine hydrochloride introduced into the environment through the production, use and disposal of the drug product. Since there are no adverse environmental impacts identified for the proposed action, no alternatives are proposed in this document. An alternative of "no action" with respect to the manufacturing of Astelin® Nasal Spray is an alternative which is available.

12. **Preparer**

K.B. Clarke, J.D., B.S.Ch

Supported by:

CARTER-WALLACE, INC.

Dr. David E. Auslander*	Director, Pharmaceutical Development
Mr. Gul Balwani*	Group Leader, Process Development
Dr. Naresh Chand*	Director, Pharmacology

Dr. Jeffrey J. Freitag*	Director, Clinical Research, Pulmonary Drugs
Mr. James A. Givens	Production Manager
Dr. Steven A. Gordziel	Vice President, Developmental Research
Ms. Elizabeth Hagstad*	Environmental Affairs Specialist
Mr. James E. Harrison*	Senior Pharmacologist
Mr. Larry D. Hearn	Director Pharmaceutical Manufacturing, Decatur
Mr. Nelson J. Ivins	Director, GLP Monitoring
Mr. Robert Kowal	Manager, Process Development
Mr. Peter J. Marshall	Manager, Environmental Affairs
Dr. James H. McGee	Director, Toxicology
Dr. James L. Perhach	Vice President, Clinical Pharmacology and Pharmacokinetics
Dr. Li-Chun C. Wang	Manager, Pharmaceutics
Dr. Joseph K. Wichmann*	Associate Director, Biochemistry
Ms. Beverly C. Wilson	Manager, Stability and Packaging Evaluation

SPRINGBORN LABORATORIES, INC.

Dr. Paul H. Fackler	Director, Environmental Chemistry

*An asterisk indicates that the person assisted in providing information for this environmental assessment but is no longer employed with the company.

13. **References**

Environmental Assessment Technical Assistance Handbook C. Eirkson, M. Harrass, C. Osbourne, P. Sayre, M. Zeeman. Food and Drug Administration, PB87-175345.

21 CFR Ch. 1, Subpart C; Preparation of Environmental Documents (4-1-92).

Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA. Pharmaceutical Manufacturers Association, V7 July, 1991.

14. **Certification**

The undersigned certifies that to the best of his knowledge and based on data provided by company personnel and other sources, the information provided in this environmental assessment and true and accurate and represents the best assessment of the company's understanding of the environmental impacts from the manufacture, use and disposal of azelastine hydrochloride at this time.

Name Richard J. Majos

Title Vice President, Safety Health and Environment

Date 9-29-95

Signature Richard J. Majos

ASTA MEDICA
Ein Unternehmen der Degussa

ASTA Medica AG · Postfach 10 01 05 · 60001 Frankfurt am Main

ASTA Medica Aktiengesellschaft
Weismüllerstraße 45
60314 Frankfurt am Main

Telefon (0 69) 40 01-0
Telex 41 71 13 asta d
Telefax (0 69) 40 01-27 40
Telegramme Astamedica Frankfurtmain

Bank
Degussa Bank Frankfurt am Main
(BLZ 500 107 00) Konto 560 200
SWIFT: DEGUDEFF

Ihr Zeichen	Ihre Nachricht	Unser Zeichen	Durchwahl-Nr. (069) 4001-	Datum
			2775	May 10, 1995

"ENVIRONMENTAL ASSESSMENT"
AZELASTINE HYDROCHLORIDE

ASTA Medica Aktiengesellschaft, as the manufacturer of Azelastine Hydrochloride having the official address:

ASTA Medica Aktiengesellschaft
An der Pikardie 10
D-01277 Dresden
Federal Republic of Germany

herewith certifies that the manufacture of Azelastine Hydrochloride in

Werk Künsebeck
Kantstraße 2
D-33790 Halle-Künsebeck

is carried out according to the current laws and regulations of the Federal Republic of Germany for the purposes of environmental protection.

The construction and the operation of plants for the manufacture of pharmaceutical products is principally subject to approval according to § 4 of the Bundesimmissionsschutzgesetz (BImSchG) (Federal Law of Immissions). This requirement is based on the regulations concerning plants subject to approval (4th BImSchV = Regulations of the Federal Law of Immissions), which are given in the enclosures under subparagraph

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Ein Unternehmen der Degussa

4.1: Plants for the manufacture of products by chemical conversion ...

and under subparagraph

4.3: Plants for the manufacture of medicinal products or medicinal product intermediates ...

