CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-120

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Labeling review

NDA 20-120	**REVIEWER:** Young-Moon Choi, Ph.D.
DRUG: Tri-Nasal (triamcinolone acetonide nasal solution 0.05 %) spray	**Submit:** 7/22/99
SPONSOR: Muro Pharmaceutical Inc.	**REVIEWED:** 12/16/99

1. SYNOPSIS

Tri-Nasal spray is a metered dose manual pump spray containing 0.05% w/v (0.5 mg/ml) triamcinolone acetonide (TAA). This is intended for topical administration to nasal mucosa. The proposed indications are for the nasal treatment of patients, 12 years and older, with seasonal and perennial allergic rhinitis symptoms. The recommended starting dose of Tri-nasal spray is 200 mcg/day given as 2 sprays (50 mcg/spray) in each nostril once a day. The active ingredient in Tri-Nasal spray, TAA, is a glucocorticosteroid which has been widely used for treatment of allergic disorders. It has potent anti-inflammatory activity. Tri-Nasal is a new dosage form (solution) of the approved drug product Nasacort (suspension).

The present labeling review is concentrated mostly on the format of the labeling. Please refer to the original clinical pharmacology and biopharmaceutics review (dated 7/15/96 by Dr. Uppoor) for detailed information.

2. RECOMMENDATION

The proposed labeling format of the pharmacokinetics section is not in accord with the currently recommended format. The labeling should be changed as follows:

Pharmacokinetics

Absorption: The pharmacokinetics of Tri-Nasal Spray was evaluated in a single dose study in 24 patients with perennial allergic rhinitis. Following a single intranasal dose of 400 mcg of triamcinolone acetonide (twice the recommended starting dose of Tri-Nasal Spray), the mean Cmax of the drug was 1.12 ng/ml (SD=0.38) with a median Tmax of 0.5 hours (range: 0.08 – 1.0).

A pharmacokinetic study to demonstrate dose proportionality was conducted in patients with perennial allergic rhinitis. The Cmax and AUC of the 200 and 400 mcg doses increased less than proportionally when compared to the 100 mcg dose. Following multiple dosing (100 or 200 or 400 mcg QD for 7days), there was no evidence of drug accumulation.

Distribution: The volume of distribution (Vd) reported was 99.5 L (SD=27.5).

Metabolism: In animal studies using rats and dogs, three metabolites of triamcinolone acetonide have been identified. They are 6β-hydroxytriamcinolone acetonide, 21-carboxitriamcinoloneacetonide and 21-carboxy- 6β-hydroxytriamcinolone acetonide. All three metabolites are expected to be substantially less active than the parent compound due to (a) the dependence of anti-inflammatory activity on the presence of a 21-hydroxyl group, (b) the decreased activity observed upon 6-hydroxylation, and (c) the markedly increased water solubility favoring rapid elimination. There appeared to be some quantitative differences in the metabolites among species. No differences were detected in metabolic pattern as a function of route of administration.

Elimination: After a single intranasal dose of 400 mcg of triamcinolone acetonide (twice the recommended starting dose of Tri-Nasal Spray), the mean observed elimination half-life was 2.26 hours (SD=0.77). Based upon intravenous dosing of triamcinolone acetonide phosphate ester, the half-life of triamcinolone acetonide was reported to be 88 minutes. The reported clearance was 45.2 L/hour (SD=9.1) for triamcinolone acetonide.

Special populations

Age: The effect of age, specifically in geriatric and pediatric patients, on the pharmacokinetics of triamcinolone acetonide has not been studied.

Gender: Gender did not significantly influence the pharmacokinetics of Tri-Nasal Spray.

Race: The effect of race on the pharmacokinetics of Tri-Nasal Spray has not been studied.

Renal/Hepatic Insufficiency: No specific pharmacokinetic studies have been conducted in renally or hepatically impaired subjects.

Drug-Drug Interactions: No specific drug-drug interactions have been investigated.

/S/ - 12/16/99

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

/S/ 12/17/99

Ramana Uppoor, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC: HFD-570 (NDA 20-120, DIV FILE, and Barnes)
HFD-870 (Huang, Hunt, Uppoor, Choi)
CDR Attn: Barbara Murphy

SEP 1 1 1997

Clinical Pharmacology & Biopharmaceutics Review

NDA 20-120
Tri-Nasal™ (triamcinolone acetonide nasal solution, 0.05%) nasal spray

Muro Pharmaceuticals, Inc.
Tewksbury, MA 01876

Type of Submission: Revised Labeling
Submission Date: 4/15/97

Reviewer:
Brad Gillespie, PharmD

Background Tri-Nasal spray is a metered dose manual pump spray containing 0.05% w/v (0.5 mg/ml) triamcinolone acetonide (TAA). This product is intended for topical administration to nasal mucosa. The proposed indications are for the nasal symptoms of seasonal and perennial allergic rhinitis in patients 12 years of age and older. The recommended starting dose of Tri-Nasal spray is 200 mg/day given as 2 sprays (50 mg/spray) in each nostril once a day. The active ingredient in Tri-Nasal spray, TAA, is a glucocorticosteroid which has been widely used for treatment of allergic disorders. It has potent antiinflammatory activity.

