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RESEARCH**

APPLICATION NUMBER:

20-120

MEDICAL REVIEW

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MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #: IND NDA 20,120

APPLICATION TYPE: Labeling amendment

SPONSOR: Muro Pharm

PRODUCT/PROPRIETARY NAME: Tri-Nasal

USAN Established Name: Triamcinolone acetonide

CATEGORY OF DRUG: Corticosteroid

ROUTE OF ADMINISTRATION: Intranasal spray

MEDICAL REVIEWER: Nicklas

REVIEW DATE: 17 December 1999

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
22 July 1999	22 July 1999	Supplement	see overview below

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
None	None	None

Overview of Application/Review: The proposed labeling for Tri-Nasal was reviewed. The labeling appears acceptable (with the exception of the section dealing with growth velocity) and consistent with the labeling for Nasacort AQ. The sponsor has also incorporated the recommendations made by the original review team. In regard to growth velocity, the same changes in the labeling as were requested for the sponsor of Nasacort AQ should be required of the sponsor for Tri-Nasal, i.e. that a statement about growth velocity should be included in the first paragraph under General Precautions and that the Pediatric Use section under Precautions be revised consistent with the class labeling statement on growth and inhaled corticosteroid use. Specifically, the following sentence should be included in the first paragraph following the "General" subsection heading, "_____ corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS, Pediatric Use section)". In addition, the Pediatric Use subsection under the PRECAUTIONS section should contain the following paragraph, "Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including _____ should be monitored routinely (e.g. via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including _____ each patient should be titrated to the lowest dose that effectively controls his/her symptoms."

Recommended Regulatory Action: The labeling is acceptable with the changes noted above.

N drive location: n:\trinasal2

NDAs:

Efficiency / Label Supp.: _____ Approvable with changes _____ Not Approvable

Signed: Medical Reviewer: */S/* *LD*

Date: 12/17/99

Medical Team Leader: */S/*

Date: 1/24/00

cc: Orig NDA 20-120
HFD-570/Div File
HFD-570/Nicklas, Barnes, Hifiker

MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #: NDA 20,120

APPLICATION TYPE: Supplement

SPONSOR: Muro

PRODUCT/PROPRIETARY NAME: Tri-Nasal

USAN Established Name: Triamcinolone
acetonide

CATEGORY OF DRUG: Corticosteroid

ROUTE OF ADMINISTRATION: Nasal solution

MEDICAL REVIEWER: Nicklas

REVIEW DATE: 9 November 1999

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
22 July 1999	22 July 1999	Supplement	see overview below

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
None	None	None

Overview of Application/Review: The sponsor has submitted a proposed modification of the original formulation for this drug product, _____

_____ Chemistry requested clinical input in regard to whether clinical studies were needed with this new formulation. Historically, reformulation of _____ was associated with increased reporting of AEs-related to bronchospasm or irritation of the lower respiratory tract. This precedent raises questions about nasal irritation and even mucosal changes related to _____

Clinical studies with the new formulation are not needed because: 1) nasal irritation would most likely be a function of the pH of the formulation which has not changed; 2) a clinical study would not detect the type of mucosal changes, e.g. metaplasia, that are of greatest concern; 3) the formulation and particle size are such that this drug product would not be expected to produce an adverse effect in the lower respiratory tract; and 4) a review of the literature failed to find any reports of adverse events from inhalation of citric acid in either the upper or lower respiratory tract.

Outstanding Issues: none

Recommended Regulatory Action: formulation change does not require any clinical studies

N drive location: n:\trinasal

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: Approvable _____ Not Approvable

Signed: Medical Reviewer:

/S/ /S/

Date: 11/10/99

Medical Team Leader

Date: 11/10/99

BARNES

AUG 21 1996

Medical Officer Review

NDA 20120

Medical Officer Review #1

Medical Officer Reviewer: Ana M. Saavedra-Delgado, M.D.

Date of original Review: June 28, 1996

GL comments incorporated: July 25, 1996

IS/ 7/25/96 U
see supervisor's memo
IS/ 8/21/96

1. General Information

Drug: Triamcinolone acetonide nasal solution, 0.05%

Sponsor: Muro Pharmaceutical, Inc.

Proposed trade name: Tri-nasal spray

Chemical name: 9-Fluoro-11 β , 16 α , 17, 21-tetrahydroxy pregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with acetone

Pharmacologic category: glucocorticosteroid

Proposed Indication: nasal treatment of seasonal and perennial allergic rhinitis symptoms

Dosage form: solution

NDA Drug Classification: 5S

Important Related drugs: NDA 19,798: Nasacort Nasal Aerosol
NDA 18,117: Azmacort
Tri-nasal is a new dosage form of the approved drug Nasacort, whose application references the approved drug Azmacort.

Related reviews: The statistical, biopharm, chemistry and pharmacology reviews have not been completed to date.

**APPEARS THIS WAY
ON ORIGINAL**

2. Table of Contents

1.	General Information	1
2.	Table of contents	2
3.	Material Reviewed	3
4.	Chemistry/Manufacturing Controls	4
5.	Animal Pharmacology/Toxicology	4
6.	Human Pharmacokinetics and Bioavailability	4
7.	Biostatistics	6
8.	Clinical Background	6
9.	Description of Clinical Data Sources	7
10.	Clinical Studies	
	a. 100-309	8
	b. 100-204	40
	c. 0501	78
	d. 100-305	94
	e. 1-0501	123
	f. Other Studies	140
11.	Overview of Efficacy	146
12.	Integrated Safety Summary	152
13.	Labeling review	186
14.	Recommended Regulatory Action	190
15.	Recommendations to Sponsor	190
16.	Appendices	195

3. Material Reviewed

Re-submission of NDA 20,120 dated October 31, 1995 consisting of 155 volumes

N(BZ)- 2/12/96 Response to FDA requests for indices of tables in the NDA, case report forms for Study 100-204

N(AZ)-2/15/96 Final report for Study 100-309, consisting of 36 volumes

C-3/6/96 Response to FDA requests regarding studies 100-204, 100-305 and 100-309 from the 2/23/96 teleconference

N(SU)-3/7/96 Update of tables for the Integrated Safety Update from study 100-309.

N(BZ)-4/1/96 Revised report for Study 100-204, consisting of 14 volumes; pages 1-3 from volume 1 and Tables 10A-D were reviewed.

C- 4/18/96 Response to FDA requests regarding study 100-309 from the 4/12/96 teleconference

N(BZ) 4/24/96 Revised evaluable for efficacy subset for study 100-309 consisting of 2 volumes, cover letter and page 01 0000 of volume 1 were reviewed.

N(EM) 5/7/96 Response to FDA requests from the May 2, 1996 teleconference

N(EM) 6/4/96 Response to FDA requests from the May 21, 1996 teleconference

Telephone facsimile dated 6/17/96- Response to questions 1, 2, 3, 4, 7, and 8 of the 6/4/96 teleconference.

Telephone facsimile dated 6/25/96- Response to the laboratory analyses requested in the 6/4/96 teleconference.

N(AK) 7/1/96- Response to the 6/6/96 and 6/10/96 teleconferences' requests and the previously faxed responses to the 6/4/96 requests.

Telephone facsimile dated 7/18/96 - Response to the questions from the teleconference dated 7/16/96.

Telephone facsimiles dated 7/23/96 and 7/24/96- Response to the questions from the teleconference dated 7/22/96.

4. Chemistry/Manufacturing Controls

The chemistry review has not been completed to date. The formulation that was used in the clinical studies 100-309, 100-204, 100-305, 0501, 100-307 and 1-0501 was the same as the to be marketed formulation, 39-050-2. The intended $\mu\text{g}/\text{volume}$ to be delivered by actuation for the 200 and 400 μg doses was 50 $\mu\text{g}/\text{spray}$. Except for Study 100-305, the other studies adjusted the dosing by varying the number of actuations used. In Study 100-305, for the 200 μg dose the actuation was $\text{---} \mu\text{g}/\text{spray}$. In studies 100-305 and 100-204 for the 50 μg dose the actuation was $\text{---} \mu\text{g}/\text{spray}$.

According to the sponsor's table in page 053 in volume 4.1, the to be marketed unit pump, --- with a --- nasal actuator is not the same pump that was used in any of the clinical studies. The average pump delivery for this pump is listed as 56 mg/mL. This dose would be higher than the average pump delivery with the pump used in the clinical studies 100-309, 100-204, 100-305 and 100-307, as well as the Biopharm studies 100-105 and 100-106. For these clinical studies a --- pump was used with an average pump delivery of 51 mg/mL. Study 1-0501 used a different --- pump with an average pump delivery of 58 mg/mL. A --- pump was used for study 0501 but it had a different actuator and has an average pump delivery of 59 mg/mL. Chemistry is aware of these issues and is in communication with the sponsor. The characteristics of the to be marketed pump need to be supported by comparative data from the unit pumps used in the pivotal clinical studies.