Approval for these plants is to be obtained by submitting a detailed written application to the relevant authorizing body. Only after thorough inspection is a notice of approval conferred by the authorizing body (for ASTA Medica AG, plant Künsebeck, Staatliches Umweltamt Bielefeld) (Federal Environmental Office Bielefeld). This notice may only be conferred if the relevant permit requirements have been satisfied according to § 6 BImSchG (see enclosure).

It is therefore essential to guarantee the fulfillment of the obligations in § 5 BImSchG which are incumbent on the operator of plants subject to approval. In addition, the construction and operation of the plants should not contravene further regulations under public law and the interests of industrial safety.

In accordance with § 5 BImSchG plants subject to approval are to be constructed and operated in such a manner that

1. harmful environmental effects and other hazards, considerable disturbance and considerable inconvenience to the community and vicinity cannot be evoked,

2. provisions are made against harmful environmental effects, in particular through the use of state-of-the-art measures for the limitation of emissions,

3. residues are avoided where possible, or are processed and rendered harmless according to regulations, or, where avoidance and processing is not technically feasible or is unreasonable, they are removed as waste without harm to the well-being of the community, and

4. any resulting heat is used in the operator's plant or transferred to a third party that has declared itself as willing to accept, provided that the process involved is technically possible and acceptable, and that it is compatible with the obligations according to subparagraphs 1 to 3.

However, where plants not subject to approval the respect to the BImSchG, approvals according to other laws may be binding (e.g. according to building regulations, according to industrial code and others). Moreover, § 22 and § 23 of the BImSchG lay down the obligations for the operator and also the requirements for the construction and the operation of such plants (see enclosure). Accordingly, such plants are to be constructed and operated so that

1. harmful environmental effects are prevented through the use of state-of-the-art technology,

ASTA MEDICA
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2. unavoidable harmful effects on the environmentall are minimized through the use of state-of-the-art technology, and

3. waste arising from the operation of the plants can be removed according to regulations.

We will enforce strict measures, in cooperation with the authorities responsible, in order to ensure compliance with the legal rulings described herein. Intentional violation of these regulations consitutes a legal irregularity which is punishable by fines.

Additionally, we draw attention to the fact that we are subject to the constant supervision of the civil Industrial Inspection Board.

Yours faithfully

ASTA Medica Aktiengesellschaft

ppa. Letmathe

i.V. Dr. Groeger

Enclosures

The accuracy of the given details is hereby confirmed.

Bielefeld, 17.05.1995

Staatliches Umweltamt Bielefeld

Staatliches Umweltamt Bielefeld 2

Mit freundlichen Grüßen
Im Auftrag

(Dr. de Groot) (Schapitz)

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Plants Subject to Approval

§ 4
Approval

(1) The construction and the operation of plants which, due to their nature or their function on certain scales, evoke harmful environmental effects or, by other means, endanger the community or the vicinity, or considerably inconvenience or disturb, require an approval. Plants which do not serve industrial purposes and have no utilization within the scope of commercial enterprises only require the approval when they are capable, at certain scales, to evoke harmful environmental effects through impurities in the air or noise. The Federal Government designates, after hearings with the groups concerned (§ 51), by statutory order, with affirmation of the Bundesrat (Upper House of Parliament), the plants which require an approval (plants subject to approval).

(2) Plants for mining or parts of these plants only require the approval according to paragraph 1 when they are constructed and operated above ground. No approval according to paragraph 1 is required for opencast mines nor for plants required for the operation or for the ventilation of opencast mines.

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Plants Subject to Approval

§ 5
Obligations of the Operator
of Plants Subject to Approval

(1) Plants subject to approval are to be constructed and operated in a such a manner that

1. harmful environmental effects and other hazards, considerable disturbance and considerable inconvenience to the community and the vicinity can not be evoked,
2. provisions are made against harmful environmental effects, in particular throught the use of state-of-the-art measures for the limitation of emissions,
3. residues are avoided where possible, or are processed and rendered harmless according to regulations, or, where avoidance and processing is not technically possible or is unreasonable, they are removed as waste without harm to the well-being of the community, and
4. any resulting heat is used in the operator's plant or transferred to a third party that has declared itself as willing to accept, provided that the process involved is technically possible and acceptable, and that it is compatible with the obligations according to subparagraphs 1 to 3.

