

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-784

MEDICAL REVIEW(S)

DIVISION DIRECTOR'S MEMORANDUM

Date: April 7, 2004

To: NDA 20-784

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Nasacort HFA (triamcinolone acetonide) Nasal Aerosol

Applicant: Aventis Pharma Ltd.,

Administrative and Introduction

NDA 20-784 for Nasacort HFA (triamcinolone acetonide) Nasal Aerosol was originally submitted by Rhone-Poulenc Rorer on December 17, 1996, as a 505(b)(1) application intended to be a replacement product for Nasacort Nasal Inhaler (triamcinolone acetonide CFC formulation) for the treatment of seasonal and perennial allergic rhinitis in patients 6 years of age and older. The original application received an approvable action on December 17, 1997, due to many CMC deficiencies. All other disciplines had recommended an approval action at that time. Over the intervening years the application has undergone multiple review cycles but remained approvable due to continued CMC deficiencies. In the interim the ownership of the NDA was assumed by Aventis Pharma due to merger and acquisition. Since last year Aventis has stopped marketing of Nasacort Nasal Inhaler because CFC based nasal spray products are not considered to be medically essential any more and therefore do not receive any CFC allocation. On October 7, 2003, Aventis submitted a complete response to a previous action on this NDA. The CMC deficiencies are now resolved and the CMC discipline is recommending an approval action on this application. The recommendation from other disciplines remains an approval action. Therefore, the NDA will be approved in this review cycle.

The clinical program for Nasacort HFA Nasal Aerosol consisted of one PK study (study RG 5029T-123) and two clinical studies (studies RG 5029T-311, and RG 5029T-405) designed to show therapeutic comparability of the Nasacort HFA Nasal Aerosol to Nasacort Nasal Inhaler. These studies were reviewed with the original submission, and this memorandum refers to those previous reviews. Aventis or its predecessor Rhone-Poulenc Rorer has not submitted any new studies conducted with Nasacort HFA Nasal Aerosol or Nasacort Nasal Inhaler to this NDA since the original submission in 1996.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug substance is triamcinolone acetonide and the DMF associated with the manufacture of the drug substance is adequate. The drug product is a microcrystalline suspension of triamcinolone acetonide in HFA-134a and dehydrated alcohol contained in an aluminum canister affixed to a plastic nasal actuator. Each actuation meters 100 mcg

of triamcinolone acetonide in 65 mg of suspension from the valve and delivers 55 mcg of triamcinolone acetonide from the nasal actuator to the patient. The drug product is manufactured in Holmes Chapel, UK. All manufacturing sites related to this application have acceptable evaluation status.

There were several CMC deficiencies that precluded approval of this application in previous cycles. These have been listed in previous CMC reviews and action letters. The applicant resolved most of the deficiencies during subsequent review cycles. One of the major deficiencies that remained was that of particle size distribution and dose content uniformity, which were outside the range that the Agency has accepted in the past for nasal or orally inhaled drug products. The applicant has made reasonable effort to tighten those as much as feasible. A judgment call was made to accept the applicant's proposed specifications given that the product is intended for nasal topical administration and is not for acute relief of serious symptoms. Wider acceptance criteria are reasonable for such a product.

Clinical Pharmacology and Biopharmaceutics

The applicant conducted study 123 to assess the degree of systemic triamcinolone acetonide (TAA) exposure from the Nasacort HFA Nasal Aerosol (the HFA formulation) and compare that to the then marketed Nasacort Nasal Inhaler (the CFC formulation). The study was conducted on 24 healthy male subjected 19-47 years of age. The study was a randomized two-period cross-over study where every subject received either Nasacort Nasal Aerosol 440 mcg or Nasacort Nasal Inhaler 440 mcg with a 7 day washout between treatments. Serial blood samples were collected to assess the TAA pharmacokinetics. Many plasma samples had TAA level below the quantitative limits following the 12-hour sample time-point, hence it was not possible to establish terminal phase. Therefore, AUC_{0-12hr} was only calculated. The exposure to TAA from both formulations was generally comparable, with the HFA formulation resulting in slightly lower exposure compared to the CFC formulation. For Nasacort HFA Nasal Aerosol the AUC_{0-12hr} was 1.362 ng.hr/ml and C_{max} was 0.205 ng/ml. For Nasacort Nasal Inhaler the AUC_{0-12hr} was 1.309 ng.hr/ml and C_{max} was 0.196 ng/ml. The point estimate and 90% confidence interval for the non-transformed data for AUC 0-12hr were 97.6 and 83.5-111.7, and for C_{max} were 96.7 and 82.1-111.3.

The applicant had conducted a study (study 101) comparing the PK of Nasacort Nasal Inhaler (CFC formulation) with Nasacort AQ Nasal Spray. In that study the systemic bioavailability of Nasacort AQ Nasal Spray was 4-5 folds higher than Nasacort Nasal Inhaler.

Clinical and Statistical

The clinical program for Nasacort HFA Nasal Aerosol consisted of one PK study (discussed above) and two clinical studies designed to show comparability of Nasacort HFA Nasal Aerosol (the HFA formulation) to the then marketed Nasacort Nasal Inhaler (the CFC formulation). The two clinical studies included one 2-week double-blind, double-dummy, placebo-controlled, parallel-group efficacy and safety study comparing

Nasacort HFA Nasal Aerosol and Nasacort Nasal Inhaler in patients 18 years of age and older with seasonal allergic rhinitis (SAR) (study 311), and one 12-month open-label safety study with Nasacort HFA Nasal Aerosol in patients 12 years of age and older with perennial allergic rhinitis (PAR) (study 405). These studies were reviewed in depth in 1996-1997 with the review of the original NDA. The reader is referred to the clinical review of Dr. Cheung Kwong and statistical review of Dr. Stephen Wilson for details, and also to the clinical team leader memorandum of Dr. Peter Honig and the Division Director memorandum of Dr. John Jenkins for summary comments. The team at that time concluded that clinical program had adequately demonstrated comparability of the CFC and the HFA formulations, and therefore the Nasacort HFA Nasal Aerosol could be approved down to the age of 6 years for both SAR and PAR although clinical efficacy study was only conducted in SAR patients 18 years of age and older. I concur with the conclusions made in 1997 because there are no new data or information available on Nasacort and on the use of nasal corticosteroids in allergic rhinitis that require a change in position. Brief comments on the two studies are made in the subsequent section that supports the conclusion.

Study 311 was conducted by the applicant to demonstrate that Nasacort HFA Nasal Aerosol was safe and effective versus placebo and also to demonstrate therapeutic comparability of the HFA and the CFC formulations. The study was conducted in patients 18 years of age older with seasonal (fall ragweed) allergic rhinitis. The study consisted of a screening phase, a baseline phase, and a 2-week double-blind treatment phase. A total of 780 patients were enrolled in the study in 16 centers in the United States. The active treatments were 440 mcg, 110 mcg, and 14 mcg per day for both Nasacort HFA Nasal Aerosol (the HFA formulation) and Nasacort Nasal Inhaler (the CFC formulation). The 440 mcg/day and 110 mcg/day were known effective doses of Nasacort Nasal Inhaler. For enrollment into the double-blind treatment phase of the study, patients were required to have a total rhinitis symptom score (sum of scores of nasal discharge, nasal stuffiness, sneezing, and nasal itching; each scored by reflection over the preceding 12 hours on a 0 to 3 scale) of 42 out of a possible maximum score of 84 for 3 days prior to randomization and the morning of randomization. The primary efficacy analyses was mean reduction of nasal index score (scores of nasal discharge, nasal stuffiness, and sneezing; each scored by reflection over the preceding 12 hours on a 0 to 3 scale) over the 2-week treatment period compared to baseline. There were various secondary variables; including assessment based on "snap-shot" score recorded in the morning to represents the symptom score at approximately 24 hours after the previous dose. All symptoms were scored by patients. Results of the primary efficacy analyses are shown in Table 1, and results of the "snap-shot" analyses are shown in Table 2. Doses of 440 mcg/day and 110 mcg/day were more effective than placebo based on the reflective symptom score, with a numerical trend of 440 mcg/day providing greater efficacy than 110 mcg/day, and a numerical trend of CFC formulation providing slightly greater efficacy than the HFA formulation. The 14 mcg/day dose was also more effective than placebo (Table 1), but that dose is not supported because of lack of maintenance of efficacy at the end of dosing interval (Table 2). These results support comparability of Nasacort HFA Nasal Aerosol (the HFA formulation) to Nasacort Nasal Inhaler (the CFC formulation).

Table 1: Analyses of change from baseline in reflective symptom score for all treated patients in study 311

Treatment Group (n)	Baseline Mean Score*	Mean Change from Baseline (SEM)**	Placebo Comparison (p-value)
Nasacort HFA 440 mcg Once Daily (111)	6.78	-2.64 (0.18)	<0.05
Nasacort HFA 110 mcg Once Daily (105)	6.41	-2.29 (0.18)	<0.05
Nasacort HFA 14 mcg Once Daily (113)	7.06	-2.11 (0.17)	<0.05
Nasacort CFC 440 mcg Once Daily (108)	6.73	-2.84 (0.18)	<0.05
Nasacort CFC 110 mcg Once Daily (114)	6.65	-2.55 (0.17)	<0.05
Nasacort CFC 14 mcg Once Daily (113)	6.99	-2.06 (0.17)	<0.05
Placebo (113)	6.75	-1.39 (0.18)	

* Baseline score was an average of the morning and evening score of 3 symptoms of allergic rhinitis (nasal discharge, nasal stuffiness, and sneezing) for 3 days preceding randomization and the morning of randomization. Each symptom was scored by patients 2 times a day by reflection over the preceding 12 hours on a scale of 0 to 3 where 0=no symptom and 3=severe symptoms.
** Changes were averaged over the 2-week treatment period compared to the baseline. Symptom scoring during treatment period was the same as that for baseline.

Table 2: Analyses of change from baseline in “snap shot” symptom score for all treated patients in study 311

Treatment Group (n)	Baseline Mean Score*	Mean Change from Baseline (SEM)*	Placebo Comparison (p-value)
Nasacort HFA 440 mcg Once Daily (76)	6.21	-2.07 (0.23)	<0.05
Nasacort HFA 110 mcg Once Daily (68)	5.49	-1.20 (0.24)	0.43
Nasacort HFA 14 mcg Once Daily (73)	6.46	-1.08 (0.23)	0.67
Nasacort CFC 440 mcg Once Daily (72)	5.87	-1.80 (0.23)	<0.05
Nasacort CFC 110 mcg Once Daily (77)	6.18	-1.93 (0.23)	<0.05
Nasacort CFC 14 mcg Once Daily (75)	6.45	-1.35 (0.23)	0.21
Placebo (71)	6.17	-0.94 (0.24)	

* Baseline score was an average of the morning and evening score of 3 symptoms of allergic rhinitis (nasal discharge, nasal stuffiness, and sneezing) for 3 days preceding randomization and the morning of randomization. Each symptom was scored by patients in the morning only and represents the symptom score at approximately 24 hours after the previous dose. Scoring was on a scale of 0 to 3 where 0=no symptom and 3=severe symptoms. Six investigators did not participate in the “snap shot” rating.
** Changes were averaged over the 2-week treatment period compared to the baseline. Symptom scoring during treatment period was the same as that for baseline.

Study 405 was conducted by the applicant to demonstrate long term safety of Nasacort HFA Nasal Aerosol. The study was conducted in patients 12 years of age older with perennial allergic rhinitis. Patients were treated with 220 mcg/day for the first 2 weeks, and then all patients continued treatment with 440 mcg/day dose with the intent to maximize exposure to triamcinolone. A total of 396 patients were enrolled in the study in 10 centers in the United States. The most significant adverse events noted in the study were epistaxis, nasal septal ulceration and erosion. A total of 8 patients discontinued from the study due to epistaxis (Patients 028, 086, 114, 196, 246, 263, 297, and 321), and 9 patients discontinued from the study due to application site reaction or nasal septal discomfort or both (Patients 064, 079, 086, 087, 311, 364, 371, 383, and 411). A high percentage of patients who reported to have nasal septum discomfort had ulceration or erosion of the anterior septum on physical examination. These local adverse events will be mentioned in the package insert and will need to be monitored post-approval.

Pharmacology and Toxicology

The applicant conducted a bridging pre-clinical toxicology program to link the Nasacort HFA Nasal Aerosol to the Nasacort Nasal Inhaler (the CFC formulation). The data from the bridging studies were reviewed previously and were found to be acceptable. There were some outstanding issues with extractables and leachables noted during previous review cycles, which has now been resolved. The applicant has rights to the preclinical data for HFA-134a.

On September 5, 2003, the applicant submitted a labeling supplement to NDA 20-468 to include language based on results of two in vitro mutation assays. A review of the studies was completed on February 4, 2004, and the team concluded that the labeling language is supported by the submitted data. Since the results of the studies also apply to this NDA, same language will be included to this product label as well.

Data Quality, Integrity, and Financial Disclosure

DSI audited two sites involved in the 2-week clinical trial. No serious deficiencies were noted at either site. During review of the studies no irregularities that would raise concerns regarding data integrity were found. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. No financial disclosure statements were submitted because the studies were conducted before that requirement went into effect.

Pediatric Consideration

The applicant is proposing use of Nasacort HFA Nasal Aerosol in patients 6 years of age and older. The Division has previously determined that nasal corticosteroids should be developed down to the age of 2 years. Although seasonal allergic rhinitis exists down to the age of 2 years and perennial allergic rhinitis exists in even younger patients, the Division considers that for nasal corticosteroids a lower age bound of 2 years would be appropriate because of availability of other forms of treatment for allergic rhinitis for

patients below 2 years of age, and because of safety concerns with the use of nasal corticosteroids in the very young children. Aventis will need to develop Nasacort HFA Nasal Aerosol down to the age of 2 years.

Linear growth suppression is a concern with all corticosteroids including nasal corticosteroids. The Agency and the scientific community consider linear growth as a marker for systemic effect of corticosteroids. This issue was discussed at an Advisory Committee meeting held on July 30 and 31, 1998. All nasal and orally inhaled corticosteroids have a class labeling to indicate that these drugs can cause growth suppression. Nasacort HFA will also have the same class labeling. Aventis will be asked to conduct a linear growth study with Nasacort HFA as a phase 4 commitment.

Product Name

The proprietary name of Nasacort is approved and has been used by Aventis for the nasal spray product formulations containing triamcinolone acetonide. The suffix HFA Nasal Aerosol is appropriate for this dosage form.

Labeling

The product label that was submitted with this application in this complete response was essentially similar to the label submitted with the original application in 1996. The language is similar to the language that was used for Nasacort Nasal Inhaler (the CFC product). That labeling language did not conform to the current science that is reflected in the language of some more recent nasal corticosteroid labels. The Nasacort HFA Nasal Aerosol label was substantially modified by the Division to bring it up to date, and also to reflect on data specific for Nasacort HFA Nasal Aerosol and other Nasacort products as appropriate. Specifically, the Clinical Trials section explains the extrapolation of efficacy from the now no-longer marketed Nasacort Nasal Inhaler to Nasacort HFA Nasal Aerosol. In addition, the Adverse Reactions section captures adverse events observed during clinical practice with Nasacort Nasal Inhaler. This labeling will need updating as adverse events are reported for this drug product. The Division and Aventis have agreed on a final labeling text that adequately reflects the data and the drug class.

Action

The clinical pharmacology study and the clinical efficacy and safety studies are sufficient to link the Nasacort HFA Nasal Aerosol to Nasacort Nasal Inhaler (the CFC formulation) and support the efficacy and safety of Nasacort HFA Nasal Aerosol for use in patients 6 years of age and older for the treatment of seasonal and perennial allergic rhinitis. Aventis and the Division have agreed to several post-approval agreements to address outstanding CMC issues which do not impact safety and efficacy. Aventis will also conduct a pediatric growth study as a phase 4 commitment. The action on this application will be APPROVAL.

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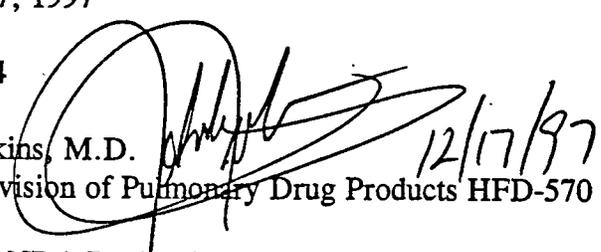
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Badrul Chowdhury
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MEDICAL OFFICER
Div Dir Memo

MEMORANDUM

DATE: December 17, 1997

TO: NDA 20-784

FROM: John K. Jenkins, M.D.  12/17/97
Director, Division of Pulmonary Drug Products HFD-570

SUBJECT: Overview of NDA Review Issues

Administrative

NDA 20-784 for Nasacort HFA (triamcinolone acetonide nasal aerosol) was originally submitted by Rhone-Poulenc Rorer on December 17, 1996. The current user fee goal date for NDA 20-784 is December 17, 1997. Nasacort HFA is the first nasal MDI propelled by HFA propellants submitted to the Agency. Its development was spurred by the Montreal Protocol on Substances that Deplete the Ozone Layer which mandates a worldwide phaseout of the use of CFCs.

Clinical

The proposed indication for Nasacort HFA is treatment of the nasal symptoms of seasonal and perennial allergic rhinitis. This is the same indication that is currently carried by the CFC-based MDI formulation of Nasacort and Nasacort AQ. The clinical development program for Nasacort HFA represented a "switch program" from the currently approved Nasacort CFC formulation and was modeled on the Division's "Points to Consider: Clinical Development Programs for New Nasal Spray Formulations." The program consisted of three clinical trials; 1) a single dose crossover pharmacokinetic comparison of Nasacort HFA and Nasacort CFC, 2) a two-week, double-blind, placebo-controlled comparison of Nasacort HFA and Nasacort CFC in patients with seasonal allergic rhinitis which was designed to demonstrate the safety and efficacy of Nasacort HFA versus placebo as well as its therapeutic comparability to the Nasacort CFC formulation, and 3) a one-year open label study to demonstrate the long-term safety of Nasacort HFA. For more complete details of the clinical review of this application, please refer to the Team Leader's Memorandum by Dr. Honig and the Medical Officer Review by Dr. Kwong.