Tri-nasal is a new dosage form (solution) of TAA. Since the approval of this product is to be partially based on clinical studies, it has been submitted as a 505(b)(2) application instead of an ANDA. This submission relies, at least partly, on the safety database of Nasacort, an approved intranasal TAA suspension. The human pharmacokinetic portion of this application was reviewed by the Office of Clinical Pharmacology & Biopharmaceutics (see Dr. Uppoor's 7/15/96 review). Dr. Uppoor recommended approval of this application with labeling comments. These comments were communicated to the sponsor in a 9/17/96 Not Approvable (NA) letter from the Division of Pulmonary Drug Products. The sponsors response to these comments is the subject of this review.

Discussion The sponsor has incorporated all of the Office of Clinical Pharmacology & Biopharmaceutics labeling comments into their current label.

Recommendation The Office of Clinical Pharmacology & Biopharmaceutics has reviewed the revised labeling for Tri-Nasal and has found it acceptable for approval.

/S/ 9/11/97
Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

FT /S/ 9/11/97 Dale P. Conner, PharmD, Team Leader

cc:
HFD-570 (NDA 20-120, Divisional File, Barnes, Nicklas)
HFD-870 (ChenME, Conner, Hunt)
HFD-850 (Lesko, Huang)
CDR (Barbara Murphy)

JUL 15 1996

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,120 **Submission Date:** October 31, 1995
June 4, 1996

Drug Name and Formulation: Tri-nasal® (triamcinolone acetonide nasal solution, 0.05%) spray

Sponsor: Muro Pharmaceutical Inc., Tewksbury, MA 01876

Reviewer: Venkata Ramana S. Uppoor, Ph.D.

Type of Submission: New Drug Application (Amendment)

I. BACKGROUND

Tri-nasal spray is a metered dose manual pump spray containing 0.05% w/v (0.5 mg/ml) triamcinolone acetonide (TAA). This is intended for topical administration to nasal mucosa. The proposed indications are for the nasal treatment of patients, 12 years and older, with seasonal and perennial allergic rhinitis symptoms. The recommended starting dose of Tri-nasal spray is 200 μg/day given as 2 sprays (50 μg/spray) in each nostril once a day. The active ingredient in Tri-nasal spray, TAA, is a glucocorticosteroid which has been widely used for treatment of allergic disorders. It has potent antiinflammatory activity.

Tri-nasal is a new dosage form (solution) of the approved drug product Nasacort (suspension). Since the approval of this product is to be based on clinical studies, it has been submitted as a 505(b)(2) application instead of an ANDA. This submission relies, at least partly on the safety database of Nasacort. This NDA (for Tri-nasal spray) was previously submitted and was not approved (08/14/92) due to several deficiencies.

II. OBJECTIVES

The sponsor submitted this amendment to the NDA to gain approval of Tri-nasal spray (a nasal solution formulation of TAA).

III. STUDIES SUBMITTED

The sponsor submitted 3 pharmacokinetic studies along with several clinical safety and efficacy studies in this application. The 3 pharmacokinetic studies are listed below:

1. Pilot study to compare the pharmacokinetics of nasal TAA solution (Tri-nasal) and intramuscular TAA suspension in perennial allergic rhinitis patients.
2. Pharmacokinetic analysis of the bioavailability of Tri-nasal nasal TAA relative to a reference standard (Nasacort) in male and female patients with perennial allergic rhinitis.
3. Dose proportionality of Tri-nasal nasal TAA solution, in male and female patients with perennial allergic rhinitis.

IV. SUMMARY OF HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SECTION

A. Formulation:

The details of formulation of Tri-nasal spray are given below.

COMPOSITION OF Tri-nasal SPRAY

COMPONENTS	COMPOSITION	
	g/100 ml (%)	Per spray
Triamcinolone acetonide, USP	0.05	50 µg
Propylene glycol, USP	[redacted]	[redacted]
Polyethylene glycol 3350, NF		
Edetate disodium, USP		
Citric acid, USP		
Sodium citrate, USP		
[redacted] benzalkonium chloride [redacted] NF		
Purified water, USP	[redacted]	[redacted]

B. PHARMACOKINETICS OF TRI-NASAL VS. KENALOG:

Study 100-104 was conducted to compare the pharmacokinetics of 200 and 400 µg of Tri-nasal vs. 4 and 8 mg Kenalog (intramuscular injection). This was done to select an appropriate dose of Kenalog and Tri-nasal to be used in the topical vs. systemic effects study. The sponsor concluded that 400 µg Tri-nasal produces comparable plasma TAA levels as that of 4 mg Kenalog. Results indicate, however, that peak plasma concentrations for the Tri-nasal, intranasal administration are much higher than those obtained after IM injection. These differences are compounded by differences in dosing regimen, in that, the IM is administered once a week vs. the intranasal product is administered once a day. Hence the selected doses for the topical vs. systemic effects study are inappropriate.