5. Animal Pharmacology/Toxicology

The pharmacology review has been completed (7/16/96). This NDA is considered to be a 505 (b) (2) submission. FDA has agreed that Muro does not need to conduct carcinogenicity or toxicology studies prior to marketing (pre-NDA conference dated 3/9/95).

6. Human Pharmacokinetics and Bioavailability

The biopharm review has been completed (7/15/96). In it, the submission was found to be acceptable provided there is adequate safety and efficacy data on this product to make this a stand alone application, since systemic exposure of TAA following Tri-nasal administration is higher than the reference product Nasacort. The bioavailability of TAA from Trinasal was found to be at least 5 times greater than Nasacort. In the topical vs systemic effects study, higher plasma concentrations were achieved after administration of Tri-nasal on each day, compared to Kenalog. The selected doses for the topical vs. systemic effect study were not found to be satisfactory and therefore the topical effect claim was not found to be substantiated.

Nasacort 440 μg is an approved intranasal suspension of TAA

indicated for the nasal treatment of seasonal and perennial allergic rhinitis symptoms. The labeling for Nasacort 440 μg also references safety data from the approved drug Azmacort. Azmacort is indicated for the control of symptoms of bronchial asthma and the recommended doses in adults are 200 μg three to four times per day, not to exceed 1600 μg .

The following information was obtained from Dr. C. Kwong's MOR for Nasacort Nasal Inhaler Pediatric Supplement (N19798).

TAA Product	Study #	Age	Dose ($\mu\text{g}/\text{day}$)	Cmax (ng/ml)	AUC _{0-∞} (ng·hr/mL)	Relative systemic bioavailability (among adults)
Nasacort CFC	Study 101	18-50	220	0.07	0.65 (projected)	1
			440	0.14	1.31	2
Azmacort CFC	Study 119	19-50	600	0.95	6.07	9.3
			800	1.36	9.49	14.6

The following table show the mean PK parameters for TAA obtained after intranasal dosing with Tri-nasal or Nasacort - Study 100-105. From Table 2, page 087 in volume 4.1

	Tri-nasal 400 μg Mean (SD)	Nasacort 440 μg Mean (SD)
C max (ng/mL)	1.12 (0.38)	0.14 (0.13)
T max (h)	0.47 (0.26)	2.28 (0.68)
AUC _{0-∞} (ng·h/mL)	3.31 (1.59)	0.63 (0.95)

The expected exposure to TAA from the intranasal administration of Tri-nasal 400 μg would be higher than the exposure to the intranasal administration of Nasacort 440 μg but within the exposure to Azmacort CFC at the recommended doses.

TAA is primarily metabolized by hepatic oxidative pathways resulting in three major metabolites. These metabolites are 6 β -hydroxytriamcinolone acetonide, 21-carboxy-triamcinolone and 21-carboxy-6 β -hydroxytriamcinolone acetonide. Because of increased water solubility, these metabolites are eliminated more rapidly than TAA, and they are also substantially less active. Since the major route of elimination is hepatic metabolism, TAA is only

minimally excreted by the kidneys. Page 058, vol 4.1.

7. Biostatistics

Although the completed statistical review is not available at the date of this review, Dr. Ted Guo's draft review concludes that adequate statistical methods were used in the intent-to-treat analyses of the studies that support efficacy, including those with baseline differences between active drug and placebo.

Dr. Ted Guo's Addendum to the Statistical Review and Evaluation dated July 22, 1996 is included in this review as Appendix 3. In this review Dr. Guo answers a list of specific questions that were asked on 7/15/96 by the medical reviewer.

8. Clinical Background

Triamcinolone acetonide (TAA) is a long acting corticosteroid that is approximately eight times more potent than prednisone and one to two times as potent as prednisone in animal models of inflammation (Nasacort labeling). It has been marketed in the USA for systemic intramuscular administration, for intra-articular injection, topical application to the skin, as a meter dose inhaler for the treatment of asthma, and a topical nasal aerosol. Topical nasal glucocorticoids are indicated to reduce the inflammation and relieve the symptoms of allergic rhinitis. The intranasal aerosol suspension, Nasacort, was approved in 1991 and the intranasal aerosol AQ suspension, Nasacort AQ, was approved in 1996.

NDA 20120, re-submitted in October 31, 1995, is the application in support of Tri-nasal Spray (triamcinolone acetonide nasal solution, 0.05%). Tri-nasal is a non-CFC nasal spray intended for the treatments of seasonal and perennial allergic rhinitis in doses of \sim to 400 μ g per day.

The original submission dated January 17, 1992 received a non-approval letter. The major clinical deficiencies were: lack of long term safety data on Trinasal patients (At least 300 patients with safety data up to 6 months will be needed); lack of an acceptable clinical topical effect study at the appropriate oral dose (the design and dosing should be discussed with the division); inadequate efficacy analysis; i.e., lack of an appropriate placebo symptomatic day analysis and lack of therapeutic dose response study.

Tri-nasal has no foreign marketing history and no foreign applications are pending.

There are different dosage forms of TAA and of its different salts in the U.S. and in the foreign market. To the best of Muro's knowledge no TAA nasal product has been withdrawn from the market related to safety or efficacy, page 043, vol 4.1,

10/31/96.

9. Clinical Data Sources

The results from a total of 14 clinical U.S. studies were submitted for review in this NDA, to support the efficacy and safety of Tri-nasal Spray, for the nasal treatment of seasonal and perennial allergic rhinitis symptoms.

The sponsor considered the following three studies pivotal for the demonstration of efficacy and safety: 100-309 (SAR -2 weeks), 100-204 (SAR- 4 weeks) and 100-305 (SAR-4 weeks).

The results from three studies that were submitted in the original application(1/17/92) were also submitted in this application. These studies were 1-0501-adrenal suppression study, 3-0501- once a day dose study in perennial allergic rhinitis and 0501 -seasonal allergic rhinitis.

In this application, the sponsor seeks to demonstrate that Tri-nasal used as recommended, has a lack of adverse effect in the HPA axis function (Study 1-501), compares in terms of efficacy to other currently marketed comparators in the treatment of allergic rhinitis (100-309, 100-204, 38-050 and 0485), has a topical rather than a systemic mode of action (100-204), and is safe in long-term use (3-0501 and 100-307).

No foreign studies are included in this application.

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10.a. Study 100-309

Title: An evaluation of the safety and efficacy of Tri-nasal (Nasal Triamcinolone Acetonide) 200 μ g and 400 μ g qd versus placebo and Nasacort 440 μ g qd in patients suffering from seasonal allergic rhinitis during the grass season.

Objective: To compare the efficacy and safety of Tri-nasal nasal spray at doses of 400 μ g qd and 200 μ g qd for two weeks of treatment of SAR due to grass pollen sensitivity in adults 18 to 65 years of age.

Study Protocol: Submission dated February 15, 1996, Vol 6.2, Appendix A Protocol.

Design

This is a double-blind, parallel trial that will compare the safety and efficacy of Tri-nasal, nasal triamcinolone acetonide (TAA) solution, 200 μ g and 400 μ g daily versus Tri-nasal placebo and Nasacort (Nasacort will not be blinded), TAA-aerosol suspension 440 μ g daily, during a two week period in seasonal allergic rhinitis patients 18-65 years of age.

Approximately 416 patients in thirteen sites are expected to participate in the study. Patients will be randomized to treatment within a 5 day window after a 7 day baseline period. Patients will evaluate treatment keeping a daily diary of symptom severity. Physicians will evaluate the treatment at weekly clinic visits.

Population

Approximately 416 patients at thirteen study sites will be enrolled in the study.

Inclusion criteria

18-65 years of age, male and female

Patients must meet criteria for diagnosis of seasonal allergic rhinitis to grass pollen: have positive skin test to grass, hx of at least moderate SAR symptoms to grass pollen for a minimum of 2 yrs prior to the study season. If there is concomitant hx of PAR, these symptoms have to be mild and would not be expected to contribute to a significant change in the patients symptoms during the study. Prior to randomization to treatment these patients must have a total score of 6/12 for the three symptoms of rhinorrhea, nasal congestion and sneezing on at least 4 of 7 days of baseline.

Exclusion criteria

Disease or condition that may interfere with the evaluation of safety or efficacy (pregnancy, infection, active TB, nasal obstruction, asthma, DM requiring drug therapy, hypertension >140/90, malignancy, clinically significant abnormal labs, etc.) and use of restricted concomitant medication as presented in section 3.4 of the protocol.

Study Plan

Visit 1 (screening): obtain medical history, physical exam, allergy skin testing, clinical labs, and a serum pregnancy test for females; patients will be given a diary to evaluate symptom severity.

The start of the baseline period will be timed to coincide as closely as possible with the start of significant grass pollen count defined as greater than 20 grains per cubic meter. Rain and grass pollen counts will be documented daily by each study site, the method used will be documented.