(2) The Federal Government designates, after hearings with the groups concerned (§ 51), by statutory order with affirmation of the Bundesrat (Upper House of Parliament), the plants where effective heat can evolve in non-insignificant quantities and which have to be constructed and operated corresponding to the requirements, given in the statutory regulations, according to paragraph 1 No. 4.

(3) The operator has also to ensure after the shut down of operations that

1. from the plant or the plant site no harmful environmental effects and other hazards, considerable disturbances and considerable inconveniences to the community and the vicinity can be evoked, and
2. residues are processed and rendered harmless according to regulations, or are removed as waste without harm to the well-being of the community.

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Plants Subject to Approval

§ 6

Approval Requirements

The approval is to be conferred when

1. it has been guaranteed that the obligations in § 5 and those in a statutory regulation issued on the basis of § 7 are satisfied, and

2. the construction and operation of the plants should not contravene further regulations under public law and the interests of industrial safety.

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Plants Not Subject to Approval

§ 22
Obligations of the Operator
of Plants Not Subject to Approval

(1) Plants not subject to aporoval are to be constructed and operated in a such a manner that

1. harmful environmental effects are prevented through the use of state-of-the-art technology,

2. unavoidable harmful effects on the environment are minimized through the use of state-of-the-art technology, and

3. waste arising from the operation of the plants can be removed according to regulations.

For plants which do not serve industrial purposes and have no utilization within the scope of commercial enterprises the obligation in clause 1 is only applicable when it is concerned with the reduction or limitation of harmful environmental effects from impurities in the air or noise.

(2) Further-reaching regulations under public law remain effective.

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Plants Not Subject to Approval

§ 22
Requirements for the Construction, the Condition and the Operation of Plants Not Subject to Approval

(1) The Federal Government is empowered, after hearings with the groups concerned (§ 51), by statutory order, with affirmation of the Bundesrat (Upper House of Parliament), to order that the construction, the condition and the operation of plants not subject to approval must fulfill certain requirements for the protection of the community and the vicinity against harmful environmental effects and also for the provision against harmful environmental effects, in particular that

1. the plants comply with certain technical requirements,

2. the emissions from plants do not exceed certain limits,

3. the operators of plants have to carry out measurements of emissions and imissions according to the procedures given in the statutory regulation or have them carried out by an agency named in the statutory regulation.

For the requirements in clause 1, Nos. 1 to 3, cf. § 7 paragraph 3.

(2) Where the Federal Government makes no use of the empowerment, the governments of the Länder are empowered by statutory regulation to issue regulations according to paragraph 1. The regional governments may delegate the empowerment to one or more principal authorities of the Länder.

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4.1

Plants for the manufacture of products by chemical conversion, in particular

a) for the manufacture of inorganic chemicals such as acids, alkalies, salts,

b) for the manufacture of metals or non-metals by wet-process or by the use of electrical power,

c) for the manufacture of corundum or carbide,

d) for the manufacture of halogens or halogen products, or of sulphur or sulphur products,

e) for the manufacture of phosphorus or nitrogenous fertilizers,

f) for the manufacture of pressurized liquid acetylene (dissolved acetylene cylinder gas plants),

g) for the manufacture of organic chemicals or solvents such as alcohols, aldehydes, ketones, acids, esters, acetates, ethers,

(the remainder of this subparagraph is not applicable and has therefore not been translated)

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4.2

Plants for the manufacture of medicinal products or medicinal-product intermediates, where

a) plants, parts of plants or plant components are extracted, distilled or treated in a similar way, excluding extraction plants with ethanol without heating,

b) animal bodies, including living animals, and also parts of the body, body components and metabolic products of animals are used,

c) microorganisms and also their components or metabolic products are used,

(the remainder of this subparagraph is not applicable and has therefore not been translated)

Degussa

Degussa
Corporation

MATERIAL SAFETY DATA SHEET

Essentially similar to OSHA Form 20

Degussa Emergency #: (205) 653-0
CHEMTREC Emergency #: (800) 424-9

SECTION I - MANUFACTURER'S NAME / ADDRESS

Degussa AG, ASTA Pharma AG, Weismüllerstraße 45, D-6000 Frankfurt, West Germany

Chemical Name: AZELASTINE HYDROCHLORIDE — CAS #: 37932-96-0

Trade Name & Synonyms: Azelastine-Hydrochloride — Synonyms:

Chemical Family: Phthalazinone-Derivative — Formula: $C_{22}H_{24}ClN_3O$

SECTION II - HAZARDOUS INGREDIENTS

Name	CAS #	%	TLV (Units)	Name	CAS #	%	TL (Ur

SECTION III - PHYSICAL DATA

Boiling Point (°C)	NA	Specific Gravity (H_2O = 1)	NA
Vapor Pressure (mmHg.)	NA	Percent Volatile by Volume (%) Not combustible	NA
Vapor Density (AIR = 1)	NA	Evaporation Rate (Butyl Acetate = 1)	NA
Solubility in Water	slightly soluble	Decomposition Temperature (°C) m.p.	225-22

Appearance and Odor:

Colorless, crystalline powder, almost odorless.

NOTICE: The data contained herein is based on information that Degussa believes to be reliable, but no expressed or implied warranty with regard to the accuracy or such data or its suitability for a given situation. Such data relates only to the specific product c and not to such product in combination with any other product and no agent of Degussa is authorized to vary any of such data. Corporation and its agents disclaim all liability for any actions taken or foregone on reliance upon such data.

SECTION IV - FIRE AND EXPLOSION HAZARD DATA

Flash Point (Closed Cup):	Flammable Limits	Lel	Uel
NA	NA	—	—

Extinguishing Media:
Water, CO_2 Standard Chemical, foam, water mist

Special Fire Fighting Procedures
Azelastine might become electrostatically loaded.

Unusual Fire & Explosion Hazards:
NA

SECTION V - HEALTH HAZARD DATA

Threshold Limit Value:	PEL (OSHA)	LD 50 Mouse	LC 50
N/A		male 124 mg/kg female 139 mg/kg	
Effects of Overexposure (Acute & Chronic):		Rat:	
N/A		male 310 mg/kg female 411 mg/kg	

Emergency First Aid Procedures

Eyes: Wash with plenty of water.

Skin: Wash with plenty of water.

Respiratory: Prevent breathing of azelastine by application of a suitable dust protection mask (filter P2).

Ingestion: After oral ingestion of toxic doses, remove th drug by gastric lavage or induce vomiting in case re-absorption has yet taken place. Only gastric lavage with intubation, afterwards according to symptoms.

Clothing: Change contaminated clothes and wash with plenty of water.

SECTION VI - REACTIVITY DATA

Stability	Unstable		Conditions to Avoid:
	Stable	X	

Incompatability (Materials to Avoid):
N/A

Hazard Decomposition Products:
N/A

Hazardous Polymerization	May Occur		Conditions to Avoid:
	Will Not Occur	X	

SECTION VII - SPILL OR LEAK PROCEDURES

Steps to be Taken in Case Material is Released or Spilled:
Collect substance to avoid dust formation.

Waste Disposal Method (Including Neutralization):
Disposal via local disposal station (combustion).

SECTION VIII - SPECIAL PROTECTION INFORMATION

Respiratory Protection (Specify Type):
Dust mask

Ventilation	Local Exhaust Recommended	Special
	Mechanical (General)	Other

Protective Gloves: As needed	Eye Protection: Goggles

Other Protective Equipment:

SECTION IX - SPECIAL PRECAUTIONS

Precautions to be Taken in Handling & Storage:
Store dry and protect from heat and light.

Other Precautions:

SECTION X - SHIPPING INFORMATION

Primary Hazard: | Secondary Hazard:

Proper DOT Shipping Name:
Not regulated for transportation purposes

Hazard Class | 49 CFR Section Reference

Hazardous Substance? | Reportable Quantity

Label(s)	Placard(s)	UN Number:
		UN Class:
		STCC Number: 2899991
		NMFC Item: 60000/439
		UFC Item: 33800/2331
		Shipping Restrictions:

Container/Packaging Data
Authorized Container Type(s):