C. PHARMACOKINETICS OF TRI-NASAL VS. NASACORT:

Study 100-105 was conducted to determine the relative bioavailability of Tri-nasal compared to the reference, currently approved, product Nasacort. Results show that TAA is rapidly absorbed from Tri-nasal as indicated by shorter T_{max} (0.47 hr for Tri-nasal vs. 2.28 hr for Nasacort). Statistically significantly higher C_{max} and AUC were obtained with Tri-nasal compared to Nasacort (90% confidence intervals for ln AUC_{0-t} : 430.2 - 978.2; for ln C_{max} : 584.4 - 920.4). This study also showed no gender effect on pharmacokinetics of TAA administered via Tri-nasal nasal spray.

D. DOSE PROPORTIONALITY OF TRI-NASAL:

Study 100-106 was conducted to determine the dose proportionality in pharmacokinetics of TAA from Tri-nasal upon both single and multiple dosing (for 7 days). 100, 200 and 400 µg daily doses of Tri-nasal spray were administered for 7 days and plasma concentrations of TAA determined on days 1 and 7. Results show that TAA plasma concentrations increase with increasing doses of Tri-nasal. However, examination

of dose-normalized pharmacokinetic parameters suggested that C_{max} and AUC increased less than proportionally with increasing doses. This study also demonstrated that there was no accumulation of TAA upon multiple dosing.

V. COMMENTS TO THE MEDICAL REVIEWER:

1. Bioavailability of TAA from Tri-nasal is at least 5 times greater than Nasacort. Hence, the use of safety database of Nasacort is not appropriate. However, this may not be of a major concern, if the clinical safety and efficacy studies with this product are adequate to make this NDA a stand-alone application. The studies submitted in the Human Pharmacokinetics and Bioavailability section are adequate to meet the requirements for this section.
2. The sponsor claims that the 400 µg Tri-nasal and 4 mg Kenalog produce similar plasma levels of TAA. However, pharmacokinetics of Tri-nasal are clearly different from Kenalog. The data indicates that the peak plasma concentrations and in turn the $AUC_{(0-12)}$ for the Tri-nasal, intranasal administration are much higher than those obtained after IM injection. These differences are compounded by differences in dosing regimen, in that, the IM is administered once a week vs. the intranasal product is administered once a day. Higher plasma concentrations are achieved after administration of Tri-nasal on each day. Hence, the selected doses for topical vs. systemic effect study are not satisfactory. If similar levels were obtained following both Tri-nasal and IM administration and if Tri-nasal showed greater efficacy, this could be attributed to topical effect of Tri-nasal. However, higher levels are achieved after Tri-nasal. Hence, superior efficacy (if any) obtained following Tri-nasal administration cannot solely be attributed to topical effects. This could as well have been due to systemic absorption of TAA from Tri-nasal. It is very difficult to separate the topical vs. systemic effects with the selected doses. Hence, the selected dose for the topical effect study is not acceptable. Therefore, the topical effect claim for this product is not substantiated.

   It should also be noted that even with reduced doses of Tri-nasal, the plasma profiles of TAA following administration via intranasal vs. IM will not be similar. Hence, the selection of IM route for this study, which acts as a depot, seems to be the problem. Instead, an alternate route of administration that produces similar plasma profile as Tri-nasal, such as TAA suspension or solution given via oral route, would have been beneficial.
3. The to-be marketed pump device is different from those used in clinical and PK studies. No pharmacokinetic bridging studies were conducted to compare the clinical and to-be marketed device. Since, the formulation under consideration is a solution, the chemist should be consulted on the comparability of these two devices based on in vitro data.

VI. COMMENTS TO THE SPONSOR:

1. In the topical vs. systemic effects study, higher plasma concentrations are achieved after administration of Tri-nasal on each day compared to Kenalog. Hence, the selected doses for topical vs. systemic effect study are not satisfactory. Therefore, the topical effect claim for this product is not substantiated.

2. It should also be noted that even with reduced doses of Tri-nasal, the plasma profiles of TAA following administration via intranasal vs. IM will not be similar. Hence, the selection of IM route for this study, which acts as a depot, seems to be the problem. Instead, an alternate route of administration that produces similar plasma profile as Tri-nasal, such as TAA suspension or solution given via oral route, would have been beneficial.

VII. LABELING COMMENTS: For proposed label, see attachment 1.

1. In the pharmacokinetics section of the label, the sponsor should include information regarding relative bioavailability of Tri-nasal [redacted]

2. Information regarding dose proportionality should be included in the label as follows:
   A pharmacokinetic study to demonstrate dose proportionality was conducted in perennial allergic rhinitis patients. The C_{max} and AUC of the 200 and 400 µg doses increased less than proportionally when compared to the 100 µg dose.
3. Information regarding absence of gender effect on pharmacokinetics of TAA from Tri-nasal should also be incorporated in the label.
4. The statement regarding topical effects [redacted] should be removed from the label.
5. The statement [redacted] should either be removed or should state that TAA levels obtained following 400 µg Tri-nasal are [redacted] than [redacted]

VIII. RECOMMENDATION

This submission has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. This submission is acceptable provided there is adequate safety and efficacy data on this product to make this a standalone application. Systemic exposure of TAA following Tri-nasal administration is higher than the reference product Nasacort.