Pharmacokinetic comparisons demonstrate that the systemic exposure to triamcinolone following a nominal 440 mcg dose of Nasacort HFA is similar to that following 440 mcg from Nasacort CFC and substantially less than that observed from 440 mcg of Nasacort AQ. This observation supports the systemic safety of Nasacort HFA given that the Nasacort AQ formulation at dose of a 440 mcg/day for 42 days has previously been shown to have no significant effect on HPA axis function as assessed by a 6-hour ACTH stimulation test. It should be noted, however, that the division has recently reviewed a growth study in pre-pubescent children which demonstrated a significant effect on growth velocity of beclomethasone dipropionate at doses of 336 mcg/day, a dose that had no significant effect on

HPA axis function by conventional testing. This has led to a tentative conclusion that conventional testing of HPA axis functioning, (e.g., ACTH stimulation) may not be as sensitive for detection of systemic corticosteroid effects as growth studies in children. These new findings are currently being assessed by the division and will likely result in a significant strengthening of the statements in the labeling for intranasal and inhaled corticosteroids with regard to potential adverse effects on growth in children. There may also be a need for the sponsor to conduct a study to assess the impact of long-term use of Nasacort on growth in children.

This study may be a Phase 4 commitment that will be required of the sponsor prior to approval of this NDA. This decision will require further discussion within the division and with the sponsor.

A two-week clinical trial was conducted by the sponsor to demonstrate that Nasacort HFA was safe and effective versus placebo and also to demonstrate the therapeutic comparability of the HFA and CFC formulations. This study clearly demonstrated that doses of 110 and 440 mcg/day of Nasacort HFA and CFC were more effective than placebo for both reflective and instantaneous nasal symptom scores (individual and combined). With regard to demonstration of a dose response, the 440 mcg doses of HFA and CFC provided numerically greater efficacy versus the 110 mcg/dose of the same formulation; however, this difference was not statistically significant. For some of the analyses of symptoms, there was a trend that the HFA formulation was numerically slightly less effective than the CFC formulation; none of these comparisons were statistically significant. The sponsor conducted a number of analyses of the two one-sided 90% confidence intervals of the ratio of HFA/CFC for the various symptom scores; all of the confidence interval estimates spanned 1.0. Overall, it is clear that both the CFC and HFA formulations were effective versus placebo and demonstrated very similar numerical dose response patterns with regard to relief of symptoms. Failure to demonstrate a statistically significant dose response for the products complicates the assessment of therapeutic comparability of the HFA and CFC formulations; however, it is not unusual for studies of intranasal corticosteroids to fail to demonstrate a significant dose response in patients with allergic rhinitis. Given the general flat dose-response curve for intranasal corticosteroids, the low incremental mean benefit of a quadrupled dose of either the CFC or the HFA formulation, the very similar numerical trends for absolute response and dose-response observed for the HFA and CFC products, and the product indication, I concur with the assessment made by Drs. Kwong and Honig that the results of this study adequately demonstrate the "comparability" of these two formulations.

From a local safety perspective, the results of the 4-week controlled trial and the one year open-label extension demonstrate the Nasacort HFA is generally well tolerated. Information from the long-term exposure indicated some tendency toward development of nasal septum bleeding, discomfort, ulceration, etc. Similar adverse effects have been demonstrated for other intranasal corticosteroids and given the uncontrolled nature of the long-term exposure it is not possible to estimate the incidence of these findings. The adverse event data for nasal septal

adverse events will need to be included in the package insert and will need to be monitored post-approval.

The sponsor did not conduct clinical trials using the HFA formulation in patients with perennial allergic rhinitis or in patients less than 12 years of age. In accordance with the Division's "Points to Consider" document, and given the fact that the Nasacort CFC formulation is approved for perennial allergic rhinitis and use in patients 6 years of age and older and the fact that the HFA and CFC formulations have been determined to be clinically "comparable", the HFA product can be approved with labeling that includes use in patients 6 years of age and older with seasonal and perennial allergic rhinitis.

Detailed review of the labeling will be deferred pending the sponsor's correction of the below noted CMC deficiencies. The sponsor will be provided general guidance to reformat the package insert based on the more recently approved Nasacort AQ. Note also that the labeling with regard to the potential effects of Nasacort HFA on growth in children may need to be modified to comply with any "class labeling" the Division may develop.

There are no outstanding clinical issues and the NDA is approvable from a clinical perspective with appropriate labeling.

Preclinical

In support of the switch from Nasacort CFC to Nasacort HFA, the sponsor conducted a bridging pre-clinical toxicology program as recommended by the Division. For further details of the review of this program, please refer to the review prepared by Dr. Pei. Overall the bridging toxicology program did not identify any new toxicologic concern and generally supported a conclusion that the CFC and HFA formulations were comparable with regard to toxicity. In addition, RPR is a member of IPAC which has conducted extensive preclinical testing of HFA-134a which have demonstrated a favorable safety profile of this propellant for long-term use in humans. The sponsor has not provided a complete profile of the extractables and leachables for the drug product to allow a complete safety assessment. The sponsor will be reminded of the need to submit the data on extractables and leachables along with supporting safety information in the action letter.

The NDA is approvable from a preclinical perspective with appropriate labeling and pending review of data for the full extractables and leachables profile for the drug product and supporting safety information. Labeling negotiations with the sponsor will be deferred until the application is otherwise approvable.

CMC

Nasacort HFA is a self-pressurized metered-dose inhaler (MDI) containing a suspension of triamcinolone acetonide in HFA-134a and dehydrated alcohol. Each actuation delivers 55 mcg of triamcinolone acetonide from the nasal actuator. The sponsor proposes to market a 100 actuation trade unit. There are numerous outstanding deficiencies with regard to CMC issues. These deficiencies will be communicated to the

sponsor in the action letter. Preliminary labeling comments will also be provided, however, more detailed comments will be deferred pending resolution of the other deficiencies.

The application is not approvable from a CMC perspective. Outstanding CMC deficiencies which must be addressed prior to approval of the application will be included in the action letter to the sponsor.

Clinical Pharmacology and Biopharmaceutics

The sponsor submitted one PK study comparing the systemic absorption of the HFA and CFC products when administered at nominal doses of 440 mcg in healthy volunteers. Please refer to the review prepared by Dr. Chen and the discussion in the clinical section, above for further details of this study. In summary, this study failed to demonstrate bioequivalence of the two formulations using standard BE criteria (failure based on AUC), however, the plasma concentration profiles were very similar for the two products. In general, the HFA formulation appeared to slightly less bioavailable than the CFC formulation. Based on a cross study comparison, systemic bioavailability of the Nasacort AQ is substantially greater than either the HFA or CFC MDI formulations. As noted above under the clinical section the lack of BE for the HFA and CFC products does not preclude approval.

There are no outstanding clinical pharmacology and biopharmaceutics issues and the application is approvable with acceptable labeling.

Data Verification

The Division of Scientific Investigations (DSI) conducted audits of two of the clinical study sites that participated in the two-week controlled trial. No serious deficiencies were noted at either site (one was rated NAI and one was rated VAI) which raise any serious concerns regarding the integrity of the overall clinical database.

Labeling

The sponsor has not officially proposed a trademark for this product. The Division's preferred nomenclature system of HFA replacement products will result in adoption of "Nasacort HFA" if the sponsor chooses to continue with the "Nasacort" name. The sponsor will be informed that the established name for the product should be "triamcinolone acetonide nasal aerosol" rather than the _____ . The sponsor will be referred to the recently approved Nasacort AQ NDA for general comments on labeling. Final review of the labeling will be deferred pending successful resolution of the other outstanding deficiencies.

Conclusion

There are significant outstanding issues related to the CMC review of this product which must be resolved before this application can be approved, however, the NDA is approvable from the standpoint of other disciplines. Therefore, the sponsor should receive an APPROVABLE letter listing the outstanding CMC deficiencies. Labeling comments will be deferred pending acceptable resolution of these CMC issues.

cc:

NDA 20-784

HFD-570 Division Files

HFD-570/Jenkins

HFD-570/Schumaker

HFD-570/Barnes

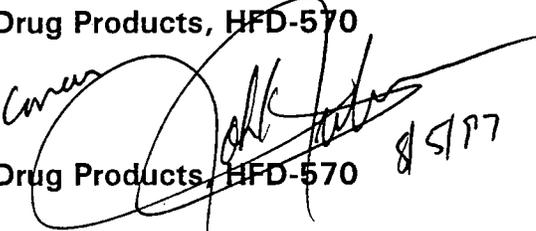
HFD-570/Honig

Team Leader Memorandum

TO: NDA 20,784

FROM: Peter K Honig, MD
Medical Team Leader
Division of Pulmonary Drug Products, HFD-570

THROUGH: John K. Jenkins, MD
Division Director
Division of Pulmonary Drug Products, HFD-570



8/5/97

RE: Nasacort-HFA Nasal Inhaler

DATE: July 29, 1997

Nasacort-HFA is a corticosteroid metered dose inhaler (MDI) developed with an alternative propellant to CFC and intended for once-daily, intranasal administration in the treatment of seasonal and perennial allergic rhinitis in patients six years of age and older. The clinical development program consisted of three clinical studies and was conducted in accordance with the *Points to Consider Document: Clinical Development Programs for New Nasal Spray Formulations*. Study 123 was an open-label, randomized, cross-over pharmacokinetic trial which demonstrated comparable systemic exposures resulting from single, 440 ug doses of Nasacort-HFA and the currently marketed Nasacort MDI (CFC). The summary results of this study are shown later in this memorandum.

Study 311 was a randomized, two-week, double-blind, double-dummy, placebo-controlled, parallel-group, study of patients with seasonal allergic rhinitis. The objective of the study was to demonstrate therapeutic comparability of the currently marketed Nasacort MDI (CFC) and the Nasacort-HFA. 780 patients aged 18 and older were randomized to one of 8 treatment groups. The six active treatments were 14 ug, 110 ug and 440 ug of Nasacort MDI or Nasacort-HFA. The placebo group was equally divided into placebo CFC and placebo HFA arms. The primary efficacy variables consisted of the twice-daily, 'reflectively'-scored, rhinitis symptoms of congestion, rhinorrhea and sneezing. These were also combined into the Nasal Index Score. End-of-dosing-interval symptom scores ('snapshot') were obtained and served as a secondary endpoint. All were analyzed as mean change from baseline evaluated over the entire double-blind treatment period. The results of the primary efficacy analysis are summarized in the table below.

Symptom	Dose	NASACORT-CFC		NASACORT-HFA	
		n	Mean change from baseline	n	Mean change from baseline
Congestion	14 ug	113	0.62	113	0.64
	110 ug	114	0.83	106	0.72
	440 ug	108	0.88	111	0.75
Rhinorrhea	14 ug	113	0.71	113	0.68
	110 ug	114	0.84	106	0.75
	440 ug	108	0.94	111	0.90
Sneezing	14 ug	113	0.70	113	0.77
	110 ug	114	0.87	106	0.83
	440 ug	108	1.02	111	1.00
Nasal Index	14 ug	113	2.04	113	2.09
	110 ug	114	2.54	106	2.30
	440 ug	108	2.84	111	2.65

These data indicate that there is rank-ordering of therapeutic response to increasing nominal doses of Nasacort. It also appears that it may be difficult to demonstrate significant dose-response above 110 ug/day using this endpoint in this patient population. The 'snapshot' scoring (i.e. end of dosing interval assessments) allowed for greater discrimination between daily doses of Nasacort-HFA above 110 micrograms. This endpoint analysis did not, however, allow for discrimination between doses 110 and 440 ug doses of the Nasacort-CFC. The reason for this discrepancy is not clear. Nevertheless, even though the sponsor has not adequately controlled the Type II within-treatment error in this study, the sponsor has achieved the goals of the study and demonstrated therapeutic comparability between the same nominal doses of triamcinolone delivered from the two MDI devices in patients with SAR and greater than 18 years of age. Although not an approval issue, the biostatistic consultant has been asked to evaluate the post-hoc defined 'equivalency' criteria proposed by the sponsor in his review.

An efficacy and safety study involving children down to six years of age was not conducted. Since this is a switch program and the CFC formulation is indicated in the pediatric population down to six years of age, such a study is not required if the safety, efficacy and pharmacokinetics of the HFA formulation are comparable to the reference formulation (*Points to Consider* document).

The safety of Nasacort-HFA was assessed both in the double-blind Study 311 and in the one-year, open-label, safety trial (Study 405) in 396 patients 12 years of age and older. In this long-term study, the initial dose selection was

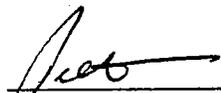
based upon current approved doses for Nasacort-CFC. Following input from the Division, the protocol was amended to allow at least 200 patients to receive 440 ug daily for six months. Nasacort-HFA appeared to be well tolerated in both studies. There was, however, a concern of local nasal effects occurring in the long-term study. There were a total of 23 incidences of "nasal septum bleeding or discomfort". Seven of these patients had objective evidence of nasal septum ulceration, abrasion, erosion or excoriation. Further information to allow clarification of the duration of exposure to Nasacort-HFA before the event was noted has been requested of the sponsor. Since this was an uncontrolled trial without comparator arms, it is difficult to determine whether the local irritation problems are specific to this drug product. It may very well be a class effect that remains underestimated in controlled clinical studies due to limited dosing durations and underreported after these drugs are marketed and used chronically for longer periods of time.

The systemic safety of Nasacort-HFA is based on single-dose, pharmacokinetic comparisons with the CFC and aqueous triamcinolone drug products. These parameters are summarized in the table below.

Drug Product	Age	Dose	Cmax (ng/mL)	AUC ₀₋₁₂ (ng*hr/mL)
NASACORT-HFA	19-47	440 ug	0.196	1.309
NASACORT-CFC	19-47	440 ug	0.205	1.362
NASACORT AQ	18-50	440 ug	0.73	4.07
	6-12	440 ug	0.89	4.06

Since the systemic effects of the Nasacort AQ formulation (i.e. lack of HPA effects) has been demonstrated in the relevant patient populations and the systemic exposure of this formulation is demonstrated to be greater than the Nasacort-HFA drug product, the systemic safety concerns for the Nasacort-HFA application are adequately addressed.

Team Leader Recommendation: The Nasacort-HFA should be approved for the treatment of seasonal allergic rhinitis down to six years of age. Labeling remains to be negotiated with the sponsor and reviewer comments are contained in a separate review.



Peter K Honig, MD
Medical Team Leader

cc:

HFD-570/NDA 20-784/Division File
HFD-570/MO/Nicklas/Honig/Jenkins
HFD-570/Stat/Wilson
HFD-570/PM/Barnes

MEDICAL OFFICER REVIEW

Division Of Pulmonary And Allergy Drug Products (HFD-570)

Application & Number: NDA #20-784	Trade Name: Nasacort® HFA
Applicant/Sponsor: Aventis Pharmaceuticals Inc.	Generic Name: Triamcinolone acetonide nasal spray
Medical Officer: Raymond F. Anthracite, MD	
Team Leader: Peter Starke, MD	Category: Corticosteroid
Date: March 17, 2004	Route: Intranasal

SUBMISSION REVIEWED IN THIS DOCUMENT

<u>Submission Date & Type</u>	<u>CDER Stamp Date</u>	<u>Comments</u>
10/6/2003 (N-000 AZ)	October 7, 2003	CMC complete response
12/19/2003 (N-000 BL)	December 22, 2003	labeling update
1/7/2004 (N-000 BL)	January 8, 2004	labeling (same as 12/19/03) & package update
2/11/2004 (N-000 BL)	February 11, 2004	labeling update with new clinical trials section

RELATED APPLICATIONS

<u>Submission Date & Type</u>	<u>CDER Stamp Date</u>	<u>Comments</u>
IND 43,841	November 2, 1993	IND for Nasacort® HFA
NDA 20-784, N-000	December 17, 1996	Nasacort® HFA Nasal Aerosol
NDA 19-798, N-000	December 27, 1988	Nasacort® Nasal Inhaler (CFC)
NDA 20-468, N-000	June 29, 1994	Nasacort® AQ Nasal Spray

REVIEW SUMMARY

This document is a brief labeling review for NDA 20-784 for Nasacort® HFA Nasal Aerosol (triamcinolone acetonide nasal aerosol). The PDUFA user fee goal date for the first cycle submission was December 17, 1997. At that time, it was considered as "approvable" based on a host of CMC deficiencies, with all other disciplines recommending "approval." After several submissions addressing the CMC deficiencies, the most recent CMC response was submitted on 10/6/2003 (N-000 AZ). This response is considered to have addressed the remaining CMC deficiencies, and NDA 20-784 is now considered for an "approval" action. This review addresses specific labeling issues that were not addressed in previous reviews. However, the final label is not complete, and is therefore not included in this review.

OUTSTANDING ISSUES

Labeling negotiations are ongoing, and the final label is not complete at the time of this review. The Division's made extensive labeling edits of the applicant's proposed PI (proposed.doc, 2/11/04). The Division's edits are summarized in this document.

RECOMMENDED REGULATORY ACTION

NDA/Supplements:	<input type="checkbox"/> Fileable	<input type="checkbox"/> Not Fileable
	<input checked="" type="checkbox"/> Approval:	<input type="checkbox"/> Approvable <input type="checkbox"/> Not Approvable
Other Action:		

Note: This review was begun by Medical Reviewer Dr. Ray Anthracite, but the review and recommendations were substantially modified and entered into DFS by his team leader, Dr. Peter Starke. The assessments and recommendations made herein reflect a compilation of efforts of both reviewers.

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I. EXECUTIVE SUMMARY

This document is a brief labeling review for NDA 20-784 for Nasacort® HFA Nasal Aerosol (triamcinolone acetonide nasal aerosol). The PDUFA user fee goal date for the first cycle submission was December 17, 1997. At that time, it was considered as “approvable” based on a host of CMC deficiencies, with all other disciplines recommending “approval.” After several submissions addressing the CMC deficiencies, the most recent CMC response was submitted on 10/6/2003 (N-000 AZ). This response is considered to have addressed the remaining CMC deficiencies, and NDA 20-784 is now considered for an “approval” action. This review addresses specific labeling issues that were not addressed in previous reviews.

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II. CONTACT INFORMATION

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

/s/

Peter Starke
3/17/04 02:57:22 PM
MEDICAL OFFICER
MO labeling review

Badrul Chowdhury
3/17/04 04:49:48 PM
MEDICAL OFFICER
I concur

Nasacort HFA
-Medical Review

Cheung Kwong M.D., Ph.D.

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	N20-784	APPLICATION TYPE:	NDA
SPONSOR:	Rhone-Poulenc Rorer	PRODUCT/ PROPRIETARY NAME:	Nasacort HFA Nasal
		USAN / Established Name:	Triamcinolone Acetonide
CATEGORY OF DRUG:	Corticosteroid	ROUTE OF ADMINISTRATION:	Intra-nasal
MEDICAL REVIEWER:	C. Kwong	REVIEW DATE:	June 17, 1997

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
Dec. 16, 1996.	Dec. 19, 1996.	NDA	
June 10, 11, 12 of 1997 (facsimile)		NDA	These data were submitted in response to our request.