Patients will record the overall symptom severity (on average for the past 24 hrs) of each allergy symptom: nasal congestion, rhinorrhea (runny nose/post nasal drip), sneezing, itchy nose/throat/palate and itchy red watery eyes, at approximately 07:00 AM during the baseline period, or just prior to dosing, during the treatment phase.

In addition, patients will record in the diary: any and all medical events, concomitant medications and hours of outdoor air exposure.

The following scale will be used to score symptom severity:

- 0= not present
- 1= mild; present, but not annoying
- 2= moderate; present and annoying
- 3= severe; interferes with daily activities
- 4= very severe; unable to participate in daily activities

Visit 2 (Day 1, start of treatment phase): determination of eligibility for enrollment; physician's assessment of patient's symptoms; for females, obtain urine for pregnancy test; past diary review with patient present; review of adverse events (ask patient and review diary); review concomitant medications taken; weight study drug; dispense study drug (if Nasacort arm, dispense bottle #1); instruct patient in correct use of spray bottles; and dispense new diary.

All patients at a given site will be randomized and will start medication over a 5 day period.

On Visit 3 (Day 8) and on Visit 4 (Day 15) the patient will make

a global evaluation of symptom relief. The patient will compare the past treatment week to the baseline treatment week. The following scale will be used:

- 6= symptoms are markedly worse
- 5= symptoms are moderately worse
- 4= symptoms are slightly worse
- 3= symptoms are the same
- 2= symptoms are slightly better
- 1= symptoms are moderately better
- 0= symptoms are markedly better

The physician assessment will be done after the patient completes the global patient assessment. It will rate the severity of the symptoms at that visit. The symptoms to be rated are: nasal congestion, rhinorrhea (runny nose/post nasal drip), sneezing, itchy nose/throat/palate and itchy red watery eyes.

The following scale will be used:

- 0= none; symptoms not present at this assessment
- 1= mild; symptom is present but would usually not be annoying to most patients
- 2= moderate, symptoms is present and would be annoying to most patients
- 3= severe, symptom would interfere with most patients' daily activities
- 4= very severe, symptom would make most patients unable to participate in daily activities

Visit 3 (Day 8 \pm 2 days): same as in Visit 2, plus obtain patient's global evaluation and retrieve study drug, weight bottle/canister, record weight in CRF, and return bottle to the patient. For patients on the Nasacort arm, dispense bottle #2.

Visit 4 (Day 15 \pm 2 days) same as in Visit 3 except that no new medication will be dispensed. In addition, repeat physical examination and clinical labs will be done. A serum pregnancy test will be repeated on women that participated in the study.

Study medication:

Each patient randomized into the Tri-nasal group will receive two bottles of study drug. Each dose will require patients to take 2 sprays per nostril, daily, from both bottles. For patients randomized to Nasacort, each dose requires the patient to take four sprays per nostril.

Tri-nasal, Triamcinolone acetonide 0/05% Nasal Solution.

Delivery system: metered dose nasal spray pump manufactured by Each actuation delivers a 100 μ l volume containing 50 μ g of triamcinolone acetonide. For patients

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11

receiving the 400 μg dose, both bottles will contain active medication. For those patients receiving the 200 μg dose, the second bottle will contain placebo.

Nasacort. Triamcinolone acetonide in a microcrystalline suspension for nasal delivery. Delivery system: CFC-12 propellant aerosol canister manufactured by Rhone-Poulenc Rorer Inc. Each actuation releases approximately 55 μg of triamcinolone acetonide.

Placebo Nasal Solution. Delivery system: metered dose nasal spray pump manufactured by ~~_____~~. Each actuation delivers a 100 μl volume.

The patients will be given instructions on how to prime the spray bottles (pump in upright position 5 times each) and the canister (shaken well and pumped 2 times).

Rescue medication was not allowed. The protocol was later modified to allow the use of saline eye drops.

Compliance

All nasal spray bottles and canisters will be weighed prior to dispensing them to the patients and at each return clinic visit.

Early withdrawal criteria

- clinically significant abnormal laboratory value or one of uncertain clinical significance
- intolerable side effects
- patient non-compliance
- positive pregnancy test
- consent withdrawal
- investigator's judgement
- sponsor terminates study

Statistical Methods

Sample size estimation

A minimum of 92 patients per treatment arm will be needed to detect a difference of 1 in the weekly averages of the diary symptom severity index, defined as the sum of the three scores (sneezing, rhinorrhea and nasal congestion), using a two tailed t-test with 80% power, at 0.05 level of significance. This calculation was done based on previous studies, considering the pairwise comparison between the 400 μg and placebo for symptom severity index, assuming a value of 5.81 for the common population variance.

Missing values

When calculating weekly averages of daily scores, the average score will be based on the non missing observations during a given week.

Efficacy

Primary efficacy measure

Symptom severity scores based on patient diary evaluation of the severity of nasal symptoms. Efficacy evaluations will be made based on the analysis of the weekly averages of the Symptom Severity Index (SSI). Treatment group comparisons for each treatment week will be made using an ANCOVA model, adjusting for study site, with the corresponding baseline serving as the covariate in each model.

Baseline calculation: the average of the corresponding diary measurements for the seven days prior to the first dose of study medication.

Secondary efficacy variables:

-For the patient's diary evaluation of individual allergy symptoms, the weekly scores will be analyzed separately, using an ANCOVA model, adjusting for study site, with the corresponding baseline serving as the covariate in each model.

-The patient's global evaluation will be analyzed for each treatment week using an ANOVA model adjusting for study site.

-For the physician's assessment, treatment group comparisons for SSI scores and individual symptoms for each treatment week, will be made using an ANCOVA model, adjusting for study site, with the corresponding baseline serving as the covariate in each model.

Safety

Primary variables:

-Changes in physical and nasal examination from baseline to final visit. Shift in category (normal to abnormal etc.) will be compared among treatments, using the Cochran-Mantel-Haenszel test controlling for study site. For each vital sign parameter, treatment group comparisons with respect to final evaluation will be done using an ANCOVA model adjusting for study site, with baseline as a covariate.

-Changes in clinical laboratory from baseline to final visit

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13

for hematology, blood chemistry and urinalysis. Treatment group comparisons with respect to final evaluation will be done using an ANCOVA model adjusting for study site with baseline as a covariate. For comparisons among treatments in category shift the Cochran-Mantel-Haenszel test controlling for study site will be used.

- Adverse events will be analyzed individually and by body systems.

Number and % of patients will be displayed by treatment group. Treatment groups will be compared with respect to number of patients who experienced the adverse event (by preferred name and by body system category) using Cochran-Mantel-Haenszel statistic controlling for study site.

Analysis of pollen count and rainfall data

Graphs and descriptive statistics will be use to describe pollen count by study site. For each study week, at each study site, counts of number of days with and without rain will be presented.

Reviewer's comments to the Protocol

The Nasacort treatment arm was not blinded. The patient's and physician's evaluations of Nasacort's treatment effects (efficacy and safety) could be biased.

The protocol does not clearly define what are the medical events that the patients are asked to capture in their daily diary other than the efficacy assessments.

The protocol does not specify the percent of drug weight used that will be considered adequate for the assessment of patient's compliance and how it may be used in the assessment of efficacy or safety.

The protocol does not specify a uniform method to be used for pollen collection at the individual study sites.

RESULTS

REVIEWER'S COMMENTS

The results of this study are reported in Volumes 6.1-6.36 of the NDA submission dated 2/15/96. The study result summary is reported in volume 6.1.

Modifications to the Protocol as indicated in the Study Report, vol 6.1:

Page 37. The use of saline nasal spray was not allowed, the use

of saline eye drops was acceptable.

Study medication used

This study used the to be marketed formulation: 39-050-2. The pump used was the _____ pump. The to be marketed pump is the _____ with _____ Nasal Actuator.

The medication was used as described earlier in the study protocol. The following batches were used:

Placebo Nasal Solution:	Batch 51504	—
Tri-nasal 0.0.5% Nasal Solution:	Batch 51704	—
Nasacort Nasal suspension:	— 650	
	— 640	

Blinding

To blind the Tri-nasal treatments, placebo was supplied in containers identical to the active drug. All evaluated medications were blind-labeled. The person dispensing the medication had no role in the patient's evaluation. The Nasacort canisters were not blinded.

Randomization code used

The sponsor used a computer generated code. It was based on a total sample size of 416, 32 patients/site, and it used a block size of four.