Please forward comments 1 - 2 and labeling comments 1 - 5 to the sponsor.

/S/ 07/12/96

Venkata Ramana S. Uppoor, Ph.D.
Division of Pharmaceutical Evaluation II

FT Initialed by Dale Conner, Pharm.D. /S/ 7/15/96

CC list:
HFD-570: NDA 20,120; HFD-570: Division file; HFD-570: CSO\Sandy Barnes;
HFD-570: Medical Reviewer\Ana Maria Saavedra; HFD-570: Chemist\Linda Ng;
HFD-570: Pharmacologist\Virgil Whitehurst; HFD-870: Dale Conner;
HFD-870: John Hunt; HFD-870: ChenMe; HFD-860: Malinowski; HFD-880: FleischerN;
HFD-850: Lesko; HFD-850: Chron; HFD-850: Drug;
HFD-870: Venkata Ramana S. Uppoor; HFD-340: Viswanathan; HFD-205: FOI.

IX. STUDY SUMMARIES:

a. STUDY 100-104: (DOSE SELECTION FOR TOPICAL EFFECT STUDY)

COMPARATIVE PHARMACOKINETICS OF TRI-NASAL SOLUTION AND IM TRIAMCINOLONE ACETONIDE SUSPENSION (KENALOG-40) IN PATIENTS WITH PERENNIAL ALLERGIC RHINITIS

Reference: Volume 4
Investigator: [redacted]
Study Location: [redacted]

Objective:

To determine the pharmacokinetic profile of TAA from 200 and 400 μg intranasal doses relative to 4 and 8 mg intramuscular (IM) doses, and to compare the plasma TAA levels from the two delivery routes. This will enable the determination of equivalent doses of Tri-nasal and IM TAA (Kenalog) for use in the topical vs. systemic effect study.

Study design:

This is a randomized, open-label, 4-way crossover study of single doses of 200 μg Tri-nasal or 400 μg Tri-nasal or 4 mg Kenalog IM or 8 mg Kenalog IM. 9 male subjects with perennial allergic rhinitis between 18 and 47 years of age participated in the study (8 subjects completed the study). There was a washout period of 10 days between each of the 4 treatments. The 4 treatments are listed below:

Treatment 1: Tri-nasal TAA nasal solution 0.5 mg/ml, 4 actuations per nostril 50 μg/actuation, for a total dose of 400 μg.
Treatment 2: Kenalog-40 injection, sterile TAA suspension, 0.1 ml IM, for a total dose of 4 mg.
Treatment 3: Kenalog-40 injection, sterile TAA suspension, 0.2 ml IM, for a total dose of 8 mg.
Treatment 4: Tri-nasal TAA nasal solution 0.5 mg/ml, — actuations per nostril — μg/actuation, for a total dose of 200 μg.

Batch numbers of Drug supplies:
1. Tri-nasal (TAA) 0.5 mg/ml nasal solution, 50 μg/100 μl actuation, Muro Pharmaceutical, Inc., Lot # 20608 —
2. Tri-nasal (TAA) 0.5 mg/ml nasal solution, —— μl actuation, Muro Pharmaceutical, Inc., Lot # 20608 —
3. Kenalog-40 injection, sterile TAA suspension, 40 mg/ml, West-wood Squibb Pharmaceuticals, Inc., Buffalo, NY, Lot # 2A58071.

Blood was collected for determination of plasma concentrations of TAA at 0, 2, 5, 10, 20, 30 and 45 minutes, and at 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 72 and 168 hours after each treatment dose. Urine samples were collected and pooled for the intervals of 0-2, 2-4, 4-8, 8-12 and 12-24 hours after each treatment. Plasma and urine samples were assayed for TAA using [redacted] methods. Pharmacokinetic analysis of data

was performed using model-independent techniques. As this was a pilot study, no statistical analysis was performed on the PK parameters.

Results:

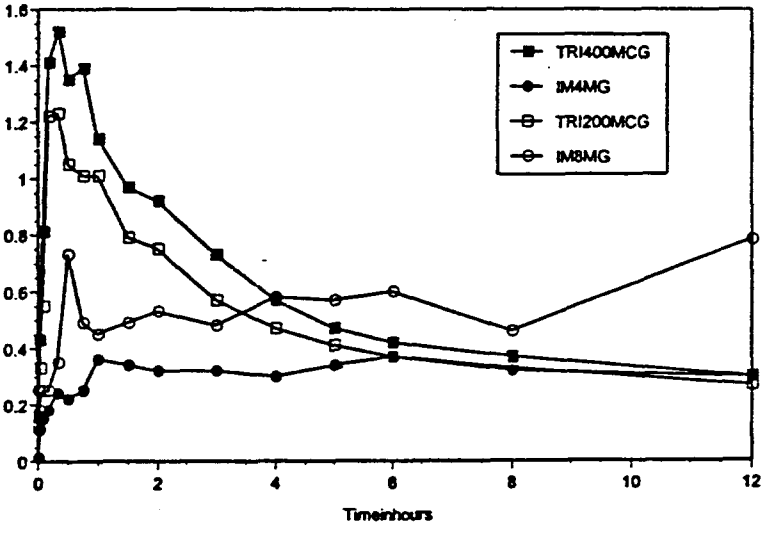
ASSAY PERFORMANCE:

1. For TAA in plasma:

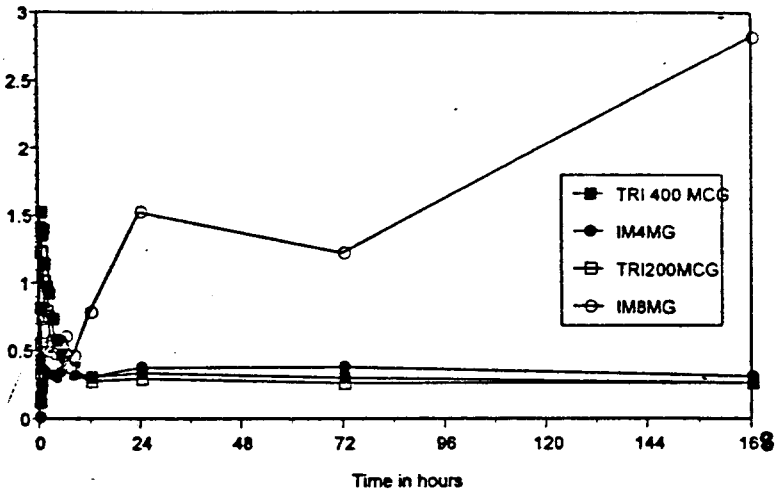
2. For TAA in urine: Method used: ———————
LOQ = ———
Assay validation report for TAA assay in urine was not submitted.

Mean plasma concentration profiles for TAA following administration of Tri-nasal and Kenalog are shown in the figures below:

Plasma TAA concentration, ng/ml



Plasma TAA concentration, ng/ml



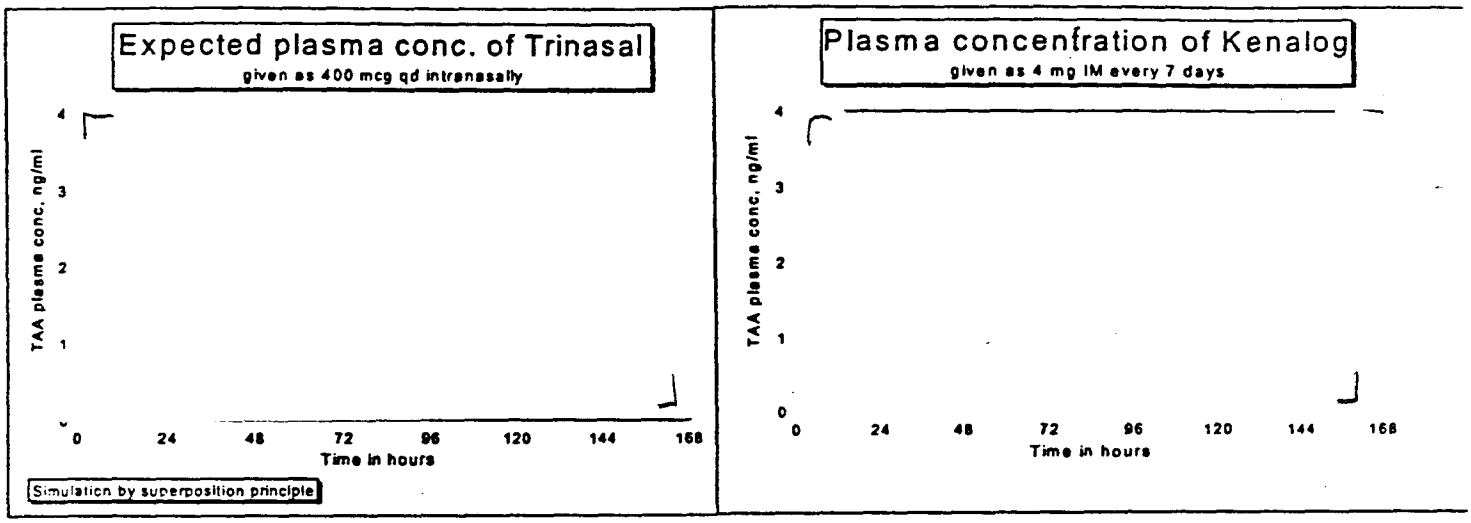
The mean plasma concentration profiles were different for the two delivery routes, with C_{max} being higher for the intranasal formulation.