SECTION XI - EMERGENCY RESPONSE

Evacuation:
NA

Containment - Immediate & Follow-up:
NA

EMERGENCY RESPONSE CONTACT(S): | Phone #:
Degussa Corporation | (205) 653-0632

SECTION XII - PRODUCT INFORMATION CONTACTS

	Contact(s)	Address	Business Phone: 069-4001-27
Degussa AG	ASTA Pharma AG	Weismüllerstraße 45 D-6000 Frankfurt West Germany	Business Phone:
Degussa Corporation	Contact(s) Tech. & Bus. Dev.	Address Rt. 46 @ Hollister Rd. Teterboro, N.J. 07608 U.S.A.	Business Phone: (201)

Date: 1/86

Prepared By: PSCC
Product Safety Compliance Committ
Degussa Corporation

D-144

AZELASTINE

MATERIAL SAFETY SHEET - Effects of Overexposure

No overdosage experience in human subjects. Azelastine has histamine (H_1) receptor blocking property and antagonist activity also against serotonin, acetylcholine, SRS-A and bradykinin; the biologic half-life with therapeutic dosage was approximately 16 hours.

Overdosage manifestations in human subjects could be expected to vary from CNS depression (sedation, apnea, cardiovascular collapse) to stimulation (insomnia, hallucinations, convulsions). Stimulation is more likely to occur in children. Gastrointestinal symptoms, dizziness, ataxia, blurred vision, hypotension, and atropine-like effects (dry mouth, fixed dilated pupils, flushing, hyperthermia) may occur.

Treatment is symptomatic and supportive. Stimulants (analeptics) should not be used. Vasopressors may be used to treat hypotension, and short-acting barbiturates or diazepam to control seizures. -- The mean oral LD_{50} was 124 mg/kg in mice, 310 mg/kg in rats and 40 mg/kg in dogs.

NDA 20114

JUN 17 1997

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA:	20-114	**DATE REVIEWED:**	June 16, 1997
REVIEW #:	9	**RECOMMEND ACTION:**	See p. 4
REVIEWER:	Linda Ng, Ph.D.		

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	March 26, 1991	March 27, 1991	June 3, 1991
AMENDMENT	December 18, 1992	December 22, 1995	December 23, 1995
AMENDMENT	May 7, 1993	May 10, 1993	May 10, 1993
AMENDMENT	August 6, 1993	August 11, 1993	August 11, 1993
AMENDMENT N(BZ)	June 30, 1995	July 3, 1995	July 10, 1995
AMENDMENT N(BC)	August 31, 1995	September 6, 1995	
AMENDMENT N(BC)	September 22, 1995	September 25, 1995	
AMENDMENT N(AZ)	May 13, 1996	May 14, 1996	
AMENDMENT N(BC)	June 7, 1996	June 10, 1996	
AMENDMENT N(AZ)	July 10, 1996	July 12, 1996	
AMENDMENT N(BC)	August 20, 1996	August 21, 1966	
AMENDMENT N(BC)	September 18,1996	September 18, 1996	
AMENDMENT N(BC)	September 30, 1996	October 4, 1996	
AMENDMENT N(BC)	October 9, 1996	October 10, 1996	
Subject of this review:			
Phase 4 Commitments	December 13, 1996	December 16, 1996	December 23, 1996
Phase 4 Commitments	December 20, 1996	December 23, 1996	January 2, 1997

NAME & ADDRESS OF APPLICANT:
Wallace Laboratories
Div. of Carter-Wallace, Inc.
Cranbury, New Jersey 08512

DRUG PRODUCT NAME

Proprietary:	ASTELIN® Nasal Spray, 137 mcg
Nonproprietary/Established/USAN:	azelastine hydrochloride
Code Name/#:	W-2979M, A-5610, E-0659
Chem.Type/Ther.Class:	1C

PHARMACOLOGICAL CATEGORY/INDICATION: Allergic rhinitis

DOSAGE FORM: Nasal Spray solution

STRENGTHS: 0.1 % (w/v); 0.137 mL = 0.137 mg azelastine hydrochloride per actuation.

ROUTE OF ADMINISTRATION: Nasal; 2 actuations per nostril twice per day

DISPENSED: X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(±)-1-(2H)-Phthalazinone,4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride

NDA 20-114

CONCLUSIONS & RECOMMENDATIONS:

The applicant has responded to the phase IV commitments outlined in the approval letter. Outstanding issues can only be resolved with the the receipt of acceptable methods verification from the FDA laboratories and completion of studies by the applicant. The comments in the draft of the chemist's part of letter should be forwarded to the applicant.