Patient Disposition

Patient Numbers

There were 377 patients that enrolled in the study. The patients were studied in 13 sites located in different geographical areas, Table 1A, vol 6.1:

		Patients enrolled/site
Site 2:	W. Berger (CA)	33
Site 3:	E.A. Bronsky (UT)	30
Site 4:	R.J. Dockhorn (KS)	32
Site 5:	P.E. Korenblat (MO)	18
Site 6:	K. Lampl (MD)	32
Site 7:	W. Lumry (TX)	27
Site 8:	S.J. Pollard (KY)	32
Site 9:	G. Raphael (MD)	32
Site 10:	C.M. Rohr (OR)	24
Site 11:	R. Rosenthal (MD)	29
Site 12:	M. Valentine (MD)	29
Site 13:	A.A. Wanderer (CO)	28

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15

Site 14: G. Shapiro (WA)

31

The study report does not indicate that an additional site, site #1, was used. This information is not reported in Table 1A, vol 6.1 or in the text of the report under the section Patients number; Patient Disposition. The study report only mentions that the 377 patients that enrolled in the study did so in 13 centers and presents the patient distribution by center as shown above.

The IND for this drug, IND _____ was searched for additional information. In the sponsor's correspondence dated 5/16/96 N-042 (PC, PI) information FDA 1572 was provided for an additional investigator not included in the above list: Dr. _____ M.D. _____. In the list the name precedes that of Dr. William Berger (Site #2). At a later date, on the correspondence to the IND dated 6/1/95 N(PI) 044, an additional investigator was added to study 100-309, Dr. Gail Shapiro.

The sponsor was asked to clarify whether there were any patients enrolled at Dr. _____ site, and whether any of the patients received study medication in teleconference dated 7/16/96. In the telephone facsimile dated 7/18/96 it is explained that Dr. _____ was recruited as a potential site for study 100-309. However, Dr. _____ withdrew from the study prior to screening patients and no patients received drug at his site. Correspondence from Muro's CRO for 100-309, _____ to the IFE documenting the withdrawal of Dr. _____ was included.

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Patient numbers from Table 1A, vol 6.1.

	Placebo	Tri-nasal 200 µg	Tri-nasal 400 µg	Nasacort 440 µg	Total
Intent-to treat	96	94	95	92	377
Completed study	89	89	90	87	355
Did not complete study	7	5	5	5	22
Evaluable efficacy	59 (62%)	60 (64%)	62 (65%)	79 (86%)	260 (69%)
Not evaluative for efficacy	37	34	33	13	117

Among the patients in the four treatment groups, a larger percentage of patients in the Nasacort treated group were considered to be evaluable for efficacy. There was no difference in the number of patients that were evaluable for efficacy among those patients treated with placebo or Tri-nasal, Table 1A, vol 6.2.

Patient numbers and Reasons for Non-Evaluability for efficacy, from Table 1A, vol. 6.1

	Placebo	Tri-nasal 200 µg	Tri-nasal 400 µg	Nasacort 440 µg	Total
Violation Inc. crit/ baseline skin-test	0	2	1	0	3
Study medication Non- compliance	32 (33%)	27 (29%)	28 (29%)	9 (10%)	96 (26%)
Restricted medication	0	2	0	2	4

Med.non-compliance restricted med.	5	1	4	2	12
Baseline sev. criteria/ med. non compliance	0	2	0	0	2

The criteria used by the sponsor to assess compliance with study medication was not clearly specified in the protocol for this study. In response to a telephone conversation with the sponsor dated 2/23/96, referring to this same subject in study 100-204 the sponsor clarified in correspondence dated 3/6/96, that after review of the calculations for study 100-309, a usage of 83% spray bottle weight was the criterion used to assess compliance for Tri-Nasal treated patients and that a usage of 67% canister weight was the compliance criterion used for the Nasacort treated patients. It had been their intention to have a 2/3 (67%) usage weight for the Tri-Nasal treatments. The sponsor decided to retain the 83% usage weight and thus the results for all the evaluable for efficacy Tri-Nasal groups will not change. The Nasacort patient compliance criterion for this study will be revised to 83%. The sponsor chose to submit an update of the analysis for the evaluable for efficacy subset for this study in the correspondence dated 4/24/96, after correcting the Nasacort compliance criterion to 83% of expected medication use.

The following Table was provided in the correspondence dated 3/6/96:

Percentage of Non-Compliant patients by treatment group (as a percent of the treatment group totals:

Compliance criteria	Placebo	Tri-Nasal 200	Tri-Nasal 400	Nasacort
67% Usage	19%	19%	19%	11%
83% Usage	36%	34%	32%	29%

Therefore, this difference in the compliance criterion used for the active treatment, could explain why Nasacort treated patients showed better compliance taking the study medication than patients in the other treatment groups, as depicted in Table 1A.

Discontinued patients

There were no differences between treatment groups for the number of patients discontinuing the study, Table 1B, vol 6.1. Of the 22 patients that discontinued the study, three patients discontinued the study due to adverse events, Section V.C.b., vol 6.1.

Nasacort (Pt. #231): 28 y/o Caucasian female patient that discontinued the study due to sore throat before taking any of the study medication. The patient was treated with amoxicilin and acetaminophen and the symptoms resolved.

Tri-nasal 200 μ g (Pt. #724): 24 y/o Caucasian male patient that discontinued the study due to sore, irritated, burning throat, classified as been of mild severity and probably related to study drug, after approximately 4 days of treatment.

Placebo (Pt. #1216): 43 y/o Hispanic male patient that discontinued the study due to an asthma exacerbation. The asthma was rated as moderate in severity and lasted for three days before the patient discontinued the study. Concomitant medication were: Robitussin for coughing and prednisone for the asthma exacerbation.

Number of patients that discontinued the study and reason for study discontinuation, in the intent-to-treat population, from Table 1B, vol 6.1.

	Placebo	Tri-nasal 200 μ g	Tri-nasal 400 μ g	Nasacort 440 μ g	Total
Adverse event	1	1	0	1	3
Failed to return	2	0	1	1	4
Restricted medication	4	0	3	1	8
Patient Withdrew	0	1	1	2	4
Other	0	3	0	0	3

Demographics and patients characteristics

The mean age range for the patients that participated in this study was 34-36 years of age. Forty eight percent of the patients were male and the majority were Caucasian (87%). There were no statistical differences between treatment groups for age,

gender and race, Table 2, vol 6.1.

Patient's past medical history. There was a statistically significant difference among the randomized treatment groups for the past medical history of skin related conditions. There were twelve percent of patients randomized to the Tri-Nasal 400, Placebo (16%), Tri-Nasal 200 (19%) and Nasacort (26%) that had a past medical history of integumentary problems. Table 3, vol. 6.1.

Physical exam. Although there were no significant differences between treatment groups with respect to any vital sign or body systems evaluated, the abnormalities were most frequently found in the nose (in 93% of patients), eyes (31%) and throat (18%), Table 4B, vol 6.1.

EFFICACY

Reviewer's comments

The reviewer's comments will discuss the efficacy and safety results of the intent-to-treat-population.

Intent-to-Treat Population

Symptom Severity Index (SSI)- Patient Diary

Baseline

The baseline includes 7 days of diary recording prior to active treatment. There were no statistically significant differences between treatments or treatment-by-site interactions at baseline for SSI scores, Table 5A1 and 5G1, vol 6.1.

Patient Diary- Adjusted Mean, Symptom Severity Index (SSI), from Table 5A1, vol 6.1.

	Placebo	Tri-nasal 200 µg	Tri-nasal 400 µg	Nasacort 440 µg	P-Value
Baseline	7.57 N=96	7.52 N=94	7.41 N=95	7.37 N=92	0.882*
Week 1	5.98 N=94	5.33 N=93	5.08 N=94	4.90 N=91	0.002**
Week 2	5.30 N=91	4.14 N=90	3.83 N=91	3.90 N=89	<.001**

* Results are based on an ANOVA model with effects for treatment and site.

** Results are based on an ANCOVA model with baseline covariate and

effects for treatment and site.

According to Dr. Guo's review, pages 1-2, Appendix 3, the reason why the intent to treat population for week 1 and 2 include less patients than the ITT population for each group is because there were missed observations on 17 patients that were enrolled in the following groups: 6-placebo, 4-Tri-nasal 200 μg , 4-Tri-nasal 400 μg and 3-Nasacort. The distribution of the patients and missed data is shown in Dr. Guo's review. A crude analysis was done using the nonmissing patients and the results were similar. Biometrics would not expect a significant impact on the efficacy results due to the missed observations on these patients.

Patient Diary- Summary of Symptom Severity Analyses for Symptom Severity Index (SSI), for the values at each week, from Table 5G1, vol 5.1

	Placebo vs. Tri-Nasal 200 μg	Placebo vs. Tri-Nasal 400 μg	Placebo vs. Nasacort 440 μg	Tri-Nasal 200 μg vs. Tri-Nasal 400 μg	Tri-Nasal 200 μg vs. Nasacort 440 μg	Tri-Nasal 400 μg vs. Nasacort 440 μg
Baseline	0.836	0.510	0.399	0.653	0.526	0.851
Week 1	0.026	0.002	<.001	0.402	0.144	0.525
Week 2	<.001	<.001	<.001	0.344	0.475	0.820

The symptom severity index scores of patients on active treatment (both Tri-Nasal treatments and Nasacort) improved significantly versus the scores of placebo treated patients, for Weeks 1 and 2. There were no statistically significant differences between the scores of the active treated patients for the two weeks of treatment. According to this measure (primary endpoint), the active treatments had comparable efficacy and they all showed superiority over placebo for the two weeks of treatment.