Mean (± standard deviation) pharmacokinetic parameters for TAA obtained after IM and intranasal dosing are shown in the table below:

Parameter	*4 mg IM*	8 mg IM	200 µg Tri-nasal	*400 µg Tri-nasal*
C_{max}, ng/ml	*0.40 (0.30)*	3.33 (6.67)	1.46 (0.74)	*1.91 (0.73)*
T_{max}, hr	18.67 (24.31)	43.06 (59.01)	0.31 (0.24)	0.36 (0.19)
AUC_{0-168}, ng.hr/ml	*44.89 (45.79)*	279.79 (558.83)	29.18 (29.57)	*33.22 (35.65)*
AUC_{0-12}, ng.hr/ml	*3.22 (2.40)*	6.61 (3.22)	5.35 (2.89)	*6.92 (3.64)*
$t_{1/2}$, hr	5.30	4.86	1.94	2.81
A_{μ}, µg	4.7 (4.2)	8.3 (4.5)	5.4 (3.33)	6.0 (5.3)

Comments:

1. The sponsor concluded that the 400 µg Tri-nasal and 4 mg Kenalog produce comparable plasma levels of TAA. However, the data indicates that the peak plasma concentrations and in turn the $AUC_{(0-12)}$ for the Tri-nasal, intranasal administration are much higher than those obtained after IM injection. These differences are compounded by differences in dosing regimen, in that, the IM is administered once a week vs. the intranasal product is administered once a day (see the figures below). Higher plasma concentrations are achieved after administration of Tri-nasal on each day (this occurs even after taking into consideration carry over effect from IM that has occurred in this study). Hence, the selected doses (400 µg Tri-nasal qd and 4 mg Kenalog q7days) for topical vs. systemic effect study are not satisfactory. If similar levels were obtained following both Tri-



nasal and IM administration and if Tri-nasal showed greater efficacy, this could be attributed to topical effect of Tri-nasal. However, higher levels are achieved after Tri-nasal. Hence, superior efficacy (if any) obtained following Tri-nasal administration cannot solely be attributed to topical effects. This could as well have been due to systemic absorption of TAA from Tri-nasal. It is very difficult to separate the topical vs. systemic effects with the selected doses.

2. It should also be noted that even with reduced doses of Tri-nasal, the plasma profiles of TAA following administration via intranasal vs. IM will not be similar. Hence, the selection of IM route for this study, which acts as a depot, seems to be the problem. Instead, an alternate route of administration that produces similar plasma profile as Tri-nasal, such as TAA suspension or solution given via oral route, would have been beneficial.

Conclusion:

The sponsor concluded that comparable plasma TAA levels are achieved upon administration of 400 µg Tri-nasal and 4 mg Kenalog-40. Results indicate, however, that higher concentrations are achieved following administration of Tri-nasal. Hence, these doses that are selected for topical vs. systemic effects study are not suitable.

b. STUDY 100-105: (TRI-NASAL VS. REFERENCE PRODUCT NASACORT)

PHARMACOKINETIC ANALYSIS OF THE BIOAVAILABILITY OF TRI-NASAL NASAL TRIAMCINOLONE ACETONIDE RELATIVE TO A REFERENCE STANDARD (NASACORT) IN MALE AND FEMALE PATIENTS WITH PERENNIAL ALLERGIC RHINITIS

Reference: Volume 5
Investigator:
Study Location: [ ]

Objective:

To determine the pharmacokinetic profile and bioavailability of TAA from a single 400 μg intranasal dose of Tri-nasal relative to a 440 μg dose of Nasacort, a currently marketed form of nasal TAA.

Study design:

This is a randomized, open-label, 2-way crossover single dose study of 400 μg Tri-nasal or 440 μg Nasacort. 27 male and female subjects with perennial allergic rhinitis between 20 and 40 years of age participated in the study (24 subjects (14 males and 10 females) completed the study). There was a washout period of 14 days between the two treatments. The 2 treatments are listed below:

Treatment 1: Tri-nasal TAA nasal solution, 4 actuations per nostril 50 μg/actuation, for a total dose of 400 μg.
Treatment 2: Nasacort TAA nasal inhaler, 4 actuations per nostril 55 μg/actuation, for a total dose of 440 μg.

Batch numbers of Drug supplies:
1. Tri-nasal (TAA) 0.5 mg/ml nasal solution, 50 μg/100 μl actuation, Muro Pharmaceutical, Inc., Lot # 31701
2. Nasacort (TAA) nasal inhaler, 55 μg/actuation, Rhone-Poulenc Rorer (Collegeville, PA), Lot # 95544.

On each dosing day, the patients received their assigned treatment following an 8 hour fast. No food or beverage other than water was consumed until after the collection of the 2 hour blood sample. A light breakfast was served after the 2 hour blood sample; lunch was served 5 - 6 hours after dosing and dinner at 10 - 12 hours after dosing.