Linda Ng, Ph.D.
Review Chemist, HFD-570

cc: Org. NDA 20-114 & Division File.
HFD-570/LNg/6-16-97
HFD-570/GPoochikian
HFD-570/CSO GStrange

File: 20114I.REV
R/D by: 6/17/97

ORIGINAL

WALLACE LABORATORIES
DIVISION OF CARTER-WALLACE, INC.
Cranbury New Jersey 08512

ANA M. FONTANA
VICE PRESIDENT
DRUG REGULATORY AFFAIRS

609-655-6880
FAX: 609-655-6564

December 20, 1996

Re: NDA 20-114

John K. Jenkins, MD, Director
Division of Pulmonary Drug Products
FDA-CDER
HFD-570; Room 10B03
5600 Fishers Lane
Rockville, Maryland 20857

Astelin® (azelastine hydrochloride) Nasal Spray

"PHASE 4 COMMITMENTS"

RECD
DEC 2 3 1996
HFD-570
EVALUATION AND RESEARCH

Dear Dr. Jenkins:

References are made to our approved New Drug Application for Astelin® (azelastine hydrochloride) Nasal Spray, NDA 20-114, and to our Phase 4 chemistry commitment contained in item 2 of the November 1, 1996 approved letter which follows.

This submission is a progress report providing the status of our investigative efforts to explore the cause of particulate matter increase during storage in an attempt to eventually reduce particulate matter and improve product quality.

SUMMARY

Based on our joint investigative efforts, Wallace and [redacted] agree

CONTENTS OF SUBMISSION

This submission includes the following information:

We will continue to explore the possibility of and another progress report will be submitted upon completion of the six month evaluation of particulates, approximately July 1997.

If you have any comments, please do not hesitate to contact me at 609-655-6880.

Sincerely,

Ana M. Fontana
Vice President
Drug Regulatory Affairs

crs/ar/s:jenkins.d21
cc: Dr. Linda Ng (with attachment)
Dr. Guiragos Poochikian (letter only)
Ms. Gretchen Trout (letter only)

Food and Drug Administration
Rockville MD 20857
NOV - 7
DR. GEORGE R. HEMSWORTH
NOV - 1 1996

NDA 20-114

Wallace Laboratories
Division of Carter-Wallace, Inc.
Half Acre Road
Box 1001
Cranbury, New Jersey 08512-0181

Attention: George R. Hemsworth, Ph.D.
Director, Regulatory Affairs

Dear Dr. Hemsworth:

Please refer to your March 26, 1991, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Astelin (azelastine hydrochloride) Nasal Spray.

We acknowledge receipt of your amendments dated June 25, October 25, and December 19, 1991, February 28, April 22, May 4, June 10, July 5, September 28, October 23, November 2 and 20, and December 18 and 21, 1992, January 7, February 19 and 24, May 7, August 6 and 18, and September 9, 1993, April 6, June 29, and October 28, 1994, June 30, July 7, August 31, September 22 and 29, 1995, and May 13 and 22, June 7, July 10 and 19, August 20, September 18, 27, and 30, and October 9 and 31, 1996.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for the treatment of the symptoms of seasonal allergic rhinitis, such as rhinorrhea, sneezing, and nasal pruritus, in adults and children 12 years and older, as recommended in the draft labeling submitted on October 31, 1996. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the October 31, 1996, draft physician labeling and the September 27, 1996, final printed carton and container labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 16 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this

submission should be designated "FPL for approved NDA 20-114." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you of your Phase 4 commitments specified in your submission dated October 9, 1996. These commitments, and their associated schedules for completion, are listed below.

Protocols, data, and final reports related to the Phase 4 commitments should be submitted to this NDA as correspondence. For administrative purposes, all submissions, including supplements, relating to these Phase 4 commitments must be clearly labeled "Phase 4 Commitments." In addition, we request that each annual report to this NDA include a section that summarizes the status of each Phase 4 commitment, identifying each submission and its related commitment. If you feel the situation has changed and the data the Phase 4 study was designed to provide are no longer necessary, fully explain why you believe you should be released from the commitment. All annual reports to this NDA should include an update on Phase 4 studies until you are notified that we consider all commitments to be satisfactorily fulfilled or canceled.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Gretchen Strange
Project Manager
(301) 827-1058

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research