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
June 29, 1994	NDA 20468	Study subjects ≥ 12 years of age
Aug. 12, 1996	NDA 20468	Study subjects < 12 years of age
Nov. 22, 1994	NDA 19798	Pediatric supplement of Nasacort P12

Overview of Application/Review:

This product was developed by reformulating the currently marketed Nasacort Nasal Inhaler

with HFA-134a. The sponsor stated that their development program was created based on input from our Division (pre-NDA meeting) and the FDA document entitled "Points to Consider: Clinical Development Programs for New Nasal Spray Formulation". This NDA application consists of one two-week SAR efficacy study in adults, one 12 month safety study in subjects 12 years of age and older, and one pharmacokinetic study in adults. In these studies, the sponsor took the 'comparability' approach as defined by the Points-to-Consider document using the Nasacort P-12 (CFC) as their reference product. Basing on the results from these studies, the established efficacy of Nasacort Nasal Inhaler (CFC) in both the adult and the pediatric population, and the previous pharmacokinetic study and the HPA axis study of Nasacort AQ, the sponsor is seeking the approval of Nasacort HFA for the treatment of both SAR and PAR in subjects 6 years of age and older.

Efficacy

The to-be-marketed doses of Nasacort HFA-134a are 110, 220 and 440 mcg once daily for patients 12 years of age and older, which are the same as that of Nasacort P12. A single placebo controlled dose-ranging efficacy trial on SAR (Study 311) was performed in subjects 18 years of age and older comparing the efficacy of Nasacort HFA-134a with that of Nasacort P-12. The efficacy of three doses of each formulation (i.e. 14 mcg, 110 mcg and 440 mcg) were evaluated, and comparisons were made within and between formulations.

Both reflective symptom scores and snap shot symptom scores were collected, and the efficacy analysis was performed on all-treated and on all evaluable patients. The primary efficacy analysis is the mean reduction from baseline of nasal stuffiness, nasal discharge, sneezing and nasal index for the overall double-blind period. As requested by our Division in a pre-NDA meeting, the sponsor made their efficacy comparison of these two Nasacort products using the evaluable population. In principle, the efficacy data of the evaluable population have a lower variability than that of the all treated. As such, it is more difficult to demonstrate comparability using data from this population. In practice, the number of subjects excluded from evaluability was small, and no discernible difference in outcome was appreciated regardless of which population one used.

Within formulation analysis indicates that the mean change from baseline of reflective rhinitis scores of the 110 and 440 mcg groups of each formulation was statistically significantly different from that of the placebo. When end of dosing interval scores were analysed, significant effect was noted only for the 440 mcg dose but not the 110 mcg dose. This finding supports the labeling of the higher dose, and the adequacy of the once daily dosing interval.

Between formulation analysis indicates that the mean changes from baseline of rhinitis scores in subjects who took Nasacort P-12 were within +/- 30% of those who took the corresponding doses of Nasacort HFA-134a. Point estimates suggested that the mean change from baseline of the 440 mcg dose of Nasacort HFA was closest to that of the 220 mcg dose of Nasacort P12. However, the numerical difference was small between the same doses of the two formulations, and this is due to the fact that both doses were at the plateau phase of the dose response curves. Numerical superiority in symptom severity reduction in the 440 mcg triamcinolone acetonide group as compared to the 110 mcg group was observed for each formulation, however, the difference was not statistically significant.

No efficacy study was performed in the pediatric population as such study is not required if the sponsor is able to demonstrate comparability between the new and the reference product in adults.

Pharmacokinetics

Intrasubject comparison of the pharmacokinetics of a single intranasal dose of 440 mcg of each of the two Nasacort products were performed in adults. The $AUC_{0-\infty}$ and C_{max} of these products were very similar in magnitude. In addition, cross-study comparison indicates that they are lower than that of the same dose of Nasacort AQ. As the systemic safety of Nasacort AQ in children has been demonstrated, these pharmacokinetic findings exempt the sponsor from evaluating the effects of Nasacort HFA-134a on the HPA axis.

Long Term Safety Studies

Study 405 was a 12 month, open-label study on 396 patients 12 years of age and older. The starting dose was 220 mcg per day, and after the first two weeks, patients were allowed to adjust the daily dose to 110 mcg or to 440 mcg as needed for adequate symptom relief. On recommendation of FDA, the sponsor modified their protocol so that the daily triamcinolone acetonide dose was standardized at 440 mcg for all subjects. This is intended to maximize the chance of capturing the adverse effects of triamcinolone acetonide and the HFA. This study is particularly useful for evaluating the safety of the propellant since there is not a vast experience on the topical effect of this excipient in the nasal cavity. There were 296 patients who were treated with the highest to-be-marketed dose of triamcinolone acetonide (i.e. 440 mcg dose) for 6 months or more. The most significant topical adverse events noted were epistaxis and nasal septum ulceration and erosion, findings likely attribute to the effect of the corticosteroid. As the adverse effects of Nasacort HFA-134a are not expected to differ markedly between adults and the pediatric population, long term safety study of Nasacort HFA-134a in the pediatric

population was not required, and was not performed.

Outstanding Issues:

None.

Recommended Regulatory Action: approval

N drive location:

NDA/20784/clin/96-12-16.rev

NDAs:

Efficacy / Label Supp.: X Approvable Not Approvable

Signed: Medical Reviewer: Cheung Hing Kwong

Date: June 18, 1997

Medical Team Leader: [Signature]

Date: 6/19/97

Excellent review. Agree i conclusions of recommendations.

See Team Leader Memo for more details

[Signature] 6/19/97

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I. INTRODUCTION

This product contains the same active ingredient as Nasacort AQ, and Nasacort® Nasal Inhaler, which are approved for patients 6 years of age and older. Neither Nasacort® Nasal Inhaler nor Nasacort® AQ Nasal Spray have been withdrawn from any market. Unlike these products, the clinical development of Nasacort HFA is based on the FDA *Points to Consider* document dated 23 January 1996 as it relates to the switching of a CFC based to a non-CFC based formulation.

II. Overview of the Clinical Studies

As recommended by the *Points to Consider Document*, the sponsor conducted a pharmacokinetic study (Study RG 5029T-123) and a dose-ranging study (Study RG 5029T-311) to establish the comparability between the two formulations (CFC P-12 and HFA-134a). In addition, long-term safety was assessed in subjects 12 years of age and older in a one-year, open-label safety study (Study RG 5029T-405).

A specific efficacy and safety study of Nasacort HFA-134a was not conducted in pediatric populations (children ages 6 to 11 years) since, as specified in the *Points to Consider*, it is not required if the safety, efficacy, and pharmacokinetics of the new formulation (HFA-134a) are comparable to that of the reference formulation (CFC P-12) in adults and if the reference formulation had been approved for use in children. The sponsor felt that Nasacort HFA-134a Nasal Inhaler met these criteria. Additionally, it was agreed upon by both the Division of Pulmonary Drug Products and Rhône-Poulenc Rorer that "one study of the response to a rapid cosyntropin stimulation in children treated with Nasacort® AQ for six weeks, with plasma triamcinolone acetonide concentration determinations made at three timepoints, could sufficiently address safety in children for Nasacort® AQ and Nasacort HFA-134a". The aqueous formulation was chosen for this study because it has a higher systemic bioavailability than other Nasacort formulations.

This NDA includes the reports from one double-blind, dose-ranging and placebo-controlled trial conducted in patients 18 years of age and older with seasonal allergic rhinitis (Study 311) and one long-term, open-label safety trial conducted in patients 12 years of age and older with perennial allergic rhinitis (Study 405). Study 405 was conducted primarily to assess the safety of the HFA-134a formulation of Nasacort, although efficacy was evaluated through global assessments by the patients and physicians. Additionally, safety data from the pharmacokinetic study (Study RG 123) were presented to support the safe use of Nasacort HFA-134a in pediatric patients (ages 6 through 11 years).

Study 311, was designed to establish the short term safety as well as to confirm the effectiveness of Nasacort HFA-134a in patients with seasonal allergic rhinitis. It was designed to demonstrate a comparability between RG 5029T (HFA-134a formulation) and the reference Nasacort® (CFC P-12) formulation. The sponsor intended to use this study as the basis for attaining a label claim for children 6-12 years of age as permitted by the *Points to Consider* document if the reference product was approved for this age group. The study design incorporated doses of the original product that were known to be effective (110 and 440 mcg per day) and a sub-optimal dose (14 mcg per day) for comparison with the new formulation.

The primary variables were the mean change from baseline averaged over the double-blind period for the following "reflective" rhinitis symptom scores: nasal stuffiness, nasal discharge, sneezing, and the nasal index (the sum of the scores for nasal discharge, nasal stuffiness, and sneezing) for the reflective 24-hour score (average of the PM reflective 12 hour scores on a given day and the AM reflective 12-hour score on the following day). Upon commencement of the Study 311, our Division requested that "snap shot" symptom severity rating be performed to assess the patient's symptoms at the end of dosing interval. This was intended to evaluate the adequacy of the once daily dosing interval.

Study 405 was a 12-month, open-label study conducted in 396 patients 12 years of age and older at 10 centers throughout the United States. Included as one of these centers, was a site (US00299, William Ziering, M.S.)

To support retaining patients from this site as part of the overall study population, RPR conducted a comparison evaluating the adverse event profile for the study population with and without Dr. Ziering's patients.

In this long-term study, the initial dose selection was based upon current labeling for Nasacort® Nasal Inhaler. Patients initiated treatment with Nasacort HFA-134a at 220 mcg/day for two weeks. After the initial two-week period, patients adjusted their medication down to 110 mcg/day or up to 440 mcg/day as needed to control their allergy symptoms. Following the recommendation our Division that safety information be obtained for at least 200 patients receiving 440 mcg/day over at least six months—the dose was standardized at 440 mcg/day for all patients. Safety was evaluated in all 396 patients enrolled in Study 405.

The safety data from these two studies (Study 311 and Study 405) were not combined due to the differences in trial design (e.g., controlled vs. uncontrolled, seasonal allergic rhinitis vs. perennial allergic rhinitis, short-term vs. long-term).

The following table is a summary of the controlled and uncontrolled clinical studies of Nasacort HFA-134a in patients with seasonal or perennial allergic rhinitis.

A Summary of All Completed Controlled and Uncontrolled Nasacort HFA-134a Clinical Studies

Study Number	Design	Indication	Number of Investigators (Location)	Duration of Drug Treatment (Frequency)	Age Range (Mean)	% M:F C:O	Total Daily Dose	Total Patients Enrolled	Medical Summary Location, Volume, Page
RG 5029T-123	Open-Label, Randomized, PK Comparison in Healthy Adult Male Subjects	N/A	1 (USA)	2 days active treatment	19-47 (26)	100:0 71:29	P-12 440 mcg HFA-134a 440mcg	24	Vol. 1.21 Page 8-1-20
RG 5029T-311	Randomized, Placebo-Controlled, Double-Blind, Double-Dummy, Parallel Group	SAR	16 (USA)	2 weeks (once daily)	18-83 (36)	55:45 84:16	P-12 14 mcg 110 mcg 440 mcg HFA-134a 14 mcg 110 mcg 440 mcg	780	Vol. 1.23 Page 8-3-2
RG 5029T-405	Open-Label, Long-Term	PAR	10 (USA)	12 months (once daily)	12-69 (32)	53:47 92:8	HFA-134a 440 mcg	396	Vol. 1.41 Page 8-21-1

III. Pharmacokinetic Study

A. Objective

This study was conducted to assess the degree of systemic triamcinolone acetonide (TAA) exposure from the new metered dose HFA-134a non-CFC propellant delivery system and to compare it with that of the currently marketed product (Nasacort CFC propellant delivery system).

Reviewer's Comment:

Comparison between the pharmacokinetics of Nasacort HFA and Nasacort AQ can be made indirectly as there are intrasubject data comparing the pharmacokinetics of Nasacort P12 and Nasacort AQ pharmacokinetics of Nasacort AQ. This comparison is useful to determine whether a study to evaluate the effect of Nasacort HFA on the HPA axis is necessary in the pediatric population.

B. Study Design

Subjects were randomly assigned to one of two treatment sequences of two periods in duration. Each treatment period was separated by a seven-day washout period. Subjects were randomly assigned to one of two treatment sequences listed below.

Treatment Sequences

<u>N</u>	<u>Period 1</u>	<u>Period II</u>
12	A	B
12	B	A

Subjects reported to the investigation site on the evening of Day 1 and were fasted overnight beginning no later than 10:00 p.m. The dose of study medication was administered in the morning on Day 2 of each period. Subjects were dosed intranasally with four sprays per nostril (approximately 55 µg per actuation), alternating nostrils between each spray to give a total dose of approximately 440 µg.

Serial blood samples (approximately 10 ml) were collected from each subject using heparinized vacutainers at 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post dose.

Subjects were released from the investigation site following the 12-hour blood draw. They were instructed to return the next morning for the 24-hour blood collection.

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ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

C. Results

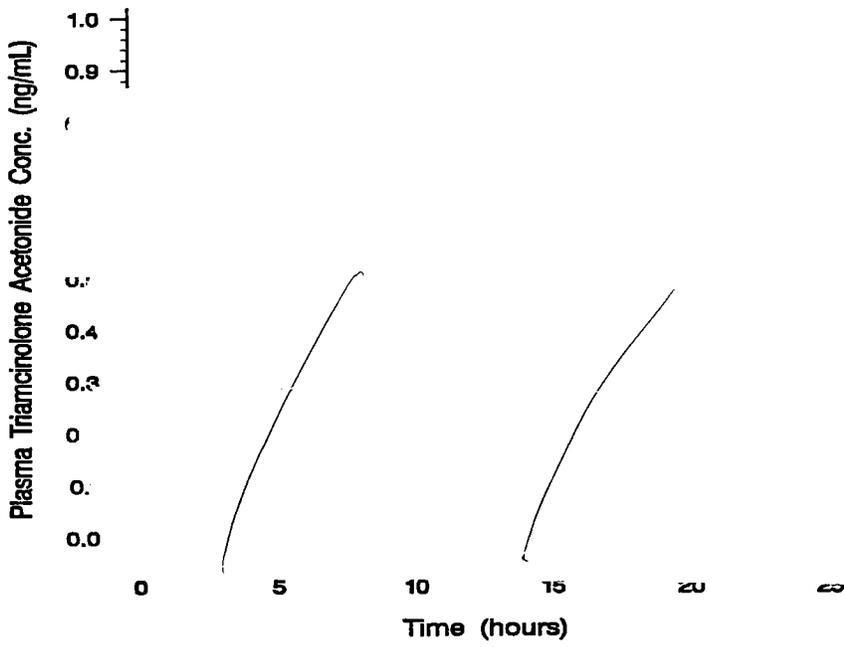
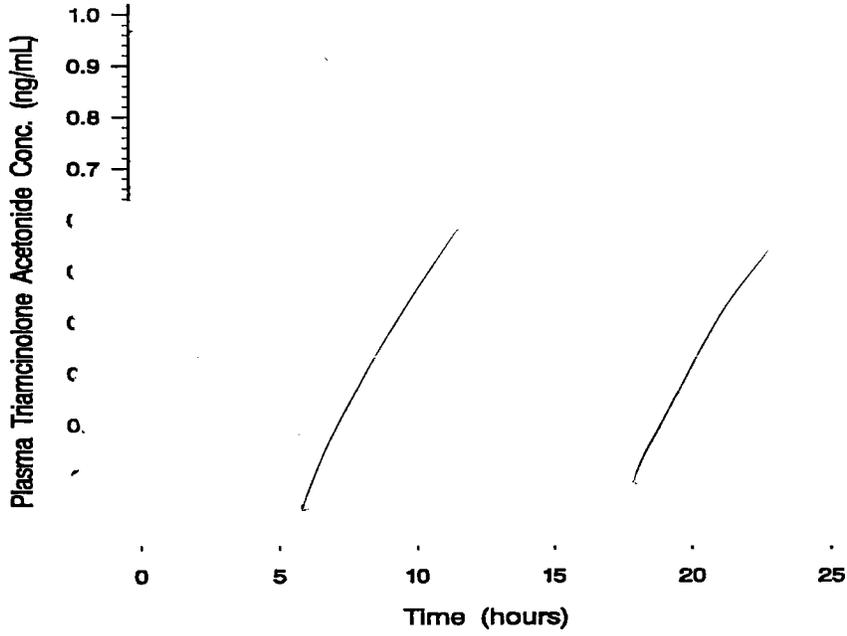


Figure 1. Individual Plasma TAA Composite Plots Following Administration of TAA from the Nasacort CFC Propellant Delivery System (top) and the Nasacort non/CFC Propellant Delivery System (bottom).

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Many plasma TAA concentrations were below the minimum quantitative limit following the 12-hour blood sample time. Hence, for several subjects, it was not possible to establish a terminal phase. K_{term} and $AUC_{0-\infty}$ were not determined for Subjects #2, 3, 7, 11, 14 (Treatment A) and for Subjects #1, 3, 4, 9, 14 (Treatment B). The plasma TAA concentration-time profiles for these individuals either exhibited poorly defined terminal phases or there were insufficient concentration data points. This is a consequence of the minimal systemic exposure associated with intranasal administration of TAA from volatile propellant systems. Therefore, for this study, the sponsor had decided to assess the extent of systemic TAA exposure from AUC_{0-12} and C_{max} only.

1. Mean (%CV) TAA Biopharmaceutic Parameters

Parameter	Treatment A Nasacort Nasal Inhaler with CFC P12 Propellant	Treatment B Nasacort Nasal Inhaler with HFA-134a Propellant
AUC_{0-12} (ng*hr/ml)	1.362 (70.2)	1.309 (63.1)
C_{max} (ng/ml)	0.205 (68.2)	0.196 (58.1)
T_{max} (hr)	2.7 (47.7)	3.8 (63.8)
k_{term}^b (1/hr)	0.134 (34.6)	0.168 (39.6)
$t_{1/2}^c$ (hr)	5.2	4.1

^a Excluding Subject #13 who was identified as a statistical outlier.

^b Excluding Subjects #1, 2, 3, 4, 9, 11, and 14. For these subjects, it was not possible to establish a terminal phase.

^c Harmonic mean half-life.

Reviewer's Comment:

- 1). The mean values of AUC_{0-12} and C_{max} were similar between the two formulations.
- 2). The mean T_{max} value following administration of TAA from the Nasacort HFA-134a non-CFC propellant delivery system was approximately 1 hour longer than that following administration of TAA from the Nasacort CFC propellant delivery system.