Individual symptoms- Patient Diary .

Sneezing, Adjusted Mean Scores, Intent-to-Treat, from Table 5B1, vol. 6.1

	Placebo	Tri-Nasal 200 μg	Tri-Nasal 400 μg	Nasacort 440 μg
Baseline	2.36 N=96	2.35 N=94	2.31 N=95	2.17 N=92

Week 1	1.79 N=94	1.56 N=93	1.47 N=94	1.41 N=91
Week 2	1.62 N=91	1.16 N=90	1.04 N=91	1.02 N=89

Summary of symptom severity analyses for **Sneezing**, from Table 5G1, vol. 6.1

	Overall P Value	P vs T200	P vs T400	P vs 440 Nasacort	T200 vs T400	T200 vs 440 Nasacort	T400 vs 440 Nasacort
Baseline	0.247	0.874	0.596	0.066	0.712	0.095	0.190
Week 1	0.004	0.036	0.004	<.001	0.414	0.182	0.595
Week 2	<.001	<.001	<.001	<.001	0.308	0.231	0.850

There were no statistically significant differences at baseline between treatment groups for the individual symptom severity score of sneezing. On Week 1 and 2, all patients on active treatment had a significant improvement in symptom severity scores ($p \leq 0.05$) for sneezing, compared to those patients treated with placebo. There were no significant differences among the active treatment groups.

For the other two individual symptoms of the SSI, rhinorrhea and nasal congestion, a statistically significant improvement was demonstrated for all active groups versus placebo for week 1 (except for the Tri-Nasal 200 treatment group) and week 2 of treatment. No significant differences between the active treatment groups were observed for the two weeks of treatment. For rhinorrhea, the Tri-Nasal 200 group did not show a statistically significant difference versus placebo for week 1. On the other hand, a significant improvement in nasal congestion was demonstrated in Week 1 for all active treatment group versus placebo.

Rhinorrhea- Adjusted Mean Scores, Intent-to-Treat, from Table 5C1, vol. 6.1

	Placebo	Tri-Nasal 200 μg	Tri-Nasal 400 μg	Nasacort 440 μg
Baseline	2.61 N=96	2.59 N=94	2.47 N=95	2.53 N=92

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Week 1	2.02 N=94	1.84 N=93	1.72 N=94	1.66 N=91
Week 2	1.78 N=91	1.41 N=90	1.34 N=91	1.36 N=89

Summary of symptom severity analyses for **Rhinorrhea**, from Table 5G1, vol. 6.1

	Overall P Value	P vs T200	Pvs T400	P vs 440 Nasacort	T200 vs T400	T200 vs 440 Nasacort	T400 vs 440 Nasacort
Baseline	0.412	0.824	0.125	0.386	0.191	0.521	0.511
Week 1	0.009	0.100	0.008	0.002	0.314	0.131	0.608
Week 2	<.003**	0.006	0.001	0.002	0.579	0.713	0.850

** Significant treatment-by-site interaction

Biometrics was asked to comment on the significant treatment-by-site interaction in the above table. Biometrics considers that the approach taken by the sponsor was correct. After finding a treatment by-site interaction a by-site analysis of treatment effects was done. The sponsor also reported that at two of the sites (Bronsky and Lumry) all the active treatments demonstrated statistical superiority to placebo. Please refer to Dr. Guo's review, page 3 in Appendix 3.

Nasal Congestion- Adjusted Mean Scores, Intent-to-Treat, from Table 5E1, vol. 6.1

	Placebo	Tri-Nasal 200 µg	Tri-Nasal 400 µg	Nasacort 440 µg
Baseline	2.59 N=96	2.59 N=94	2.64 N=95	2.67 N=92
Week 1	2.19 N=94	1.94 N=93	1.88 N=94	1.81 N=91
Week 2	1.94 N=91	1.56 N=90	1.47 N=91	1.51 N=89

Summary of symptom severity analyses for **Nasal Congestion**, from Table 5E1, vol. 6.1

	Overall P Value	P vs T200	Pvs T400	P vs 440 Nasacort	T200 vs T400	T200 vs 440 Nasacort	T400 vs 440 Nasacort
Baseline	0.766	0.952	0.581	0.398	0.542	0.368	0.766
Week 1	0.003	0.019	0.004	<.001	0.566	0.237	0.537
Week 2	<.001	0.003	<.001	<.001	0.466	0.655	0.780

Itchy Nose/Throat/Palate

There were no statistically significant differences at baseline or at week 1 among treatment groups. The scores for this symptom complex improved during week 1, for all treatments. After one week of treatment, on Week 2, a statistically significant improvement was demonstrated in patients receiving active treatment versus those patients treated with placebo. During week 2, there were no significant differences in the improvement of this symptom complex, among active treatment groups.

Itchy Nose/Throat/Palate, Adjusted Mean Scores, Intent-to-Treat, from Table 5E1, vol. 6.1

	Placebo	Tri-Nasal 200 µg	Tri-Nasal 400 µg	Nasacort 440 µg
Baseline	2.24 N=95	2.30 N=94	2.29 N=95	2.16 N=92
Week 1	1.72 N=94	1.48 N=93	1.46 N=94	1.48 N=91
Week 2	1.44 N=91	1.03 N=90	0.96 N=91	1.05 N=89

Summary of symptom severity analyses for Itchy Nose/Throat/Palate, from Table 5G1, vol. 6.1

	Overall P Value	P vs T200	Pvs T400	P vs 440 Nasacort	T200 vs T400	T200 vs 440 Nasacort	T400 vs 440 Nasacort
Baseline	0.704	0.673	0.705	0.529	0.964	0.296	0.315
Week 1	0.088	0.042	0.028	0.045	0.868	0.989	0.858
Week 2	<.001	0.002	<.001	0.002	0.570	0.924	0.509

During the first week of treatment, although no overall statistically significant difference was demonstrated among treatments for itchy nose/throat/palate, there were statistically significant differences between the three active treatments and placebo. Biometrics was asked to comment on this discrepancy. At the time of this review Biometrics considers that it could be related to confounding factors within the patients; but that they would need more time to conduct additional research, refer to Dr. Guo's review, page 3, Appendix 3.

Itchy Red/Watery Eyes

There were no statistically significant differences at baseline among treatment groups. Only for Week 2, the Tri-Nasal 400 group demonstrated a significant improvement over placebo. Otherwise, the active treatment groups did not show any statistical significant improvement versus placebo during the two weeks of treatment. The placebo treated group had a progressive improvement in this symptom complex and so did the active treated groups.

Itchy Red/Watery Eyes, Adjusted Mean Scores, Intent-to-Treat, from Table 5F1 vol. 6.1

	Placebo	Tri-Nasal 200 µg	Tri-Nasal 400 µg	Nasacort 440 µg
Baseline	2.41 N=95	2.25 N=94	2.38 N=95	2.19 N=92
Week 1	1.80 N=94	1.82 N=93	1.66 N=94	1.62 N=91
Week 2	1.49 N=91	1.34 N=90	1.24 N=91	1.28 N=89

Summary of symptom severity analyses for **Itchy Red/Watery Eyes**, from Table 5G1, vol. 6.1

	Overall P Value	P vs T200	Pvs T400	P vs 440 Nasacort	T200 vs T400	T200 vs 440 Nasacort	T400 vs 440 Nasacort
Baseline	0.277	0.214	0.833	0.096	0.302	0.667	0.145
Week 1	0.264	0.869	0.244	0.147	0.185	0.106	0.765
Week 2	0.225	0.226	0.053	0.102	0.468	0.666	0.770

Patient Diary- Symptom severity index for treatment Days 1 and 2

Both Tri-Nasal 400 μg and Nasacort 440 μg showed statistical significant improvement over placebo in the symptom severity index by Day 2 of treatment. The improvement in the SSI scores for these two days for Tri-Nasal 200 μg treated patients, was not different from placebo, even though there was a numerical improvement in the SSI scores for the Tri-Nasal 200 μg treated group. A statistical significant difference was also demonstrated between the patient group that received 440 μg of Nasacort and those patients that received Tri-Nasal 200 μg .