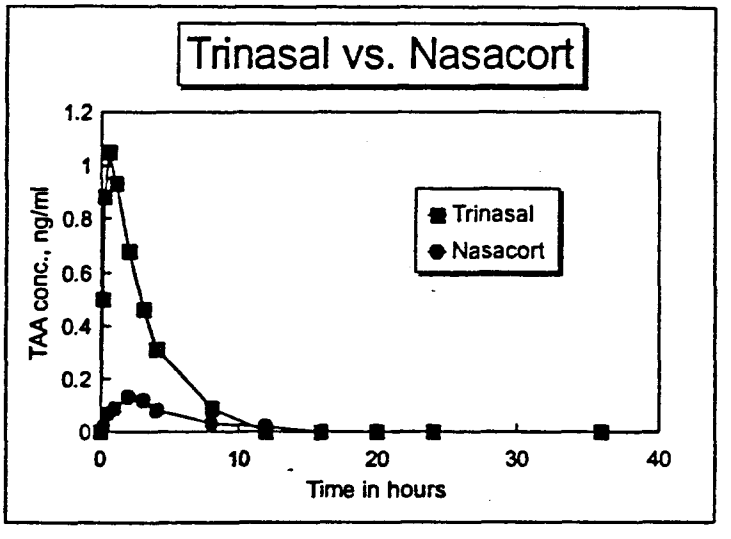
Blood was collected for determination of plasma concentrations of TAA at 0, 5, 10, and 30 minutes, and at 1, 2, 3, 4, 8, 12, 16, 20, 24 and 36 hours after each treatment dose. Plasma samples were assayed for TAA using ———— methods. Pharmacokinetic analysis of data was performed using model-independent techniques. ANOVA was carried out on log transformed AUC and C_{max} using sequence, subjects within sequence, treatment and period as factors.

Results: Of the 27 patients randomized to treatment, 24 completed the study. Data from one of the patients was not used in data analysis since TAA concentrations were measurable in the predose samples. Sponsor attributed this to the patient continuing to take the medication during washout periods.

ASSAY PERFORMANCE:

For TAA in plasma:

Mean plasma concentration profiles for TAA following administration of Tri-nasal 400 µg and Nasacort 440 µg are shown in the figure below:



Mean (± standard deviation) pharmacokinetic parameters for TAA obtained after intranasal dosing via Tri-nasal and Nasacort are shown in the table below:

Parameter	*TRI-NASAL 400 µg*	*NASACORT 440 µg*
C_{max}, ng/ml	*1.12 (0.38)*	*0.14 (0.13)*
T_{max}, hr	*0.47 (0.26)*	*2.28 (0.68)*
AUC_{0-t}, ng.hr/ml	*3.31 (1.59)*	*0.63 (0.95)*
$AUC_{0-\infty}$, ng.hr/ml	3.84 (1.67)	
$t_{1/2}$, hr	2.04	
K_e, hr^{-1}	0.3394 (0.1065)	

The 90% confidence intervals for AUC and C_{max} calculated using the log transformed parameters and using Nasacort as reference are as follows:

FOR LN AUC_{0-T} : 430.2 - 978.2; FOR LN C_{MAX} : 584.4 - 920.4

Results obtained in this study show that higher plasma concentrations of TAA were achieved following administration of Tri-nasal than Nasacort. These differences in C_{max} and AUC were statistically significant. This indicates enhanced absorption following Tri-nasal administration. Also, absorption following Tri-nasal is rapid, as shown by shorter T_{max} compared to Nasacort. An aspect to be noted is the lower % coefficient of variation obtained with Tri-nasal, which indicates better reproducibility in absorption.

Comparison of mean (± st. dev.) PK parameters for Tri-nasal in male and female patients is shown in the table below:

Parameters	Female	Male
C_{max}, ng/ml	1.14 (0.32)	1.10 (0.42)
T_{max}, hr	0.46 (0.11)	0.48 (0.33)
AUC_{0-t}, ng.hr/ml	3.16 (1.71)	3.40 (1.56)

These results indicate the lack of gender effect on pharmacokinetics of TAA when administered as Tri-nasal nasal spray.

Conclusion: Pharmacokinetics of TAA administered as Tri-nasal nasal spray have been determined. Results show enhanced absorption of TAA from Tri-nasal compared to currently approved product Nasacort. Significantly higher C_{max} and AUC (4 to 10 times higher) are obtained with Tri-nasal. Pharmacokinetics of TAA did not differ between male and female patients.

c. STUDY 100-106: (SINGLE AND MULTIPLE DOSE, DOSE PROPORTIONALITY STUDY)

DOSE PROPORTIONALITY OF TRI-NASAL NASAL TRIAMCINOLONE ACETONIDE SOLUTION, IN MALE AND FEMALE PATIENTS WITH PERENNIAL ALLERGIC RHINITIS

Reference: Volumes 6 and 7
Investigator:
Study Location: [ ]
Objective:

To determine the linearity of TAA pharmacokinetics and the extent of TAA accumulation after administration of Tri-nasal.

Drug dosage forms:

Tri-nasal (TAA) 0.5 mg/ml nasal solution, 50 µg per actuation, Muro Pharmaceutical, Inc., Tewksbury, MA, Lot # 31701 —

Study Design:

This is an open-label, randomized, 3-way crossover study, with single and multiple dose administration of Tri-nasal at 3 doses, 100 (1 actuation/nostril), 200 (2 actuations/nostril) and 400 µg (4 actuations/nostril) daily for 7 days. There was a 16 day washout period between treatments. 29 male and female patients, age range 19 - 40 years, with a history of perennial allergic rhinitis enrolled in the study.