2. Confidence Intervals Derived from TAA Biopharmaceutic Parameters

Ninety percent confidence limits calculated from the two one-sided test were determined for nontransformed mean AUC_{0-12} and C_{max} values.

	90% Confidence Interval (Percent of Reference)		
	Test:Reference		
	Nasacort Nasal Inhaler With HFA-134a:Nasacort Nasal Inhaler With P12		
Parameter	Lower Limit	Ratio	Upper Limit
AUC_{0-12}	83.5	97.6	111.7
C_{max}	82.1	96.7	111.3

Subject #13 was not included in the calculation of these parameters because this subject was identified as a statistical outlier.

The Wilcoxon signed rank test did show a significant difference between the two propellant delivery systems for T_{max} .

Reviewer's Comment:

Based upon the 80% to 120% criterion for nontransformed data, the systemic bioavailability of the two products were bioequivalent. Though this differs from the current bioequivalent standard of the Biopharmacology Division at CDER which is based upon the 80-125% criterion for transformed data, the exact choice of criterion is not particularly critical in this case. Based on

the above analysis, the overall extent and rate of systemic exposure to TAA were similar between the two formulations.

Pharmacokinetics of various triamcinolone acetonide-containing products in adult and children

	Study #	Age	Dose (µg/day)	C _{max} (ng/mL)	AUC ₀₋₁₂ (ng X hr/mL)	AUC _{0-∞} (ng X hr/mL)
Nasacort AQ	Study 125	6-12	440	0.89	4.06 (projected)	4.54 (projected)
Nasacort AQ	Study 101	18-50	220	0.44	2.42	2.64
			440	0.73	4.07	4.54
Nasacort (P12)			220	0.07	0.505	0.65
			440	0.14	1.01	1.31
Nasacort (P12)	Study 123	19-47	440	0.205	1.362	
Nasacort HFA				0.196	1.309	
Azmacort P12)	Study 119	19-50	600	0.95	5.17	6.07

* After the last dose (steady-state)

Shaded Cells: data requested of the sponsor after the initial submission of their NDA. These data were received in facsimile dated May 9, 1997.

Reviewer's Comment:

1. Study was not performed to permit a direct comparison between the pharmacokinetics of Nasacort HFA-134a and that of the Nasacort AQ. In Study 123, the pharmacokinetics of Nasacort P-12 in adults were compared with that of the Nasacort HFA-134a. In Study 101, the pharmacokinetics of Nasacort P-12 was compared with that of Nasacort AQ. An

indirect comparison between Nasacort HFA-134a and Nasacort AQ can be made using the Nasacort P-12 as the reference product.

Intrasubject comparison among adults in Study 123 indicates that the C_{max} and AUC_{0-12} were comparable between Nasacort HFA and Nasacort P-12, whereas Study 101 indicates that the systemic bioavailability of Nasacort AQ is 4-5 fold higher than that of Nasacort P-12. Taken together, the systemic bioavailability of Nasacort AQ is 4-5 fold higher than that of Nasacort HFA.

2. *Cross study comparison suggests that the systemic bioavailability of Nasacort AQ was comparable between adults and children 6-12 years of age, and the same relationship is expected to apply also to Nasacort HFA-134a. As the systemic bioavailability of Nasacort AQ was 4-5 fold higher than that of Nasacort HFA-134a in adults, a qualitatively similar relationship is expected to apply also to children 6-12 years of age. Previous study (Study 125) showed that treatment of children 6-12 years of age with 440 mcg dose of Nasacort AQ once daily for six weeks did not affect the HPA axis. The same should apply also for Nasacort HFA as it has a lower systemic bioavailability.*

IV. EFFICACY AND SHORT TERM SAFETY TRIAL- STUDY 311

The efficacy claim on Nasacort HFA-134a in adults is based solely on this study.

A. Objective

To demonstrate therapeutic comparability of the currently marketed Nasacort® P12 Nasal Inhaler propellant and the new Nasacort HFA-134a Nasal Inhaler.

B. Participating Investigators

Investigators'	No. of Patients
<u>Names/Locations</u>	<u>Randomized</u>
Peter Boggs, M.D.	53
Joseph D. Diaz, M.D.	53
Robert Dockhorn, M.D.	53

Investigators' Names/Locations	No. of Patients Randomized
Elliot Ginchansky, M.D.	54
David Golden, M.D.	52
Andrew Green, M.D.	31
Gary Gross, M.D.	53
William Howland, M.D.	57
Robert L. Jacobs, M.D.	60
Zev Munk, M.D.	42
Scott L. Osur, M.D.	25
Eric J. Schenkel, M.D.	55
Loren Southern, M.D.	42
Sheryl Talbot, M.D.	48
Julius Van Bavel, M.D.	54
Suzanne Weakley, M.D.	48
<hr/> Total	<hr/> 780

Reviewer's Comment:

None of these investigators were found in the FDA's Disqualified Investigator List.

C. CLINICAL METHODS

1. Design and Plan of Study

This was a two-week, double-blind, double-dummy, parallel group, randomized therapeutic comparability study in adult patients with seasonal (fall ragweed) allergic rhinitis. The study consisted of a screening phase, a baseline phase, and a two-week double-blind treatment phase.

Reviewer's Comment:

The design of this trial is similar to that of Nasacort AQ.

a) Treatment Assignment

A total of 780 patients were enrolled in the study at 16 centers located in the United States. The patients were randomly assigned to one of eight (8) parallel treatment groups. The six active treatments were 14 mcg, 110 mcg, and 440 mcg/day for both the Nasacort[®] P12 and HFA-134a Nasal Inhalers. The placebo group was equally divided between P12 and HFA-134a propellants. Blocks of fourteen patients were randomly assigned, two patients for each of the active treatments and one patient for each of the placebo treatments. The randomization schedule was provided by the Biostatistics Department of Rhône-Poulenc Rorer Research and Development.

b) Clinical Visits

(1) Screening (Visit 1)

The patients were screened by means of medical and drug history, skin prick test to fall ragweed allergens, physical examination and vital signs, examination of mucous membranes of the nose, mouth, and throat for fungal infection, and laboratory tests. All inclusion/exclusion criteria were reviewed and diary cards were distributed at this time to record daily rhinitis symptoms.

(2) Baseline (Visit 2)

Visit 2 was scheduled for all patients when the seasonal (fall ragweed) pollen counts in the vicinity of the investigational site had been elevated over a period of at least seven days prior to the visit. In an attempt to expose all patients at each site to similar pollen levels, the period allowed for enrollment of patients into the double-blind portion of the study was four consecutive days. In addition, no medication for the relief of rhinitis symptoms was permitted for the six days preceding this visit and throughout the treatment period.

Daily rhinitis symptom scores were reviewed for the morning (AM rating

only) of the baseline visit and for the three days (AM and PM ratings) that immediately preceded this visit. The patient was randomized to treatment only if the aggregated sum of the reflective scores for the four nasal symptoms (discharge, stuffiness, itching, and sneezing) over the previous three days preceding randomization, plus the morning of the randomization visit (7 total AM/PM ratings), was at least 42 points (out of a possible 84). Adverse experiences and concomitant medication use were also reviewed.

(3) Week 1 - Interim Visit (Visit 3)

Diary cards were reviewed for completeness and correctness and the patient was interviewed for reports of adverse experiences and the use of study and concomitant medications.

(4) Week 2 - Final Visit (Visit 4)

The patient was interviewed for reports of adverse experiences and the use of study and concomitant medications. Additionally, unused study medication and medication containers were collected, physical exam and vital signs were performed, and mucous membranes of the nose, mouth, and throat were examined for fungal infections. Blood and urine samples were collected for laboratory tests. Independent global evaluations of treatment were also recorded by the patient and investigator.

c) Study Population

(1) Inclusion Criteria

- (a) Eligible patients were males and nonpregnant, nonlactating females at least 18 years of age.
- (b) All patients had historical exacerbations of seasonal (fall ragweed) allergic rhinitis, for at least two years, and were candidates for treatment with nasal steroids based on the study physician's assessment of either a) inadequate control of their allergy symptoms with antihistamines, decongestants and/or immunotherapy, or b) prior successful treatment with nasal steroids.

- (c) Each patient also had a positive response to a skin prick test for seasonal (fall ragweed) allergen.
- (d) The patients were required to refrain from concomitant medication use for the specific purpose of alleviating rhinitis symptoms during the specified period.
- (e) A minimum qualifying total rhinitis symptom (discharge, stuffiness, itching, and sneezing) score was 42 points out of a possible 84. This total was the summation of the previous three days preceding randomization plus the morning of the randomization visit.

(2) Exclusion Criteria (pre-randomization)

- (a) medical conditions that might significantly interfere with the study
- (b) clinically relevant deviations from normal in either the general physical exam or laboratory parameters
- (c) nasal candidiasis
- (d) acute or chronic sinusitis
- (e) significant nasal polyposis, or other gross anatomical deformity of the nose sufficient to impair nasal breathing
- (f) systemic corticosteroid use within 42 days of screening
- (g) nasal cromolyn sodium use within 28 days of screening
- (h) nasal or inhaled corticosteroid use within 30 days of screening
- (i) astemizole use within 60 days of screening
- (j) initiation of immunotherapy within six months of screening
- (k) received an investigational drug within 60 days of screening

- (l) use of medication for other conditions that may produce/relieve the signs and symptoms of allergic rhinitis or affect their ability to subjectively rate their allergic rhinitis symptoms
 - (m) use of loratidine (Claritin®) within 10 days of screening
 - (n) females with childbearing potential without acceptable birth control practices
 - (o) hypersensitivity to corticosteroids
 - (p) previous participation in a RG 5029T study
 - (q) travel planned outside the pollen area during the study.
- (3) Post-admission exclusion criteria.
- (a) use of medication for the specific purpose of alleviating the symptoms of seasonal allergic rhinitis from six days (Claritin® is excluded for 10 days) preceding Visit 2 until completion of the study.
 - (b) use of medication (i.e., antihypertensive) for another indication that could produce or relieve the signs and symptoms of seasonal allergic rhinitis (SAR) or affect their ability to subjectively rate their rhinitis symptoms. Any patient who used any disallowed medications during the study could be discontinued at the sponsor's discretion.
 - (c) patients who developed any illness during the study that interfered with their assessment of SAR symptoms were discontinued from the study.

d) Rationale for Dose Selection and Dose-Interval

Qualified patients were randomly assigned to receive daily administration of Nasacort® P12 Nasal Inhaler, Nasacort HFA-134a Nasal Inhaler or Placebo.

Treatment Groups

Study Medication	Total Daily Dose	Daily Regimen	
		Canister A	Canister B
Placebo	0	2 sprays (HFA-134a or P12)	6 sprays (HFA-134a or P12)
Nasacort® P12	14 mcg	2 sprays * 7 mcg	6 sprays Placebo
Nasacort® P12	110 mcg	2 sprays * 55 mcg	6 sprays Placebo
Nasacort® P12	440 mcg	2 sprays * 55 mcg	6 sprays * 55 mcg
Nasacort HFA-134a	14 mcg	2 sprays * 7 mcg	6 sprays Placebo
Nasacort HFA-134a	110 mcg	2 sprays * 55 mcg	6 sprays Placebo
Nasacort HFA-134a	440 mcg	2 sprays * 55 mcg	6 sprays * 55 mcg

The study design incorporated doses of the original product that were known to be effective (110 and 440 mcg per day) and sub-optimal (14 mcg per day) for comparison with the new formulation. The use of these doses in both P12 and HFA-134a formulations, compared to placebo, 1) provided evidence of comparability between the formulations, and 2) demonstrated the sensitivity of the clinical model to discriminate between the active treatment doses.

Reviewer's Comment:

All treatment arms received the same number of puffs of inhaler.

e) Blinding

This was a double-blind and double-dummy study. Patients received placebo and/or Nasacort® P12 or Nasacort HFA-134a canisters that were identical in appearance and labeling. Each patient was supplied with two canisters, and this allowed the sponsor to blind the various treatment regimens in a double-dummy fashion.

2. EFFICACY AND SAFETY VARIABLE

a) Clinical Measurement

(1) Skin Test

A skin prick test for seasonal allergens prevalent in the patient's environment was applied and interpreted. A test was considered positive if the wheal diameter caused by the allergen was equal to or greater than that caused by the positive control (histamine) or was at least 5 mm greater than the wheal diameter of the negative control (saline).

(2) Physical Examination

A physical examination was performed at the initial visit (Visit 1, screening) and at the final study visit (Visit 4), or upon discontinuation.

(3) Fungal Examination

The mucous membranes of the nose, mouth, and throat were visually examined for fungal infection at Visits 1 and 4. A suspected infection at Visit 4 was confirmed by a laboratory culture.

(4) Diary Cards

The following information was recorded by the patient on the daily symptom diary cards:

(a) Rhinitis Symptom Scores

The following reflective rhinitis symptoms were rated prior to dosing each day in the morning (AM) and in the evening (PM):

1. Nasal discharge (anterior and/or posterior drainage)
2. Nasal stuffiness
3. Nasal itching
4. Sneezing
5. Total eye symptoms (itchiness, tearing, redness)

The "reflective" symptom ratings assessed the patient's symptoms over approximately the previous 12 hours. The "snap shot" symptom ratings assessed the patient's symptoms at the

exact time of recording at the end of the dosing interval in the AM only. The inclusion of this "snap shot" rating was at the request of the FDA's Division of Pulmonary Drugs. However, six of the sixteen investigators had already initiated the study prior to our request to include this "snap shot" rating. Therefore the following investigators were unable to include "snap shot" ratings at their site: Golden, Green, Osur, Schenkel, Southern, and Talbot.

Severity of each symptom was rated according to the following scale:

0 = Symptom absent

1 = Mild, present but not annoying to self

2 = Moderate, present and annoying to self but does not interfere with sleep or daily living

3 = Severe, interferes with/or unable to carry out activities of daily living or sleep.

(5) Global Evaluations

A global evaluation assessing treatment effectiveness was made at Visit 4. The physician and patient recorded their opinion independently and blinded from each other according to the following scale:

0 = greatly improved

1 = somewhat improved

2 = no change

3 = somewhat worsened

4 = greatly worsened

(6) Study Medication

The number of sprays of each canister (A and B) of study medication was recorded daily.

(7) Outdoor Exposure

The patient recorded on a daily basis the total number of hours that the patient was exposed to outdoor air during the preceding 24 hours. This included time spent outdoors, in a building with open windows, or in an automobile with open windows.

b) Laboratory Measurements

Basic chemistry, CBC and a urine collection were obtained at Visits 1 and 4 (or upon discontinuation).

3. Concomitant Therapy

Patients were not permitted to use medication (over the counter or prescription) for the specific purpose of alleviating the symptoms of seasonal allergic rhinitis from six days preceding Visit 2 until the completion of the study. Topical vasoconstrictor/decongestant eye preparations for severe eye symptoms were allowed. All concomitant medication was recorded on the case report form and diary card.

4. Prohibited Medication

Patients were not permitted to take medication for another indication that could produce or relieve the signs or symptoms of allergic rhinitis or affect their ability to subjectively rate their symptoms consistently. Patients were not permitted to take medication for another indication that could produce or relieve the signs or symptoms of allergic rhinitis or affect their ability to subjectively rate their symptoms consistently.

5. STATISTICAL METHODS

a) Statistical and Analytical Plans

(1) Efficacy Variables

(a) Variables Recorded in the Daily Diary

The reflective symptom ratings were done prior to dosing each day in the morning (AM) and in the evening (PM). The "reflective" score reflects the patients symptoms over the previous 12 hours. The 24 hour score was the average of the PM measurement on a given day and the AM measurement on the following day.

The "snap shot" symptom ratings assessed the patient's symptoms at the time of recording. In this study the "snap shot" rating was made in the AM only and represented the responses at approximately 24 hours after the previous day's dose. Six of the investigators had already initiated the study prior to the our request to include the "snap shot" rating. The investigators who did not include snap shot ratings were: Golden, Green, Osur, Schenkel, Southern, and Talbot.

Reviewer's Comment:

These centers account for 32% of the enrolled subjects for this trial

(b) Primary Variables

The primary variables were the mean change from baseline averaged over the double-blind period of the following reflective symptom scores: nasal stuffiness, nasal discharge, sneezing and nasal index (the sum of the scores for nasal discharge, nasal stuffiness, and sneezing) for the reflective 24 hour score.

(c) Secondary Variables

- (i) The mean change from baseline of the reflective primary variables was averaged over each week separately, as well as on Days 1 through 4 for the 24 hour, PM (1st 12 hours), and AM (2nd 12 hours) scores.
- (ii) Additional secondary variables were the mean changes from baseline of itchy nose and total eye symptoms. These variables were analyzed over and at the same time points as the primary variables.
- (iii) AM "snap shot" scores

The mean changes from baseline in the AM "snap shot" scores were averaged over each week, the overall double-blind period, and Days 1 through 4 for nasal stuffiness, nasal discharge, sneezing, the nasal index, itchy nose, and total eye symptoms.

(2) Global Evaluation of Efficacy

Patients' Global Evaluation of Efficacy, and Physicians' Global Evaluation of Efficacy were recorded during the last double-blind visit.

b) **Statistical Methodology**

(1) For all analyses to assess treatment differences

A two-way analysis of variance model was used with treatment and investigator as the main effects and no interaction term at the 0.05 level of significance.

Also, for the primary efficacy variables, the following two-sided, Bonferroni adjusted pairwise comparisons was performed within each formulation: placebo versus 14 mcg, placebo versus 110 mcg, placebo versus 440 mcg, 14 mcg versus 110 mcg, 14 mcg versus 440 mcg and 110 mcg versus 440 mcg. Under the assumption that the P12-placebo group and the 134a-placebo group were similar, the placebo group in the analysis would be the combination of the P12-placebo and 134a-placebo groups. Except where noted, the two placebo groups were combined and the analysis of variance was based on seven treatment groups. To justify the combination, a two sample t-test comparing the change from baseline of the nasal index of the two inhaler placebo groups was performed.

(2) To assess equivalence

The two one-sided confidence interval approach was used to assess equivalence between the following: 14(P12) versus 14(134a), 110 (P12) versus 110 (134a), and 440(P12) versus 440(134a) mcg of RG 5029 for the

primary efficacy variables. The primary comparisons would be between the 110 (P12) versus 110 (134a) and 440 (P12) versus 440 (134a) mcg formulations of RG 5029. The P12 and HFA-134a formulations are considered by the sponsor to be therapeutically comparable if the resulting clinical responses, as measured by the primary efficacy parameters, are statistically within thirty percent (30%) of each other.