Patient Diary -Symptom Severity Index for Treatment Day 1 and 2
Adjusted Mean Scores, Intent-to-Treat, from Table 5H1 vol. 6.1

	Placebo	Tri-Nasal 200 μg	Tri-Nasal 400 μg	Nasacort 440 μg
Baseline	7.68 N=95	7.43 N=89	7.75 N=91	7.22 N=87
Treatment Day 1	6.69 N=94	6.35 N=92	6.10 N=94	6.18 N=91
Treatment Day 2	6.54 N=94	6.12 N=93	5.60 N=93	5.38 N=90

Summary of symptom severity analyses for **Symptom Severity Index for Treatment Day 1 and 2**, from Table 5I1 vol. 6.1

	Overall P Value	P vs T200	Pvs T400	P vs 440 Nasacort	T200 vs T400	T200 vs 440 Nasacort	T400 vs 440 Nasacort
Baseline	0.300	0.408	0.815	0.137	0.294	0.512	0.089
Treatment Day 1	0.258	0.293	0.064	0.117	0.436	0.606	0.799
Treatment Day 2	0.006	0.235	0.008	0.001	0.150	0.044	0.547

Biometrics was asked why does these analyses have more patients on Day 1 and Day 2 for the three active treatments than at baseline. Please refer to Dr. Guo's review page 4, Appendix 3. The data collection and recording process may be responsible. The number of patients for baseline, day 1 and day 2 were calculated by merging several data files and by subsetting based on the value of the variable called "DAY" which was calculated from the difference between DOD and RDATE. It would take more time to carry out additional research to assess the effect of those missing data on the efficacy analysis.

Physician Weekly Assessment of Symptom Severity

Intent-to Treat**Physician Weekly assessments - Symptom Severity Index -**

There were no statistically significant differences detected at baseline among treatment groups for the physician assessment of symptom severity index scores.

The results of the physician assessments using the symptom severity index scores parallel the results of the patient's diary scores.

The symptom scores of the patients on active treatment show significant improvement over placebo for weeks 1 and 2. No significant differences are demonstrated among active treatments for these two weeks. There were significant treatment-by-site interactions for Week 2 for the individual sites of Bronsky ($p < .001$), Lampl ($p = 0.007$) and Lumry ($p = 0.016$), Appendix B, Table E.05, vol 6.3.

Physician weekly assessment of the Symptom Severity Index, Adjusted Mean Scores, Intent-to-Treat, from Table 6A1

	Placebo	Tri-Nasal 200 μ g	Tri-Nasal 400 μ g	Nasacort 440 μ g
Baseline	7.01 N=96	7.02 N=94	6.92 N=95	6.67 N=92
Week 1	5.32 N=94	4.09 N=92	4.13 N=94	3.70 N=91
Week 2	4.42 N=89	3.69 N=89	3.19 N=90	3.36 N=87

Summary of symptom severity analyses for the Symptom Severity Index from the Physician Weekly Symptom Assessment, from Table 6G, vol. 6.1

	Overall P Value	P vs T200	P vs T400	P vs 440 Nasacort	T200 vs T400	T200 vs 440 Nasacort	T400 vs 440 Nasacort
Baseline	0.596	0.957	0.775	0.244	0.735	0.226	0.379
Treatment Day 1	<.001	<.001	<.001	<.001	0.890	0.244	0.190
Treatment Day 2	0.002**	0.032	<.001	0.002	0.142	0.332	0.622

** Significant treatment-by-site interaction. These were the Bronsky, Lampl and Lumry sites. At each of these sites both Tri-Nasal

treatments showed significant improvement over placebo. Biometrics was asked to comment about the significant treatment-by-site interaction. They referenced their comments to a similar question from Table 5G1 (Patient's assessment of rhinorrhea), Dr. Guo's review, page 5 in Appendix 3.

Individual Symptom Scores from the Physician Weekly Assessments

There were no statistical significant differences at baseline between treatment groups.

The results of this assessment parallel that of the patients' scores during Week 1. However, during Week 2 this assessment was not able to demonstrate significant improvement of patients receiving the Tri-Nasal 200 µg treatment versus those on placebo for nasal congestion, Itchy N/T/P or Itchy R/Watery eyes. The same can be said for the Nasacort 440 µg treatment versus placebo for these same symptoms.

As can be seen in the following Table, even though no statistical significant differences were demonstrated over placebo for Week 2 for these individual symptom scores, these scores were numerically lower than those on Week 1.

Physician weekly assessment of individual symptom severity, adjusted mean scores, from Table 6B1, 6C1, 6D1, 6E1, 6F1 and 6G in volume 6.1.

	Baseline	Week 1	Week 2
Sneezing			
T 200	2.02	1.05*	1.02
T 400	2.03	1.10*	0.71*(200 vs 400)#
N 440	1.81	0.80*(400vs440)	0.81*
Placebo	2.06	1.53	1.25
Rhinorrhea			
T 200	2.44	1.34*	1.23
T 400	2.26	1.35*	1.02*
N 440	2.30	1.23*	1.13*
Placebo	2.32	1.79	1.49
Nasal Congestion			
T 200	2.56	1.70*	1.47
T 400	2.63	1.69*	1.36*
N 440	2.56	1.65*	1.43
Placebo	2.63	2.02	1.68
Itchy N/T/P			
T 200	2.18	1.05*	0.94
T 400	2.25	1.20*	0.88*
N 440	2.10	1.18*	1.02
Placebo	2.14	1.63	1.14

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28

Itchy R/W eyes			
T 200	2.13	1.39*	1.05
T 400	2.22	1.44*	1.01*
N 440	2.17	1.24*	1.16
Placebo	2.25	1.75	1.31

*p<0.05 between active treatment and placebo

#p<0.05 between active treatments

Patient Global Assessment

The Patient's global assessment rated all the active treatments better than placebo for the two weeks of the study; Table 7A and Table 7B in volume 6.1.

No one active treatment was found to be significantly better than the others.

There were treatment by site interactions during Week 1 (Bronsky, p=0.001; and Lumry p=0.053), Appendix B, Table B.10 and during Week 2 (Bronsky, p=0.005 and Rosenthal, p=0.045), Appendix B, Table B.11, vol 6.3.

Pollen count and Frequency of Rain during the study period

The site with the highest mean pollen count during the study period was Site 8 (Pollard, KY) with means of 133 and 114 pollen counts/cubic meter, during Week 1 and Week 2 respectively.

Sites 2 (Berger, CA), 7 (Lumry, TX) and 13 (Wanderer, Co) had the lowest pollen counts with daily averages of less than 20 counts/cubic meter, Figure 5 (1 figure/site) in volume 6.3. The comparison of symptom scores in the placebo treated patients at the individual sites with pollen counts is made in Figure 6, volume 6.3. Even though, Lumry's site (TX,) had low pollen counts, the placebo patient's symptom scores were higher at this center than at other centers that had higher pollen counts, suggesting that Lumry's patients were exposed to their relevant allergens.

Site 8 (Pollard, KY) and Site 3 (Bronsky, UT) had the highest number of rainy days during the study (9, 38%); nine days, page 01 0072, vol 6.1. In Bronsky's site the majority of the rain days were during the baseline period. For Pollard's site (KY) even though there was rain recorded during the treatment period, the grass counts recorded during those days were in general above 20 counts/cubic meter, Data Listing 11, vol 6.25.

SAFETY**Reviewer's comments:****Extent of exposure**

A total of 377 patients were enrolled in the study. Of these:

94 received Tri-Nasal 400 μ g
 95 received Tri-Nasal 200 μ g
 96 received Placebo
 92 received Nasacort 440 μ g

daily for two weeks.

Adverse events

The number of patients with adverse events by treatment (intent-to-treat), was very similar, Table 9A, vol 6.1:

Placebo	79.2% (76/96)
Tri-Nasal 200 μ g	87.2% (82/94)
Tri-Nasal 400 μ g	78.9% (75/95)
Nasacort 440 μ g	81.5% (75/92)

There were no statistically significant differences among treatment groups in the overall frequency of adverse events.

The total number of occurrences of adverse events by treatment arm was (Table 9C, vol 6.1):

Placebo	294
Tri-Nasal 200 μ g	376
Tri-Nasal 400 μ g	320
Nasacort 440 μ g	302

The treatment group with the highest frequency of adverse events per patient and largest number of occurrences was the Tri-Nasal 200 μ g group.

The majority of adverse events were classified to be of mild or moderate severity.

The list of the most common adverse events by treatment in decreased order of frequency is presented in Table 9E, vol 6.1. The most common adverse events listed were: headache, application site reaction, rhinitis, pharyngitis, taste perversion, dysmenorrhea, back pain and asthma.

The study report does not list any statistical significant difference in the frequency of individual adverse events by

treatment, for the most common adverse events listed in page C1 0073, vol 6.1.

The following Table, from Table 9E in vol 6.1, depicts the adverse events that were reported at a higher frequency in any of the active groups compared to the placebo treated group and that were also reported by more than 2% of the patients.

Percent of patients with adverse experiences by preferred term, (Intent-to-Treat) from Table 9E in vol 6.1.