On each blood-sampling day, the patients received their assigned treatment following an 8 hour fast. No food or beverage other than water was consumed until after the collection of the 2 hour blood sample. A light breakfast was served after the 2 hour blood sample; lunch was served 5 - 6 hours after dosing and dinner at 10 - 12 hours after dosing. On non-blood-sampling days, meal timings were not controlled prior to or after treatment administration.

Blood was collected for determination of plasma concentrations of TAA, at 0, 5, 10, and 30 minutes, and at 1, 2, 3, 4, 8, 12, 16, 20, and 24 hours after each treatment dose, on days 1 and 7. Trough plasma samples, therefore, were collected on days 1, 2, 6, 7 and 8. Plasma samples were assayed for TAA using ———— methods.

Data Analysis:

The primary pharmacokinetic variables were AUC, C_{max} and t_{max} of TAA. Data was analyzed by model independent methods. Statistical analysis for dose proportionality was conducted on dose-normalized parameters (log transformed) and then tested for differences between treatment groups using analysis of variance and pairwise comparisons. This analysis was conducted for the parameters after both single dose and repeated dosing.

Results:

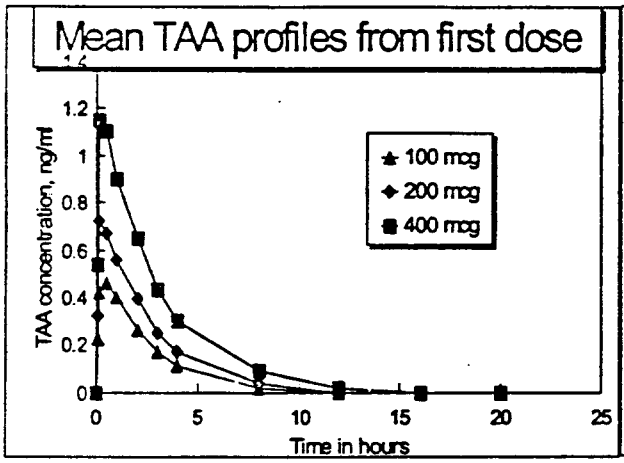
Of the 29 patients randomized to treatment, 28 completed the study.

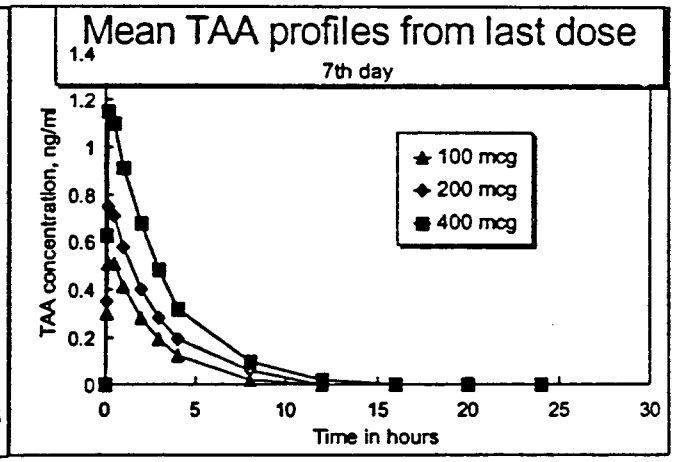
ASSAY PERFORMANCE:

For TAA in plasma:

Pharmacokinetics:

Plasma concentration time profiles of TAA after single dose and after 7 days of treatment with 100 μg, 200 μg and 400 μg daily via Tri-nasal nasal spray are shown in the figures below:





The derived pharmacokinetic parameters, mean (and standard deviation) are shown in the following table:

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Treatment	Single (day 1) or multiple dose (day 7)	AUC $_{0-\infty}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max} (hr)
Tri-nasal 100 μg qd	SD	1.54 (1.30)	0.52 (0.34)	0.41 (0.30)
	MD	1.68 (0.95)	0.57 (0.31)	0.38 (0.24)
Tri-nasal 200 μg qd	SD	2.25 (1.29)	0.77 (0.42)	0.48 (0.62)
	MD	2.58 (1.26)	0.80 (0.37)	0.39 (0.24)
Tri-nasal 400 μg qd	SD	3.83 (2.27)	1.27 (0.85)	0.40 (0.28)
	MD	4.09 (2.21)	1.26 (0.67)	0.42 (0.29)

TAA showed an increase in AUC and C_{max} with increasing dose after both single dose and after repeated dosing. However, this increase with dose was less than proportional, as seen from the dose-normalized parameters. Tukey test showed the dose-adjusted parameters (AUC and C_{max}) from the 100 μg doses to be greater than those for the 200 and 400 μg doses. This lack of dose proportionality could be due to administration of larger volumes into the nose at higher doses. After a large intranasal dose (large volume), some of the dose may be lost from the nostrils.

The data obtained from single dose and after multiple dose indicate that there is no accumulation of TAA upon multiple dosing.

Conclusions:

Results of this study demonstrate lack of dose proportionality in pharmacokinetics of TAA (after both single and repeated dosing). With increase in dose, there was less than proportional increase in plasma TAA concentrations. No accumulation of TAA was observed upon multiple dosing.