Reviewer's Comment:

The protocol did not specify a priori the criteria of equivalence. Such criteria are not needed as the Points to Consider document did not require a proof of equivalence between the new and the reference formulation. Our method is based on visual inspection comparing the dose response curves of the two active formulations. The goals are the assessment of the degree of similarity between the potency of the two products and to identify the doses of these two products which yielded comparable efficacy.

c) RESULTS

Most patients were Caucasian (84%) with more males (55%) than females (45%). The mean age was 36 years and ranged from 18 to 83 years. There were no important differences in demographics between the treatment groups.

**APPEARS THIS WAY
ON ORIGINAL**

(1) Disposition Of Patients Entered

Reasons Patients Discontinued

	P12				HFA-134a			
	Placebo	14 mcg	110mcg	440mcg	Placebo	14 mcg	110mcg	440mcg
	All Treated Patients N=780							
Reason Discontinued	n=54	n=113	n=115	n=108	n=57	n=113	n=107	n=113
Lost to Follow-up	1	0	1	0	0	1	2	0
Test Drug Ineffective	3	6	1	1	4	1	1	2
Adverse Clinical Experience	0	0	1	0	1	2	0	0
Deviation from Protocol	0	1	2	2	0	0	1	3
Consent Withdrawn	0	0	0	0	0	1	0	1
Other	2	3	2	0	0	1	1	0
Total Discontinued N=48	6	10	7	3	5	6	5	6

Reviewer's Comment:

- 1). A total of 780 patients were enrolled in the study and 732 (94%) completed the study.
- 2). The number of subjects who withdrew prematurely from the trial for the reasons listed above was comparable between these two products.
- 3). The most frequent reason for patient withdrawal (19/48) was the perceived ineffectiveness of the test drug.

d) Patient Evaluability

(1) All Treated Population

All patients who had double-blinded diary data, including baseline data, were included in the All Treated population. Excluded days were also included. The All Treated population was 775/780 (99%) of the patients.

(2) Evaluable Patients

Patient study days were excluded from the evaluable analyses if concomitant medication was taken on that day or the test medication was not taken on that day. 98% of the enrolled patients were classified as the

evaluable population. In addition to the five patients without double blind data (listed above), 13 patients were determined to be not evaluable. The reasons for nonevaluability were: 6/13 due to questionable baseline symptom scores, 5/13 due to disallowed baseline therapy, and 2/13 due to interfering conditions during baseline. All of these conditions were considered major protocol violations. Nonevaluable patients are summarized by treatment group in the following table.

Reasons Patients Were Considered Not Evaluable

	All Treated Patients With Data N=775								
	P12 Inhaler				HFA-134a Inhaler				Total
	Placebo	14 mcg	110mcg	440mcg	Placebo	14 mcg	110mcg	440mcg	
No Double-blind Efficacy Data	1	0	1	0	0	0	1	2	5
	n=53	n=113	n=114	n=108	n=57	n=113	n=106	n=111	
Reason Not Evaluable	Evaluable Patients With Data N=762								
	n=52	n=112	n=112	n=106	n=57	n=111	n=105	n=107	
Excluded Baseline Therapies	1	0	0	0	0	0	0	0	1
Baseline Scores Questionable	0	1	2	1	0	0	0	2	6
Excluded Baseline Therapies	0	0	0	1	0	0	1	2	4
Interfering Condition	0	0	0	0	0	2	0	0	2
Total Nonevaluable with Data	1	1	2	2	0	2	1	4	13

Reviewer's Comment:

As requested by our Division in a pre-NDA meeting, the sponsor performed their statistical comparison of the efficacy of the two Nasacort products using the evaluable population. This is our preference at that time because it is more difficult in principle to establish comparability using the evaluable population as compared to using the all-treated population due to the expected lower variability of symptom scores of the evaluable population. In reality, the number of subjects excluded from evaluation is small, and it makes little difference in our conclusion regardless of whether or not the all-treated or the evaluable population was used for the comparison.

e) Demography

Demographic Data Summary

All-Treated Patients

Treatment Group	N	Sex		Race		Age (years)		Height	Weight
		M (%)	F (%)	Caucasian (%)	Other (%)	Mean	Range	Mean (cm.)	Mean (kg.)
P12 Nasal Inhaler									
Placebo	54	52	48	85	15	35	19-68	169	76
14 mcg	113	56	44	86	14	35	19-71	172	79
110 mcg	113	54	46	89	11	36	19-83	171	82
440 mcg	108	56	44	81	19	36	19-77	172	80
HFA-134a Nasal Inhaler									
Placebo	57	56	44	82	18	37	18-65	171	76
14 mcg	113	59	41	77	23	38	18-76	172	79
110 mcg	107	54	46	89	11	36	18-62	172	77
440 mcg	113	53	47	83	17	36	18-72	171	79
All Placebo	111	54	46	84	16	36	18-68	170	76
Total	780	55	45	84	16	36	18-83	171	79

Reviewer's Comment:

The demography of the Nasacort P12 and the Nasacort HFA-134a groups were similar.

D. EFFICACY OUTCOME

1. Efficacy Variables at Baseline

**Summary of Mean Baseline Efficacy Scores for Reflective Variables
All Treated Patients**

Variable	Time	Placebo	P12 Inhaler			HFA-134a Inhaler		
			14 mcg	110mcg	440 mcg	14 mcg	110mcg	440 mcg
Number of Patients		110	113	114	108	113	106	111
Nasal Stuffiness	1st 12 hr.	2.3	2.5	2.4	2.4	2.4	2.3	2.4
	2nd 12 hr.	2.3	2.5	2.4	2.4	2.5	2.3	2.3
	24 hr.	2.3	2.5	2.4	2.4	2.4	2.3	2.3
Nasal Discharge	1st 12 hr.	2.3	2.4	2.2	2.3	2.4	2.2	2.4
	2nd 12 hr.	2.3	2.4	2.3	2.2	2.4	2.2	2.3
	24 hr.	2.3	2.4	2.3	2.3	2.4	2.2	2.3
Sneezing	1st 12 hr.	2.1	2.1	2.0	2.2	2.3	2.0	2.2
	2nd 12 hr.	2.0	2.0	1.9	2.0	2.2	1.8	2.0
	24 hr.	2.1	2.1	2.0	2.1	2.2	1.9	2.1
Nasal Index ^a	1st 12 hr.	6.8	7.0	6.7	6.9	7.1	6.4	6.9
	2nd 12 hr.	6.7	6.9	6.6	6.6	7.0	6.3	6.6
	24 hr.	6.7	7.0	6.7	6.7	7.1	6.4	6.8
Itchy Nose	1st 12 hr.	2.1	2.1	2.1	2.1	2.2	2.0	2.1
	2nd 12 hr.	2.1	2.1	2.0	2.1	2.2	1.9	2.0
	24 hr.	2.1	2.1	2.1	2.1	2.2	2.0	2.1
Eye Symptoms	1st 12 hr.	2.0	2.0	1.9	2.1	2.0	1.8	2.0
	2nd 12 hr.	2.0	2.0	1.9	2.0	2.0	1.8	1.9
	24 hr.	2.0	2.0	1.9	2.0	2.0	1.8	2.0

^a Nasal Index = sum of scores for nasal stuffiness, nasal discharge, and sneezing.

Total Symptoms Score = sum of score for nasal index plus score for itchy eyes.

Each symptom was rated on a four-point severity scale: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe

Reviewer's Comment:

The baseline reflective rhinitis symptoms were similar across treatments for all variables.

**Summary of Mean Baseline Efficacy Scores for "Snap Shot" Variables
All Treated Patients**

Variable	Time	Placebo	P12 Inhaler			HFA-134a Inhaler		
			14 mcg	110mcg	440 mcg	14 mcg	110mcg	440 mcg
Number of Patients		72	75	77	72	73	69	76
Nasal Stuffiness	2nd 12 hr	2.2	2.4	2.3	2.3	2.4	2.1	2.4
Nasal Discharge	2nd 12 hr	2.2	2.3	2.2	2.1	2.2	1.9	2.1
Sneezing	2nd 12 hr	1.7	1.8	1.7	1.5	1.8	1.5	1.7
Nasal index	2nd 12 hr	6.1	6.5	6.2	5.9	6.5	5.5	6.2
Itchy Nose	2nd 12 hr	1.9	2.0	2.0	1.8	2.0	1.8	1.9
Eye Symptoms	2nd 12 hr	2.0	2.1	1.9	1.9	1.9	1.8	1.8

Reviewer's Comment:

1. *The baseline reflective rhinitis symptom scores were similar across treatment groups. The baseline symptom severity of the enrolled subjects were moderate.*
2. *Whereas the "snap shot" nasal index of the 14 mcg treatment arm and 440 mcg treat arm at baseline were comparable between the P12 group and the HFA group, there was a discernible difference for the 110 mcg treatment arms between these two groups (6.5 versus 5.5). This difference might account for the failure to demonstrate a significant difference in efficacy outcome between the 110 mcg group and the placebo.*
3. *The number of subjects who had collection of their "snap shot" scores was approximately three quarter of those who were enrolled. By the time that our Division recommended the sponsor to collect "snap shot" scores, one fourth of the centers had already started the trial. This reduction in the number of study subjects with the snap shot score analysis reduced the ability of the trial to demonstrate the adequacy of the once daily dosing interval.*

2. Between Placebo Group Analysis

The placebo groups were found not to be significantly different from each other at the 0.10 level of significance. On this basis, the sponsor combined the P12 and

HFA-134a placebo groups in the primary and secondary analyses.

Summary of Comparison of Placebo Groups

Variable	Treatment Group	N	Adjusted^a Mean (S.E.)	P-Value^b versus Placebo
Nasal Index	Placebo P12	57	-1.48 (0.23)	0.38
	Placebo HFA-134a	52	-1.21 (0.22)	

a Means adjusted for differences among investigators.

b: p- values are computed from t-tests for a two-way analysis of variance model with treatment and center as main effects and no interaction term.

Reviewer's Comment:

The pooling of these two placebo groups is acceptable as the placebo responses were similar.

**APPEARS THIS WAY
ON ORIGINAL**

3. **Primary Efficacy Analysis**

a) **Within formulation analysis**

Analysis of Change From Baseline in Reflective Symptom Score

All Treated Patients

Overall Double-Blind Period for 24 Hours

Variable	Treatment	N	Baseline Mean	Adjusted Mean ^b Change from Baseline (S.E.)	Within Formulation P-value ^c versus		
					Placebo	14 mcg	110 mcg
Nasal Stuffiness	14 mcg P12	113	2.48	-0.62 (0.06)	0.01*		
	110 mcg P12	114	2.40	-0.83 (0.06)	0.00#	0.02*	
	440 mcg P12	108	2.41	-0.88 (0.06)	0.00#	0.00#	0.61
	14 mcg HFA-134a	113	2.44	-0.64 (0.06)	0.00#		
	110 mcg HFA-134a	106	2.28	-0.71 (0.06)	0.00#	0.46	
	440 mcg HFA-134a	111	2.35	-0.75 (0.06)	0.00#	0.23	0.66
	Placebo	109	2.34	-0.38 (0.06)			
Nasal Discharge	14 mcg P12	113	2.44	-0.72 (0.06)	0.00#		
	110 mcg P12	114	2.26	-0.84 (0.06)	0.00#	0.17	
	440 mcg P12	108	2.26	-0.94 (0.07)	0.00#	0.02*	0.29
	14 mcg HFA-134a	113	2.40	-0.69 (0.06)	0.01*		
	110 mcg HFA-134a	106	2.21	-0.75 (0.07)	0.00#	0.50	
	440 mcg HFA-134a	111	2.34	-0.89 (0.06)	0.00#	0.02*	0.11
	Placebo	109	2.33	-0.44 (0.07)			
Sneezing	14 mcg P12	113	2.06	-0.72 (0.07)	0.17		
	110 mcg P12	114	1.98	-0.88 (0.07)	0.00#	0.11	
	440 mcg P12	108	2.07	-1.03 (0.07)	0.00#	0.00*	0.12
	14 mcg HFA-134a	113	2.22	-0.79 (0.07)	0.04*		
	110 mcg HFA-134a	105	1.90	-0.83 (0.07)	0.01*	0.67	
	440 mcg HFA-134a	111	2.09	-1.01 (0.07)	0.00#	0.03*	0.08
	Placebo	109	2.09	-0.58 (0.07)			
Nasal Index ^a	14 mcg P12	113	6.99	-2.06 (0.17)	0.01*		
	110 mcg P12	114	6.65	-2.55 (0.17)	0.00#	0.04*	
	440 mcg P12	108	6.73	-2.84 (0.18)	0.00#	0.00#	0.24

Variable	Treatment	N	Baseline Mean	Adjusted Mean ^b Change from Baseline (S.E.)	Within Formulation P-value ^c versus		
					Placebo	14 mcg	110 mcg
	14 mcg HFA-134a	113	7.06	-2.11 (0.17)	0.00#		
	110 mcg HFA- 134a	105	6.41	-2.29 (0.18)	0.00#	0.47	
	440 mcg HFA- 134a	111	6.78	-2.64 (0.18)	0.00#	0.03*	0.16
	Placebo	109	6.75	-1.39 (0.18)			

Abstracted from Appendix IV, Section A, Table 7.1.1A.

- a Nasal Index is the sum of Nasal Stiffness, Nasal Discharge, and Sneezing.
- b Means adjusted for differences among investigators.
- c p-values are computed from t-tests for a two-way analysis of variance model with treatment and center as main effects and no interaction term.
- * p < 0.05 for 2-tailed test.
- # Also significant for p < 0.05 for 2-tailed, adjusted for multiple comparison..

Reviewer's Comment:

- 1). For within formulation efficacy analysis, the population of choice is the all-treated population.
- 2). For both formulations:
 - a). The mean changes from baseline of each rhinitis symptom score in the 110 mcg group and the 440 mcg group were significantly different from that of the placebo.
 - b). The mean changes from baseline of each of the rhinitis symptom score of the 440 mcg groups are numerically greater, but not significantly different, than that of the 110 mcg group.

b) Comparison of Nasacort HFA-134a with Nasacort P-12

Between Formulation Analysis on Reduction From Baseline for Reflective Symptom Scores
by Dose for Overall Double-Blind Period
24 HOUR TIMEPOINT

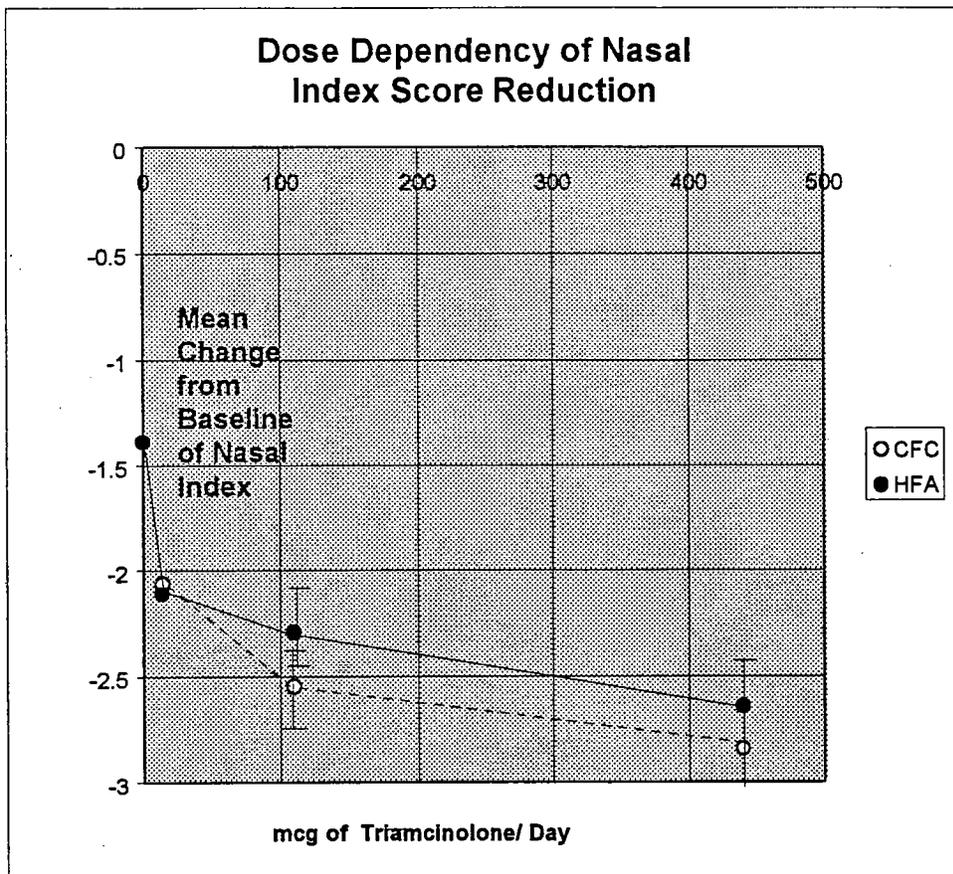
All Treated Analysis								
Variable	Treatment	Nasacort [®] P12		Nasacort HFA-134a		Mean ^b Squared Error (DF)	Ratio of HFA-134a/ P12	Two one-sided 90% Confidence Interval of Ratio HFA-134a/P12
		N	Mean Reduction From Baseline	N	Mean Reduction From Baseline			
Nasal	14 mcg	113	0.62	113	0.64	0.44 (209)	1.03	(0.79 1.26) #
Stuffiness	110 mcg	114	0.83	106	0.72	0.44 (203)	0.86	(0.68 1.04)
	440 mcg	108	0.88	111	0.75	0.46 (202)	0.86	(0.69 1.03)
Nasal	14 mcg	113	0.71	113	0.68	0.48 (209)	0.95	(0.74 1.16) #
Discharge	110 mcg	114	0.84	106	0.75	0.44 (203)	0.90	(0.72 1.07) #
	440 mcg	108	0.94	111	0.90	0.52 (202)	0.96	(0.79 1.13) #
Sneezing	14 mcg	113	0.70	113	0.77	0.54 (209)	1.10	(0.87 1.33)
	110 mcg	114	0.87	105	0.83	0.58 (202)	0.96	(0.76 1.15) #
	440 mcg	108	1.02	111	1.00	0.57 (202)	0.98	(0.82 1.15) #
Nasal Index ^a	14 mcg	113	2.04	113	2.09	3.58 (209)	1.03	(0.82 1.23) #
	110 mcg	114	2.54	105	2.30	3.38 (202)	0.91	(0.75 1.07) #
	440 mcg	108	2.84	111	2.65	3.72 (202)	0.93	(0.78 1.09) #

Evaluable Patients								
Variable	Treatment	Nasacort [®] P12		Nasacort HFA-134a		Mean ^b Squared Error (DF)	Ratio of HFA-134a/ P12	Two one-sided 90% Confidence Interval of Ratio HFA-134a/P12
		N	Mean Reduction From Baseline	N	Mean Reduction From Baseline			
Nasal Stuffiness	14 mcg	112	0.63	111	0.63	0.44 (206)	1.01	(0.77 1.24) #
	110 mcg	112	0.84	105	0.72	0.45 (200)	0.85	(0.67 1.03)
	440 mcg	106	0.87	107	0.77	0.46 (196)	0.89	(0.71 1.06) #
Nasal Discharge	14 mcg	112	0.71	111	0.68	0.49 (206)	0.95	(0.74 1.17) #
	110 mcg	112	0.84	105	0.75	0.45 (200)	0.89	(0.72 1.07) #
	440 mcg	106	0.93	107	0.92	0.52 (196)	0.99	(0.81 1.16) #
Sneezing	14 mcg	112	0.71	111	0.77	0.54 (206)	1.08	(0.85 1.31)
	110 mcg	112	0.88	104	0.83	0.59 (199)	0.95	(0.75 1.14) #
	440 mcg	106	1.02	107	1.02	0.57 (196)	1.00	(0.83 1.17) #
Nasal Index ^a	14 mcg	112	2.05	111	2.08	3.62 (206)	1.01	(0.81 1.22) #
	110 mcg	112	2.56	104	2.31	3.48 (199)	0.90	(0.74 1.06) #
	440 mcg	106	2.82	107	2.70	3.76 (196)	0.96	(0.80 1.11) #

^a Nasal Index is the sum of Nasal Stuffiness, Nasal Discharge, and Sneezing.