Adverse event	Placebo	Tri-nasal 200	Tri-Nasal 400	Nasacort 440
Headache	49	56	60	50
Rhinitis	15	17	6	11
Pain -	14	15	6	10
Pharyngitis	6	9	11	13
Taste Perversion	9	13	13	3
Back Pain	2	9	6	8
Asthma	4	7	5	5
Conjunctivitis	3	5	1	9
Vomiting	3	2	6	3
Myalgia	2	3	5	3
Nausea	1	2	4	2
Abdominal Pain	1	0	4	2
Photosensitivity reaction	1	3	0	0
Eye disorder	2	1	1	3

After reviewing the adverse event Table 9E, vol 6.1, the following adverse events were noted. These were reported in patients treated with Tri-Nasal 400 and were classified to be of moderate severity (Table 9B, vol 6.1): parotid gland enlargement, herpes simplex,

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31

pyelonephritis, and neoplasm. In a patient treated with Tri-Nasal 200, bilirubinemia of moderate severity was reported. The study report does not include a short clinical summary of these cases. Although it would be unlikely that the use of study drug for two weeks would be related to these adverse events, in teleconference with the sponsor dated 4/12/96, we asked the sponsor to provide us with either a brief clinical history of these cases or with the CRF.

A brief summary of these cases was provided in the sponsor's correspondence dated 4/12/96. According to this summaries: The neoplasm was the Costart term used for a nasal polyp. The patient with pyelonephritis, had a past history of severe urinary tract infections. At the time of the study initiation and at the final visit her urinalysis was normal. The onset of signs and symptoms of pyelonephritis was two days after the final visit. The patient with genital herpes had a negative history at the screening visit. However, 3 days prior to starting the study medication she was started on Acyclovir for genital herpes. The screening history did not capture a hx of parotid gland enlargement for a patient that was found to have enlarged parotid glands at final exam. Upon questioning the patient it was learned that he had a 5 yr hx. of intermittent parotid gland enlargement. The patient with hyperbilirubinemia was found to have a bilirubin of 1.5 mg/dL at screening. By the end of treatment it was 0.1 mg/dL and five days later, 1.4 mg/dl. It was attributed by the sponsor to be most likely due to Gilbert's syndrome.

For the common adverse events, the local reaction listed with the preferred name of "application site reaction", was reported by a large number of patients using the Tri-Nasal preparations, 23-26%, including placebo. For the Nasacort formulation, the reported frequency of this adverse event was less, 15%. The sponsor suggests that this difference in the adverse event rate for this local reaction may be due to the -based-vehicle employed in the formulation for Tri-Nasal.

From the list of most common adverse events, the following adverse events with a reported with a reported frequency >2%, were also reported in Table 9F, vol 6.1, to be at least possibly related to study medication.

Percent of patients that experienced at least one adverse event that was considered to be at least possibly related to study drug, (Intent-to-Treat), Table 9F, vol 6.1.

Adverse event	Placebo	Tri-Nasal 200	Tri-Nasal 400	Nasacort 440
Headache	27	33	36	29
Application site reaction	25	26	23	15
Rhinitis	12	10	4	8

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32

Pain	1	2	1	5
Pharyngitis	5	5	6	8
Taste perversion	9	13	13	3
Back pain	0	3	1	2
Conjunctivitis	2	1	0	4
Vomiting	3	2	3	0

In addition to the adverse events listed above as possibly related to study drug, the following two adverse events were also reported as possibly related to study drug in patients using Tri-Nasal 400 µg: pyelonephritis and neoplasm. The study report does not include a section that describes these two cases, nor does it give the patient's identifier.

A table showing the percent of adverse event occurrences that were considered to be at least possibly related to study medication for the most common adverse events, based on the sponsor's reported table on page 01 0075 of vol 6.1, follows.

Percent of the most commonly reported adverse event occurrences that were considered to be at least possibly related to study drug by treatment group.

Adverse event	Placebo	Tri-Nasal 200	Tri-Nasal 400	Nasacort 440
headache	45	44	40	44
application site reaction	100	100	100	100
rhinitis	80	52	50	73
pain	6	8	13	50
pharyngitis	86	63	69	64
taste perversion	100	100	100	100
dysmenorrhea	0	0	0	0
back pain	0	19	14	25
asthma	38	20	21	20

In teleconference with the sponsor dated 4/12/95 we asked the sponsor

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33

to clarify what terms were grouped under the term application site reaction and to list by treatment the frequency of the patient's reported term.

Dropouts due to adverse events

The summary of these 3 cases was included under the results section for patient disposition.

Deaths and serious adverse events

There were no deaths reported during the course of the study. A serious, not related adverse event was reported. A patient (#618, in pages 02 0288 to 02 0344 in vol 6.2) that had received placebo for 12 days developed what was described by the investigator as an adverse/anaphylactic reaction occurring 30 minutes after eating "Doritos corn chips with cool ranch flavor" and 5 hrs after using the study drug. The reaction involved symptoms of angioedema of the throat and airway involvement with decreased peak flow measurements. Patient's symptoms responded to an epinephrine injection. Ninety minutes later symptoms had totally resolved and the patient went back to work. The CRF does not record the patient's previous history of allergy to this or to other foods. After this episode the patient continued to receive the study drug for the following two days without problems.

Clinical Laboratory Evaluations

Hematology

There were no statistically significant changes when the between-treatment groups comparisons were made, taking baseline as a covariate (Table 11A, vol 6.1).

There were numerically small changes in hematology parameters that were statistically significant when the within-group comparisons were made from final evaluation to baseline. These were not considered to be clinically significant. From these parameters, the results for % eosinophils follow.

Change in mean % eosinophils from baseline to final evaluation, from Table 11A in vol 6.1.

	Placebo	Tri-Nasal 200	Tri-Nasal 400	Nasacort 440
Baseline	2.85 N=96	2.88 N=92	2.78 N=95	2.57 N=91
Final value	2.65 N=95	2.50 N=92	2.02 N=93	2.30 n=89
within group p value	0.492 N=95	0.038 N=90	0.000 N=93	0.124 N=88

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Even though the within group decrease in % eosinophil count for the Trinasal treated groups are statistically significant they are not clinically significant. In this study, for this parameter, a greater effect is shown with an increase in dose in the Tri-Nasal treated patients. The Nasacort treated group does not show a statistically significant decrease (within-group) on this parameter.

Chemistry

When the changes in mean values from baseline were evaluated there were a few statistically significant changes that are depicted in page 01 0083 of volume 6.1, but they are not clinically significant (Table 12A, vol 6.1). These are decreases total protein (<0.2 g/dl), ALT/SGPT (<2U/L), AST/SGOT (<2 U/L), and cholesterol (<4 mg/dl).

The study report does not discuss any individual abnormal blood chemistry lab report.

The following abnormal lab reports from patients on active treatment were obtained from the review of the Data Listing 16B in volumes 6.31 and 6.32:

Test	screening	final-retest	Treatment	Pt. #	sex	DOB
SGOT(U/L)	36	96 (6/22/95) 36 (6/28/95)	Nasacort 440	207	M	
SGPT(U/L) *T bilirubin normal	73	82 (6/22/95) 76 (6/28/95)	"	"	"	
s. glucose (mg dl)	84	147 (6/27/95) 93 (6/30/95)	Nasacort 440	1307	M	
s. glucose (mg/dl)	94	148 (7/11/95)*	Tri-Nasal 400	1414	M	
s. glucose (mg'dl)	141	198(6/23/95)*	Tri-Nasal 400	326	F	
s. glucose (mg'dl)	122	271 (6-06-95) 153 (6-10-95)	Tri-Nasal 200	811	M	
T. bilirubin (mg/dl)	1.5	2.5 (6/13/95)*	Tri-Nasal 400	1202	M	

* the last lab was obtained on the final study day, no repeat labs found

Pt. #811 was on Furosemide, K-dur and Zaroxolyn prior to treatment and continued on them during the study. He took Exedrin for 5 days during

treatment. This patient also had abnormal high triglyceride and uric acid at screening and at the final visit.

Patients #207, 1202, 1307, and 1202 are not listed as taking any concomitant meds in Data Listing 14 A, volume 6.26. Patient 1414 is listed as having used Tylenol for only one day. patient 326 is listed as having used Tagamet for two days and Advil for one day.

Transient elevations in serum glucose were observed during treatment in a few patients with normal and elevated values at screening. Upon retest these values came back to screening levels when a retest was done. Transient changes in glucose levels could also be attributed to when these labs were done in relation to meals, since this was not specified in the protocol.

Pt. #207 had an elevated SGPT at screening and a transient elevation during treatment of both the SGOT and SGPT. These went back down to screening levels after 6 days post d/c of treatment.

Pt. #1202 had an elevated level of T. bilirubin at screening. At final evaluation this lab was further elevated with no abnormal changes in other chemistry lab including liver function tests. No retest was done and no clinical summary for this patient was included in the study report.

Urinalysis

There were no statistically significant differences in ph or specific gravity at baseline or final evaluation within groups or among groups. For categorical parameters there were no statistically significant differences between treatment groups at either baseline or final evaluation.