^b Model is a two-way analysis of variance model with investigator and center as main effects and no interaction term

Ratio between (0.7,1.3, open interval)



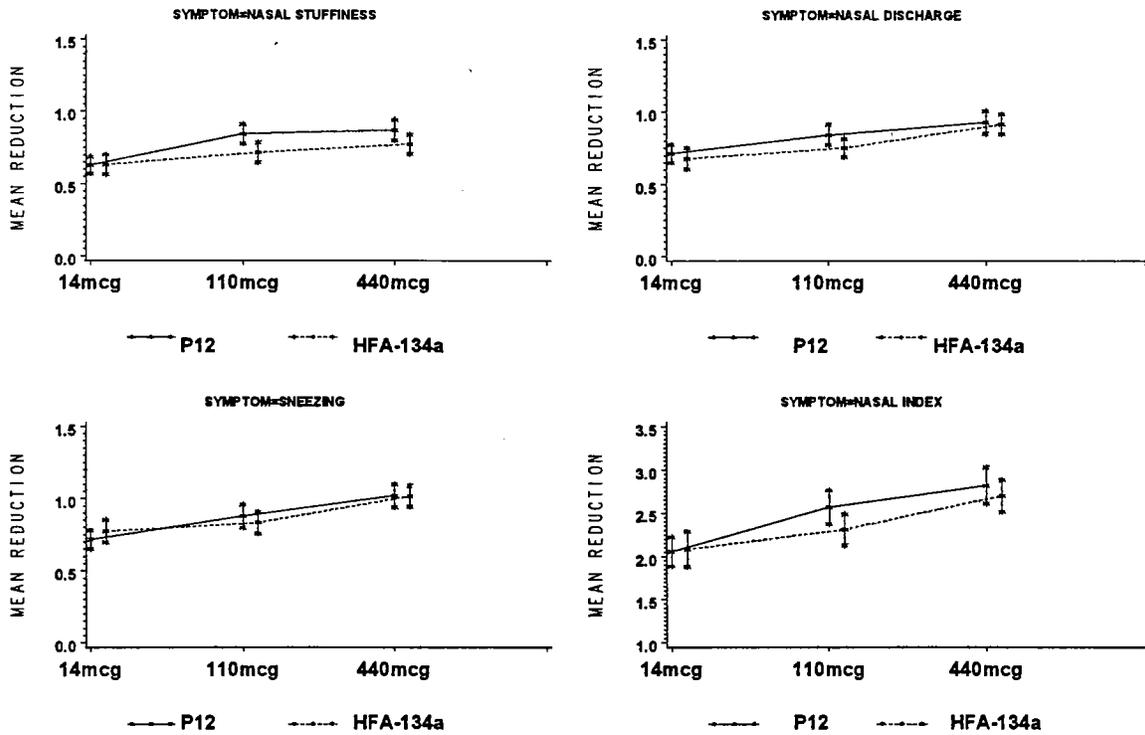
Bars: indicate range of standard error

Reviewer's Comment:

Though the efficacy of 110 & 440 mcg dose of Nasacort HFA-134a appears to approximate closest to that of 55 & 220 mcg dose of Nasacort P-12 respectively, the differences in efficacy between these two formulations were small. Patients who took a given dose of Nasacort P-12 experienced treatment effect similar to that of the same dose of Nasacort HFA-134a.

FIGURE 1

BETWEEN FORMULATION MEAN REDUCTION FROM BASELINE FOR OVERALL
REFLECTIVE WITH STANDARD ERROR
EVALUABLE PATIENTS (REFLECTIVE)
WEEK = OVERALL TIME = 24hrs



Comparison of Nasacort HFA-134a and Nasacort P-12 by Confidence Interval Analysis

Between Formulation Analysis on Reduction From Baseline for Reflective Scores

by Dose and 12 hour Timepoint for Overall Double-Blind Period

Evaluable Patients

Variable	Time	Treatment	Nasacort® P12		Nasacort HFA-134a		Mean ^b Squared Error (DF)	Ratio of HFA- 134a/ P12	Two one-sided 90% Confidence Interval of Ratio HFA-134a/P12
			N	Mean Reduction From Baseline	N	Mean Reduction From Baseline			
Nasal Stuffiness	1st 12 Hours	14 mcg	112	0.67	111	0.66	0.54	0.98	(0.74 1.22) #
		110 mcg	112	0.89	105	0.74	0.54	0.83	(0.65 1.02)
		440 mcg	106	0.94	107	0.83	0.56	0.89	(0.70 1.07) #
	2nd 12 Hours	14 mcg	111	0.54	111	0.59	0.45	1.09	(0.82 1.37)
		110 mcg	112	0.79	104	0.69	0.46	0.88	(0.68 1.07)
		440 mcg	106	0.82	107	0.70	0.46	0.85	(0.66 1.03)
Nasal Discharge	1st 12 Hours	14 mcg	112	0.76	111	0.71	0.57	0.94	(0.72 1.16) #
		110 mcg	112	0.85	105	0.77	0.55	0.91	(0.71 1.10) #
		440 mcg	106	0.99	107	1.00	0.62	1.01	(0.83 1.19) #
	2nd 12 Hours	14 mcg	111	0.64	111	0.62	0.50	0.96	(0.72 1.20) #
		110 mcg	112	0.82	104	0.72	0.48	0.88	(0.69 1.07)
		440 mcg	106	0.88	107	0.83	0.56	0.95	(0.75 1.14) #
Sneezing	1st 12 Hours	14 mcg	112	0.76	111	0.82	0.61	1.07	(0.84 1.30) #
		110 mcg	112	0.91	104	0.86	0.63	0.94	(0.75 1.14) #
		440 mcg	106	1.09	107	1.10	0.72	1.01	(0.83 1.19) #
	2nd 12 Hours	14 mcg	111	0.65	111	0.72	0.59	1.12	(0.85 1.38)
		110 mcg	112	0.84	104	0.80	0.67	0.96	(0.74 1.17) #
		440 mcg	106	0.97	107	0.91	0.58	0.93	(0.76 1.11) #
Nasal Index ^a	1st 12 Hours	14 mcg	112	2.19	111	2.19	4.18	1.00	(0.79 1.20) #
		110 mcg	112	2.64	104	2.37	3.85	0.90	(0.73 1.06) #
		440 mcg	106	3.02	107	2.93	4.51	0.97	(0.81 1.13) #
	2nd 12 Hours	14 mcg	111	1.83	111	1.93	3.62	1.05	(0.82 1.29) #
		110 mcg	112	2.45	104	2.21	3.67	0.90	(0.73 1.08) #
		440 mcg	106	2.67	107	2.44	3.69	0.91	(0.75 1.07) #

Abstracted from Appendix IV, Section A, Table B.2.1.

- a Nasal Index is the sum of Nasal Stuffiness, Nasal Discharge, and Sneezing
- b Model is a two-way analysis of variance model with investigator and center as main effects and no interaction term.
- # Ratio between (0.7,1.3 open interval)

Reviewer's Comment:

1. *These two formulations meet the sponsor's criteria of bioequivalence when the comparisons were made with efficacy data at the 24 hours time point, the first or the second 12 hour time point. Though our Division has no predefined criteria of comparability or bioequivalence for topical products, the sponsor's confidence interval analysis does serve to quantify the similarity between the dose response curves of these formulations.*

2. *The mean change from baseline of nasal index of the 440 mcg dose of Nasacort HFA is:*
 - a). *Numerically larger than that of the 110 mcg dose of the same product, thus supporting the superiority of the higher dose. However, this increment in the benefit of the higher dose is small and statistically insignificant.*
 - b). *Numerically closer to that of the 110 mcg dose of Nasacort P-12 than that of the 440 mcg dose, and probably closer to that of 220 mcg dose of Nasacort P-12 which was not evaluated in this study.*

4. Secondary Efficacy Analysis

- a) **Efficacy Analysis of the Symptom Severity at The End of Dosing Interval**

The mean reduction from baseline in the "snap shot" variables for nasal stuffiness, nasal discharge, and nasal index for the 440 mcg dose was significantly greater than that of the placebo.

**Analysis of Mean Change From Baseline in "Snap Shot" Symptom Score
for All Treated Patients Over the 2 Week Double blind period**

Variable	Treatment	N	Baseline Mean	Adjusted Mean ^b Change from Baseline (S.E.)	Within Formulation P-value ^c versus		
					Placebo	14 mcg	110 mcg
Nasal Stuffiness	14 mcg P12	75	2.43	-0.47 (0.08)	0.08		
	110 mcg P12	77	2.33	-0.60 (0.08)	0.00#	0.27	
	440 mcg P12	72	2.25	-0.59 (0.08)	0.01*	0.30	0.95
	14 mcg HFA-134a	73	2.41	-0.39 (0.08)	0.29		
	110 mcg HFA-134a	69	2.14	-0.39 (0.09)	0.29	1.00	
	440 mcg HFA-134a	76	2.36	-0.67 (0.08)	0.00#	0.02*	0.02*
	Placebo	71	2.25	-0.26 (0.08)			
Nasal Discharge	14 mcg P12	76	2.27	-0.48 (0.08)	0.23		
	110 mcg P12	77	2.17	-0.63 (0.08)	0.01*	0.20	
	440 mcg P12	72	2.07	-0.64 (0.09)	0.01*	0.18	0.94
	14 mcg HFA-134a	73	2.21	-0.30 (0.09)	0.80		
	110 mcg HFA-134a	69	1.87	-0.37 (0.09)	0.76	0.58	
	440 mcg HFA-134a	76	2.14	-0.67 (0.08)	0.01*	0.00#	0.01*
	Placebo	71	2.22	-0.33 (0.09)			
Sneezing	14 mcg P12	76	1.78	-0.45 (0.10)	0.44		
	110 mcg P12	77	1.69	-0.70 (0.10)	0.01*	0.07	
	440 mcg P12	72	1.54	-0.57 (0.10)	0.11	0.39	0.35
	14 mcg HFA-134a	73	1.84	-0.39 (0.10)	.76		
	110 mcg HFA-134a	68	1.45	-0.45 (0.10)	0.48	0.68	
	440 mcg HFA-134a	76	1.72	-0.74 (0.10)	0.00*	0.01*	0.04*
	Placebo	71	1.70	-0.35 (0.10)			
Nasal Index ^a	14 mcg P12	75	6.45	-1.35 (0.23)	0.21		
	110 mcg P12	77	6.18	-1.93 (0.23)	0.00#	0.08	
	440 mcg P12	72	5.87	-1.80 (0.23)	0.01*	0.17	0.70
	14 mcg HFA-134a	73	6.46	-1.08 (0.23)	0.67		
	110 mcg HFA-134a	68	5.49	-1.20 (0.24)	0.43	0.71	
	440 mcg HFA-134a	76	6.21	-2.07 (0.23)	0.00#	0.00#	0.01*
	Placebo	71	6.17	-0.94 (0.24)			

^a Nasal Index is the sum of Nasal Stuffiness, Nasal Discharge, and Sneezing

^b Means adjusted for differences among investigators.

^c p-values are computed from t-tests for a two-way analysis of variance model with treatment and center as main effects and no interaction term.

* p < 0.05 for 2-tailed test. # Also significant for p < 0.05 for 2-tailed, adjusted for multiple comparison.

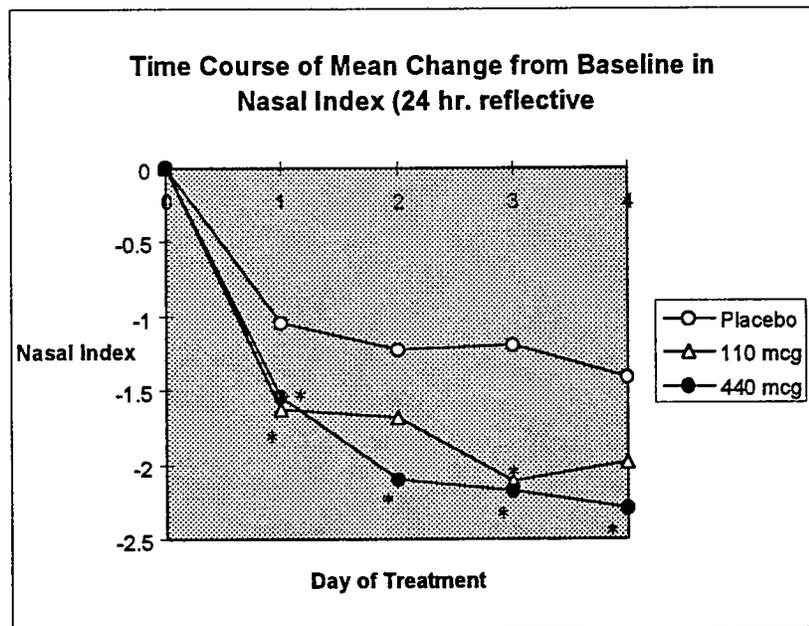
Reviewer's Comment:

This end of dosing interval analysis yields a different result from that based on reflective symptom scores. The mean change from baseline of each of the rhinitis symptom scores of the 440 mcg dose of Nasacort HFA-134a is significant greater than that of the 110 mcg dose and that of the placebo. These findings support the following:

1. Nasacort HFA-134a is effective against these rhinitis symptoms.
2. The superiority of the 440 mcg dose over the 110 mcg dose.
3. The adequacy of the once daily dosing interval of Nasacort HFA-134a for the 440 mcg dose.

b) Time Course of Treatment Response in Nasacort HFA-134a Treatment Groups

(1) Reflective Symptom Scores



* $P < 0.05$ for a 2-tailed t-test.

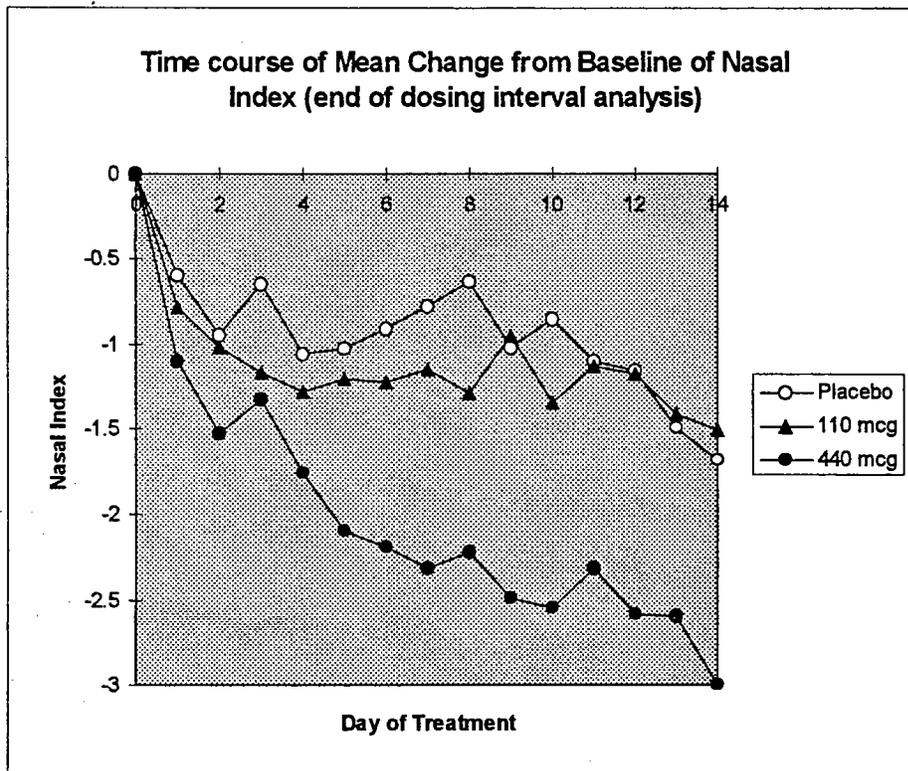
Reviewer's Comment:

There was a significant reduction in the mean change from baseline in the nasal index scores for both triamcinolone acetonide treatment groups. These findings suggested that the onset of action for Nasacort HFA-134a is Day 1. A more stringent criteria for determining the day of onset is based on the mean change from baseline of nasal index scores collected at the end of

dosing interval. However, it is debatable that the day of onset of action requires demonstration of significant reduction of symptoms at the end of dosing interval. The time course of the change in nasal index as determined at the end of dosing interval is presented below.

(2) End of Dosing Interval Analysis

Nasacort HFA

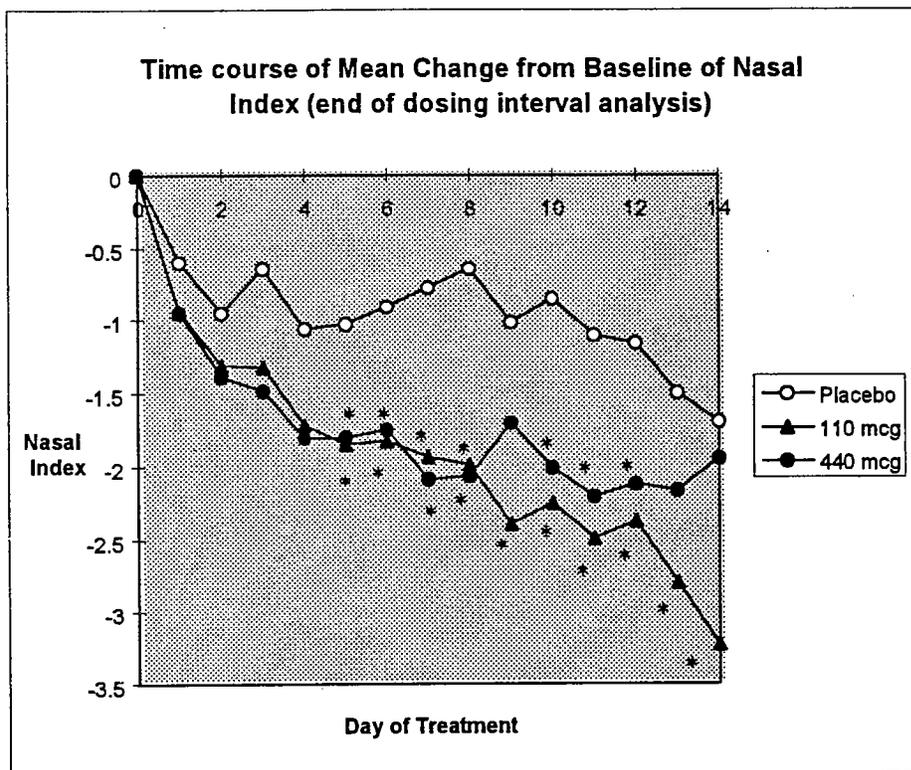


Reviewer's Comment:

Statistical significant reduction in the mean change from baseline nasal index scores was observed on Day 5 and later days for the 440 mcg group, but on none of the days for the 110 mcg group. These data support the adequacy of the once daily dosing interval for the 440 mcg dose, but not for the 110 mcg dose. A point of caution in this conclusion is that the analysis above did not take into account the difference in baseline symptom scores for the 110 mcg group as compared to the 440 mcg group and the placebo group. The mean baseline index score of the 110 mcg group was 1 point lower than that of the placebo group (see page 29), and

adjustment of the baseline difference by ANCOVA might yield a more favorable finding for the 110 mcg group.

Nasacort P12



Comment

The day of onset was Day 5 based on end of dosing interval analysis.

APPEARS THIS WAY
ON ORIGINAL

c) Efficacy Analysis for the Second 12 hour Period Post Dosing

Analysis of Change From Baseline in Reflective Symptom Score
All Treated Patients
Overall Double-Blind Period for Second 12 Hours (AM)

Variable	Treatment	N	Baseline Mean	Adjusted Mean ^b Change from Baseline (S.E.)	Within Formulation		
					Placebo	14 mcg	110 mcg
Nasal Stuffiness	14 mcg HFA-134a	113	2.46	-0.59 (0.06)	0.00#		
	110 mcg HFA-134a	106	2.29	-0.67 (0.07)	0.00#	0.36	
	440 mcg HFA-134a	111	2.32	-0.66 (0.06)	0.00#	0.48	0.84
	Placebo	109	2.32	-0.31 (0.06)			
Nasal Discharge	14 mcg HFA-134a	113	2.37	-0.62 (0.07)	0.01*		
	110 mcg HFA-134a	106	2.19	-0.71 (0.07)	0.00#	0.34	
	440 mcg HFA-134a	111	2.28	-0.82 (0.07)	0.00#	0.03*	0.24
	Placebo	109	2.31	-0.38 (0.07)			
Sneezing	14 mcg HFA-134a	113	2.18	-0.74 (0.07)	0.12		
	110 mcg HFA-134a	105	1.84	-0.80 (0.08)	0.04*	0.56	
	440 mcg HFA-134a	111	1.98	-0.90 (0.07)	0.00#	0.11	0.32
	Placebo	109	2.06	-0.57 (0.07)			
Nasal Index ^a	14 mcg HFA-134a	113	7.00	-1.95 (0.17)	0.01*		
	110 mcg HFA-134a	105	6.34	-2.20 (0.18)	0.00#	0.33	
	440 mcg HFA-134a	111	6.57	-2.38 (0.18)	0.00#	0.09	0.47
	Placebo	109	6.68	-1.26 (0.18)			

Abstracted from Appendix IV, Section A, Table 7.1.1A

^a Nasal Index is the sum of Nasal Stuffiness, Nasal Discharge, and Sneezing

^b Means adjusted for differences among investigators.

^c p-values are computed from t-tests for a two-way analysis of variance model with treatment and center as main effects and no interaction term.

* p < 0.05 for 2-tailed test.

Also significant for p < 0.05 for 2-tailed, adjusted for multiple comparison; refer to Appendix IV, Section A, Table 7.1.1 for p-value.

Reviewer's Comment:

The mean changes from baseline of each rhinitis score of both the 110 mcg dose and the 440 mcg dose were statistically significantly different from that of the placebo. These findings suggest a significant treatment effect during the second 12 hour period post dosing in subjects treated with 110 mcg dose of Nasacort HFA inspite of the fact that significance difference was not noted when the analysis was based on the end of dosing interval.

**APPEARS THIS WAY
ON ORIGINAL**

E. SAFETY

This trial compared the safety of Nasacort HFA-134a with that of Nasacort P-12, and the HFA-containing placebo. This comparison provides opportunity to identify the adverse effects associated with the excipients in Nasacort HFA-134a, including the propellant.

1. Serious Adverse Events
There were none.
2. Non-serious adverse events

**Adverse Events with Incidence \geq 3% Irrespective of Drug Relationship
by Dose and Treatment Group
Seasonal Allergic Rhinitis**

Frequently Reported AEs ^a	Treatment Group						
	Placebo	P12 14 mcg	P12 110 mcg	P12 440 mcg	HFA-134a 14 mcg	HFA-134a 110 mcg	HFA-134a 440 mcg
Headache	8.1%	8 (7.1%)	8 (7.0%)	17 (15.7%)	10 (8.8%)	11 (10.3%)	7 (6.2%)
Rhinitis	2 (1.8%)	2 (1.8%)	7 (6.1%)	3 (2.8%)	6 (5.3%)	5 (4.7%)	4 (3.5%)
Application site reaction	9 (8.1%)	14 (12.4%)	8 (7.0%)	6 (5.6%)	14 (12.4%)	16 (15.0%)	17 (15.0%)
Sinusitis	2 (1.8%)	4 (3.5%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)

Abstracted from Study 311, Appendix V, Table 19 (Vol. 1.33, Page 8-13-109).

^a Present in at least 3% of patients in any treatment group.

Reviewer's Comment:

Of particular interest to us are adverse events that occurred in Nasacort HFA-134a groups at incidence comparable to or higher than that of the placebo. The only adverse event above that meets this criterion is application site reaction, which will be analyzed further as follows.

3. Topical Effect

Overall nasal AEs were categorized by synonym term into the following (RPR terms): dry mucous membranes, epistaxis, nasal irritation, naso-sinus congestion, sneezing, throat discomfort, and URI.

ADVERSE CLINICAL EXPERIENCES RELATED TO TOPICAL EFFECTS (CONSIDERED POSSIBLY RELATED TO STUDY MEDICATION)

Adverse Experiences (AE)	Placebo	P12 Inhaler			HFA-134a Inhaler		
		14 mcg	110 mcg	440 mcg	14 mcg	110 mcg	440 mcg
Nasal AEs (overall)	14 (12.6%)	21 (18.6%)	18 (15.7%)	10 (9.3%)	23 (20.4%)	22 (20.6%)	21 (18.6%)
Dry Mucous Membranes	0%	0%	0%	0%	0%	0.9%	0%
Epistaxis	1.8%	2.7%	2.6%	0%	0.9%	1.9%	1.8%
Nasal Irritation	3.6%	5.3%	6.1%	0.9%	8.8%	7.5%	6.2%
Naso-Sinus Congestion	0%	0%	0.9%	1.9%	3.5%	0.9%	1.8%
Sneezing	7.2%	9.7%	10.4%	5.6%	11.5%	14.0%	15.9%
Throat Discomfort	1.8%	2.7%	1.7%	0.9%	0.9%	0.9%	0%

Abstracted from Appendix VI, Table 34.

When comparing the P12 and HFA-134a formulations for sneezing, there is a slight increase in incidence in the HFA-134a group. Nasal irritation, for the 440 mcg groups, was higher for the HFA-134a formulation. However, when compared within formulations, the 440 mcg groups reported the lowest incidence of nasal irritation among the three active treatment groups.

Reviewer's Comment:

1. Nasacort HFA-134a versus placebo

The difference between these two formulations is triamcinolone acetonide, and the presence of a dose dependency supports a causal relationship. Nasal irritation,

nasal sinus congestion, and sneezing occurred at slightly higher incidence than the placebo. Of these, only sneezing showed dose dependency.

2. Nasacort HFA-134a versus Nasacort P-12

The differences between these two formulations are the excipients, including the propellant. Comparison between them in the same randomized trial provides clue on excipient-related adverse events. As compared to those who received Nasacort P-12, subjects treated with Nasacort HFA-134a had slightly higher incidence of nasal irritation and sneezing.

4. Laboratory Findings

Abnormal changes observed were small and no excess in incidence of abnormal findings were observed in the Nasacort HFA-134a treatment groups as compared to other treatment groups.

**APPEARS THIS WAY
ON ORIGINAL**

V. Long Term Safety Trial- Study 405

A. Primary Objective

To study the long term safety of Nasacort HFA-134a Nasal Inhaler in adolescent and adult patients with perennial allergic rhinitis.

Reviewer's Comment:

- 1). *Although this long-term study was primarily for the evaluation of safety, an overall assessment of rhinitis symptoms was recorded independently by both the patient and investigator at each visit, following enrollment, throughout the open-label period. In the absence of a placebo control, efficacy evaluation is not meaningful.*

- 2). *The adverse event profile of triamcinolone acetonide has been evaluated extensively in the past using other products containing this active ingredient. The primary purpose of this trial would be to evaluate the safety of the excipients, i.e. HFA propellant.*

B. Participating Investigators

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In-house and field audits were performed by the sponsor in order to verify the information collected at Dr. Ziering's site. Following the review of these audits as well as all study source documentation, it was determined that a comparison should be conducted to evaluate the adverse event profiles for the study populations with and without Dr. Ziering's patients. The

results from this comparison support the inclusion of Dr. Ziering's site for consideration of the overall safety profile of this product. Furthermore, two serious adverse events were reported by Dr. Ziering. Both events (spinal fluid leak and staph infection) occurred in the same patient after an elective back surgery.

Reviewer's Comment:

C. Clinical Methodology

This is an open-label long-term safety study which consisted of a screening phase, a baseline period, and a twelve month open-label treatment period.

1. Inclusion Criteria

- a) Male or non-pregnant, non-lactating females at least 12 years of age
- b) At least a two year history of perennial allergic rhinitis (may also have seasonal allergic exacerbations.), who, in the opinion of the investigator, were candidates for treatment with nasal steroids based on a history of inadequate control of symptoms with antihistamines, decongestants and/ or immunotherapy, or prior successful treatment with nasal steroids.
- c) Positive skin prick test for perennial allergens present in the patient's environment.
- d) Was able to participate in the study without taking concomitant medications for rhinitis symptoms during specified period (baseline).
- e) Demonstrated eosinophilia in nasal secretions at screening.
- f) Had an aggregated sum of at least 24 points for four nasal symptoms (discharge, stuffiness, itching, sneezing) over the four day period immediately preceding the baseline visit (Visit 2).

2. **Exclusion criteria**

- a). The use of medications for the specific purpose of alleviating the symptoms of PAR from the six days preceding Visit 2 (baseline visit) until completion of the study except for severe allergy symptoms. Patients could not receive medication for another indication that could produce or relieve the signs and symptoms of PAR or effect their ability to subjectively rate their rhinitis symptoms. Any patient who used disallowed medications during the study may have been discontinued at the sponsor's discretion. Patients were permitted to use oral antihistamines and/or decongestants as well as topical vasoconstrictor/decongestant eye preparations on an as needed basis for severe allergy symptoms only. Each use of the medication was to be recorded by the patient on the diary card.
- b). The development of any illness that interfered with the patient's assessment of PAR symptoms (e.g. acute sinusitis, influenza, or upper respiratory tract infection) would not be cause for discontinuation of that patient unless the illness required disallowed medication (e.g. oral or injected corticosteroids).

3. **Dosing of Nasacort HFA-134a**

Nasacort HFA-134a Nasal Inhaler, 55 mcg per actuation, was administered once daily in the morning. Initially, following 2 weeks of fixed 220 mcg/day, patients were allowed to adjust dose up to 440 mcg/day or down to 110 mcg/day. However, following recommendations of our Division, approximately 4 months post study initiation, the dose was standardized to 440 mcg/day for all patients. This maximization of the daily dose was intended to maximize the opportunity to capture triamcinolone acetonide related adverse events. The number of puffs of study drug, the concomitant medications, and the indications for their use were recorded on the diary cards.

4. **Criteria for Evaluation**

Physical examinations; measurements of vital signs; observed changes in the mucous membranes of the nose, mouth, and throat; laboratory assessments; and reports of adverse experiences. Suspected fungal infection of oral cavity was confirmed by a laboratory culture. Patients recorded any adverse experience or unusual health-related event on the diary card.

5. Interim visits

During interim visits (Week 2, 1st month, second month, and every other month henceforward, patients returned to the clinic, and both patient and investigator independently assessed the degree of symptom relief for the period since the previous visit. Diary cards were reviewed for completeness and correctness, and patients were interviewed for reports of adverse experiences and the use of study and concomitant medications. Mucous membranes of the nose, mouth, and throat were examined for fungal infection. Sufficient study medication and calendar diaries were dispensed to last until the next visit.

6. Global Symptom Assessments

A global evaluation assessing treatment effectiveness was made at Visits 3-10. The physician and patient recorded their opinion independently, blinded from each other according to the following scale:

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- 0 =No Relief
- 1 =Slight Relief
- 2 =Moderate Relief
- 3 =Marked Relief
- 4 =Complete Relief

7. Statistical Analysis

No statistical analysis of efficacy was intended or performed for this study

8. **RESULTS**

a) **Demography**

The mean age was 32 years with a range from 12 to 69 years. Most patients were Caucasian (92%) with more males (53%) than females (47%).

Treatment Group	N	Sex		Race		Age (years)		Height	Weight
		M (%)	F (%)	Caucasian (%)	Other (%)	Mean	Range	Mean (cm.)	Mean (kg.)
RG 5029T	396	52.8	47.2	92.4	7.6	31.9	12-69	169.9	73.2

b) **Extent of Exposure**

The average number of days treated was 267.7 with a range from 1 to 393 days.

Two hundred ninety-six (75%) patients received treatment of 440 mcg/day for more than 6 months.

MONTHS	TOTAL PATIENTS (N)	PERCENT OF PATIENTS (%)
≤ 2	43	10.9
>2 and ≤6	57	14.4
>6	296	74.7

c) **Patient Disposition**

SUMMARY OF PATIENT STUDY COMPLETION STATUS

Enrollment Status	RG 5029T 440 mcg
<u>TOTAL ENROLLED</u>	396
Completed, Study	256
Percent (%) Completed	64.6
<u>Total Discontinued</u>	140 (35.4%)
Lost To Follow - up	23 (5.8%)
Adverse Clinical Experience	34 (8.6%)
Protocol Deviation	17 (4.3%)
Therapy Ineffective	8 (2.0%)
Consent Withdrawn	29 (7.3%)
Other	29 (7.3%)

Patients that completed Visit 9 (month 10) were to be designated as "completed study". Patients not having completed Visit 9 were discontinued as "other-sponsor's request". At the time that the site was notified to discontinue the study, 40 patients had been enrolled. Of these patients, 13/40 completed the study and 27/40 were dropped from the study. Of the 27 patients that were dropped, 16/27 were designated as "other - sponsor's request".

d) **Safety Findings**

Of the 396 patients included in the safety population, 349 (88.1%) patients reported adverse experiences. Review of adverse experiences by body system revealed the highest percentage (70.5%) of patients experienced respiratory system-related adverse experiences. The most frequently reported adverse experiences were pharyngitis (36.1%), rhinitis (28.8%), application site reaction (26.5%), headache (25.5%), epistaxis (21.7%), and sinusitis (16.7%).

e) Patients discontinued due to adverse experiences

Pt. No.	Age/ Sex	Adverse Experience (COSTART)	Study Day ^a	Duration	Severity	Relationship to Study Drug	Outcome
012	28/F	Rhinitis	136	26 days	moderate	probable	recovered
028	33/F	Rhinitis	168	58 days	moderate	probable	recovered
		Epistaxis	182	12 days	mild	probable	recovered
064	12/M	Application site reaction	121	23 days	mild	probable	recovered
079	14/M	Application site reaction	104	64 days	mild	probable	recovered
		Application site reaction	104	64 days	mild	probable	recovered
080	39/M	Rhinitis	1	95 days	mild	probable	recovered
086	34/M	Application site reaction	126	8 days	moderate	probable	recovered
		Epistaxis	133	3 days	mild	probable	recovered
087	47/M	Nasal Septum Discomfort	57	ongoing	mild	probable	ongoing
095	23/F	Pneumothorax	22	ongoing	mild	possible	ongoing
104	46/F	Infection	134	22 days	moderate	probable	recovered
112	25/M	Headache	2	20 days	severe	possible	recovered
113	30/F	Headache	8	13 days	severe	possible	recovered
114	21/F	Epistaxis	205	55 days	mild	possible	recovered
133	28/F	Pregnancy-Unintended ^c	258	235 days	mild	none	recovered
164	24/F	Pregnancy-Unintended ^c	278	249 days	mild	none	recovered
190	43/M	Rhinitis	126	23 days	mild	probable	recovered
196	46/F	Epistaxis	245	15 days	mild	probable	recovered

Abstracted from Appendix VI, Table 20.