One patient (#623) was noted to have hematuria that was confirmed on retest. The patient was referred to a urologist for follow up. The follow up report is not included in the submission. According to Data Listing 16B in vol 6.31 this 30 y/o male patient on Tri-Nasal 200 did not have any abnormal blood chemistry labs at final visit (Data Listing 16A, vol 6.31) nor was he on any concomitant medications (Data Listing 14A, vol 6.26). A decrease in WBC count from 4,320 (screening) to 4,170/ μ L at final visit was the only abnormal hematology lab result reported(Data Listing 16A, vol 6.29).

Physical examination

There were no statistical differences in weight at baseline or at final evaluation within groups or among groups (Table 14A, vol 6.2). In the systolic and diastolic blood pressure measurements there was a decrease of 3 mmHg from baseline for the Nasacort 440 treated group that was statistically significant. These mean changes are not clinically significant.

There were no statistically significant differences between treatments in shifts from the categorical physical examination results (Table 14B in vol 6.2).

Concomitant medication

No rescue medication was allowed in this study. The percent of patients taking concomitant medications is presented in Table 15, vol 6.2.

The percent of patients taking the most common concomitant medication at a >10% frequency from those listed in Table 15, vol 6.2, follows. Only one medication of each type is counted for each patient.

	Placebo N=96	Tri-Nasal 200 N=94	Tri-Nasal 400 N=95	Nasacort 440 N=92
Concurrent meds.	73 (76%)	69 (73%)	66 (70%)	71 (77%)
Propionic acid derivatives	30 (31%)	35 (37%)	28 (29%)	32 (35%)
Anilides	27 (28%)	32 (34%)	34 (36%)	23 (25%)
Progesterones and estrogens	16 (17%)	16 (17%)	10 (11%)	14 (15%)
Salicylic Acid and derivatives	11 (12%)	15 (16%)	10 (11%)	10 (11%)

The study report does not include the necessary linking tables or figures for the reviewer to make the assessment as to whether the use of the most commonly used concurrent medications had any clinical interactions with the study drugs, particularly as it refers to adverse events. In the review of specific abnormal labs there were no particular safety concerns raised with the use of the above concomitant medications.

Overall conclusions

This was a double-blind, parallel study that compared the efficacy and safety of Tri-nasal, nasal triamcinolone acetonide (TAA) solution, 200 µg and 400 µg daily versus Tri-nasal placebo and Nasacort (not blinded), TAA-aerosol suspension 440 µg daily, during a two week period in seasonal allergic rhinitis patients, 18-65 years of age.

A total of 377 patients were enrolled in the study. Patients had a baseline period of at least seven days and during 4/7 days the patients needed to have moderate symptoms that were defined as a score ≥6 of a possible total of 12 for the sum of the scores of the individual

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37

symptoms of sneezing, rhinorrhea and nasal congestion. This symptom complex was designated as the symptom severity score (SSI) and this score recorded daily by the patient averaged by treatment week was considered to be the primary efficacy endpoint. No rescue medication was allowed in this study.

The study results, using the intent to treat population, support the efficacy of both doses of Tri-nasal 200 and 400 μg over placebo.

The symptom severity index score (SSI) in patients on both Tri-Nasal treatments and Nasacort improved significantly versus the scores in placebo treated patients, for Weeks 1 and 2. There were no statistically significant differences at baseline between treatment groups. There were no statistically significant differences between the scores of the active treated patients for the two weeks of treatment. According to this measure (primary endpoint), all the active treatments had comparable efficacy and they all showed superiority over placebo for the two weeks of treatment.

There were no statistically significant differences at baseline between treatment groups for the individual symptom severity score of sneezing, rhinorrhea or nasal congestion. On Week 1 and 2, all patients on active treatment had a significant improvement in sneezing ($p \leq 0.05$), compared to those patients treated with placebo. There were no significant differences among the active treatment groups.

For the other two individual symptoms of the SSI, rhinorrhea and nasal congestion, a statistical significant improvement was demonstrated for all active groups versus placebo for both symptoms, for week 1 (except for the Tri-Nasal 200 treatment group) and week 2 of treatment. There were no significant differences between the active treatment groups for the two weeks of treatment.

During the first week of treatment, although no overall statistically significant difference was demonstrated among treatments for itchy nose/throat/palate, there were statistically significant differences between the three active treatments and placebo. Biometrics was asked to comment on this discrepancy. At the time of this review they consider that it could be related to confounding factors within the patients; but that they would need more time to conduct additional research. For the symptom complex of itchy/red/watery eyes there were no statistically significant differences between treatments or between the specific active treatments and placebo.

For the second week of treatment the three active treatments improved significantly versus placebo for the symptom complex of itchy nose/throat/palate. However, for the symptom complex of itchy red/watery eyes, only Trinalasal 400 μg treated patients had significant improvement versus those patients treated with placebo.

Both Tri-Nasal 400 μg and Nasacort 440 μg showed statistical significant improvement over placebo in the symptom severity index by Day 2 of treatment. The improvement in the SSI scores for these two

days for Tri-Nasal 200 μg treated patients, was not different from placebo, even though there was a numerical improvement in the SSI scores for the Tri-Nasal 200 μg treated group. A statistical significant difference was also demonstrated between the patient group that received 440 μg of Nasacort and those patients that received Tri-Nasal 200 μg . Therefore, it may take patients treated with Tri-Nasal 200 μg longer than 2 days to achieve demonstrable significant efficacy.

In general, the secondary efficacy endpoints also support the efficacy of the active treatments versus placebo for the two weeks of treatment. The results of the physician's weekly assessments parallel the results obtained using the patient's daily diary for the symptom severity index for the two weeks of treatment. However, in terms of the individual symptoms, the results support the efficacy of all the active treatments for week 1 but not for week 2, with the exception of the Tri-Nasal 400 treatment. The patient's global assessment rated all the active treatments better than placebo for the two weeks of the study.

The study results support the safety of the two doses of Tri-Nasal used once/day for two weeks of treatment.

A total of 377 patients were considered to be evaluable for safety. Of these, 94 patients received Tri-Nasal 400 μg and 95 were treated with Tri-Nasal 200 μg .

The percent of patients reporting adverse events in all treatment groups ranged from 79-87%. Patients treated with Tri-Nasal 200 reported the highest frequency of adverse events per patient and the largest number of occurrences. The majority of patients experienced adverse events that were mild or moderate in severity. The most common adverse events considered to be at least possibly related to study medication and that at the same time were reported in a higher frequency in active treated groups than in placebo were: headache, application site reaction, taste perversion and pharyngitis.

Two adverse events were also reported as possibly related to study drug in one patient each, using Tri-Nasal 400 μg : pyelonephritis and neoplasm. The study report does not include a section that describes these two cases, nor does it give the patient's identifier. The following adverse events, classified to be of moderate severity: parotid gland enlargement and herpes simplex, were reported in one patient each, treated with Tri-Nasal 400. A case of bilirubinemia was reported in a Tri-Nasal 200 treated patient. The study report does not include a short clinical summary of these cases. Although it is unlikely that the use of this nasal steroid inhaler for two weeks, would be related to these adverse events, we would want to see a brief clinical history of these cases or the CRFs. The sponsor was asked to provide this information in a teleconference dated 4/12/96.

An unrelated serious adverse event, anaphylactic/adverse reaction to food, was reported during the study. Placebo patient (#618) was treated for this reaction and recovered. Treatment with the study drug was continued. There were no reported deaths.

10.b. Study 100-204

Title: Evaluation of the topical vs systemic efficacy of nasal and IM Triamcinolone acetonide in patients with seasonal allergic rhinitis.

Study Protocol: (Appendix A.1, vol 4.17)

Objective

Compare the topical efficacy of Triamcinolone Acetonide (TAA) nasal spray solution (Trinasal) at doses of 50 and 400 μ g qd against a systemic form of TAA (4 mg IM Kenalog-40) and placebo in the treatment of seasonal allergic rhinitis.

Design

Multicenter(5), four week, double-blind, placebo controlled, randomized study that compares the efficacy of nasal TAA, IM TAA, and placebo in patients 18-65 with seasonal allergic rhinitis secondary to mountain cedar sensitivity.

After a one week baseline period, patients will be randomized to receive nasal TAA 50 and 400 mcg qd, TAA 4 mg IM/wk, or placebo. Patients will keep a daily diary of allergy symptoms, medications taken, and adverse events. The use of up to 4 mg of chlorpheniramine qid will be allowed during the treatment phase.

Population:

The study plans to enroll approx. 300 patients in 5 study sites.

Inclusion criteria:

-Symptoms of SAR for at least 2 years prior to study season, of moderate severity requiring antihistamine therapy for control.

-PAR if present must be of minor severity, fully characterized prior to study baseline, and not expected to contribute significant change for the patient during the study period

- Symptom score of at least 8 of a possible of 16 for the following 4 symptoms, on a minimum of 4/7 days during the baseline period:

- 1) nasal congestion,
- 2) rhinorrhea,