- ^a Refers to study day from beginning of active treatment.
^b Serious adverse experience for which the patient discontinued the study.
^c Pregnancy resulted in a normal delivery.
^c Pneumothorax follow up revealed that it resolved after 293 days

TABLE 5
PATIENTS DISCONTINUED DUE TO ADVERSE EXPERIENCES
(CONTINUED)

Pt. No.	Age/Sex	Adverse Experience (COSTART)	Study Days ^a	Duration	Severity	Relationship to Study Drug	Outcome
246	38/F	Epistaxis	93	4 days	moderate	possible	recovered
263	35/M	Epistaxis	44	63 days	mild	possible	recovered
276	65/M	Rhinitis	161	73 days	mild	probable	recovered
282	43/M	Rhinitis	169	22 days	moderate	probable	recovered
288	65/F	Carcinoma-Breast ^b	196	ongoing	severe	none	ongoing
291	60/M	Rhinitis	78	117 days	moderate	probable	recovered
297	26/M	Epistaxis	63	25 days	moderate	probable	recovered
299	51/M	Rhinitis	120	28 days	moderate	probable	recovered
311	19/F	Application Site Reaction	8	107 days	mild	probable	recovered
321	23/M	Epistaxis	18	86 days	moderate	probable	recovered
341	40/F	Rhinitis	70	85 days	severe	probable	recovered
364	28/F	Application Site Reaction	4	12 days	mild	probable	recovered
		Application Site Reaction	4	12 days	mild	probable	recovered
		Nasal Septum Discomfort	15	21 days	mild	probable	recovered
371	13/M	Application Site Reaction	96	13 days	mild	probable	recovered
379	20/M	Headache	49	6 days	moderate	probable	recovered

383	26/M	Application Site Reaction	36	22 days	moderate	probable	recovered
407	15/M	Sinusitis	200	32 days	moderate	none	recovered
408	14/M	Depression ^b	49	ongoing	moderate	none	ongoing
411	39/F	Nasal Septum Discomfort	119	113 days	moderate	probable	recovered

Abstracted from Appendix VI, Table 20.

- a Refers to study day from beginning of active treatment.
- b Serious adverse experience for which the patient discontinued the study
- c. Pregnancy resulted in a normal delivery.
Pneumothorax follow up revealed that it resolved after 293 days

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Reviewer's Comment:

None of the serious adverse events that led to the premature withdrawal of patients from the trial were plausibly related to Nasacort HFA-134a treatment. Nasal septum discomfort as used by the sponsor obscured more serious conditions including ulceration and excoriation of the septum (see below).

f) **Summary of adverse clinical experience (open - label period)**

Variables	HFA-134a 440 mcg	HFA-134a 440 mcg ^a
Total Number of Patients	396	356
Number of Patients with AEs	349	325
% of Patients with AEs	88.1%	91.3%
Frequently Reported AEs (≥3%)	N (% of Patients)	N (% of Patients)
Pharyngitis	143 (36.1%)	138 (38.8%)
Rhinitis	114 (28.8%)	110 (30.9%)
Application Site Reaction	105 (26.5%)	95 (26.7%)
Headache	101 (25.5%)	98 (27.5%)
Epistaxis	86 (21.7%)	84 (23.6%)
Sinusitis	66 (16.7%)	66 (16.7%)
Injury Accident	36 (9.1%)	34 (9.6%)
Flu Syndrome	35 (8.8%)	35 (9.8%)
Cough - Increased	30 (7.6%)	28 (7.9%)
Pain	25 (6.3%)	25 (7.0%)
Pain Back	23 (5.8%)	22 (6.2%)
Reaction Unevaluable	23 (5.8%)	22 (6.2%)
Tooth Discomfort	21 (5.3%)	21 (5.9%)
Dyspepsia	20 (5.1%)	20 (5.6%)
Bronchitis	20 (5.1%)	17 (4.8%)
Infection	18 (4.5%)	17 (4.8%)
Nasal Septum Discomfort	18 (4.5%)	18 (5.1%)
Otitis Media	14 (3.5%)	13 (3.7%)
Nausea	13 (3.3%)	13 (3.7%)
Pain Abdomen	12 (3.0%)	11 (3.1%)
Dysmenorrhea	12 (3.0%)	12 (3.4%)

Abstracted from Appendix VI, Table 19 and Appendix VII, Table 3

^a Excluding Ziering's patients

ADVERSE CLINICAL EXPERIENCES RELATED TO TOPICAL EFFECTS

Adverse Event ^a	Number of Patients (%)	Number of Patients (%) ^b
Overall Naso-Pharyngeal AEs	173 (43.7%)	160 (44.9%)
Nasal Irritation	89 (22.5%)	79 (22.2%)
Naso-Sinus Congestion	5 (1.3%)	5 (1.4%)
Throat Discomfort (Pharyngitis)	3 (0.8%)	3 (0.8%)
Dry Mucous Membranes	16 (4.0%)	13 (3.7%)
Sneezing	82 (20.7%)	77 (21.6%)
Epistaxis	77 (19.4%)	75 (21.1%)

Abstracted from Appendix VI, Table 36, and Appendix VII, Table 4, AEs considered possibly or probably related to study medication.

^a Adverse experience decoding terms for Application Site Reaction, Rhinitis, Epistaxis, Pharyngitis, and Sinusitis COSTART terms.

^b Excluding Zierring's patients

Reviewer's Comment:

1). Usefulness of this open-label study

In the absence of a placebo control group, or a reliable historical incidence of adverse events in a comparable patient population, the usefulness of the safety data above is very limited. The principal function of this trial would be to generate signals for serious or severe adverse events which are possibly related to Nasacort HFA-134a treatment.. No drug-related serious adverse events were observed, but clinically significant topical reactions were identified.

2). Clinically Significant Topical reactions

Upon my request, the sponsor submitted a list of all patients who reported nasal septum discomfort, and based on this a number of patients who developed nasal septum injury during the trial were identified. 7 of these 18 patients who reported nasal septum discomfort had objective evidences of ulceration, abrasion, erosion, or excoriation of the nasal septum. These topical reactions are clinically significant as one or more these conditions are expected to precede the perforation of the nasal septum.

Table 2 Literal adverse event terms for nasal septum discomfort

(facsimile received on June 10, 1997)

Physical findings indicative of physical damage to the nasal septum among the 18 patients who complained of nasal septum discomfort

Patient Code	AECOS	AESYN
00053	<i>Nasal septum discomfort</i>	<i>erosion septum anterior</i>
00067	<i>Nasal septum discomfort</i>	<i>nasal septal ulceration</i>
000364	<i>Nasal septum discomfort</i>	<i>nasal septal ulceration</i>
000369	<i>Nasal septum discomfort</i>	<i>nasal septal ulceration</i>
000165	<i>Nasal septum discomfort</i>	<i>abrasion septum nasal</i>
000405	<i>Nasal septum discomfort</i>	<i>excoriation nasal septum</i>
000411	<i>Nasal septum discomfort</i>	<i>excoriation nasal septum</i>

The list above includes only those who had nasal septum damage. Of the patients who experienced nasal septum discomfort, a high percentage had erosion or ulceration of their nasal septums. It is advisable for Nasacort users who experience nasal septum discomfort to reevaluate their technique in the application of the Nasacort to minimize the deposition of triamcinolone onto their septums.

Upon inspection of the adverse event line listings of all patients in Study 405 (Vol 1.44: 8-24-7 to 8-24-97), more patients with adverse events at the nasal septum were identified. The following list includes all patients who experienced either nasal septum epistaxis or erosion/ ulceration.

Patients who experienced nasal septum bleeding or damage during the clinical trial

Patient Allocation Number	Adverse Experience (synonym term)	Onset Day (Study Day)	With complaint of nasal septum discomfort during clinical trial	Study Day that the Event started	Comments
33	nasal septal bleeding		--		
40	nasal septal bleeding		--		
44	nasal septal bleeding		--		
49	nasal septal bleeding		--		
52	nasal septal bleeding		--		
53	erosion of septum anterior		yes	169	
87	ulceration septum nasal		no	57	
127	nasal septal bleeding		--		Took beconase prior t
130*	nasal septal bleeding		--		
134	nasal septal bleeding		--		
140	nasal septal bleeding		--		
141*	nasal septal bleeding		--		Took vancenase prior enrollment
143*	nasal septal bleeding		--		Took beconase prior t
165	abrasion nasal septum		yes	236	
341*	nasal septal bleeding		--		Took Nasacort prior t
345*	nasal septal bleeding		--		Took beconase prior t
348	nasal septal bleeding		--		
364	ulceration septum nasal		yes	15	

Patient Allocation Number	Adverse Experience (synonym term)	Onset Day (Study Day)	With complaint of nasal septum discomfort during clinical trial	Study Day that the Event started	Comments
369	ulcer anterior nasal septum		yes	15	
405	excoriation nasal septum		yes	188	
411	excoriation nasal septum		yes	119	
427	ulceration nasal		no		

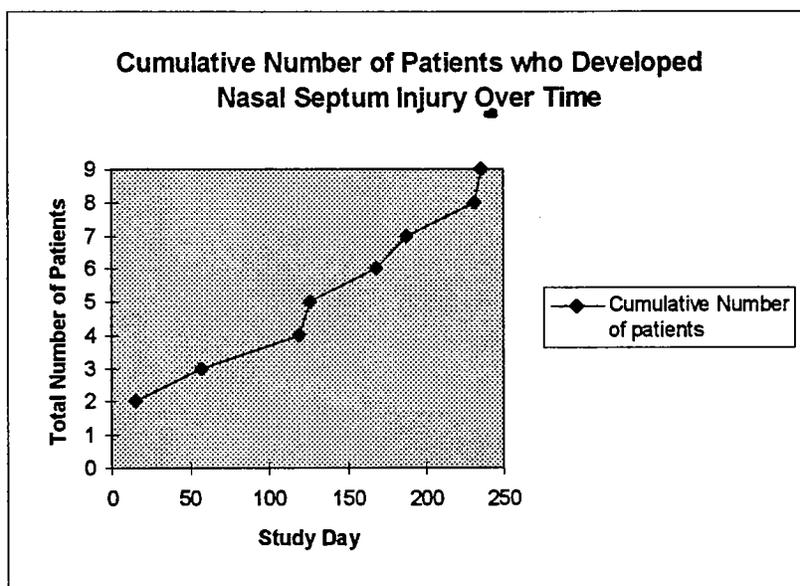
Shaded cells: nasal septum injury (excluding bleeding)

-- : indicates nasal septal adverse event that was not categorized by the sponsor under the term 'nasal septum discomfort'.

a). Nasal Septum Injury

22 of the 396 (or 5.5%) enrolled subjects developed nasal septum disorders during this 12 month trial. 8 of these (2%) had ulceration, erosion or excoriation of their septums, and the earliest occurrences took place less than 16 days after the initiation of Nasacort HFA-134a treatment. The rest (14 patients) had bleeding at the nasal septum.

Nasal Injury excluding epistaxis



There was no evidence of leveling off of occurrence of this event over this study period.

b). Relevant Past Medical History pertaining to Nasal Septum Disorders

Of the 8 subjects who developed nasal septum ulceration, abrasion or excoriation, only two gave a recent history of epistaxis prior to their enrollment, and none of these gave a recent history of topical corticosteroid use at the time they were screened for enrollment into this trial.

Of the 14 patients who reported epistaxis during the trial, 5 took nasal steroids prior to enrollment but none reported recent history of epistaxis.

3). 'Reaction Unevaluable'

As requested the sponsor submitted a list of all adverse events classified by the sponsor as 'reaction unevaluable' (facsimile dated June 10, 1997), and review of this list did not unveil any drug-related adverse reactions.

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VI. CONCLUSIONS

1. The sponsor had conducted all the required studies outlined in our Division's Points-to-Consider Document for the switching of nasal spray products.

2. Systemic Bioavailability

The systemic bioavailability of Nasacort HFA-134a is very similar to that of Nasacort P-12. Based on the pharmacokinetic data, as a group subjects who take the to-be-marketed dose of Nasacort HFA-134a will not be exposed to a higher systemic levels of triamcinolone acetonide than those who take the same dose of Nasacort P-12.

3. Efficacy

- a. Efficacy of Nasacort HFA-134a as compared to the placebo

The mean change from baseline of rhinitis symptom scores in the 110 mcg and 440 mcg groups were statistically different from than that of the placebo. Nasacort HFA-134a is therapeutically superior to the placebo.

- b. Comparability between formulations

For all practical purposes, patients on Nasacort P-12 can be switched to the same dose of Nasacort HFA-134a to attain similar level of relief of their rhinitis symptoms.

- c. Adequacy of the once daily dosing interval

Efficacy analysis based on symptom scores collected at the end of dosing interval supports the adequacy of the once daily dosing interval for the 440 mcg dose but not for the 110 mcg dose. However, the mean change from baseline of the reflective symptom scores for the second 12 hour period post dosing was statistically different from that of the placebo for both the 110 and 440 mcg doses. As long as patients whose symptoms at the end of dosing interval are not adequately managed by the 110 mcg dose have the recourse to attain a greater level of relief of their symptoms at the higher doses (220 and 440 mcg per day), the once daily dosing interval is acceptable for this product.

- d. The Day of Onset of Action

Based on the 24 hour reflective symptom scores, Day 1 was the first day of onset of action. However, based on the end of dosing interval scores, Day 5 is the day of onset of action. The day of onset of action depends on the definition. If the definition demands that the day be the one that Nasacort HFA-134a users achieve statistically greater reduction in symptom severity for the entire day as compared to the placebo, then the day of onset is Day 5.

4. Safety

From the standpoint of safety, the to-be-marketed doses of Nasacort HFA-134a are acceptable. As the 440 mcg once daily dose of Nasacort AQ, a product with higher systemic bioavailability than Nasacort HFA-134a, did not affect the hypothalamic, the to-be-marketed doses of Nasacort HFA-134a are not expected to have a clinically significant effect on this axis.

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MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY DRUG PRODUCTS (HFD-570)

APPLICATION #: N20-784 SPONSOR: Rhone-Poulenc Rorer CATEGORY OF DRUG: Corticosteroid MEDICAL REVIEWER: C. Kwong	APPLICATION TYPE: NDA PRODUCT/PROPRIETARY NAME: Nasacort HFA Nasal Inhaler USAN / Established Name: Triamcinolone Acetonide ROUTE OF ADMINISTRATION: Intra-nasal REVIEW DATE: January 14, 1997
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SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
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Dec. 16, 1996.	Dec. 19, 1996.	NDA	
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RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
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Overview of Application/Review:

This is a 60-Day review of this application. This product was developed by reformulating the currently marketed Nasacort Nasal Inhaler with HFA-134a. The sponsor claimed that the development program was created with input from our Division (pre-NDA meeting) and in accordance with the FDA document entitled "Points to Consider: Clinical Development Programs for New Nasal Spray Formulation". This NDA application consists of one two-week SAR efficacy trial in adults, one 12 month safety trial in subjects 12 years of age and older, and one pharmacokinetic study in adults. In each of these studies, the sponsor took the 'comparability' approach as proposed in the points-to-consider document. Comparison was made with Nasacort P-12 (CFC). Basing on the results from these studies, the established efficacy of Nasacort Nasal Inhaler (CFC) in both adults and the pediatric population, the pharmacokinetic and HPA axis study with Nasacort AQ, the sponsor is seeking approval for the labeling of Nasacort HFA for the treatment of both SAR and PAR in subjects 6 years of age and older.

Efficacy

The single pivotal trial was a dose-ranging efficacy study in SAR (Study 311) in subjects 18 years of age and older. The sponsor included a placebo and three doses of triamcinolone acetonide for each formulation (i.e. 14 mcg, 110 mcg and 440 mcg), though only two active doses are required. The to-be-marketed doses are 110, 220 and 440 mcg once daily.

Both reflective symptom scores and snap shot symptom scores were attained, and efficacy analysis was performed on all-treated and all evaluable patients. The primary efficacy analysis is the mean reduction from baseline of nasal stuffiness, nasal discharge, sneezing and nasal index for the overall double-blind period. As requested by our Division in a pre-NDA meeting, the sponsor had elected to make efficacy comparison between triamcinolone acetonide products using the evaluable population. This is our preference, because it is more difficult or vigorous to establish comparability using the evaluable population as compared to using the all-treated population because the former typically has lower variability in efficacy outcome as compared to the latter.

The duration of the SAR trial (2 weeks) is acceptable. Preliminary inspection of the primary efficacy analysis suggests that the mean reduction of the primary nasal parameters in subjects who took either triamcinolone acetonide product are comparable for each of the dose studied. This fulfills the requirement that the trial be designed to permit determination of a dose of the new formulation that is comparable to the highest marketed dose of the old formulation. Numerical superiority in symptom severity reduction in the 440 mcg triamcinolone acetonide group as compared to the 110 mcg group was observed, though the difference was not statistically significant. Nonetheless, this forms an adequate basis to support the approval of the higher dose as far as efficacy is concerned.

No efficacy study was performed in the pediatric population in accordance with the points-to-consider document which stated that efficacy and safety study in pediatric population in addition to what were done in adults are not required if the safety, efficacy, and pharmacokinetics of the new formulation are comparable to that of the reference formulation in adults. As described below, this situation applies for this product.

Pharmacokinetics

The pharmacokinetics of a single intranasal dose of 440 mcg of each product were compared among the same group of adults. These AUC_{0-∞} were comparable, and were lower than that of the same dose of Nasacort AQ in a cross-study comparison. This latter finding exempts the sponsor from the requirement to assess the effect of Nasacort HFA-134a on HPA axis.

Long Term Safety Studies

Study 405 was a 12 month, open-label study on 396 patients 12 years of age and older. The starting dose was 220 mcg per day, and after the first two weeks, patients were allowed to adjust the daily dose to 110 mcg or to 440 mcg as needed for adequate symptom relief. On recommendation of FDA, the sponsor modified their protocol while the trial was in progress so that the daily dose of triamcinolone acetonide was standardized to 440 mcg once daily. The intent was to maximize the chance of capturing adverse effect of triamcinolone acetonide and HFA. This study is particularly useful for evaluating the safety of the propellant since there is not a vast experience on the local effect of this excipient in the nasal cavity. There were 296 patients who were treated with the highest to-be-marketed dose of triamcinolone acetonide (i.e. 440 mcg dose) for 6 months or more. This meets even our minimum requirement for NME. As great difference between the adults and the pediatric population in the adverse response to the excipients is not expected. Additional long term safety study in children to evaluate the safety of these excipients in a long term safety trial is not required.

Outstanding Issues:

No outstanding issues have been identified at this stage of the review process. Two centers from Study 311 and two from Study 405 were recommended to DSI on February for inspection; final selection of two of these are at the discretion of DSI.

Recommended Regulatory Action: none at present

N drive location:

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDA:

Efficacy / Label Supp.: _____ Approvable _____ Not Approvable

Signed: Medical Reviewer: Cheng Kwong Date: 4/16/97

Medical Team Leader: [Signature] Date: 4/16/97

CC: NDA 20-784
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